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**.

Mechanisms
Mechanisms
Mechanisms

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.

Patient safety

4. Relate the selection of antibiotic therapy for the individual patient to the treatment goal, the specific infectious bacteria targeted by the drugs, and individual patient factors.

Bacterial pathogens to know by name and type for this course

Antimicrobial therapeutic use requires knowledge of the pathogens.

Basics
Patterns
Chunking

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Gram-positive

Cocci

Skin flora
- Streptococcus pneumoniae
- Group A strep (GAS)
- Staphylococcus aureus
- Staph. epidermidis

Gut flora
- Enterococcus faecalis
- Enterococcus faecium

Bacilli (soil, water, food, etc)
- Listeria monocytogenes
- Corynebacterium diphtheriae

Obligate Anaerobic Bacilli
- Clostridia spp
- Clostridioides difficile

Gram-negative aerobes

Pseudomonas aeruginosa (soil, water, vegetation)

Enterobacterales (gut flora)
- Escherichia coli
- Proteus mirabilis
- Klebsiella spp

and many more

Respiratory flora
- Haemophilus influenzae
- Moraxella catarrhalis
- N. meningitidis (cocci)

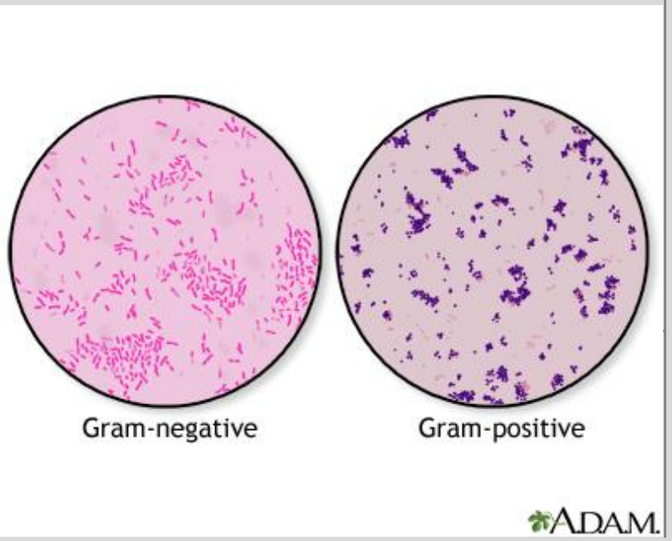
STD
- N. gonorrhoeae (cocci)

N= Neisseria

Obligate Anaerobic GNB
- Bacteroides fragilis

Spirochetes

Gram-negative, thin-walled spiral-shaped flexible organisms
- Treponema pallidum (syphilis)
- Leptospira
- Borrelia burgdorferi (Lyme disease)



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.

Pharmacology of beta-lactam antibiotics you need to know and understand:

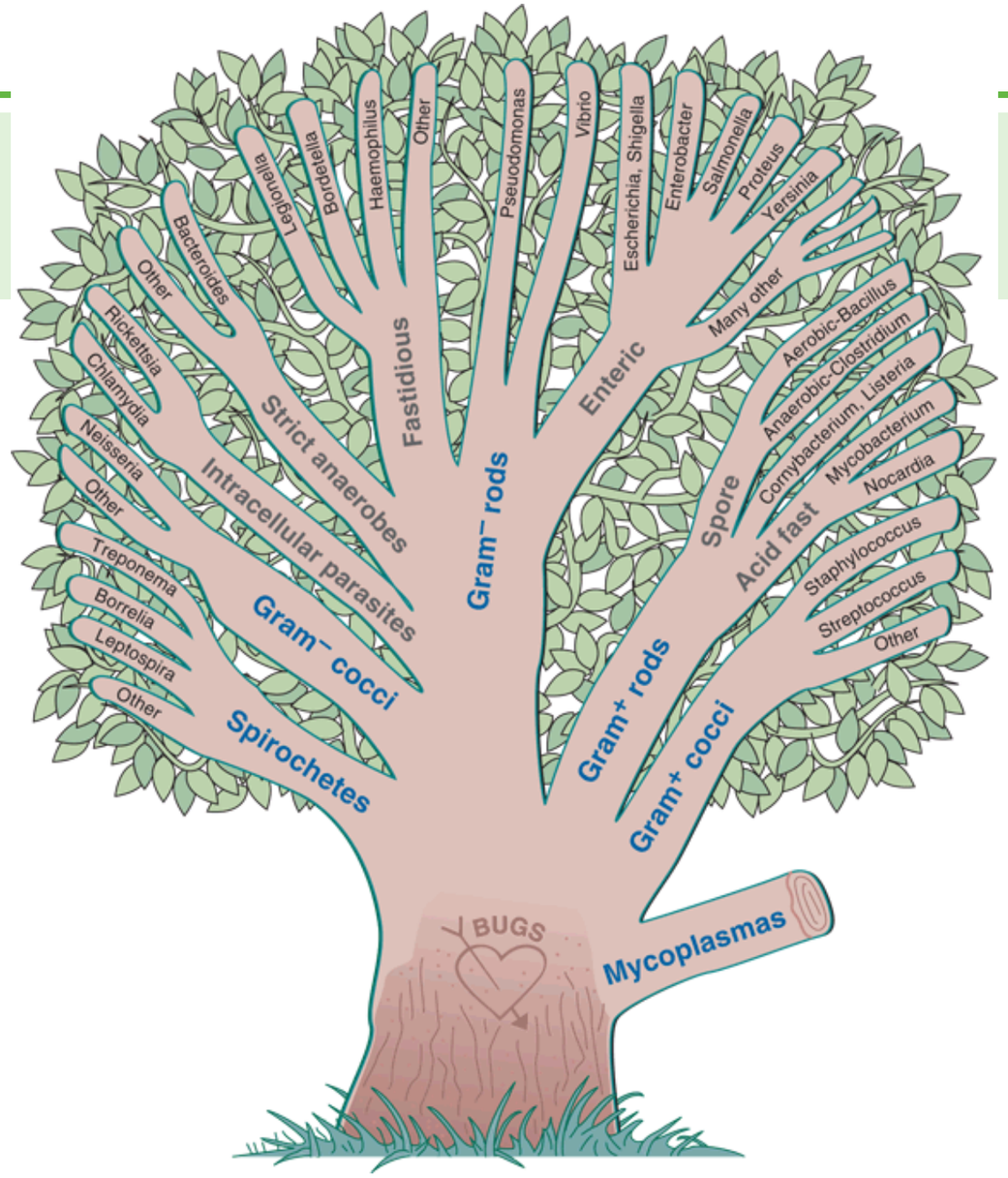
- Structure-activity relationship: An intact beta-lactam ring is essential for antibacterial activity.
- Pharmacokinetics: Know the class properties and the one or two differences in the “starred” drugs.

  Routes of administration (and why), absorption, distribution in body water and penetration of tissues, elimination (metabolism and/or excretion), half-life, onset and duration of action.
- Pharmacodynamics: Bactericidal effects (and sometimes bacteriostatic effects)
- PK-PD profile: T>MIC and minimal persistent effects
- Target: Transpeptidases, also known as “penicillin binding proteins – PBPs”
- Mechanism of action: Covalently bind PBPs inhibiting the final step in bacterial cell wall synthesis – peptide cross linking, which triggers bacterial autolysins, leading to osmotic rupture of the bacterial cell. Non-lytic mechanisms causing collapse of membrane potential also appear to be involved.
- Mechanisms of resistance: Drug inactivation by beta-lactamases, low-affinty PBPs, reduced penetration to target by alterations of porin proteins or expression of efflux pumps. Intrinsic resistance by organisms without cell wall and obligate intracellular bacteria.

