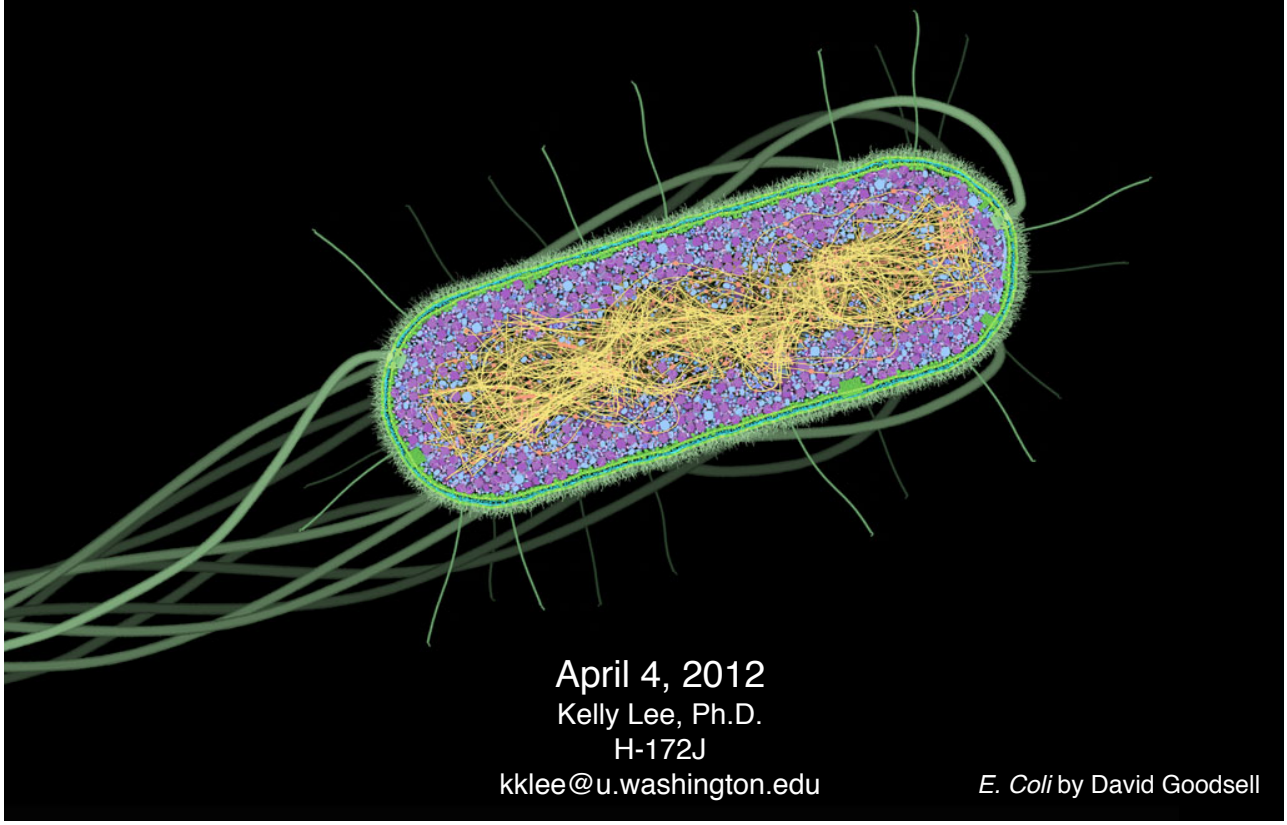
Mechanisms of action of antibacterial therapeutics

MEDCH 561P



April 4, 2012

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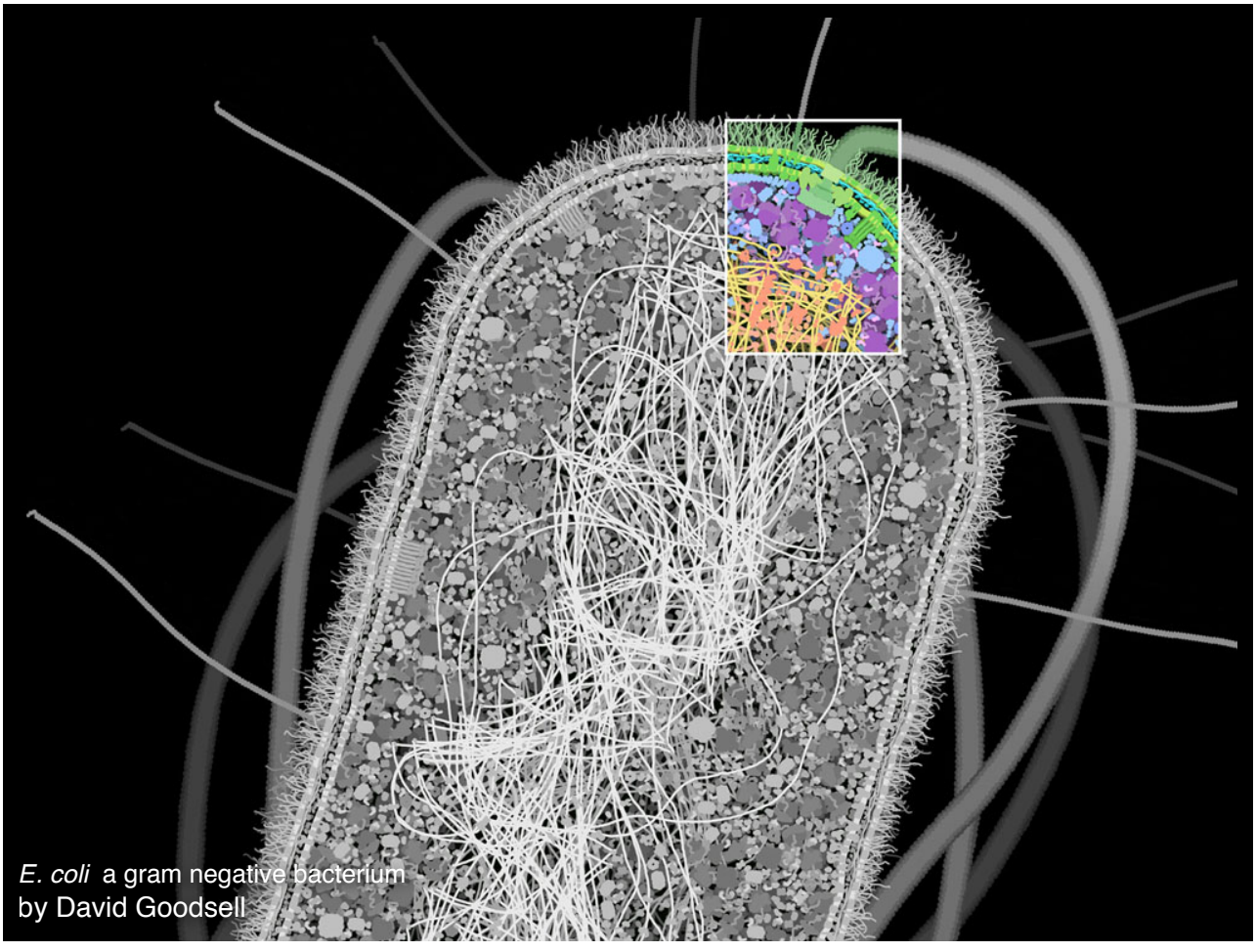
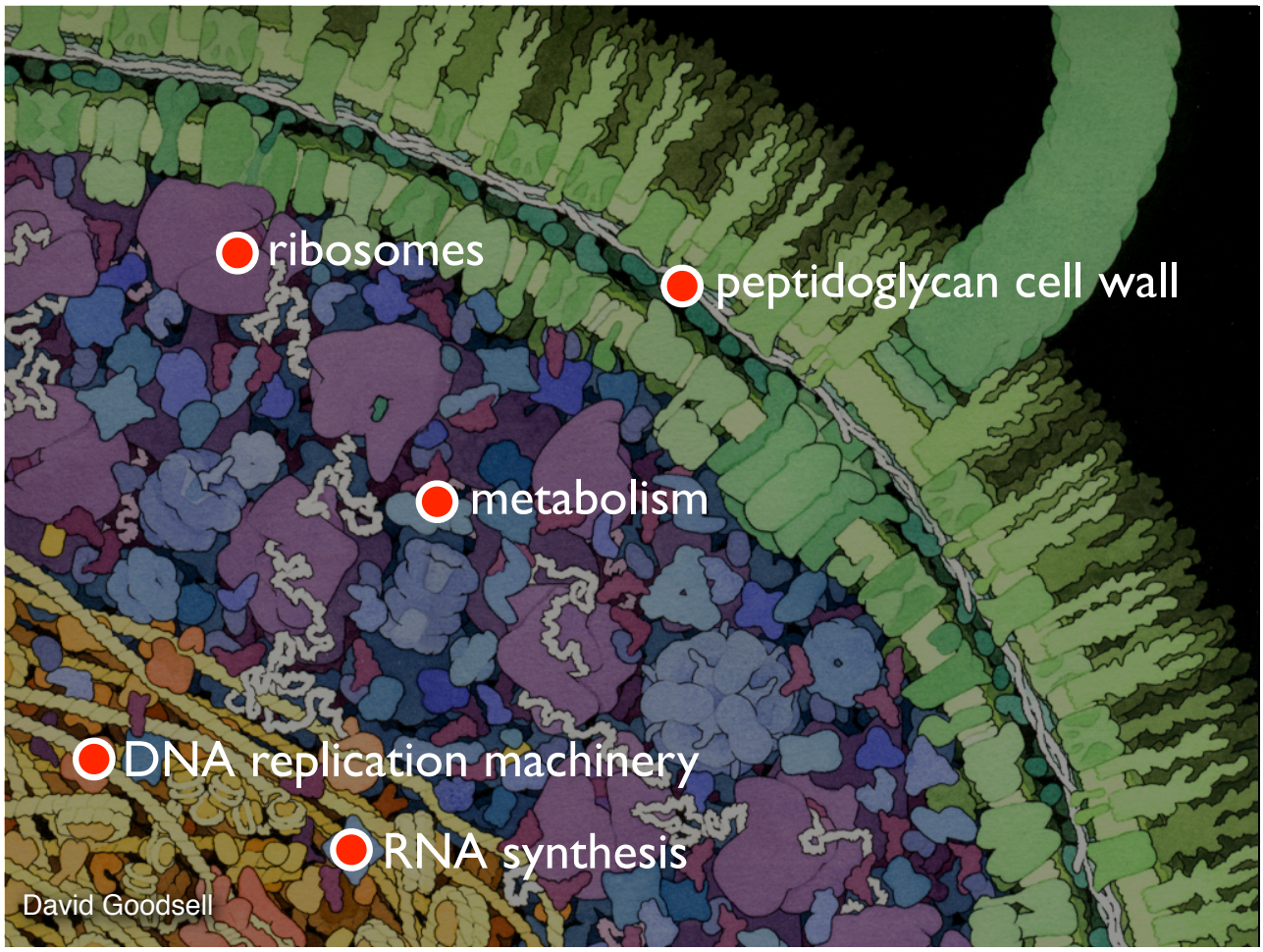
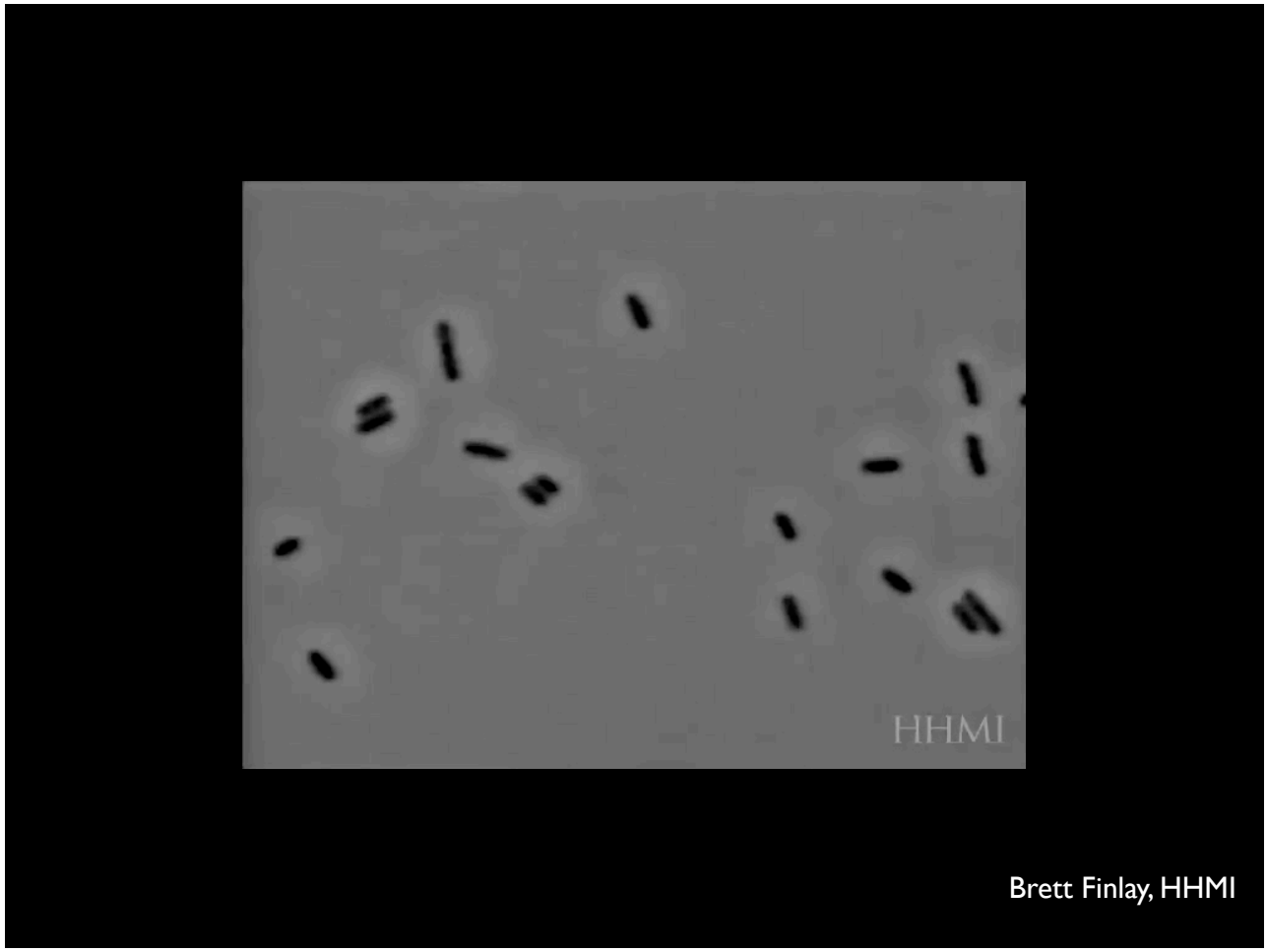
E. Coli by David Goodsell



E. coli a gram negative bacterium
by David Goodsell


ribosomes
peptidoglycan cell wall
metabolism
DNA replication machinery
RNA synthesis
David Goodsell


HHMI
Brett Finlay, HHMI

E. coli treated with ampicillin (a beta-lactam drug)

Brett Finlay, HHMI

Targets are unique to bacteria, not found in humans

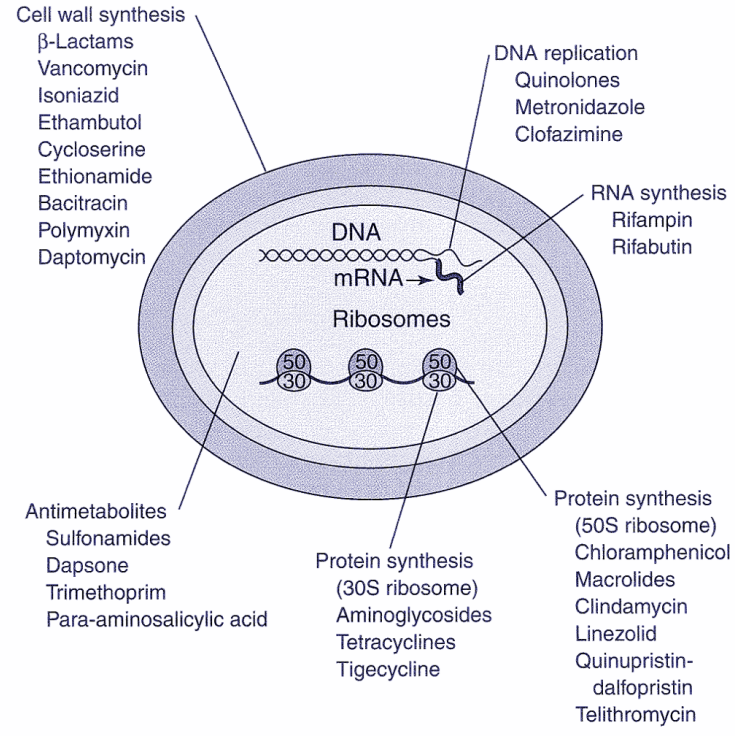


Figure 20–1. Basic sites of antibiotic activity.

