



Mechanisms of bacterial resistance to antibiotics:

1. Methods of drug modification:

- Hydrolysis (β -lactams, macrolides)
- Acetylation (quinolones, aminoglycosides, chloramphenicol, streptograminA)
- Phosphorylation (macrolides, aminoglycosides)
- ADP-ribosylation (rifampin)
- Nucleotidylation (aminoglycosides, lincosamide)
- Mono-oxygenation (tetracycline, tigecycline)
- Glycosylation (macrolides, rifamycins)
- Glutathione S-transferase (fosfomycin)

2. Altered target site:

- Penicillin binding proteins -altered or novel PBPs with low affinity (β -lactams, glycopeptide)
- Alterations in DNA gyrase, topoisomerase IV (quinolones)
- Posttranscriptional 16S rRNA methylation (aminoglycosides), Posttranscriptional 23S rRNA methylation (Macrolide, lincosamide, streptograminB)

3. Membrane impermeability:

- Naturally impermeable porins
- Natural lack of porins
- Mutational loss of non-essential transporters
- Mutational narrowing of porin channels

4. Active efflux

- Mutational overexpression of efflux pumps
- Plasmid mediated novel efflux pumps
- Mutations making efflux-pump more efficient at export

5. Antibiotic sequestration: Multilayered thick cell wall binds to antibiotics (glycopeptide resistance in VRSA), Biofilm formation in *P.aeruginosa* may sequester antibiotics in biofilm and prevent its reach.

6. Overproduction of targets: increase expression of PBPs

7. Target protection: gene encoding a protein with pentapeptide repeats that protects DNA (quinolone); ribosomal protection proteins promote GTP dependent release of tetracyclines from the ribosomal A site leading to dissociation of the antibiotic-target interaction. FusB-type proteins bind to elongation factor G and rescue translation from fusidic acid-mediated inhibition.

8. Modified metabolic pathway: Mutations permitting bacteria to obtain readymade folic acid. (trimethoprim-sulphamethoxazole)

Mechanism of resistance to classes of antibiotics:

Antibiotic class	Mechanisms of resistances
β -lactams	<ul style="list-style-type: none"> ▪ Antibiotic inactivation (hydrolysis by β-lactamases) ▪ Altered target (novel PBP with reduced affinity) ▪ Active efflux
Glycopeptides	<ul style="list-style-type: none"> ▪ Altered target (production of low affinity PBPs - synthesis of peptidoglycan by an alternative pathway, which produces modified peptidoglycan precursors ending in D-Ala⁴-D-Lac⁵ or D-Ala⁴-D-Ser⁵ instead of D-Ala⁴-D-Ala⁵) ▪ Sequestration of drug in thick cell wall
Bacitracin	<ul style="list-style-type: none"> ▪ Increased phosphorylation of C55-isoprenyl phosphate, due to elevated intracellular levels of the lipid kinase
Fosfomycin	<ul style="list-style-type: none"> ▪ Antibiotic inactivation (fosfomycin glutathione S-transferase converts fosfomycin into a glutathionyl derivative, via the opening of its epoxide group).
Colistin	<ul style="list-style-type: none"> ▪ Altered target (changes in the outer membrane) ▪ Active efflux
Daptomycin	<ul style="list-style-type: none"> ▪ Altered target
Aminoglycosides	<ul style="list-style-type: none"> ▪ Altered target (point mutations in the gene encoding 16S rRNA, Posttranscriptional 16S rRNA methylation) ▪ Antibiotic inactivation (aminoglycoside phosphoryltransferase, aminoglycoside acetyltransferase, aminoglycoside nucleotidyltransferase) ▪ Active efflux
Tetracycline	<ul style="list-style-type: none"> ▪ Membrane impermeability (alteration of porin proteins limits the diffusion of tetracycline into the periplasm in Gram-negative bacteria) ▪ Active efflux ▪ Target protection (ribosomal protection proteins promote GTP dependent release of tetracyclines from the ribosomal A site leading to dissociation of the antibiotic-target interaction) ▪ Altered target (point mutation in ribosomal RNA) ▪ Antibiotic inactivation (tetracycline-degrading mono-oxygenase)
Chloramphenicol	<ul style="list-style-type: none"> ▪ Antibiotic inactivation (chloramphenicol acetyltransferases, chloramphenicol phosphotransferases) ▪ Altered target (target site mutation/modification) ▪ Active efflux ▪ Decrease membrane permeability
Macrolides	<ul style="list-style-type: none"> ▪ Altered target (mutations in 23S rRNA; a post-transcriptional modification of the 23S rRNA component of the 50S ribosomal subunit involving methylation) ▪ Antibiotic inactivation(hydrolysis, glycosylation, and phosphorylation) ▪ Active efflux
Lincosamides	<ul style="list-style-type: none"> ▪ Antibiotic inactivation(nucleotydilation, phosphorylation) ▪ Altered target (mutations in 23S rRNA; a post-transcriptional modification of the 23S rRNA component of the 50S ribosomal subunit involving methylation) ▪ Active efflux

