Antibiotic Targets and Antibiotic Resistance

- Antibiotics are antimicrobials naturally produced by microbes.
  - kill or inhibit bacterial growth
  - target essential molecular processes

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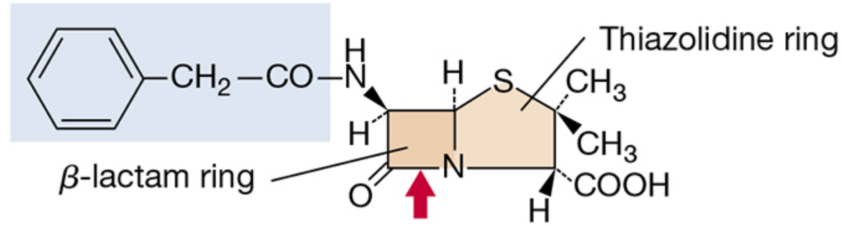
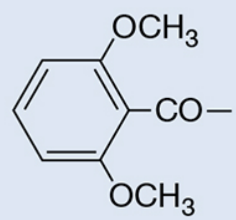
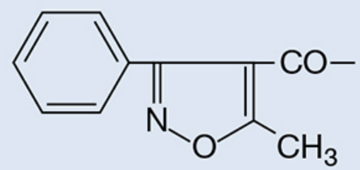
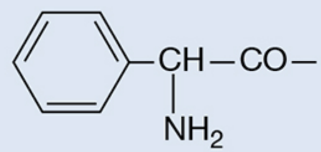
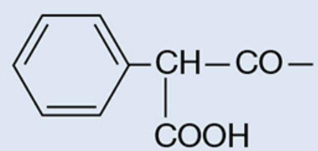
Antimicrobial Drugs

- Antibiotics are.....
- Semisynthetic vs. Synthetic

Natural penicillin (penicillin G)
Gram-positive activity; β-lactamase and acid-sensitive



N-acyl group modification	Semisynthetic penicillins
	**Methicillin** acid-stable, β-lactamase-resistant
	**Oxacillin** acid-stable, β-lactamase-resistant
	**Ampicillin** broadened spectrum of activity (especially against gram-negative *Bacteria*), acid-stable, β-lactamase-sensitive
	**Carbenicillin** broadened spectrum of activity (especially against *Pseudomonas aeruginosa*), acid-stable but ineffective orally, β-lactamase-sensitive

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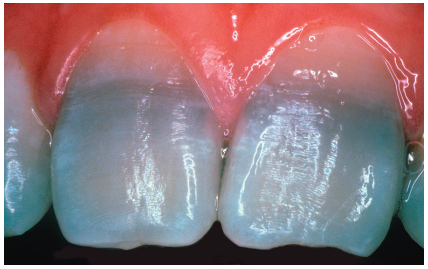
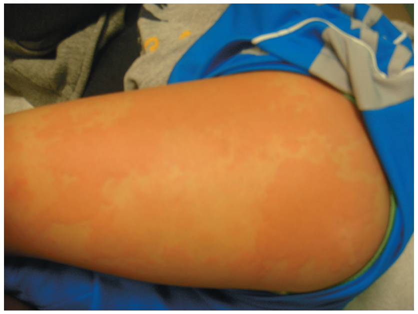
Antimicrobial Drugs

- In order to be useful, antibiotics need to.......
  - exhibit selective toxicity....?
  - be administered properly
    - Target cells
      - Broad vs. narrow spectrum
    - Drug stability
    - Side effects and interactions
    - Half-life





- Antibiotics are classified by their mechanism of action, as each group targets different parts of bacterial anatomy or physiology.