Murray PR, Rosenthal KS, Pfaller MA, (2009) Medical Microbiology 6th Edition

Natural product antibiotics and their derivatives

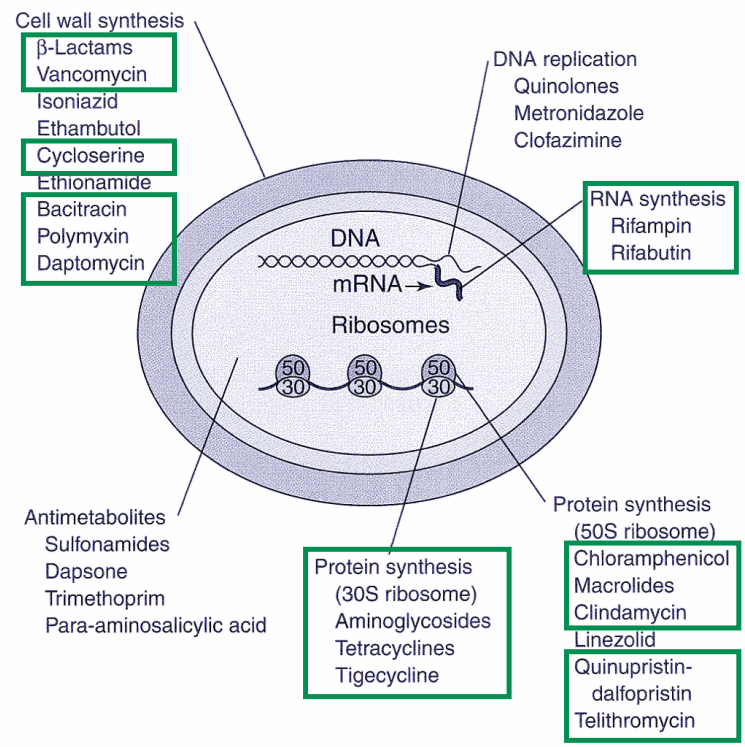


Figure 20–1. Basic sites of antibiotic activity.

Murray PR, Rosenthal KS, Pfaller MA, (2009) Medical Microbiology 6th Edition

Synthetic antimicrobial agents

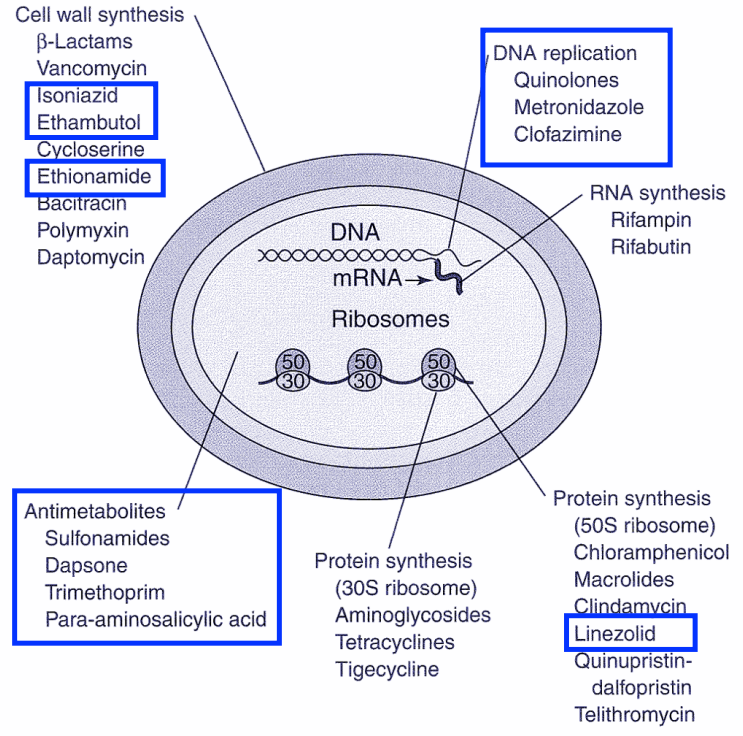
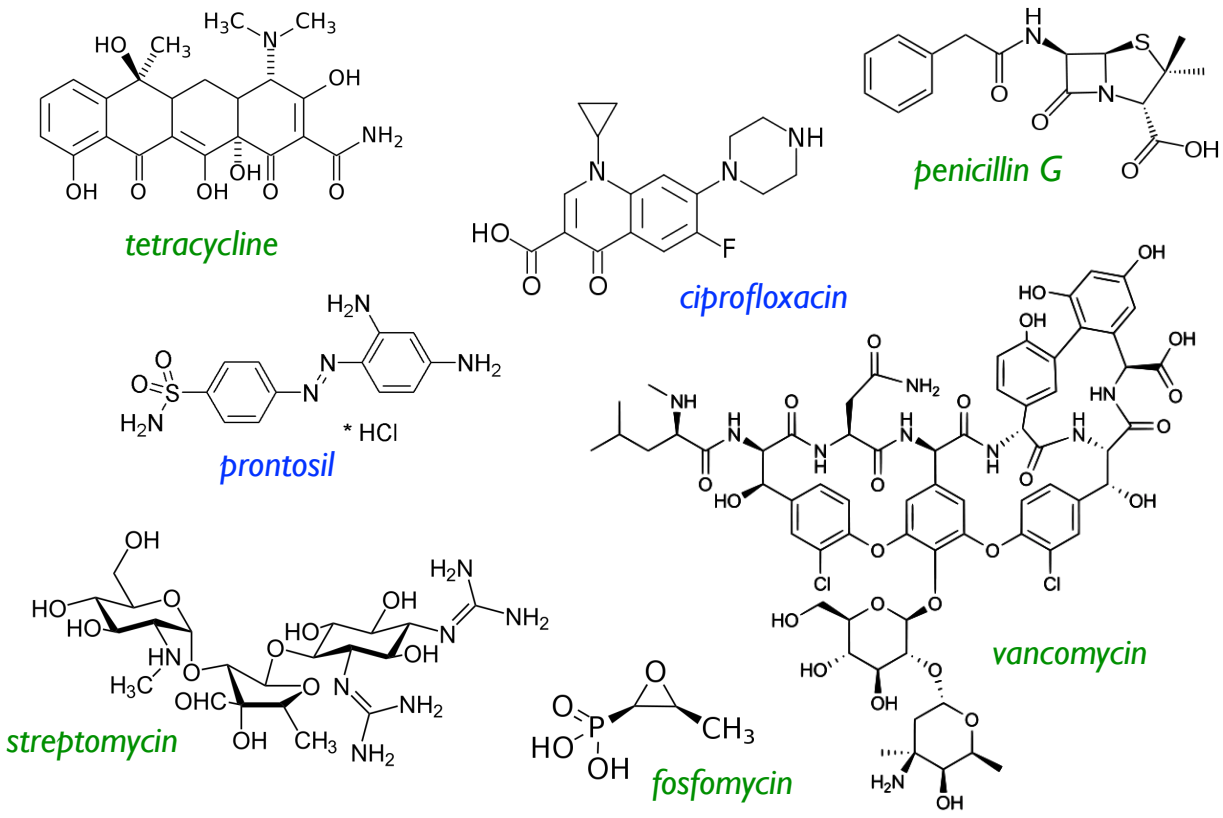


Figure 20–1. Basic sites of antibiotic activity.

Murray PR, Rosenthal KS, Pfaller MA, (2009) Medical Microbiology 6th Edition

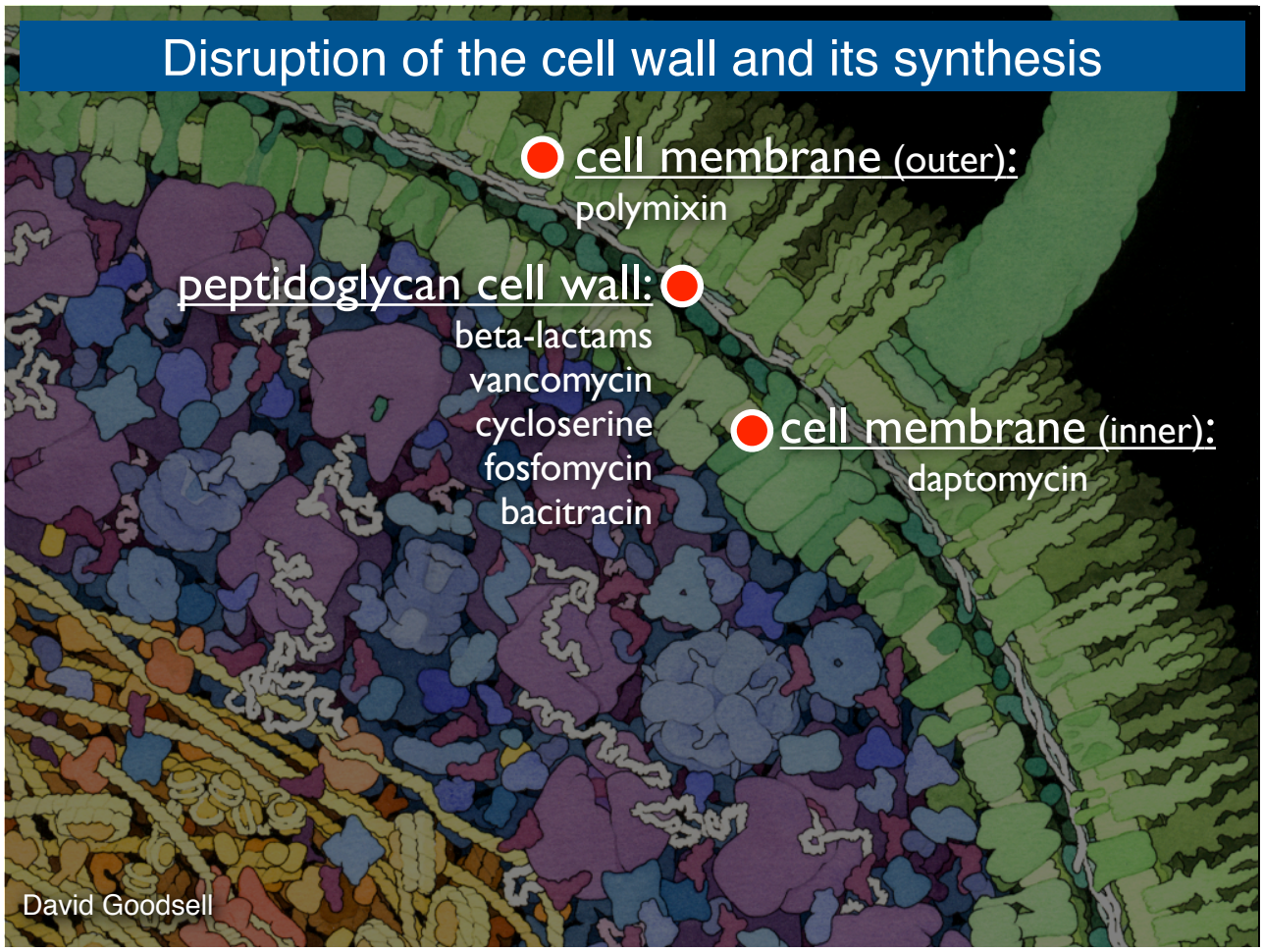
Mechanisms of action: broad array of drug classes



Narrow or broad spectrum

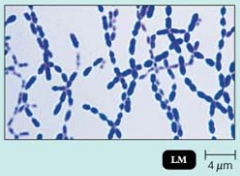
- Differences among bacterial species mean a drug will only be active against certain types of bugs
  - Narrow vs. broad spectrum
  - gm(+) vs gm(-)
  - target expressed?
  - details of target enzyme structure
  - differences in resistance mechanisms

Disruption of the cell wall and its synthesis

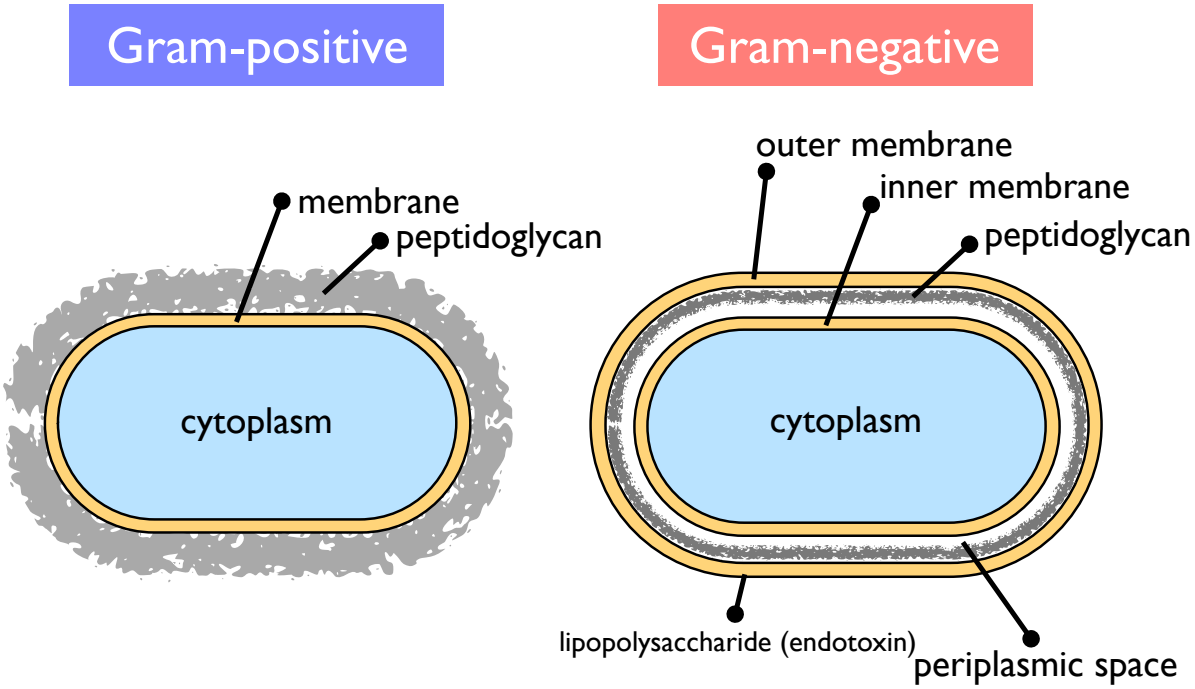


Gram-positive vs. Gram-negative bacteria

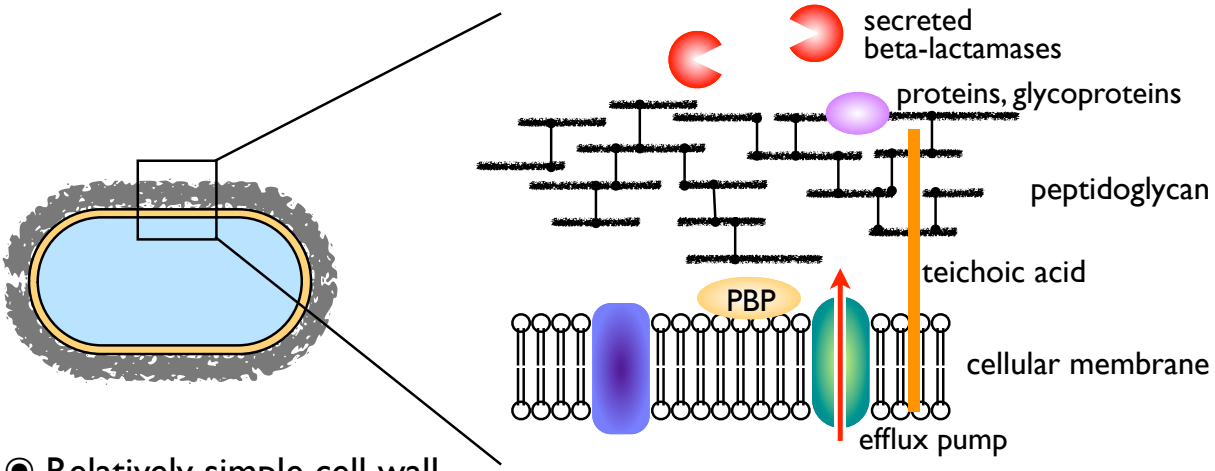
TABLE 4.1 Some Comparative Characteristics of Gram-Positive and Gram-Negative Bacteria