Streptogramin	<ul style="list-style-type: none"> ▪ Altered target (modification of 23 rRNA ribosomal proteins due to point mutations, a post-transcriptional modification of the 23S rRNA component of the 50S ribosomal subunit involving methylation) ▪ Antibiotic inactivation(streptogramin acetyltransferases inactivate type A streptogramins by O-acetylation; C-O lyases inactivate Streptogramin B) ▪ Active efflux
Fusidic acid	<ul style="list-style-type: none"> ▪ Altered target (point mutations) ▪ Target protection (FusB-type proteins bind to elongation factor G and rescue translation from fusidic acid-mediated inhibition)
Oxazolinidones	<ul style="list-style-type: none"> ▪ Altered target (mutations in chromosomal genes encoding 23S rRNA ribosomal protein, posttranscriptional methylation of the 23S rRNA by methyltransferase)
Quinolones	<ul style="list-style-type: none"> ▪ Altered target (mutations in the genes encoding subunits of DNA gyrase or topoisomerase IV) ▪ Antibiotic inactivation(acetylation) ▪ Target protection (a protein with pentapeptide repeats that protects DNA) ▪ Active efflux ▪ Reduced permeability
Rifamycins	<ul style="list-style-type: none"> ▪ Antibiotic inactivation(ADP-ribosyl transferase (ARR), glycosylation, monooxygenase) ▪ Altered target (chromosomal mutations)
Novobiocin	<ul style="list-style-type: none"> ▪ Altered target (accumulation of point mutations in the gene gyrB, encoding the DNA gyrase B subunit)
Mupirocin	<ul style="list-style-type: none"> ▪ Altered target (low level resistance due to mutations in isoleucyl tRNA synthetase gene; high level resistance due to expression of alternate isoleucyl-tRNA synthetase)
Trimethoprim - Sulphamethoxazole	<ul style="list-style-type: none"> ▪ Altered target (production of an additional drug-resistant dihydrofolate reductase; chromosomal mutation resulting in the production of a dihydrofolate reductase enzyme which is less vulnerable to trimethoprim inhibition) ▪ Ability to use alternative pathway by uptake of extracellular thymidine

Mechanism of action of antibiotics

Site of action	Antibiotics	Mechanism
Cell wall	β -lactams (penicillin, cephalosporins, cephamycins, monobactam, carbapenem)	Bind to penicillin binding protein (PBP) and inactivate them
	Glycopeptides (vancomycin, teicoplanin)	Inhibits transglycosylation of d-alanine-d-alanine; prevents formation of cross-linkages between two peptidoglycan chains
	Bacitracin (a cyclic polypeptide)	Binds to a phosphorylated lipid carrier (C55-isoprenyl phosphate) that transfers sugar-peptide units, prevents its dephosphorylation
	Fosfomycin	Binds to phosphoenolpyruvate UDP-N-acetylglucosamine-3-O-enolpyruvyl transferase, an enzyme which catalyzes the first step of peptidoglycan biosynthesis.
Cell membrane	Polymyxin B, colistin (cationic polypeptide)	By binding to Lipid A moiety of the gram negative outer cell membrane's lipopolysaccharide, polymyxin B disrupts the membrane's function.
	Lipid peptides (daptomycin)	Binds to cell membrane in a calcium dependent manner and causes depolarization of bacterial membrane potential resulting in release of potassium ions. Inhibits synthesis of lipoteichoic acid in gram positive bacteria
Protein synthesis	Aminoglycosides (amikacin, streptomycin, gentamicin)	Binds to 16sRNA of the 30S subunit near site A, blocking the 30S initiation complex, result in premature termination of translation of mRNA
	Tetracycline, doxycycline	Binds to 16sRNA of the 30S subunit near site A, prevent binding of tRNA to A site
	Chloramphenicol	Binds to 23sRNA of the 50S subunit, prevent binding of tRNA to A site
	Macrolides (erythromycin, roxithromycin)	Binds to 23sRNA of the 50S subunit, result in detachment of peptide chain
	Lincosamides (clindamycin)	Binds to 23sRNA of the 50S subunit, result in disassociation of peptidyl tRNA
	Streptogramins (quinupristin & dalfopristin)	Binds to 23sRNA of the 50S subunit, interferes with functioning of peptidyl tRNA, act synergistically to prevent peptide chain elongation
	Fusidic acid	Inhibits Elongation Factor G
	Oxazolidinone (linezolid)	Inhibits formation of 70S initiation complex, inhibits translocation of peptidyl tRNA from site A to P
Nucleic acid	Quinolones (nalidixic acid, ciprofloxacin, norfloxacin)	Inactivate DNA gyrase (topoisomerase II), prevents uncoiling and causes breaks in DNA
	Rifampicin	Inhibits DNA dependent RNA polymerase, block mRNA synthesis
	Novobiocin	Inhibits ATPase of DNA gyrase
	Mupirocin (Psuedomonic acid)	Inhibits isoleucyl tRNA synthetase
Metabolic pathways	Sulphamethoxazole	Block folic acid synthesis, a precursor of purine synthesis. Being analogous to PABA, it binds to dihydropteroate synthase and prevent formation of dihydropteroate
	Trimethoprim	Blocks later steps of purine synthesis; inhibits dihydrofolate reductase