

Pharmacology of Antibiotics: Beta-Lactams, Other Cell Wall Inhibitors and Cell Membrane Inhibitors

Part 2

Cephalosporins, Carbapenems, Monobactam, Vancomycin, and Daptomycin

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Make.
Heal.
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Reinvent the Future.

I am available to groups and individuals for pharmacology help and discussions by appointment.

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

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

Preparation Materials (links are in the CPG and on the next slide)

Required

- ScholarRx Bricks | Practice Questions

Optional materials:

- Video Lecture | Dr. Goldstein's Word handout | Guided reading questions (GRQs)
- Textbooks and Examination Review Books (please see next slide)

SUGGESTIONS:

- *Use the resources that work best for you.*
- *You do not need to study all of them. (ScholarRx Bricks & Practice Questions are required.)*
- *Work through the GUIDED READING QUESTIONS with pen/pencil and paper.*

Try answering them in your OWN WORDS first without looking at the readings, and then again after reviewing.

- *Practice questions (not graded): Simple Recall and Case Vignettes*

Resources listed in the class preparation guide (CPG):

Scholar Rx Bricks: (required)

General Microbiology > Antimicrobial Agents > Antibacterial Drugs > Penicillins

<https://exchange.scholarrx.com/brick/penicillins>

Suggested supplemental resources:

Access Medicine Katzung's Basic & Clinical Pharmacology, 16e, 2024; Chapter 43: Beta-Lactams and Other Cell Wall- & Membrane-Active Agents

<https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3382§ionid=281754499>

Access Medicine Katzung's Pharmacology: Examination & Board Review, 14e, 2024; Chapter 43: Beta-Lactams and Other Cell Wall- & Membrane-Active Agents

<https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3461§ionid=285597666>

LWW Health Library, Premium Basic Sciences: Lippincott's Illustrated Reviews: Pharmacology, 8e, 2023; Chapter 29: Cell Wall Inhibitors

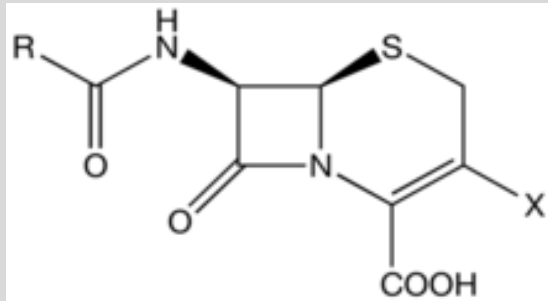
<https://premiumbasicsciences-lwwhealthlibrary-com.nyit.idm.oclc.org/content.aspx?sectionid=253328533&bookid=3222>

To understand the actions and uses of antimicrobials, students will need to know and understand basic microbiology concepts of medically important bacterial and fungal microorganisms.

- Medical Microbiology textbooks are available on NYITCOM Library website

What you need to know:

Please see Beta-Lactams, Other Cell Wall Inhibitors and Cell Membrane Inhibitors Part 1.



Cephalosporins

Cephalosporin Generations

First-gen	Second-gen	Third-gen	Fourth-gen	Advanced-gen
<ul style="list-style-type: none"> *Cefazolin *Cephalexin 	<ul style="list-style-type: none"> *Cefuroxime 	<ul style="list-style-type: none"> *Ceftriaxone *Cefotaxime *Oral: Cefdinir 	<ul style="list-style-type: none"> *Cefepime 	<ul style="list-style-type: none"> *Ceftaroline <ul style="list-style-type: none"> • anti-MRSA
	Cephamycins group <ul style="list-style-type: none"> *Cefoxitin anti- <i>Bacteroides</i> (anaerobic GNBs)	anti- <i>P. aeruginosa</i> : <ul style="list-style-type: none"> *Ceftazidime *Ceftazidime-avibactam Ceftolozane-tazobactam <ul style="list-style-type: none"> • ESBL-producing GNBs 		MDR GNBs <ul style="list-style-type: none"> *Cefiderocol including <i>P. aeruginosa</i>

There are several other drugs in each subclass.

***Students should know the starred drugs by name and their specific characteristics.**

MDR: multidrug resistant | GNB: Gram-negative bacteria


Class Pharmacokinetic Properties of Cephalosporins

Typical of the beta-lactams class effects.

	General Properties	Comments
A	IM or IV; oral	<ul style="list-style-type: none"> • CSF penetration poor • Exceptions: Better CSF penetration with cefuroxime, cefotaxime, ceftriaxone, ceftazidime, cefepime • Note: Higher CSF concentrations are achieved when meninges are inflamed. <p>Important</p>
D	Distribute in most body fluids and tissues including <ul style="list-style-type: none"> • bile and gallbladder • liver and kidneys • bone and synovial fluid • cross placenta, enter breast milk 	
E	Glomerular filtration and secretion of unchanged drug	
t_{1/2}	Average: ~1 hour to 8 hours depending on agent Ceftriaxone 1x daily dose (2x daily for CNS infections)	<ul style="list-style-type: none"> • 3rd-gen ceftriaxone biliary excretion Dose adjustment for renal impairment not required. • Current advanced-gen agents are excreted in urine as active drug <p>Important</p>

Cephalosporin Generations and Spectrums of Activity

(in the ideal world of no bacterial resistance)

<div>Increasing activity against gram-negative bacteria</div> 	Generation	Gram-positive	Gram-negative
	1st Generation	Streptococci Staph, MSSA ie, penicillinase-producing	PEcK (<i>Proteus</i> , <i>E coli</i> , <i>Klebsiella</i>)
	2nd Generation	Streptococci Staph (MSSA)	Expanded gram-negative PEcK & <i>H. influenzae</i> , <i>M. catarrhalis</i> Cephamycins: <i>B. fragilis</i> (obligate anaerobe)
	3rd Generation	Good activity, as above (except ceftazidime)	Highly active against Enterobacterales, <i>H. influenzae</i> , <i>Neisseria</i> spp. Ceftazidime, Ceftaz-avibactam, Ceftolozane-tazo: <i>Pseudomonas</i> (obligate aerobe)
	4th Generation	Good activity, as above	Extended spectrum of aerobic and anaerobic enteric and non-enteric GNBs <i>plus</i> activity against <i>Pseudomonas</i>
	Cefepime more stable against certain chromosomal β -lactamases of GNBs.		
	Advanced Generation	Each agent has its drug-specific features	Drug-specific

First-generation Cephalosporins' Narrow Spectrum of Activity

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

Gram-positive

Cocci

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

*Cefazolin is the preferred cephalosporin for treatment of penicillinase-producing *S. aureus* infections (MSSA).

