MICROBIOLOGY/
INFECTIOUS DISEASE

PHARMACOLOGY

Introduction to Antibiotics

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WASHINGTON STATE UNIVERSITY
Elson S. Floyd College of Medicine

Disclosure

None

USE STATEMENT

Collaboration

We would love to have an interactive session - if you have a question, let me know!

Raising hands is always good.

The room is big so if I don't see you, please speak up!!!

You can also email us after class:
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Objectives

- [1] Describe the five basic mechanisms of action of antimicrobials against bacterial cells (inhibition of cell wall synthesis, inhibition of protein synthesis, alteration of cell membranes, inhibition of nucleic acid synthesis, and antimetabolite activity)
- [2] Define empiric versus directed antimicrobial therapy and describe the basic principles behind selecting an empiric antimicrobial regimen
- [3] Discuss the pharmacokinetic (static versus cidal) and pharmacodynamic (time-dependent versus concentration-dependent) principles of antimicrobial therapy
- [4] Describe three main mechanisms by which bacteria resist the activity of antimicrobials

JAMBOARD ACTIVITY

Antibiotics – What to Know

Mechanism of Action

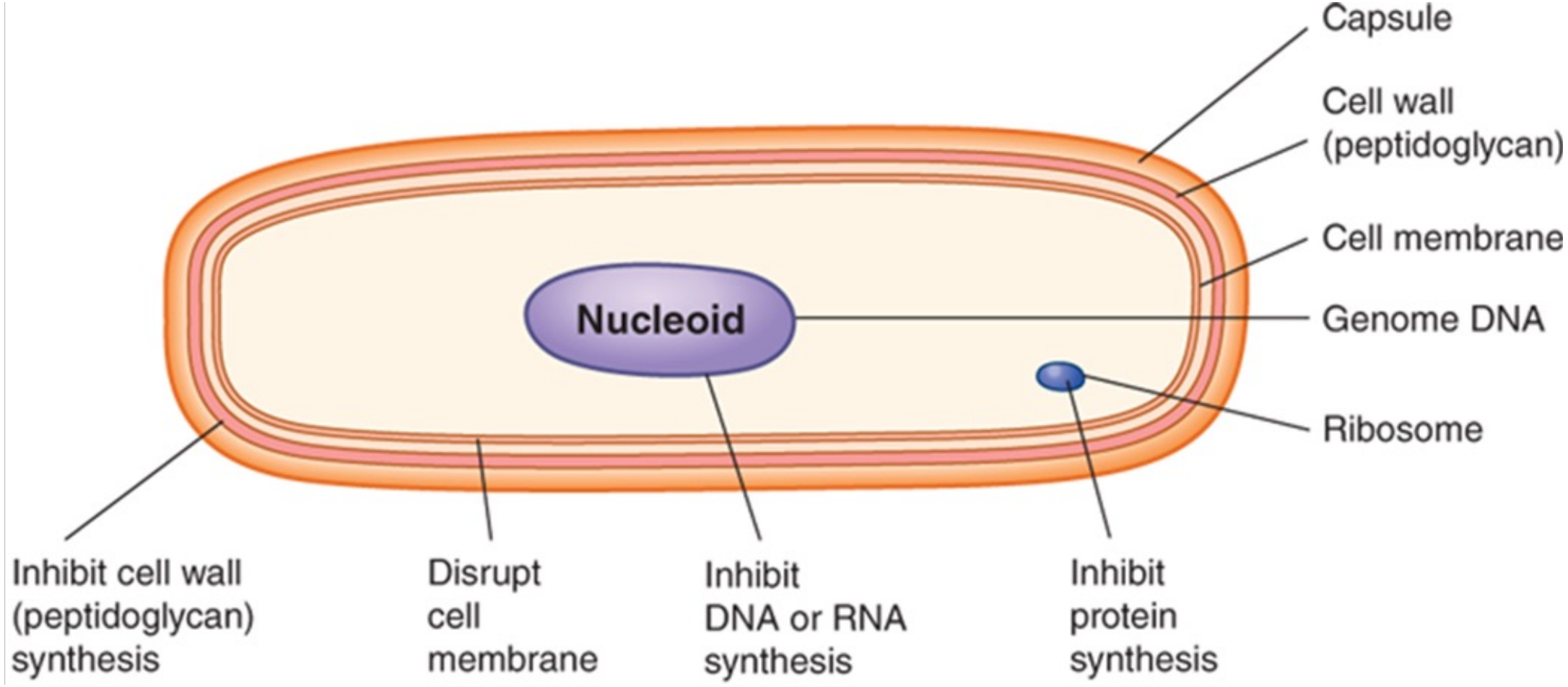
Spectrum of Activity

Mechanisms of Resistance

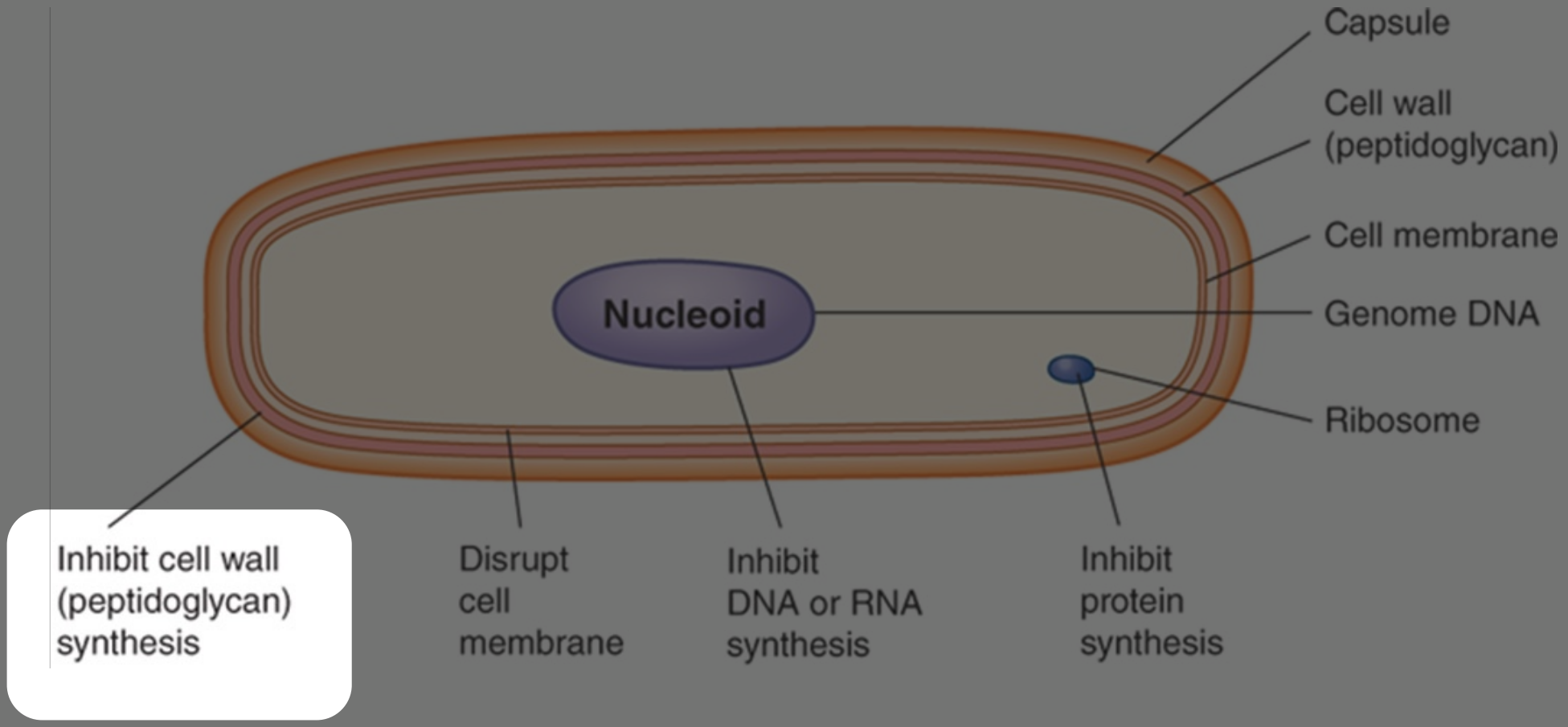
Pharmacology: Absorption/bioavailability, metabolism, distribution, elimination

Adverse effect profile

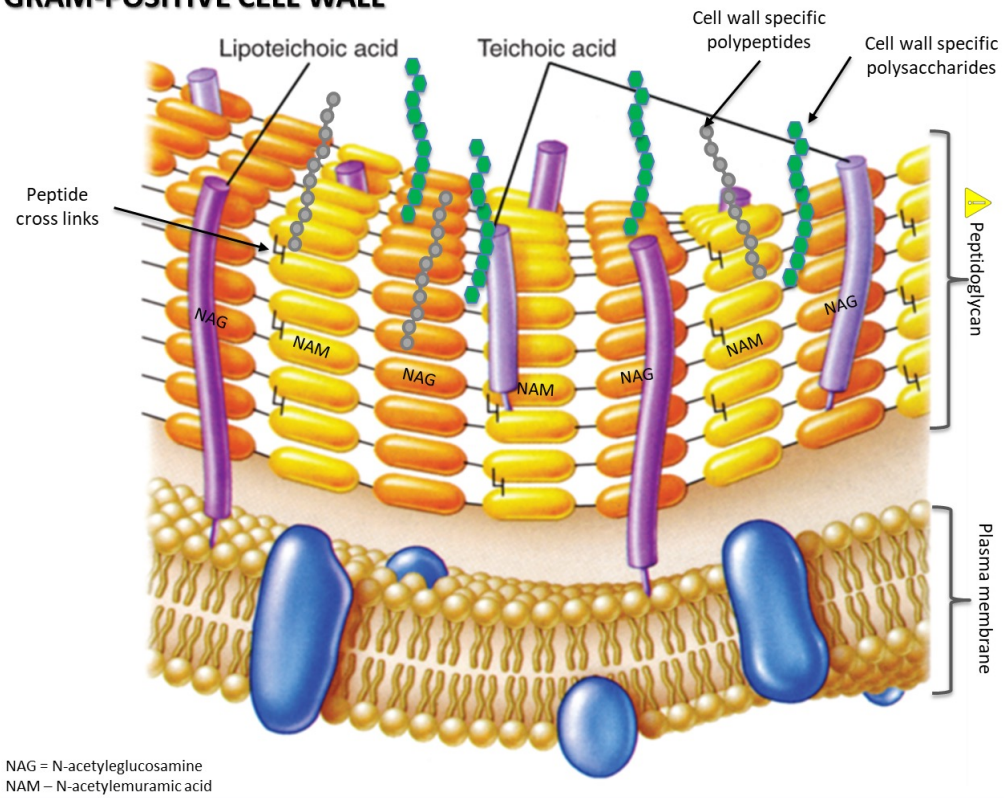
Model of Typical Bacterial Cell Showing Sites of **Action Of Important Antibacterial Drugs**



Model of typical bacterial cell showing sites of action of important antibacterial drugs