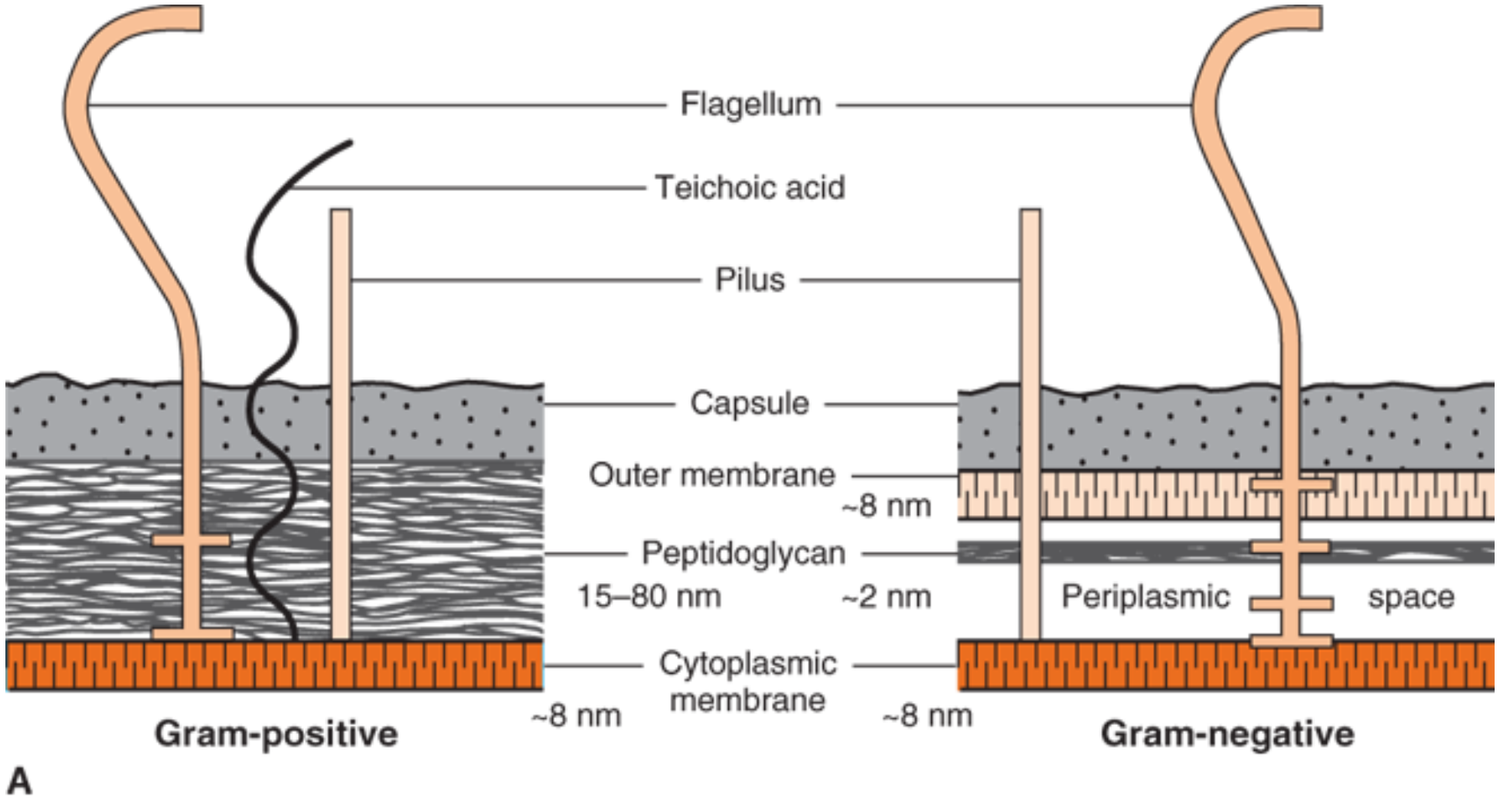
What you need to know and understand:

- Classification of gram-negative bacterial beta-lactamases: Ambler Class A, B, C, and D categorize the main resistance patterns.
- The mechanisms and effects of the beta-lactamase inhibitors when partnered with a beta-lactam antibiotic
- The properties of each of the beta-lactam subclasses:
  - The penicillins group: natural, penicillinase-resistant, aminopenicillins, antipseudomonal
  - The cephalosporins group: first-, second-, third-, fourth-, and advanced-generation drugs
  - The carbapenems
  - The monobactam
- Therapeutic uses of each subclass of beta-lactam antibiotics based on their spectrums of activity and bacterial resistance patterns
- Adverse effects associated with beta-lactam antibiotics: Hypersensitivity reactions, GI side effects, secondary infection by *C. difficile* and *Candida*, injection reactions, and drug-specific effects
- Mechanisms of drug interactions.

From: **Chapter 10 Introduction to the Pathogenic Bacteria**
Schaechter's Mechanisms of Microbial Disease, 5e, 2012



The major groups of medically important bacteria.



Bacterial cell wall structure.

A: Cell walls of gram-positive and gram-negative bacteria. Note that the peptidoglycan in gram-positive bacteria is much thicker than in gram-negative bacteria. Note also that only gram-negative bacteria have an outer membrane containing endotoxin (lipopolysaccharide [LPS]) and thus have a periplasmic space where β-lactamases are found. Several important gram-positive bacteria, such as staphylococci and streptococci, have teichoic acids. (Reproduced with permission from Ingraham JL, Maaløe O, Neidhardt FC. Growth of the Bacterial Cell. Sunderland, MA: Sinauer Associates; 1983.)

Antibiotics Classes

<table>
<tr><th colspan="4">Beta-Lactam Antibiotics</th></tr>
<tr><td><u>Penicillins</u>

Narrow spectrum

Extended spectrum

Antipseudomonas
Broad spectrum</td><td><u>Cephalosporins</u>

Narrow spectrum

Extended spectrum

Anti-MRSA</td><td><u>Carbapenems</u>

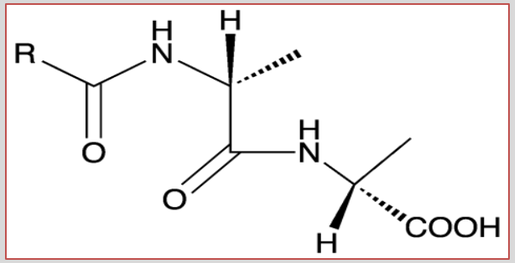
Broad spectrum</td><td><u>Monobactam</u>

Gram-negative aerobes only</td></tr>
<tr><td colspan="2">Other Cell Wall Active Antibiotics

Vancomycin and others</td><td colspan="2">Cell Membrane Active Antibiotic

Daptomycin</td></tr>
</table>

Beta-lactams are analogs of D-Ala-D-Ala



D-alanyl-D-alanine

CLASS PROPERTIES

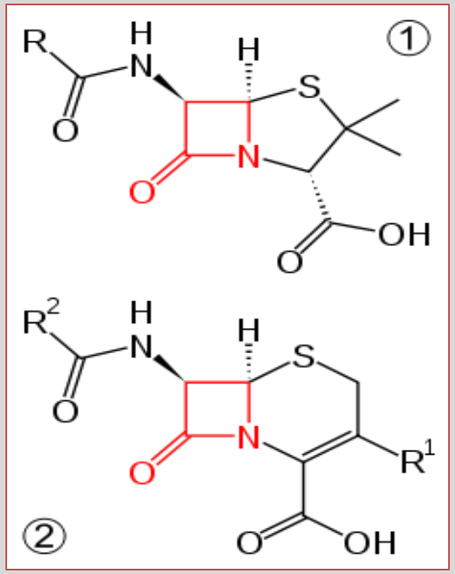
Beta-Lactam Antibiotics

Penicillins

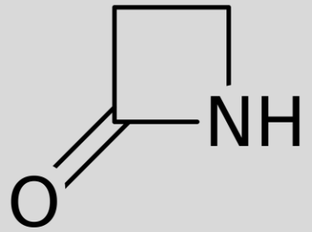
Cephalosporins

Carbapenems

Monobactam



core stuctures of penicillin (1) and cephalosporins (2)



β-lactam ring

Beta-Lactam Antibiotics Structure-Activity Relationship

- **Activity:** β-lactam ring (B in figure)
- **Inactivation:** Bacterial β-lactamases cleave the β-lactam ring.
- **Pharmacologic properties:**

Different side chains/rings (R groups) determine:

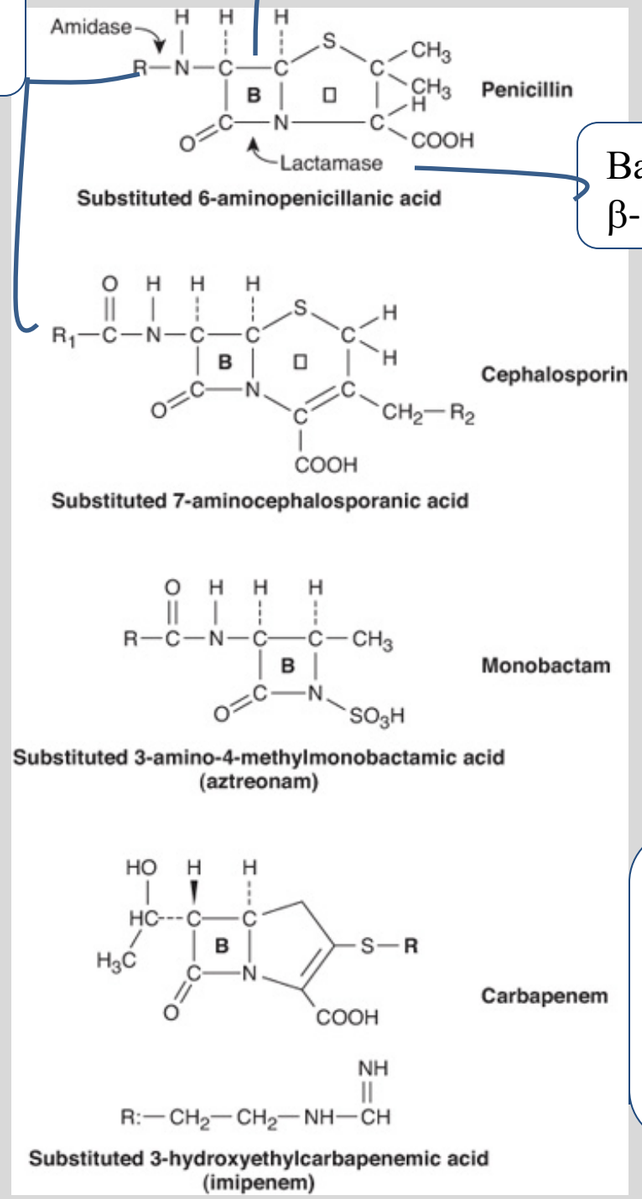
1- **Spectrum of action** – penetration and affinity for target – and

2- **Stability** to enzymatic or acidic hydrolysis by β-lactamases.

- Amidase: Cleaves side chain amide bond; penicillin amidase is used in the manufacture of semisynthetic β-lactam antibiotics.

β-lactam ring

R groups change the properties of drug.



Carbapenems resist β-lactamases due to their different stereochemical features.

Basic & Clinical Pharmacology Figure 43-1

Pharmacokinetics: Beta-lactams class properties

PK properties are related antibacterial to efficacy.

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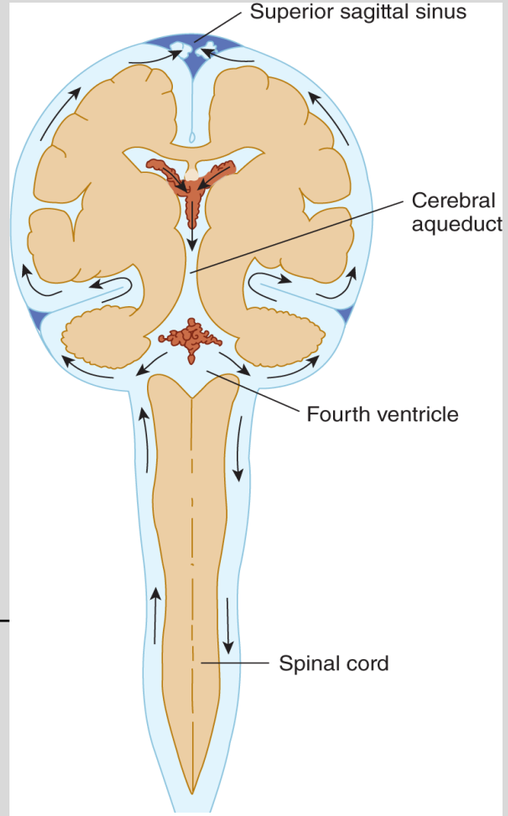
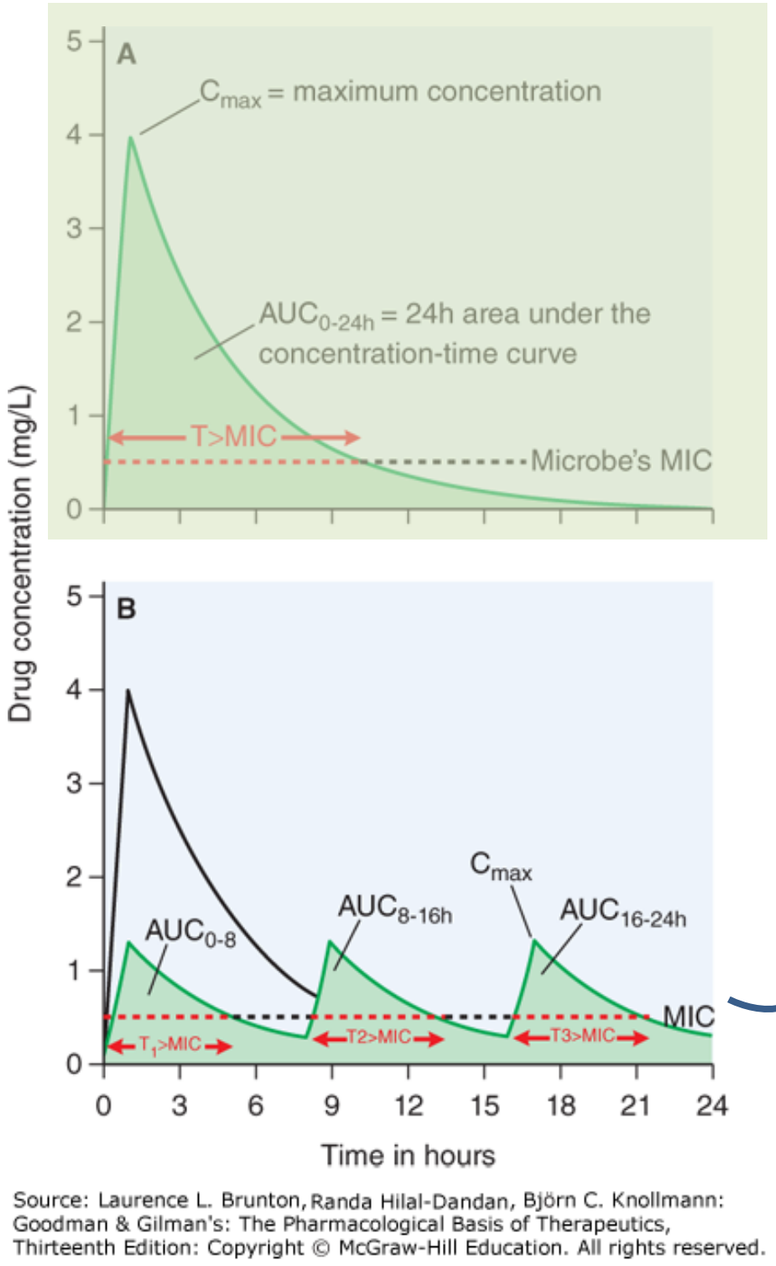
A	Oral; IM; IV Intrathecal is **contraindicated**. IT admin can cause arachnoiditis and severe and fatal encephalopathy.
D	Widely distributed in body fluids and tissues Poor penetration in CSF (non-inflamed); vitreous fluid; prostate; phagocytic cells Therapeutic concentrations are achieved when meninges are inflamed Ceftriaxone, cefotaxime, cefuroxime, cefepime → good penetration even when meninges are not inflamed
E	Renal elimination (glomerular filtration / secretion) Penicillinase-resistant ("antistaphylococcal"): hepatic metabolism
t½	short ~30-60 minutes (ceftriaxone is an exception)



Schematic illustration, in coronal projection, of the circulation (arrows) of CSF.

Figure: http://www.fpnotebook.com/legacy/Neuro/Exam/CrbrlSpnlFld.htm



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.

Beta-Lactams PK-PD Profile: **T>MIC**

The amount of time during the dosing interval that the serum drug concentration stays above the MIC.