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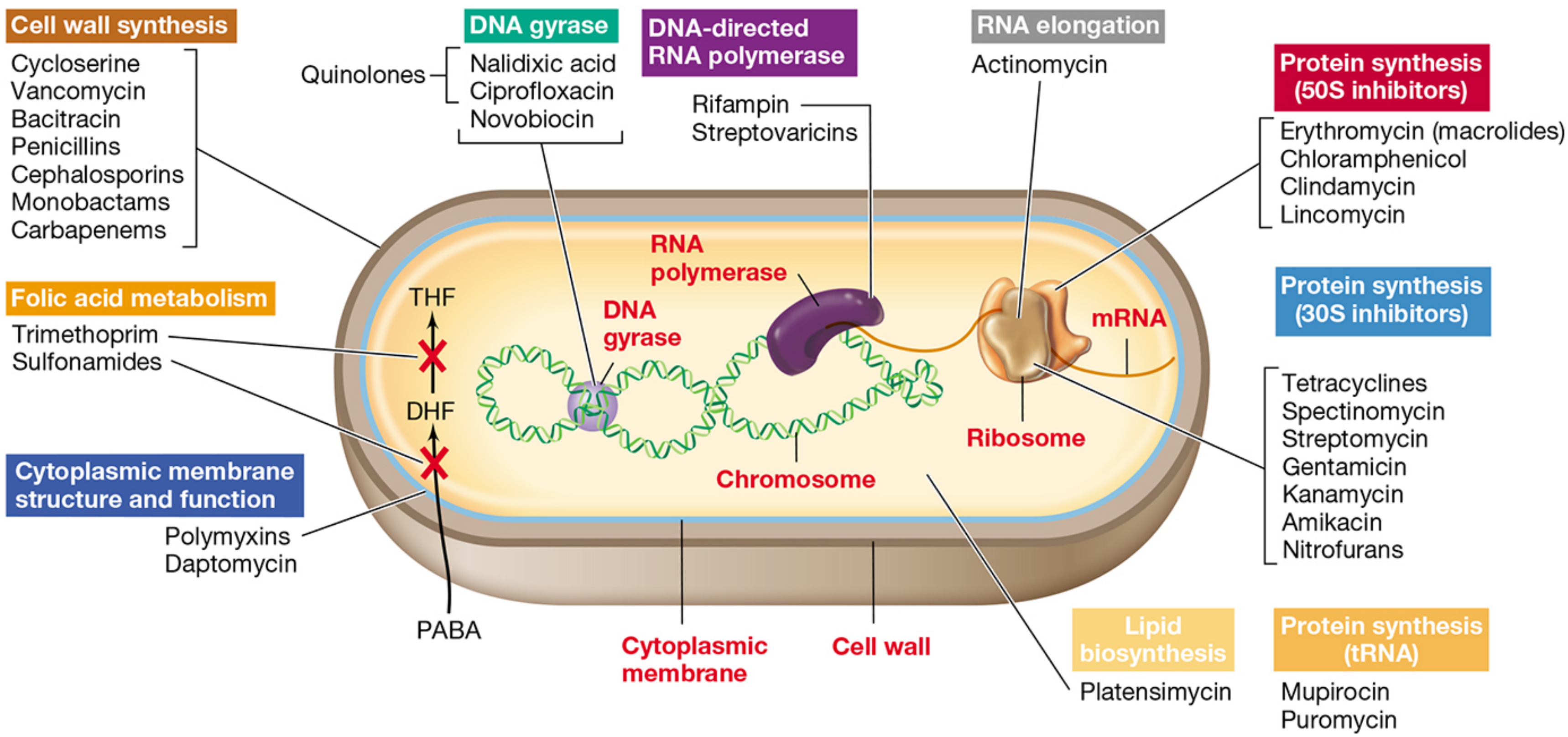
Antimicrobial Drug Targets

- Major cell targets?
  - Cell wall synthesis, nucleic acids, folic acid synthesis, protein synthesis, cell membrane



