

# Pharmacology of Antibiotics

## Beta-Lactams, Other Cell Wall Inhibitors and Cell Membrane Inhibitors

### Part 1

## The Penicillins Class & Beta-Lactamase Inhibitors

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Do.  
Make.  
Heal.  
Innovate.  
Reinvent the Future.

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

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Do.  
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Reinvent the Future.

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.
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.

Mechanisms  
Mechanisms  
Mechanisms

Patient  
safety

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

### Required

- ScholarRx Bricks | Practice

### 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&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

## Study hints – Basics → Patterns → Chunking

- Pharmacology is about drugs.
- Drugs are for treating patients.
- To treat infection, you need to understand the causative agents and goals of therapy.

### How

- Brush up on the **basics** of bacteriology. What you need to know for this course is in my handout and ScholarRx (link provided on the previous slide).
- Look for **patterns**.
- “**Chunk**” concepts together. This practice reduces the volume to be learned.
- There are only 4 main categories of bacteria related to the antibiotics lectures:  
Gram-positive, Gram-negative, Spirochetes, “Atypicals”
- There are 4 main subcategories:  
Cocci, Bacilli (rods), Aerobic and Anaerobic
- You don’t need to memorize every single bacterial pathogen for this course. You do need to be able to fit very common pathogens into their categories.
- **Then use the same method – patterns, chunking, spectrums of action – for learning the antibiotic classes and subclasses and the specific starred drugs.**

Antibiotic  
Spectrums  
of action



<https://www.fairmanstudios.com/project/otitis-media-2/>

The following microbiology concepts are touched on in this lecture.

An understanding of them is ESSENTIAL for understanding the pharmacology of antibacterial drugs. (Detailed explanations are in the Notes Handout.)

Differentiation of the bacteria based on their Gram stains (Gram-positive or Gram-negative) and growth environments is important for understanding antibacterial mechanisms of action and microbial mechanisms of resistance.

- Prokaryote structure and Gram stain | cocci (spheres), bacilli (rods), spirochetes (spiral)
- Gram-positive bacteria | Gram-negative bacteria including spirochetes | Atypical bacteria
- Some bacteria require an aerobic or anaerobic environment for growth. These are categorized as “obligate aerobes” and “obligate anaerobes”, respectively.
- Facultative anaerobic organisms can proliferate in both aerobic and anaerobic environments. They are categorized as “aerobes”. Enterobacterales is an important group of Gram-negative facultative anaerobic bacilli (GNBs) that can cause serious infections.
- Some microbes proliferate only within host cells. These are “obligate intracellular” organisms.
- Microbes develop drug resistance by selection pressure – mutations in the genes of structural or metabolic proteins that occur in the presence of a drug and confer the ability to proliferate in the presence of the drug.
- Bacteria develop resistance through chromosomal mutations and by plasmid transfer of resistance genes among and between bacterial species.

You may find ScholarRx Bricks General Microbiology helpful with these topics.

# Bacterial pathogens to know by name and type for this course

Antimicrobial therapeutic use requires knowledge of the pathogens.

**Basics  
Patterns  
Chunking**

## 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*

## Gram-negative aerobes

- Pseudomonas aeruginosa* (soil, water, vegetation)
- Enterobacterales (gut flora)
  - *Escherichia coli*
  - *Proteus mirabilis*
  - *Klebsiella spp*
- Respiratory flora
  - *Haemophilus influenzae*
  - *Moraxella catarrhalis*
  - *N. meningitidis* (cocci)
- STD
  - *N. gonorrhoeae* (cocci)
  - N= *Neisseria*