- Time-dependent

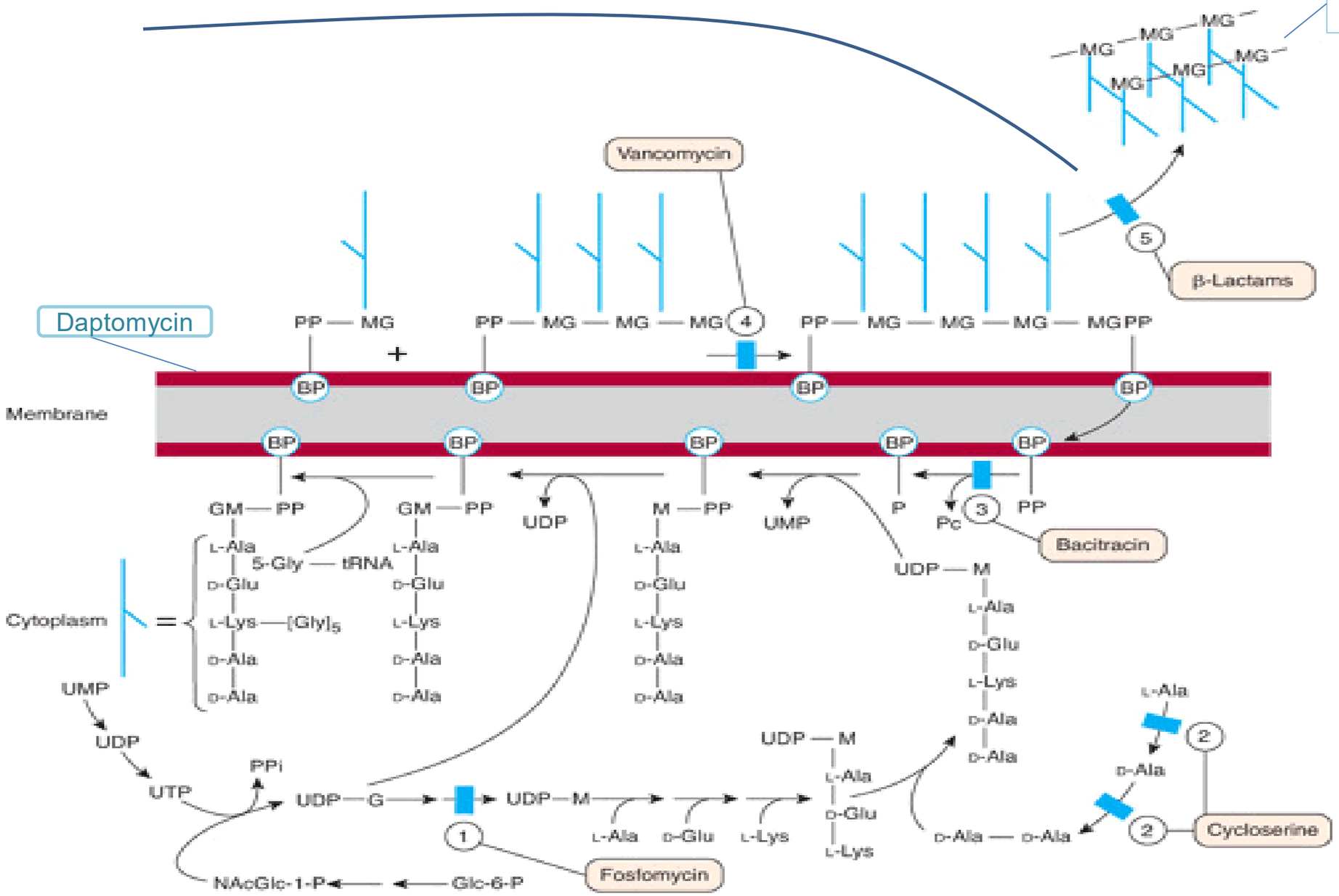
and concentration-independent

- Minimal persistent effects
- Bactericidal

Effect of different dose schedules on shape of the concentration-time curve. The same total dose of a drug was administered as a single dose (panel A) and in three equal portions every 8 h (panel B). The total AUC for the fractionated dose in B is determined by adding $AUC_{0–8h}$, $AUC_{8–16h}$, and $AUC_{16–24h}$, which totals to the same $AUC_{0–24h}$ in A. The time that the drug concentration exceeds MIC in B is also determined by adding T_1 > MIC, T_2 > MIC, and T_3 > MIC, which results in a fraction greater than that for A.

Citation: Chapter 52 General Principles of Antimicrobial Therapy, Brunton LL, Hilal-Dandan R, Knollmann BC. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e;* 2017 Figure 52-4. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=2189&sectionid=172483986 Accessed: September 23, 2021

Target of Beta-Lactams: Peptidoglycan cell wall

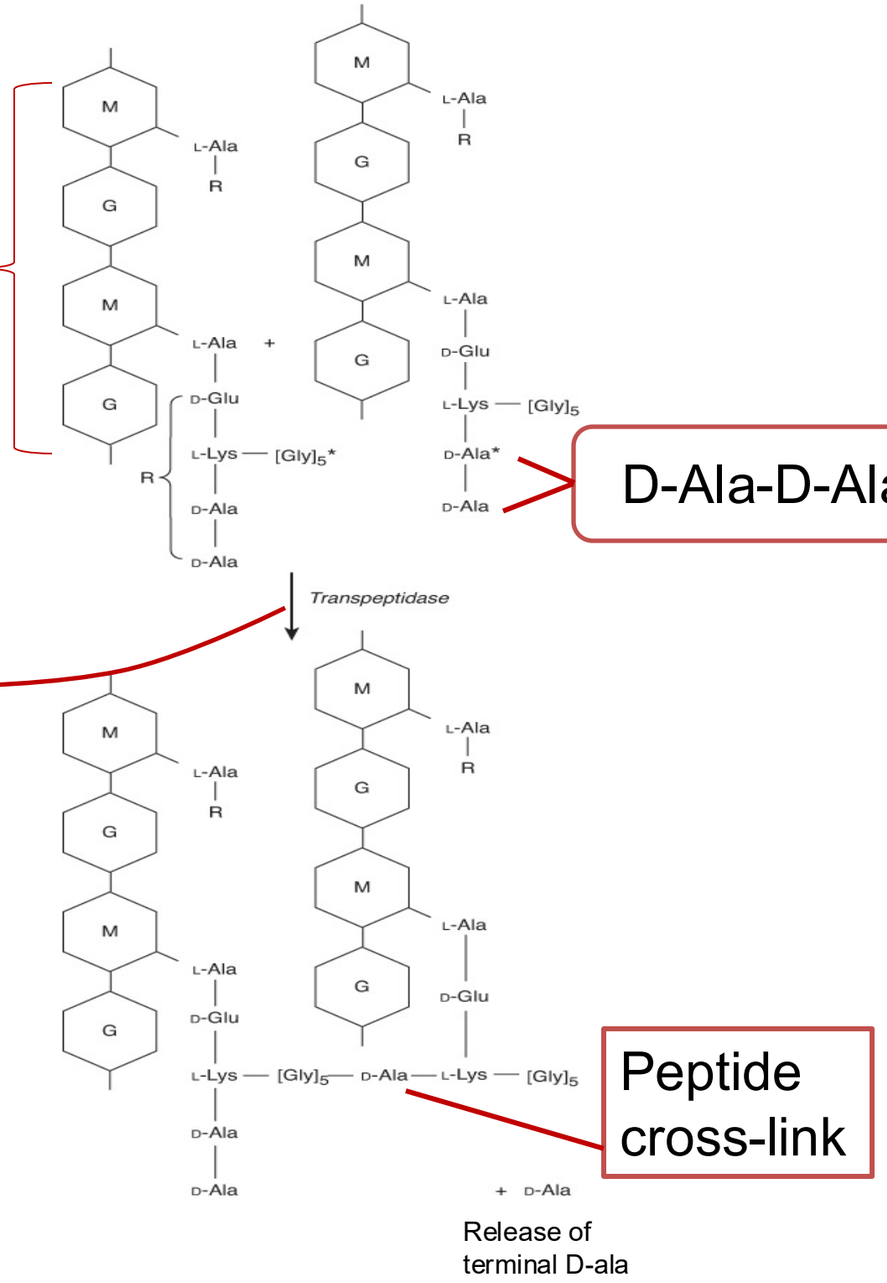


- The peptidoglycan cell wall is built molecule by molecule in the cytoplasm.
- The NAM/NAG-pentapeptide subunits are ferried across the plasma membrane by bactoprenol (BP).
- Cell wall construction is completed externally.