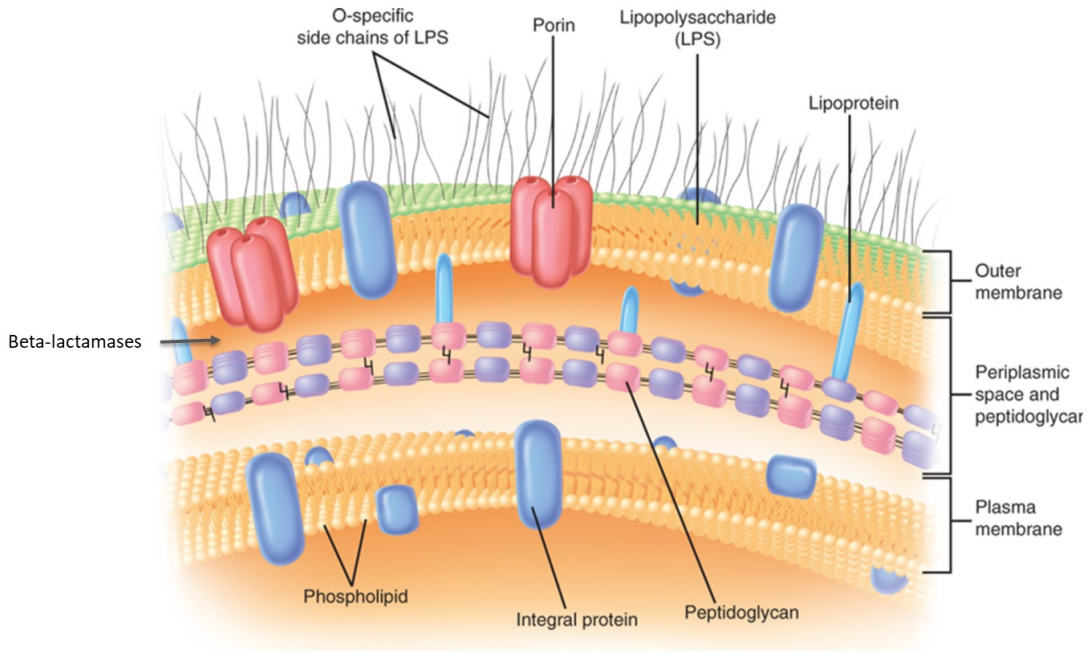


GRAM-POSITIVE CELL WALL



NAG = N-acetyleglucosamine
NAM – N-acetylemuramic acid

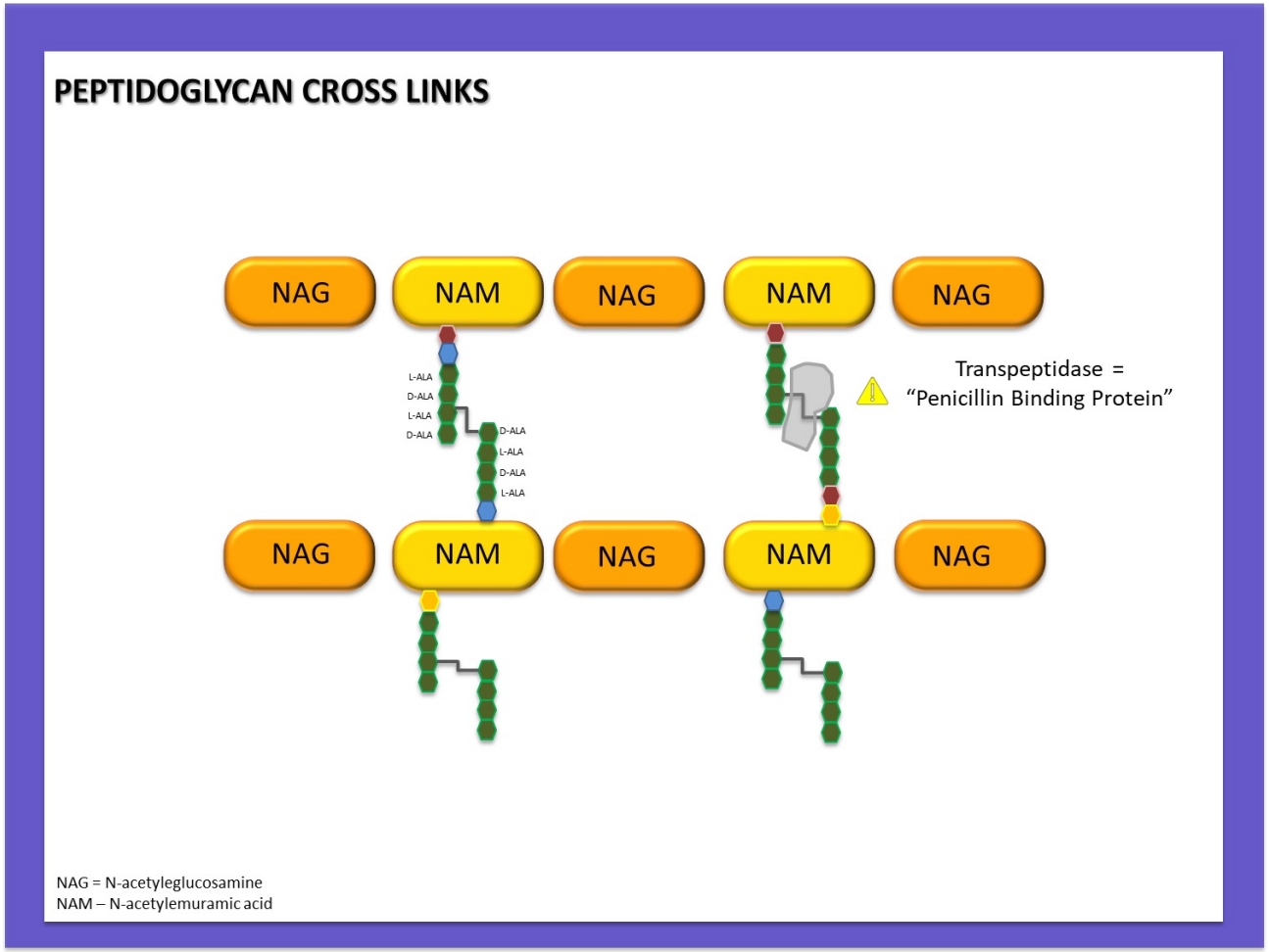
GRAM-NEGATIVE CELL WALL



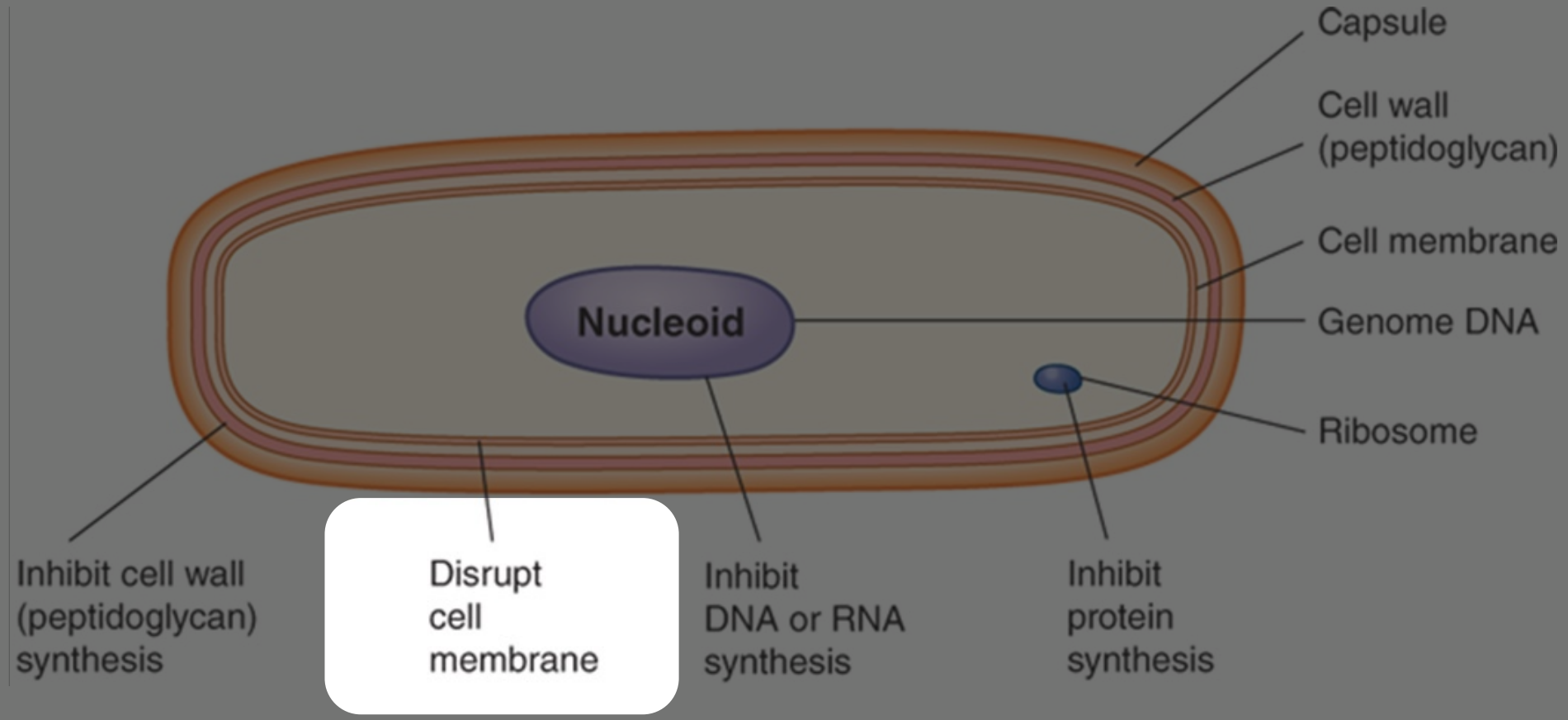
Beta-lactams: Inhibition of Cell-wall Cross-linking

Beta-lactam antibiotics, structural analogs of the natural D-Ala-D-Ala substrate, covalently binds to the active site of PBPs. The binding inhibits the transpeptidation reaction and stops the peptidoglycan synthesis and the cell dies

- Penicillins
- Cephalosporins
- Carbapenems
- Vancomycin



Model of typical bacterial cell showing sites of **action of important antibacterial drugs**



