also reduced in strains that exhibit resistance or intermediate susceptibility to vancomycin, although in some cases strains may still be classified as susceptible on the basis of clinical interpretive criteria.

Aminoglycosides The most common mechanism of resistance is due to acquisition of plasmid genes encoding transferase enzymes that modify aminoglycosides by the addition of acetyl, adenyl, or phosphate groups; these added groups decrease the drugs' binding affinity to their ribosomal target site. Transferases differ in which aminoglycosides they modify, and amikacin resistance occurs less often than resistance to gentamicin or tobramycin. More recently, plasmids encoding methyltransferases that modify the ribosomal site of aminoglycoside binding and confer resistance to all aminoglycosides have been found in enteric gram-negative bacteria. For streptomycin, a ribosomal protein mutation may cause resistance. In *Pseudomonas aeruginosa*, resistance may also occur through mutations causing increased expression of a chromosomally encoded efflux pump, MexXY.

Tetracyclines and Glycylcyclines For tetracyclines, resistance is most often plasmid mediated and attributable either to active efflux pumps, which are generally specific for tetracyclines, or to proteins that protect the ribosome from tetracycline action. Resistance to the glycylcycline tigecycline, which is not affected by the usual tetracycline resistance mechanisms, can occur through mutations that cause overexpression of certain broad-spectrum efflux pumps in *Proteus* species.

Macrolides, Ketolides, Lincosamides, and Streptogramins Resistance to macrolides, clindamycin, and quinupristin is most often due to plasmid-acquired methylases that modify the drug binding site on the ribosome. Resistance to quinupristin by this mechanism renders the quinupristin-dalfopristin combination bacteriostatic rather than bactericidal. Telithromycin, a ketolide, has an additional binding site on the ribosome and remains active in the presence of these methylases. Acquired genes encoding active efflux pumps can also contribute to resistance to macrolides in streptococci and resistance to macrolides, clindamycin, and dalfopristin in staphylococci. Plasmid-acquired drug-modifying enzymes in staphylococci can also cause resistance to quinupristin and dalfopristin. Macrolide resistance due to 23S rRNA mutations is uncommon in staphylococci and streptococci because of the multiple copies of the rRNA genes on the chromosomes of these species; such resistance may occur more frequently, however, in mycobacteria and *Helicobacter pylori*, which have only single chromosomal copies of these rRNA genes.

Chloramphenicol Resistance to chloramphenicol is most often due to a plasmid-encoded drug-modifying acetyltransferase.

Oxazolidinones Linezolid resistance has been seen in enterococci more often than in staphylococci and, in both organisms, is due to mutations in multiple copies of the 23S rRNA genes that reduce drug binding to the ribosome. A plasmid-acquired ribosomal methylase gene that confers resistance to both chloramphenicol and linezolid has also been found in some strains of staphylococci but is not yet widespread. Tedizolid may still be active against some but not all linezolid-resistant strains.

Mupirocin Resistance to mupirocin occurs by either mutation in the target leucyl-tRNA synthetase (low-level resistance) or the acquisition of a plasmid-encoded resistant tRNA synthetase (high-level resistance).

Sulfonamides and Trimethoprim Resistance to both of these antimetabolites is due to plasmid-acquired genes encoding resistant enzymes that bypass the inhibition of the native sensitive enzymes—a resistant dihydropteroate synthetase in the case of sulfonamides and a resistant dihydrofolate reductase in the case of trimethoprim.

Quinolones Resistance to quinolones is most often due either to chromosomal mutations altering the target enzymes DNA gyrase and DNA topoisomerase IV, with consequent reduction in drug binding, or to mutations that increase the expression of native broad-spectrum efflux pumps for which quinolones (among other compounds) are substrates. In addition, three types of genes can confer reduced susceptibility or low-level resistance by protecting target enzymes, modifying some quinolones, or pumping quinolones out of the cell (efflux). These genes are located on multidrug resistance plasmids that have spread worldwide. Their presence can promote the selection of higher levels of quinolone resistance linked to resistance to other antibacterial drugs that is encoded on the same plasmid.

Rifampin and Rifabutin Single mutations in the β subunit of RNA polymerase can cause high-level resistance to rifampin. Thus rifampin and other rifamycins are used for treatment of infections only in combination with other antibacterial drugs in order to prevent resistance.

Metronidazole Acquired resistance to metronidazole in *Bacteroides* species is rare. Such resistance has been reported in strains that lack endogenous nitroreductase activity or that have acquired *nim* genes responsible for further reduction of DNA-damaging nitroso intermediates to an inactive derivative. Active efflux and enhanced DNA repair mechanisms also have been associated with resistance.

Nitrofurantoin Resistance to nitrofurantoin in *Escherichia coli* can emerge through a series of mutations that progressively decrease the nitroreductase activity necessary for generating active nitrofuran metabolites.

Polymyxins Because of emerging multidrug resistance in gram-negative bacteria, colistin and polymyxin B are being used increasingly for infections due to resistant Enterobacteriaceae, *P. aeruginosa*, and *Acinetobacter* species. Rates of resistance vary. Resistance can emerge during therapy through mutations that cause reductions in the negative charge of the gram-negative bacterial cell surface, thereby reducing binding of the positively charged colistin.

Daptomycin The mechanisms of resistance to daptomycin are complex and involve mutations in several genes that can alter cell membrane charge and reduce daptomycin binding. Resistance to daptomycin is relatively infrequent but has emerged in some *S. aureus* strains with intermediate vancomycin susceptibility from patients treated with vancomycin but not with daptomycin. In some methicillin-resistant *S. aureus* (MRSA) strains, daptomycin resistance has been linked to acquired susceptibility to β-lactams; combinations of daptomycin and nafcillin have been successful for treatment of patients infected with resistant strains when daptomycin alone or in combination with other agents has failed. The mechanism of this effect is not yet clear.

PHARMACOKINETICS AND PHARMACODYNAMICS

The term *pharmacokinetics* describes the disposition of a drug in the body, whereas *pharmacodynamics* describes the determinants of drug action on the pathogen in relation to pharmacokinetic factors. An understanding of the principles governing these two areas is required for effective drug selection, dosing, and prevention of toxicities.

PHARMACOKINETICS

The process of drug disposition has four principal phases: absorption, distribution, metabolism, and excretion. These components determine the time course of drug concentrations in serum and subsequently the concentrations in other tissues and body fluids.

Absorption When a drug is given by a particular route, *absorption* is defined as the percentage of the dose that reaches the systemic circulation. For example, since IV administration provides direct access to the systemic circulation, 100% of a drug dose given IV is usually absorbed. The level of absorption becomes more relevant when non-IV routes are used—e.g., the oral, IM, SC, and topical routes. The percentage of a drug that is absorbed is termed its *bioavailability*. Examples of antibacterial agents with a high oral bioavailability include metronidazole, levofloxacin, and linezolid. IV administration and oral dosing for highly bioavailable agents usually give equivalent results. Many factors can affect a drug's oral bioavailability, including the timing of food consumption relative to drug administration, drug-metabolizing enzymes, efflux transporters, concentration-dependent solubility, and acid degradation. Underlying conditions such as diarrhea or ileus can also affect the site of drug absorption and thereby alter bioavailability. Certain orally administered drugs have lower bioavailability because