in DNA, resulting in bactericidal activity. Although mammalian cells also have type II DNA topoisomerases like gyrase and topoisomerase IV, the structures of the mammalian enzymes are sufficiently different from those of the bacterial enzymes that quinolones have substantially selective antibacterial activity.

RIFAMYCINS Rifampin, rifabutin, and rifapentine are semisynthetic derivatives of rifamycin B and bind the β subunit of bacterial RNA polymerase, thereby blocking elongation of mRNA. Their action is highly selective for the bacterial enzyme over mammalian RNA polymerases.

NITROFURANTOIN The reduction of nitrofurantoin, a nitrofuran compound, by bacterial enzymes produces highly reactive derivatives that are thought to cause DNA strand breakage. Nitrofurantoin is used only for the treatment of lower urinary tract infections.

METRONIDAZOLE Metronidazole is a synthetic nitroimidazole with activity limited to anaerobic bacteria and certain anaerobic protozoa. Reduction of its nitro group by the electron-transport system in anaerobic bacteria produces reactive intermediates that damage DNA and result in bactericidal activity. Both nitrofurantoin and metronidazole have selective antibacterial activity because the reducing activity needed to generate active derivatives is generated only by bacterial and not mammalian enzymes.

Disruption of Membrane Integrity The integrity of the bacterial cytoplasmic membrane—and, in gram-negative bacteria, the outer membrane—is important for bacterial viability. Two bactericidal drugs have membrane targets.

POLYMYXINS The polymyxins, including polymyxin B and polymyxin E (colistin), are cationic cyclic polypeptides that disrupt the cytoplasmic membrane and the outer membrane (the latter by binding lipopolysaccharide).

DAPTOMYCIN Daptomycin is a lipopeptide that binds the cytoplasmic membrane of gram-positive bacteria in the presence of calcium, generating a channel that leads to leakage of cytoplasmic potassium ions and membrane depolarization.

MECHANISMS OF RESISTANCE

Bacteria use a wide variety of mechanisms to block or circumvent the activity of antibacterial agents. Although myriad, these mechanisms can generally be grouped into three categories: (1) altered or bypass targets that exhibit reduced binding of the drug, (2) altered access of the drug to its target by reductions in uptake or increases in active efflux, and (3) a modification of the drug that reduces its activity. These mechanisms result from either mutations in bacterial chromosomal genes occurring spontaneously during bacterial DNA replication or the acquisition of new genes by DNA transfer from other bacteria or uptake of exogenous DNA. New genes are most often acquired on self-replicating plasmids or other DNA elements transferred from other bacteria. However, some bacteria, such as *Streptococcus pneumoniae* and *Neisseria gonorrhoeae*, can also take up fragments of environmental DNA from related species and recombine that DNA directly into their own chromosomes, a process called *transformation*. Not uncommonly, resistant bacteria have combinations of resistance mechanisms either within one category or among categories, and many plasmids contain more than one resistance gene. Thus, plasmid acquisition itself can in many cases confer resistance to multiple antibacterial agents.

Many antibacterial drugs are derived from natural products of microbial species. Some genes encoding resistance to these drugs may have evolved and been mobilized onto plasmids from a protection mechanism in the producer organism or in other surviving bacteria in the exposed environment. Exposure to antibacterial agents either in nature or from human or animal use results in the selection of resistant strains within an otherwise susceptible bacterial population. Because the patterns and extent of resistance may differ among settings, initial choices of antibacterial drugs should be based, whenever possible, on local susceptibility data and should be modified as needed as soon as specific microbiology susceptibility data become available.

β-Lactams The most common mechanism of resistance to β-lactams is their degradation by β-lactamases, enzymes that break down the core β-lactam ring and destroy drug activity. Different β-lactamases degrade different β-lactams. Some β-lactamases are encoded on the bacterial chromosome, and their activity contributes to the susceptibility profile of a particular species. Because other β-lactamases are encoded by acquired plasmids, their resistance profiles may be present in some strains of a species but not others. In gram-positive bacteria β-lactamases are secreted into the extracellular environment, whereas in gram-negative bacteria these enzymes are secreted into the periplasmic space between the cytoplasmic and outer membranes. Thus, in gram-negative bacteria, access of β-lactams both to their target PBPs and to β-lactamases requires diffusion across the outer membrane, generally through the porin channels.

Most strains of *Staphylococcus aureus* produce a plasmid-encoded β-lactamase that degrades penicillin but not semisynthetic penicillins, such as oxacillin and nafcillin. The most common plasmid-encoded β-lactamases of gram-negative bacteria are able to inactivate all penicillins and most earlier-generation cephalosporins. Extended-spectrum β-lactamase (ESBL) variants of these early enzymes that can degrade later-generation cephalosporins (ceftriaxone, cefotaxime, ceftazidime) as well as the monobactam aztreonam have now emerged and are widely disseminated. Some ESBLs also degrade the fourth-generation cephalosporin cefepime. Carbapenems (imipenem, meropenem, ertapenem, doripenem) are not degraded by ESBLs, but additional β-lactamases, called *carbapenemases*, that degrade carbapenems and most if not all other β-lactams have begun to emerge.

The chromosomal β-lactamase of *Klebsiella pneumoniae* preferentially degrades penicillins but not cephalosporins. In contrast, the chromosomal β-lactamase of *Enterobacter* and related genera, AmpC, can degrade almost all cephalosporins but is normally expressed in small amounts. Mutations that cause increased amounts of AmpC to be produced confer full resistance to penicillins and cephalosporins; the exceptions are cefoxitin and cefepime, which are relatively stable to AmpC. Resistance to cefepime can develop, however, through the combined effects of increased AmpC production and decreased porin diffusion channels. Genes encoding AmpC have also been found on plasmids but are less common than plasmid-encoded ESBLs.

Inhibitors of β-lactamases such as clavulanate, sulbactam, and tazobactam have been developed and paired with amoxicillin and ticarcillin, ampicillin, and piperacillin, respectively. These inhibitors have little or no antibacterial activity of their own but inhibit plasmid-mediated β-lactamases, including ESBLs but not AmpC enzymes.

Resistance to β-lactams also occurs through alterations in their target PBPs. In *S. pneumoniae*, *N. gonorrhoeae*, and *Neisseria meningitidis*, resistance to penicillin occurs by recombination of transformed DNA from related species. In staphylococci, resistance to methicillin and other β-lactams occurs by the acquisition of the *mec* gene, which encodes PBP2a with reduced drug affinity. Ceftaroline is the only β-lactam that has affinity for PBP2a and is thus active against methicillin-resistant staphylococcal strains.

Glycopeptides Resistance to vancomycin in enterococci is due to the acquisition of a set of *van* genes that result in (1) the production of D-alanine-D-lactate—instead of the normal D-alanine-D-alanine—at the end of the peptidoglycan stem peptide and (2) the reduction of existing D-alanine-D-alanine terminated peptides. Vancomycin binds D-alanine-D-lactate with a thousandfold lower affinity than D-alanine-D-alanine. In a small number of cases, the *van* gene cassettes have been transferred from enterococci to *S. aureus*, with the consequent generation of full vancomycin resistance. Particularly in patients receiving prolonged courses of vancomycin, intermediate resistance to this drug has developed in *S. aureus* by a different mechanism: multiple chromosomal mutations that result in a thickened and poorly cross-linked cell wall in which multiple distant D-alanine-D-alanine stem peptide termini exist and bind vancomycin, impeding its access to the binding sites proximal to the cell membrane where new cell-wall synthesis occurs and where binding would block transpeptidase and transglycosylase enzymes. Susceptibility to telavancin, dalbavancin, and oritavancin is