This is one lecture in two parts. These learning objectives apply to both.

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After completing the preparation materials, students should be able to:

1. Identify the interrelationship between bacteriology and the pharmacology of antibiotics.
2. Illustrate the microbial characteristics of gram-positive, gram-negative, aerobic, and anaerobic bacteria that are relevant to antibiotic mechanisms and therapy.
3. Apply the structure-activity relationship of the beta-lactam antibiotics, vancomycin, and daptomycin to their mechanisms of **action**, antibacterial **spectrums**, and mechanisms of **resistance**.
4. Describe the class and drug-specific pharmacokinetics properties of the beta-lactams, vancomycin, and daptomycin.
5. Apply the pharmacokinetics-pharmacodynamics (PK-PD) profile of the beta-lactams, vancomycin, and daptomycin to dosing considerations for optimizing therapy.
6. List the class and drug-specific adverse effects of the beta-lactams, vancomycin, and daptomycin.
7. Relate the selection of antibiotic therapy for the individual patient to the treatment goals, the specific infectious bacteria targeted by the drugs, and individual patient factors.

Mechanisms
Mechanisms
Mechanisms

Class Pharmacokinetic Properties of Cephalosporins

Typical of the beta-lactams class effects.

	General Properties	Comments
A	IM or IV; oral	• **CSF penetration poor** **Exceptions:** Better CSF penetration with cefuroxime, cefotaxime, ceftriaxone, ceftazidime, cefepime • Note: Higher CSF concentrations are achieved when meninges are inflamed.
D	Distribute in most body fluids and tissues including • bile and gallbladder • liver and kidneys • bone and synovial fluid • cross placenta, enter breast milk	
E	Glomerular filtration and secretion of unchanged drug	• 3rd-gen **ceftriaxone** biliary excretion Dose adjustment for renal impairment not required. • Current advanced-gen agents are excreted in urine as active drug
t½	Average: ~1 hour to 8 hours depending on agent **Ceftriaxone** 1x daily dose (2x daily for CNS infections)	

Important

Important

First-generation Cephalosporins' Narrow Spectrum of Activity

Remember the potential for acquired resistance due to TEM/SHV beta-lactamases and KPC.

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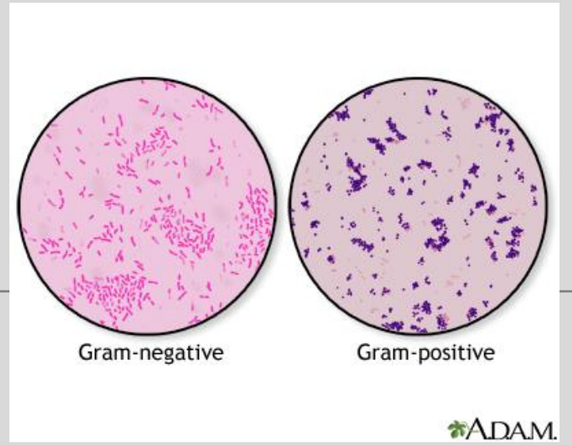
Gram-positive	Gram-negative aerobes	Spirochetes	Atypicals*
Cocci • Streptococcus pneumoniae • Group A strep (GAS) • S. aureus: MSSA • S. epidermidis: MSSE	Pseudomonas aeruginosa Enterobacterales (rods) (facultative anaerobes) • Proteus mirabilis • Escherichia coli • Klebsiella spp only these	Gram-negative, thin-walled spiral-shaped flexible organisms • Treponema pallidum • Leptospira • Borrelia burgdorferi	Bacteria remain colorless when gram-stained • Mycoplasma • Chlamydiaceae • Legionella • Rickettsia STD • Chlamydia trachomatis *Not visible on Gram stain
✳Cefazolin is the preferred cephalosporin for treatment of penicillinase-producing *S. aureus* infections (MSSA).	Respiratory • Haemophilus influenzae • Moraxella catarrhalis • Neisseria meningitidis STD • Neisseria gonorrhoeae		
Obligate G+ Anaerobic • Clostridia spp low activity • Clostridioides difficile	Obligate G– Anaerobic • Bacteroides fragilis		



Beta-lactams are ineffective in the treatment of infection caused by the atypicals.

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Second-generation Cephalosporins' Moderate Spectrum of Activity

Remember the potential for acquired resistance (including by KPCs).

Gram-positive

Cocci
- Streptococcus pneumoniae
- Group A strep (GAS)
- S. aureus: MSSA
- S. epidermidis: MSSE
- Enterococcus faecalis
- Enterococcus faecium

Bacillus (rod)
- C. diphtheriae
- Listeria monocytogenes

Obligate G+ Anaerobic
- Clostridia spp low activity
- Clostridioides difficile

Gram-negative aerobes

Pseudomonas aeruginosa

Enterobacterales (rods)

(facultative anaerobes)
- Proteus mirabilis
- Escherichia coli
- Klebsiella spp

and a few others

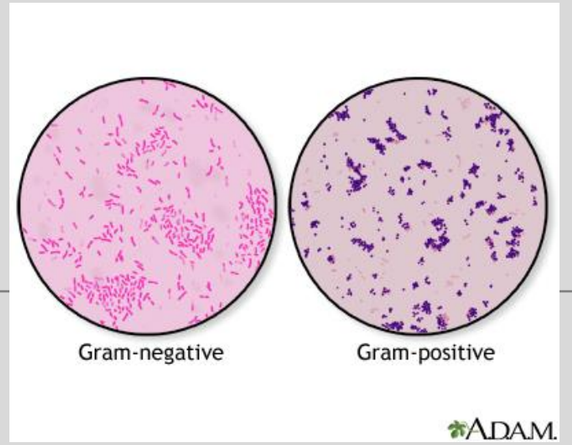
Respiratory
- Haemophilus influenzae
- Moraxella catarrhalis
- Neisseria meningitidis