Obligate G+ Anaerobic

- Clostridia spp low activity
- Clostridioides difficile

Gram-negative aerobes

Pseudomonas aeruginosa

Enterobacterales (rods)
(facultative anaerobes)

- Proteus mirabilis
- Escherichia coli
- Klebsiella spp

only
these

Respiratory

- Haemophilus influenzae
- Moraxella catarrhalis
- Neisseria meningitidis

STD

- Neisseria gonorrhoeae

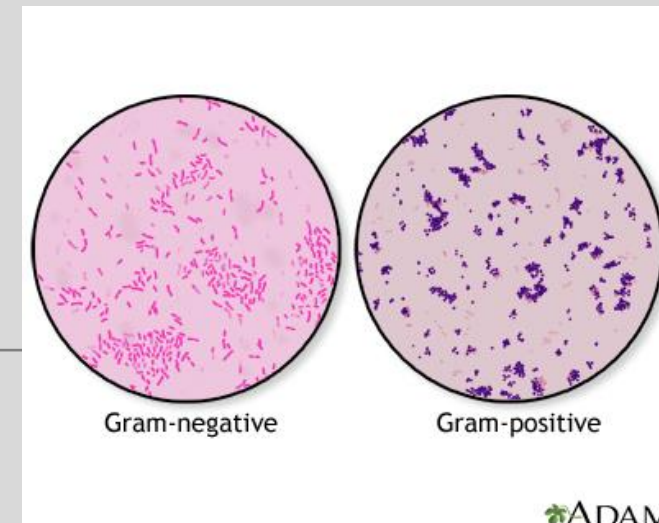
Obligate G– Anaerobic

- 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

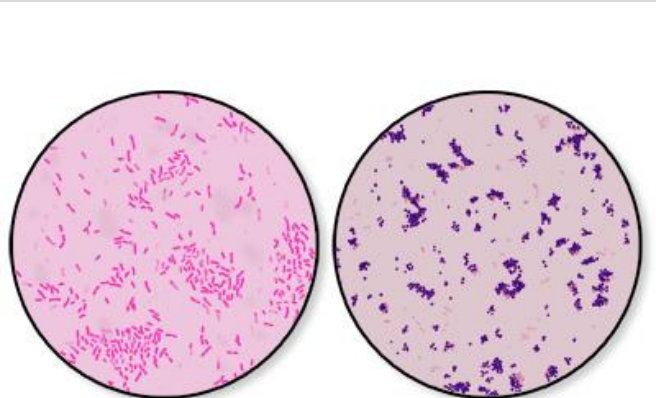
- Chlamydia trachomatis

*Not visible on Gram stain

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

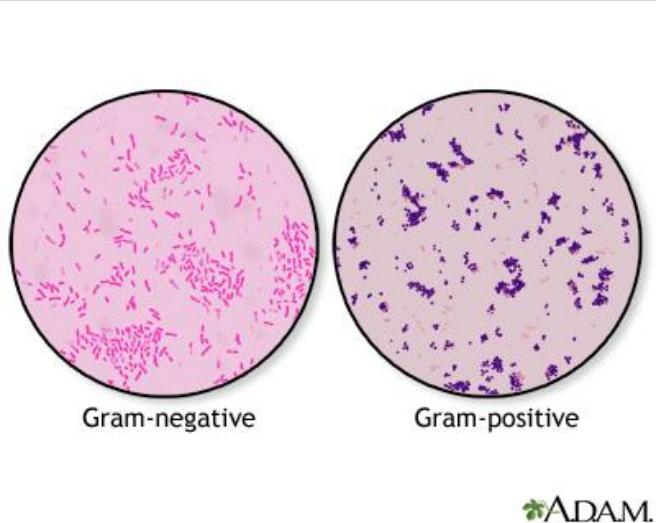
Second-generation Cephalosporins' Moderate Spectrum of Activity

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

Gram-positive	Gram-negative aerobes	Spirochetes	Atypicals*
<p>Cocci</p> <ul style="list-style-type: none"> Streptococcus pneumoniae Group A strep (GAS) S. aureus: MSSA S. epidermidis: MSSE 	<p>Pseudomonas aeruginosa</p> <p>Enterobacterales (rods) (facultative anaerobes)</p> <ul style="list-style-type: none"> Proteus mirabilis Escherichia coli Klebsiella spp <p>and a few others</p>	<p>Gram-negative, thin-walled spiral-shaped flexible organisms</p> <ul style="list-style-type: none"> Treponema pallidum Leptospira Borrelia burgdorferi 	<p>Bacteria remain colorless when gram-stained</p> <ul style="list-style-type: none"> Mycoplasma Chlamydiaceae Legionella Rickettsia
<p>Bacillus (rod)</p> <ul style="list-style-type: none"> Enterococcus faecalis Enterococcus faecium C. diphtheriae Listeria monocytogenes 	<p>Respiratory</p> <ul style="list-style-type: none"> Haemophilus influenzae Moraxella catarrhalis Neisseria meningitidis <p>STD</p> <ul style="list-style-type: none"> Neisseria gonorrhoeae 	 <p>Gram-negative Gram-positive</p>	<p>STD</p> <ul style="list-style-type: none"> Chlamydia trachomatis <p>*Not visible on Gram stain</p>
<p>Obligate G+ Anaerobic</p> <ul style="list-style-type: none"> Clostridia spp low activity Clostridioides difficile 	<p>Obligate G– Anaerobic</p> <ul style="list-style-type: none"> Bacteroides fragilis cephamycins only (cefoxitin) 		<p>Beta-lactams are ineffective in the treatment of infection caused by the atypicals.</p>

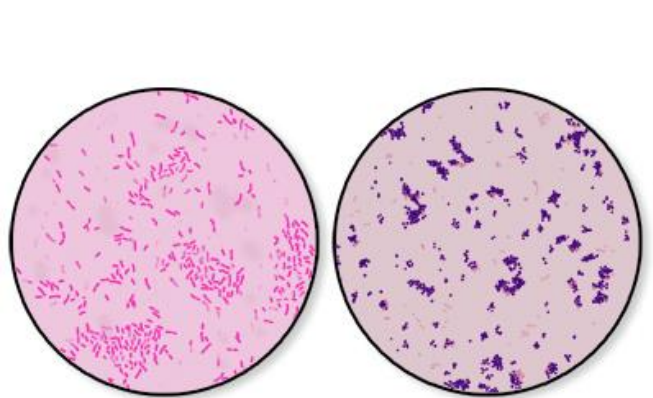
Third-generation Cephalosporins' Extended-Spectrum Activity

Remember: ESBLs and KPCs confer resistance.

