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Bacterial Resistance to Antimicrobial Agents ■ ■DEFINITION OF RESISTANCE The action of antimicrobial agents on a range of targets within the bacterial cell can result in inhibition of bacterial growth or in killing of the bacterial cell (Chap. 149). Reduction in or loss of an agent's antibacterial effect is referred to as resistance, and the properties of or alterations in the bacterium that result in reduced antimicrobial activity are termed resistance mechanisms. Bacteria can be resistant to single or multiple antimicrobials, as detailed in the sections that follow. The occurrence and magnitude of resistance are often assessed in clinical microbiology laboratories by measurement of the lowest drug concentration that inhibits growth of a bacterium (minimal inhibitory concentration, or MIC) with a standardized inoculum and growth conditions. MIC values are generally interpreted as represent ing bacterial susceptibility, intermediate susceptibility, or resistance; the interpretation is based on correlations of the MIC values with the pharmacokinetics and delivery of a drug to the site of infection in the body as well as with data from clinical trials. Thus, a clinical laboratory result of "susceptible" for a bacterium predicts a likely clinical response to an appropriately dosed antimicrobial drug by a patient infected with that organism, whereas a result of "resistant" predicts poor or no clinical response to that drug. Breakpoint MIC values for categoriza tion of bacteria as susceptible, intermediate, or resistant are generally developed by regulatory and advisory groups and are often based on the distribution of MIC values from a large collection of recent clinical bacterial isolates. Research studies on the mechanisms and epidemiol ogy of resistance may in some cases use different and less rigid defini tions of resistance based on determination of a reproducible increase in an MIC value relative to a baseline reference MIC, independent of clinical breakpoints. ■ ■MECHANISMS OF RESISTANCE Bacteria use a wide variety of mechanisms to interrupt or circumvent the activity of antibacterial agents (Table 150-1 and Fig. 150-1). Although myriad, these mechanisms can generally be grouped into three categories: (1) alteration or bypassing of 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 modi fication 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 gonor rhoeae, can also take up fragments of environmental DNA from related bacterial species and recombine that DNA directly into their own chro mosomes, a process called transformation. Not uncommonly, resistant bacteria have combinations of resistance mechanisms either within one category or among categories; many plasmids contain more than one resistance gene; and bacteria can acquire multiple plasmids. Thus, plasmid acquisition itself can in many cases confer resistance to mul tiple antibacterial agents. Resistance to multiple, structurally unrelated antibiotics can also occur by mutations that cause increased expression or, less often, expanded substrate profiles of certain bacterial efflux pumps, some of which are able to transport multiple antibacterial agents as well as other compounds out of the cell. Many antibacterial drugs are derived from natural products of envi ronmental microbial species. Some genes encoding resistance to these drugs originate in the drug-producer organism to protect it from its own product and have then been mobilized onto plasmids that spread to other organisms. Surviving nonproducer bacteria in the exposed

natural environment may also have evolved resistance under selection pressure that adds to the reservoir of resistance mechanisms. Exposure to antibacterial agents either in nature or during human, animal, or other use then results in the selection of resistant strains within an otherwise susceptible bacterial population. In some cases, resistance mechanisms may confer disadvantages that render bacterial growth or survival fitness inferior to that of susceptible strains. In a number of examples, however, fitness defects are often mitigated over time by compensatory mutational mechanisms that make the bacteria both resistant and fit and thereby more likely to persist in a reservoir even in the absence of continued antimicrobial selection pressures. Discussed below are the major classes of antimicrobial agents currently in clinical use and the most important mechanisms of resistance encountered in clinical infections.

β-Lactams β-lactams, the largest class of antibiotics, inhibit bac terial cell-wall synthesis by binding to cell-wall transpeptidases, cross-linking enzymes that are also called penicillin-binding proteins (PBPs); PBPs are targets that are unique to bacteria and have no mam malian counterpart. The most common mechanism of resistance to β-lactams, particularly in gram-negative bacteria, is their degradation by β-lactamases, enzymes that break down the core β-lactam ring and destroy drug activity. β-Lactamases differ in the spectrum of β-lactams they can degrade. Some β-lactamases are encoded on the bacterial chromosome, and their activity contributes to the intrinsic susceptibility profile of a particular species. Chromosomally encoded β-lactamases can be produced in varying amounts that affect the degree of resistance. In some cases, enzyme expression is physiologi cally induced by exposure to certain β-lactams; in other cases, enzyme expression can become constant or constitutive through mutations in genes that encode the regulators of expression of a β-lactamase gene. Other β-lactamases are encoded by genes on acquired plasmids and are usually constitutively expressed. The resistance profiles due to plasmids may be present in some strains of a species but not others, depending on which plasmids the strain has acquired. In gram-positive bacteria, β-lactamases are secreted into the extracellular environment, whereas in gram-negative bacteria these enzymes are secreted into the periplas mic space between the cytoplasmic and outer membranes—a limited space that enables the presence