STD
- Neisseria gonorrhoeae

Obligate G– Anaerobic
- Bacteroides fragilis
  cephamycins only (cefoxitin)

Spirochetes

Gram-negative, thin-walled spiral-shaped flexible organisms
- Treponema pallidum
- Leptospira
- Borrelia burgdorferi



Atypicals*

Bacteria remain colorless when gram-stained
- Mycoplasma
- Chlamydiaceae
- Legionella
- Rickettsia

STD
- Chlamydia trachomatis

*Not visible on Gram stain

Beta-lactams are ineffective in the treatment of infection caused by the atypicals.

Third-generation Cephalosporins' Extended-Spectrum Activity

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Remember: ESBLs and KPCs confer resistance.

Gram-positive

Cocci
- Streptococcus pneumoniae
- Group A strep (GAS)
- S. aureus: MSSA
- S. epidermidis: MSSE
- Enterococcus faecalis
- Enterococcus faecium

Bacillus (rod)
- C. diphtheriae
- Listeria monocytogenes

Obligate G+ Anaerobic
- Clostridia spp low activity
- Clostridioides difficile

Gram-negative aerobes

Pseudomonas aeruginosa
ceftazidime, ceftolozane-tazo only

Enterobacterales (rods)

(facultative anaerobes)
- Proteus mirabilis
- Escherichia coli
- Klebsiella spp

and many others

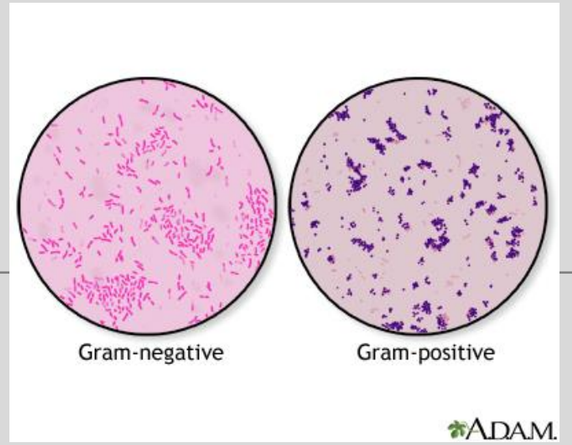
Respiratory
- Haemophilus influenzae
- Moraxella catarrhalis
- Neisseria meningitidis

STD
- Neisseria gonorrhoeae

Obligate G– Anaerobic
- Bacteroides fragilis

Spirochetes

Gram-negative, thin-walled spiral-shaped flexible organisms
- Treponema pallidum
- Leptospira
- Borrelia burgdorferi



Atypicals*

Bacteria remain colorless when gram-stained
- Mycoplasma
- Chlamydiaceae
- Legionella
- Rickettsia

STD
- Chlamydia trachomatis

*Not visible on Gram stain

Beta-lactams are ineffective in the treatment of infection caused by the atypicals.

Fourth-generation: Cefepime's Broad Spectrum of Activity

Remember: ESBLs and KPCs confer resistance.

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Gram-positive

Cocci
- Streptococcus pneumoniae
- Group A strep (GAS)
- S. aureus: MSSA
- S. epidermidis: MSSE
- Enterococcus faecalis
- Enterococcus faecium

Bacillus (rod)
- C. diphtheriae
- Listeria monocytogenes

Obligate G+ Anaerobic
- Clostridia spp low activity
- Clostridioides difficile

Gram-negative aerobes

Pseudomonas aeruginosa

Enterobacterales (rods)

(facultative anaerobes)
- Proteus mirabilis
- Escherichia coli
- Klebsiella spp

Respiratory
- Haemophilus influenzae
- Moraxella catarrhalis
- Neisseria meningitidis

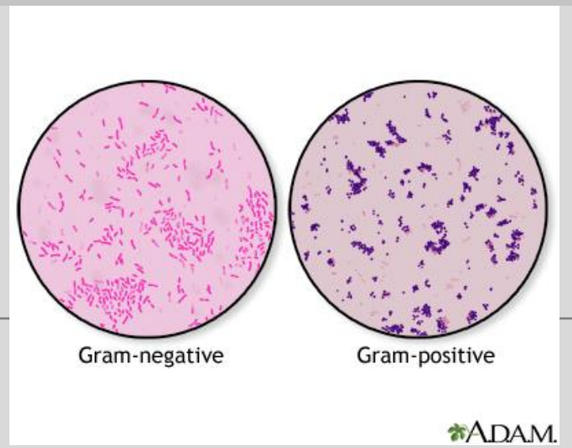
STD
- N. gonorrhoeae-cefepime not approved for use

and more: stable to many β-lactamases

Obligate G– Anaerobic
- Bacteroides fragilis

Spirochetes

Gram-negative, thin-walled spiral-shaped flexible organisms
- Treponema pallidum
- Leptospira
- Borrelia burgdorferi



Atypicals*

Bacteria remain colorless when gram-stained
- Mycoplasma
- Chlamydiaceae
- Legionella
- Rickettsia

STD
- Chlamydia trachomatis

*Not visible on Gram stain

Beta-lactams are ineffective in the treatment of infection caused by the atypicals.

Ceftriaxone and cefotaxime have the same spectrum of activity, are both administered parenterally, and are widely distributed in body fluids and tissues, including the cerebral spinal fluid.

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Know this

What are the main differences between ceftriaxone and cefotaxime?