Gram-positive	Gram-negative aerobes	Spirochetes	Atypicals*
<div>Cocci<ul style="list-style-type: none">Streptococcus pneumoniaeGroup A strep (GAS)S. aureus: MSSAS. epidermidis: MSSE</div> <div><ul style="list-style-type: none">Enterococcus faecalisEnterococcus faecium</div> <div>Bacillus (rod)<ul style="list-style-type: none">C. diphtheriaeListeria monocytogenes</div>	<div>Pseudomonas aeruginosa ceftazidime, ceftolozane-tazo only</div> <div>Enterobacterales (rods) (facultative anaerobes)<ul style="list-style-type: none">Proteus mirabilisEscherichia coliKlebsiella spp</div> <div>Respiratory<ul style="list-style-type: none">Haemophilus influenzaeMoraxella catarrhalisNeisseria meningitidis</div> <div>STD<ul style="list-style-type: none">Neisseria gonorrhoeae</div>	<div>Gram-negative, thin-walled spiral-shaped flexible organisms<ul style="list-style-type: none">Treponema pallidumLeptospiraBorrelia burgdorferi</div>	<div>Bacteria remain colorless when gram-stained<ul style="list-style-type: none">MycoplasmaChlamydiaceaeLegionellaRickettsia</div> <div>STD<ul style="list-style-type: none">Chlamydia trachomatis</div> <div>*Not visible on Gram stain</div> <div>Beta-lactams are ineffective in the treatment of infection caused by the atypicals.</div>
<div>Obligate G+ Anaerobic<ul style="list-style-type: none">Clostridia spp low activityClostridioides difficile</div>	<div>Obligate G– Anaerobic<ul style="list-style-type: none">Bacteroides fragilis</div>	<div></div>	

Fourth-generation: Cefepime's Broad Spectrum of Activity

Remember: ESBLs and KPCs confer resistance.

Gram-positive	Gram-negative aerobes	Spirochetes	Atypicals*
<p>Cocci</p> <ul style="list-style-type: none"> Streptococcus pneumoniae Group A strep (GAS) S. aureus: MSSA S. epidermidis: MSSE <p>Enterococcus faecalis</p> <p>Enterococcus faecium</p> <p>Bacillus (rod)</p> <ul style="list-style-type: none"> C. diphtheriae Listeria monocytogenes 	<p>Pseudomonas aeruginosa</p> <p>Enterobacterales (rods) (facultative anaerobes)</p> <ul style="list-style-type: none"> Proteus mirabilis Escherichia coli Klebsiella spp <p>Respiratory</p> <ul style="list-style-type: none"> Haemophilus influenzae Moraxella catarrhalis Neisseria meningitidis <p>STD</p> <ul style="list-style-type: none"> N. gonorrhoeae-cefepime not approved for use 	<p>Gram-negative, thin-walled spiral-shaped flexible organisms</p> <ul style="list-style-type: none"> Treponema pallidum Leptospira Borrelia burgdorferi  <p>Gram-negative Gram-positive</p>	<p>Bacteria remain colorless when gram-stained</p> <ul style="list-style-type: none"> Mycoplasma Chlamydiaceae Legionella Rickettsia <p>STD</p> <ul style="list-style-type: none"> Chlamydia trachomatis <p>*Not visible on Gram stain</p> <p><i>Beta-lactams are ineffective in the treatment of infection caused by the atypicals.</i></p>
<p>Obligate G+ Anaerobic</p> <ul style="list-style-type: none"> Clostridia spp low activity Clostridioides difficile 	<p>Obligate G– Anaerobic</p> <ul style="list-style-type: none"> Bacteroides fragilis 		

and more:
stable to
many
 β -
lactamases

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

Advanced-generation agents: Spectrums of Activity

Mechanisms

Ceftaroline

Binds PBP2a → MRSA activity

Cefiderocol

- Chelation of extracellular free iron allows iron transport systems to deliver cefiderocol across the outer membrane of gram-negative bacilli.
- The cephalosporin moiety binds PBPs, inhibiting transpeptidase activity.

Organisms	Ceftaroline	Cefiderocol*
Gram-positive		
S. pneumoniae, pcn-resistant	✓	
MSSA	✓	
MRSA	✓	
Gram-negative		
GNB, aerobic enteric	✓	✓
GNB, ESBL- and AmpC-producing		✓
GNB, MDR		✓
GNB, aerobic, non-enteric	✓	in vitro
Pseudomonas aeruginosa		✓
Anaerobic GNBs		

	Ceftaroline	Cefiderocol
Clinical applications	infants, children, adults	adults only ≥18 years old
Pneumonia, community-acquired	✓	
Pneumonia, hospital-acquired	✓	✓
Pneumonia, ventilator-associated	✓	✓
Bacteremia	✓	
Intra-abdominal		
Urinary tract infection, complicated		✓
P aeruginosa, MDR		✓
Skin/Soft tissue infection	✓	

GNB Gram-negative bacteria; aerobic, non-enteric GNBs: *Haemophilus influenzae*, *Moraxella catarrhalis* (colonizers of the respiratory tract)

Acquired resistance: β -lactamase production and altered PBPs

The newer agents were developed to overcome resistance by ESBLs and modified PBPs.

β -lactamases

ESBLs: Plasmid-encoded, constitutively-expressed

E. coli, *Klebsiella* spp. and other Enterobacterales → resistance to all penicillins and cephalosporins

ESBL: extended-spectrum beta-lactamase

***Bacteroides fragilis*:** Multidrug resistance

- Cefoxitin and cefotetan cephamycins (2nd-gen subset) have been effective but significant reduction in susceptibility has occurred over time.