Disruption of Cell Membrane

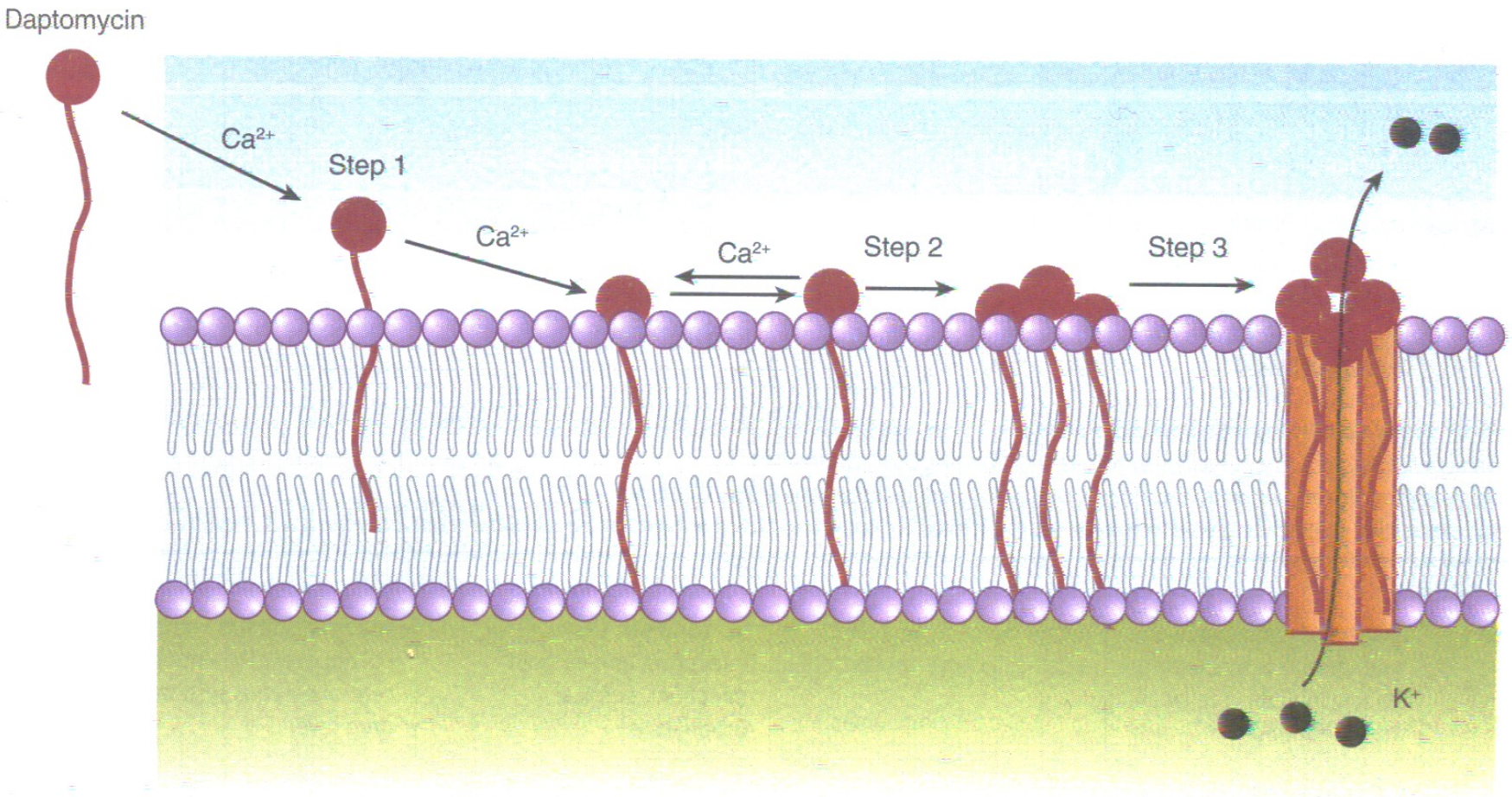
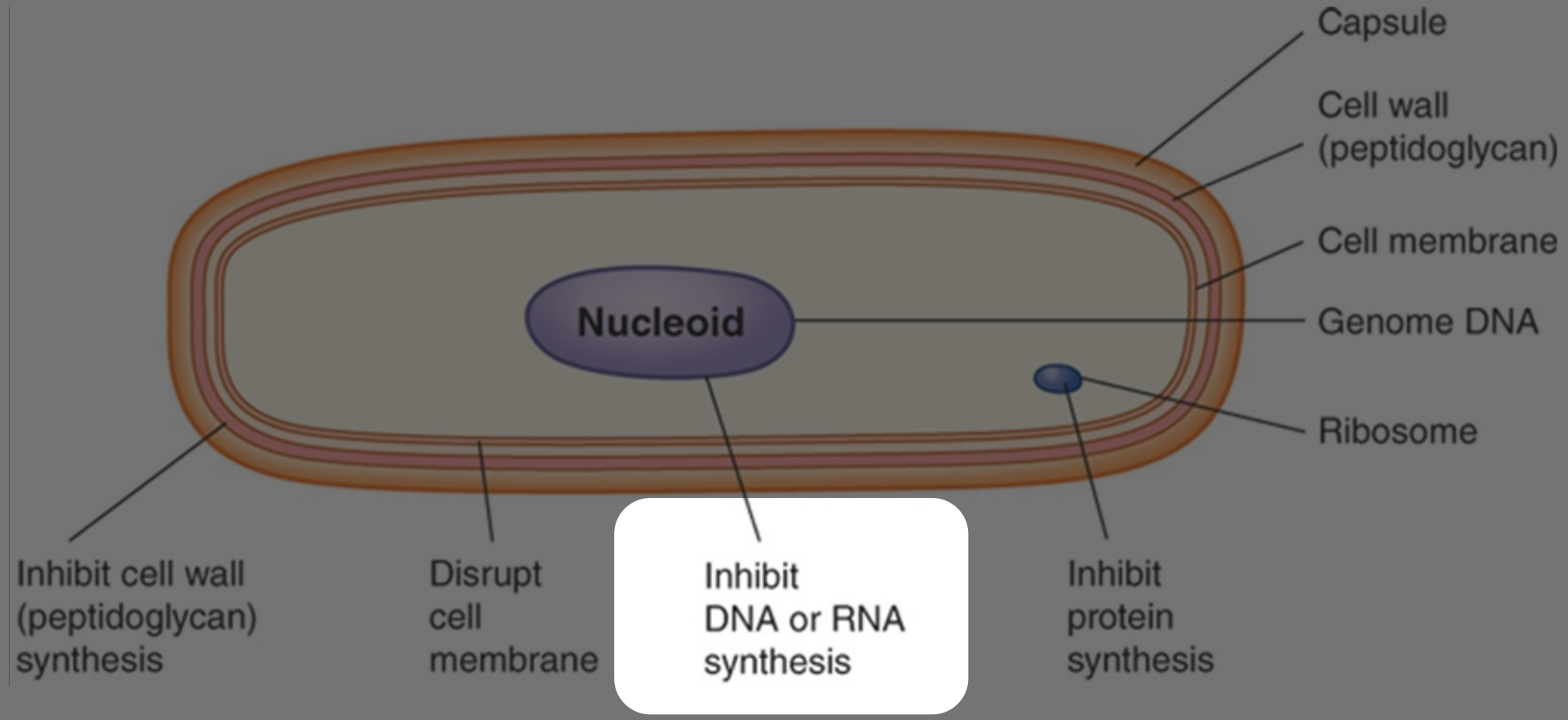
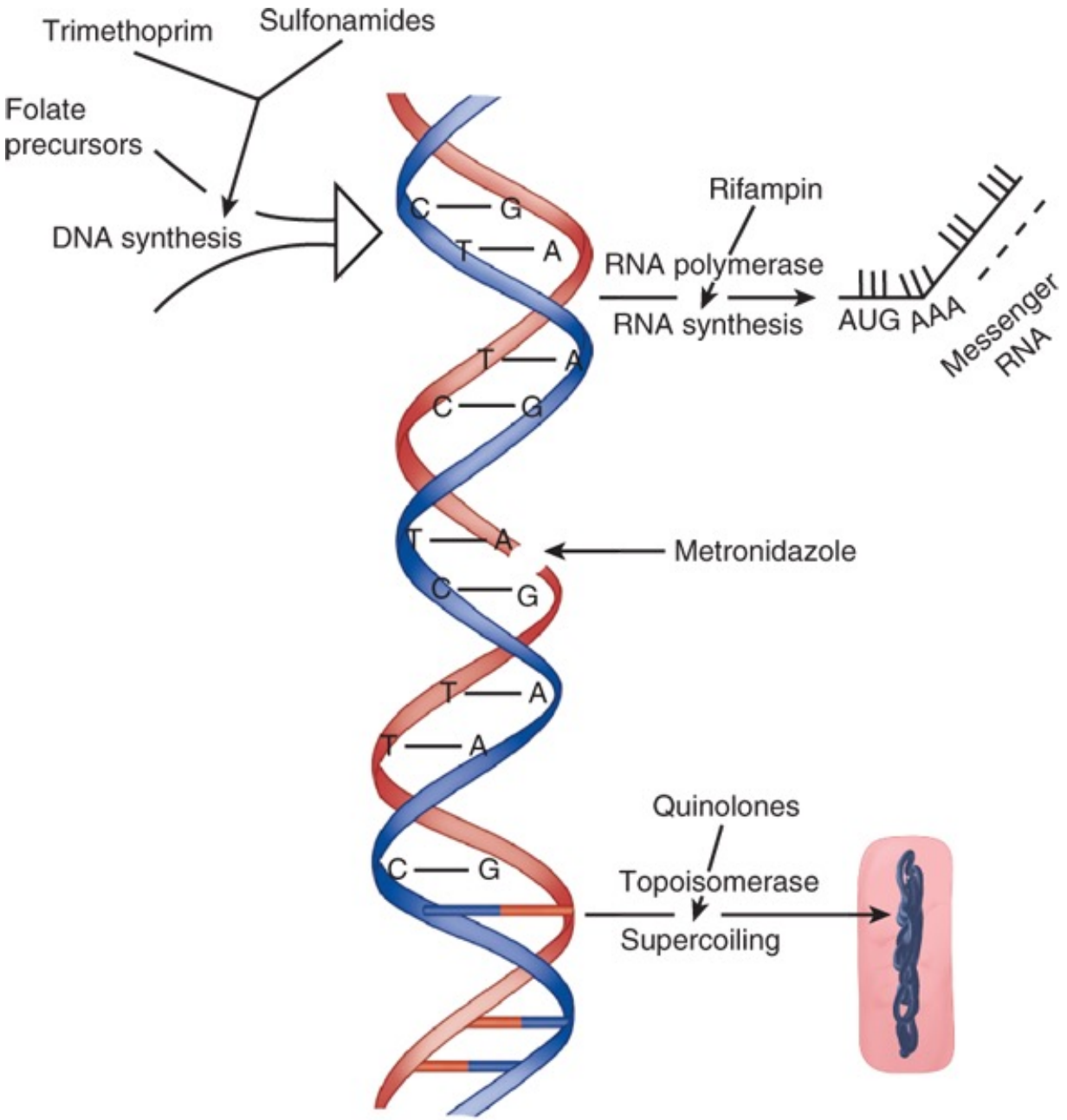


FIGURE 43–10 Proposed mechanism of action of daptomycin. Daptomycin first binds to the cytoplasmic membrane (step 1) and then forms complexes in a calcium-dependent manner (steps 2 and 3). Complex formation causes a rapid loss of cellular potassium, possibly by pore formation, and membrane depolarization. This is followed by arrest of DNA, RNA, and protein synthesis resulting in cell death. Cell lysis does not occur.

Model of typical bacterial cell showing sites of **action of important antibacterial drugs**

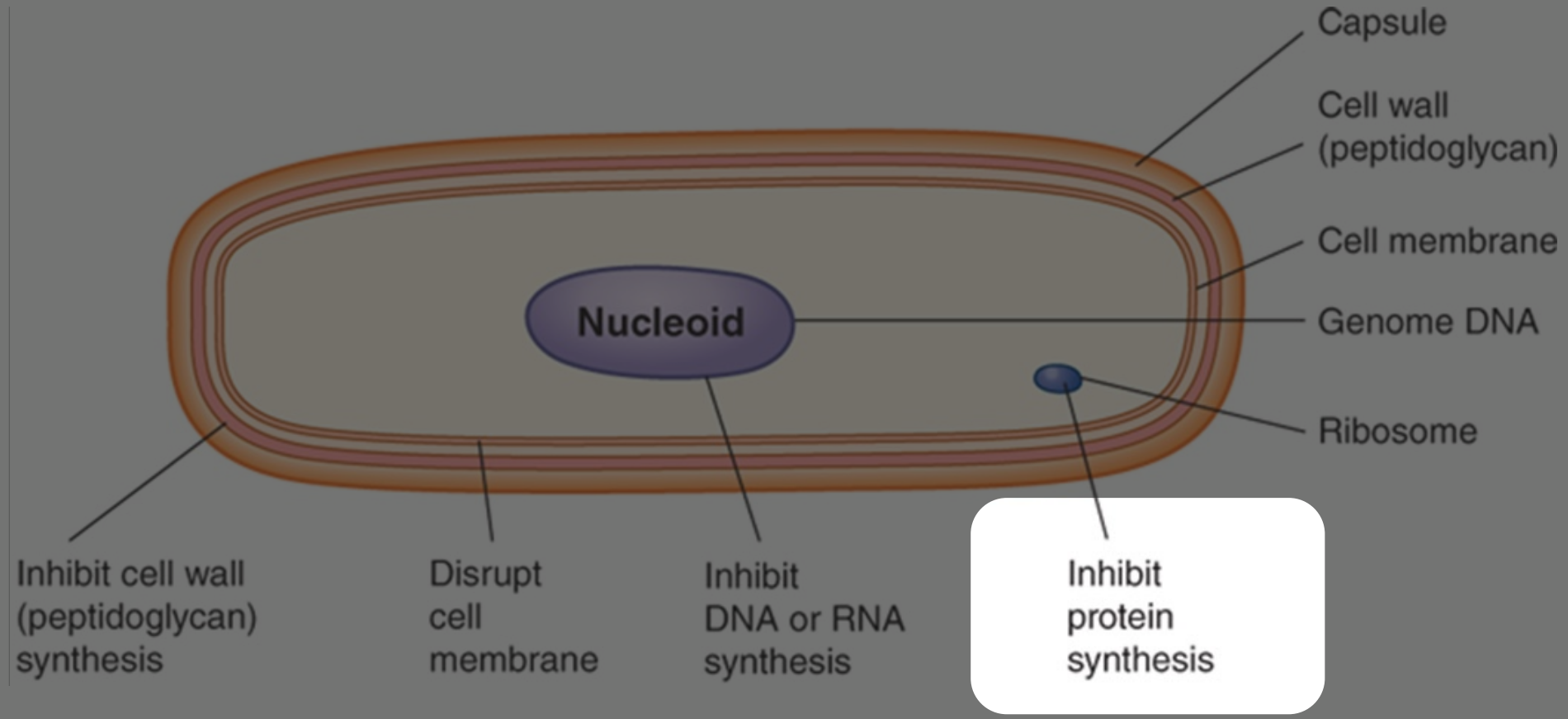




Inhibit DNA or RNA Synthesis

- Block the formation of DNA 'building blocks'
- Damage to DNA itself
- Inhibition of transcription
- Prevention of uncoiling/supercoiling

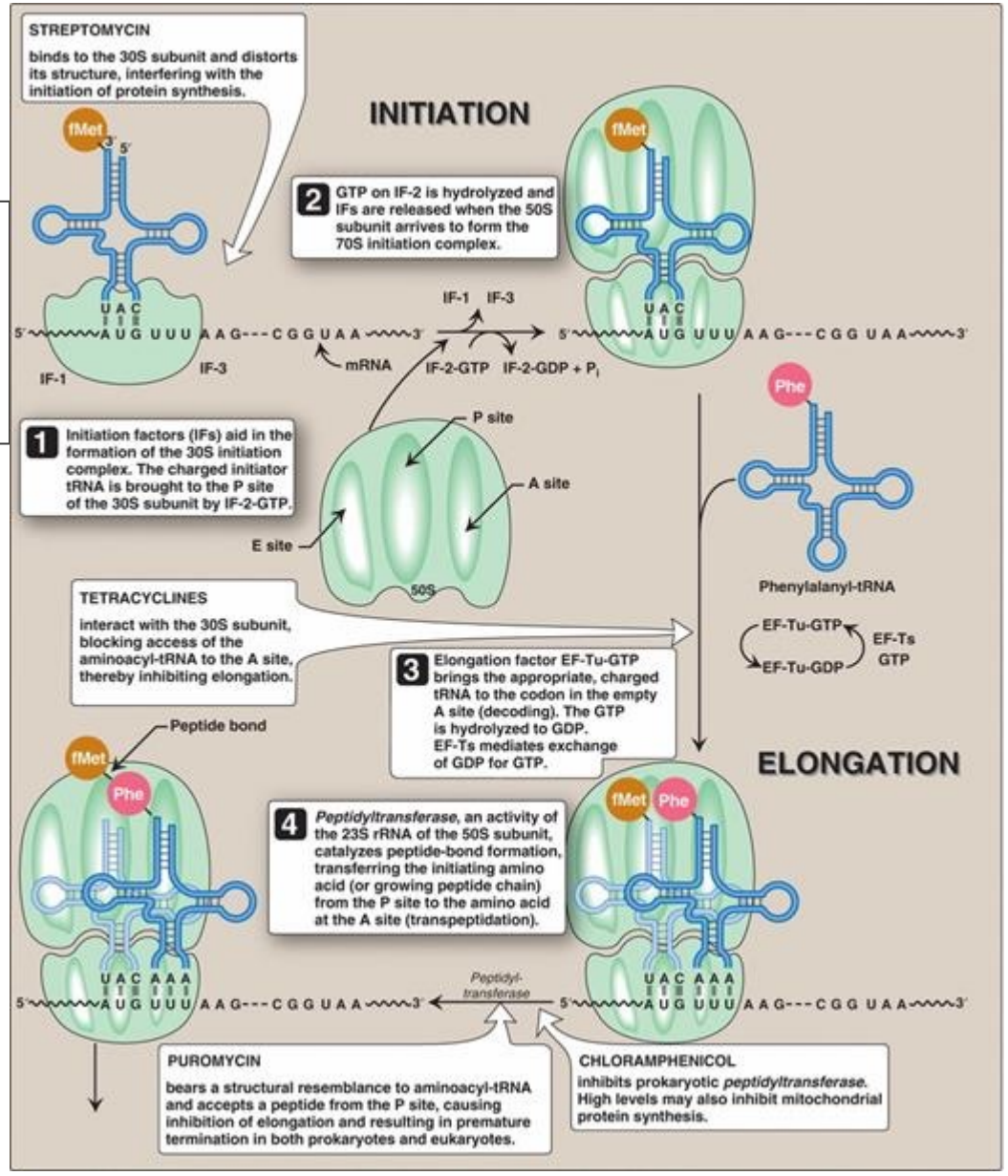
Model of typical bacterial cell showing sites of **action of important antibacterial drugs**

