

2.1 Principles of antimicrobial chemotherapy and the routes to resistance

Antimicrobial chemotherapy rests on **selective toxicity**: the drug hits a target the pathogen has and the host lacks, or a shared target in a form the host tolerates. Four target families organise the whole field: the bacterial cell wall (absent from human cells), the bacterial ribosome (70S against the host 80S), bacterial enzymes of folate synthesis and DNA handling (different from the host versions), and the fungal membrane sterol ergosterol (cholesterol's counterpart). A drug is **bactericidal** if it kills and **bacteriostatic** if it arrests growth and lets immunity finish the work, a distinction that matters in endocarditis, meningitis and the neutropenic patient, where there is no immunity to finish anything.

Resistance is the syllabus's second theme in this unit, and every class below is read through it. Bacteria resist by four general routes:

THE FOUR GENERAL ROUTES TO ANTIMICROBIAL RESISTANCE

1. Destroy or modify the drug
beta lactamases hydrolyse beta lactams
aminoglycoside modifying enzymes acetylate, adenylate, phosphorylate
2. Change the target
altered penicillin binding proteins (MRSA), methylated ribosomes (erm genes), mutated DNA gyrase, changed dihydrofolate reductase
3. Keep the drug out, or throw it out
lost porins (Gram negative outer membrane), efflux pumps (mex systems of Pseudomonas, mef pumps of pneumococci)
4. Bypass the blocked pathway
an alternative enzyme the drug cannot inhibit (the mecA product PBP2a still builds wall when the native PBPs are blocked)

Spread: mutation under selection, and horizontal gene transfer on plasmids, transposons and integrons, which is why resistance travels between species and between hospitals faster than mutation alone allows.

The Four Routes to Antimicrobial Resistance

1. Destroy or modify the drug

beta lactamases hydrolyse beta lactams
aminoglycoside modifying enzymes

2. Change the target

PBP2a in MRSA, methylated ribosomes
mutated DNA gyrase

3. Keep the drug out, or throw it out

lost outer membrane porins
efflux pumps: Mex, Mef

4. Bypass the blocked step

an alternative enzyme the drug
cannot inhibit takes over

Spread: by mutation under selection, and by horizontal gene transfer on plasmids and transposons.

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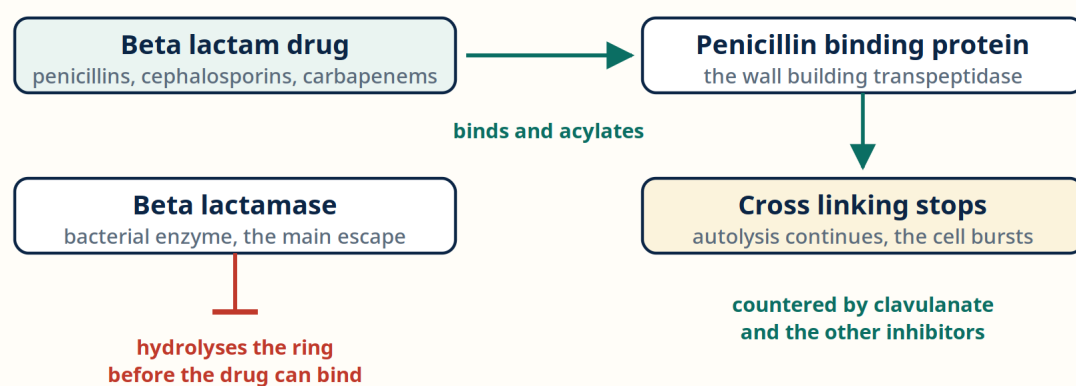
Figure: The four general routes by which bacteria resist antimicrobial drugs. Every class specific resistance in this unit is one of these four, wearing a class uniform.

2.2 Beta lactams: penicillin binding proteins and the beta lactamases

The **beta lactams** (penicillins, cephalosporins, carbapenems, monobactams) share a four membered beta lactam ring that mimics the D alanine D alanic acid end of the peptidoglycan precursor. They bind the **penicillin binding proteins (PBPs)**, the transpeptidases that cross link the cell wall, and acylate them irreversibly. Wall synthesis stops while autolytic enzymes keep working, and the growing bacterium bursts. Killing therefore needs growth, and beta lactams are the classic **time dependent, bactericidal** agents. The classes differ in spectrum and stability: benzylpenicillin is narrow and acid labile, amoxicillin adds Gram negative reach, the later cephalosporin generations trade Gram positive for Gram negative power (ceftriaxone, ceftazidime), carbapenems (meropenem, imipenem) are the broadest and most beta lactamase stable, and aztreonam covers Gram negatives only.