AmpC β -lactamases: chromosomally-encoded; inducible during therapy

Citrobacter; *Morganella*; *Providencia*; *Serratia*; *Enterobacter*

- **mnemonic:**

Cephalosporins May Prove Sub-Efficacious Plus *Acinetobacter* and *Pseudomonas*

ALTERED PBPs

- MRSA, MRSE
- *S. pneumoniae*
- Enterococci

Intrinsically resistant

- *Enterococcus*; *Listeria monocytogenes* – PBPs with low-affinity for cephs.
- Atypical respiratory pathogens *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Chlamydophila pneumoniae* – resistant to all beta-lactams
- *C. difficile* and *Campylobacter jejuni* (important cause of acute diarrhea)

Resistance: In general, cephalosporins are **Ineffective** against:

Gram-positive	<ul style="list-style-type: none"> • MDR <i>S. pneumoniae</i> Except ceftaroline • MRSA, MRSE Except ceftaroline • <i>Enterococcus</i> spp Various infections • <i>Listeria monocytogenes</i> Food-borne illness, meningitis • <i>C. difficile</i> Secondary infection
Gram-negative	<ul style="list-style-type: none"> • KPC-producing Enterobacterales.. Class A beta-lactamases • <i>Campylobacter jejuni</i>..... Food-borne illness • <i>Stenotrophomonas maltophilia</i>..... MDR nosocomial infections • <i>Acinetobacter</i> spp..... MDR nosocomial infections <p>KPC: <i>Klebsiella pneumoniae</i> carbapenemase</p>
“Atypical”	<ul style="list-style-type: none"> • <i>Mycoplasma pneumoniae</i> (lacks peptidoglycan, intracellular) • <i>Legionella pneumophila</i> (gram-negative, intracellular pathogen) • <i>Chlamydiaceae</i> (obligate intracellular pathogens)

Cephalosporins Therapeutic Uses

Hint: Think about the types of infections bacteria cause and a drug's spectrum of action and ability to penetrate the site of infection.

Medicine

1st Generation Gram-positive PEcK	Skin and soft tissue infections (<i>S. pyogenes</i> (GAS); MSSA) Urinary tract infections (uncomplicated) Cefazolin : surgical prophylaxis Cephalexin is oral for uncomplicated infections.	
2nd Generation	Cefuroxime : URI– <i>H. influenzae</i> , <i>M. catarrhalis</i> Not preferred due to delayed responses and treatment failures. Third-generation cephalosporins are more effective.	Cephamycin: Cefoxitin Common aerobic GNBs and <i>B. fragilis</i> → abdominal/pelvic inf.
3rd Generation	Ceftriaxone / Cefotaxime : Serious infections, including meningitis, gonorrhea, Lyme disease (disseminated) Ceftazidime : GNB, including <i>Pseudomonas</i> infections Ceftolozane-tazobactam : Serious infections caused by ESBL-producing GNBs or MDR <i>Pseudomonas</i>	Oral agents (eg, cefdinir): Otitis media, upper/lower respiratory infections, UTIs
4th Generation	Cefepime is usually reserved for the treatment of severe infections.	
Advanced generation		
Ceftaroline	Skin/skin structure infections (including MRSA) Community-acquired pneumonia (CAP)	
Cefiderocol (a siderophore)	Hospital-acquired / ventilator-associated pneumonia and UTI caused by MDR GNBs, including ESBL-, carbapenemase-, or metallo-β-lactamase producing aerobic and anaerobic GNBs in adults (no activity against gram-positive bacteria)	
All parenterals:	Injection site reactions: IV thrombophlebitis IM painful injection	

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Third-generation cephalosporins are the most commonly prescribed drugs in the group:

- Extended spectrum of activity
- Stability against common beta-lactamases of gram-negative bacilli
- Gram-positive bacteria: active against penicillin non-susceptible *S. pneumoniae*, and other gram-positive species
 - **Less potent activity against MSSA than first-generation cephalosporins**
- Highly active against Enterobacterales order (bowel microbiota), *N. meningitidis*, and *H. influenza* (respiratory microbiota)
 - but poor activity against *Pseudomonas aeruginosa* – except *ceftazidime*
- **Ceftriaxone and cefotaxime are agents of choice for treatment of meningitis.**
Target: gram-negative bacilli in combination antibiotic therapy.
- **Ceftriaxone (a single IM injection) is the only CDC recommended treatment of uncomplicated gonorrhea.**

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.

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	
<ul style="list-style-type: none">Hyperbilirubinemia → kernicterus Ceftriaxone is highly bound to plasma proteins and can displace unconjugated bilirubin, which can lead to kernicterus (encephalopathy) in the newborn.	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.
<ul style="list-style-type: none">Precipitation of Ca²⁺-containing solutions → lung and kidney damage in neonates	

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 Ca²⁺-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

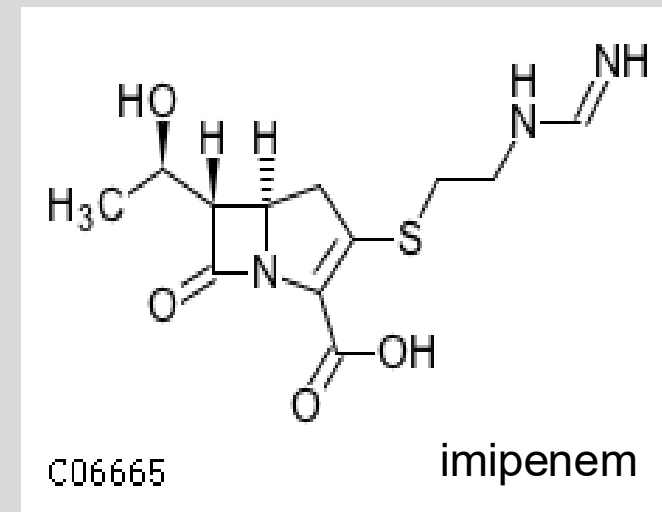
Cefotaxime has the same actions as ceftriaxone but does not displace bilirubin from plasma proteins or precipitate calcium and is preferred for neonates.

Check your knowledge:

1. Which cephalosporins have the best penetration of the CSF?
2. Which cephalosporin is most active against MSSA?
3. Which cephalosporin can be used parenterally to treat acute bacterial skin and soft tissue infections caused by MRSA?
4. The “extended spectrum” cephalosporins have broader activity against what bacteria?
5. What drug is preferred for the treatment of uncomplicated gonorrhea and administered as a single IM injection?
6. Why is cefotaxime preferred over ceftriaxone for treatment of meningitis in neonates for coverage of gram negative bacillary pathogens?
7. What is the therapeutic use of the cephalosporin that gains access to the bacterial cell wall by binding extracellular iron?
8. Which beta-lactam antibiotics are inactivated by ESBLs?
9. ESBLs are expressed mainly by which bacterial species?
10. How can antibiotic activity be restored in ESBL-expressing bacteria?
11. What cephalosporins are inactivated by KPC-expressing bacteria?
12. How can antibiotic activity be restored in KPC-expressing bacteria?
13. What is a common side effect of parenteral cephalosporins?

