

Introduction to Antimicrobials

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What are antimicrobials?

- Drugs that destroy microbes, prevent their multiplication or growth, or prevent their pathogenic action
 - Differ in physical, chemical, pharmacological properties
 - Differ in antibacterial spectrum of activity
 - Differ in their mechanism of action

Antibiotic Classes (by mechanism of action)

- Inhibit cell wall synthesis
- Inhibit protein synthesis
- Alter nucleic acid metabolism
- Inhibit folate metabolism
- Other mechanisms

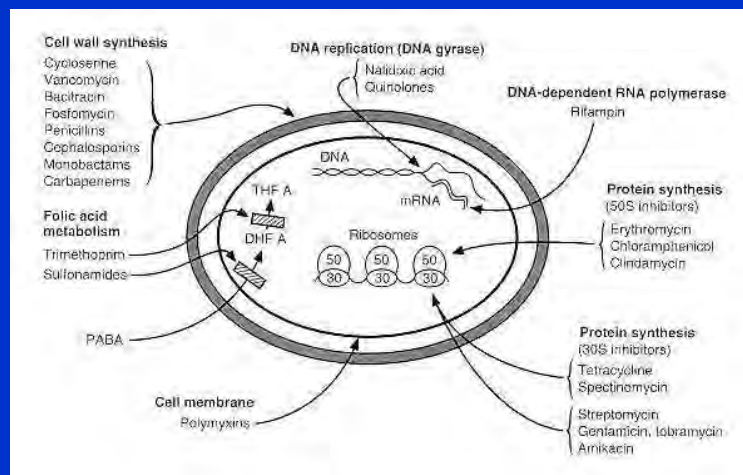
Antibiotic Classes

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|--------------|--|--|
| | <ul style="list-style-type: none">• Inhibit cell wall synthesis | <ul style="list-style-type: none">• Inhibit protein synthesis |
| Beta-lactams | <ul style="list-style-type: none">– Penicillins | <ul style="list-style-type: none">– Aminoglycosides |
| | <ul style="list-style-type: none">– Cephalosporins | <ul style="list-style-type: none">– Tetracyclines |
| | <ul style="list-style-type: none">– Monobactams (aztreonam) | <ul style="list-style-type: none">– Glycylcycline (tigecycline) |
| | <ul style="list-style-type: none">– Carbapenams | <ul style="list-style-type: none">– Macrolides (azithromycin, clarithromycin) |
| | <ul style="list-style-type: none">– Glycopeptides (vancomycin) | <ul style="list-style-type: none">– Lincosamides (clindamycin) |
| | | <ul style="list-style-type: none">– Streptogramins (quinapristin/dalfopristin) |
| | | <ul style="list-style-type: none">– Oxazolidinones (linezolid) |
| | | <ul style="list-style-type: none">– Chloramphenicol |

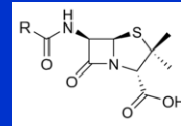
Antibiotic Classes Continued

- **Alter nucleic acid metabolism**
 - Rifamycins
 - Quinolones
- **Miscellaneous**
 - Metronidazole
 - Lipopeptides (Daptomycin)
 - Polymyxins
- **Inhibit folate metabolism**
 - Trimethoprim
 - Sulfonamides