of high concentrations of β-lactamase. 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 diffusion channels. Reductions in outermembrane diffusion channels due to mutation can further augment the efficiency of β-lactamase degradation of β-lactams: slow diffusion acts together with the high enzyme concentrations in the periplasmic space to enhance drug degradation and resistance. CHAPTER 150 Bacterial Resistance to Antimicrobial Agents Most strains of Staphylococcus aureus produce a plasmid-encoded β-lactamase that degrades penicillin but not semisynthetic penicil lins, such as oxacillin and nafcillin. The greatest diversity among β-lactamases, however, is found in gram-negative bacteria. The most common and earliest identified plasmid-encoded β-lactamases of gram-negative bacteria can inactivate all penicillins and most earlygeneration cephalosporins. Multiple extended-spectrum β-lactamase (ESBL) variants of these early enzymes have emerged and are now widely disseminated. These ESBLs can degrade later-generation cepha losporins (ceftriaxone, cefotaxime, ceftazidime) as well as the mono bactam aztreonam, and some ESBLs also degrade the fourth-generation cephalosporin cefepime. Carbapenems (imipenem, meropenem, ertapenem, doripenem) generally are not degraded by ESBLs, but additional β-lactamases, called carbapenemases, which degrade car bapenems and most if not all other β-lactams, have emerged and are increasing in prevalence. In the United States, Klebsiella pneu moniae carbapenemases (KPCs), which are usually found in strains of Escherichia coli and K. pneumoniae, are most widespread, but New Delhi metallo-β-lactamases (NDM carbapenemases), which were found initially on the Indian subcontinent, have now appeared and increased in the United States, as has an OXA group carbapen emase, OXA-48. In some cases, high levels of expression of an ESBL or an AmpC chromosomally encoded enzyme (see below), together

TABLE 150-1 The Most Common Mechanisms of Resistance to Antibacterial Agents ANTIBACTERIAL AGENT(S) MAJOR TARGET MECHANISM(S) OF ACTION MECHANISM(S) OF RESISTANCE Cell-wall synthesis Bind cell-wall cross-linking enzymes (PBPs, transpeptidases) β-Lactams (penicillins, cephalosporins, monobactams, carbapenems) Glycopeptides and lipoglycopeptides (vancomycin, teicoplanin, telavancin, dalbavancin, oritavancin) Cell-wall synthesis Block cell wall glycosyltransferases by binding d-Ala-d-Ala stem-peptide terminus Teicoplanin, telavancin, dalbavancin, and oritavancin: affect membrane function Bacitracin Cell-wall synthesis Blocks lipid carrier of cell wall precursors Active drug efflux Fosfomycin Cell-wall synthesis Blocks linkage of stem peptide to NAG by enoyltransferase Aminoglycosides (gentamicin, tobramycin, amikacin, plazomicin) Protein synthesis Bind 30S ribosomal subunit Block translocation of peptide chain Cause misreading of mRNA Tetracyclines (tetracycline, doxycycline, minocycline) Protein synthesis Bind 30S ribosomal subunit Inhibit peptide elongation Tigecycline, eravacycline, omadacycline Protein synthesis Same as tetracyclines Active drug efflux (pumps different from those affecting tetracyclines) Macrolides (erythromycin, clarithromycin, azithromycin) and the ketolide telithromycin Protein synthesis Bind 50S ribosomal subunit Block peptide chain exit Lincosamides (clindamycin) Protein synthesis Bind 50S ribosomal subunit Block peptide bond formation Streptogramins (quinupristin, dalfopristin) Protein synthesis Same as macrolides Same as macrolides Drug-modifying enzymes PART 5 Infectious Diseases Chloramphenicol Protein synthesis Binds 50S ribosomal subunit Blocks aminoacyl tRNA positioning Oxazolidinones (linezolid, tedizolid) Protein synthesis Bind 50S ribosomal subunit Inhibit initiation of peptide synthesis Pleuromutilins (lefamulin) Protein synthesis Bind 50S ribosomal subunit Blocks peptidyl transferase center Mupirocin Protein synthesis Blocks isoleucyl tRNA synthetase Acquired resistant tRNA synthetase