Carbapenems

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



Important note:

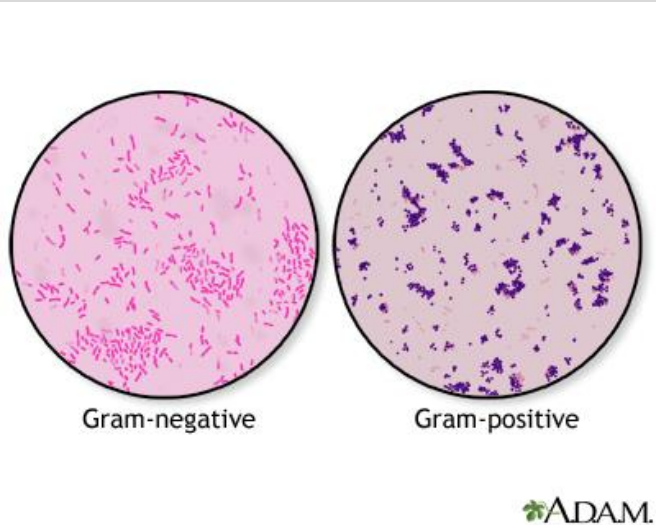
*Cilastatin inhibits dehydropeptidase I in the brush border of proximal renal tubules.

Dehydropeptidase I inactivates imipenem.

Cilastatin blocks degradation of imipenem, which increases imipenem concentrations in urine.

Carbapenem's Broad Spectrum of Activity

Strike through = once susceptible but now significant resistance

Gram-positive	Gram-negative aerobes	Spirochetes	Atypicals*
<p>Cocci</p> <ul style="list-style-type: none"> Streptococcus pneumoniae Group A strep (GAS) Staphylococcus aureus Staph. epidermidis Enterococcus faecalis Enterococcus faecium <p>Bacillus (rod)</p> <ul style="list-style-type: none"> C. diphtheriae Listeria monocytogenes 	<p>Pseudomonas aeruginosa (not ertapenem)</p> <p>Enterobacterales (rods) (facultative anaerobes)</p> <ul style="list-style-type: none"> Escherichia coli Proteus mirabilis Klebsiella spp and many more <p>Respiratory</p> <ul style="list-style-type: none"> Haemophilus influenzae Moraxella catarrhalis Neisseria meningitidis <p>STD: Neisseria gonorrhea</p>	<p>Gram-negative, thin-walled spiral-shaped flexible organisms</p> <p>Not extensively tested against spirochetes.</p> <p>Treponema pallidum</p> <p>Leptospira</p> <p>Borrelia burgdorferi</p>	<p>Bacteria remain colorless when gram-stained</p> <ul style="list-style-type: none"> Mycoplasma Chlamydiaceae Legionella Rickettsia <p>STD</p> <ul style="list-style-type: none"> Chlamydia trachomatis <p>*Not visible on Gram stain</p> <p><i>Beta-lactams are ineffective in the treatment of infection caused by the atypicals.</i></p>
<p>Obligate G+ Anaerobic</p> <ul style="list-style-type: none"> Clostridia spp Clostridioides difficile 	<p>Obligate G– Anaerobic</p> <ul style="list-style-type: none"> Bacteroides fragilis 		

stable to many β -lactamases

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

Acquired resistance

Class A KPC: *K. pneumoniae* carbapenemases

Class B metallo- β -lactamases

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

Intrinsic resistance

- 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**

Imipenem-cilastatin-relebactam

Meropenem-vaborbactam

Relebactam and Vaborbactam: Beta-lactamase inhibitors, reversible

Inhibit Ambler class A β -lactamases, including KPCs, and AmpC β -lactamases
—Not effective against Class B metallo- β -lactamases—

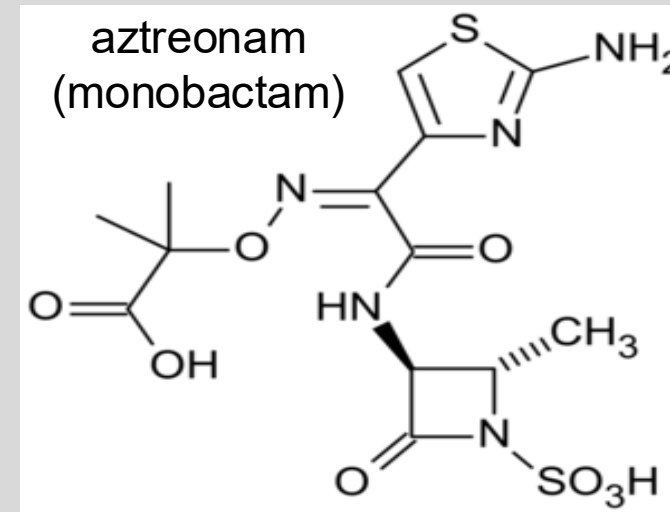
**Both are formulated in drug- β -lactamase inhibitor combinations
mainly for the treatment of infections caused by KPC-producing Enterobacterales.**

Relebactam improves imipenem activity against most Enterobacterales and some nonsusceptible <i>P. aeruginosa</i>	Vaborbactam improves meropenem activity against most Enterobacterales
Relebactam does NOT improve imipenem activity against resistant <i>Acinetobacter</i> or <i>Stenotrophomonas</i>	Vaborbactam has not shown to improve meropenem activity against resistant <i>Pseudomonas</i> , <i>Acinetobacter</i> , or <i>Stenotrophomonas</i>


Stenotrophomonas maltophilia is a difficult to treat, multidrug-resistant, gram-negative rod intrinsically resistant to antibiotics. It is an opportunistic pathogen associated with high morbidity and mortality in severely immunocompromised and debilitated patients.

Monobactam

* Aztreonam



Aztreonam Properties

PK	IV, IM; widely distributed; renal excretion
Activity	only gram-negative aerobic cocci and bacilli, including <i>P. aeruginosa</i> – highly active Caution: <i>P. aeruginosa</i> resistance arises with aztreonam monotherapy.
Resistance	Gram-positive bacteria ESBLs, KPC, and AmpC β -lactamase hydrolyze Enterobacterales (some) aztreonam <i>Pseudomonas</i> (PBPs with low affinity for aztreonam)
Uses	Urinary tract infections, lower respiratory tract infections, septicemia, skin/skin structure infections, intra-abdominal infections, and pelvic infections <i>P. aeruginosa</i> lung infection in cystic fibrosis patients → aztreonam inhalation  Aztreonam should not be used alone for empiric therapy – narrow spectrum
Adverse effects	Low immunogenic potential: limited cross-reactivity with other β -lactams Exception, ceftazidime (similar side chain): cross-reactivity reported Nausea / vomiting / diarrhea Thrombophlebitis and pain at injection site Potential for <i>C. difficile</i> superinfection.

