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

Required

- ScholarRx Bricks | Practice Questions

Pptional 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):

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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&sectionid=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&sectionid=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

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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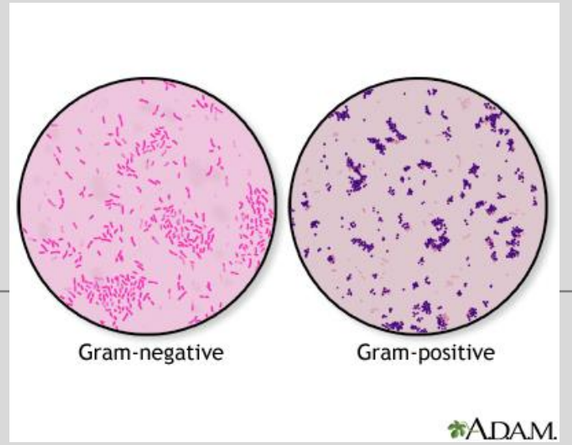
Gram-positive	Gram-negative aerobes	Spirochetes	Atypicals*
Cocci • Streptococcus pneumoniae • Group A strep (GAS) • S. aureus: MSSA • S. epidermidis: MSSE	Pseudomonas aeruginosa Enterobacterales (rods) (facultative anaerobes) • Proteus mirabilis • Escherichia coli • Klebsiella spp only these	Gram-negative, 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

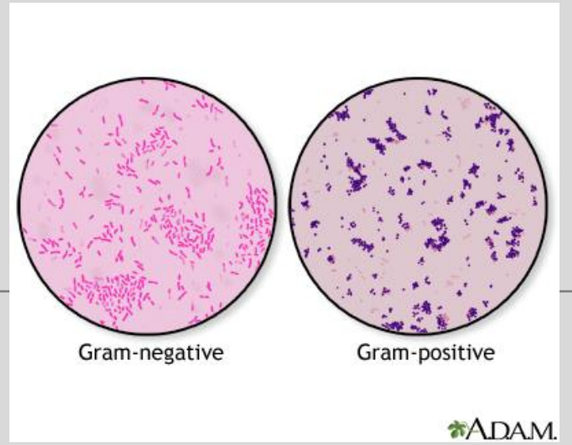
Respiratory
- Haemophilus influenzae
- Moraxella catarrhalis
- Neisseria meningitidis

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

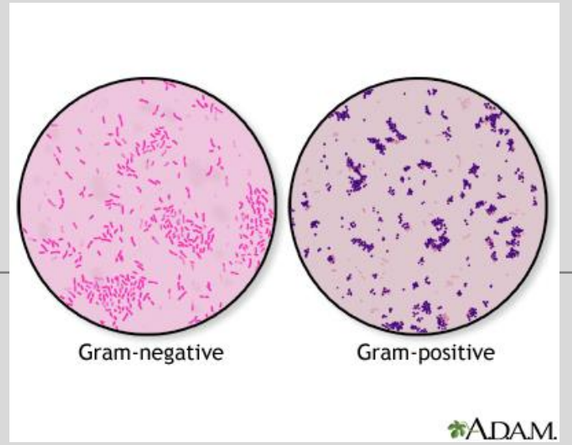
Respiratory
- Haemophilus influenzae
- Moraxella catarrhalis
- Neisseria meningitidis

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

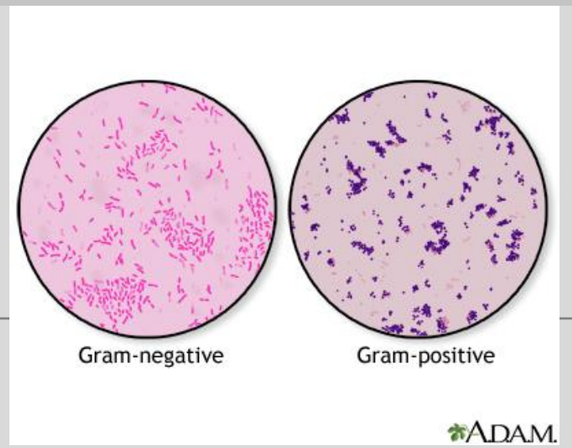
STD
- N. gonorrhoeae-cefepime not approved for use

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



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STD
- Chlamydia trachomatis

*Not visible on Gram stain

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

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.

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1st Generation Gram-positive PEcK	Skin and soft tissue infections (*S. pyogenes* (GAS); MSSA) Urinary tract infections (uncomplicated) **Cefazolin:** surgical prophylaxis | **Cephalexin** is oral for uncomplicated infections.	
2nd Generation	**Cefuroxime:** URI– *H. influenzae, M. catarrhalis* Not preferred due to delayed responses and treatment failures. Third-generation cephalosporins are more effective.	**Cephamycin: Cefoxitin** Common aerobic GNBs and *B. fragilis* → abdominal/pelvic inf.
3rd Generation	**Ceftriaxone / Cefotaxime**: Serious infections, including meningitis, gonorrhea, Lyme disease (disseminated) **Ceftazidime:** GNB, including *Pseudomonas* infections **Ceftolozane-tazobactam:** Serious infections caused by ESBL-producing GNBs or MDR *Pseudomonas*	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	

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.**

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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

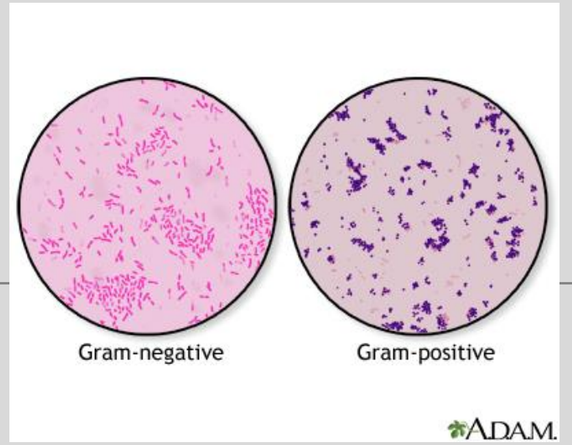
STD: Neisseria gonorrhea

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: 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**

Carbapenem-Beta-Lactamase Inhibitor Combinations

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 *P. aeruginosa*	Vaborbactam improves meropenem activity against most Enterobacterales
Relebactam does NOT improve imipenem activity against resistant *Acinetobacter* or *Stenotrophomonas*	Vaborbactam has not shown to improve meropenem activity against resistant *Pseudomonas, Acinetobacter*, or *Stenotrophomonas*
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.	

Vancomycin Spectrum of Action and Resistance Mechanisms

Spectrum	Gram-positive pathogens only	• MRSA and MRSE Note: For treatment of MSSA / MSSE, the penicillinase-resistant penicillins, nafcillin, oxacillin, dicloxacillin, have better activity than vancomycin and are preferred. • Penicillin-resistant *S. pneumoniae* • *Enterococcus faecalis* and *E. faecium* (bacteriostatic)
Intrinsic resistance	All gram-negative	Drug cannot penetrate porins of gram-negative bacteria
	Mycobacteria	Impermeable cell wall
Acquired resistance	Enterococci	**Inducible vanA and vanB gene cluster** → expresses D-Ala-D-Lactate (instead of D-alanyl-D-alanine) → ↓ vancomycin binding ↓ confers high-level resistance to vancomycin and teicoplanin
	S. aureus	1. Plasmid-mediated acquisition of VanA gene cluster confers high-level resistance 2. 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

- 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.

- 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.