## Spirochetes

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

## Atypicals\*

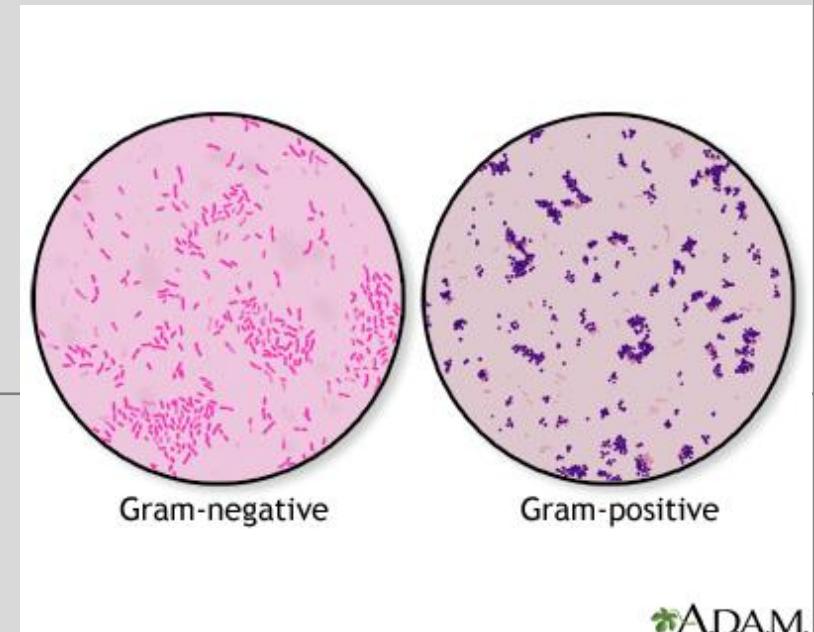
- Bacteria remain colorless when gram-stained
  - *Mycoplasma*
  - *Chlamydiaceae*
  - *Legionella*
  - *Rickettsia*
- STD
  - *Chlamydia trachomatis*

\*Not visible on Gram stain

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

- Obligate Anaerobic Bacilli
  - *Clostridia spp*
  - *Clostridioides difficile*

- Obligate Anaerobic GNB
  - *Bacteroides fragilis*



## 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.

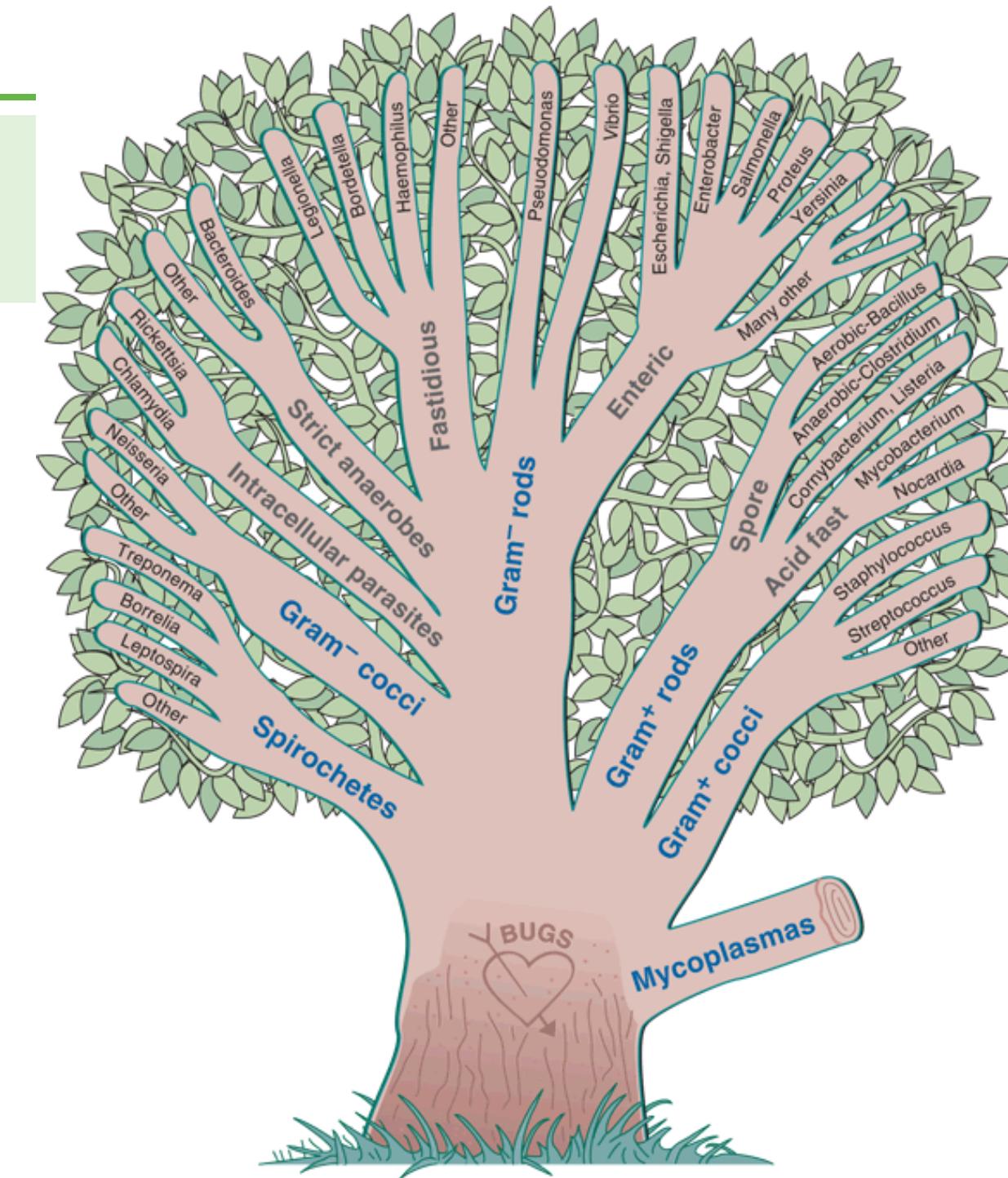
Routes of administration (and why), absorption, distribution in body water and penetration of tissues, elimination (metabolism and/or excretion), half-life, onset and duration of action.
- Pharmacodynamics: Bactericidal effects (and sometimes bacteriostatic effects)
- PK-PD profile: T>MIC and minimal 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-affinity 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.