Ceftriaxone is eliminated via the biliary system, therefore: 1. It is useful in treating acute cholecystitis. 2. It can cause biliary sludge or gallstone formation.	**Cefotaxime** is excreted in urine.
Ceftriaxone does not need dose adjustment in patients with renal impairment. (unless the patient has concomitant hepatic insufficiency).	**Cefotaxime** dose should be reduced in patients with severe renal impairment. (CrCl <20 mL/min/1.73m^2).
Ceftriaxone's longer half-life allows 1x daily dosing. (2x daily for CNS infections).	Cefotaxime's short half-life requires frequent dosing (every 6 to 8 hours).
Neonates	
• Hyperbilirubinemia → kernicterus **Ceftriaxone** is highly bound to plasma proteins and can displace unconjugated bilirubin, which can lead to kernicterus (encephalopathy) in the newborn. • Precipitation of Ca^{2+}-containing solutions → lung and kidney damage in neonates	**Cefotaxime is preferred in neonates.** Cefotaxime does not displace bilirubin from plasma proteins or precipitate calcium and is preferred for neonates. **Cefotaxime does not cause kernicterus**. Cefotaxime does not form drug-calcium precipitate.

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Adverse effects of Cephalosporins

In addition to class effects…

Injection reactions: I.M. painful injection; I.V. thrombophlebitis

Rare but serious: Renal tubular necrosis; Interstitial nephritis

Ceftriaxone

- Biliary stasis / cholestatic hepatitis

Neonates:

- Hyperbilirubinemia → kernicterus
- Precipitation of Ca^{2+}-containing solutions → lung and kidney damage in neonates

Cefotetan (cephamycin) (Board-relevant)

- Hypoprothrombinemia

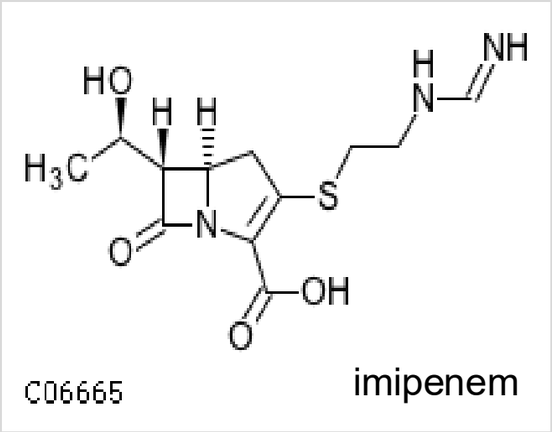
Vitamin K administration prevents this AE

- Disulfiram-like reaction with alcohol consumption

Cefotaxime has the same actions as ceftriaxone but does not displace bilirubin from plasma proteins or precipitate calcium and is preferred for neonates.

Carbapenems

- ✳ Imipenem-cilastatin*
- ✳ Imipenem-cilastatin-relebactam
- ✳ Meropenem
- ✳ Meropenem-vaborbactam
  - Ertapenem
  - Doripenem (not available in US)



Important note:

*Cilastatin inhibits dehydropeptidase I in the brush border of proximal renal tubules.
Dehydropeptidase I inactivates imipenem.
Cilastatin blocks degradation of imipenem, which increases imipenem concentrations in urine.

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Carbapenem's Broad Spectrum of Activity

Strike through = once susceptible but now significant resistance

Gram-positive

Cocci

- Streptococcus pneumoniae
- Group A strep (GAS)
- Staphylococcus aureus
- Staph. epidermidis
- Enterococcus faecalis
- Enterococcus faecium

Bacillus (rod)

- C. diphtheriae
- Listeria monocytogenes

Gram-negative aerobes

Pseudomonas aeruginosa (not ertapenem)

Enterobacterales (rods)

(facultative anaerobes)

- Escherichia coli
- Proteus mirabilis
- Klebsiella spp
- and many more

stable to many β-lactamases

Respiratory

- Haemophilus influenzae
- Moraxella catarrhalis
- Neisseria meningitidis

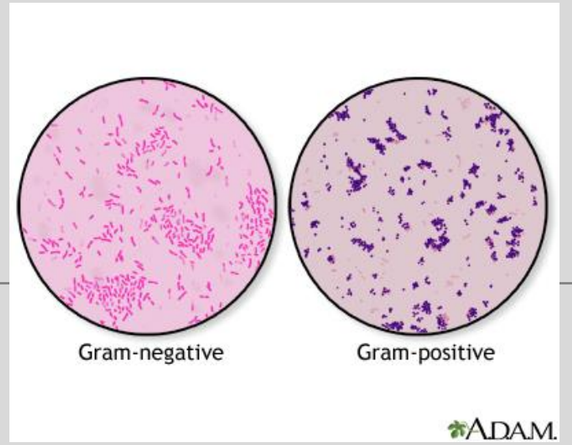
STD: Neisseria gonorrhea

Spirochetes

Gram-negative, thin-walled spiral-shaped flexible organisms

Not extensively tested against spirochetes.

- Treponema pallidum
- Leptospira
- Borrelia burgdorferi



Atypicals*

Bacteria remain colorless when gram-stained

- Mycoplasma
- Chlamydiaceae
- Legionella
- Rickettsia

STD

- Chlamydia trachomatis

*Not visible on Gram stain

Beta-lactams are ineffective in the treatment of infection caused by the atypicals.