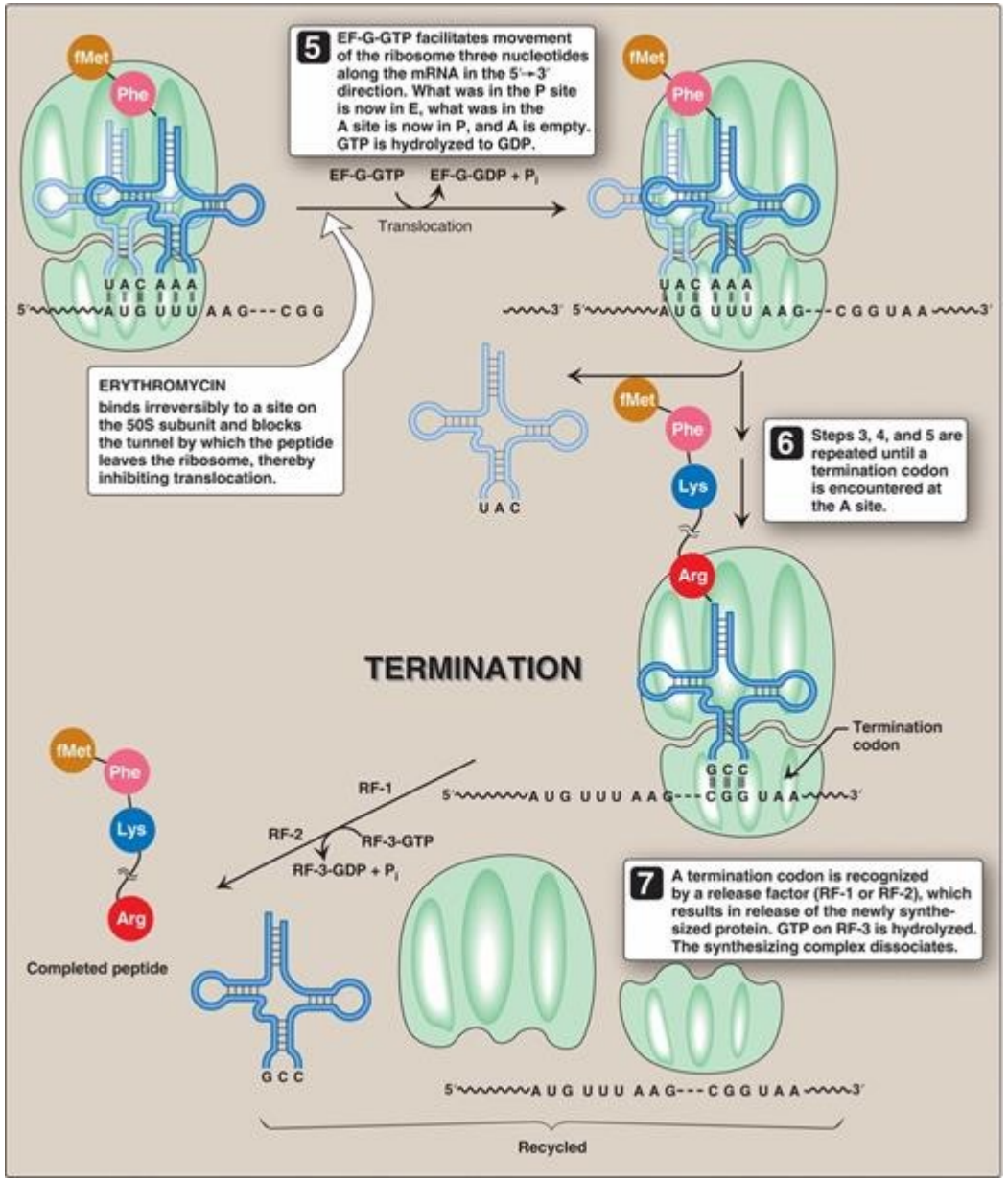


INHIBITION PROTEIN SYNTHESIS

30S interference

50S interference





Antibiotics – What to Know

Mechanism of Action

Spectrum of Activity

Mechanisms of Resistance

Pharmacology: Absorption/bioavailability, metabolism, distribution, elimination

Adverse effect profile

Framework for Spectrum of Activity

GRAM-POSITIVE	GRAM-NEGATIVE RODS
❑ *Staphylococcus* ❑ *MRSA* ❑ *Streptococcus* ❑ *Enterococcus*	❑ *Enterics (Enterobacteriaceae)* ❑ *Respiratory* ❑ *GI* ❑ *Pseudomonas*
ATYPICALS	**ANAEROBE**
❑ Atypical cell wall ❑ Mycobacteria	❑ Oral ❑ Bowel

Antibiotics – What to Know

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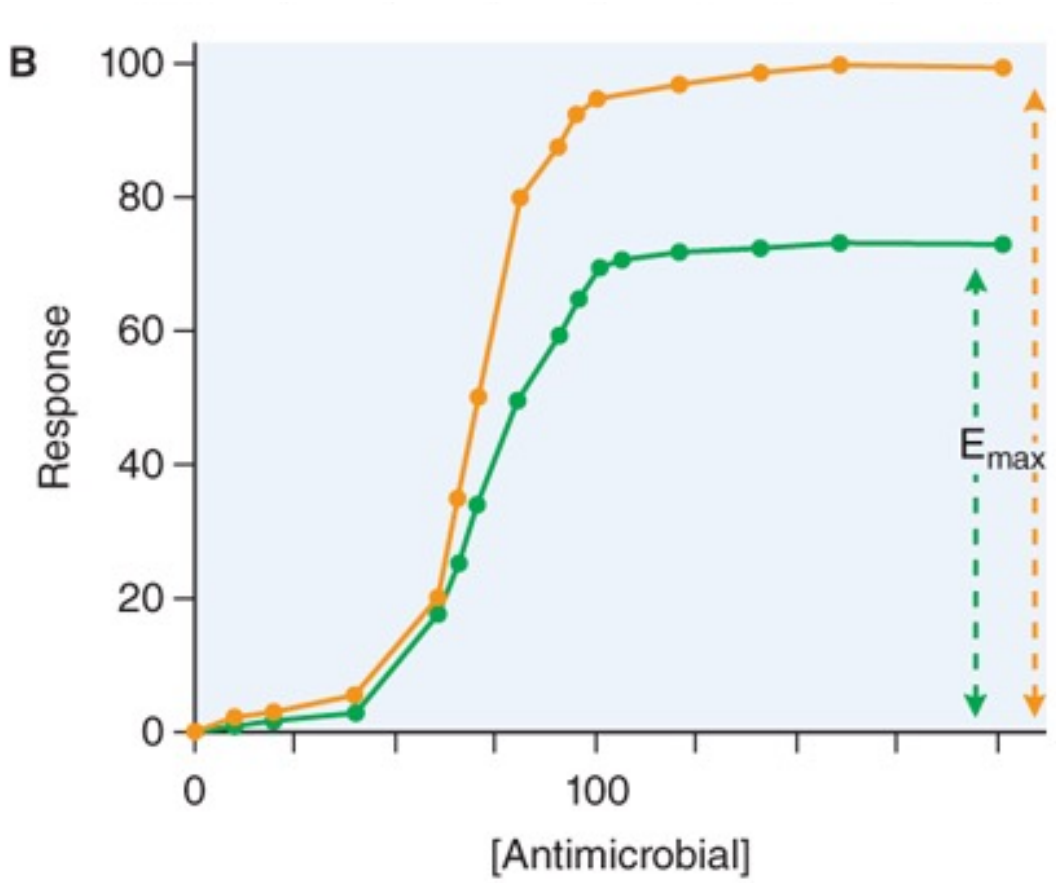
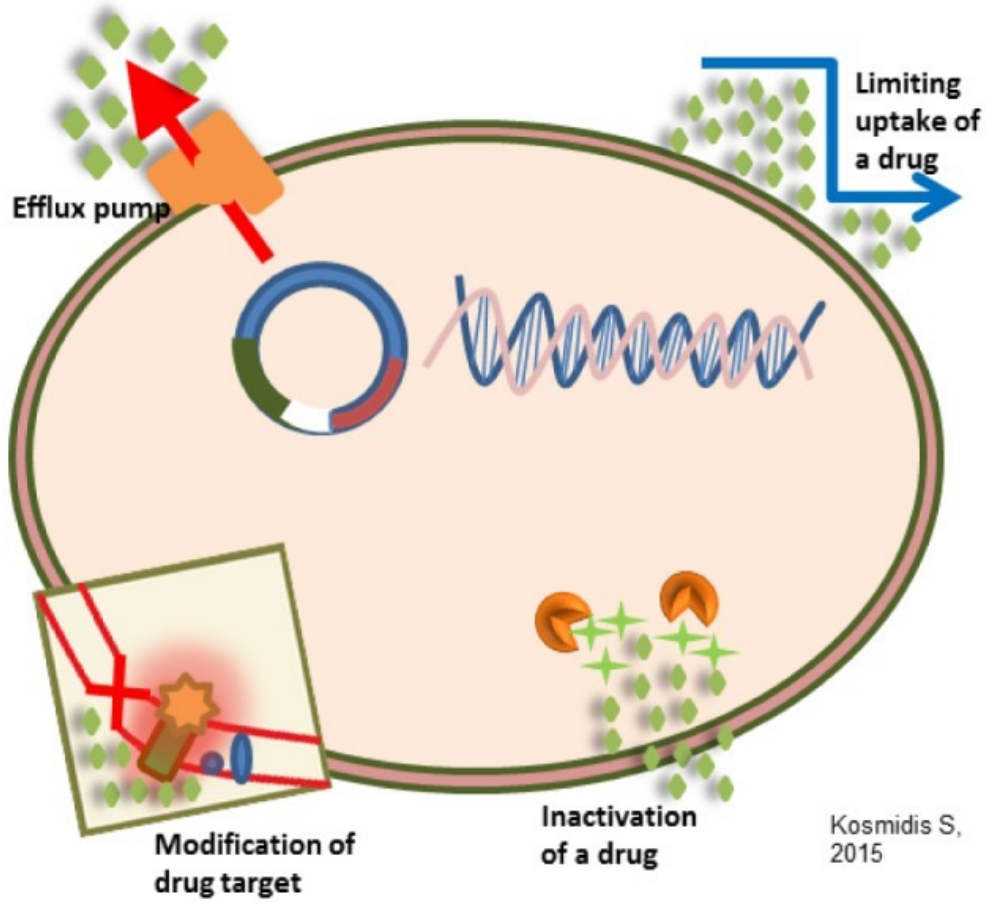
Active Learning

Consider the following dose response curves for two different antimicrobials against the same microorganism. Draw a star next to the curve of the drug with the lower efficacy.



