

Exercise walk-through

8.6

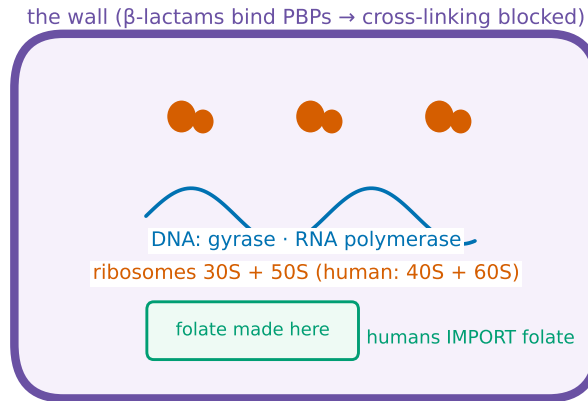
Antimicrobials and resistance

University Medicine

Antimicrobials: four targets, resistance arithmetic

- 1 **Targets** Wall (β -lactams $\rightarrow$ penicillin-binding proteins), ribosome (30S/50S vs our 40S/60S), gyrase/RNA polymerase, folate (bacteria make it, we import it).
- 2 **Arithmetic** Resistance mutations 10^{-7} - 10^{-9} per cell per generation; $\sim 10^9$ cells per mL overnight $\rightarrow$ mutants against any single drug; two hits multiply to 10^{-14} - 10^{-18} .
- 3 **Report read** β -lactamase opens the ring (hydrolysis); PBP2a is the altered target - different mechanisms, different reports.

Drug targets on a bacterium



**selective toxicity = a target
human cells lack**

wall

β -lactams $\rightarrow$ PBPs (cross-linking)

ribosome

30S/50S blocked; ours untouched

DNA enzymes

gyrase · RNA polymerase

folate

blocked; humans import it

resistance: mutation 10^{-7} – 10^{-9} /cell/generation
+ plasmids moving genes between species

Wall, ribosome, DNA enzymes, folate - four bacteria-specific targets on one cell.

Exercises 2.1-2.3

2.1 Why is an anti-folate selectively toxic? [3]

2.2 A 1 mL culture holds 10^9 cells; resistance arises at 10^{-8} per cell per generation – expected resistant mutants? [3]

2.3 β -lactamase resistance vs PBP2a resistance: one difference. [3]

Exercises 2.1-2.3

2.1 Why is an anti-folate selectively toxic? [3]

2.1

- Bacteria synthesise folate; humans import it in the diet – the pathway is the difference ✓.

2.2 A 1 mL culture holds 10^9 cells; resistance arises at 10^{-8} per cell per generation – expected resistant mutants? [3]

2.2

- $10^9 \times 10^{-8} = 10^1 \approx 10$ mutants ✓.

2.3 β -lactamase resistance vs PBP2a resistance: one difference. [3]

2.3

- β -lactamase hydrolyses (opens) the drug ring; PBP2a is an altered target that still builds the wall ✓.

Exercise 3.1

3.1 A fictional broth culture of 4×10^9 cells faces drug X; resistance mutations arise at 10^{-8} per cell per generation.

Calculate the expected resistant mutants ($4 \times 10^9 \times 10^{-8} \approx 40$). For a two-drug combination with independent targets at 10^{-8} each, calculate the double-mutant expectation (10^{-16} per cell pair – effectively zero in the culture) and explain in one line why combinations exist. [8]

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3.1

- $4 \times 10^9 \times 10^{-8} = 40$ resistant mutants expected ✓.
- Double mutant: $10^{-8} \times 10^{-8} = 10^{-16}$ per cell pair ✓.
- $4 \times 10^9 \times 10^{-16} = 4 \times 10^{-7}$ – effectively zero in the culture ✓.
- Combinations exist because two independent probabilities multiply: the resistant fraction collapses ✓.

Exercise 3.2

3.2 A fictional ward sees rising resistance tracked to broad spectrum use.

Explain the mechanism chain from drug pressure to a resistant ward flora (selection of the pre-existing 10^{-7} – 10^{-9} fraction, then plasmid spread between species). Explain why narrowing the drug to the reported susceptibility reduces selective pressure. [7]

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3.2

- Every large population already carries the resistant fraction (10^{-7} – 10^{-9} per cell per generation) ✓.
- The drug SELECTS it: sensitive cells die, resistant cells fill the niche; plasmids then move genes between species ✓.
- Narrowing to the reported susceptibility removes needless pressure on the rest of the ward flora – stewardship is the mechanism applied ✓.