Obligate G+ Anaerobic

- Clostridia spp
- Clostridioides difficile

Obligate G– Anaerobic

- Bacteroides fragilis

Carbapenems: Broad spectrum of activity | Some resistance

- gram-positive and gram-negative
- aerobic and anaerobic
  - Penicillin-resistant *S. pneumonia*
  - Penicillin-sensitive *Enterococcus faecalis* (but NOT *E. faecium*)
- stable to most β-lactamases
  - But not carbapenemases or metallo-β-lactamases

Treatment of choice for:

- ESBL-expressing Enterobacterales
- Anaerobes, including *B. fragilis*
- *Pseudomonas aeruginosa* (resistance may arise during therapy)
  - except ertapenem, which is ineffective against *Pseudomonas*

mnemonic: EE – except ertapenem

<u>Acquired resistance</u>

Class A KPC: *K. pneumoniae* carbapenemases

Class B metallo-β-lactamases

- **hydrolyze penicillins, cephalosporins, carbapenems, and aztreonam** (monobactam)
- **not inhibited by β-lactamase inhibitors**

<u>Intrinsic resistance</u>

- MRSA
- *Enterococcus faecium*
- *Clostridioides difficile*
- *Stenotrophomonas maltophilia* (a multidrug resistant gram-negative rod – MDR GNB)

Carbapenems: Treatments and Adverse Effects

Therapeutic Uses

Empiric treatment of serious infections in hospitalized patients who have recently received other beta-lactam antibiotics:

- **lower respiratory**
- **intra-abdominal**
- **pelvic**
- **skin, soft tissue, bone, joint**

caused by:

- **gram-positive bacteria**
- **Enterobacterales**
- ***Pseudomonas aeruginosa*** (except ertapenem)
- **anaerobes including *B. fragilis***

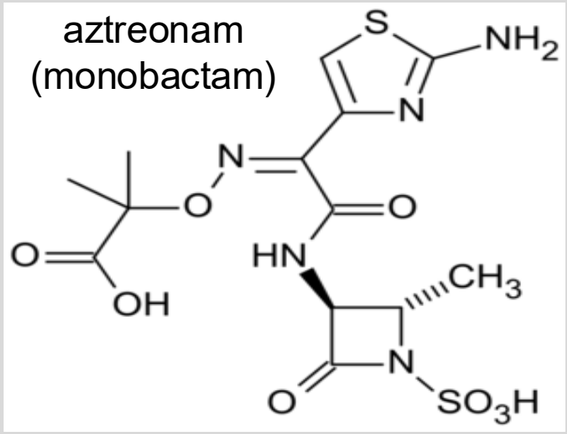
Adverse Effects

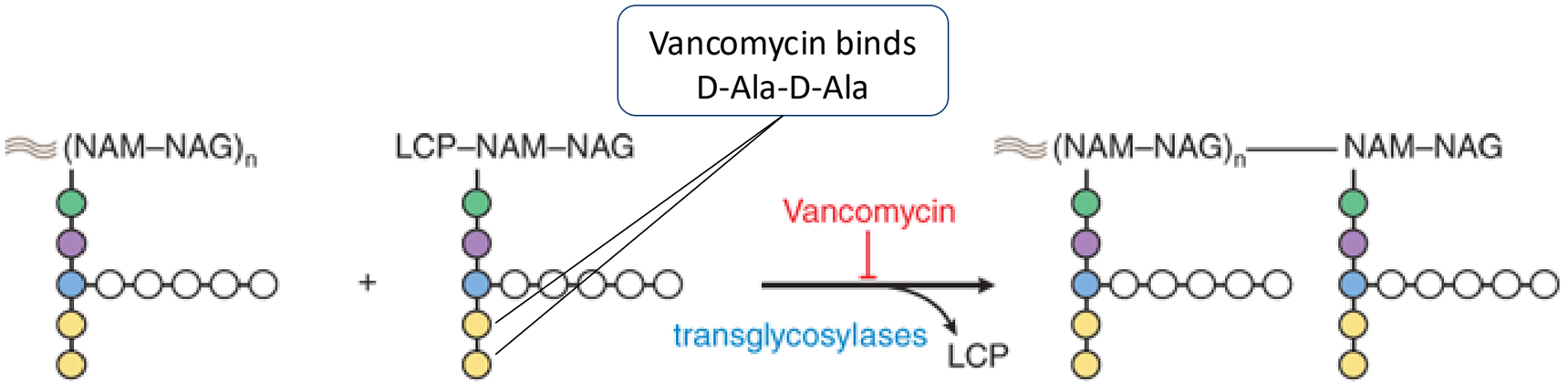
In addition to hypersensitivity reactions and other side effects common to the class:

- **Seizures:** greatest risk with the use of imipenem
  - **patients with renal insufficiency are at increased risk**
- **Hematologic:** Bleeding, agranulocytosis, leukopenia (reported)
- **GI:** Nausea, vomiting, diarrhea are relatively common
- ***C. difficile* superinfection**

Monobactam

* Aztreonam

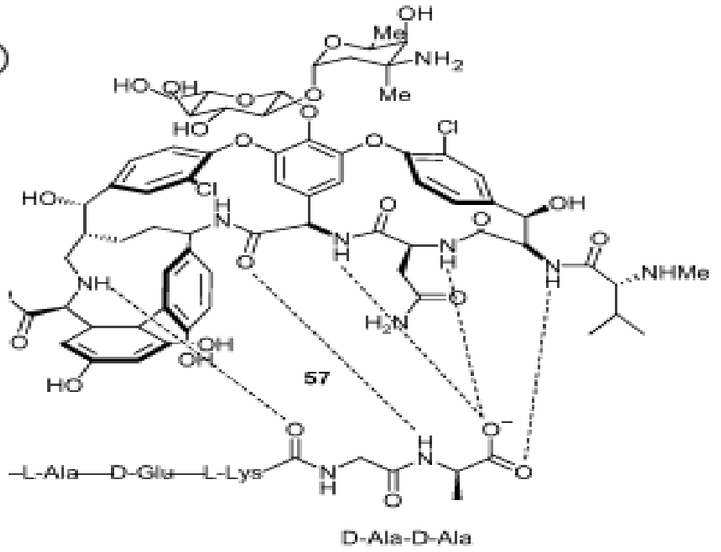




KEY

- L–Alanine
- D–Glutamate
- L–Lysine
- D–Alanine
- Glycine

NAM = N–Acetylmuramic acid
NAG = N–Acetylglucosamine
LCP = Lipid carrier bactoprenol
≈ cell wall



of vancomycin to the D-Ala-D-Ala terminus of recursor.