Characteristic	Gram-Positive	Gram-Negative
	 LM 4 μm	 LM 4 μm
Gram Reaction	Retain crystal violet dye and stain dark violet or purple	Can be decolorized to accept counterstain (safranin) and stain pink
Peptidoglycan Layer	Thick (multilayered)	Thin (single-layered)
Teichoic Acids	Present in many	Absent
Periplasmic Space	Absent	Present
Outer Membrane	Absent	Present
Lipopolysaccharide (LPS) Content	Virtually none	High
Lipid and Lipoprotein Content	Low (acid-fast bacteria have lipids linked to peptidoglycan)	High (due to presence of outer membrane)
Flagellar Structure	2 rings in basal body	4 rings in basal body
Toxins Produced	Primarily exotoxins	Primarily endotoxins
Resistance to Physical Disruption	High	Low
Cell Wall Disruption by Lysozyme	High	Low (requires pretreatment to destabilize outer membrane)
Susceptibility to Penicillin and Sulfonamide	High	Low
Susceptibility to Streptomycin, Chloramphenicol, and Tetracycline	Low	High
Inhibition by Basic Dyes	High	Low
Susceptibility to Anionic Detergents	High	Low
Resistance to Sodium Azide	High	Low
Resistance to Drying	High	Low

Gram-positive vs. Gram-negative bacteria

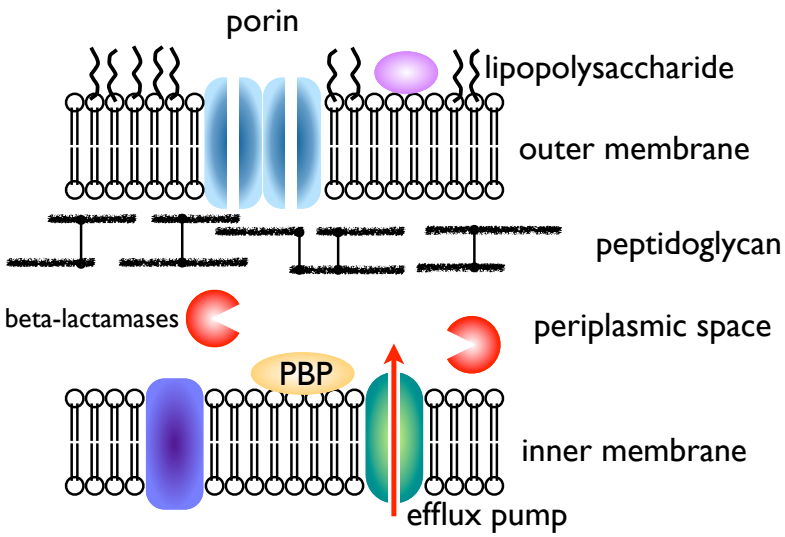


Gram-positive bacteria

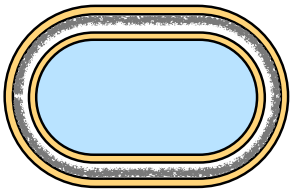


- Relatively simple cell wall
  - Single membrane
  - Thick (20-80nm) peptidoglycan layer, can be up to 40 layers thick
- High internal osmolality
- Less developed biosynthetic capability
- Lysozyme, a protein in our innate immune defense, digests peptidoglycan; found in tears, mucus, saliva

Gram-negative bacteria

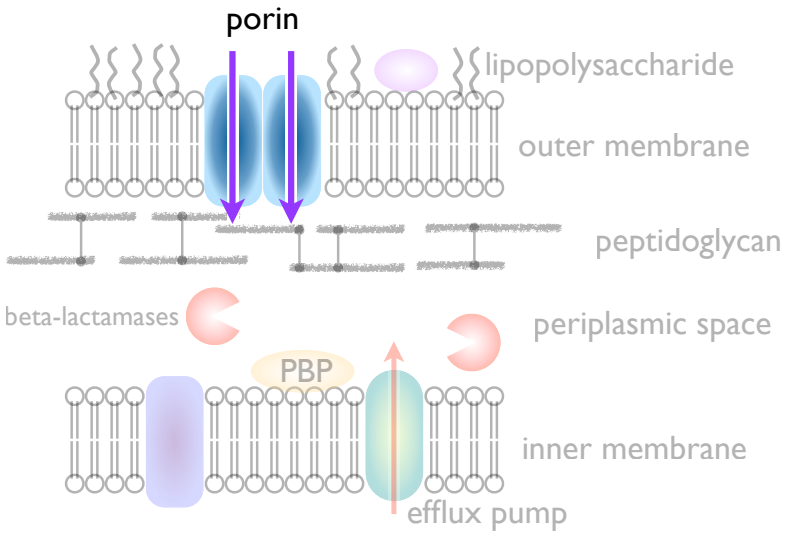


Gram-negative bacteria



- Complex cell wall
  - Outer and inner membranes
  - Thin (7-8nm) peptidoglycan layer only 1 or 2 layers in thickness
  - Periplasmic space separating the two membrane barriers
  - Porin channels in outer membrane can restrict uptake of drug
- Low internal osmolality
- Highly developed synthetic capability
- Highly adaptive

Outer membrane can drastically limit drug uptake: Porins



- Large, bulky drugs (e.g. vancomycin), >700 Daltons excluded
- Apolar compounds tend to be excluded
- Smaller, polar compounds may cross outer membrane *via* porins

Pages JM et al., "The Porin and the Permeating Antibiotic: a selective diffusion barrier in Gram-negative Bacteria" (2008) *Nature Reviews Microbiology* **6**: 893-903

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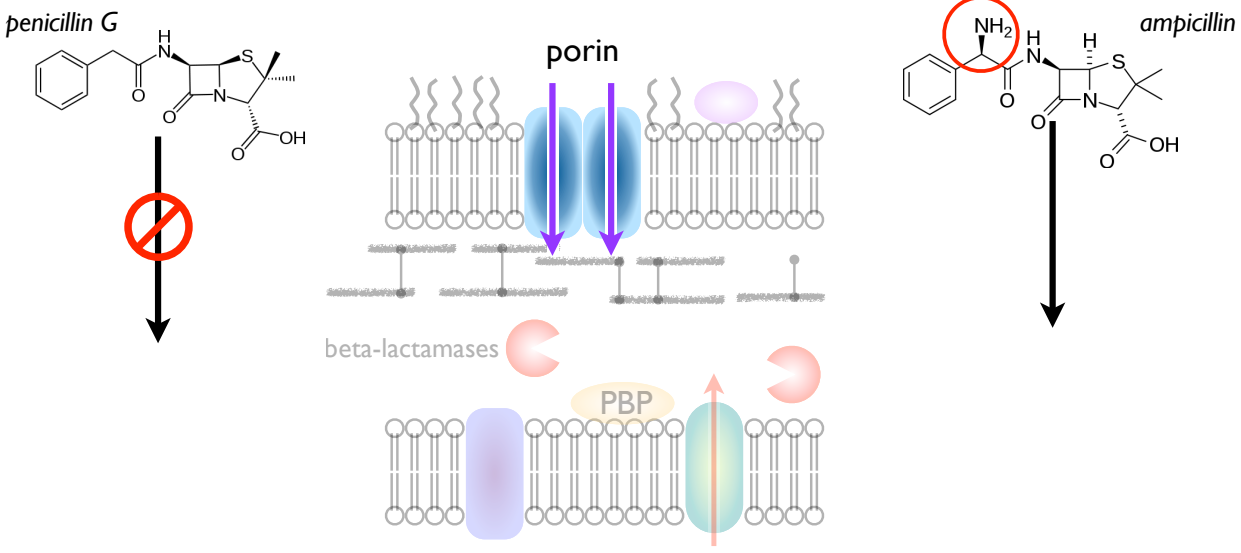

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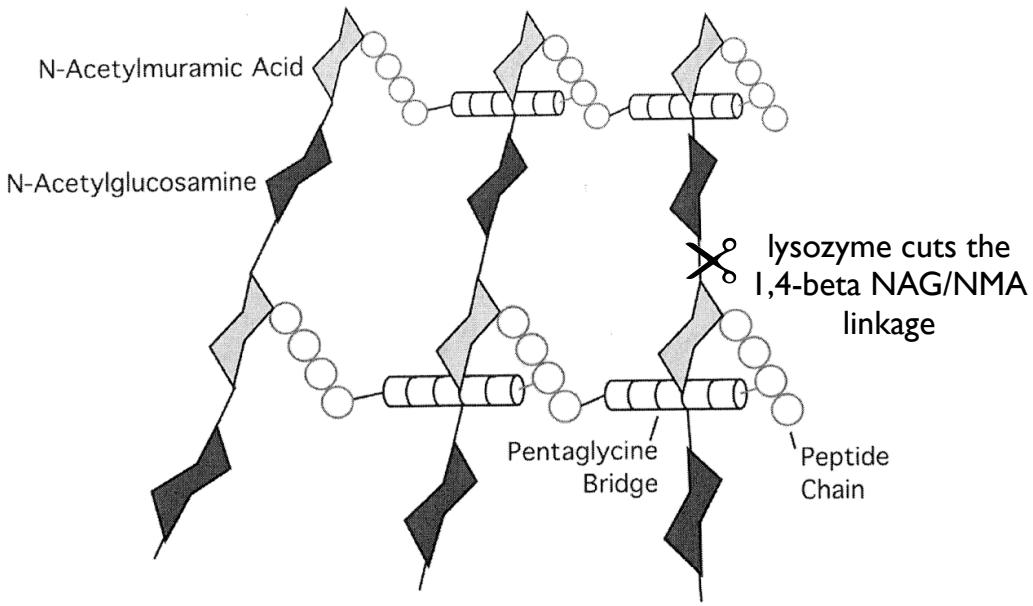
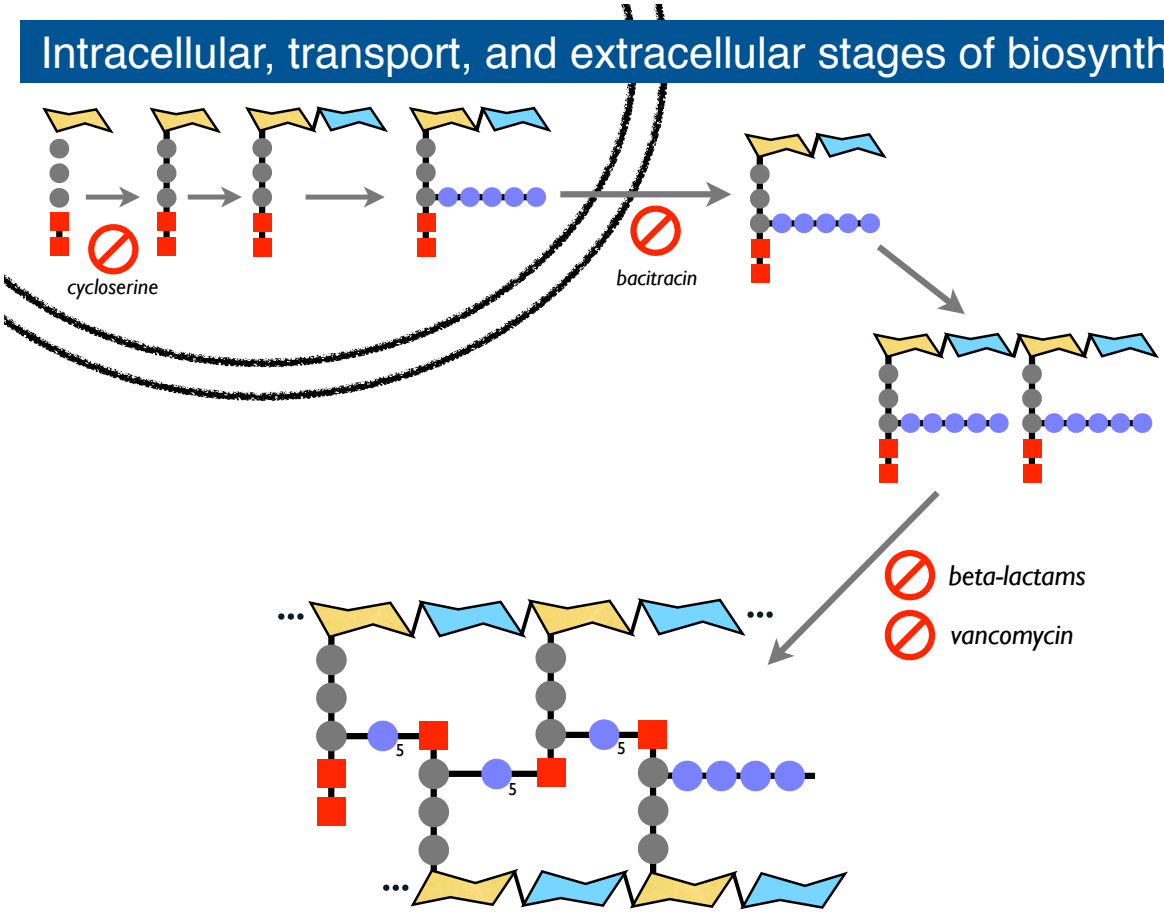
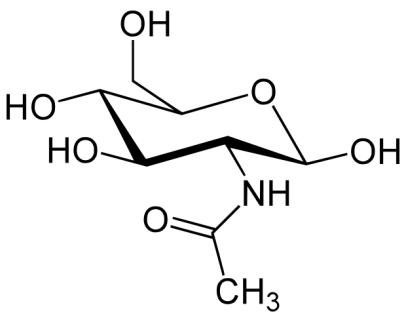
Peptidoglycan networks



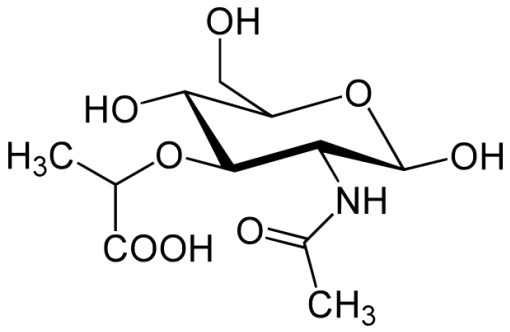
Intracellular, transport, and extracellular stages of biosynthesis



