
Antibiotics

Antibiotic drugs

Overview of antibiotics

Antibacterial classes		Examples	Mechanism of action	Bacteriostatic/bactericidal	Mechanisms of resistance
Inhibition of cell wall synthesis					
β-lactams	Penicillins	• Natural penicillins (penicillin G and penicillin V) • Anti-staphylococcal penicillins (e.g., oxacillin, nafcillin, dicloxacillin) • Aminopenicillins (amoxicillin, ampicillin) • Antipseudomonal penicillins (e.g., piperacillin, ticarcillin)	• Bind to penicillin-binding proteins (PBPs) → ↓ crosslinking of peptidoglycan layer	• Bactericidal	• Cleavage of β-lactam ring by β-lactamases (penicillinases) • PBP mutations (e.g., MRSA)
	Cephalosporins	• 1st generation (e.g., cephalexin) • 2nd generation (e.g., cefaclor) • 3rd generation (e.g., cefixime) • 4th generation (e.g., cefepime) • 5th generation (ceftaroline)			• Cleavage of β-lactam ring by β-lactamases (cephalosporinases) • PBP mutations
	Carbapenems	• Imipenem • Meropenem • Ertapenem • Doripenem			• Cleavage of β-lactam ring by β-lactamases (carbapenemases)
	Monobactams	• Aztreonam			• Cleavage by β-lactamases (less suceptible than other ß-lactams)

Glycopeptides		• Vancomycin
		• Bacitracin
		• Teicoplanin
		• Telavancin
		• Dalbavancin
		• Oritavancin
			• Bind to D-alanyl-D-alanine section of peptidoglycan precursor → inhibited peptidoglycan synthesis	• Bactericidal
				• Bacteriostatic against C. difficile
					• Reduced penetration in gram-negative bacteria
					• Change in peptidoglycan precursor structure
					  ○ D-alanyl-D-alanine → D-alanyl-D-lactate
					  ○ Glycopeptides do not bind to the altered precursor.

Epoxides		• Fosfomycin	• Inactivate enolpyruvate transferase (MurA) → inhibition of N-acetylmuramic acid formation → disruption of peptidoglycan synthesis [3]	• Bactericidal	• Reduced penetration • Enzyme gene overexpression • Enzymatic inactivation
Disruption of cell membrane integrity					
Lipopeptides		• Daptomycin	• Lipid portion binds to bacterial cytoplasmic membrane → formation of ion-conducting channels → intracellular K+ efflux → bacterial cell membrane depolarization	• Bactericidal	• Not fully understood • Altered cell membrane potential
Polymyxins		• Polymyxin E (colistin) • Polymyxin B	• Cationic detergents (polypeptides) bind to outer cell membrane (phospholipids on gram-negative bacteria) → ↑ permeability → bacterial lysis • Bind to and inhibit lipopolysaccharides → ↓ effect of bacterial endotoxins	• Bactericidal	• Not fully understood • Altered lipid A portion of lipopolysaccharides (LPSs) • Efflux pumps