Glycopeptides: Cell wall inhibitors

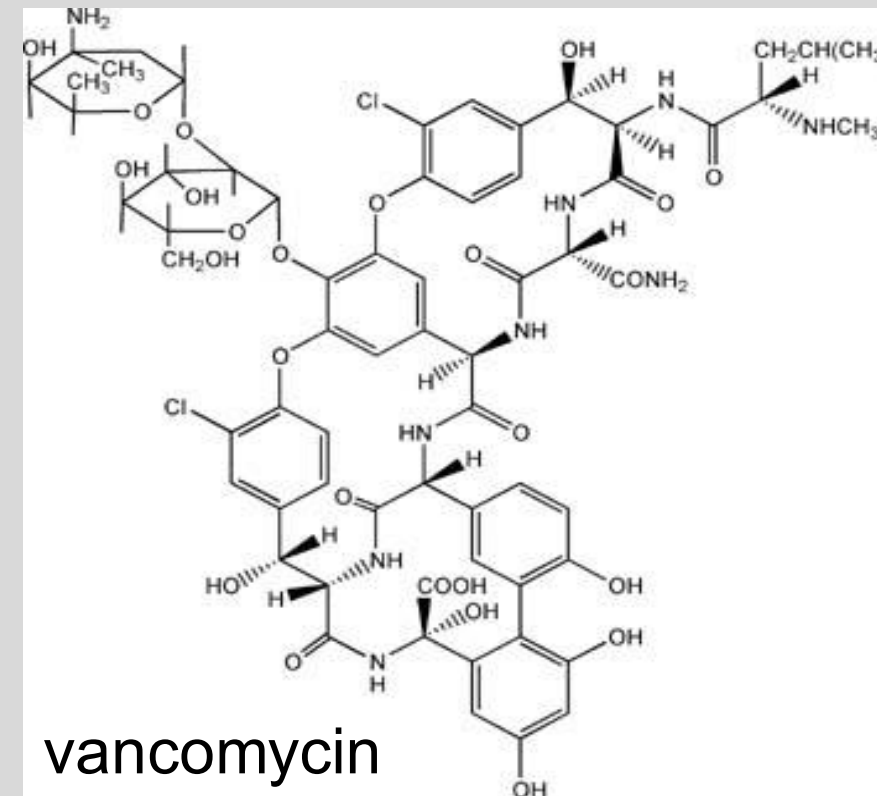
*Vancomycin

Telavancin

Dalbavancin

Oritavancin

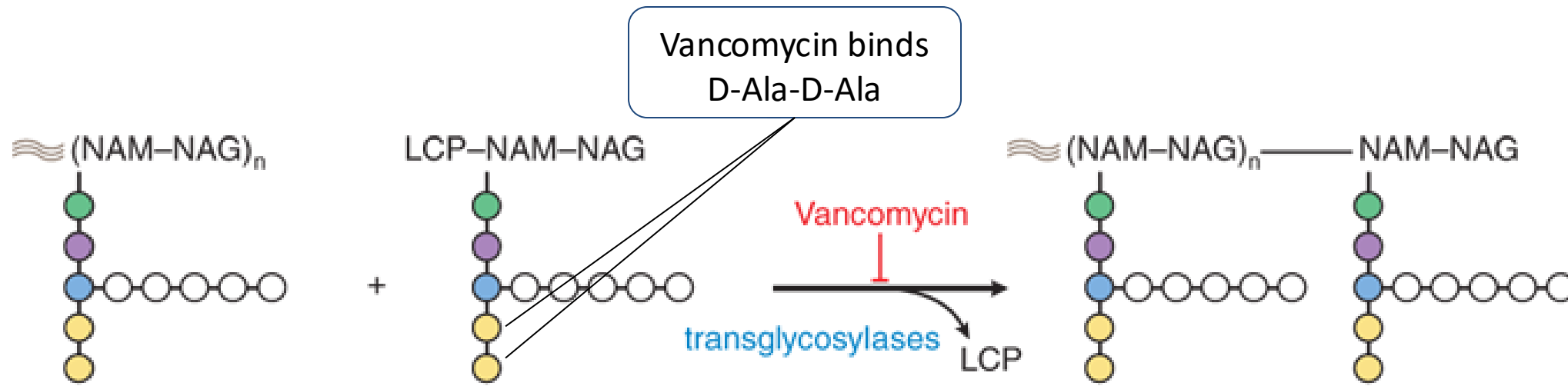
and more



vancomycin

Vancomycin Profile

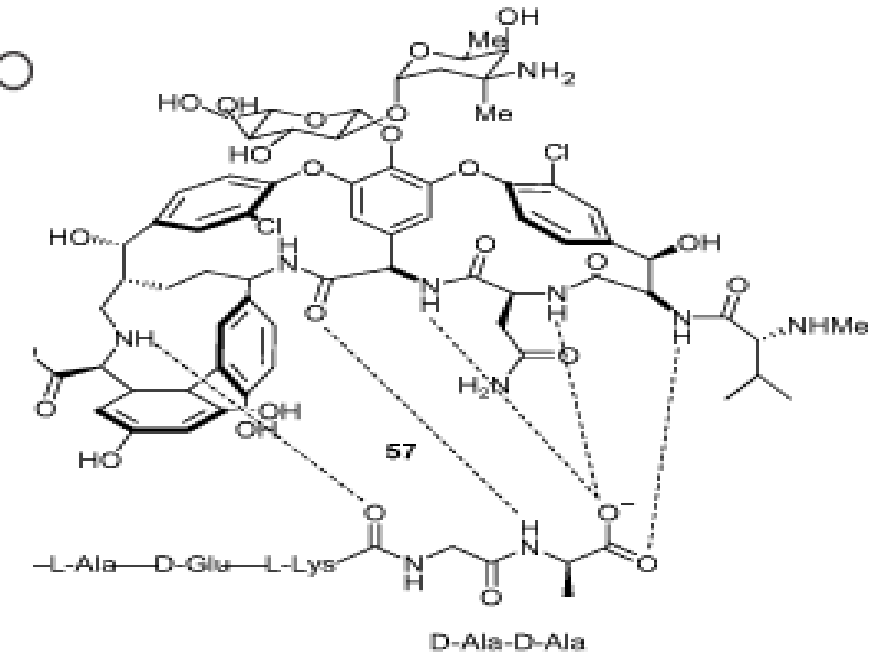
GI Absorption	Poor (oral for local action in gut)
Administration	IV only for systemic infections slow infusion to avoid non-immune anaphylactoid infusion-related reaction (“red man syndrome”)
Distribution	Wide distribution to tissues and fluids
CNS distribution	CSF low penetration except inflamed meninges
Excretion:	Glomerular filtration unchanged drug
t _{1/2} serum	~6 hours (normal renal function) ➤ Renal impairment: Extended dosing interval / Lower doses
PK-PD	T>MIC; short post-antibiotic effect. Clinical efficacy correlates with 24-h AUC/MIC ratio. Example: ≥400 – 600 for MRSA treatment to maximize efficacy and minimize risk of nephrotoxicity
Killing effect	Bactericidal



KEY

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

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



3 of vancomycin to the D-Ala-D-Ala terminus of precursor.