Peptidoglycan networks

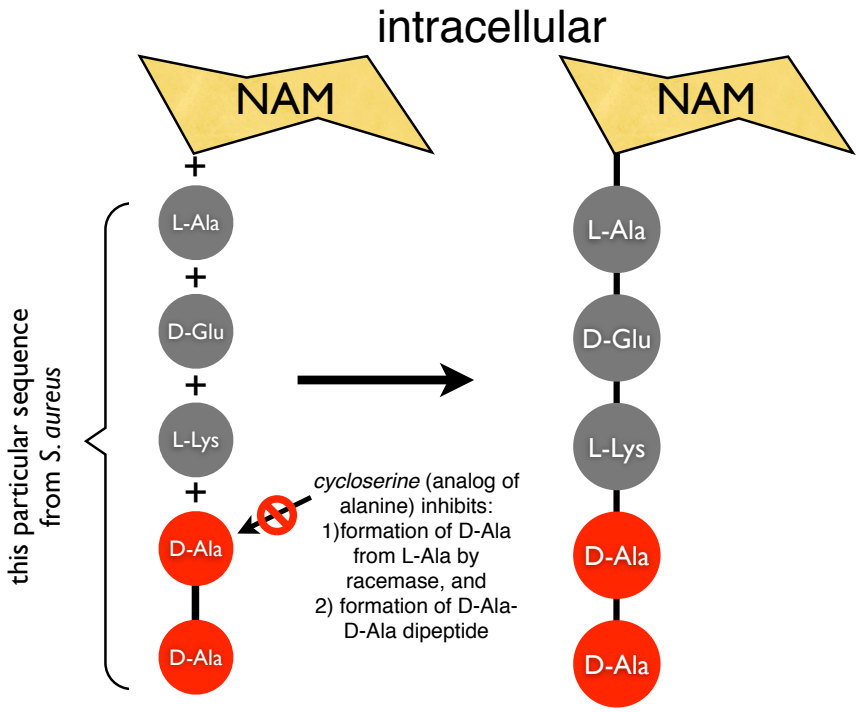


N-acetylglucosamine (NAG)



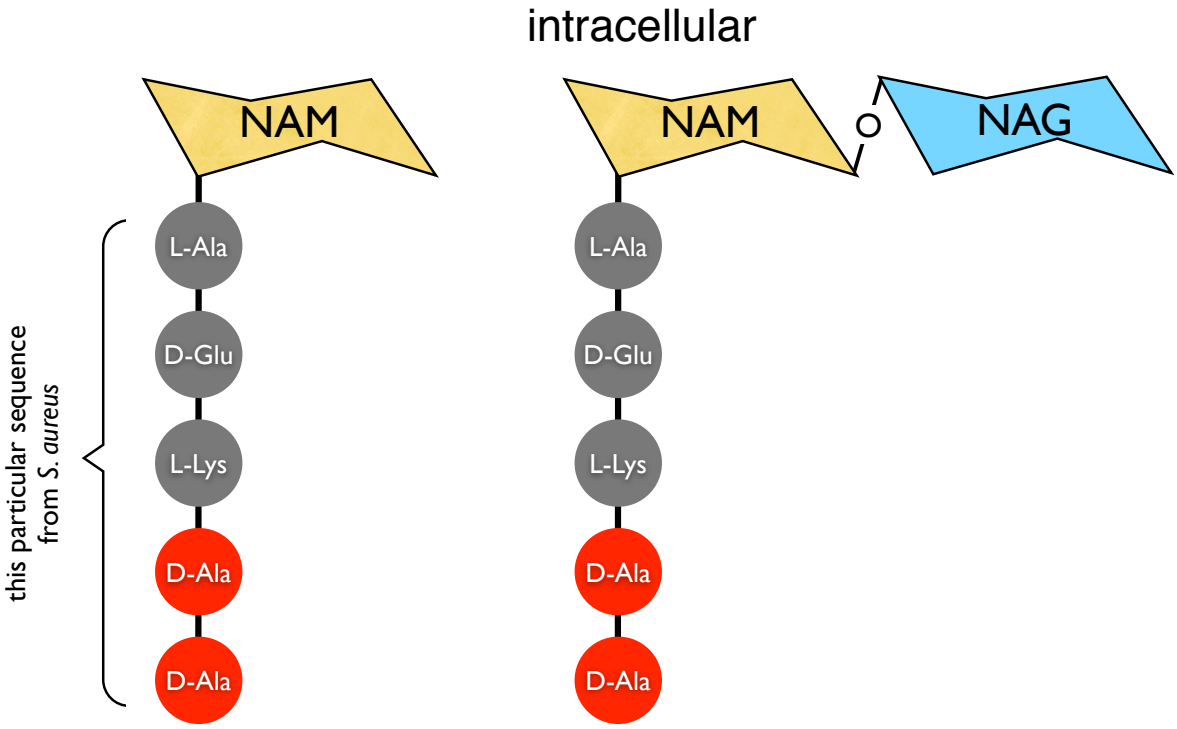
N-acetylmuramic acid (NAM)

Enzymatic (MurC-F) peptide linkage

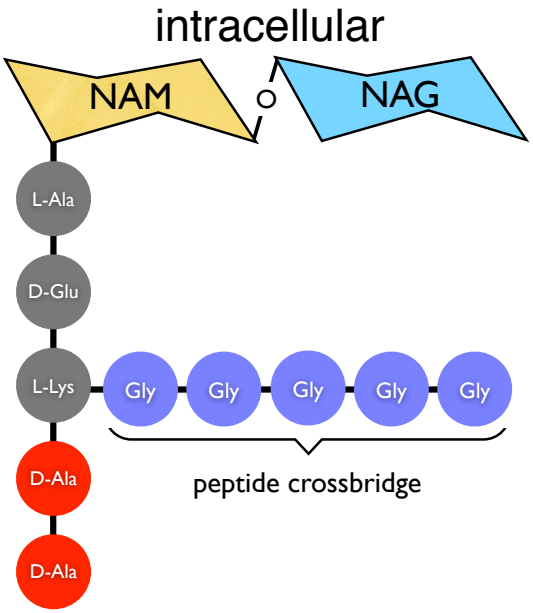


- Peptide contains D amino acids: likely resistant to proteolytic degradation
- Peptide chain formed enzymatically, not by ribosome

MurG enzyme catalyzes formation of the NAM-NAG disaccharide

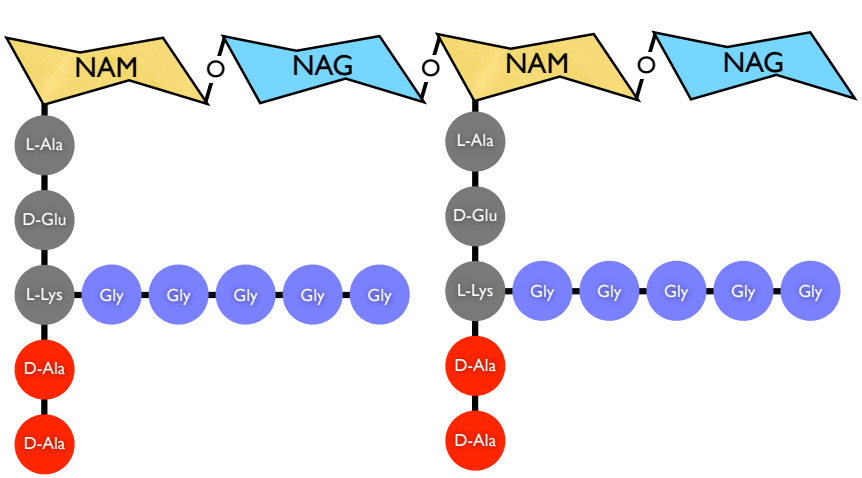


Penta-glycine crossbridge attached to residue 3 (Lys) of NAM-linked pentapeptide chain

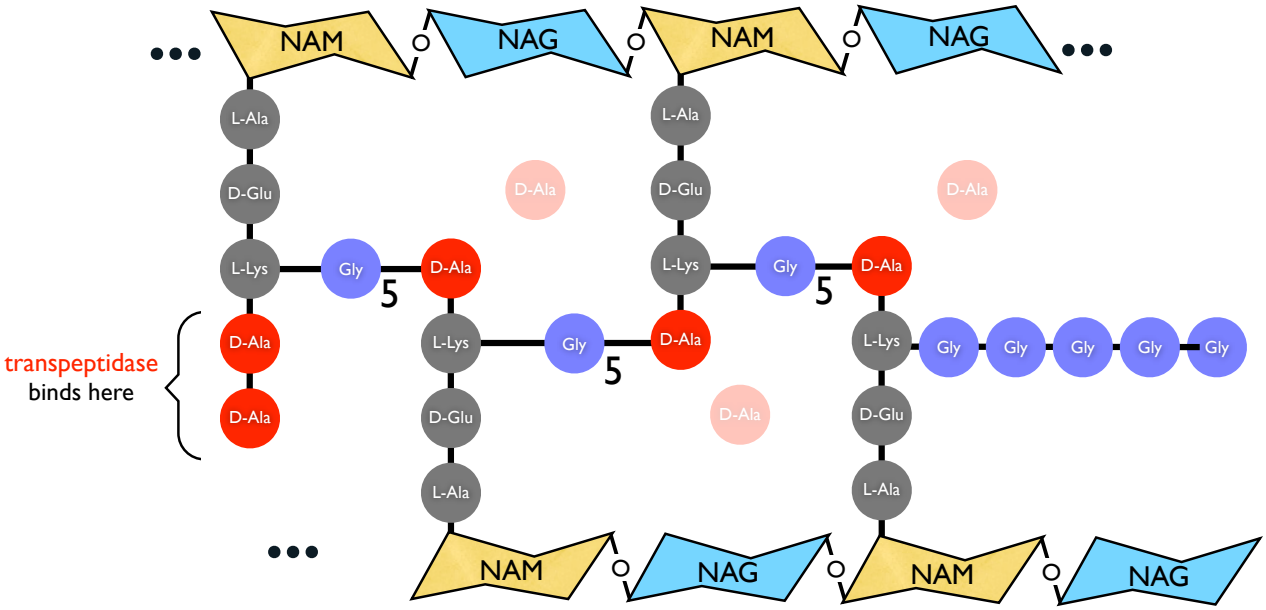


- Penta-glycine added onto sidechain of 3rd residue of peptide chain
- The disaccharide with penta-peptide chain and penta-glycine is translocated across the cytoplasmic membrane (*bacitracin* knocks out the translocator protein)

Extracellular transglycosylases polymerize the carbohydrate chains

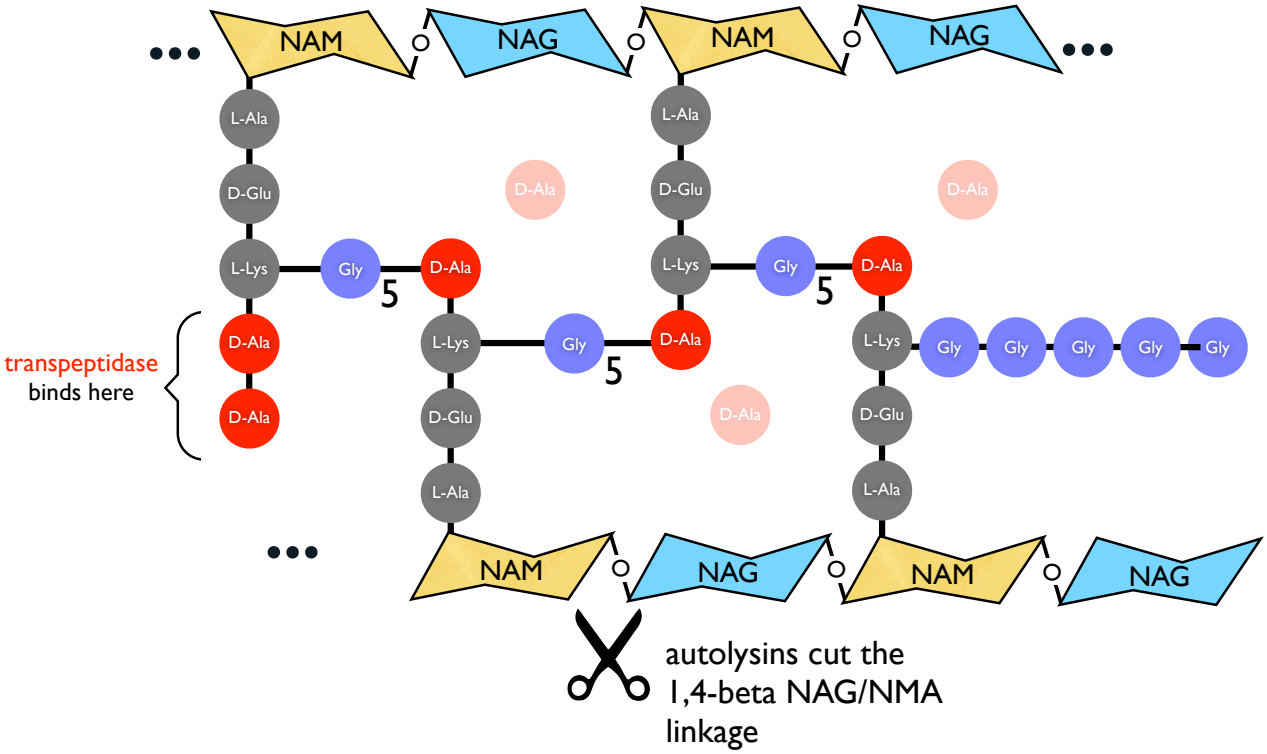


Crosslink the peptide chains to form the peptidoglycan network Transpeptidase catalyzes the Gly-D-Ala link are targets of beta-lactam antibiotics: "Penicillin-binding proteins" (PBP)

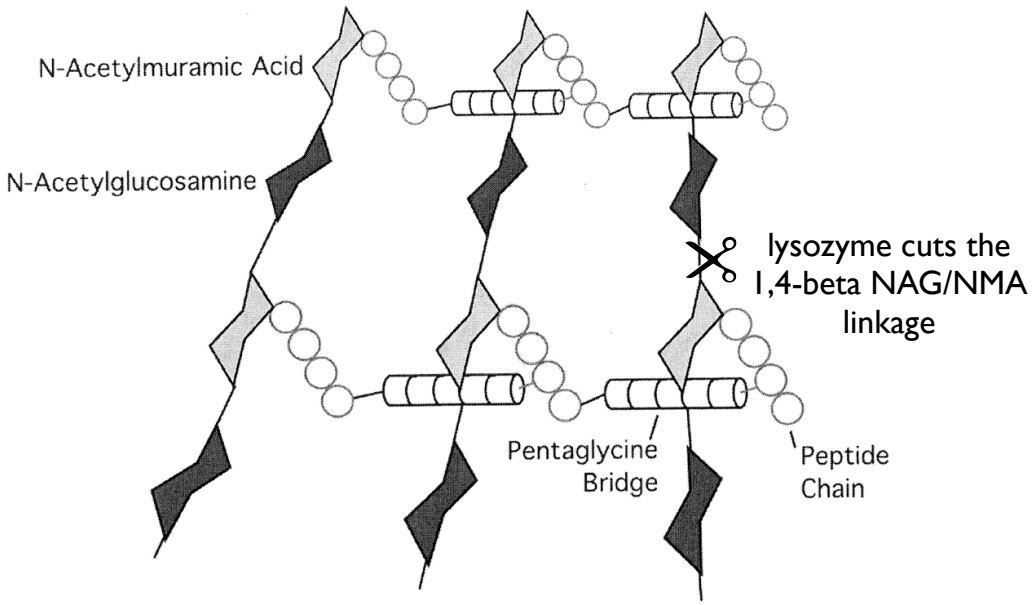


- Extracellular
- Beta-lactams inhibit this step by binding to transpeptidase. Prevent cell wall maintenance and regeneration. Bactericidal.