Basic & Clinical Pharmacology, 2013 Figure 43-5

NAG-NAM-pentapeptide subunits

PBP = bacterial enzymes involved in final stages of peptidoglycan synthesis (drug target)



D-Ala-D-Ala

Peptide cross-link

Release of terminal D-ala

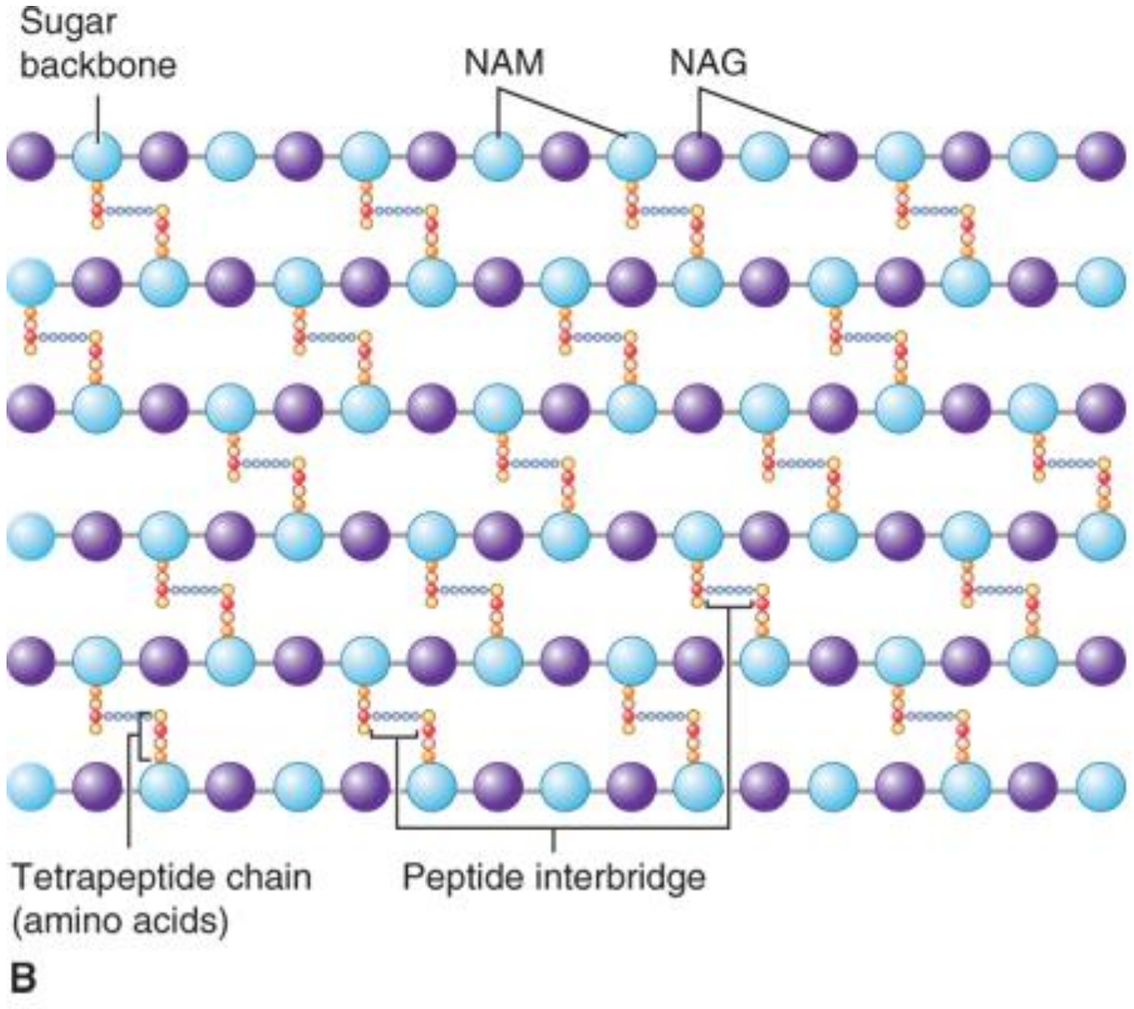
Beta-lactams
bind transpeptidase (PBP)
↓
blocks peptide cross-linking
↓
blocks cell wall synthesis
↓
triggers bacterial autolysins
↓
Osmotic rupture

plus, probable non-lytic mechanisms

This figure shows *Staphylococcus aureus* cell wall synthesis.

The Legend for this slide is in the notes section of this PowerPoint slide.

Citation: Chapter 43 Beta-Lactam & Other Cell Wall- & Membrane-Active Antibiotics, Katzung BG, Vanderah TW. *Basic & Clinical Pharmacology, 15e;* 2021, Figure 43-4. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=2988&sectionid=250601638 Accessed: September 24, 2021



Source: W. Levinson, P. Chin-Hong, E.A. Joyce, J. Nussbaum, B. Schwartz: Review of Medical Microbiology & Immunology: A Guide to Clinical Infectious Diseases, Seventeenth Edition: Copyright © McGraw Hill. All rights reserved.

Peptidoglycan structure. A: Peptidoglycan is composed of a glycan chain (NAM and NAG), a tetrapeptide chain, and a cross-link (peptide interbridge). B: In the cell wall, the peptidoglycan forms a multilayered, three-dimensional structure. NAG, N-acetylglucosamine; NAM, N-acetylmuramic acid. (Reproduced with permission from Nester EW, Anderson D, Roberts CE, et al: Microbiology: A Human Perspective, 6th ed. New York, NY: McGraw Hill; 2009.)

Mechanisms of resistance to the Beta-lactams

Acquired resistance

Enzymatic degradation of the drugs.

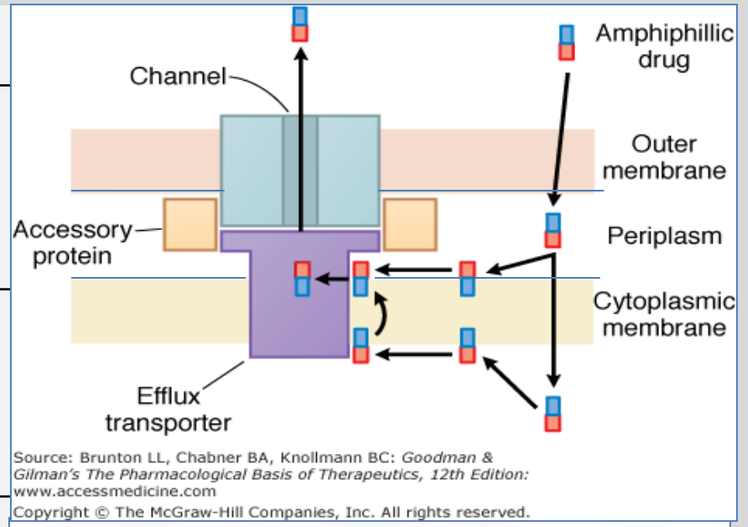
- β-lactamases cleave the beta-lactam ring, which inactivates the drugs.
- Staphylococcus (MSSA), GNBs (major mechanism of resistance)

Modification of penicillin binding protein (PBP) drug target

- Mutations in the transpeptidase (PBP) genes result in low affinity binding of drug.
- *Staphylococcus* (MRSA), *S. pneumoniae*, *Enterococcus*

Reduced drug concentration at the site of action.

- Changes in the aqueous channels (porins) of Gram-negative bacteria that prevent the drugs from penetrating the outer membrane → the drug does not reach the target PBP
- Antibiotic efflux by Gram-negative bacteria → drug is transported out of periplasmic space back across cell wall outer membrane



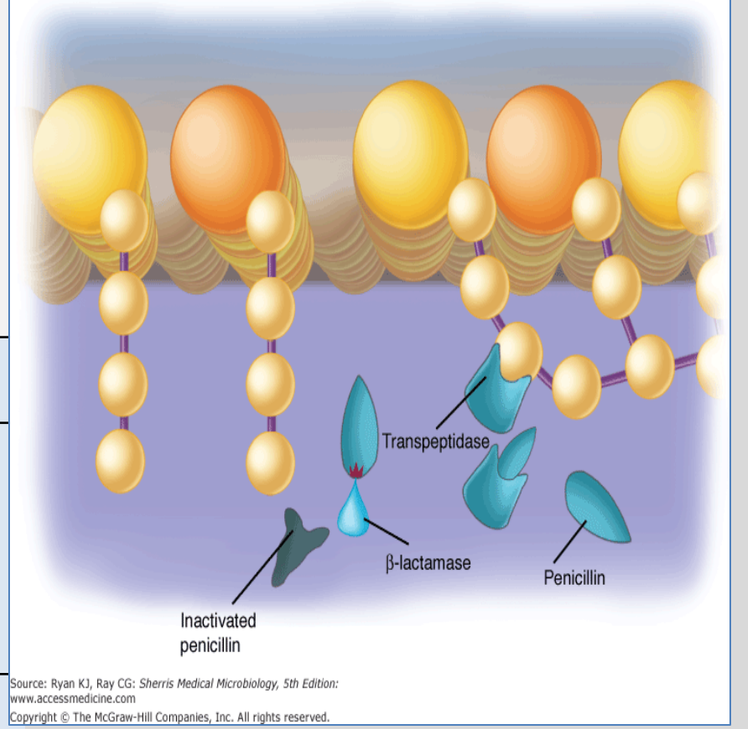
Intrinsic resistance

Obligate intracellular bacteria

- Beta-lactams do not penetrate into host cells.
- "Atypicals": Chlamydiaceae, Legionella, Rickettsia

Bacteria that lack peptidoglycan cell wall: *Mycoplasma*

Mnemonic: 6 Ps
Penicillinases
(= β-lactamases)
PBPs
Porins
Pumps
Penetration
Peptidoglycan



Beta-Lactams are useful in the treatment of SUSCEPTIBLE bacterial infections involving all organ systems.