Inhibition of bacterial cell wall synthesis by glycopeptides such as vancomycin. Vancomycin inhibits the polymerization or transglycosylase reaction by binding to the D-alanyl-D-alanine terminus of the cell wall precursor unit attached to its lipid carrier and blocks linkage to the glycopeptide polymer (indicated by the subscript n). These $(NAM–NAG)_n$ peptidoglycan polymers are located within the cell wall.

vanA and vanB-type resistance is due to expression of enzymes that modify cell wall precursor by substituting a terminal D-lactate for D-alanine → D-Ala-D-Lac, reducing affinity for vancomycin by 1000-fold.

Vancomycin Cautions

Adverse Effects

- Nephrotoxicity: Acute kidney injury (usually in patients with multiple risk factors)
- Non-immune anaphylactoid infusion-related reaction
- Hypersensitivity reaction (immunogenic)
- Phlebitis at injection site
- Neutropenia with prolonged therapy (7 to 12 days)
- Ototoxicity (rare): hearing loss, vertigo

Drug Interactions

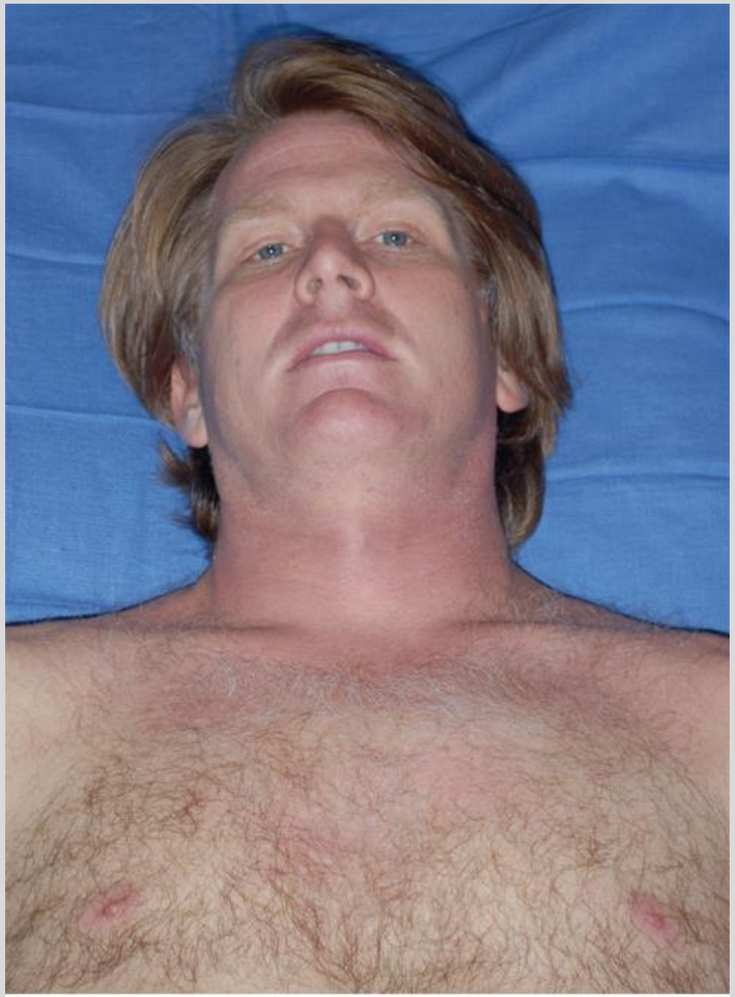
Increased risk when drugs with the same toxicities are given together:

- Nephrotoxicity: Aminoglycosides, loop diuretics, amphotericin B, NSAIDs

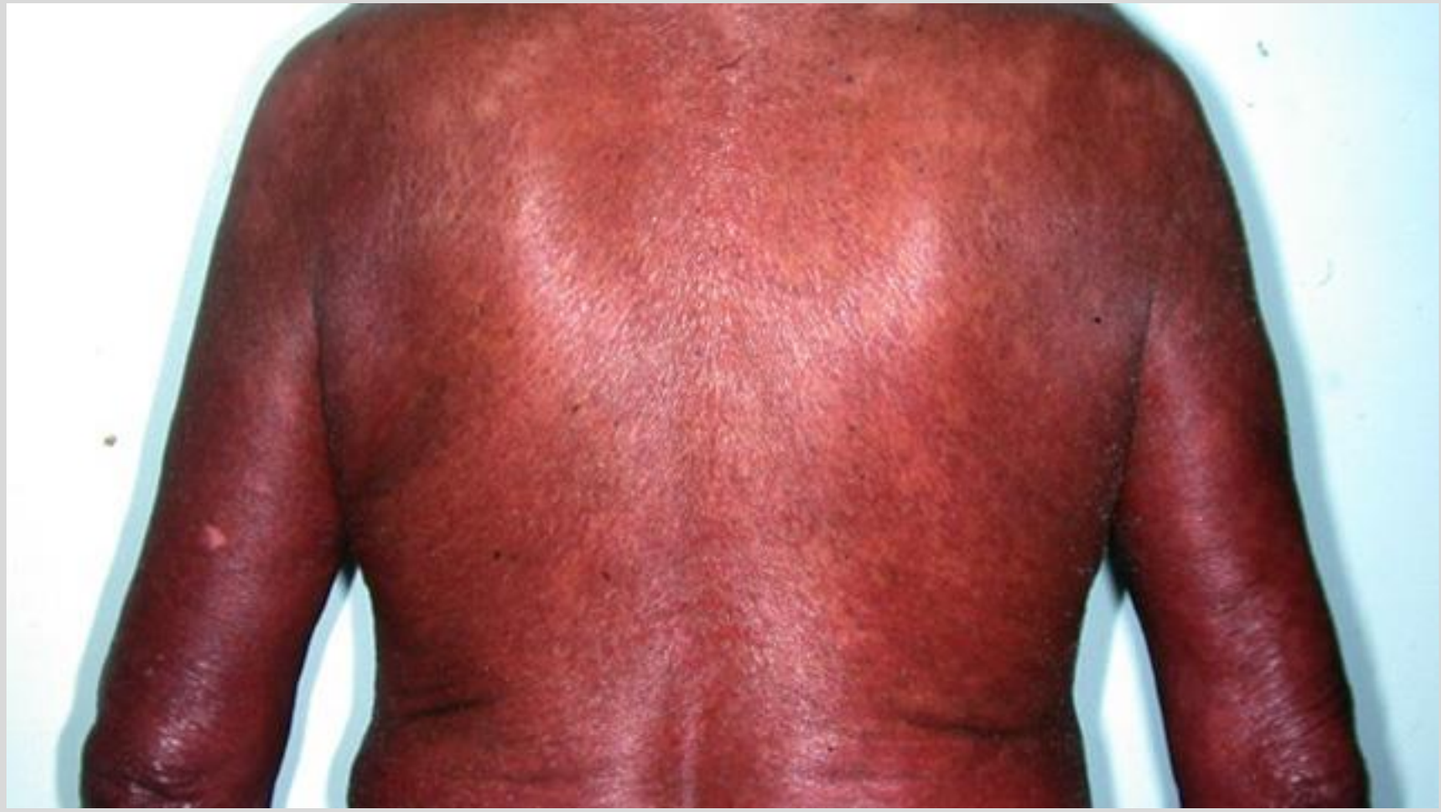
Mitigation: Monitor vancomycin serum levels. Monitor for signs/symptoms of adverse effects.

Non-immune anaphylactoid infusion-related reaction ("red man syndrome")

Flushing on face, neck and trunk with pruritis and hypotension are manifestations that may be seen with high concentration or rapid IV vancomycin infusion.



Source: K.J. Knoop, L.B. Stack, A.B. Storrow, R.J. Thurman:
The Atlas of Emergency Medicine, 4th Edition,
www.accessemergencymedicine



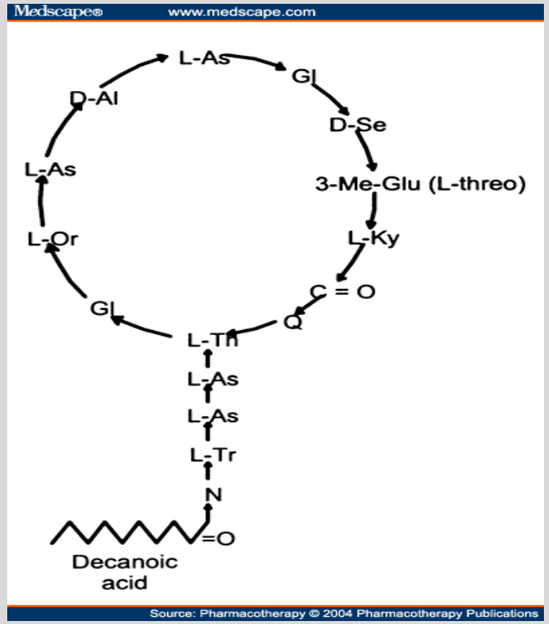
Left Photo: DermNet New Zealand

Right photo: The Atlas of Emergency Medicine, 4e, 2016: TOXICOLOGICAL CONDITIONS Figure 17.54; Photo contributor: R. Jason Thurman, MD.