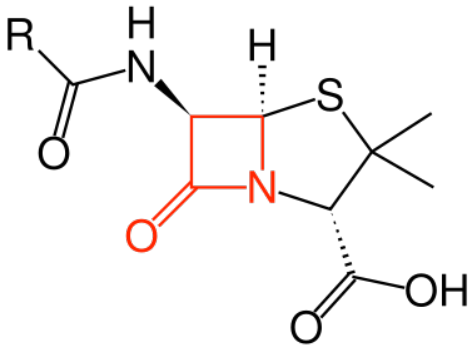
By knocking out the transpeptidase activity, beta-lactams, shift the cell wall maintenance equilibrium to degradation by autolysins: results in cells bursting



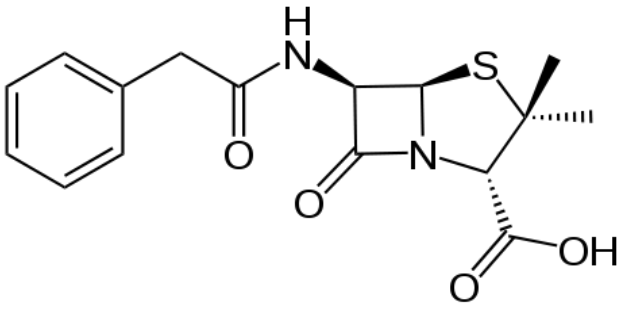
Peptidoglycan networks



Inhibition of cell-wall synthesis: beta-lactams/penicillins



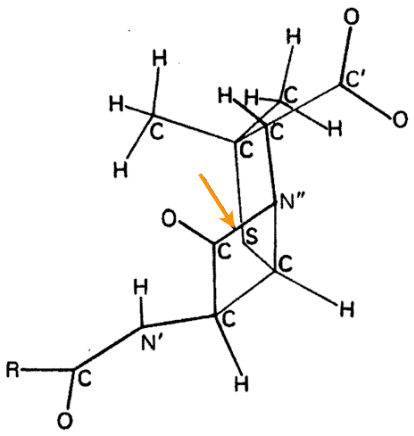
6-APA penicillin nucleus



penicillin G (benzylpenicillin)

- Produced by mold (*Penicillium chryosogenum*)
- The penicillin nucleus: a beta-lactam ring fused with the 5-membered thiazolidine ring (6-aminopenicillanic acid; 6-APA)

Beta-lactams bind to transpeptidase in place of D-Ala-D-Ala



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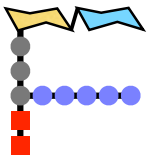
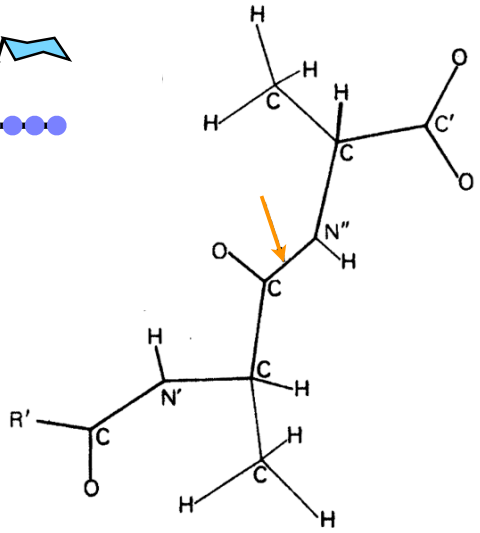




D-alanyl-D-alanine

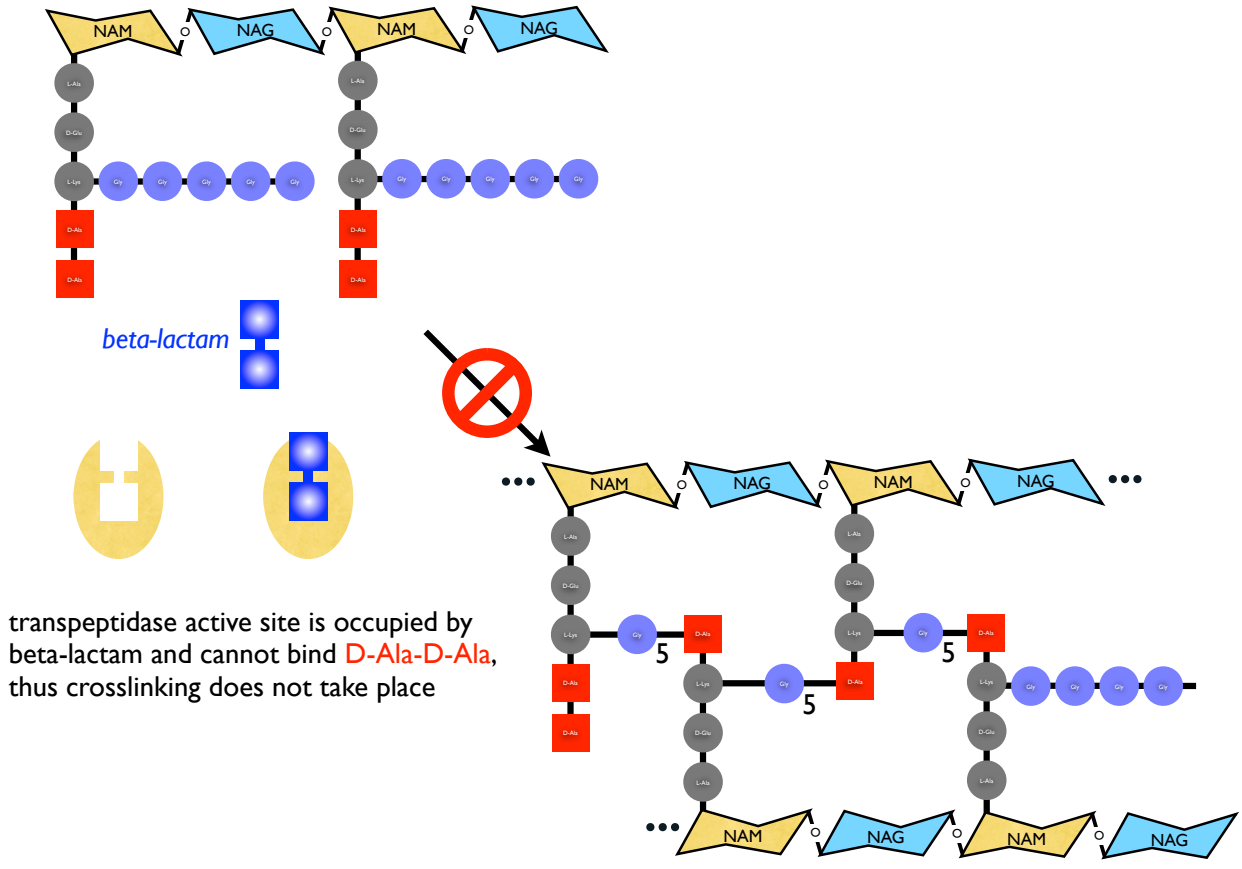
Transpeptidase (a PBP) normally binds to the D-Ala-D-Ala at the end of peptidoglycan precursors to crosslink the peptidoglycan. Beta-lactams such as penicillin mimic D-Ala-D-Ala, occupying the PBP active site and inhibiting crosslinking of peptidoglycan peptide bridges. Cell wall is weakened and this allows autolytic enzymes that degrade the peptidoglycan network to dominate, leading to lysis of the cells. Bactericidal.

"Penicillin Binding Proteins" (PBP) of *E. coli*: beta-lactam targets

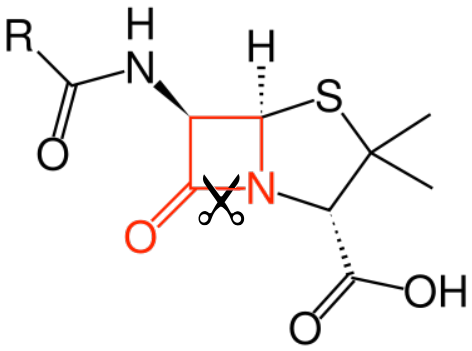
PBP	% of total PBP	Function	Inhibition lethal?
1a	8	transpeptidases; cell elongation	yes
1b			
2	0.7	maintain rod shape	yes
3	2	septum formation	no
4	4	D-alanine carboxypeptidases; limit extent of peptidoglycan crosslinking	no
5	65		no
6	2		no

Table 38.4 from Lemke TL, et al. *Foye's Principles of Medicinal Chemistry*, 6th Ed (2008)

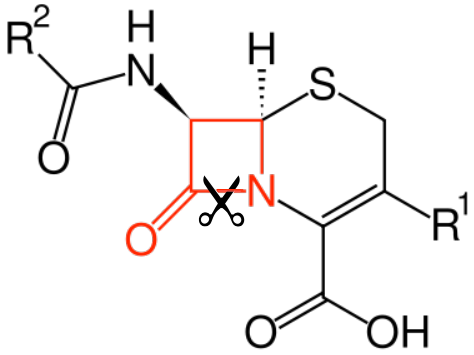
Beta-lactams bind to transpeptidase in place of D-Ala-D-Ala



beta-lactamases can inactivate beta-lactam drugs



penicillin nucleus

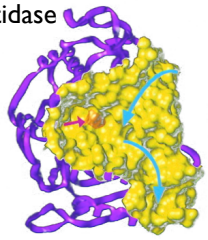


cephalosporin nucleus

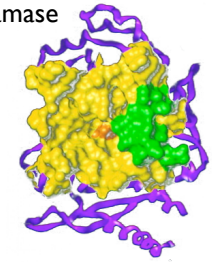
- Beta-lactamases hydrolyze the beta-lactam ring
- Enzymatic turn-over of drug inactivation (not single shot like w/ transpeptidase)
- Some specific in activity against certain classes (e.g. penicillins vs. cephalosporins), others have a broad range of activities

beta-lactamases can inactivate beta-lactam drugs

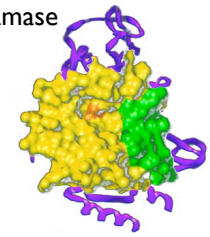
transpeptidase



class-C betalactamase



class-A betalactamase



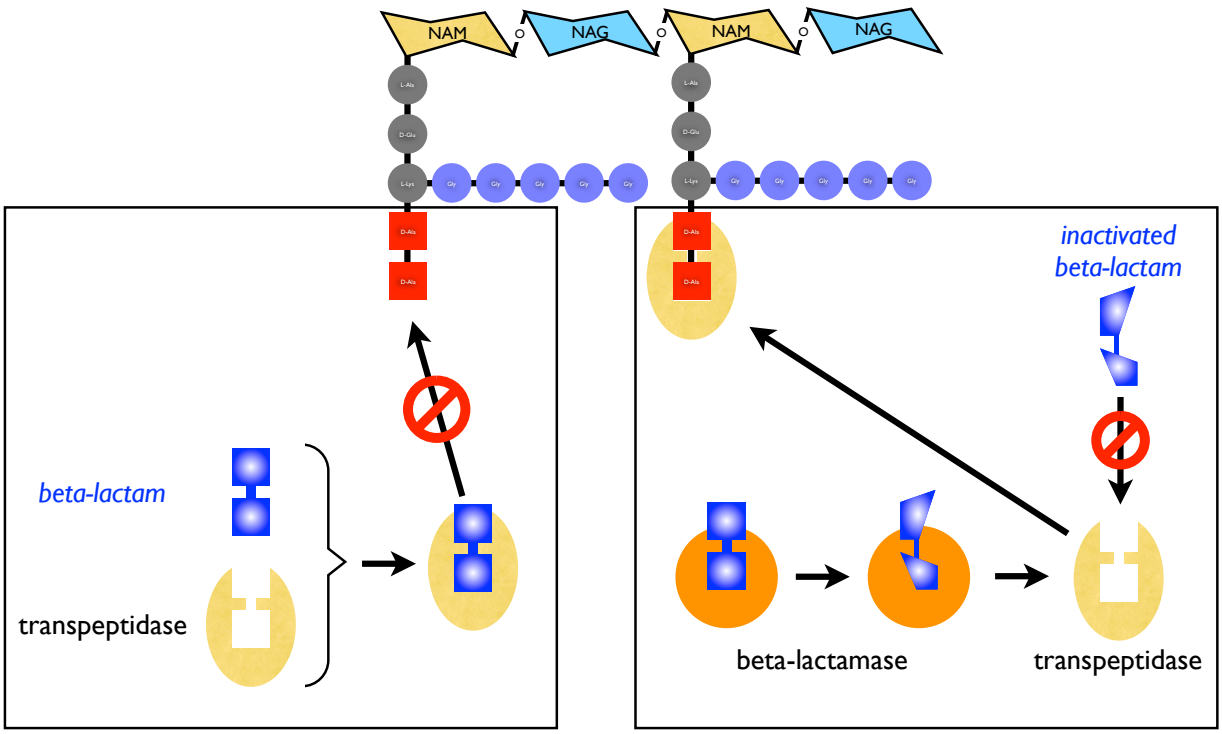
- Most share same structural family as transpeptidase (penicillin-binding proteins; PBP) that are antibiotic targets
- The drugs are bound at essentially the same active site, but beta-lactamases can hydrolyze the beta-lactam ring, inactivating the drug.

DD-peptidase-**transpeptidase** from *Streptomyces* sp. The red and blue arrows indicate the grooves where the first and second peptidoglycan strands, respectively, bind to the active site. The first peptidoglycan strand (red arrow) would approach the active-site serine, represented by the orange surface, essentially orthogonally to the plain of the figure in the depicted perspective. The yellow areas constitute the remainder of the active-site regions. The rest of each protein is depicted in the ribbon presentation in magenta.

class C beta-lactamase from *E. cloacae*

class A TEM-1 beta-lactamase from *E. coli*

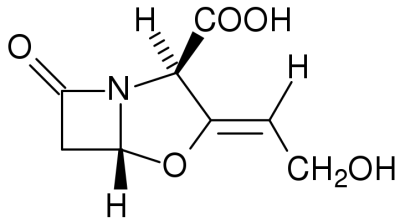
beta-lactamases can inactivate beta-lactam drugs



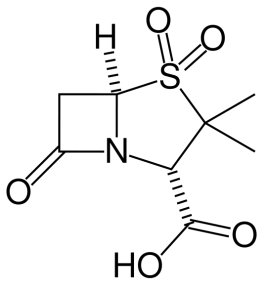
transpeptidase blocked by beta-lactam, cannot form peptidoglycan crosslink, cell lyses

transpeptidase functional since beta-lactam inactivated by beta-lactamase, crosslinks formed, cell lives

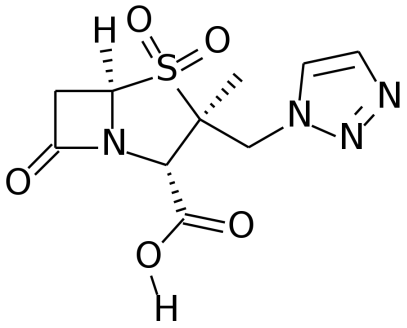
Cell-wall synthesis: beta-lactamase inhibitors



clavulanic acid



sulbactam

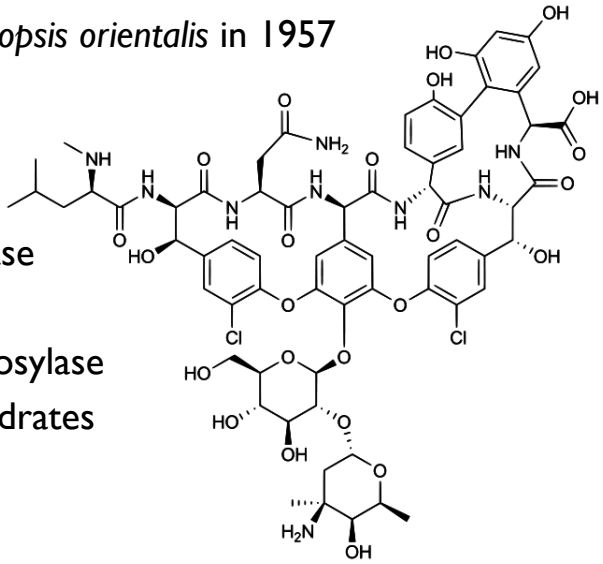


tazobactam

- Used to overcome beta-lactamase-related resistance to beta-lactams; not effective against all, however
- Bind to beta-lactamase active site and irreversibly inactivate them by forming a covalent linkage to the active site serine
- Minimal antibiotic activity by themselves
- Combination therapy with beta-lactam antibiotics
  - Augmentin (amoxicillin + clavulanic acid)