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Date of download: 9/23/2021

## Normal human microbiota

We harbor 10 times more microbial cells than human cells. They may have a symbiotic relationship that benefits the host or may simply live as commensals with a neutral relationship. Most have not (yet) been associated with disease.

**Microbiota cause infection when there is a break in the barrier. ← This is the takeaway.**

**Skin** (Know the bacteria bolded in red.)

<b><i>Staphylococcus aureus</i></b>	<b><i>Staphylococcus epidermidis</i></b>	Micrococcus species
<b><i>Streptococcus</i></b> Beta-hemolytic groups A, C, G	<i>Corynebacterium</i> species	<i>Propionibacterium acnes</i>
<i>Peptostreptococcus</i> species (anaerobic)	<i>Acinetobacter</i> species	Others, small amount (Examples: <i>Candida</i> spp, <i>P. aeruginosa</i> )

**Nasopharynx** (Know the bacteria bolded in red.)

Any amount of the following: diphtheroids, nonpathogenic ***Neisseria meningitidis*** and other *Neisseria* species, ***α-hemolytic (viridans) streptococci***; ***S. aureus*** (anterior nares), nonhemolytic ***streptococci***, anaerobes (too many species to list; varying amounts of *Prevotella* species, anaerobic cocci, *Fusobacterium* species, etc)

Lesser amounts of the following when accompanied by organisms listed above: yeasts, ***Haemophilus*** species, ***Streptococcus pneumoniae***, ***S. aureus***, ***Neisseria meningitidis***, Gram-negative bacilli

Anaerobes (too many to list); the following may be important when clearly predominant: *Prevotella*, *Clostridium*, and *Peptostreptococcus* species.

## Normal human microbiota

**Gastrointestinal tract – mainly colon:** The highest microbial density of any human-associated microbial community. The species are far too numerous to list here. Please know those bolded in red, which are related to this lecture.

In the normal adult colon, 96–99% of the resident bacterial flora consists of anaerobes:

Anaerobes: *Bacteroides* species, especially ***Bacteroides fragilis***; *Fusobacterium* species; anaerobic lactobacilli, eg, bifidobacteria; ***Clostridium*** spp; anaerobic gram-positive cocci (*Peptostreptococcus* species).

1–4% are facultative anaerobes:

**Enterobacterales:** ***Escherichia coli*, *Klebsiella*, *Proteus mirabilis*, *Salmonella enterica*, *Shigella***, others

***Enterococcus faecalis*** and ***E. faecium***, pseudomonads, lactobacilli, ***Candida (fungus)*** spp, and other microorganisms.

**Genitourinary tract** Male and female tracts, like other regions, consist of a diverse array of microorganisms.

**Secondary infections can arise from antibiotic therapy.**

**Mechanism of antibiotic adverse effect:** As the antibiotic kills the bacteria in the microbial community, microorganisms not killed by the antibiotic can proliferate and cause infection.