Resistance comes by three of the four routes. **Beta lactamases** hydrolyse the ring: hundreds exist, from simple penicillinases (why flucloxacillin was built penicillinase proof) through the extended spectrum beta lactamases (ESBLs) that destroy third generation cephalosporins, to the **carbapenemases** (KPC, NDM and others) that threaten the last line. The counter move is the **beta lactamase inhibitor**: clavulanate, sulbactam, tazobactam, and the newer avibactam, suicide or shield molecules given in fixed combination (co amoxiclav is amoxicillin plus clavulanate). **Altered targets** give methicillin resistant Staphylococcus aureus its name: the acquired mecA gene encodes **PBP2a**, a transpeptidase beta lactams bind poorly, so the wall is built anyway; treatment needs vancomycin or the anti MRSA cephalosporin ceftaroline. **Porin loss** and efflux in Pseudomonas and other Gram negatives complete the picture. The class adverse signature is hypersensitivity, up to anaphylaxis, with partial cross reactivity between penicillins and cephalosporins that modern data put far below the old ten percent teaching.

Beta Lactams at the Penicillin Binding Protein



MRSA escapes differently: its PBP2a target binds beta lactams too weakly to inhibit.

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Figure: Beta lactam action at the penicillin binding protein, and destruction of the drug by beta lactamase before it can bind.

2.3 Aminoglycosides: the 30S subunit and oxygen dependent killing

The **aminoglycosides** (gentamicin, amikacin, tobramycin, streptomycin) are polycationic sugars that must be actively transported into the bacterium, a process needing oxygen and membrane energy, which is why

they fail against anaerobes and in acidic, anaerobic abscesses. Inside, they bind the **30S ribosomal subunit** at the decoding site: the ribosome misreads messenger RNA, inserting wrong amino acids, and the abnormal proteins damage the membrane, letting still more drug in. The result is rapid, **concentration dependent bactericidal** killing with a **post antibiotic effect**, the pharmacokinetic pattern behind once daily dosing. They cover aerobic Gram negatives (and synergise with beta lactams against enterococcal endocarditis, the wall agent opening the door for them), but their toxicity is the price: **nephrotoxicity** (usually reversible) and **ototoxicity** (cochlear and vestibular, irreversible, worse with loop diuretics and in patients carrying mitochondrial mutations), plus neuromuscular blockade at high levels.

Resistance is mainly route 1 and route 2: **aminoglycoside modifying enzymes** (acetyltransferases, phosphotransferases, nucleotidyltransferases, often plasmid borne and different in spectrum, amikacin surviving many of them by its protective side chain), and, most ominously, acquired **16S ribosomal RNA methyltransferases** that methylate the binding site itself and defeat the whole class at once.

2.4 Quinolones: DNA gyrase, topoisomerase IV and target mutation

The **fluoroquinolones** (ciprofloxacin, levofloxacin, moxifloxacin) are synthetic agents that trap the bacterial enzymes **DNA gyrase** (topoisomerase II, the primary target in Gram negatives, which introduces negative supercoils ahead of the replication fork) and **topoisomerase IV** (primary in Gram positives, which separates daughter chromosomes) in their DNA cleavage complex; the trapped complexes shatter into double strand breaks and the cell dies. They are concentration dependent, bactericidal, superbly bioavailable, and concentrated in tissues, which made them oral answers to infections once needing intravenous therapy.

Resistance accumulates stepwise: **point mutations in the quinolone resistance determining regions** of gyrA and parC lower binding, each mutation raising the MIC until clinical resistance emerges; **plasmid borne qnr proteins** shield the enzymes; **efflux pumps** and a modifying enzyme variant (aac(6')-Ib-cr) add smaller contributions, important because they let bacteria survive long enough to select the chromosomal mutations. The class cautions are tendinitis and tendon rupture, QT prolongation, dysglycaemia, CNS effects and the aortic aneurysm warning, and ciprofloxacin's inhibition of CYP1A2, which raises theophylline levels.