For example:

- Skin and skin structures
- Central nervous system (meningitis)
- Respiratory tract
- Endocarditis
- Genitourinary tract infections
- Bacteremia
- Peritonitis
- Syphilis (penicillin G)

Drug selection

- A drug with activity against the infectious pathogen
- That distributes to the site of action
- At a dose that achieves adequate therapeutic concentration
- By an appropriate route of administration
- And is not contraindicated in the individual patient.

HYPERSENSITIVITY REACTIONS

- **the most important adverse effect of the penicillins**

  Hapten formation: Penicillins and other beta-lactams can covalently bind to certain proteins on the red blood cell membrane. Antibodies created against the complex can stimulate an immune attack, which can lead to hemolytic anemia.

- **potential cross-reactivity with the other beta-lactams –**

  Cross-reactivity potential with cephalosporins and other beta-lactams is related to the structural similarity of the side chains.

- Skin testing of patients who report an immediate reaction to penicillin is recommended.

  Estimated cross-reactivity in patients who reported PCN allergy (without confirmatory testing) range between 0.8% and 8.1%, based on retrospective studies.
  Up to 10% of patients report a penicillin allergy. More than 90% do not have an IgE-mediated sensitivity when skin testing is performed. Among those with positive skin testing, 97% will tolerate cephalosporins and 99% will tolerate carbapenems, according to available studies.

  Caution: Remember – Beta-lactams are among the leading causes of drug-induced anaphylaxis.

Check your knowledge

1. What are the mechanisms of resistance to the beta-lactam antibiotics?
2. What is the most important adverse effect of the beta-lactam antibiotics as a class?
3. What are two common secondary infections that can occur with antibiotic use?
4. Probenecid is an OAT inhibitor that is sometimes used with penicillin for its beneficial drug-drug interaction? What is it?
5. What is the reason for the recommendation to people taking hormonal contraceptives to prevent pregnancy for using a barrier contraceptive method during and after antibiotic therapy?
6. What route of beta-lactam administration is not recommended? Why?
7. Why is it important for clinicians and students to have a basic knowledge of the normal microbiota of the various body sites?
8. Why is it important to have a basic knowledge of the morphologic and growth classifications of bacteria?
9. Why are antibiotics not used for the treatment of viral infections, such as common upper respiratory infections?

Ambler Classification of β-Lactamases
and
Pharmacology of Beta-Lactamase Inhibitors

Thousands of β-lactamases – plasmid transmissible and chromosomal replication

What is the clinical importance of knowing the classes?

To understand mechanisms of resistance and the function and effects beta-lactamase inhibitors.

The Ambler Classification of β-Lactamases

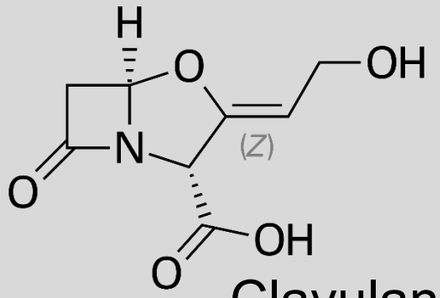
Class A	**ESBLs** (extended spectrum β-lactamases): TEM, SHV, CTX-M: Resistance to most β-lactams **KPC: Carbapenemase** *Beta-lactamase inhibitors usually block Class A β-lactamases.*	Serine β-lactamases
Class C	AmpC, CMY: Resistance to broad and extended-spectrum beta-lactam antibiotics	
Class D	OXA-type: ESBLs and Carbapenemases	
Class B	IMP, VIM, GIM, SPM, SIM: Carbapenemases New Delhi (NDM-1): Carbapenemases ***Not inhibited by any of the beta-lactamase inhibitors.***	Metallo-β-lactamases

Beta-Lactamase Inhibitors

(formulated only in fixed combinations with β-Lactam antibiotics)

1. ✳Clavulanic acid
2. ✳Sulbactam
3. ✳Tazobactam

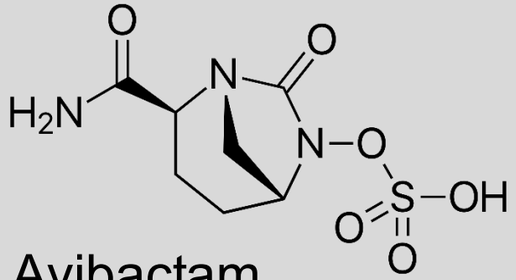
Beta-lactam structure



Clavulanic acid

4. ✳Avibactam
5. ✳Vaborbactam
6. ✳Relebactam
7. ✳Durlobactam

Non-beta-lactam structure



Avibactam

Mnemonic: (the) Cat Sleeps Tight (and has) A Very Real Dream AI-generated

Mechanisms: Beta-Lactamase Inhibitors

The antibacterial spectrum is determined by the beta-lactam antibiotic, not the beta-lactamase inhibitor.

Beta-lactamase inhibitors have only weak antibacterial activity on their own.
Adverse effects: hypersensitivity reactions; secondary *C. difficile* infection

Irreversible (suicide) inhibitors:

Clavulanic acid, Sulbactam, Tazobactam

- Inhibit mainly Ambler class A β-lactamases

Potent, reversible inhibitors:

Avibactam, Vaborbactam, Relebactam, Durlobactam

- Inhibit Ambler class A, and C β-lactamases

The reversible inhibitors lack the beta-lactam structure characteristic of the suicide inhibitors.

*Sulbactam is bactericidal against *A. baumannii.* Sulbactam binds A. baummanii transpeptidases PBP1 and PBP3. Sulbactam-durlobactam treats hospital-acquired and ventilator-associated bacterial pneumonia caused by susceptible isolates of *Acinetobacter baumannii-calcoaceticus* complex. Sulbactam-durlobactam has *no other indications*.

For context only. No need to memorize.

Wong D, van Duin D. Novel Beta-Lactamase Inhibitors: Unlocking Their Potential in Therapy. Drugs (2017), 77, 615-618; PMCID5473160; PMID28303449; doi: 10.1007/s40265-017-0725-1

Beta-Lactamase Inhibitors Activity

		Class A ESBLs	Class A KPC carbapenemases	Class D	Class C Ambler-type (AmpC)	Class B metallo-beta-lactamases
irreversible	Clavulanic acid	✓				None of the beta-lactamase inhibitors is effective.
	Sulbactam	✓				
	Tazobactam	✓				
potent reversible	Avibactam	✓	✓ (some)	✓ (some)	✓	
	Vaborbactam	✓	✓ (some)		✓	
	Relebactam	✓	✓ (some)		✓	
	Durlobactam	✓	✓ (some)	✓ (some)	✓	

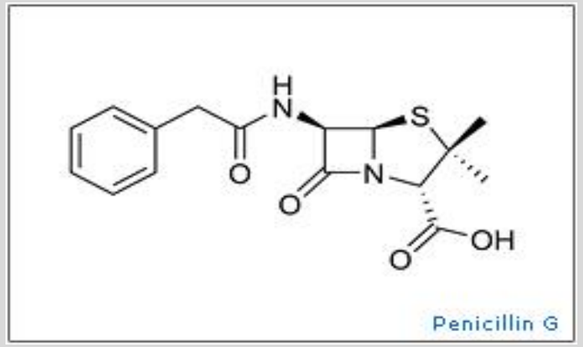
Gram-negative bacteria that express inducible chromosomal AmpC β-lactamases include: *Serratia*, *Pseudomonas, indole-positive Proteus, Citrobacter, Enterobacter* (S.P.I.C.E.)