Antibiotic Targets

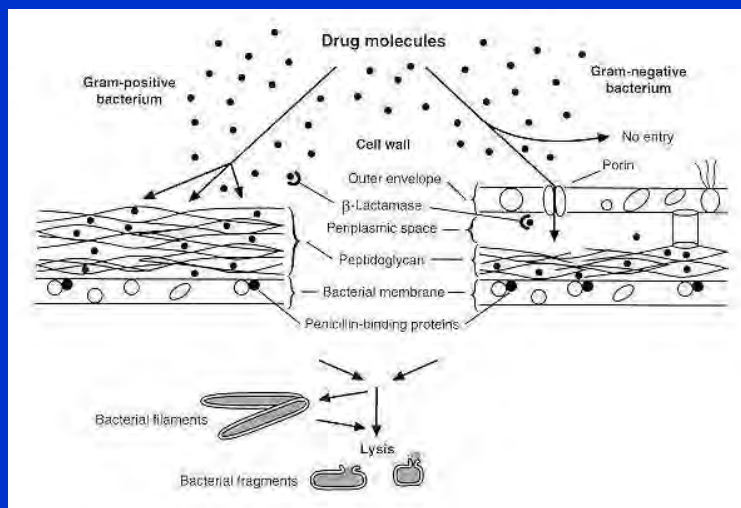


Beta-lactams



- All contain the beta-lactam ring with 3 carbon atoms and one nitrogen atom
- Inhibit synthesis of the peptidoglycan layer of the cell wall by blocking the action of transpeptidases (penicillin binding proteins)
- Includes: penicillins, cephalosporins, monobactams, and carbapenams

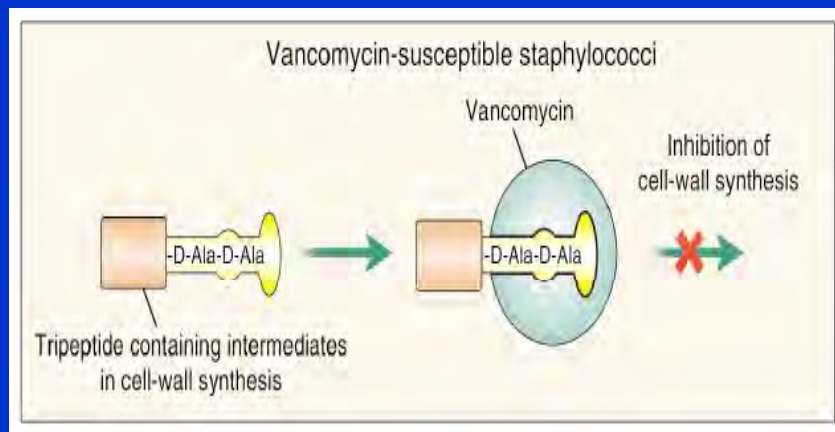
Beta-lactams



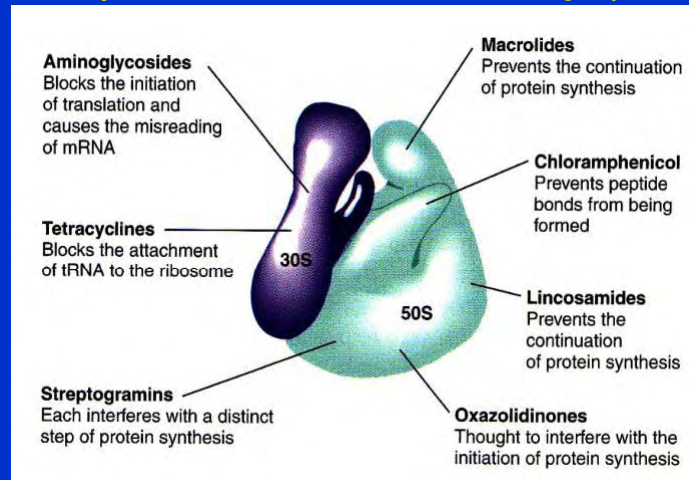
Vancomycin (Glycopeptide)

- Inhibits cell wall synthesis by interfering with peptidoglycan synthesis.
- It does this by binding to the D-Ala-D-Ala terminals of N-acetylmuramic acid (NAM)- and N-acetylglucosamine (NAG)-peptide subunits localized at the outer surface of the cell membrane.
- As a result, these subunits can not incorporate into the peptidoglycan matrix
- With a rare exception, only active against gram positive bacteria

Vancomycin



Protein Synthesis Inhibitors (inhibit translation of bacterial proteins in various ways)