Cell Membrane Active Antibiotics

Cyclic lipopeptide

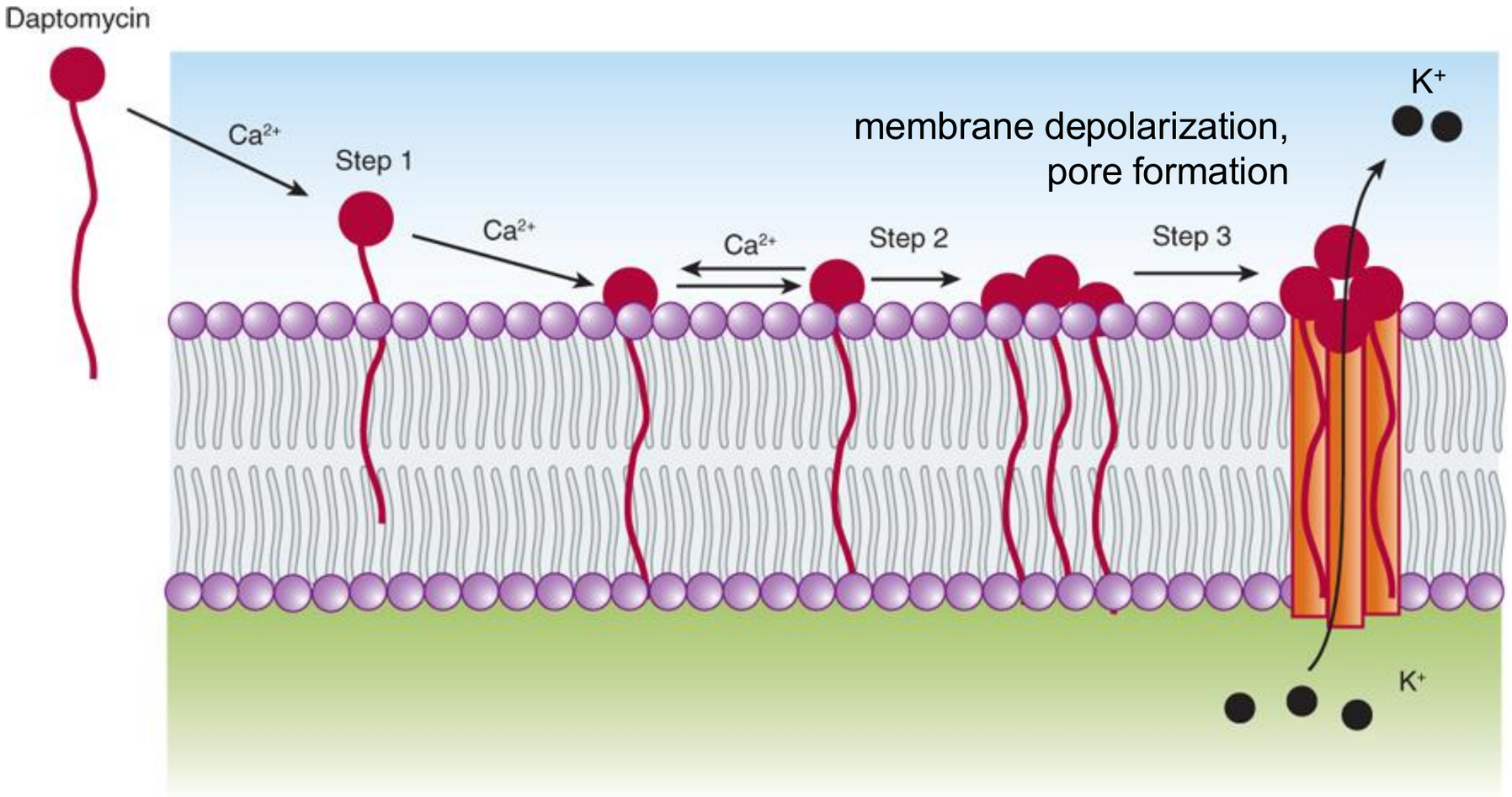
✳ Daptomycin



Other cell membrane-active drugs:

Polymyxin B: Damages bacterial cell membrane by binding to phospholipids, causing permeability and leakage of intracellular contents and cell death. Treatment of serious multidrug resistant gram-negative infections. Nephro- and neurotoxic.

Colistimethate: Hydrolyzed to colistin, which acts as a detergent that damages cell membranes causing leakage of intracellular substances in cell death. Treatment of serious multidrug resistant gram-negative infections. Nephro- and neurotoxic, causes bronchoconstriction.



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 rapid cell death. Cell lysis does not occur.**

Daptomycin Cautions

- Myopathy
- Eosinophilic pneumonia
  - Respiratory failure if not recognized
  - Develops 10 days to 4 weeks after therapy initiation
- Hypersensitivity reactions reported, immediate and delayed, with skin rash and systemic symptoms

- Pregnancy: Limited information
- Excreted in breast milk
- Pediatrics: dosing guidance is listed in the drug monograph

Drug-drug interaction:

- **HMG CoA-reductase inhibitors** (statins): Potential for additive muscle toxicity. Management: Consider temporarily stopping the HMG CoA-reductase inhibitor during daptomycin therapy.

Management → Monitor:

CK levels and for signs/symptoms of new onset or worsening muscle pain/weakness, peripheral neuropathy, fever/dyspnea/infiltrates on chest imaging studies, hypersensitivity reactions including drug reaction with eosinophilia and systemic symptoms (DRESS)

Summary of:

Cephalosporins

Carbapenems

Monobactam

Vancomycin

Daptomycin

- Cephalosporins are beta-lactam antibiotics structurally and functionally related to penicillins.
- Cephalosporins are classed as first-, second-, third-, fourth-, and advanced-generation based largely on their bacterial susceptibility and resistance to beta-lactamases.

The following descriptions refer to susceptible bacteria. Resistance is increasing.

- First-generation: Gram-positive bacteria, including MSSA, and modest activity against gram-negative *Proteus, E. coli,* and *Klebsiella* (PEcK). Cefazolin is used for surgical prophylaxis and a variety of susceptible infections
- Second-generation: Weaker activity than first-generation cephalosporins against gram-positive organisms and better activity against PEcK and gram-negative respiratory pathogens *H. influenzae* and *M. catarrhalis*. Delayed response and treatment failures have occurred. Third-generation cephalosporins are generally preferred.
- Cephamycins, a subgroup of the second-generation agents, have a spectrum of action like the other second-generation agent PLUS they are effective against the MDR gram-negative obligate anaerobe, *Bacteroides fragilis*. Cefoxitin and cefotetan may be used for surgical prophylaxis but susceptibility is decreasing over time.
- Third-generation: This group is important in the treatment of infectious diseases. They have enhanced activity against gram-negative Enterobacterales (enteric, facultative anaerobic gram-negative bacilli), β-lactamase producing strains of *H. influenzae* and *N. gonorrhoeae*, and gram-positive streptococci including *Streptococcus pneumoniae* and staphylococci (less active against MSSA than first-generation agents). They are used in the treatment of a wide variety of infections.