(drug bypass) Altered native tRNA synthetase target Sulfonamides (sulfadiazine, sulfisoxazole, and sulfamethoxazole) Folate synthesis Inhibit dihydropteroate synthetase Acquired resistant dihydropteroate synthetase (drug bypass) Trimethoprim Folate synthesis Inhibits dihydrofolate reductase Acquired resistant dihydrofolate reductase (drug bypass) Quinolones (norfloxacin, ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gemifloxacin, delafloxacin) DNA synthesis Inhibit DNA gyrase and DNA topoisomerase IV Enzyme–DNA–drug complex: blocks DNA replication apparatus Rifamycins (rifampin, rifabutin, rifapentine) RNA synthesis Inhibit RNA polymerase Altered target Nitrofurantoin Nucleic acid synthesis Reduces reactive drug derivatives that damage DNA Metronidazole Nucleic acid synthesis Reduces reactive drug derivatives that damage DNA Polymyxins (polymyxin B and polymyxin E [colistin]) Cell membrane Bind LPS and disrupt both outer and cytoplasmic membranes Daptomycin Cell membrane Produces membrane channel and membrane leakage Abbreviations: LPS, lipopolysaccharide; NAG, N-acetylglucosamine; PBP, penicillin-binding protein. with reduced porin diffusion channels, can also result in resistance to carbapenems. In Pseudomonas aeruginosa, resistance to carbapenems can occur by mutations that cause reductions in the OprD diffusion channel for imipenem or increased expression of efflux pumps that can remove meropenem from the bacterial cell.

Drug inactivation by β-lactamases Altered PBP targets Reduced diffusion through porin channels Altered iron uptake proteins (cefiderocol) Altered d-Ala-d-Ala target (d-Ala-d-Lac) Increased d-Ala-d-Ala target binding at sites distant from cell wall synthesis enzymes Target enzyme overexpression Drug-modifying enzymes Drug-modifying enzymes Methylation at ribosome binding site Decreased permeation to target due to active efflux Active drug efflux Ribosomal protection proteins Methylation at ribosome binding site Active drug efflux Methylation at ribosome binding site Drug-modifying enzymes Altered rRNA binding site Methylation of ribosome binding site Altered L3 and L4 protein binding site Methylation of ribosome binding site Altered target(s) Active efflux Protection of target from drug Drug-modifying enzyme (ciprofloxacin) Altered drug-activating enzymes Altered drug-activating enzyme Acquired detoxifying enzymes Active efflux Altered cell-membrane charge with reduced drug binding Altered cell-membrane charge with reduced drug binding The chromosomal β-lactamase of K. pneumoniae preferentially degrades penicillins over cephalosporins. In contrast, the chromo somal β-lactamase of Enterobacter and related genera, AmpC, can degrade almost all cephalosporins but is normally expressed in only small amounts. Mutations in regulatory genes that cause increased

Gram-Negative Bacterium Antibiotic a-lactamases in periplasmic space b-lactams (including carbapenems for some b-lectamases) Loss of porins carbapenems (imipenem) Porin Altered iron uptake pathways (cefiderocol) Antibiotic Plasmid with antibioticresistant genes Bypass targets trimethoprim (dihydrofolate reductase), sulfonamides (dihydropteroate synthase) Ribosomes Ribosomal mutation or modification tetracyclines, ozazolidinones, lefamulin (TetM or TetO), aminoglycosides (rRNA methylation) Mutations in lipopolysaccharide structure polymyxin antibiotic class FIGURE 150-1 Antibacterial targets and mechanisms of resistance to antibacterial agents, as illustrated in a gram-negative bacterium. Similar mechanisms are found in gram-positive bacteria, but their lack of an outer membrane causes β-lactamases to be excreted outside the cell, rather than into the periplasmic space between the inner and outer membranes, and reduces the efficiency of efflux pumps because exported drugs can re-enter the cell after crossing a single membrane, rather than the two membranes in gram-negative bacteria. Red spheres indicate antibiotics. (From AY Peleg, DC Hooper: Hospital-acquired infections due to gram-negative bacteria.

N Engl J Med 362:1084, 2010. Copyright © 2010 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.) amounts of AmpC to be produced can cause full resistance to penicil lins 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 mutations that cause 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. A recent novel cephalosporin, cefiderocol, has enhanced stability to β-lactamases and, due to a catechol side group, is actively taken up into the bacterial cell by siderophore iron uptake pathways, rather than diffusing pas sively through porin channels. It is active against many gram-negative bacteria that are resistant to other β-lactams, including carbapenems. Reduced susceptibility has been reported to occur in strains with muta tions in multiple iron transport genes. Inhibitors of β-lactamases such as clavulanate, sulbactam, tazobac tam, avibactam, vaborbactam, relebactam, and durlobactam have been developed and paired with amoxicillin and ticarcillin (clavulanate), ampicillin (sulbactam), piperacillin and ceftolozane (tazobactam), ceftazidime (avibactam), meropenem (vaborbactam), imipenem (rele bactam), and sulbactam (durlobactam), which has selective activity against Acinetobacter. These inhibitors, with the exception of sulbac tam, have little or no antibacterial activity of their own but inhibit plasmid-mediated β-lactamases, including ESBLs. Only avibactam, vaborbactam, and relebactam inhibit AmpC enzymes and some car bapenemases (KPCs but not metallo-carbapenemases, such as NDM). Resistance to β-lactams also occurs through alterations in the drugs’ target transpeptidase enzymes (PBPs) involved in cross-linking of the bacterial cell-wall peptidoglycan structure. In S. pneumoniae,