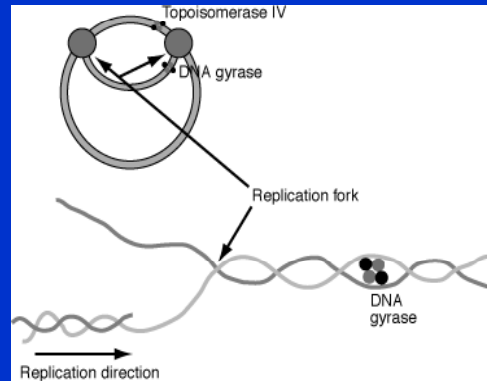


Rifamycins (rifampin)

- Mechanism of action:
 - Blocks mRNA synthesis (prevents transcription of bacterial DNA)
 - Does this by binding to the bacterial DNA-dependent RNA polymerase
- Used in combination with other antimicrobials (only used alone as prophylaxis for *N. meningitidis*)

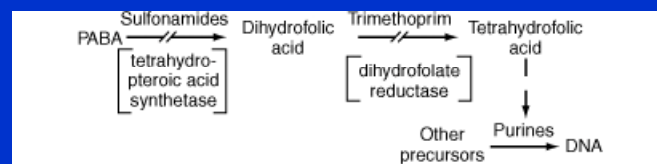
Quinolones

- Inhibit DNA synthesis
- Inhibit the topoisomerases responsible for supercoiling DNA (DNA gyrase) and relaxing the supercoiled DNA (topoisomerase IV)
- Examples: ciprofloxacin, levofloxacin, moxifloxacin



Inhibitors of Folate Metabolism

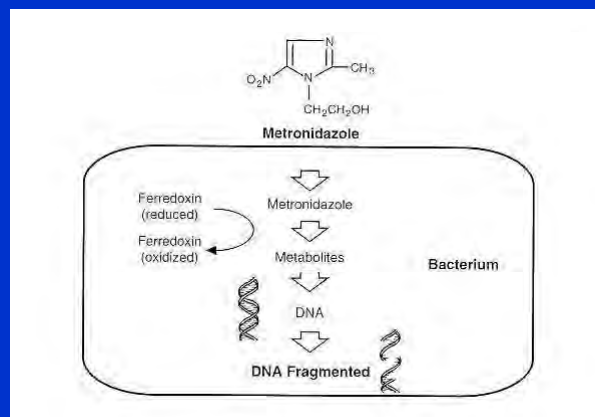
- Examples: trimethoprim, sulfonamides
- Often given in combination (example: trimethoprim-sulfamethoxazole)



Metronidazole

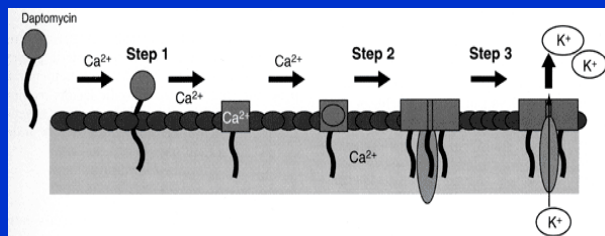
- Diffuses into the cell and is reduced
- Metronidazole free radicals interfere with organism DNA causing breakage, destabilization and cell death
- Active in anaerobes and select parasites such as Entamoeba and Giardia