Inhibition of protein synthesis - 30S ribosomal subunit				
Aminoglycosides	• Gentamicin • Amikacin • Tobramycin • Streptomycin • Neomycin	• Inhibit initiation complex → protein mistranslation	• Bactericidal	• Inactivating enzymes (via e.g., acetylation, phosphorylation, adenylation) • Removal by efflux pumps • Mutation of the bacterial ribosome binding site • Reduced penetration • Anaerobic bacteria • Acidic environment
Tetracyclines	• Tetracycline • Doxycycline • Minocycline • Eravacycline • Sarecycline • Omadacycline	• Block incoming aminoacyl-tRNA with amino acids → ↓ protein synthesis	• Bacteriostatic	• Reduced cell wall penetration • Removal by efflux pumps (plasmid-encoded) • Production of a protein that protects ribosome
Glycylcyclines (tetracyclin derivative)	• Tigecycline			• Designed to overcome the resistance of tetracycline (e.g., efflux pumps, ribosomal protection) [4]
Inhibition of protein synthesis - 50S ribosomal subunit				
Macrolides and ketolides	• Erythromycin • Clarithromycin • Azithromycin	• Bind to 23S rRNA → inhibition of transpeptidation, translocation, and chain elongation → ↓ protein synthesis	• Bacteriostatic	• Reduced penetration • Efflux pumps • Methylation of 23S rRNA binding site → inhibits binding of macrolides • Cross-resistance with clindamycin and streptogramins • Mutation of bacterial ribosome binding site
Lincosamides	• Clindamycin	• Impair transpeptidation → inhibition of chain elongation → ↓ protein synthesis • Increase opsonization and phagocytosis • Inhibit alpha toxin expression	• Bacteriostatic	• Reduced penetration • Mutation of bacterial ribosome binding site
Streptogramins	• Quinupristin-dalfopristin	• Dalfopristin binds to 23S portion of the 50S subunit → conformation change → facilitation of binding of quinupristin • Quinupristin binds to and blocks 50S subunit → inhibition of polypeptide elongation → ↓ protein synthesis [5]	• Bactericidal when used in combination • Bacteriostatic when used separately	• Alteration of bacterial ribosome binding site • Enzyme-mediated methylation • Efflux pumps
Oxazolidinones	• Linezolid	• Prevent association of 50S with 30S subunit → impairment of initiation complex formation → early interruption of protein synthesis	• Bacteriostatic • Only bactericidal against Streptococci	• Point mutation of the 23S rRNA
Amphenicols	• Chloramphenicol	• Prevent binding of amino acid-containing aminoacyl-tRNA → inhibition of peptidyltransferase → ↓ protein synthesis	• Bacteriostatic • Bactericidal in higher concentrations	• Reduced penetration • Enzymatic inactivation by acetyltransferase (plasmid-encoded)
DNA gyrase inhibition				
Fluoroquinolones	• Norfloxacin • Moxifloxacin • Gemifloxacin • Ciprofloxacin • Ofloxacin • Levofloxacin • Enoxacin	• Inhibit prokaryotic topoisomerase II (DNA gyrase) and topoisomerase IV → inhibited DNA synthesis	• Bacteriostatic and bactericidal	• Mutations (chromosome-encoded) in DNA gyrase and topoisomerase IV • ↓ Cell wall permeability • Efflux pumps (plasmid-encoded resistance)

Disruption of DNA integrity				
Nitroimidazoles	• Metronidazole • Tinidazole	• Prodrug [6] • Free radical formation → single-strand breaks in DNA molecules	• Bactericidal (and antiprotozoal)	• Reduced activation due to decreased enzymatic activity
Inhibition of folic acid synthesis and reduction				

Sulfonamides and diaminopyrimidines	• Trimethoprim-sulfamethoxazole
	• Sulfadiazine and pyrimethamine
	• Sulfisozaxole
		• Prevent bacterial tetrahydrofolate formation (THF) → ↓ DNA methylation
		• Synergistic effect
		  ◦ Sulfamethoxazole inhibits THF
		  ◦ Trimethoprim inhibits dihydrofolate reductase (DHFR).
			• Bactericidal (sulfamethoxazole)
			• Bacteriostatic (trimethoprim)
				• Overproduction of para-aminobenzoate (PABA)
				• Decreased uptake
				• Structural changes on target enzymes (e.g., dihydropteroate synthase)
				• Efflux pumps

Antimycobacterial drugs				
Rifamycins	• Rifampin • Rifabutin • Rifaximin	• Block mRNA synthesis via inhibition of bacterial DNA-dependent RNA-polymerase → ↓ protein synthesis	• Bacteriostatic and bactericidal	• Mutated RNA-polymerase → ↓ binding of rifamycins
Hydrazides	• Isoniazid	• Prodrug • Inhibits mycolic acid synthesis → ↓ cell wall synthesis	• Bactericidal	• Mutation causing ↓ KatG → ↓ expression of catalase-peroxidase
Nicotinamides	• Pyrazinamide	• Prodrug • Not completely understood	• Bacteriostatic	• Mutations in RpsA gene coding for ribosomal protein S1
Ethylenediamine derivates	• Ethambutol	• Inhibits arabinosyltransferase → ↓ cell wall synthesis	• Bacteriostatic	• Mutations in EmbCAB gene coding for arabinosyltransferase → inability of the drug to inhibit the enzyme
Sulfones	• Dapsone	• Competitive antagonism of para-aminobenzoic acid → inhibited dihydrofolic acid synthesis	• Bacteriostatic and bactericidal	• Mutations in folP1 gene coding for dihydropteroate synthase → ↓ expression of dihydropteroate synthase
Others				
Nitrofurans	• Nitrofurantoin	• Prodrug • Bind to bacterial ribosomes → inhibtion of DNA, RNA, (cell wall) and protein synthesis [7][8]	• Bacteriostatic • Bactericidal in higher concentrations	• Enzyme-mediated reduction • Efflux pumps