Overexpression of transmembrane efflux pump b-lactams (meropenem), quinolones, aminoglycosides, tetracycline antibiotics (tigecycline), and chloramphenicol Antibiotic Antibiotic-modifying enzymes aminoglycosides, ciprofloxacin Target mutations quinolones (DNA gyrase and topoisomerase IV) Proteins CHAPTER 150 Protein Lipopolysaccharide Bacterial Resistance to Antimicrobial Agents N. gonorrhoeae, and Neisseria meningitidis, resistance to penicillin occurs by recombination of transformed DNA from related species that results in mosaic PBPs with lower affinity for penicillin. A combination of increased expression of an efflux pump and a porin mutation also causes penicillin resistance in N. gonorrhoeae. In staphylococci, resis tance to methicillin and other β-lactams occurs by acquisition of the mec gene, which encodes a PBP2a with reduced drug affinity. PBP2a is a bypass target that can function in cell wall cross-linking in the pres ence of β-lactams, bypassing their effect on other PBPs. Ceftaroline is the only β-lactam that has affinity for PBP2a and is thus active against methicillin-resistant staphylococcal strains. Resistance to ceftaroline can occur, however, by mutations in the gene encoding PBP2a that reduce its affinity for the drug. Glycopeptides and Lipoglycopeptides Glycopeptides and lipoglycopeptides inhibit bacterial cell-wall synthesis by binding to the terminal two d-alanine amino acids on the cell-wall peptidoglycan stem peptides, which are involved in peptidoglycan cross-links. In doing so, these drugs block the transpeptidase cross-linking enzymes and glycosyl transferases necessary for cell-wall synthesis. 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–termi nated peptides. Vancomycin binds d-alanine-d-lactate with a 1000-fold lower affinity than d-alanine-d-alanine. The van genes originated in the organisms that naturally produce vancomycin and have been mobilized and reorganized in transposon mobile genetic elements

and onto plasmids, which can be transferred between enterococci. In rare cases, the van gene cassettes have been transferred from entero cocci to S. aureus, with the consequent generation of full vancomycin resistance. In S. aureus, intermediate resistance to vancomycin is more common than full vancomycin resistance and is due to a different mechanism that results from a series of several chromosomal muta tions leading to a thickened and poorly cross-linked cell wall. This modified cell wall contains additional d-alanine-d-alanine–terminated stem peptides that bind vancomycin at a site distant from the cell membrane, adjacent to which new peptidoglycan is synthesized and where vancomycin binding blocks transpeptidase and transglycosylase enzymes. Thus, vancomycin's binding to these distant termini impedes its access to the proximal binding sites that result in inhibition of peptidoglycan synthesis. This intermediate-resistance phenotype was first recognized in patients receiving prolonged courses of vancomycin that created an opportunity for selection of the multiple mutations needed to produce the modified cell wall. Because of the energy costs of a thickened cell wall, this intermediate-resistance phenotype may be unstable, with strains returning to susceptibility in the absence of van comycin selection pressure. Susceptibility to telavancin, dalbavancin, and oritavancin is also reduced in strains that exhibit resistance or intermediate susceptibility to vancomycin, although in some cases, the drugs remain sufficiently active that the strains may still be classified as susceptible based on standard clinical laboratory interpretive criteria.