Metronidazole: mechanism of action in anaerobes



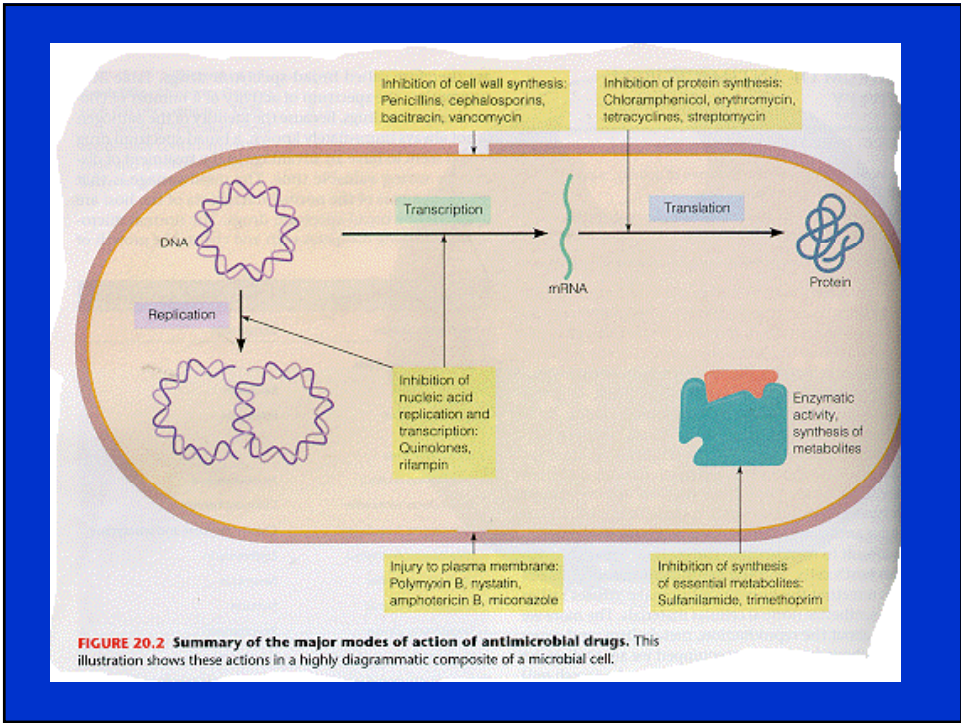
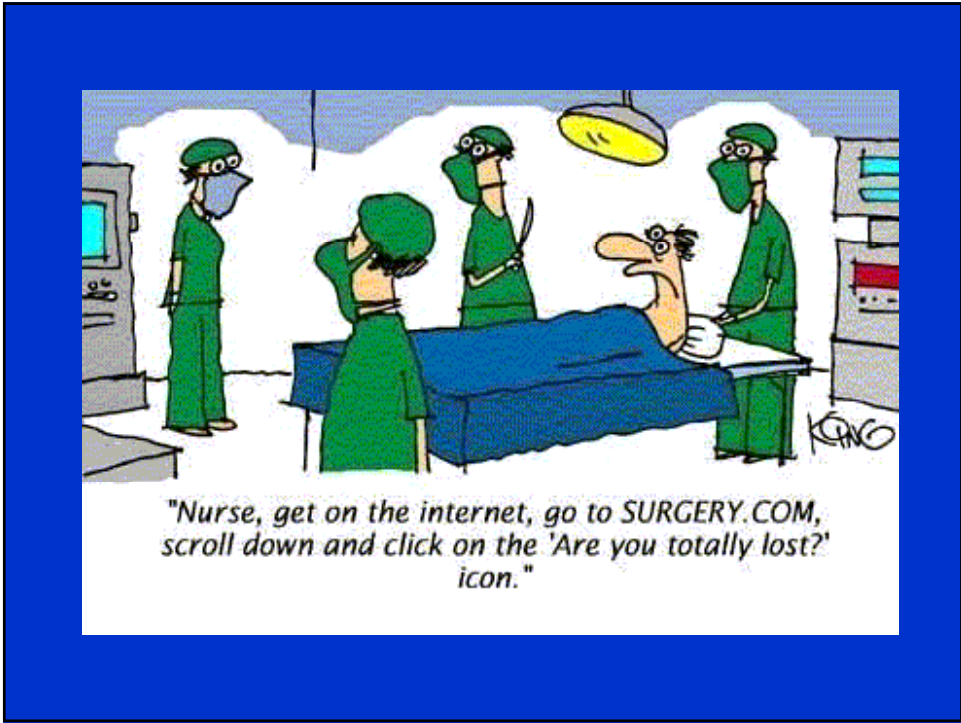
Daptomycin (Lipopeptide)

- Binds to the cell membrane of gram-positive organisms in a calcium-dependent process and disrupts the bacterial cell membrane potential causing ion leakage and cell death.