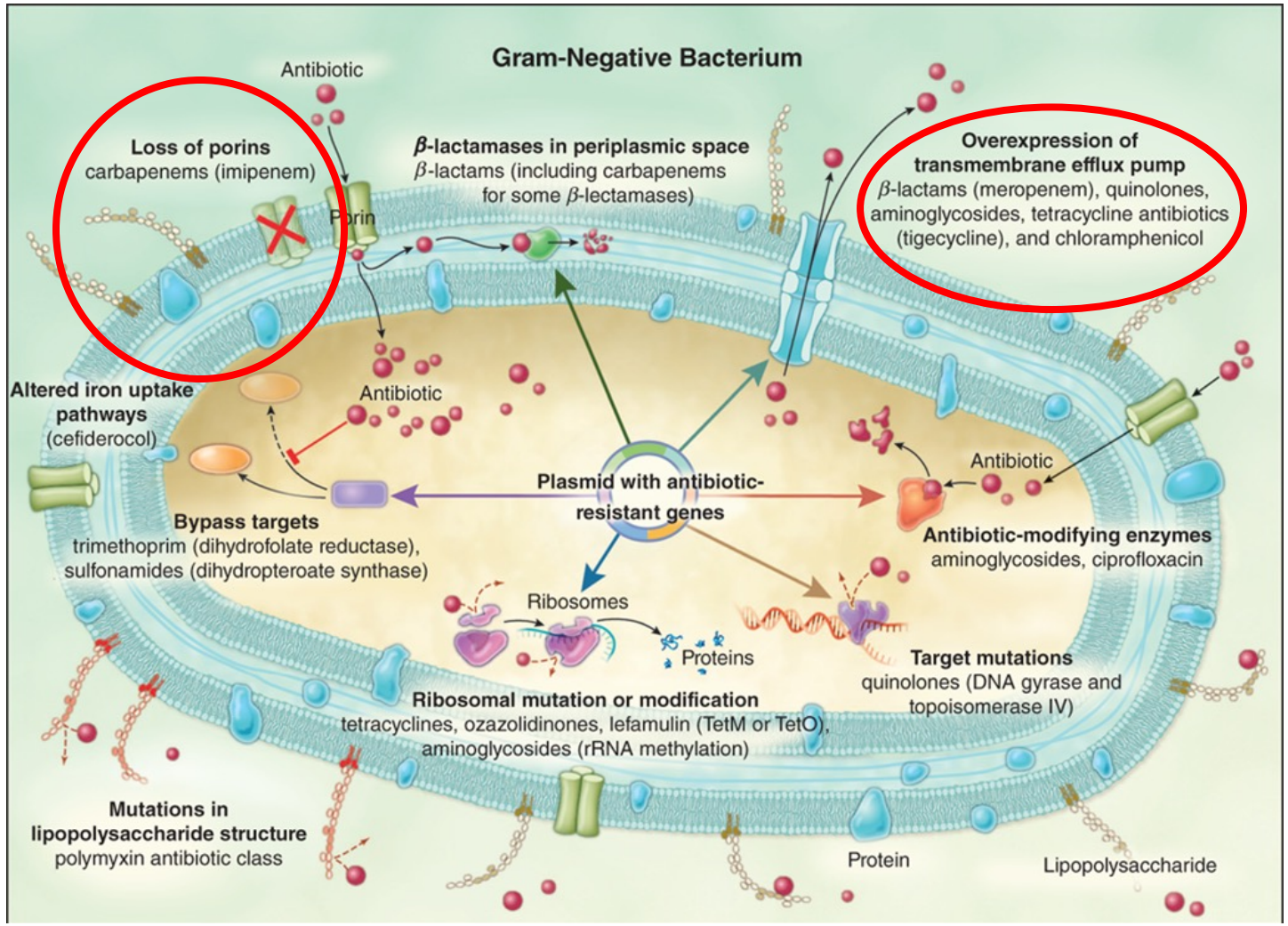
Mechanism of Resistance



1. Limiting Drug Uptake/Exclusion Barrier
2. Modification of Drug Targets
3. Enzymatic Inactivation

Mechanism of Resistance 1: Limiting Drug Uptake/Exclusion Barrier

- Natural differences
  - Bacteria that lack cell walls (*Mycoplasma*) intrinsic resistance to drugs that target cell wall (beta-lactams, glycopeptides)
- ↓ entry of drugs into pathogen
  - Antibiotics (often small polar molecules) enter the cell through protein channels called porins
  - Porin channel absence/mutation in → ↓ rate of drug entry into a cell
- Drug efflux
  - Microorganisms can overexpress efflux transporters
  - Expel antibiotics to which the microbial is susceptible

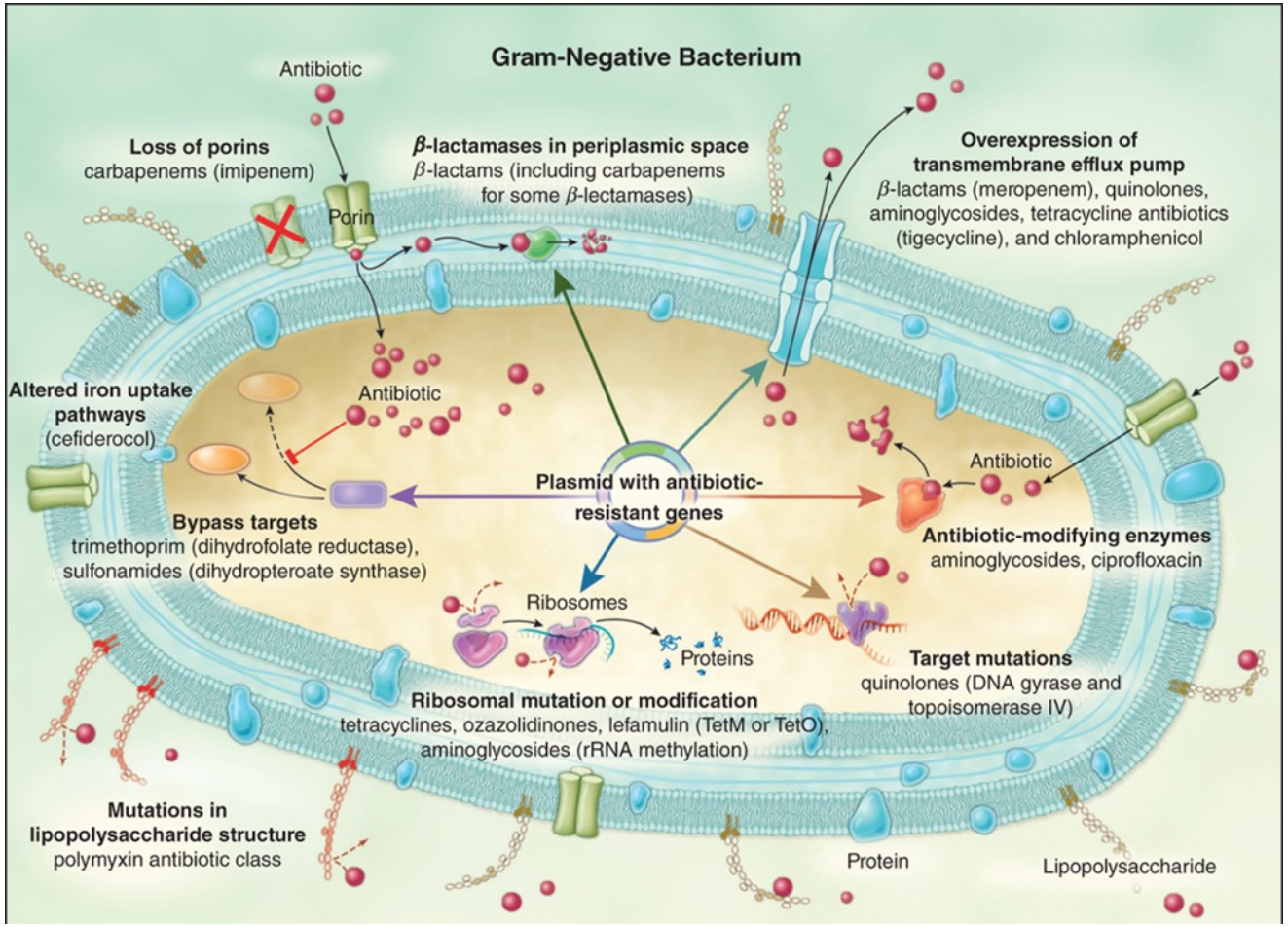

Gram-Negative Bacterium
Antibiotic
Loss of porins
carbapenems (imipenem)
Porin
β-lactamases in periplasmic space
β-lactams (including carbapenems
for some β-lectamases)
Overexpression of
transmembrane efflux pump
β-lactams (meropenem), quinolones,
aminoglycosides, tetracycline antibiotics
(tigecycline), and chloramphenicol
Altered iron uptake
pathways
(cefiderocol)
Antibiotic
Antibiotic
Plasmid with antibiotic-
resistant genes
Bypass targets
trimethoprim (dihydrofolate reductase),
sulfonamides (dihydropteroate synthase)
Antibiotic-modifying enzymes
aminoglycosides, ciprofloxacin
Ribosomes
Proteins
Target mutations
quinolones (DNA gyrase and
topoisomerase IV)
Ribosomal mutation or modification
tetracyclines, ozazolidinones, lefamulin (TetM or TetO),
aminoglycosides (rRNA methylation)
Mutations in
lipopolysaccharide structure
polymyxin antibiotic class
Protein
Lipopolysaccharide

Mechanism of Resistance 2: Modification of Drug Targets

- Beta-lactams
  - Alteration in penicillin-binding proteins (PBPs)
  - PBP structure change
- Glycopeptides
  - Acquisition of genes that change structure of peptidoglycan precursors → ↓ binding ability

- Drugs that target ribosomal subunits
  - Ribosomal mutation, subunit methylation, protection
- Drugs that target nucleic acid synthesis (fluoroquinolones)
  - Modifications in DNA gyrase or topoisomerase IV
- Drugs that target metabolic pathways
  - ↓ binding ability to active site

Mechanism of Resistance 3: Enzymatic Inactivation



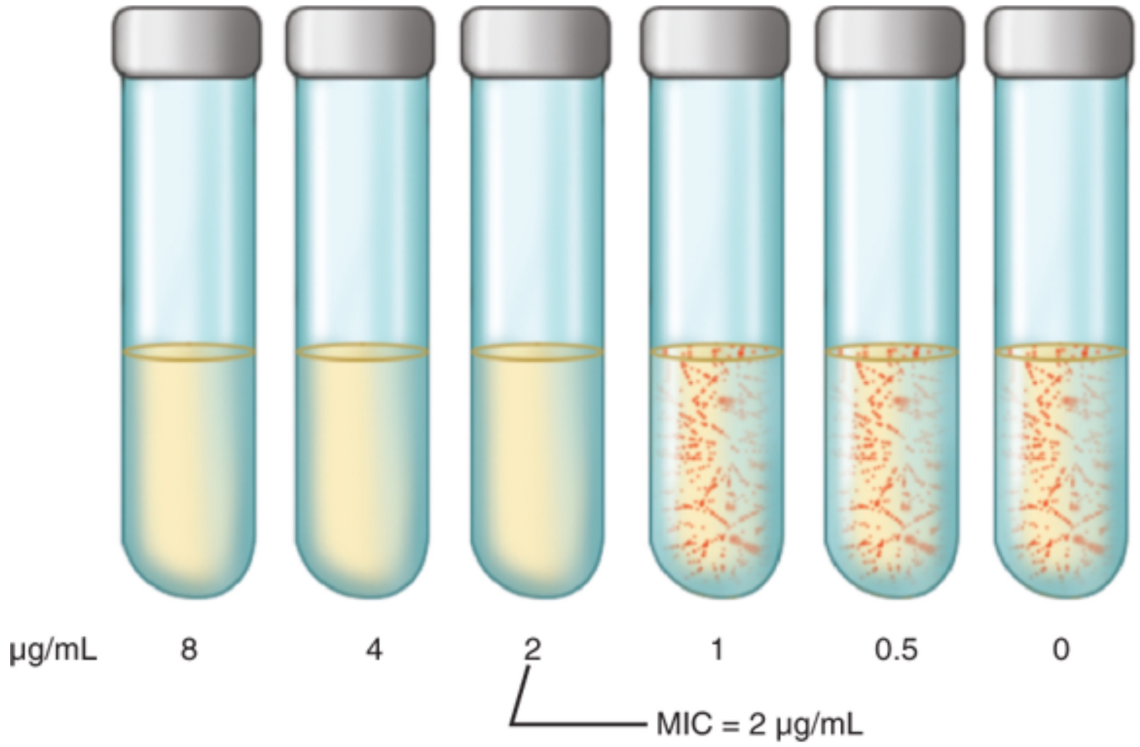
- Hydrolysis (e.g., beta-lactamases)

Other modifications

- Acetylation (aminoglycosides, chloramphenicol, fluoroquinolones)
- Adenylation, phosphorylation (fluoroquinolones)

How do we know when an organism is resistant?

Minimum Inhibitory Concentration (MIC)



- Lowest concentration of an antimicrobial that inhibits visible growth after 18-24 hours
  - Lower MIC indicates less drug is required for inhibiting growth
  - Higher MIC indicates more drugs required for inhibiting growth
- MIC scores
  - Confirm resistance of microorganisms to an antimicrobial agent
  - Allow activity monitoring of new antimicrobial agents