2.5 Macrolides: the 50S exit tunnel and ribosomal methylation

The **macrolides** (erythromycin, clarithromycin, azithromycin) are large lactone rings that bind the **50S ribosomal subunit** at the nascent peptide exit tunnel, blocking translocation so the growing chain stalls; they are generally bacteriostatic, concentrated inside cells, and therefore strong against the atypical organisms (Mycoplasma, Legionella, Chlamydia) and in respiratory infection. Azithromycin's long tissue half life supports short courses and single dose regimens; clarithromycin adds Helicobacter pylori (Unit 4) and mycobacteria; erythromycin is also a motilin receptor agonist, a prokinetic side effect used deliberately in gastroparesis and suffered as cramping in infection.

Resistance divides neatly by geography and mechanism: **erm genes** encode methylases that dimethylate a single adenine of 23S ribosomal RNA, producing macrolide lincosamide streptogramin B (MLSB) resistance, inducible or constitutive; **mef genes** encode efflux pumps giving lower level macrolide only resistance, common in pneumococci in some regions; and 23S mutations occur in Helicobacter and mycobacteria. Drug interactions define clarithromycin and erythromycin in practice: both inhibit CYP3A4 strongly (azithromycin does not), raising levels of statins, warfarin and many others, and all macrolides can prolong the QT interval.

2.6 Antifungal drugs: ergosterol and the fungal wall

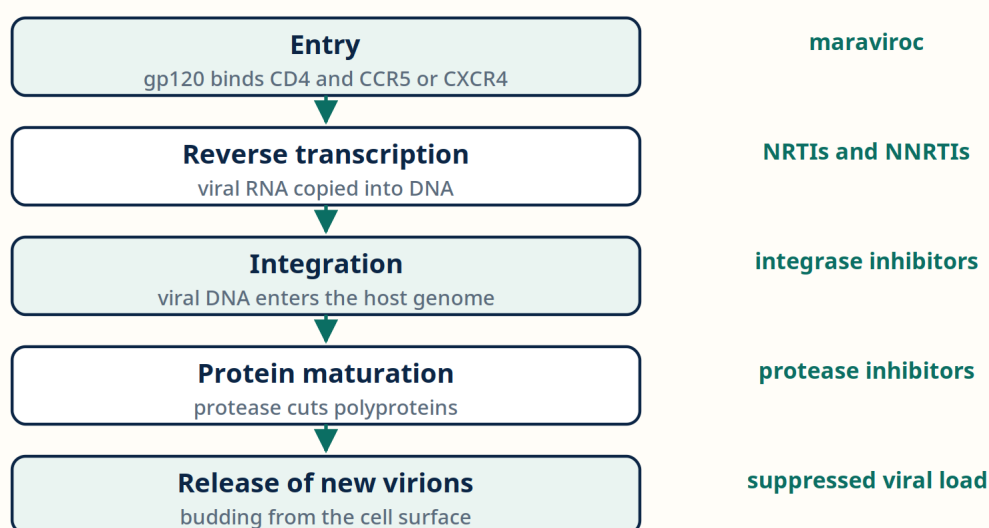
Fungi are eukaryotes, so selective toxicity is harder and the targets fewer. **Amphotericin B**, a polyene, binds **ergosterol** in the fungal membrane and forms pores; the cell leaks and dies. It remains the broadest, most reliably fungicidal agent for invasive mycoses, paid for with infusion reactions and dose limiting nephrotoxicity, which lipid formulations soften. The **azoles** (fluconazole, itraconazole, voriconazole, posaconazole) inhibit **lanosterol 14 alpha demethylase**, a fungal CYP enzyme, starving the membrane of ergosterol; they are mostly fungistatic, orally available, and themselves CYP inhibitors with rich interaction lists. The **echinocandins** (caspofungin, micafungin) inhibit **beta 1,3 glucan synthase**, dissolving the fungal cell wall that human cells do not possess at all, the cleanest selective target in the field, invaluable against *Candida* including many azole resistant strains. **Flucytosine** is converted inside the fungus to 5 fluorouracil and corrupts its RNA and DNA, used only in combination (with amphotericin for cryptococcal meningitis) because resistance emerges rapidly alone. **Terbinafine** blocks squalene epoxidase upstream of ergosterol and is the oral standard for nail infection. Resistance, once rare, now matters: azole resistant *Aspergillus* from agricultural azole use, and *Candida* species with efflux pump overexpression or target mutation, are reshaping empirical choices.