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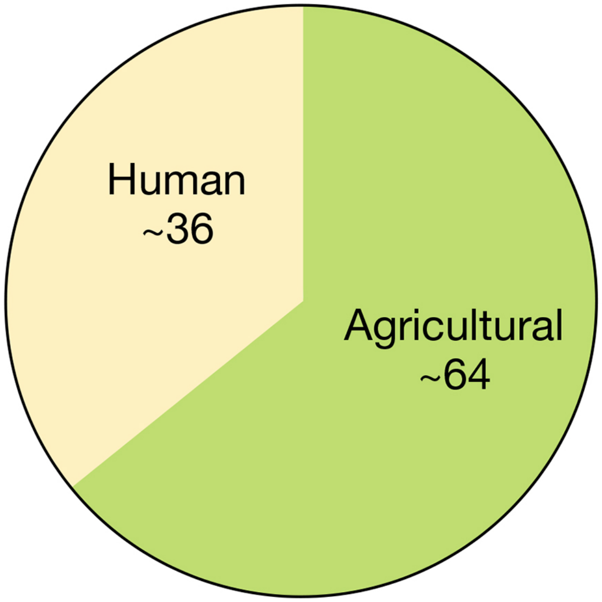
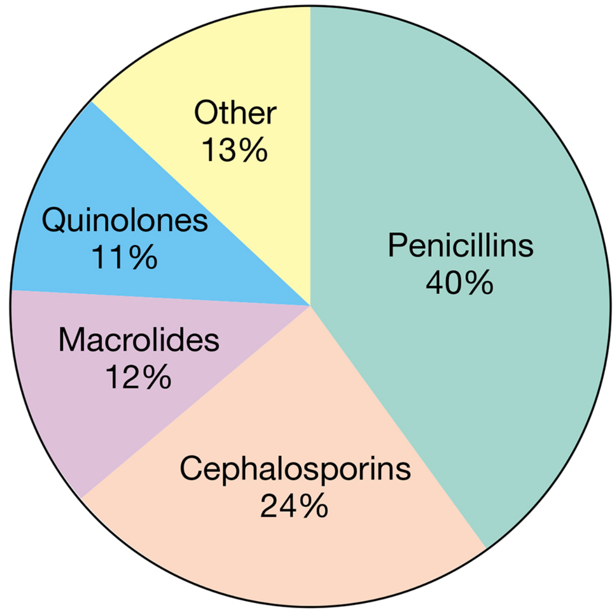
Antimicrobial Drugs

- Antibiotics that target the cell membrane
  - Polymyxins → disrupting membrane and causing leakage and death
- .....others target peptidoglycan synthesis.....
  - β-lactams (penicillin, cephalosporins, carbapenems) interfere with transpeptidation (formation of cross-links)
    - Most of the over 100,000 metric tons of antibiotics used worldwide each year are *β-lactam antibiotics*.



(a) **Antibiotic usage in metric tons**



(b) **Frequency of antibiotic usage**

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Antimicrobial Drugs

- .....others target peptidoglycan synthesis.....
  - Vancomycin binds to pentapeptide precursor and prevents interbridge formation.
  - Bacitracin binds to bactoprenol and prevents new peptidoglycan precursors from reaching site of synthesis.

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Antimicrobial Drugs

- Protein synthesis as a drug target.....Why?
  - Most of the antibiotics targeting protein synthesis will target translation by binding to the bacterial ribosome.
  - Usually bacteriostatic – Why?
  - Examples of antibiotics that target protein synthesis include:
    - Aminoglycosides (end in "mycin" or "micin)
      - Narrow range
    - Tetracyclines
      - Broad
    - Macrolides (Erythromycin, Azithromycin)
      - Broad

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Antimicrobial Drugs

- Nucleic acid synthesis as a drug target
  - Quinolones are antibacterial compounds that interfere with DNA gyrase.
    - Ciprofloxacin
    - Broad spectrum, usually bacteriocidal

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Antimicrobial Drugs

- Other antibacterial drug targets
  - Growth factor analogs are structurally similar to growth factors but do not function in the cell.
    - analogs similar to vitamins, amino acids, and other compounds
    - Sulfa drugs
  - Isoniazid is a growth analog effective only against *Mycobacterium.*
    - interferes with synthesis of mycolic acid

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Review

Match the antimicrobial drug class to its action.