Source: Laurence L. Brunton, Randa Hilal-Dandan, Björn C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, Thirteenth Edition: Copyright © McGraw-Hill Education. All rights reserved.

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 $(\text{NAM-NAG})_n$ 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 \rightarrow D-Ala-D-Lac, reducing affinity for vancomycin by 1000-fold.

Spectrum	Gram-positive pathogens only	<ul style="list-style-type: none">• MRSA and MRSE <p>Note: For treatment of MSSA / MSSE, the penicillinase-resistant penicillins, nafcillin, oxacillin, dicloxacillin, have better activity than vancomycin and are preferred.</p> <ul style="list-style-type: none">• Penicillin-resistant <i>S. pneumoniae</i>• <i>Enterococcus faecalis</i> and <i>E. faecium</i> (bacteriostatic)
	All gram-negative	Drug cannot penetrate porins of gram-negative bacteria
Intrinsic resistance	Mycobacteria	Impermeable cell wall
	Enterococci	<p>Inducible vanA and vanB gene cluster → expresses D-Ala-D-Lactate (instead of D-alanyl-D-alanine) → ↓ vancomycin binding</p> <p>↓</p> <p>confers high-level resistance to vancomycin and teicoplanin</p>
Acquired resistance	<i>S. aureus</i>	<ol style="list-style-type: none">1. Plasmid-mediated acquisition of VanA gene cluster confers high-level resistance2. Altered cell wall metabolism → abnormally thick cell wall with increased numbers of D-Ala-D-Ala → may trap vanco within the cell wall (sequesters the drug) → confers intermediate resistance

Vancomycin Clinical Uses

MRSA / MRSE infections

bacteremia, pneumonia, empyema, endocarditis, osteomyelitis, skin/soft-tissue abscess, and more

Penicillin-resistant *Enterococcus* endocarditis

Meningitis due to penicillin-resistant *S. pneumoniae*

Gram-positive infections in penicillin-allergic patients

C. difficile infection: **Oral** vancomycin acts locally in the gut

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
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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

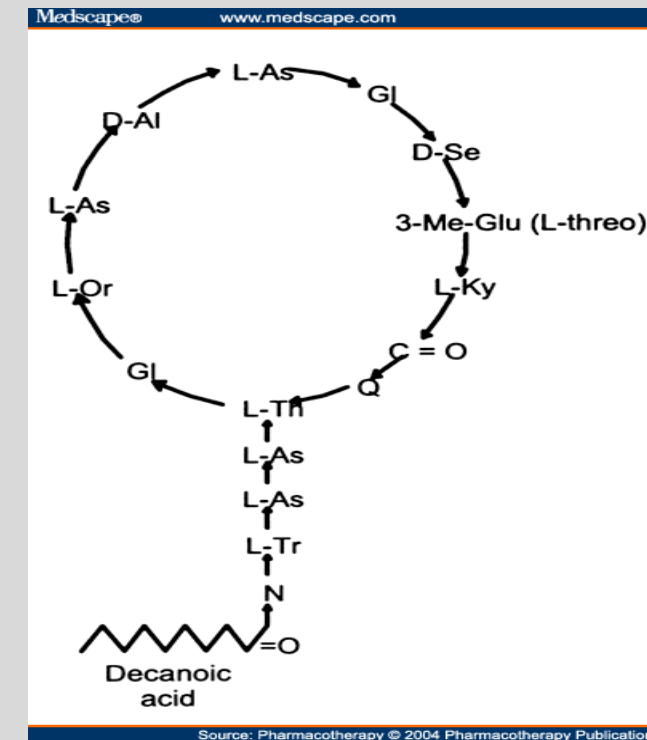
Cyclic lipopeptide

* Daptomycin

Other cell membrane-active drugs:

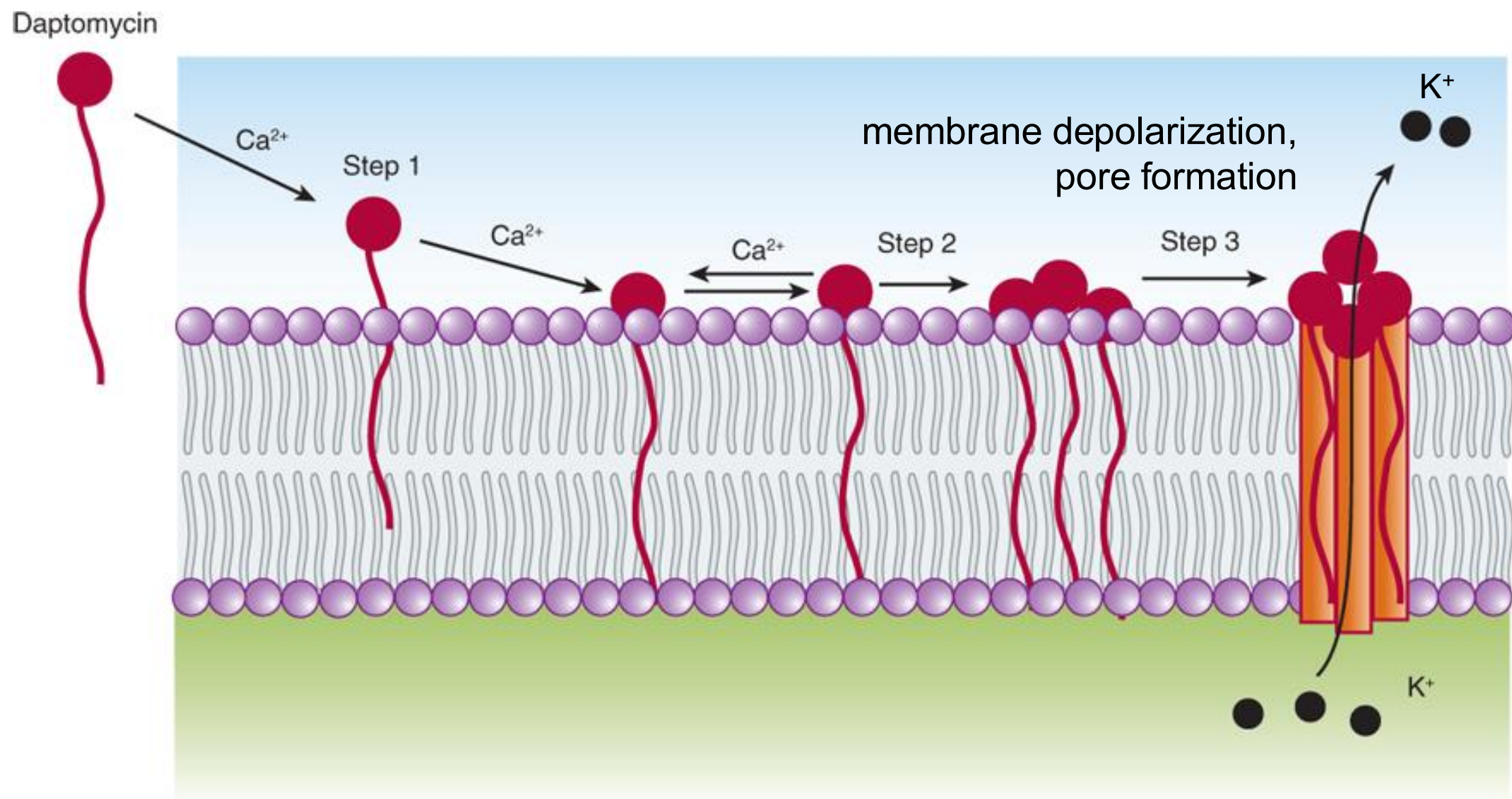
Polymyxin B: Damages bacterial cell membrane by binding to phospholipids, causing permeability and leakage of intracellular contents and cell death. Treatment of serious multidrug resistant gram-negative infections. Nephro- and neurotoxic.