2.7 Antiviral drugs: hitting a parasite that uses the host

Viruses borrow the host's machinery, so antiviral targets are the few virus specific steps: viral enzymes and entry proteins. The anti herpes agents start the story: **aciclovir** is a guanosine analogue activated first by viral thymidine kinase (the selectivity trick), then by host kinases to a triphosphate that inhibits viral DNA polymerase and terminates the chain; valaciclovir is its oral prodrug, and ganciclovir extends the pattern to cytomegalovirus at the price of marrow toxicity.

Antiretroviral therapy (ART) for HIV is the field's triumph and its discipline. The classes map onto the viral life cycle: **nucleoside reverse transcriptase inhibitors** (tenofovir, emtricitabine, zidovudine, abacavir) fake the building blocks of reverse transcription; **non nucleoside reverse transcriptase inhibitors** (efavirenz, rilpivirine) jam the enzyme's allosteric pocket; **protease inhibitors** (ritonavir or cobicistat boosted darunavir and others) stop maturation of viral proteins; **integrase strand transfer inhibitors** (dolutegravir, bictegravir) block insertion of viral DNA into the host genome and now anchor most first line regimens; entry and fusion agents (maraviroc, enfuvirtide) serve salvage situations. Viral replication is error prone and fast, so a single drug selects resistance within weeks: ART is always combination therapy, three active agents, and adherence is pharmacology, not advice, since missed doses are the selection pressure. Elsewhere: **oseltamivir** inhibits influenza neuraminidase, preventing release of new virions; hepatitis B is suppressed by tenofovir and entecavir; hepatitis C is now cured by direct acting combinations (sofosbuvir based) that inhibit the NS5B polymerase, NS5A and the NS3/4A protease; remdesivir, a nucleotide analogue of an RNA polymerase, represents the same logic in coronaviruses.

The HIV Life Cycle and the Antiretroviral Classes



Combination therapy blocks several steps at once, so no single mutation rescues the virus.

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Figure: The HIV life cycle and the antiretroviral classes. Combination therapy blocks several steps at once so that no single mutation rescues the virus.

2.8 Anti-TB drugs: four drugs against persistence and resistance

Tuberculosis combines every chemotherapy difficulty in one disease: a slow growing bacillus with a waxy mycolic acid wall, populations hiding in different states (actively dividing, semi dormant in acidic caseous foci, intracellular), and a huge bacterial load in cavitary disease within which resistant mutants already exist by chance. Standard drug sensitive TB is therefore treated with **four drugs for two months, then two drugs for four months** (the 2HRZE/4HR pattern), each drug covering the others' resistant mutants and each hitting a different bacterial population:

Drug	Mechanism	Population it kills best	Signature toxicity
Isoniazid (H)	Prodrug activated by the bacterial catalase peroxidase KatG; the activated form inhibits mycolic acid synthesis (InhA)	Actively dividing bacilli, the most potent early killer	Hepatitis; peripheral neuropathy prevented by pyridoxine (vitamin B6), worst in slow acetylators and diabetics
Rifampicin (R)	Inhibits bacterial DNA dependent RNA polymerase	Semi dormant persisters, the great sterilising drug that shortened therapy to six months	Hepatitis, orange urine and tears, and potent enzyme induction collapsing the levels of contraceptives, warfarin and transplant drugs
Pyrazinamide (Z)	Prodrug converted by bacterial pyrazinamidase; active against bacilli in acidic environments	Acidic, caseous and intracellular populations, first two months	Hepatitis, raised uric acid and arthralgia
Ethambutol (E)	Inhibits arabinosyl transferases building the arabinogalactan wall layer	Protects the regimen while susceptibilities are unknown	Optic neuritis: loss of acuity and red green colour vision, checked during therapy

Resistance follows predictably when therapy is inadequate: loss of KatG or InhA change defeats isoniazid, rpoB mutation defeats rifampicin, and **multidrug resistant TB (MDR TB)**, resistant to at least isoniazid and rifampicin) and extensively drug resistant disease need second line regimens now built around **bedaquiline** (which inhibits mycobacterial ATP synthase, a wholly new target), pretomanid, linezolid and the

fluoroquinolones, supervised for far longer. The unit's message generalises: in chemotherapy, the regimen is designed around the resistance arithmetic of the pathogen population, not around any single drug.

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