1. Macrolides
2. Tetracyclines
3. Quinolones
4. Sulfa Drugs
5. Penicillins
6. Polymyxin

A. Inhibit cell wall synthesis

B. Disrupt cell membrane integrity

C. Block folic acid synthesis

D. Interrupts nucleic acid synthesis

E. Inhibits protein synthesis

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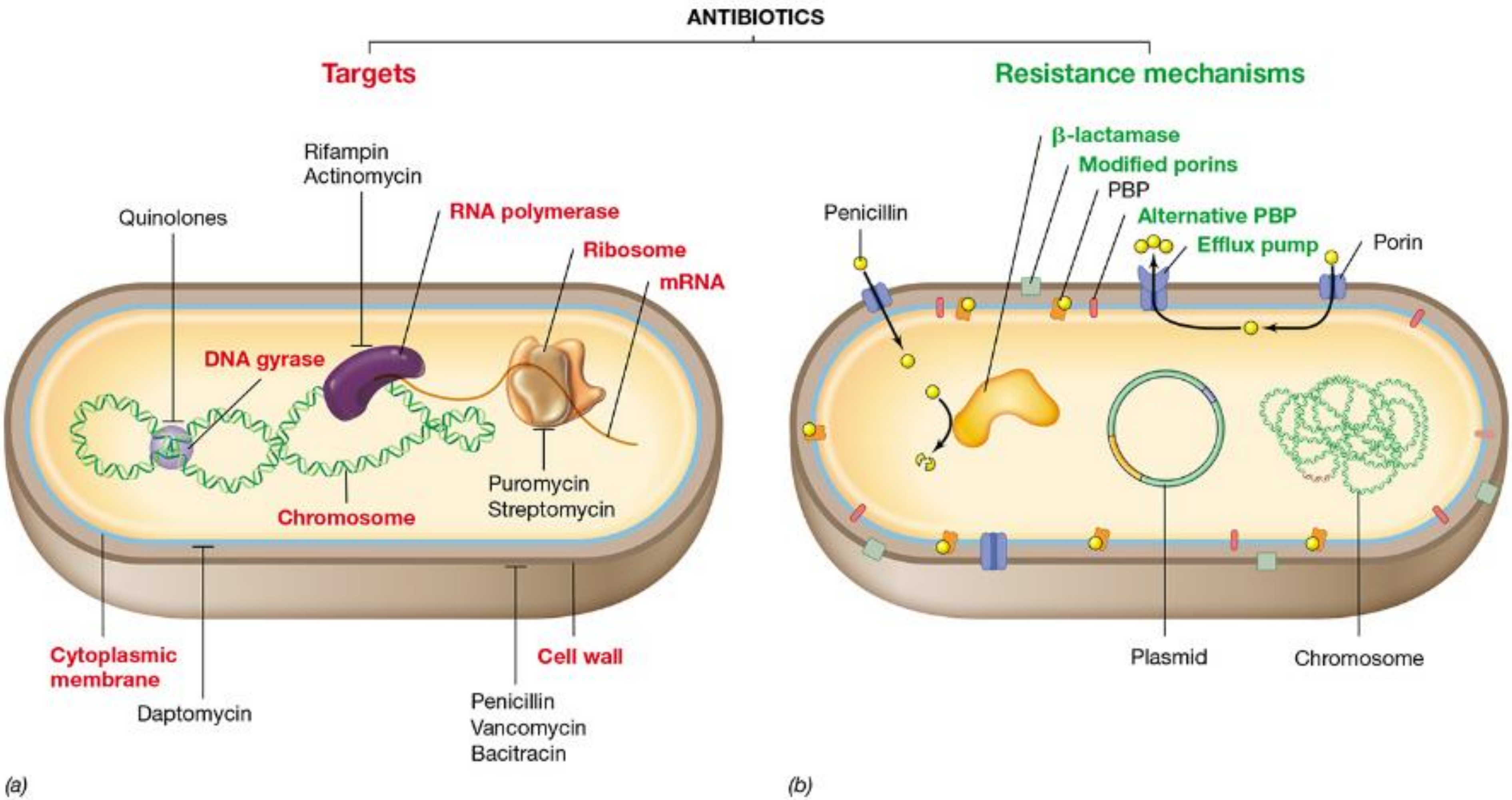
Antibiotic Resistance