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.



Daptomycin Profile

Parameter	Property
GI absorption	Poor
Administration	I.V., once daily dosing
Distribution	Distributed in body fluids Protein binding >90% Low penetration of uninflamed meninges
Elimination	Renal, primarily unchanged drug
t _{1/2}	8-9 hours (adults, normal renal function) Renal impairment: extend dosing interval
PK-PD profile	Concentration-dependent, prolonged persistent effects Clinical effect is associated with 24h AUC/MIC ratio
Killing effect	Bactericidal



Source: Bertram G. Katzung, Todd W. Vanderah:
Basic & Clinical Pharmacology, Fifteenth Edition
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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 is active against all gram-positive pathogens – aerobic, facultative anaerobic, and obligate anaerobic

Effective against MRSA, MRSE, VISA, VRSA, and VRE

Alternative to vancomycin for the treatment of infections caused by MRSA or VRE:

- Complicated skin and soft tissue infections (MRSA, streptococci, E. faecalis)
- Endocarditis, right-sided (MRSA)
- Bloodstream infections (MRSA)
- Osteomyelitis, septic arthritis, meningitis, and others

Daptomycin is INEFFECTIVE in:

- Pneumonia: Drug inactivation by pulmonary surfactants.
- Infections by gram-negative bacteria – inherent resistance

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.

- Third-generation antipseudomonal: Ceftazidime, ceftazidime-avibactam, ceftolozane-tazobactam have good gram-negative activity but weak gram-positive activity. Ceftolozane-avibactam is effective against anaerobic GNB *B. fragilis*. Both drugs are approved for complicated intra-abdominal infections, complicated urinary tract infections, hospital-acquired and ventilator-associated pneumonia.
- Fourth-generation: Cefepime is the only agent in this group. It is a broad-spectrum parenteral antibiotic with good activity against penicillin-non-susceptible *S. pneumoniae*, staphylococci (MSSA), and Enterobacterales, *P. aeruginosa*, and highly active against *H. influenzae* and *Neisseria* spp. It is used in the treatment of various serious infections in hospitalized patients.
- Advanced generation:
 - Ceftaroline has broad gram-positive activity and is the only beta-lactam with affinity for PBP2a so it is active against MRSA and is active against penicillin-resistant *S. pneumoniae*. It is used for inpatients without risk factors for *P. aeruginosa* infections: community-acquired, hospital-acquired, and ventilator-associated pneumonia (HAP and VAP), bacteremia, and skin/soft tissue infections
 - Cifiderocol is a catechol-substituted siderophore that binds extracellular free iron. It is transported across the outer membrane of GNBs by active iron transport systems and is stable in the presence of β -lactamases, including MDR β -lactamases and metallo- β -lactamases. The drug is highly active against aerobic GNBs, including MDR *P. aeruginosa*, but has no activity against gram-positive bacteria and most anaerobic bacteria. It is used for treatment of hospital-acquired and ventilator-associated pneumonia and complicated urinary tract 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 <i>Treponema pallidum</i> (syphilis); self-limited
Disulfiram-like reaction with concomitant alcohol use	Cefotetan (side chain inhibits aldehyde dehydrogenase → ↑ 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.



Unnecessary Outpatient Antibiotic Use Endangers Kids

Health systems and payers can protect patients by encouraging responsible prescribing

<https://www.pewtrusts.org/en/about/news-room/opinion/2022/08/17/unnecessary-outpatient-antibiotic-use-endangers-kids> 48

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Slide 21 answers to check your knowledge questions

1. Ceftriaxone, cefotaxime, cefepime, cefuroxime
2. Cefazolin (first-generation)
3. Ceftaroline (advanced generation)
4. GNBs: Enterobacterales, *Haemophilus influenzae*, and *Neisseria* sp. Third-generation agents have marked stability against common beta-lactamases (not class A ESBLs, KPCs).
5. Ceftriaxone
6. Slide 19: Ceftriaxone may cause kernicterus by displacing unconjugated bilirubin from albumin binding sites and precipitate with calcium causing serious organ damage.
7. Cefiderocol complexes with ferric iron, which allows use of iron transport systems to deliver the drug across the outer membrane of gram-negative bacteria. It is used for treatment of hospital-acquired and ventilator-associated pneumonia and complicated urinary tract infections caused by susceptible GNBs. Cefiderocol is more stable to various beta-lactamases, including class A, B, C, D.
8. Penicillins, cephalosporins (except cefiderocol), and aztreonam.
9. *E. coli* and *Klebsiella*
10. Combining the antibiotic with a beta-lactamase inhibitors – all of them are effective
11. All
12. Combining the antibiotic with a newer beta-lactamase inhibitors – avibactam, relebactam, or vaborbactam. (Durlobactam is combined with sulbactam for the treatment of *Acinetobacter baumannii-calcoaticus* infections.)
13. Injection site reactions: IM pain; IV thrombophlebitis

Lecture Feedback Form:

<https://comresearchdata.nyit.edu/redcap/surveys/?s=HRCY448FWYXREL4R>