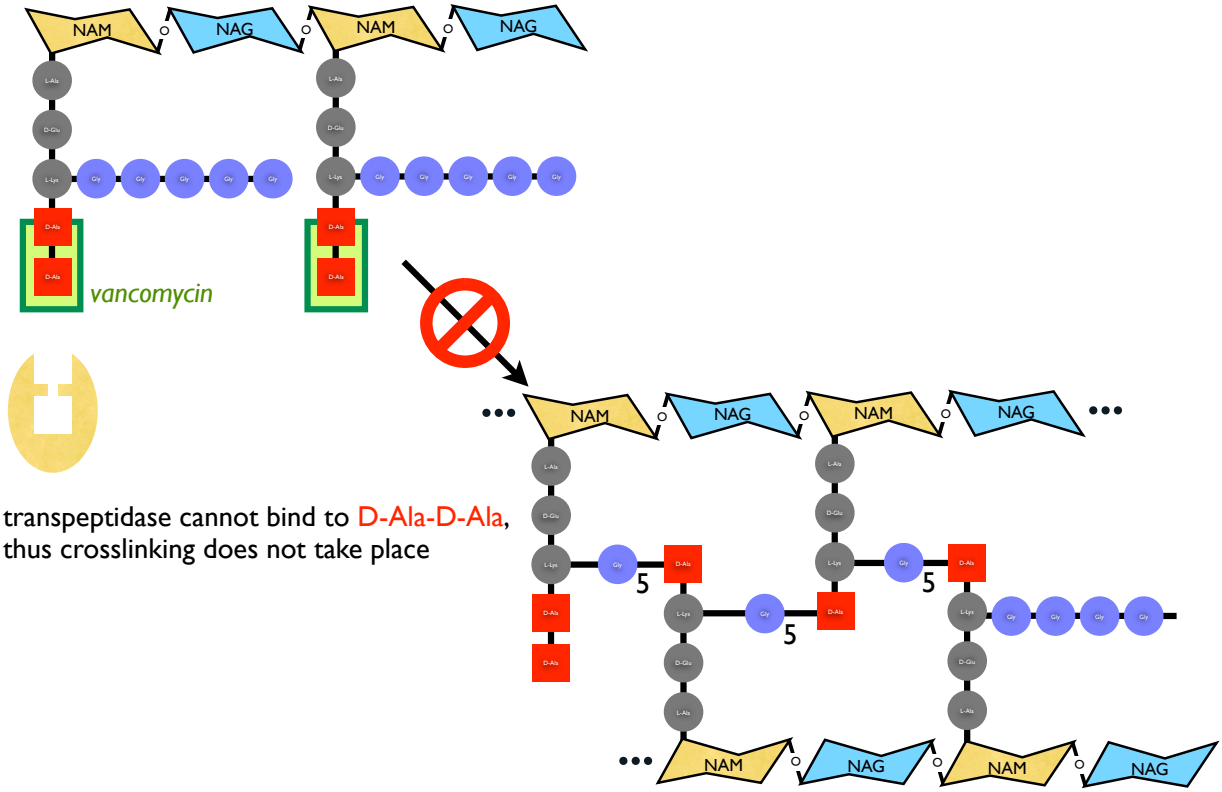
Cell-wall synthesis: vancomycin

- Isolated from Actinobacteria *Amycolatopsis orientalis* in 1957
- Cyclic glycosylated peptide
- Prevents peptidoglycan formation in Gram+ bacteria by binding to the D-Ala-D-Ala; inhibits transpeptidase (peptide crosslinking)
- Some derivatives inhibit the transglycosylase that polymerizes NAG/NAM carbohydrates

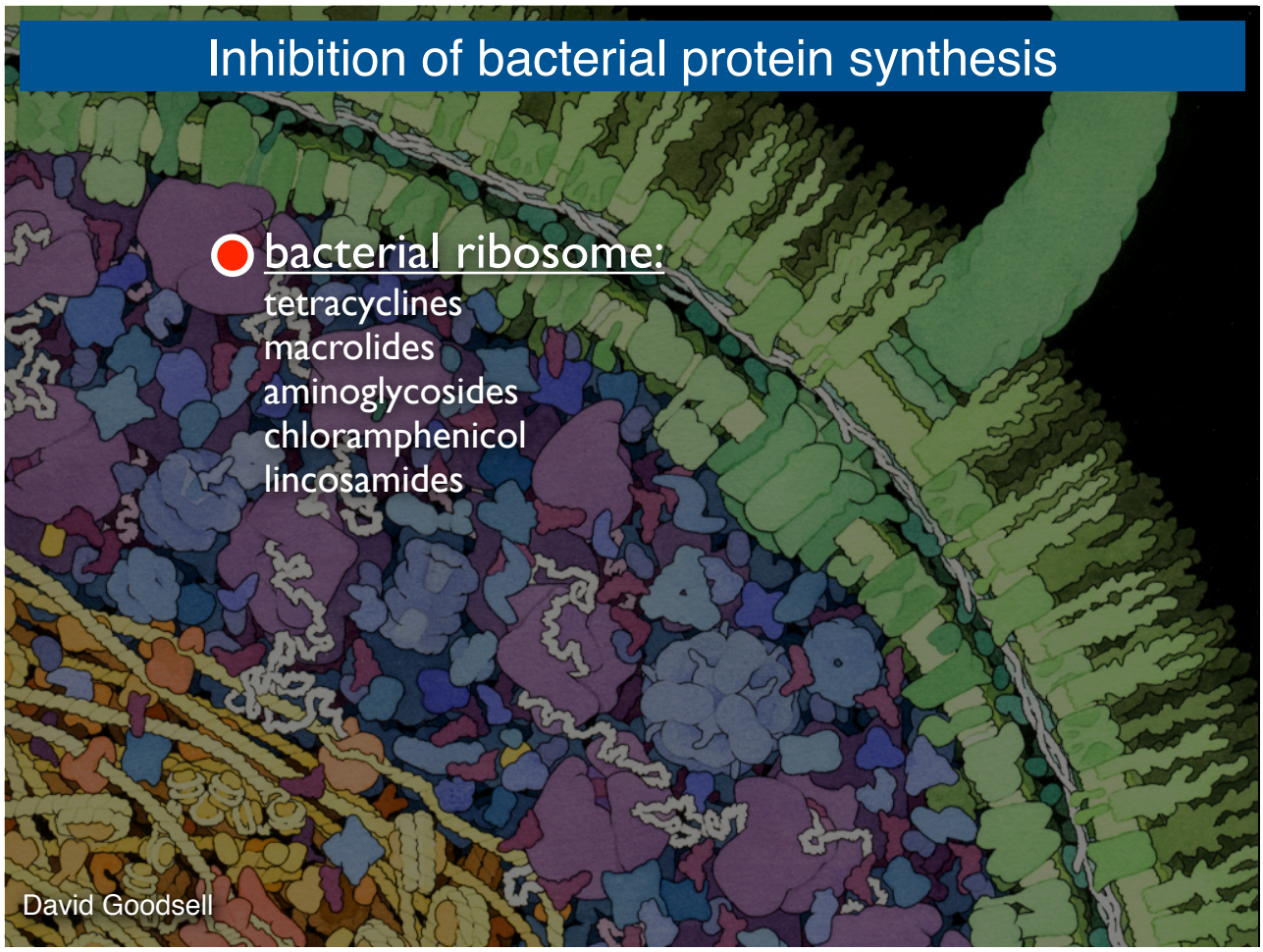


- Resistance:
  - Emergence in 1987-present:
    - VRE: vancomycin-resistant enterococcus
    - VRSA: vancomycin-resistant *Staph. aureus*
    - VISA: vancomycin-intermediate *Staph. aureus*
    - vancomycin-resistant *Clostridium difficile*

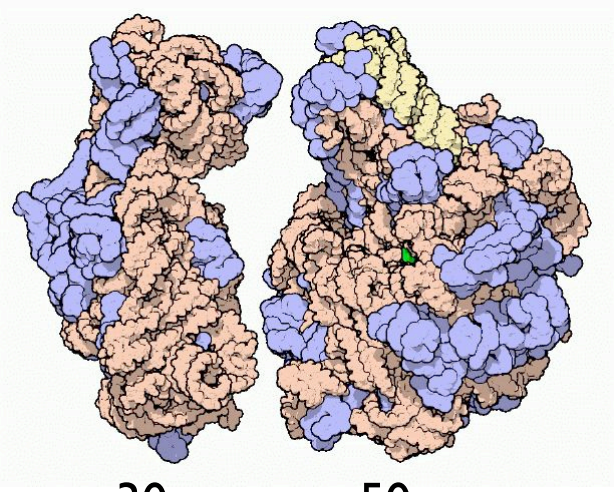
Cell-wall synthesis: vancomycin



Inhibition of bacterial protein synthesis



Inhibition of bacterial protein synthesis

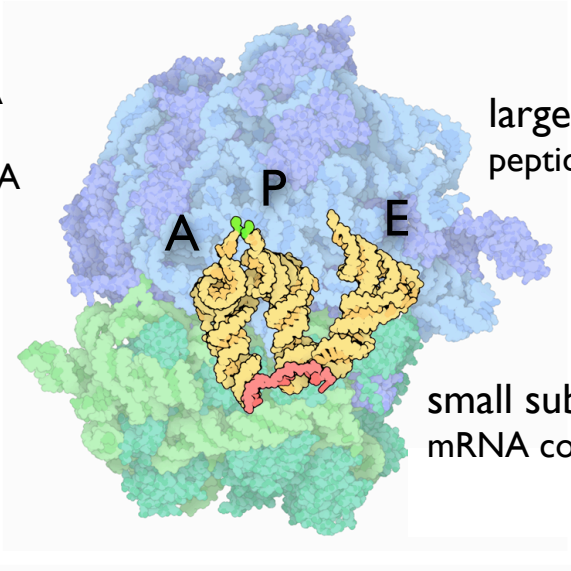


- The 70s (30s+50s) bacterial ribosomes are sufficiently different from eukaryotic 80s ribosomes (40s+60s subunits) that antimicrobials act selectively

PDB coordinate-based illustrations by David Goodsell

Inhibition of bacterial protein synthesis

A: aminoacyl-tRNA
P: peptidyl-tRNA
E: free, exiting tRNA



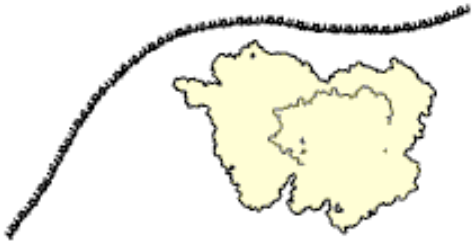
large subunit (50s):
peptide chain synthesis

small subunit (30s):
mRNA codon, anticodon pairing

- Ribosome: a protein/RNA ribozyme, functions like a machine with moving parts and substrates including mRNA, tRNA, amino acids, co-factors, the nascent polypeptide

2wdk+2wdl PDB coordinate-based illustrations by David Goodsell

Inhibition of bacterial protein synthesis



- Ribosome: a protein/RNA ribozyme, functions like a machine with moving parts and substrates including mRNA, tRNA, amino acids, co-factors, the nascent polypeptide

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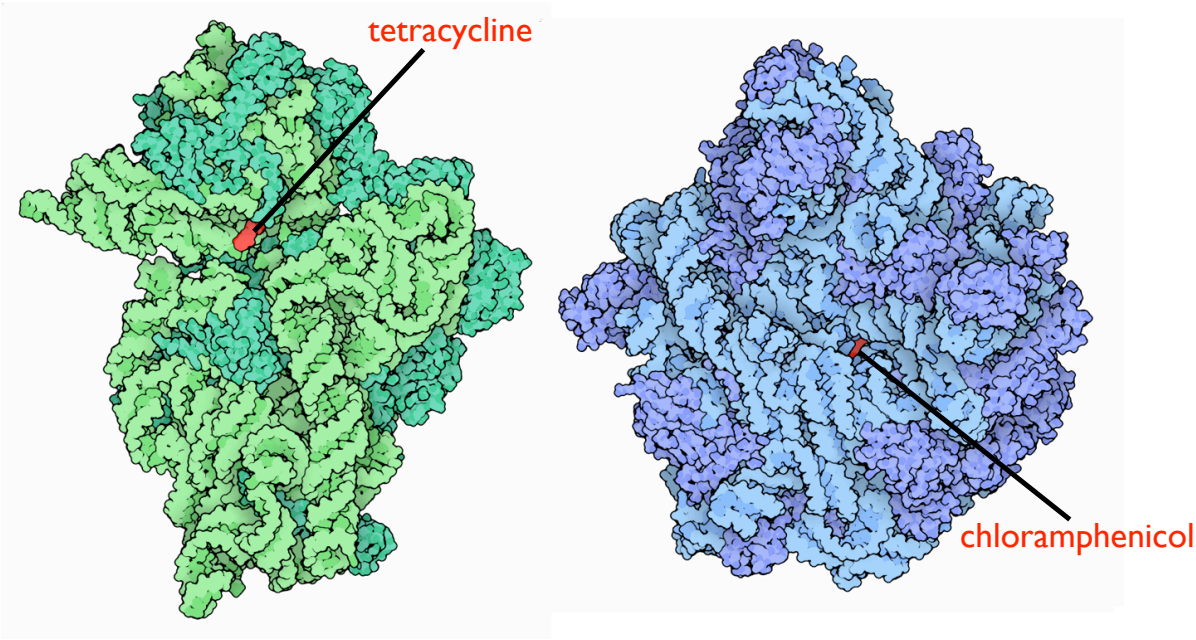
Antimicrobials directed against protein synthesis bind to the rRNA



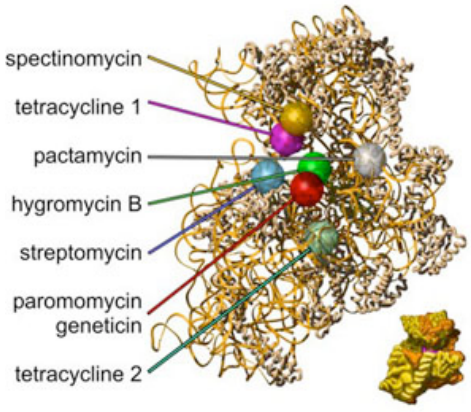
30s subunit
PDB: 1hnw

50s subunit
PDB: 1nji

PDB coordinate-based illustrations by David Goodsell

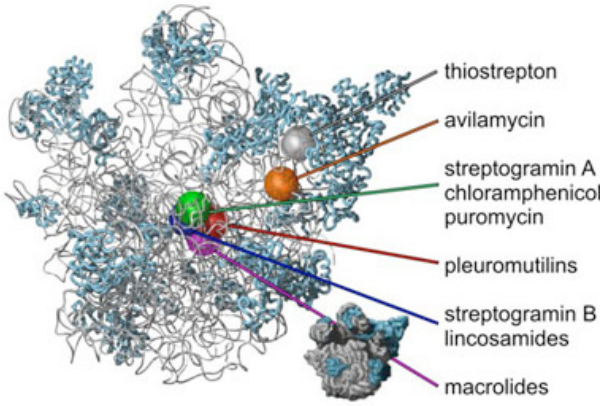
Inhibition of bacterial protein synthesis

30s



aminoglycosides
tetracycline

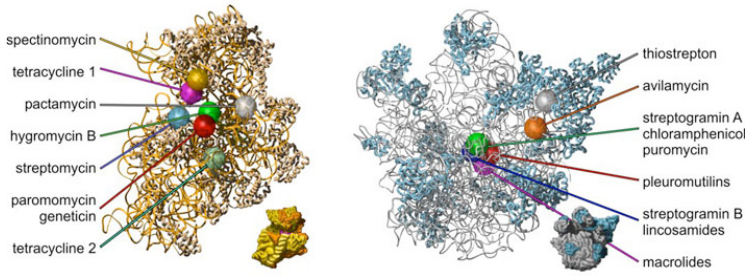
50s



macrolides
chloramphenicol
lincosamides
streptogramins
linezolid

figure by Stephen Douthwaite, University of Southern Denmark

Inhibition of bacterial protein synthesis



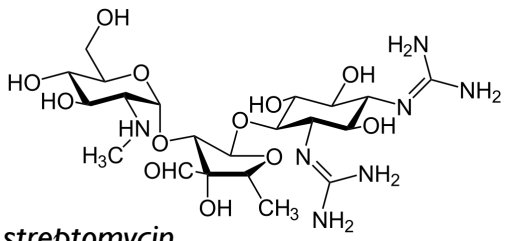
- MACROLIDES: Bind to 50s subunit:
  - Induce premature dissociation of peptidyl-tRNA from ribosome, hence premature termination
  - Prevent addition of residues onto nascent polypeptide by blocking A to P translocation

- TETRACYCLINES: Bind to 30s subunit:
  - Prevent aminoacyl-tRNA binding, hence peptide elongation

- AMINOGLYCOSIDES: Bind to 30s subunit:
  - Prevent tRNA movement from A to P site
  - Induce errors into "proofreading" and induce premature release of nonsense peptides

figure by Stephen Douthwaite, University of Southern Denmark

Inhibition of bacterial protein synthesis: aminoglycosides



streptomycin

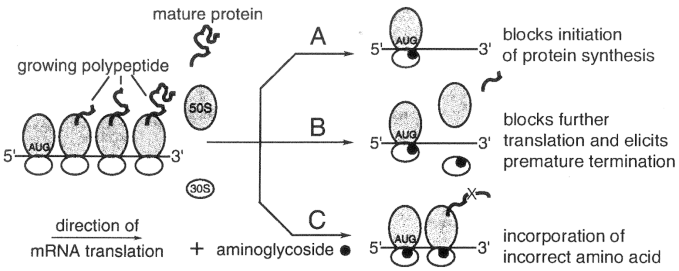
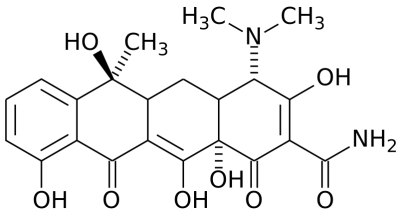


Figure 46-2. Effects of aminoglycosides on protein synthesis.