Aminoglycosides Aminoglycosides are one of several classes of antimicrobials that inhibit protein synthesis by binding to either the 30S or the 50S bacterial ribosomal subunit (both of which differ from eukaryotic ribosomal subunits), with consequent selective antibacterial activity. The aminoglycosides bind to the 30S subunit of the bacterial ribosome. The most common mechanism of resistance to aminogly cosides in gram-negative bacteria is due to acquisition of plasmids with 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. Various transferases differ in which aminoglycosides they modify, and amikacin resistance occurs less often than resistance to gentamicin or tobramycin by these mechanisms. Plazomicin, a recently developed aminoglycoside, is distinctive in that it remains active and is not modi fied by most transferases. Another mechanism of plasmid-mediated aminoglycoside resistance is due to methylase enzymes that can methyl ate the site of aminoglycoside binding on the 16S ribosomal RNA of the 30S ribosomal subunit and reduce drug binding to its ribosome target, resulting in resistance to all aminoglycosides, including plazomicin. For streptomycin, a single ribosomal protein mutation may also cause resistance. In P. aeruginosa, aminoglycoside resistance can also occur through mutations in regulatory genes causing increased expression of a chromosomally encoded efflux pump, MexXY, which reduces intracel lular drug concentrations. PART 5 Infectious Diseases Tetracyclines These antibiotics bind the 16S ribosomal RNA of the 30S ribosomal subunit at a site distinct from the binding site of the ami noglycosides and inhibit bacterial protein synthesis. For tetracyclines, including doxycycline and minocycline, resistance is often plasmidmediated and due either to active efflux pumps, which in some cases are specific for tetracyclines, or to proteins that protect the ribosome from tetracycline action. Some broad-spectrum, chromosomally encoded efflux pumps may also include tetracyclines among their substrates, and regulatory mutations that cause pump overexpression may confer tetracycline resistance together with resistance to other agents that are pump substrates. There have been recent derivatives of the tetracyclines, including the glycylcycline, tigecycline, the fluorocycline, eravacycline, and the aminomethylcycline, omadacycline, which have modifications

on the core tetracycline ring structure rendering them less affected or unaffected by the common tetracycline resistance mechanisms. Resis tance to the newer tetracyclines can occur, however, through mutations that cause overexpression of some broad-spectrum efflux pumps, partic ularly in Proteus species. An uncommon plasmid-encoded tetracycline modification mechanism can also cause resistance to the newer agents.

Macrolides, Ketolides, Lincosamides, and Streptogramins These antibiotics are also inhibitors of bacterial protein synthesis, in this case through their binding to the 23S RNA of the 50S ribosomal subunit. They are generally active against gram-positive bacteria. Resistance to macrolides, clindamycin, and quinupristin is most often due to acquired Erm methylases that modify the drug-binding site on the ribosome, reducing drug binding. Resistance to quinupristin by this mechanism renders the quinupristin-dalfopristin combination bacteriostatic rather than bactericidal. Telithromycin, a ketolide structurally related to macro lides, has an additional binding site on the ribosome and remains active in the presence of some methylases. Methylase gene expression can be induced by exposure to most macrolides but generally not ketolides (e.g., telithromycin); however, bacterial strains constitutively expressing methylase genes can display resistance to both macrolides and ketolides. Acquired genes encoding active efflux pumps can also contribute to resistance to macrolides in streptococci and to resistance to macro lides, 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 at the site of drug binding is uncommon in staphylococci and streptococci because of the multiple copies of the rRNA genes on the chromosomes of these species; such resistance mechanisms may occur more frequently, however, in mycobacteria, Helicobacter pylori, and Treponema species, which have only one or two chromosomal cop ies of these rRNA genes, thus requiring fewer mutations to generate a resistance phenotype. Among gram-negative bacteria, many of which are not susceptible to current macrolides because of inadequate drug perme ation across the outer membrane, some strains with acquired genes for macrolide-modifying enzymes have been described. Chloramphenicol Chloramphenicol inhibits bacterial protein synthesis by binding to the 23S rRNA of the 50S subunit at a site that overlaps the macrolide-binding site. Chloramphenicol is uncommonly used in human medicine because of infrequent but potentially severe bone marrow toxicity. Resistance to chloramphenicol is most often due to plasmid-encoded, drug-modifying acetyltransferases that have been found in both gram-positive and gram-negative bacteria and whose expression can be induced by drug exposure. Among staphylococci, some resistant strains have been found to have a plasmid-encoded ribosomal methylase that confers resistance to chloramphenicol, clindamycin, and oxazolidinones. As is the case for macrolides, ribo somal mutations causing resistance to chloramphenicol are uncommon because of multiple copies of rRNA genes in the common grampositive human pathogens. Plasmid-encoded efflux pumps affecting chloramphenicol specifically have been found in gram-negative bac teria, and other pumps affecting chloramphenicol and oxazolidinones have been found in gram-positive bacteria. Oxazolidinones Linezolid and tedizolid are the only members of the oxazolidinone class of antimicrobials in clinical use, and both are active against gram-positive bacteria only; lack of sufficient activity in gram-negative bacteria results from the ability of native efflux pumps in these bacteria to limit drug access to their cytoplasmic ribosome targets. Oxazolidinones target the bacterial ribosome and inhibit pro tein synthesis by binding to 23S rRNA of the 50S subunit at a distinct site that overlaps with the chloramphenicol-binding site. Resistance has been seen in enterococci more often than in staphylococci and, in both organisms, is most often due to