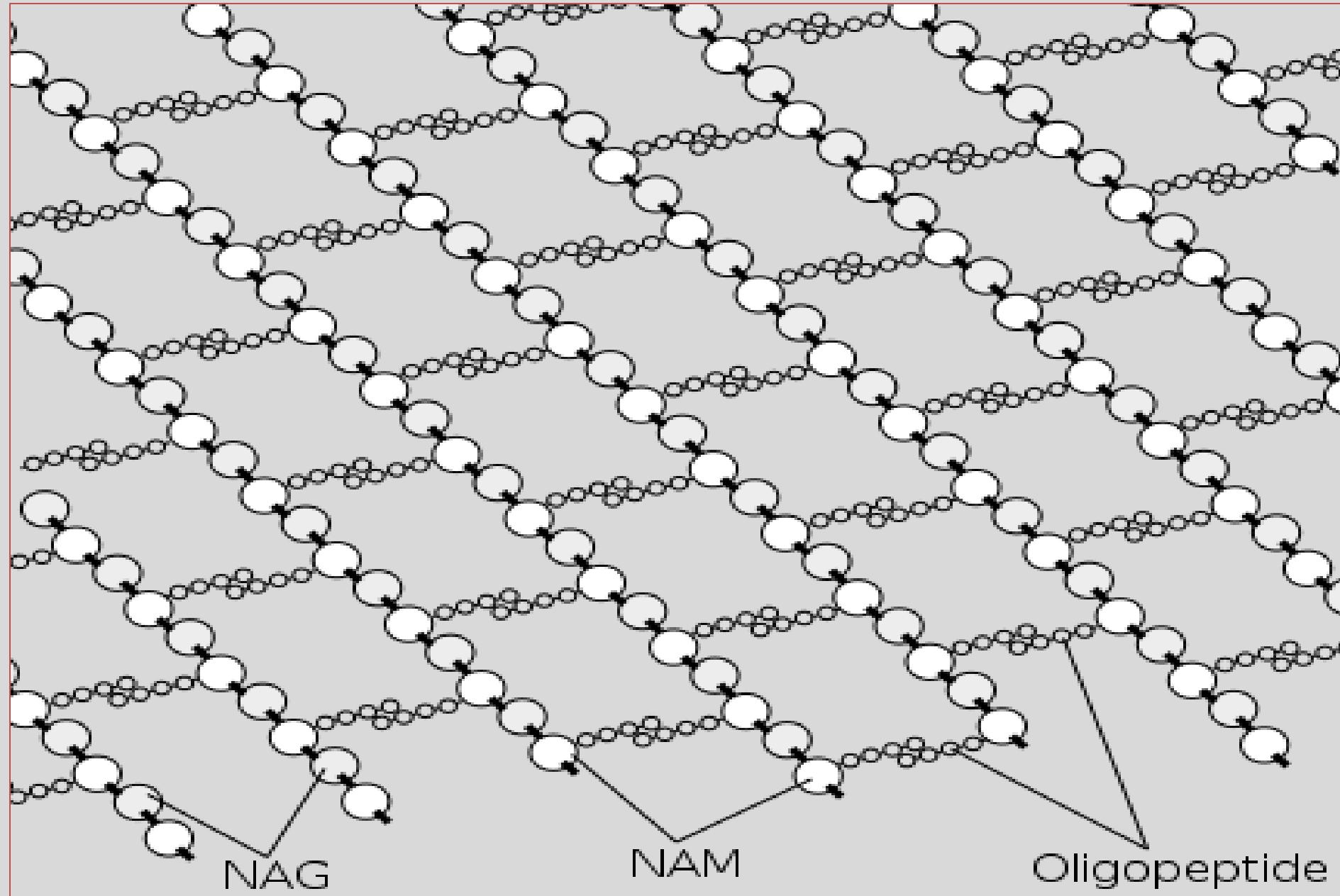
**Colon:** ***Clostridioides difficile*** is a difficult to treat spore-forming Gram-positive anaerobic coccus that occupies the gut of some individuals. Antibiotic therapy can lead to *C. difficile* overgrowth → diarrhea, pseudomembranous colitis, and life-threatening megacolon.