MONDAY PUNDAY

BY GEMMA CORRELL

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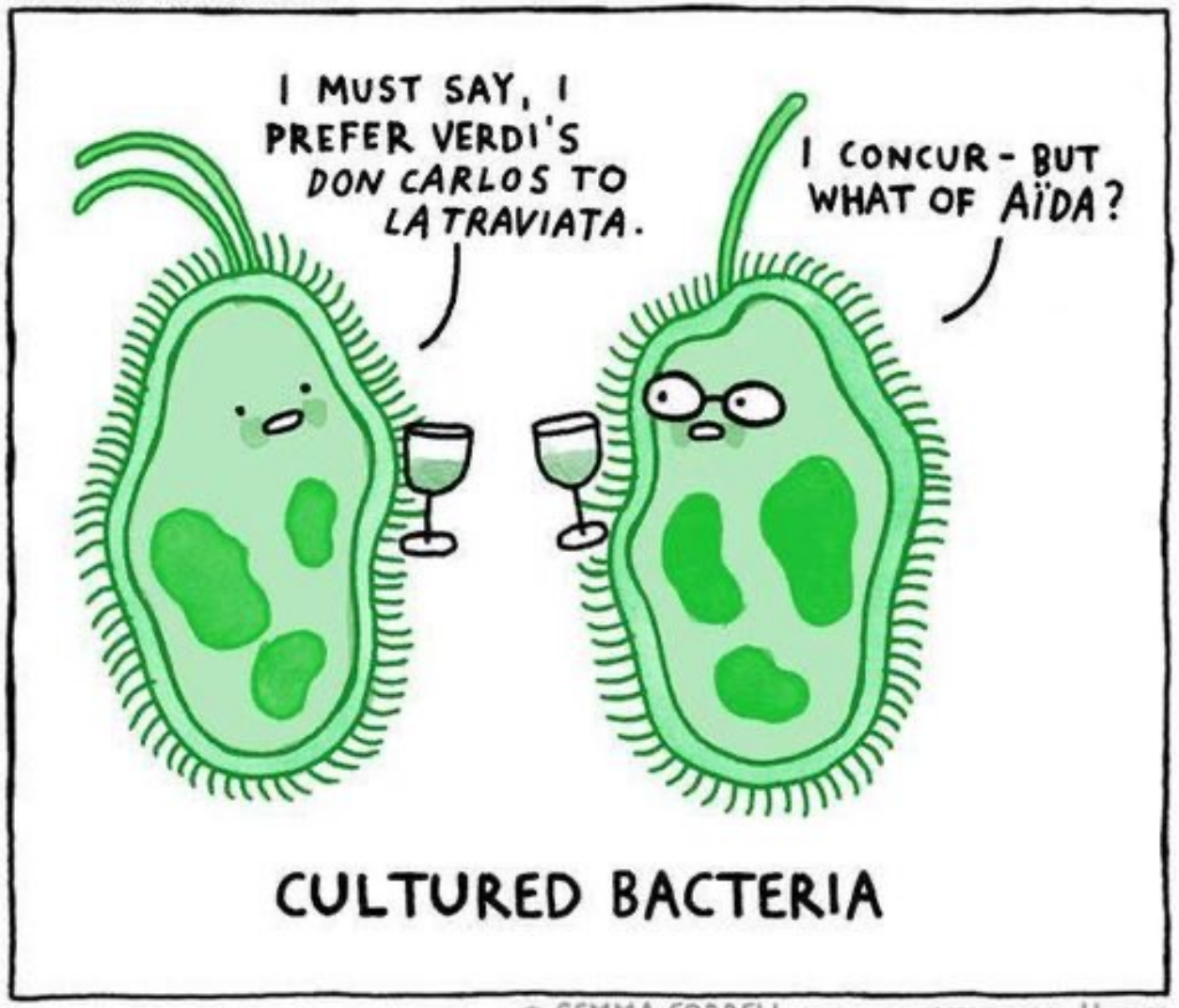
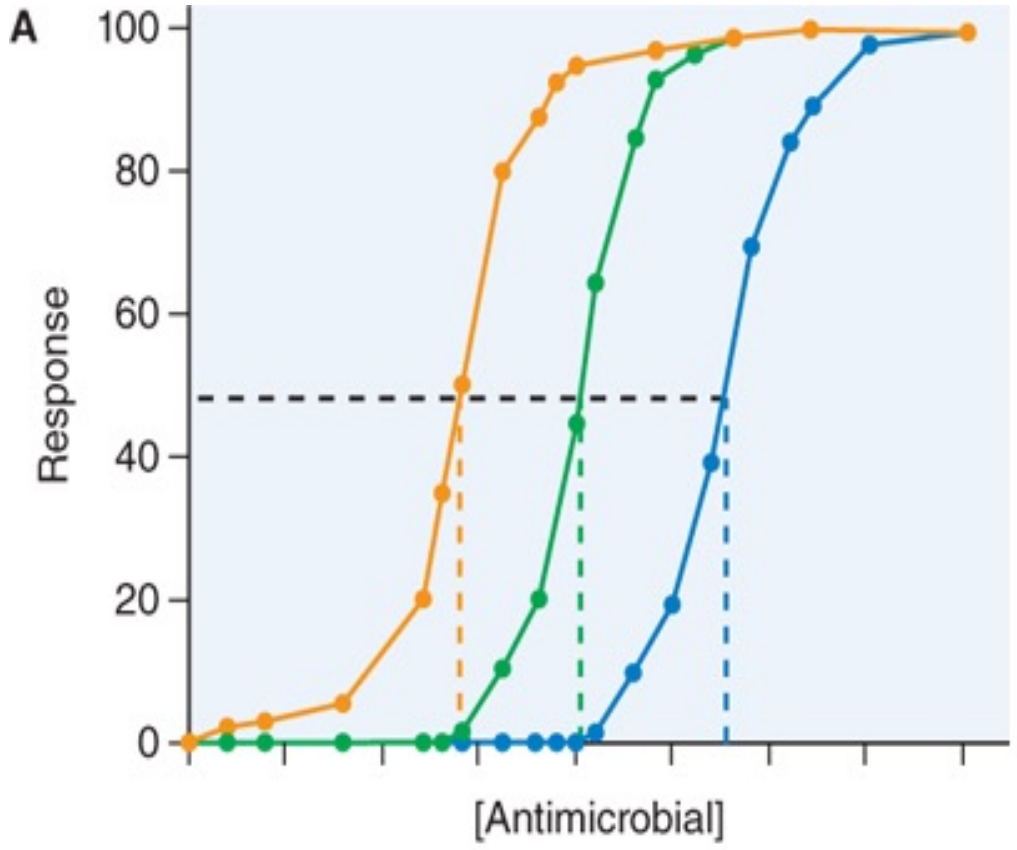


Active Learning

Consider the following dose response curves for antimicrobial A. Draw a heart next to the curve indicating the largest increase in resistance.



Antibiotics – What to Know

Mechanism of Action

Spectrum of Activity

Mechanisms of Resistance

Pharmacology: Absorption/bioavailability, metabolism, distribution, elimination

Adverse effect profile

Pharmacology & Antibiotics

Inhibit the growth of bacteria without harming the human host	• Kinetics , dynamics
Penetrate body tissues in order to reach the bacteria	• Kinetics (absorption, distribution)
Have appropriate spectrum (range of bacteria that a drug is effective against)	• Dynamics
Impact bacteria in a desired way	• Kinetics , dynamics

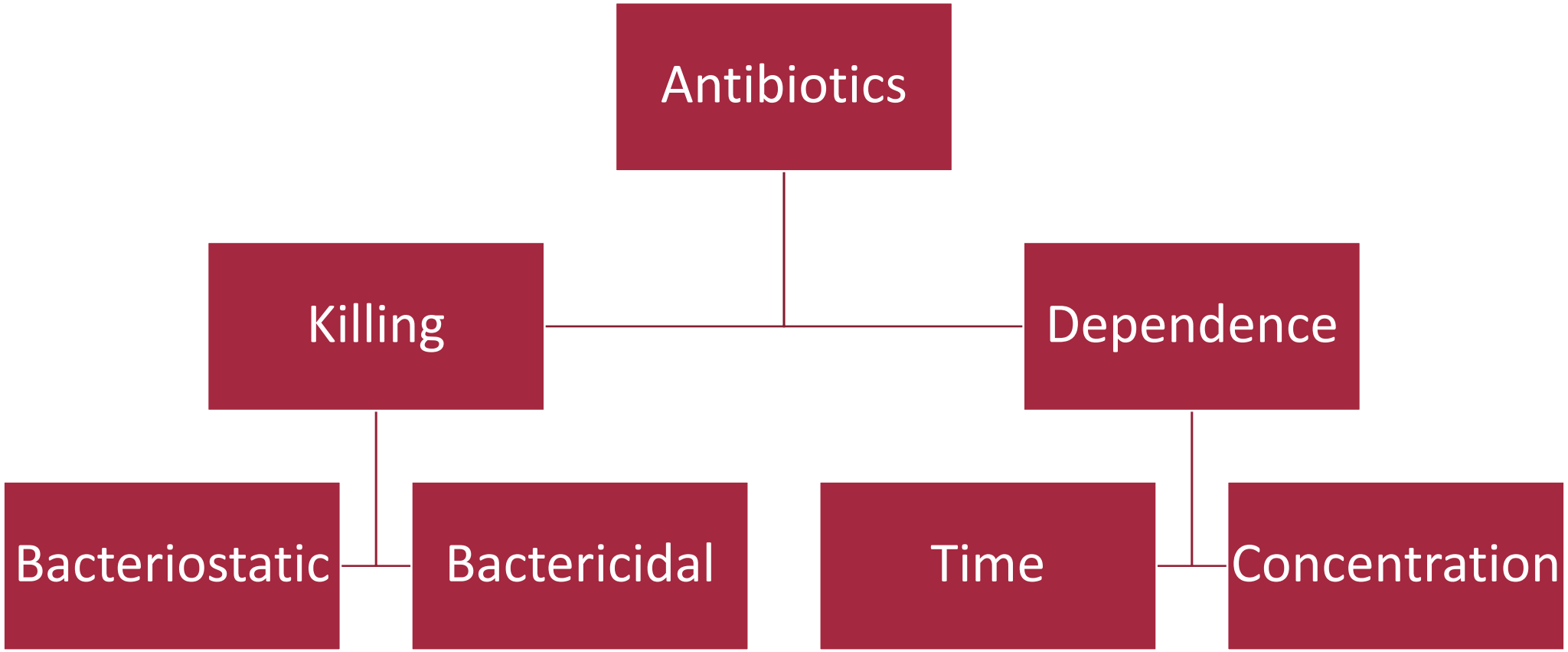
Pharmacology Considerations

Kinetic

- Route of administration
- Conditions that alter ADME
  - Renal or hepatic impairment
- Drug concentration in body fluids

Dynamic

- Susceptibility
- **Drug bactericidal versus bacteriostatic activity**
- **Drug synergism**
- Antagonism
- Postantibiotic effects (PAE)


Antibiotics
Killing
Dependence
Bacteriostatic
Bactericidal
Time
Concentration

Which of the following antibiotic categories kill bacteria?

0

Bacteriostatic

0%

Bactericidal

0%

Bacteriostatic & Bactericidal Antibiotics

BOTH bacteri**cidal** and bacterio**static** antibiotics kill bacteria

- Static requires higher concentration to achieve specific thresholds of bacterial reduction

Limitations

- Some antibiotics may be considered bacteriostatic against selected organisms and bactericidal against others
- When used as monotherapy, enterococci are inhibited but not killed by certain antibiotics (vancomycin, penicillin, or ampicillin)

Bacteriostatic vs Bactericidal Antibiotics

DEFINITIONS

- **Minimum bactericidal concentration (MBC)**
  - Lowest concentration of antimicrobial that will prevent the growth of an organism after subculture on to antibiotic-free media
- **Minimum inhibitory concentration (MIC)**
  - Concentration of antibiotic that inhibits visible growth at 24 hours

CIDAL	STATIC

• Minimum bactericidal concentration (MBC) of drug is ≤4-fold above the MIC	• Antibiotic that either:
	  • Achieve a >1000-fold ↓ in bacterial density at a concentration that is 8-fold above its MIC
	  OR
	  • 500-fold reduction in bacterial density at 4-fold above its MIC

Which of the following drug combinations would you expect to have the greatest antimicrobial effect?

0

Two drugs that affect cell wall synthesis

0%

One drug that affects cell wall synthesis and one drug that acts intracellularly

0%

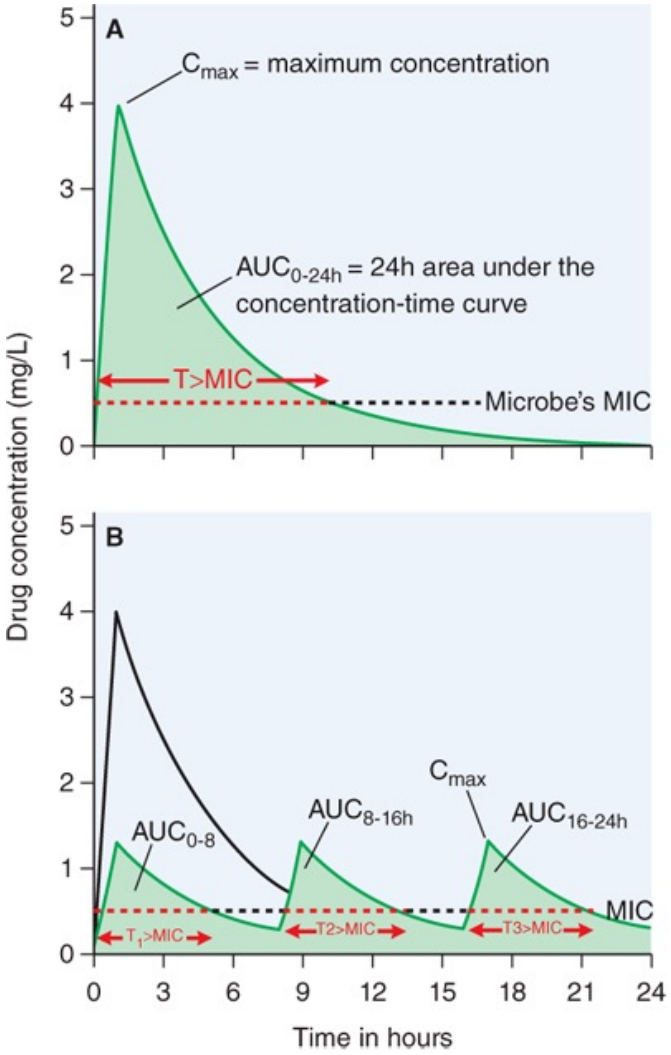
Drug Synergism

Combinations of antimicrobials can take advantage of the MOAs to produce a synergistic effect

Typically combine agents with **different** MOAs

Active Learning

Consider a dose of an antibiotic being administered once daily (A) versus divided into three equal doses every 8 hours (B). Which dosing schedule would result in the greatest microbial kill?