Questions: You may want to pause the video and think about them.

1. Why is it important when learning the pharmacology of antibiotics to be able to explain some rudimentary microbiology of the various microbes?
2. Why is it important to understand the classifications of the beta-lactamases?
3. Give examples of Ambler class A, C, D, and B β-lactamases.
4. What is the takeaway regarding pairing a beta-lactamase inhibitor in fixed combination with a beta-lactam antibiotic?
5. Name the beta-lactamase inhibitors (the Cat Sleeps Tightly and has A Very Real Dream).
6. Which beta-lactamase inhibitors stabilize the partner beta-lactam antibiotic against Ambler class A, ESBLs?
7. Which beta-lactamase inhibitors are effective against Class A KPC carbapenemases, and Class C (AmpC) β-lactamases?
8. Which beta-lactamase inhibitors are active against the Ambler class B metallo-β-lactamases?

Penicillins Class

- Natural penicillins (penicillin G)
- Penicillinase-resistant penicillins
- Aminopenicillins
- Antipseudomonal penicillins



Penicillin's Narrow 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 (high dose)

Obligate G+ Anaerobic

- Clostridia spp
- Clostridioides difficile

Gram-negative aerobes

Pseudomonas aeruginosa

Enterobacterales (rods) (facultative anaerobes)

- Escherichia coli
- Proteus mirabilis
- Klebsiella spp

Respiratory

- Haemophilus influenzae
- Moraxella catarrhalis
- Neisseria meningitidis

STD

- Neisseria gonorrhea

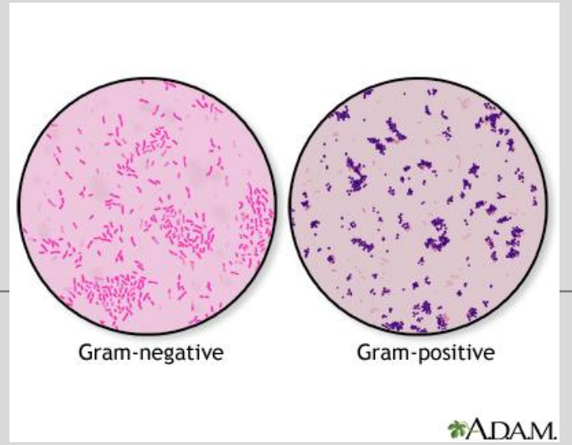
Obligate G– Anaerobic

- 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.

Natural Penicillins: Adverse Effects

Hypersensitivity reactions, anaphylaxis

Seizures	High dose penicillin
Electrolyte disturbances	Drugs are formulated as Na^+ and K^+ salts. Penicillin G aqueous has a short t½ and T>MIC with minimal persistent effects. I.V. administration 6 times daily or by continuous infusion.
Jarisch-Herxheimer reaction	Syphilis: Acute, self-limited, febrile reaction to antibiotic treatment, which often resolves 12-24 hours without intervention. Proposed mechanism: Immune reaction in response to lipoproteins released by dying *Treponema pallidum* spirochetes with subsequent proinflammatory cascade Management: Symptomatic, NSAIDs or acetaminophen

Penicillinase-Resistant Penicillins' Narrow Spectrum of Activity

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Strike through = once susceptible but now significant resistance to penicillin

Gram-positive

Cocci

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

Bacillus (rod)

- C. diphtheriae
- Listeria monocytogenes

Obligate Anaerobic

- Clostridia spp
- Clostridioides difficile

Gram-negative aerobes

Pseudomonas aeruginosa

Enterobacterales (rods)

(facultative anaerobes)

- Escherichia coli
- Proteus mirabilis
- Klebsiella spp

Respiratory

- Haemophilus influenzae
- Moraxella catarrhalis
- Neisseria meningitidis

STD

- Neisseria gonorrhea

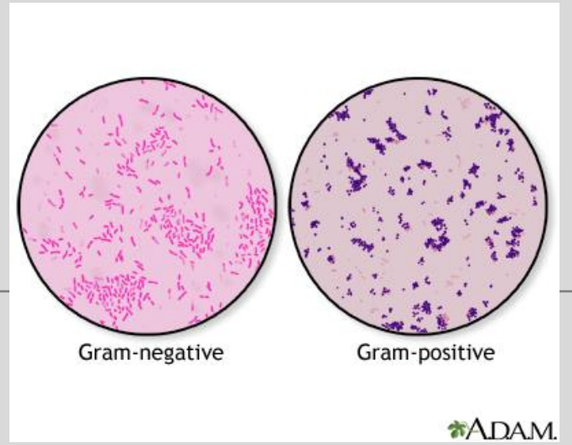
Obligate Anaerobic

- 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
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Penicillinase-resistant penicillins

PK	Nafcillin, Oxacillin: IM, IV; Dicloxacillin, Cloxacillin: oral Hepatic elimination (nonrenal clearance) Dose adjustment not necessary for renal impairment • Caution in patients with hepatic impairment
Activity	MSSA / MSSE: Penicillinase-producing *S. aureus*, *S. epidermidis*
Resistance (common)	MRSA / MRSE: Modification of staphylococcal PBPs **PBP2a (*MecA* gene)** → very low affinity for all beta-lactam antibiotics
Therapeutic use	MSSA / MSSE infections only (Penicillin-susceptible strains of streptococci are also susceptible but penicillin is more active against them, therefore preferred.)
Adverse effects	Hepatitis: direct toxicity and hypersensitivity reaction Acute interstitial nephritis (rare)

MSSA / MSSE: Methicillin sensitive *S. aureus*, *S. epidemidis*
MRSA / MRSE: Methicillin resistant *S. aureus*, *S. epidemidis*

Aminopenicillin's Spectrum of Activity

(without beta-lactamase inhibitor combination)

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Gram-positive

Cocci

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

Bacillus (rod)

- C. diphtheriae (PCN preferred)
- Listeria monocytogenes

Obligate G+ Anaerobic

- Clostridia spp
- Clostridioides difficile

Gram-negative aerobes

Pseudomonas aeruginosa

Enterobacterales (rods)

(facultative anaerobes)

- ~~Escherichia coli~~
- ~~Proteus mirabilis~~
- Klebsiella spp

and several others

Respiratory

- Haemophilus influenzae
- Moraxella catarrhalis
- Neisseria meningitidis

STD

- Neisseria gonorrhea

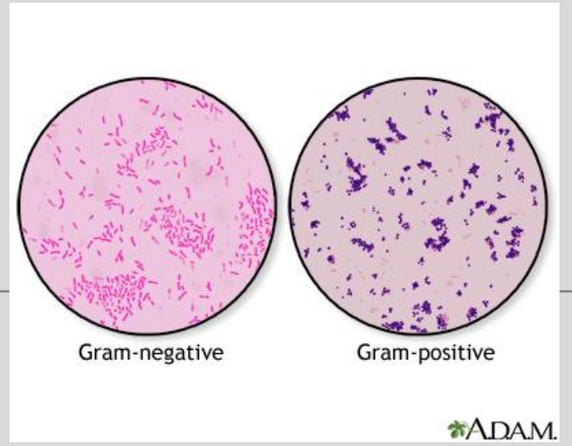
Obligate G– Anaerobic

- Bacteroides fragilis

Spirochetes

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

- Treponema pallidum
- Leptospira
- Borrelia burgdorferi



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Extended-spectrum penicillins

Antipseudomonal Penicillins

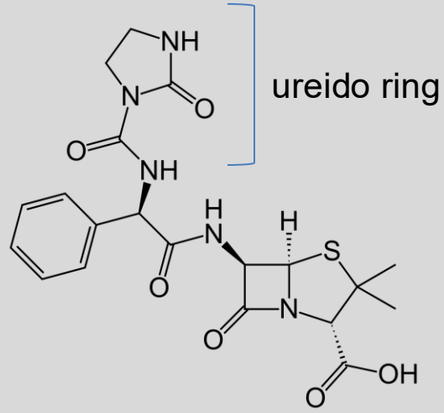
Piperacillin-tazobactam (parenteral only)

Piperacillin
Ticarcillin-clavulanate } No longer available

Structure: Piperacillin is a ureidopenicillin.

Class PK properties

- Not metabolized
- High concentrations excreted in urine.
- Short half-life: IV may be administered by continuous infusion.