mutations in multiple copies of the 23S rRNA genes that reduce drug binding to the ribosome. A plasmidacquired ribosomal methylase gene that enables ribosomal alteration at a site that confers resistance to both linezolid and chloramphenicol has also been found in some strains of both S. aureus and coagulasenegative staphylococci but is not yet widespread. A plasmid-encoded active efflux pump conferring resistance to oxazolidinones (both line zolid and tedizolid) and chloramphenicol has been described in animal isolates and a small number of human isolates of Enterococcus faecalis. Pleuromutilins Lefamulin is the only systemic pleuromutilin in clinical use. Retapamulin has been available for topical use in skin infections. Pleuromutilins inhibit bacterial protein synthesis by

 binding to the peptidyl transferase center in the 50S ribosomal sub unit, and lefamulin is generally active against gram-positive bacteria, Haemophilus influenzae, Moraxella catarrhalis, and atypical respira tory pathogens, such a Mycoplasma pneumoniae and Legionella spp. Although there is partial overlap in the site of binding of lefamulin and those of other antibacterials binding the 50S ribosomal subunit, cross-resistance with macrolides, oxazolidinones, lincosamides, and streptogramins is uncommon. Resistance to lefamulin can occur by mutations in L3 and L4 proteins of the 50S subunit that alter the lefamulin binding site. In addition, the plasmid-encoded Cfr methyl ase, which confers resistance to chloramphenicol and oxazolidinones, can also cause resistance to lefamulin by disrupting its binding site. Vga efflux transporters, which cause resistance to lincosamides and streptogramins, also affect pleuromutilins. Mupirocin Mupirocin is used only in topical formulations, most often for elimination of nasal carriage of S. aureus. It targets bacterial leucyl-tRNA synthetase and inhibits protein synthesis. Resistance to mupirocin occurs by either mutation in the target leucyl-tRNA syn thetase (low-level resistance) or the acquisition of a plasmid-encoded resistant tRNA synthetase (high-level resistance), which bypasses drug inhibition of the native, sensitive synthetase. Sulfonamides and Trimethoprim These agents inhibit the folate biosynthesis pathway at different steps. Sulfonamides are structurally similar to para-aminobenzoic acid (PABA) and competitively inhibit dihydropteroate synthetase, which, in an early step in the pathway, uses PABA to synthesize dihydropteroate, a precursor of dihydrofolate. Trimethoprim inhibits dihydrofolate reductase at a later step in the pathway that generates tetrahydrofolate. Clinical use of folate pathway inhibitors most often consists of the combination of sulfamethoxazole and trimethoprim; on occasion, however, trimethoprim or various sulfonamides are used individually. Resistance to both of these anti metabolites can result from mutation in their target enzymes or can be 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. Resistance to the combination of sulfamethoxazole and trimethoprim requires that the bacterial strain have resistance mechanisms for both agents and yet is relatively common. Resistance due to drug efflux or drug modification has been limited for both sulfonamides and trimethoprim. Quinolones Quinolones are synthetic inhibitors of bacterial DNA synthesis. They bind to two enzymes required for DNA synthesis: DNA gyrase and DNA topoisomerase IV, which alter DNA conformation and the interlinking of replicated molecules. In addition to inhibiting the enzymes’ catalytic functions of altering DNA topology, they stabilize enzyme–DNA complexes that form a barrier to the DNA replication machinery and are a precursor to lethal double-strand DNA breaks. Although related topoisomerase enzymes are involved in mammalian DNA synthesis, the mammalian and bacterial