- Originally from *Streptomyces*; large family of derivatives
- Binds to 30s ribosomal subunit and: (A) interferes with initiation, ribosome locked at AUG start codon of mRNA (at higher concentrations); (B) premature termination of translation; (C) incorporation of incorrect amino acid ("X") leading to nonsense proteins.
- Used against gm(+) and some gm(-), less effective against anaerobes
- Outer membrane disruption (interacts w/ lipopolysaccharide) in Gram-negative bacteria leads to cell permeabilization and greater antibiotic uptake.
- Bacteriostatic or bactericidal
- Synergistic with beta-lactams (e.g. ampicillin + gentamycin)

Brunton LL, et al., *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition (2005)

Inhibition of bacterial protein synthesis: tetracyclines



tetracycline

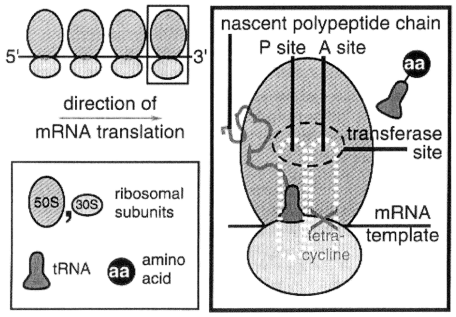
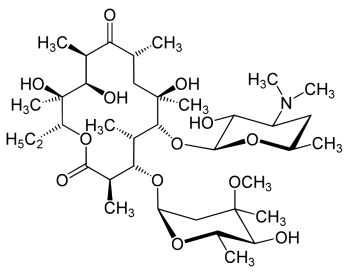


Figure 47-1. Inhibition of bacterial protein synthesis by tetracyclines.

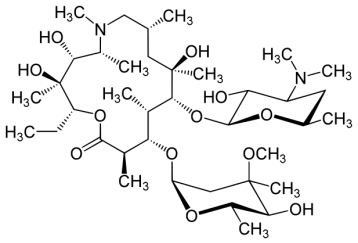
- Originally from *Streptomyces*; large family of derivatives
- Normally the aminoacyl-tRNA charged with the next amino acid would bind to the A site, but tetracycline binds to 30s ribosomal subunit to prevent binding of the amino-acylated tRNA to the "A" site; terminates peptide chain elongation.
- Gm(+) and gm(-)
- Bacteriostatic
- Resistance:
  - "protection proteins" (rescue ribosome function in presence of tetracyclines)
  - active efflux
  - rRNA mutation of binding site

Brunton LL, et al., *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition (2005)

Inhibition of bacterial protein synthesis: macrolides



erythromycin



azithromycin

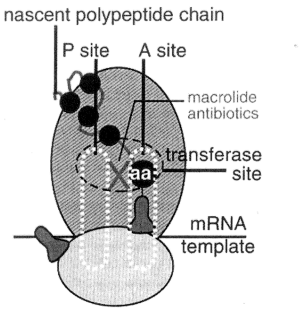


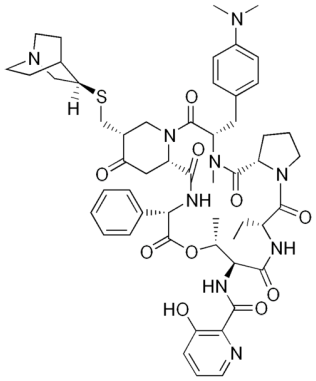
Figure 47-3. Inhibition of bacterial protein synthesis by erythromycin, clarithromycin, and azithromycin.

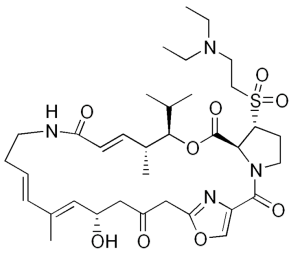
- Originally from Actinobacteria (*Saccharopolyspora erythraea*)
- 14, 15, or 16-membered lactone rings; some semi-synthetic
- Erythromycin, azithromycin (Zithromax), clarithromycin, etc.
- Binds to 50s ribosomal subunit, inhibits peptide elongation by preventing the nascent peptide chain from translocating from "A" to "P" sites
- Gm(+) and gm(-)
- Bacteriostatic
- Resistance:
  - Modify rRNA to weaken macrolide binding
  - Active efflux

Brunton LL, et al., *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition (2005)

Inhibition of bacterial protein synthesis: quinupristin/dalfopristin (Synercid)

quinupristin

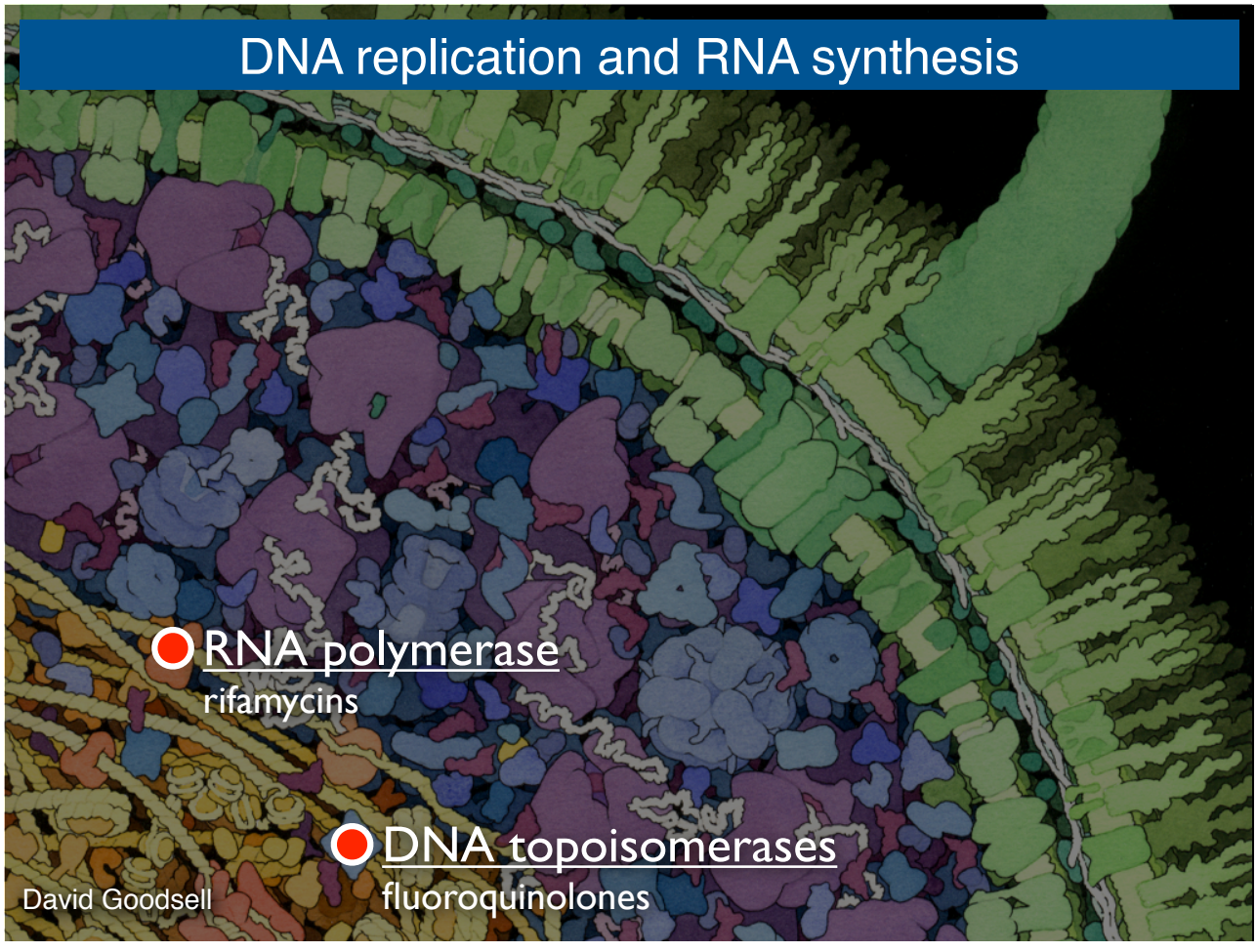




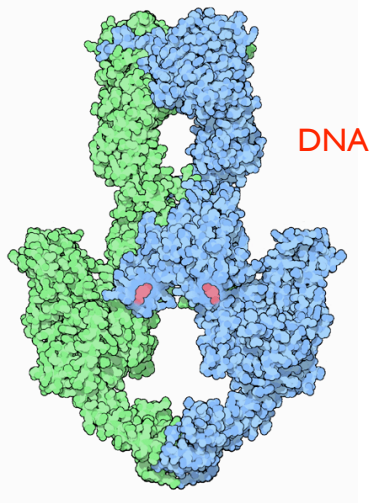
dalfopristin

- Synergistic action of two ribosome-binding compounds: quinupristin (30%), dalfopristin (70%)
- Used to treat vancomycin-resistant *Enterococcus faecium* infections (VRE), *Staph. aureus*
- Dalfopristin binds to 50s ribosomal subunit and induces a conformational change that allows quinupristin to bind, also to the 50s subunit
- They prevent peptidyl transfer (dalfopristin) and polypeptide chain elongation and release
- Individually bacteriostatic, but in combination bactericidial
- Inhibits P450, and exhibits a number of drug interactions

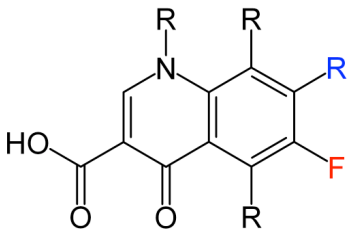
DNA replication and RNA synthesis



interfere with DNA replication: quinolones/fluoroquinolones



DNA gyrase

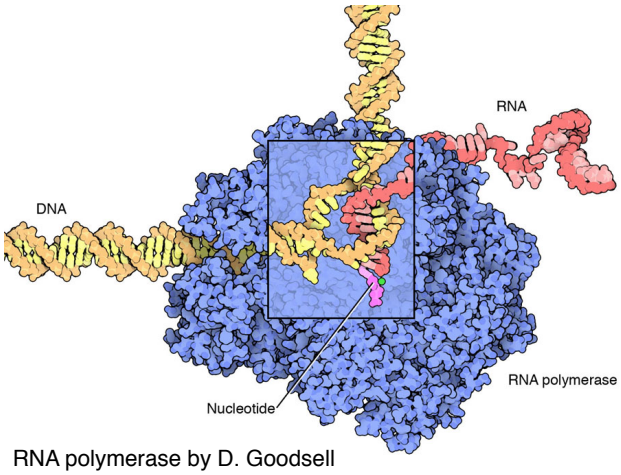


quinolone nucleus

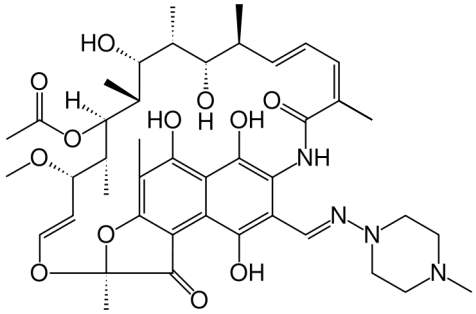
- During DNA replication, helicases and DNA polymerase introduce supercoiling into DNA, gyrase, a topoisomerase, relieves that strain, allowing replication to proceed.
- Block topoisomerases II (gyrase in gm(-)) and IV (in gm(+)): inhibits control of DNA supercoiling and hence gene regulation and nucleoid (chromosome) packaging in the cell
- Pass through porins; active against both gm(+)and gm(-)
- Bactericidal
- *E.g.* ciprofloxacin, levafloxacin

rendering of topoisomerase II by D. Goodsell

target RNA synthesis: rifamycins



RNA polymerase by D. Goodsell

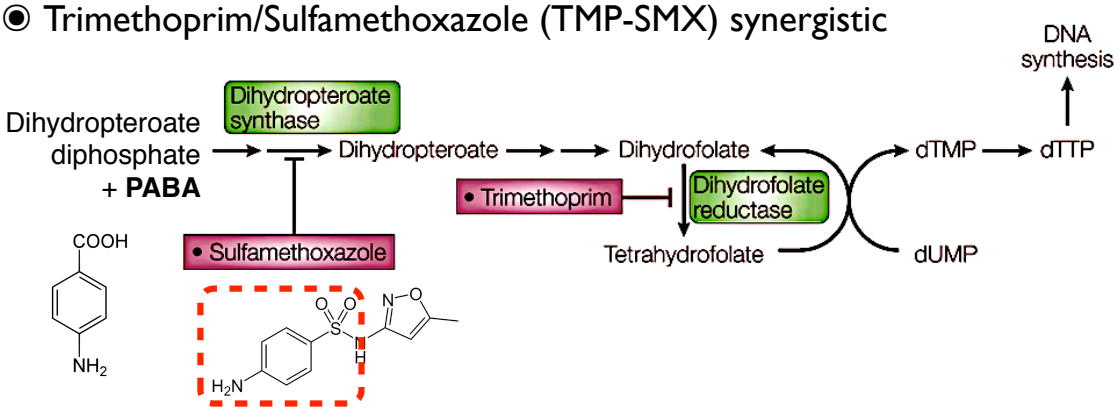


rifampin

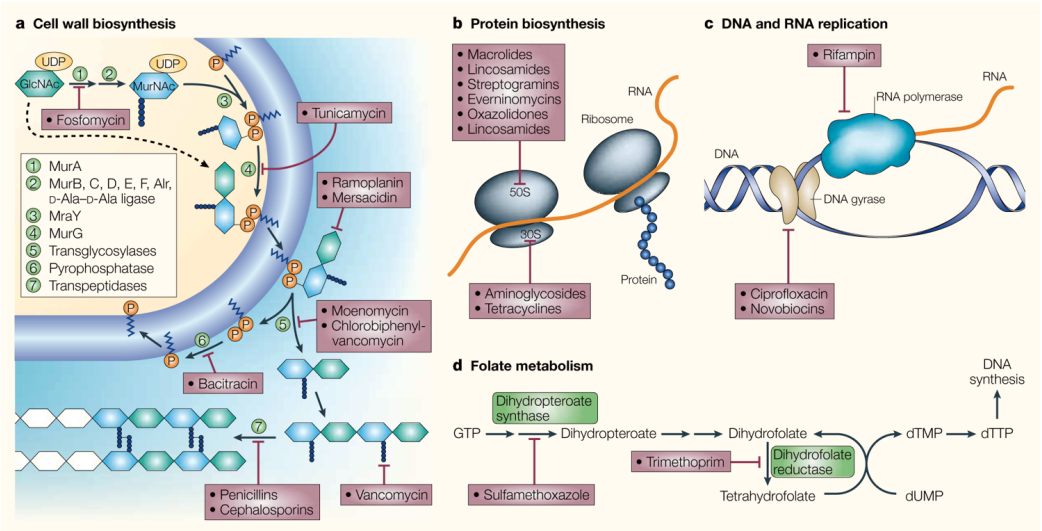
- From Actinobacteria *Amycolatopsis mediteranie*
- Binds to bacterial RNA polymerase, inhibit RNA synthesis by blocking chain elongation, blocks mRNA transcription
- Bactericidal
- Treatment of mycobacteria infection (TB, leprosy), some gm(+); drug can penetrate cell
- Some activity against HIV's reverse transcriptase (not clinically tested)