Polymyxins

- Polymyxins destroy bacterial membranes with a surface detergent-like mechanism by interacting with membrane phospholipids and increasing cellular permeability.
- Only active against Gram negative bacteria (do not have access to the bacterial cell membrane in Gram positives and resistant Gram negatives)



Antibiotic Spectrum

- *Broad Spectrum*
 - Covers many potential pathogens (example: a carbapenam which has Gram positive, Gram negative, and anaerobic coverage)
- An antibiotic with a *narrower spectrum* has a more targeted spectrum of activity
 - Example: clindamycin which only has Gram positive and anaerobic coverage—no Gram negative coverage)

How are antibiotics used?

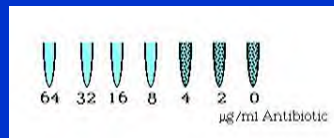
- Empiric therapy
 - Often 'broad spectrum'
- Definitive therapy
 - If possible, initial empiric therapy should be changed to an antibiotic with a narrower spectrum of activity
- Prophylactic or preventative therapy

Culture and Sensitivities

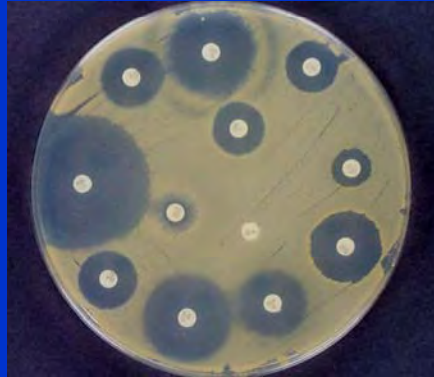
- Identify the pathogen
- Determine the sensitivity of the organism to various antibiotics
 - is it 'sensitive', 'intermediate', or 'resistant'?
- Sensitivity is determined by the interpretation of the minimum inhibitory concentration (MIC) which is the lowest concentration of antibiotic that prevents visible bacterial growth after 24 hours of incubation in the appropriate culture media

The MIC

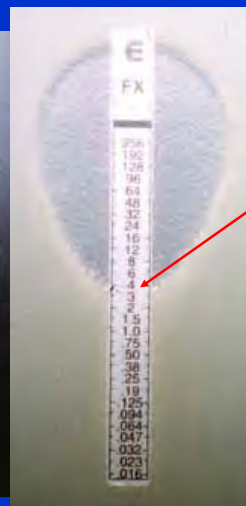
- The MIC is organism and drug specific
- 'Susceptible' implies that the concentration of antibiotic that can be achieved at the site of infection is \geq MIC
- Numerous ways to determine the MIC
 - Kirby-Bauer disk diffusion
 - Broth dilution
 - E-test



Disk Diffusion



E test



MIC



It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.

TABLE 11-2 Mechanisms of Resistance

Alteration of target
Modification to insensitivity to inhibitor
Reduction in physiologic importance of target
Synthesis of new target enzyme that duplicates function of inhibited target
Prevention of access to target
Efflux of more drug than enters cell
Failure of modified drug to enter cell
Inactivation of agent
Destruction of the agent
Modification of the agent so it fails to bind to target
Failure to convert an inactive precursor agent to its active form

When choosing and dosing an antibiotic, consider:

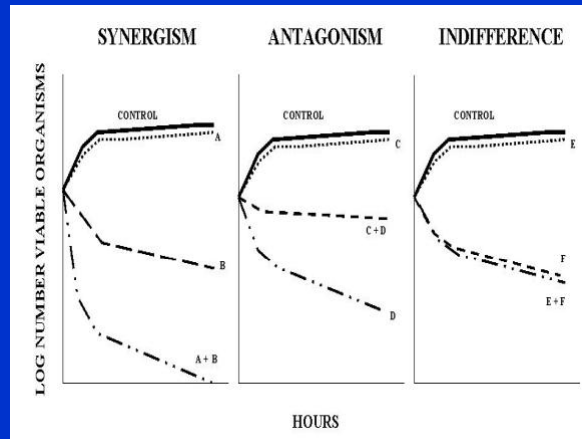
- Pharmacodynamics (what the drug does to the body/bacteria)
 - Desirable effects
 - Cidal vs static
 - Concentration vs time-dependent killing
 - Post antibiotic effect
 - Undesirable effects
 - Toxicity (e.g. nephrotoxic, hepatotoxic, ototoxic, etc)
 - Allergy
 - Antibiotic-associated diarrhea or *C. difficile* colitis

When choosing and dosing an antibiotic, also consider:

- Pharmacokinetics (what the body does to the drug):
 - Absorption (consider food/drug interactions)
 - Distribution (does it get where it needs to go in the right concentration?)
 - Metabolism (will it be metabolized properly, are there drug-drug interactions?)
 - Excretion
 - Renal vs nonrenal
 - Half life (time for the blood concentration to decrease by half)

Using antibiotics in combination

- Synergism
- Antagonism
- Indifference



Case

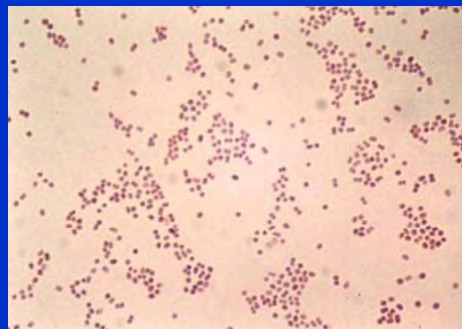
- A 19 YO college student complains to her friends that she has a headache and neck stiffness.
- The next morning her roommate is unable to wake her and EMS is called
- Exam: temp 102, RR 24, BP 90/45, P 120, patient is lethargic with nuchal rigidity, photophobia, and a petechial rash

Case Continued

- Bacterial meningitis is suspected in the ER.
- Before a lumbar puncture is performed, she is given broad spectrum coverage with vancomycin (glycopeptide) and ceftriaxone (3rd generation cephalosporin)
- Lumbar puncture draws cloudy fluid.
- CSF analysis reveals leukocytosis w/90% PMNs, low glucose and high protein, consistent with bacterial meningitis.

Case Continued

- Gram stain of the CSF reveals Gram negative diplococci
- Culture grows *Neisseria meningitidis* type B (not covered by vaccine)



Case Continued

- The diagnosis of meningococcal meningitis is made and vancomycin is discontinued (ceftriaxone is continued as definitive treatment).
- The health department is contacted and the patient's close contacts, including her roommate and boyfriend, are given rifampin for prophylaxis.

Case Continued

- The patient requires treatment in the ICU, but recovers.
- Her boyfriend is shocked to discover that his pee turned orange after taking the rifampin (this is from rifampin, but no one warned him)!

Case Continued

- A health care worker who had almost no contact with the patient is paranoid that he will get infected and takes ciprofloxacin as prophylaxis, despite health department recommendations.
- This worker develops *C. difficile* colitis requiring treatment with metronidazole
- No one tells him not to drink alcohol on the metronidazole. When he does he has a disulfuram-reaction (flushing, throbbing, headache, copious vomiting, etc!)

Heed this Warning

- Use discretion when prescribing antibiotics. Indiscriminate use promotes antibiotic resistance and unnecessarily puts patients at risk for adverse reactions.
- One of Lowy's Laws: It is always the patient who didn't need the antibiotic to begin with who has the worst reaction.