enzymes are sufficiently different from each other for quinolones to have selective activity against bacteria. 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 sub strates. In addition, three types of acquired genes can confer reduced susceptibility or low-level resistance by protecting the target enzymes, modifying some quinolones (particularly ciprofloxacin and norfloxacin) to reduce their activity, or generating an efflux of quinolones. These genes are usually located on multidrug-resistance plasmids that have spread worldwide. Their presence can promote higher levels of quino lone resistance by enhancing selection of the mutations in chromosomal target genes with exposure to quinolones and can then link quinolone resistance to resistance to other antibacterial drugs that are encoded by the same plasmid. Rifampin, Rifabutin, and Rifapentine Antimicrobials of the rifamycin class target bacterial RNA polymerase and thereby inhibit transcription of messenger RNA and gene expression. Their activity is generally limited to gram-positive bacteria because native efflux pumps in most gram-negative bacteria reduce drug access to the cytoplasmic enzyme target. Single mutations in the β subunit of RNA polymerase con stitute the principal mechanism of acquired rifampin resistance, which is high-level. Thus, rifampin and other rifamycins are used for treatment of infections only in combination with other antibacterial drugs in order to reduce the likelihood of selection of high-level resistance. Metronidazole Metronidazole is actively taken up by most anaero bic bacteria and then converted to reactive drug derivatives that nonspecifically damage cytoplasmic proteins and nucleic acids. Thus, metronidazole lacks a specific cellular target. Acquired resistance to metronidazole in Bacteroides species is rare. Such resistance has been reported in strains that lack the endogenous activating nitroreductase or that have acquired nim genes responsible for further reduction of the DNA-damaging nitroso intermediates to an inactive derivative. Active efflux and enhanced DNA repair mechanisms also have been associ ated with resistance. Nitrofurantoin Nitrofurantoin is used only for treatment of lower urinary tract infections because adequate drug concentrations are found only in urine. Its mechanism of action is not fully understood but is thought to involve generation of reactive derivative molecules (as occurs with metronidazole) that damage DNA and ribosomes. Resis tance to nitrofurantoin in E. coli can emerge through a series of muta tions that progressively decrease the nitroreductase activity required for generating active nitrofuran metabolites. These mutants are also impaired in growth; this impairment possibly explains the infrequent occurrence of resistance with clinical use of nitrofurantoin. Polymyxins Because of emerging multidrug resistance in gramnegative bacteria, colistin and polymyxin B have been used for infec tions due to resistant Enterobacterales, P. aeruginosa, and Acinetobacter species. Polymyxins are cationic cyclic peptide molecules that bind negatively charged lipopolysaccharides on the gram-negative bacterial outer membrane, with subsequent disruption and permeabilization of both outer-membrane and cytoplasmic-membrane structure. Thus, the polymyxins are bactericidal. Resistance is so far uncommon but 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. Transferable plasmid-mediated colistin resistance has also been found to be due to mcr-1 and other mcr variants that encode a gene for a phosphoetha nolamine transferase that also reduces the negative charge on the cell surface. mcr-containing enteric bacteria have now been identified in Asia, Europe, and the United States. Daptomycin Daptomycin is active against gram-positive bacteria and interacts with and disrupts the cytoplasmic membrane in a calcium-dependent manner, resulting in bactericidal activity. The mechanisms of resistance to daptomycin are

complex and involve mutations in several genes that can alter cell membrane charge and structure 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 van comycin but not exposed to daptomycin. In some strains of methicillinresistant S. aureus, daptomycin resistance has been linked to acquired susceptibility to β-lactams; combinations of daptomycin with nafcillin or ceftaroline 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 but may involve alteration in surface charge and increased daptomycin binding in the presence of β-lactams. Daptomycin resistance has also been reported in enterococci. ■ ■EPIDEMIOLOGY OF RESISTANCE AND REDUCTION OF ITS OCCURRENCE Multidrug resistance in human bacterial infections has been increasing overall in recent years, substantially limiting the number of antibiotics that can be used to treat some infections. The prevalence of resistance

to various antimicrobials among human pathogens can, however, vary greatly in different geographic areas and even at different institutions in the same area. Thus, specific local data on the occurrence of various types of resistance are an important component of the choice of anti microbials for empirical treatment of infection until the responsible pathogen is identified and its specific susceptibilities are determined by the clinical microbiology laboratory. Prompt adjustment of the initially chosen antimicrobial on the basis of species and susceptibility data to best target therapy is equally important. These principles emphasize the importance of obtaining appropriate samples for culture or other diagnostic modalities and susceptibility testing—whenever possible, prior to administration of antimicrobials. They also highlight the importance of rapid and sensitive diagnostic methods and the prompt communication of their results to clinicians to inform best choices of antimicrobials.

The overall prevalence of resistance can be affected by a number of factors, including (1) the extent of resistance reservoirs in the patient population; (2) the selection pressures from use of antimicrobials that favor resistant strains over susceptible ones; and (3) the extent by which resistance is amplified by transmission of resistant strains to patients from their environment or other persons, either directly or indirectly via the contaminated hands of health care workers when hand hygiene and other infection control practices are inadequately followed. The likelihood that an individual patient will be infected with a resistant pathogen is likewise affected by his or her history. Studies have shown that prior antibiotic treatment, prior infection with resistant pathogens, and prior hospitalizations all increase this likelihood. These factors emphasize the importance of the appropriate use of antimicrobials (particularly, the avoidance of their use in clinical conditions in which they are not needed), the use of the shortest courses of therapy sufficient for a successful clinical outcome, and the implementation of antimicrobial stewardship programs (Chap. 149) as well as careful and consistent infection control practices in short-term and long-term-care institutions. Antimicrobial agents are distinct among drug classes in human medicine in that—despite their clear clinical value when used appropriately—the extent of their use can compromise their future utility because of resistance. The remarkable ability of pathogens to acquire resistance is inherent in their biology and emphasizes the necessity for clinicians and institu tions to pay careful attention to those factors that can be controlled through judicious antimicrobial use and rigorous infection control and prevention practices. PART 5 Infectious Diseases Efforts to address the problems caused by resistance are now being made worldwide. The