PK/PD Parameters of Interest

Cmax = maximum (peak) concentration reached

Area under the curve (AUC) = total drug exposure integrated over time

MIC = mean inhibitory concentration

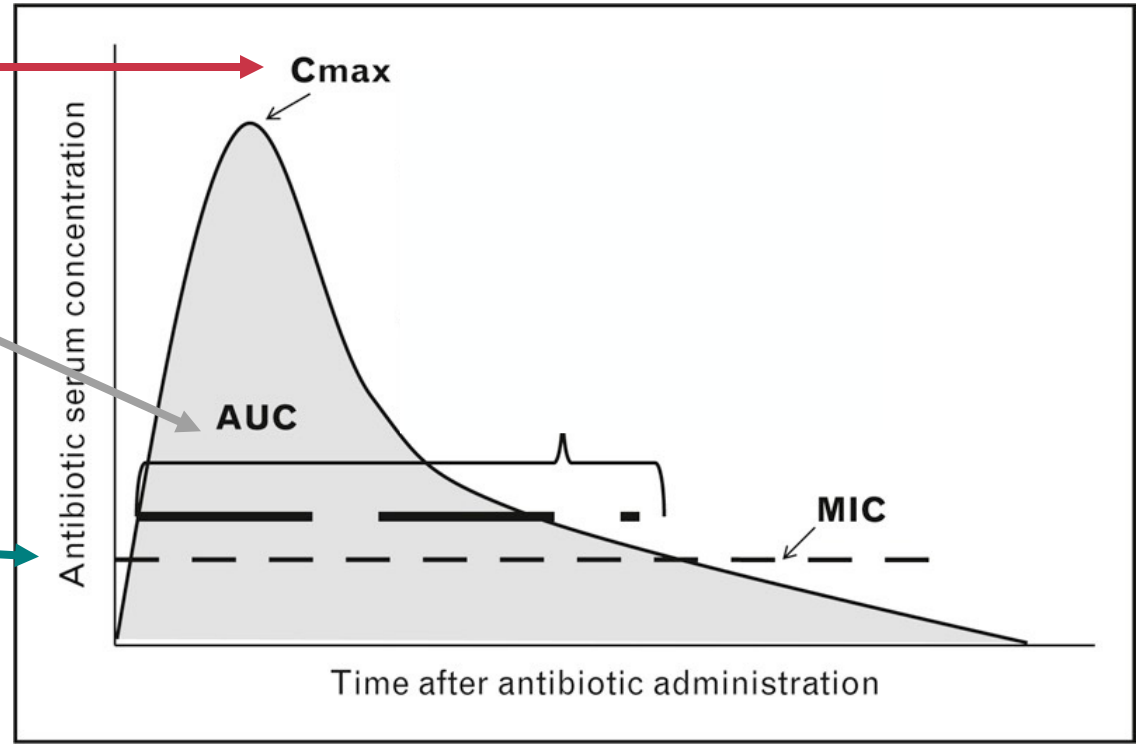


Image credit: Al-Dorzi, et al

Parameters of Importance Vary Based on Specific Antimicrobials

- **Peak** concentration matters most for some antimicrobials (**Cmax/MIC**)
- **Total antimicrobial exposure above the MIC** matters most for others (**AUC/MIC**)
- Some antimicrobials kill best when **concentration persists above MIC for longer durations** of the dosing interval (**T>MIC**)

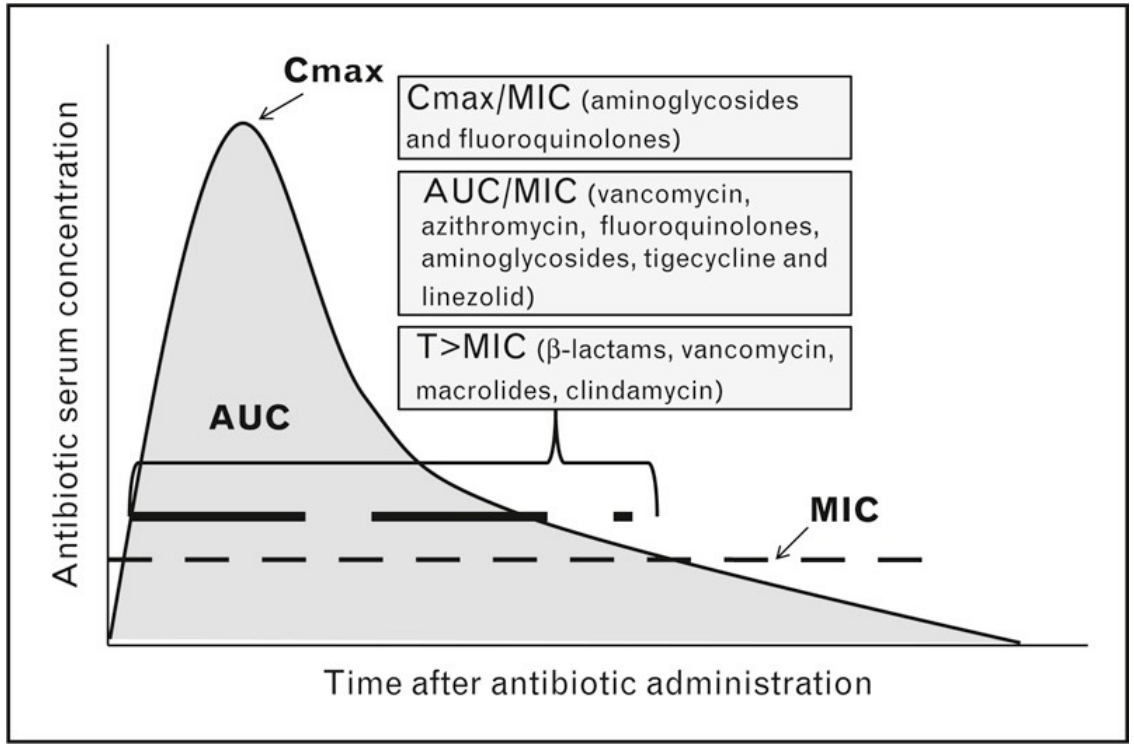
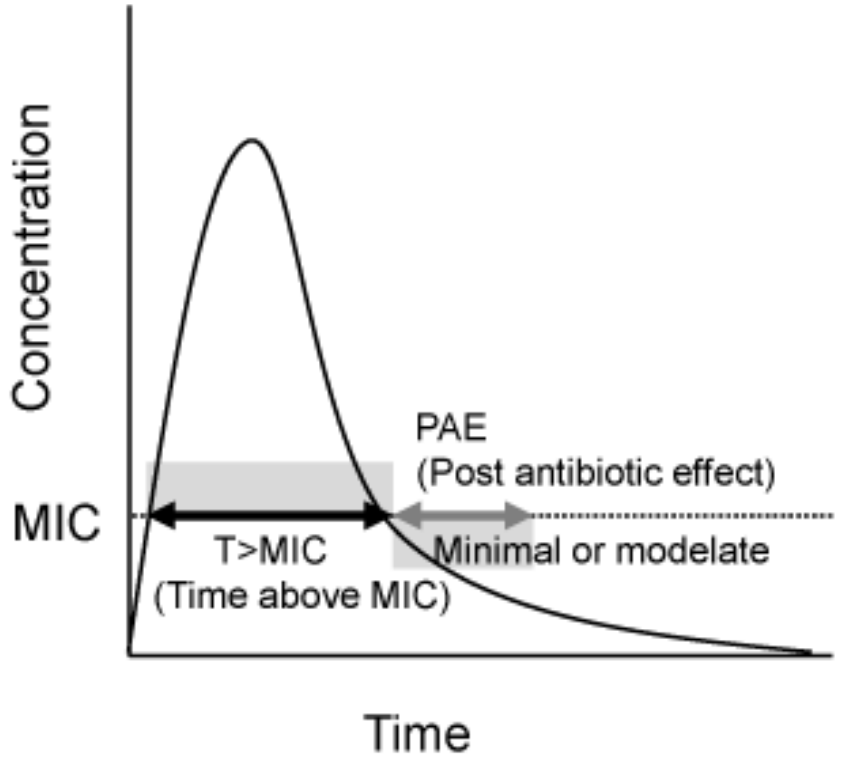


Image credit: Al-Dorzi, et al

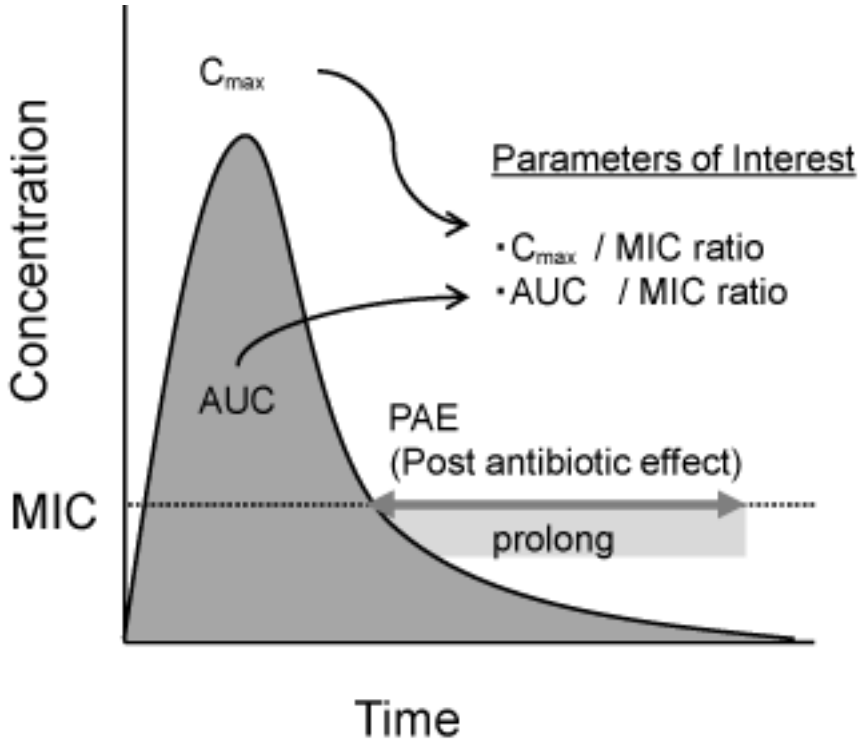
Time-Dependent Killing

- Extent of killing activity continues if plasma concentration > than MIC
- Examples
  - Beta-lactams (penicillins, cephalosporins, carbapenems, monobactams), clindamycin, macrolides (erythromycin, clarithromycin), oxazolidinones (linezolid)
- **Referred to as time-dependent antibiotics**
- Pharmacodynamic parameter = time serum concentrations remain above the MIC during the dosing interval (**T>MIC**)
  - The greater the **T>MIC** , the greater the killing



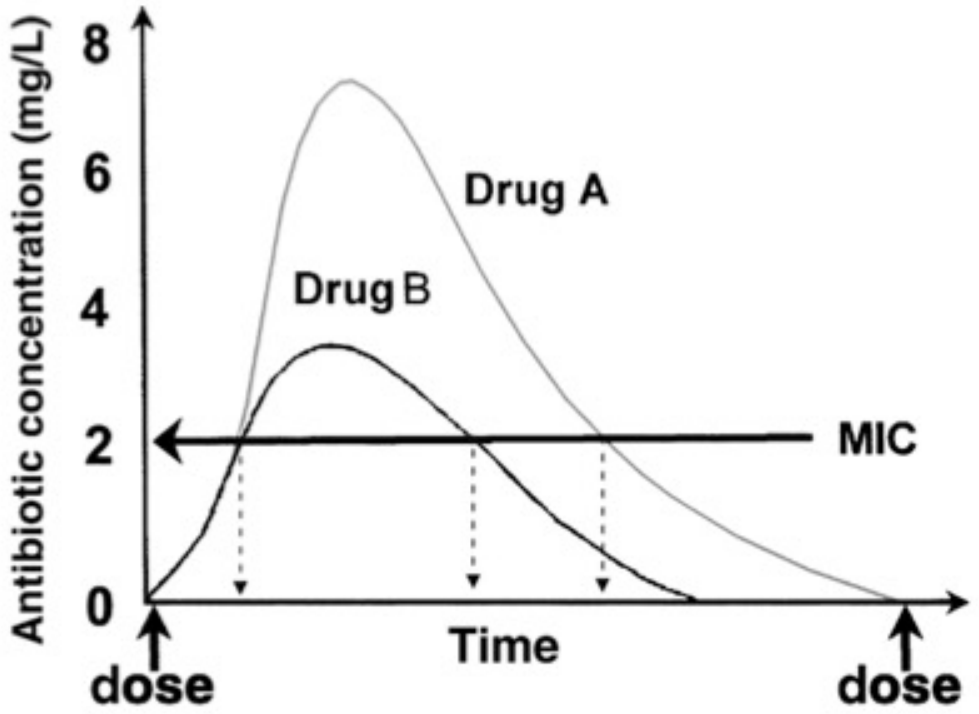
Concentration-Dependent Killing

- Rate and extent of killing increases as the peak drug concentration increases
- Examples
  - Aminoglycosides and fluoroquinolones
- Referred to as **concentration-dependent** killing
- Pharmacodynamic parameters = **Cmax**/**MIC** and **AUC**/**MIC** ratio
  - Greater the ratio, the greater the killing



Active Learning

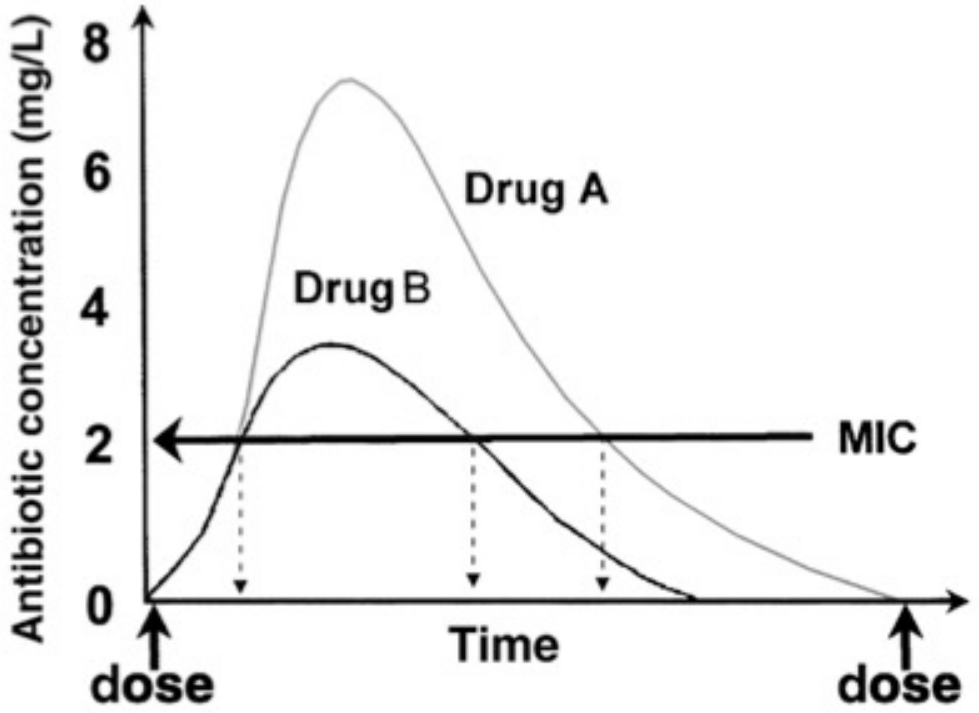
Would Drug A or Drug B be more effective if it exhibited time-dependent killing? Circle your answer.