Other targets

- Inhibition of folate synthesis in bacteria:
  - Sulfa drugs (sulfonamides): an "antimetabolite" that inhibits dihydropteroate synthase by competitive binding with p-aminobenzoic acid (PABA)
  - Folate is a critical for DNA synthesis
  - Bacteria make their own folate, we do not synthesize our own folic acid, our cells import it
  - Prontosil, the original sulfonamide drug (actually a prodrug)
  - Trimethoprim/Sulfamethoxazole (TMP-SMX) synergistic



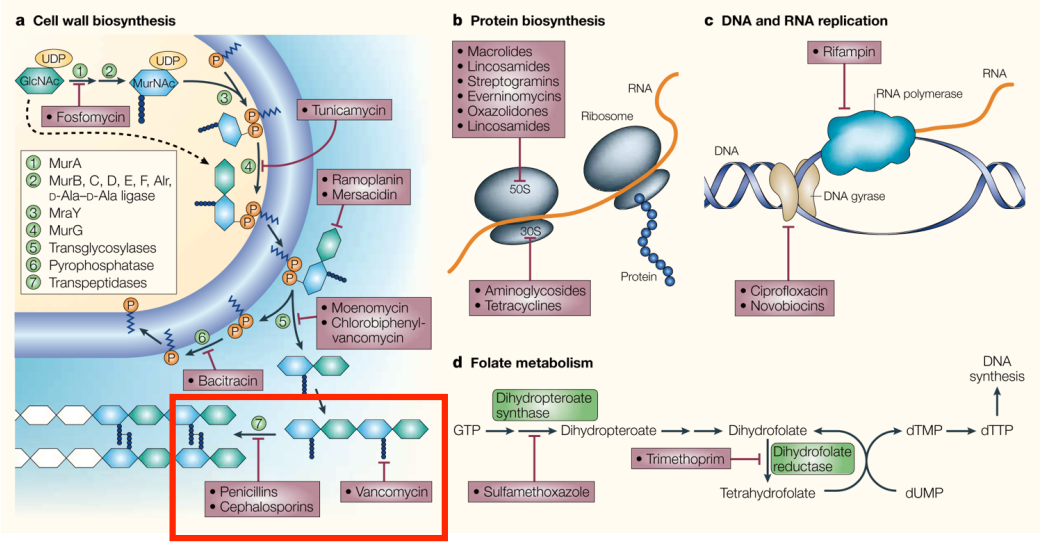
Summary of Mechanisms



a-d depict metabolic pathways in the cell that have been, or are proposed to be, targets for antibiotic action. **a** | Cell-wall biosynthesis: the intracellular steps of murein (peptidoglycan) biosynthesis are catalysed by the enzymes MurA–F and MurG (steps1–4). Peptidoglycan is a polymer of two hexoses (filled hexagons) — *N*-acetylglucosamine (GlcNac) and *N*-acetyl-muramic acid (MurNAc). Peptidoglycan units are transferred to a carrier lipid — bactoprenol-phosphate (orange circles) — which transports precursor molecules across the cell membrane, generating Lipids I and II. Sugars and phosphates are added by transglycosylation and pyrophosphorylation (steps 5 and 6), and finally, a peptide bond between the peptide chains is formed (step 7). Antibiotics that inhibit cell-wall synthesis are indicated. **b** | Protein biosynthesis: bacterial ribosomes comprise two subunits (30S and 50S) of rRNA and protein. Structural studies have identified the sites at which antibiotics bind[18, 19, 20, 21]. **c** | DNA and RNA replication: rifampin binds to RNA polymerase and prevents attachment of the polymerase to DNA, thereby inhibiting transcription. Ciprofloxacin and novobiocin bind to DNA gyrase, thereby preventing the introduction of supercoils in DNA. **d** | Folate metabolism: folate is necessary for the synthesis of thymine, which, in turn, is an essential component of DNA. The figure shows antibiotics that block steps in folate metabolism and therefore block the synthesis of thymine

Walsh C, *Nature Reviews Microbiology* (2003) 1:65-70

Summary of Mechanisms



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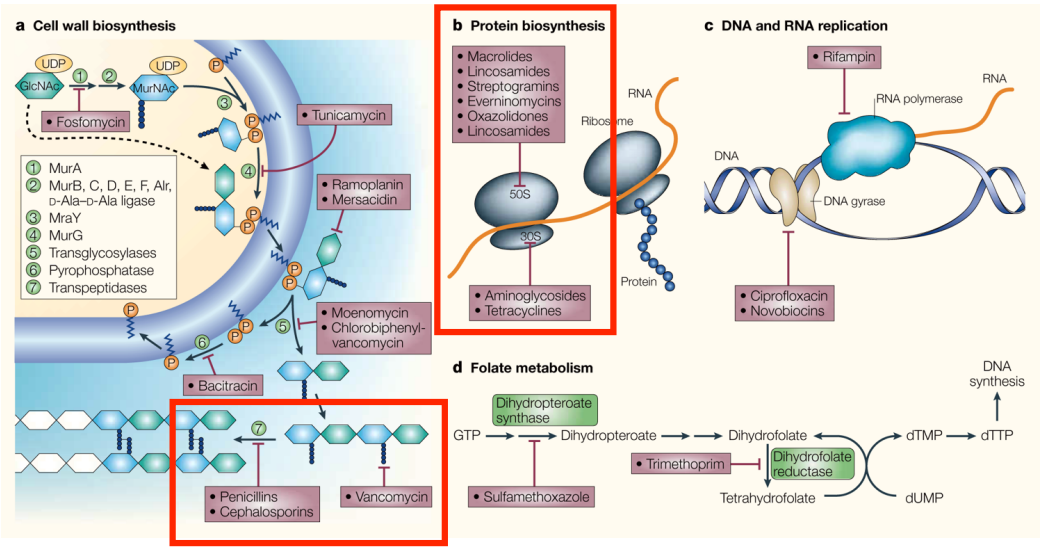
Summary of Mechanisms



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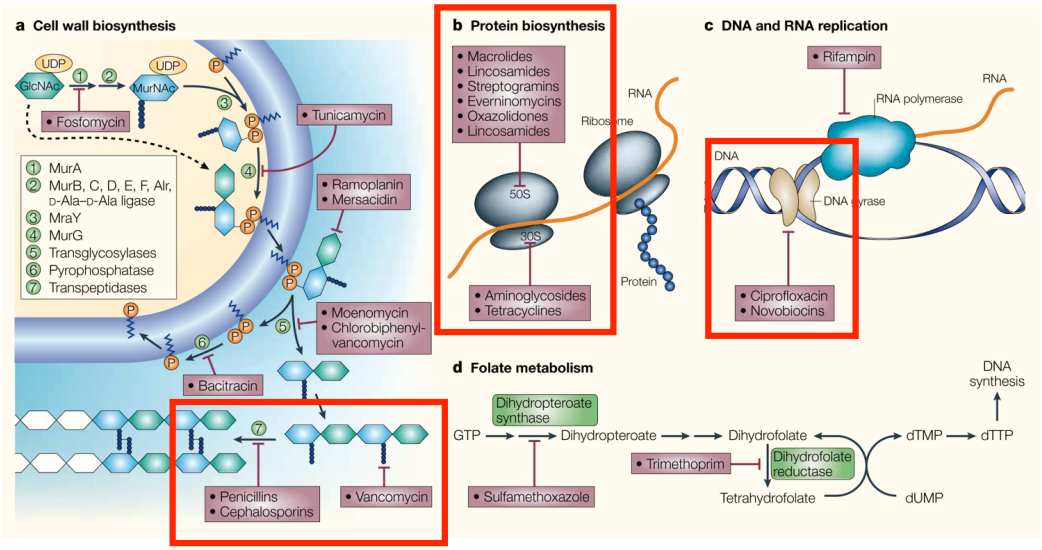
Summary of Mechanisms



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Walsh C, *Nature Reviews Microbiology* (2003) 1:65-70

Summary of Mechanisms

Table 20–1. Basic Mechanisms of Antibiotic Action

Antibiotic	Action
Disruption of Cell Wall	
Penicillins Cephalosporins Cephamycins Carbapenems Monobactams	Bind PBPs and enzymes responsible for peptidoglycan synthesis
β-lactam/β-lactamase inhibitor	Binds β-lactamases and prevents enzymatic inactivation of β-lactam
Vancomycin	Inhibits cross-linkage of peptidoglycan layers
Daptomycin	Causes depolarization of cytoplasmic membrane, resulting in disruption of ionic concentration gradients
Bacitracin	Inhibits bacterial cytoplasmic membrane and movement of peptidoglycan precursors
Polymyxins	Inhibit bacterial membranes
Isoniazid Ethionamide	Inhibit mycolic acid synthesis
Ethambutol	Inhibits arabinogalactan synthesis
Cycloserine	Inhibits cross-linkage of peptidoglycan layers
Inhibition of Protein Synthesis	
Aminoglycosides	Produce premature release of aberrant peptide chains from 30S ribosome
Tetracyclines	Prevent polypeptide elongation at 30S ribosome
Glycylcyclines	Bind to 30S ribosome and prevent initiation of protein synthesis
Oxazolidinone	Prevents initiation of protein synthesis at 50S ribosome
Macrolides Ketolides Clindamycin Streptogramins	Prevent polypeptide elongation at 50S ribosome
Inhibition of Nucleic Acid Synthesis	
Quinolones	Bind α subunit of DNA gyrase
Rifampin Rifabutin	Prevent transcription by binding DNA-dependent RNA polymerase
Metronidazole	Disrupts bacteria DNA (is cytotoxic compound)
Antimetabolite	
Sulfonamides	Inhibit dihydropteroate synthase and disrupt folic acid synthesis
Dapsone	Inhibits dihydropteroate synthase
Trimethoprim	Inhibits dihydrofolate reductase and disrupts folic acid synthesis

DNA, deoxyribonucleic acid; PBPs, penicillin-binding proteins; RNA, ribonucleic acid.

Murray PR, Rosenthal KS, Pfaller MA, (2009) Medical Microbiology 6th Edition

Beta-lactams

Table 20–2. Penicillins

Antibiotics	Spectrum of Activity
Natural penicillins: benzylpenicillin (penicillin G), phenoxymethyl penicillin (penicillin V)	Active against all β-hemolytic streptococci and most other species; limited activity against staphylococci; active against meningococci and most gram-positive anaerobes; poor activity against aerobic and anaerobic gram-negative rods
Penicillinase-resistant penicillins: methicillin, nafcillin, oxacillin, cloxacillin, dicloxacillin	Similar to the natural penicillins, except enhanced activity against staphylococci
Broad-spectrum penicillins: aminopenicillins (ampicillin, amoxicillin); carboxypenicillins (carbenicillin, ticarcillin); ureidopenicillins (piperacillin)	Activity against gram-positive cocci equivalent to the natural penicillins; active against some gram-negative rods, with piperacillin the most active
β-Lactam with β-lactamase inhibitor (ampicillin-sulbactam, amoxicillin-clavulanate, ticarcillin-clavulanate, piperacillin-tazobactam)	Activity similar to natural β-lactams, plus improved activity against β-lactamase-producing staphylococci and selected gram-negative rods; not all β-lactamases are inhibited; piperacillin/tazobactam is the most active

Table 20–3. Selected Examples of Cephalosporins and Cephamycins

Antibiotics	Spectrum of Activity
Narrow spectrum (cephalexin, cephalothin, cefazolin, cephapirin, cephradine)	Activity equivalent to oxacillin against gram-positive bacteria; some gram-negative activity (e.g., *Escherichia coli*, *Klebsiella*, *Proteus mirabilis*)
Expanded-spectrum cephalosporins (cefaclor, cefuroxime)	Activity equivalent to oxacillin against gram-positive bacteria; improved gram-negative activity to include *Enterobacter*, *Citrobacter*, and additional *Proteus* species
Expanded-spectrum cephamycins (cefotetan, cefoxitin)	Activity similar to expanded-spectrum cephalosporins but less susceptible to β-lactamases
Broad spectrum (cefixime, cefotaxime, ceftriaxone, ceftazidime)	Activity equivalent to oxacillin against gram-positive bacteria; improved gram-negative activity to include *Pseudomonas*
Extended spectrum (cefepime, cefpirome)	Activity equivalent to oxacillin against gram-positive bacteria; marginally improved gram-negative activity

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Beta-lactams

Table 20–4. Other β-Lactam Antibiotics

Antibiotics	Spectrum of Activity
Carbapenems (imipenem, meropenem, ertapenem)	Broad-spectrum antibiotics active against most aerobic and anaerobic gram-positive and gram-negative bacteria except oxacillin-resistant staphylococci, most *Enterococcus faecium*, and selected gram-negative rods (e.g., some *Burkholderia*, *Stenotrophomonas*, some *Pseudomonas*)
Monobactam (aztreonam)	Active against selected aerobic gram-negative rods but inactive against anaerobes or gram-positive cocci

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Inhibitors of Protein Synthesis

Table 20–5. Inhibitors of Protein Synthesis

Antibiotics	Spectrum of Activity
Aminoglycosides (streptomycin, kanamycin, gentamicin, tobramycin, amikacin)	Primarily used to treat infections with gram-negative rods; kanamycin with limited activity; tobramycin slightly more active than gentamicin against *Pseudomonas*; amikacin most active; streptomycin and gentamicin combined with cell-wall-active antibiotic to treat enterococcal infections; streptomycin active against mycobacteria and selected gram-negative rods
Aminocyclitol (spectinomycin)	Active against *Neisseria gonorrhoeae*
Tetracyclines (tetracycline, doxycycline, minocycline)	Broad-spectrum antibiotics active against gram-positive and some gram-negative bacteria (*Neisseria*, some Enterobacteriaceae), mycoplasmas, chlamydiae, and rickettsiae
Glycylcyclines (tigecycline)	Spectrum similar to tetracyclines but more active against gram-negative bacteria and rapidly growing mycobacteria
Oxazolidinone (linezolid)	Active against staphylococcus (including methicillin-resistant and vancomycin-intermediate strains), *Enterococcus*, *Streptococcus*, gram-positive rods, and *Clostridium* and anaerobic cocci; not active against gram-negative bacteria
Macrolides (erythromycin, azithromycin, clarithromycin)	Broad-spectrum antibiotics active against gram-positive and some gram-negative bacteria, *Neisseria*, *Legionella*, *Mycoplasma*, *Chlamydia*, *Chlamydophila*, *Treponema*, and *Rickettsia*; clarithromycin and azithromycin active against some mycobacteria
Ketolides (telithromycin)	Broad-spectrum antibiotic with activity similar to macrolides; active against some macrolide-resistant staphylococci and enterococci
Lincosamide (clindamycin)	Broad-spectrum activity against aerobic gram-positive cocci and anaerobes
Streptogramins (quinupristin-dalfopristin)	Primarily active against gram-positive bacteria; good activity against methicillin-susceptible and methicillin-resistant staphylococci, streptococci; vancomycin-susceptible and vancomycin-resistant *Enterococcus faecium* (no activity against *E. faecalis*); *Haemophilus*, *Moraxella*, and anaerobes (including *Bacteroides fragilis*); not active against Enterobacteriaceae or other gram-negative rods

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Quinolones

Table 20–6. Quinolones

Antibiotics	Spectrum of Activity
Narrow spectrum (nalidixic acid)	Active against selected gram-negative rods; no useful gram-positive activity
Broad spectrum (ciprofloxacin, levofloxacin, ofloxacin)	Broad-spectrum antibiotics with activity against gram-positive and gram-negative bacteria
Extended spectrum (gatifloxacin, clinafloxacin, moxifloxacin, trovafloxacin)	Broad-spectrum antibiotics with enhanced activity against gram-positive bacteria (particularly streptococci and enterococci) compared with early quinolones; activity against gram-negative rods similar to that of ciprofloxacin and related quinolones

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