U.S. Centers for Disease Control and Preven tion (CDC) has recently estimated that >2.8 million resistant bacterial infections occur in the United States each year, with 35,900 deaths, and has identified particular resistant pathogens that are of great est concern because of their overall effects on public health (Table 150-2). Enteric bacteria (such as E. coli, K. pneumoniae, and Entero bacter spp.) and Acinetobacter spp. that are resistant to carbapenems are included in the “urgent” category because of their increasing occurrence worldwide and because they are often highly resistant to multiple drugs, with few if any active antimicrobials available for treatment. Resistant N. gonorrhoeae is included in this category as well because of the ease with which gonorrhea can be spread from person to person and because limited active agents are now available. Other resistances are common and also affect clinical care, often requiring use of alternatives to first-line agents that can be less effective and less well tolerated. Also affecting clinical care and considered urgent are infections due to Clostridioides difficile. Although not directly due to acquired resistance, C. difficile disease, like resistant bacterial infec tions, is linked to antibacterial use (by the disruption of the normal microbiome of the gastrointestinal tract rather than direct resistance selection) and to its ability as a spore-forming bacterium to be spread in health care environments. To address the problems posed by resis tance and C. difficile disease, the CDC has emphasized a set of five core actions. (1) Infection prevention and control: These efforts focus on implementation of evidence-based activities to reduce the risks and incidence of device-related infections overall and on improvement of

TABLE 150-2 Antibiotic Resistance Threats in the United States, 2019 THREAT CATEGORY ORGANISMS Urgent Carbapenem-resistant Acinetobacter Candida auris Clostridioides difficile Carbapenem-resistant Enterobacterales Drug-resistant Neisseria gonorrhoeae Serious Drug-resistant Campylobacter Drug-resistant Candida Extended-spectrum β-lactamase–producing Enterobacterales Vancomycin-resistant Enterococcus Multidrug-resistant Pseudomonas aeruginosa Drug-resistant nontyphoidal Salmonella Drug-resistant Salmonella serotype Typhi Drug-resistant Shigella Methicillin-resistant Staphylococcus aureus Drug-resistant Streptococcus pneumoniae Drug-resistant Mycobacterium tuberculosis Concerning Erythromycin-resistant group A Streptococcus Clindamycin-resistant group B Streptococcus Watch List Azole-resistant Aspergillus fumagatis Drug-resistant Mycoplasma genitalium Drug-resistant Bordetella pertussis Source: U.S. Centers for Disease Control and Prevention. compliance with infection control practices that prevent transmis sion of resistant pathogens from one person to another, such as hand hygiene and isolation precautions in health care and long-term care settings. (2) Tracking and data: Efforts aim to increase the reporting and sharing of the occurrence of resistance to enhance epidemiologic data and inform targeting of preventive interventions. (3) Antibiotic use and access: Antimicrobial stewardship programs with specific components to track usage and educate clinicians on appropriate use have become required in hospitals, and the CDC has implemented efforts to reduce inappropriate use in outpatient settings, with particu lar attention to upper respiratory illnesses that often do not require antimicrobials because of their common self-limited viral causes. (4) Vaccines, therapeutics, and diagnostics: The U.S. Congress and the U.S. Food and Drug Administration, as well as agencies in other countries, have recently developed incentives and enhanced regulatory pathways for drug approval that pharmaceutical companies can use for develop ment of antimicrobials that specifically address particular resistant pathogens. Both small and large companies have undertaken efforts in this area. New technologies for rapid detection of resistance and sus ceptibility are also being developed by multiple diagnostics companies in order to facilitate the appropriate choice of antimicrobials earlier in the course of illness, providing an

important tool for antimicrobial stewardship programs. (5) Environment and sanitation: Reservoirs of resistant bacteria and resistance genes on mobile genetic elements can exist in agriculture and food production and domestic animals and have the potential for introduction into humans. Thus, antibiotic use in these environments can amplify resistance reservoirs and increase the chance of human exposure. Therefore, public health interventions addressing these issues in a One Health approach (https://www.cdc

.gov/onehealth/index.html) are an important component of managing resistance risks. ■ ■FURTHER READING Bush K, Bradford PA: Interplay between β-lactamases and new β-lactamase inhibitors. Nat Rev Microbiol 17:295, 2019. Centers for Disease Control and Prevention: Antibiotic resis tance threats in the United States, 2019. Available at https://www.cdc

.gov/antimicrobial-resistance/media/pdfs/2019-ar-threats-report-508. pdf. Accessed June 23, 2020.

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