Active Learning

Would Drug A or Drug B be more effective if it exhibited time-dependent killing?

A because it spends more time at a concentration greater than the MIC

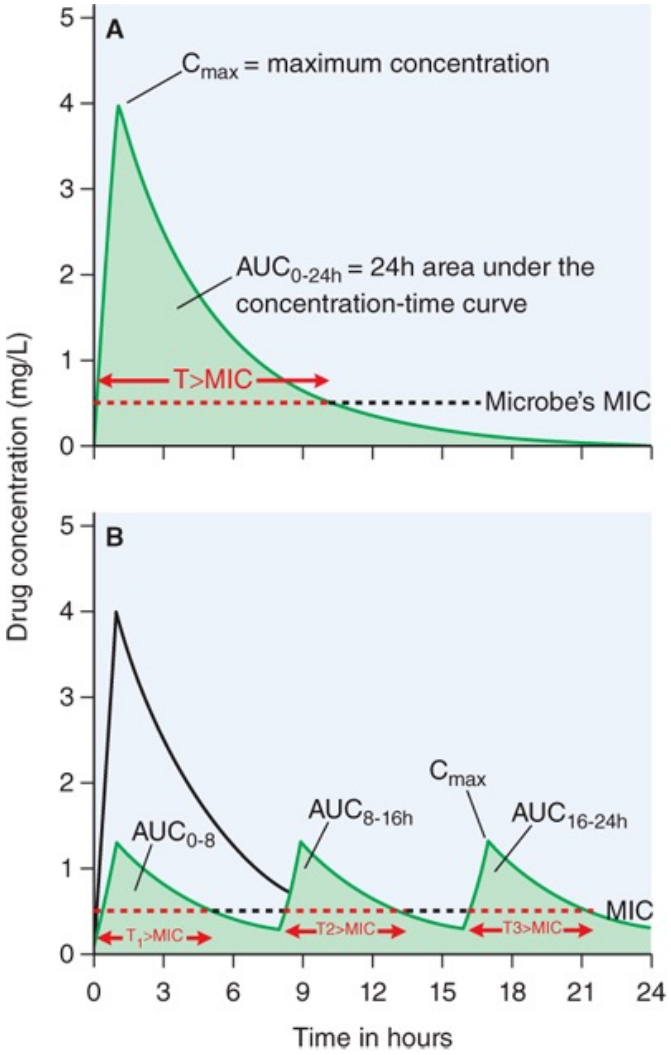


Active Learning

Consider a dose of an antibiotic being administered once daily (A) versus divided into three equal doses every 8 hours (B). Which dosing schedule would result in the greatest microbial kill for:

- Penicillin (beta-lactam)

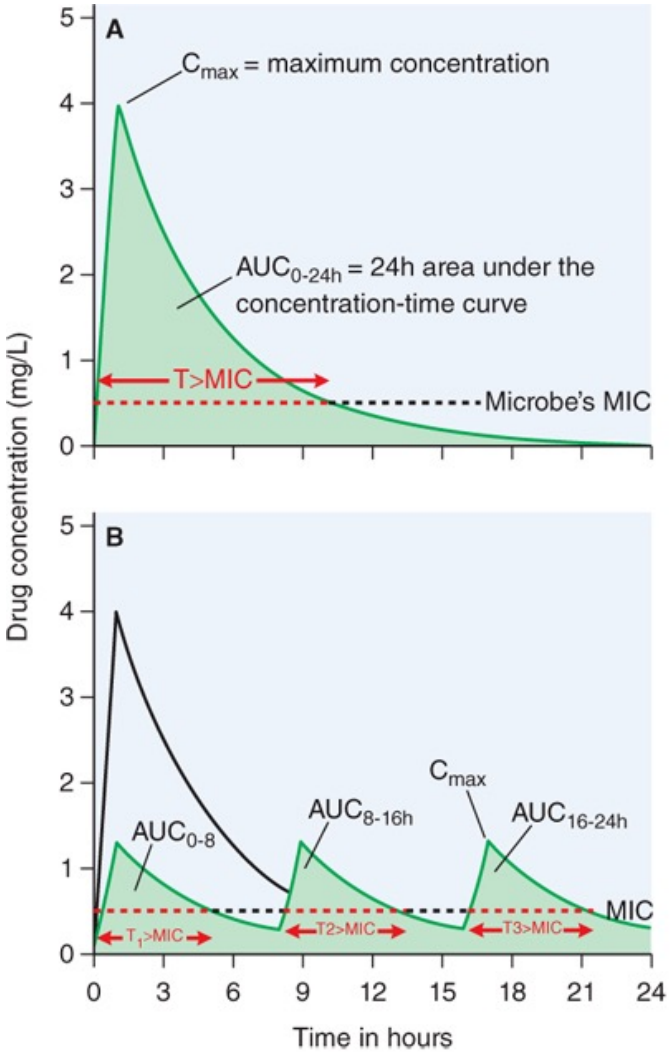
- Gentamicin (aminoglycoside)



Active Learning

Consider a dose of an antibiotic being administered once daily (A) versus divided into three equal doses every 8 hours (B). Which dosing schedule would result in the greatest microbial kill for:

- penicillin (beta-lactam) – **B**
- gentamicin (aminoglycoside) – **A**



Imagine you have patient using an antibiotic that exhibits time-dependent killing. Which of the following dosing regimens would theoretically be LEAST effective?

0

Continuous infusion 0%

Every 6 hour dosing 0%

Every 24 hour dosing 0%

Antibiotics – What to Know

Mechanism of Action

Spectrum of Activity

Mechanisms of Resistance

Pharmacology: Absorption/bioavailability, metabolism, distribution, elimination

Adverse effect profile

Adverse Effects

- Allergic
- Toxic
- Idiosyncratic
- Related to changes in the normal body flora
  - Unique to antibiotics

Pharmacologic Considerations for Antimicrobial Selection

1. Apply knowledge of the susceptibility (either MIC or IC90) of the organism to the antimicrobial agent and index drug exposure to MIC
2. Use the optimal dose of the antibiotic for the patient, that is, the dose that achieves IC80 to IC90 exposures at the site of infection.
3. Use a dosing schedule that maximizes the antimicrobial effect; recognize that optimal microbial kill by the antibiotic may be best achieved by maximizing certain shapes of the concentration-time curve.
4. Minimize adverse effect impact on patients.

CASE STUDY

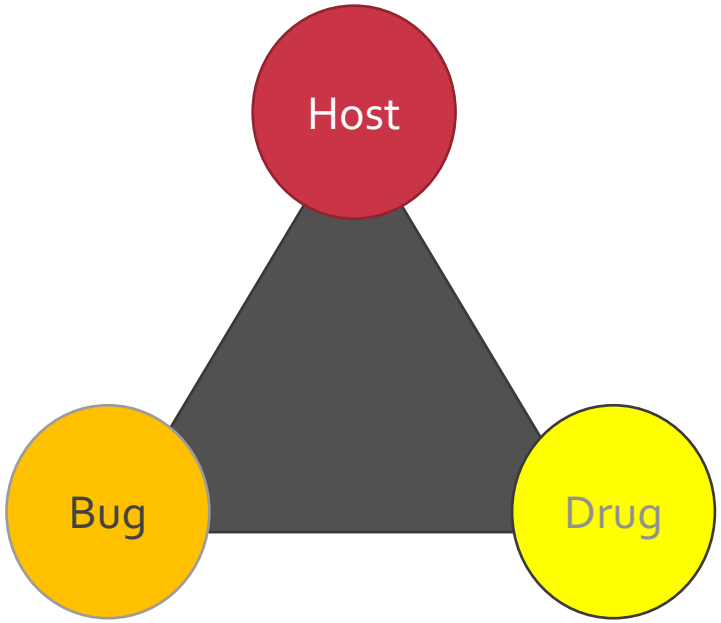
In your CBL case, Dr. Golden and you agree upon an antibiotic after I&D in the clinic.

There are roughly 74 antibiotics in use in the US.

How will you choose one?

Principles of Antibiotic Therapy

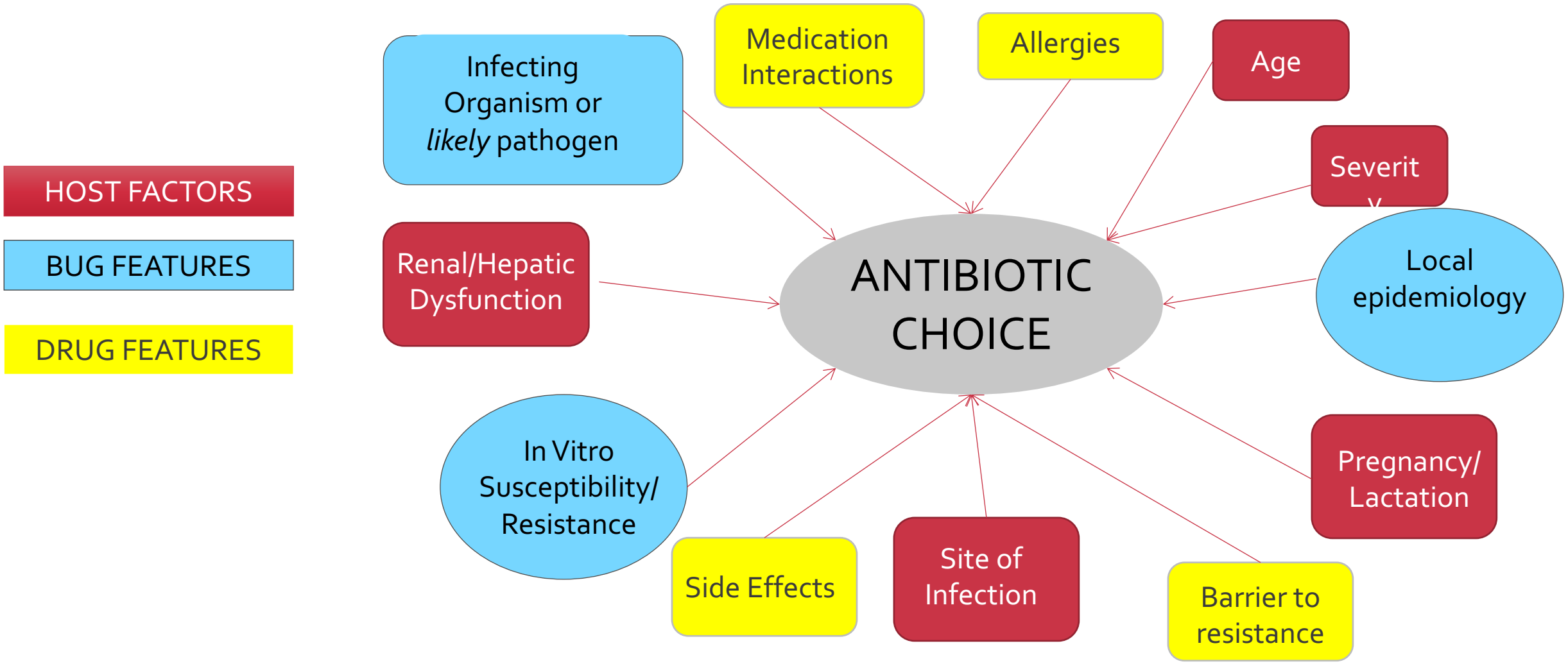
What should we take into account when selecting an antibiotic to treat an infection?



+

Evidence
Experience
Guidelines

Choosing an Antibiotic



Any questions?

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Reference List

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