Piperacillin-Tazobactam's Spectrum of Activity

(without beta-lactamase inhibitor combination)

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Gram-positive

Cocci

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

Bacillus (rod)

- C. diphtheriae (PCN preferred)
- Listeria monocytogenes

Obligate G+ Anaerobic

- Clostridia spp
- Clostridioides difficile

Gram-negative aerobes

Pseudomonas aeruginosa

Enterobacteriaceae (rods)

(facultative anaerobes)

- Escherichia coli
- Proteus mirabilis
- Klebsiella spp

and many others

Respiratory

- Haemophilus influenzae
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Obligate G– Anaerobic

- Bacteroides fragilis

Spirochetes

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

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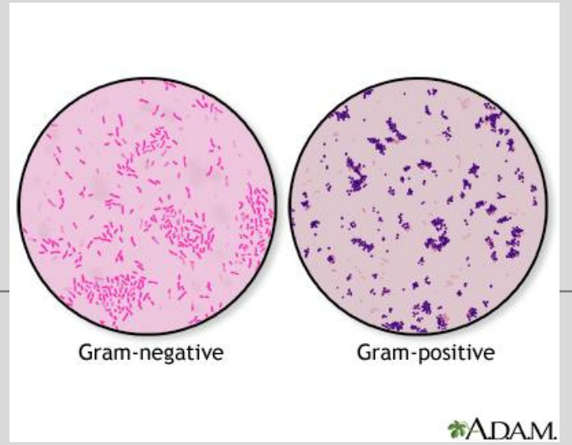

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Piperacillin-Tazobactam

The broadest antibacterial spectrum of the penicillins class

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Activity	The same activity as the aminopenicillins *plus* *Pseudomonas aeruginosa* • Polar side chains allow the drug to pass through the porins of *P. aeruginosa* and many GNBs (gram-negative bacilli).
Therapeutic uses	Bacteremia, pneumonias, burns, appendicitis, gynecologic infections, urinary tract infections

Adverse effects

Congestive heart failure exacerbation: Na^+ salts, frequent administration

Abnormal platelet aggregation, thrombocytopenia $\rightarrow$ bleeding disorders

Leukopenia/neutropenia (long-term use)

Seizure disorders (high doses; renal impairment)

Pseudomonas aeruginosa is a gram-negative rod, obligate aerobe. It is an important nosocomial pathogen that produces infection in patients with abnormal immune systems. It has intrinsic resistance to many antibiotics and it produces beta-lactamases that can inactivate penicillins, cephalosporins, and carbapenems.

Questions: You may want to pause the video to think about the answers.

1. Which drug in the penicillins class has the broadest spectrum of activity?
2. Activity against what microbe sets it apart from the other penicillins?
3. Which drug in the penicillins class has an extended spectrum of activity and 100% oral bioavailability?
4. Which drug in the penicillins class has excellent activity against, and is preferred, for the treatment of *Treponema pallidum* infection?
5. Which gram-negative coccus that causes meningitis is susceptible to intravenous penicillin G?
6. How did ampicillin, amoxicillin, and piperacillin get the name “extended-spectrum” penicillins?
7. Which drugs in the beta-lactams group are effective against the atypical organisms that cause community-acquired atypical pneumonia?
8. What is the most serious adverse effect of the penicillins class?
9. Which antibiotics are highly active against and preferred for the treatment of infections caused by penicillinase-producing *S. aureus*?

Summary of penicillins class of beta-lactam antibiotics and beta-lactamase inhibitors

- Beta-lactam antibiotics require an intact β-lactam ring for activity.
- Beta-lactam antibiotics inhibit transpeptidases (PBPs), which prevents cross-linking of the peptidoglycan subunits, the final step in cell wall synthesis. Bacterial autolysins are triggered leading to osmotic rupture of the cell. Nonlytic mechanisms causing collapse of the membrane potential may also be involved.
- The microorganisms must be proliferating – synthesizing cell walls – for the beta-lactam antibiotics to be fully effective.
- The antibacterial spectrum is determined by the drugs' ability to access the PBPs, which is determined by the drug's molecular size, charge, and hydrophobicity.
- Penicillins readily access PBPs of gram-positive bacteria. Gram-negative bacteria are surrounded by an outer lipopolysaccharide membrane. Drugs in the penicillins group active against these organisms must pass through the aquaporins inserted in the membrane to access the PBPs in the cell wall.

- Penicillin G has activity against susceptible streptococci, gram-positive anaerobes, such as *Clostridium* spp (except *C. difficile*), and *Trepanema* spirochetes. It is the drug of choice for the treatment of syphilis. Penicillin G is more potent than penicillin V. Penicillin V is more acid stabile than penicillin G and can be taken orally (empty stomach).
- Penicillinase-producing staphylococci are resistant to penicillin G (natural penicillins).
- The penicillinase-resistant penicillins, nafcillin, oxacillin, dicloxacillin, and cloxacillin, are preferred drugs for the treatment of methicillin-sensitive staphylococcal infections, MSSA and MSSE. Methicillin-resistant *S. aureus* (MRSA) expresses modified PBP2a (*mecA* gene) with low affinity for the beta-lactam antibiotics.
- The penicillinase-resistant penicillins are cleared by nonrenal elimination. Dosage adjustment in patients with renal impairment is not required. Caution should be used in patients with hepatic impairment.

- The aminopenicillins (extended-spectrum penicillins) have the gram-positive activity of penicillin G. A structural modification increases their spectrum to include gram-negative respiratory pathogens and some Enterobacterales (enteric GNBs), such as *E. coli*, *P. mirabilus*, and *Salmonella*. Ampicillin is the drug of choice for *Listeria monocytogenes* infections and susceptible enterococci (combination therapy for synergy).
- Amoxicillin and ampicillin are available with or without co-formulation with the beta-lactamase inhibitors clavulanate and sulbactam, respectively. The beta-lactamase inhibitors expand their gram-negative activity.
- Piperacillin is an extended-spectrum penicillin active against *Pseudomonas aeruginosa*, thus, the designation antipseudomonal penicillin. It is co-formulated with the beta-lactamase inhibitor tazobactam. Piperacillin-tazobactam has the broadest spectrum of action of all the penicillins.

- Clavulanic acid, sulbactam and tazobactam are irreversible inhibitors of beta-lactamase.
- Avibactam, relebactam, vaborbactam, and durlobactam are potent reversible inhibitors.
- All beta-lactamase inhibitors inhibit the activity of several plasmid-mediated Ambler class A β-lactamases of staphylococci, *H. influenzae, N. gonorrhoeae, E. coli, Klebsiella, Salmonella, Shigella*; *Bacteroides fragilis,* and *Moraxella catarrhalis.*
- Avibactam, vaborbactam, relebactam, and durlobactam inhibit Class A beta-lactamases, including some KPC carbapenemases, and plasmid- and chromosomally mediated Class C (AmpC) β-lactamases. They are not active against metallo-beta-lactamases.
- Combinations of beta-lactamase inhibitors with extended-spectrum penicillins, some cephalosporins, and carbapenems result in antibiotics with expanded spectrums of activity against many, but not all, organisms containing plasmid-mediated β-lactamases.

Answers to questions on Slide 43.

1. To understand the mechanisms of antibacterial actions, it is necessary to understand the targets – pharmacology. Antibiotics are developed to eradicate microbial infections – pharmacotherapy.
2. There are hundreds of beta-lactamases expressed by the various bacteria, especially GNBs. Resistance is a serious, worldwide challenge. Knowing what beta-lactamases are prevalent will help clinicians to select the appropriate drugs to treat drug-resistant, including MDR, bacterial infections.
3. Class A ESBLs: TEM, SHV, CTX-M, ESBLs, and also KPCs.
4. Beta-lactamase inhibitors extend the spectrum of the beta-lactam antibiotics against beta-lactamase-expressing GNBs. The antibiotics are once again effective in killing the microbes.
5. Irreversible inhibitors clavulanic acid, sulbactam, tazobactam. Potent reversible inhibitors avibactam, vaborbactam, relebactam, durlobactam.
6. All of the beta-lactamase inhibitors are active against extended-spectrum beta-lactamases, which confer resistance to extended-spectrum cephalosporins – ceftriaxone, cefotaxime, ceftazidime – and to cefepime, cefazolin, penicillins, aztreonam.
7. Avibactam, vaborbactam, relebactam, durlobactam
8. None.