- The carbapenems, imipenem-cilastatin, meropenem, and ertapenem, are broad spectrum beta-lactam antibiotics for the empiric treatment of serious complicated infections caused by β-lactamase producing gram-positive and gram-negative pathogens, including *Pseudomonas aeruginosa* (except ertapenem) and *B. fragilis*. They are inactivated by KPC carbapenemases and metallo-beta-lactamases. Relebactam and vaborbactam co-formulated with imipenem-cilastatin and meropenem, respectively, inactivate the KPCs, restoring the activity of the antibiotics.
- Carbapenems are administered IV and renally excreted. Cilastatin, coformulated with imipenem, inhibits dehydropeptidase I in the proximal tubule brush border, which prevents inactivation of imipenem by this enzyme → adequate imipenem levels are achieved in urine. Carbapenems are useful for the treatment of serious and complicated infections of various organ systems.
- High concentrations of imipenem may induce seizures.
- Aztreonam is a parenteral monobactam with aerobic gram-negative activity, including *P. aeruginosa*. It is stable to many β-lactamases but is inactivated by ESBLs, KPCs, and AmpC β-lactamases. It is available for oral inhalation in the treatment of *P. aeruginosa* infection of the lung in cystic fibrosis patients. Aztreonam has low immunogenic potential and is not cross-reactive with other beta-lactams except ceftazidime (structural similarity). Aztreonam is not used for empiric treatment because of its limited spectrum of activity. It has no activity against gram-positive bacteria.

Summary of β-lactams Adverse Effects

Cholestatic jaundice	Beta-lactams excreted in bile (ceftriaxone)
Interstitial nephritis reported rarely:	Methicillin (withdrawn from market) Nafcillin; Oxa-; Dicloxa-; Cloxacillin
Decreased coagulation	Cefotetan (pts w. hypoprothrombinemia)
Seizures	High-dose, especially Penicillin and Imipenem
Electrolyte imbalances	Drugs formulated as Na+ and K+ salts
Jarisch-Herxheimer reaction	Inflammatory response to dying *Treponema pallidum* (syphilis); self-limited
Disulfiram-like reaction with concomitant alcohol use	Cefotetan (side chain inhibits aldehyde dehydrogenase $\rightarrow\uparrow$ plasma aldehyde levels)
Secondary infection (eg C. difficile; Candidiasis)	All antibiotics can cause superinfection.

- Vancomycin is a glycopeptide that binds the D-Ala-D-Ala terminal on the lipid carrier-NAG-NAM-pentapeptide cell wall precursors, which inhibits the polymerization – transglycosylation – of the glycopeptide subunits, the penultimate step in bacterial cell wall synthesis.
- VanA and vanB gene clusters confer resistance in strains of enterococci (VRE) and staphylococci (VRSA) due to expression of enzymes that modify cell wall precursor by substituting a terminal D-lactate for D-alanine → D-Ala-D-Lactate with reduced affinity for vancomycin by 1000-fold. *S. aureus* with intermediate resistance results from sequestration of vancomycin in an unusually thickened cell wall due to increased numbers of D-Ala-D-Ala residues.
- Vancomycin has only gram-positive activity, including MRSA. It is an important antibiotic in the management of serious infections by susceptible MRSA, *Enterococcus faecalis*, and *E. faecium*. Oral vancomycin, which is not absorbed from the GI tract, is used in the treatment of *C. difficile* infection. It may also be used in penicillin-allergic patients to treat susceptible gram-positive infections.
- Vancomycin has a T>MIC PK-PD profile and a short, organism-specific post-antibiotic effect. Clinical effect is associated with 24h-AUC/MIC ratio. It is bactericidal against MRSA but bacteriostatic against enterococci.
- Non-immune anaphylactoid infusion-related reaction with flushing of the upper torso, neck, and face (“red man syndrome”) can occur with too-rapid infusion. Adverse effects are nephrotoxicity and injection site reactions. Risk increases when used with other nephrotoxic drugs. Additional potential toxicities include hypersensitivity reactions, immune thrombocytopenia, peripheral neuropathy, neutropenia, and ototoxicity.

- Daptomycin is a cyclic lipopeptide that binds to bacterial plasma membrane via calcium-dependent insertion of its lipid tail, resulting in depolarization of the cell membrane with potassium efflux. DNA, RNA, and protein synthesis arrest result in rapid cell death.
- Daptomycin has only gram-positive activity with a spectrum similar to vancomycin's. Daptomycin is active against vancomycin-resistant strains of enterococci and staphylococci.
- Daptomycin is an alternative to vancomycin for infections caused by MRSA or VRE, such as skin and soft tissue infections, bacteremia, endocarditis, meningitis, osteomyelitis, and others. The drug is inactivated by surfactant in lungs and is ineffective in the treatment of pneumonia.
- Daptomycin can cause myopathy (monitor CK) and, rarely, eosinophilic pneumonia, hypersensitivity reactions with rash and drug reaction with eosinophilia and systemic symptoms (DRESS), tubulointerstitial nephritis, peripheral neuropathy, neutropenia. Monitor CK, and for signs/symptoms muscle pain/weakness, fever, difficulty breathing, new infiltrates on chest imaging, new-onset or worsening paresthesia, and hypersensitivity reactions.