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Antimicrobial Drug Resistance and New Treatment Strategies

- Antimicrobial drug resistance
  - Intrinsic vs acquired
  - Intrinsic:
    - *Mycoplasma pneumoniae*
    - *Clostridium difficile*
    - *Mycobacterium tuberculosis*
  - Acquired:
    - Mutations
    - Horizontal gene transfer

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TABLE 28.8 **Bacterial resistance to antibiotics**

Resistance mechanism	*Antibiotic example*	*Genetic basis of resistance*	*Mechanism present in*
Reduced permeability	Penicillins	Chromosomal	Gram-negative bacteria
Inactivation of antibiotic Examples: b-lactamases; modifying enzymes, such as methylases, acetylases, phosphorylases, and others	Penicillins	Plasmid and chromosomal	*Staphylococcus aureus* Enteric bacteria
	Chloramphenicol	Plasmid and chromosomal	*Neisseria gonorrhoeae* *Staphylococcus aureus*
	Aminoglycosides	Plasmid	Enteric bacteria
Alteration of target Examples: RNA polymerase, rifamycin; ribosome, erythromycin and streptomycin; DNA gyrase, quinolones	Erythromycin	Chromosomal	*Staphylococcus aureus*
	Rifamycin		Enteric bacteria
	Streptomycin		Enteric bacteria
	Norfloxacin		Enteric bacteria *Staphylococcus aureus*
Development of resistant biochemical pathway	Sulfonamides	Chromosomal	Enteric bacteria *Staphylococcus aureus*
Efflux (pumping out of cell)	Tetracyclines	Plasmid	Enteric bacteria
	Chloramphenicol	Chromosomal	*Staphylococcus aureus* *Bacillus subtilis*
	Erythromycin	Chromosomal	*Staphylococcus*

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Table 28.8

Antimicrobial Drug Resistance and New Treatment Strategies

- Antimicrobial drug resistance
  - Because antibiotic-resistant genes are in nearly every population, physicians cannot use the same antibiotic for long.
  - Any use of antibiotics selects for resistance, increasing the number of resistant bacteria in any bacterial population.
    - Overuse accelerates this process.

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Antimicrobial Drug Resistance and New Treatment Strategies

- Antimicrobial drug resistance
  - Almost all pathogenic microbes have acquired resistance to some chemotherapeutic agents.
  - A few pathogens have developed resistance to all known antimicrobial agents.
  - Resistance can be minimized by using antibiotics correctly and only when needed.
  - Resistance to a certain antibiotic can be lost if antibiotic is not used for several years.

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Antimicrobial Drugs That Target Nonbacterial Pathogens

- Antiviral drugs
  - Most antiviral drugs also target host structures, resulting in toxicity.
  - Most successful and commonly used antivirals are the *nucleoside analogs*. (*e.g.,* AZT)
    - block reverse transcriptase and production of viral DNA
    - also called nucleoside reverse transcriptase inhibitors (NRTIs)
- Drugs that target eukaryotic pathogens
  - Fungi pose special problems for chemotherapy because they are eukaryotic. (Figure 28.32)
    - Much of the cellular machinery is the same as that of animals and humans.
    - As a result, many antifungals are topical.

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