**Vagina:** Lactobacillus is the predominant bacterium (major source of vaginal lactic acid). Other bacteria contribute.

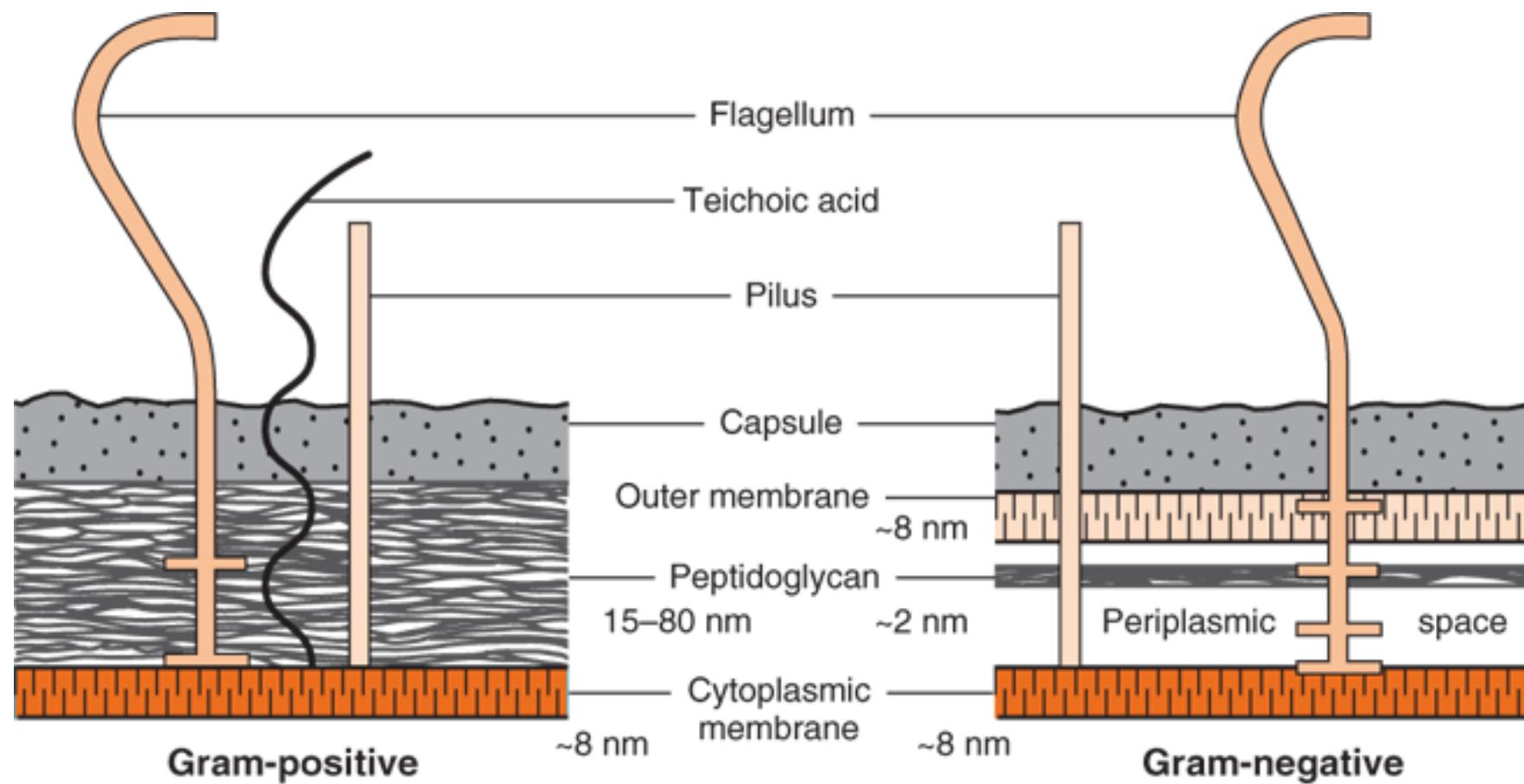
***Candida*** (yeast form) is also a component of the vaginal microbiome. Vaginal bacteria are susceptible to antibiotics. Fungi are not. ***Candida*** overgrowth can cause a secondary vaginal yeast infection.

Know this

# The Structure of Peptidoglycan Cell Wall



Amino sugars NAG: N-acetyl-glucosamine; NAM: N-acetyl-muramic acid  
Oligo: a few; Oligopeptide: a peptide consisting of a few amino acids.



A

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

## 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  $\beta$ -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

## Beta-Lactam Antibiotics

### Penicillins

Narrow spectrum

Extended spectrum

Antipseudomonas  
Broad spectrum

### Cephalosporins

Narrow spectrum

Extended spectrum

Anti-MRSA

### Carbapenems

Broad spectrum

### Monobactam

Gram-negative  
aerobes only

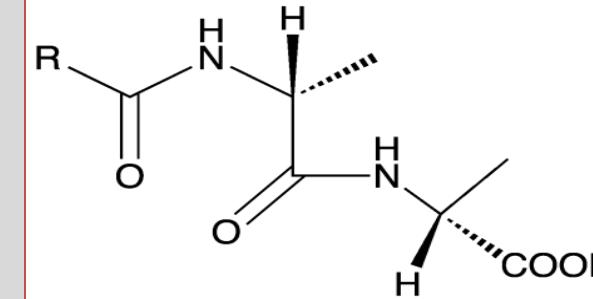
## Other Cell Wall Active Antibiotics

Vancomycin and others

## Cell Membrane Active Antibiotic

Daptomycin

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



## CLASS PROPERTIES

# Beta-Lactam Antibiotics

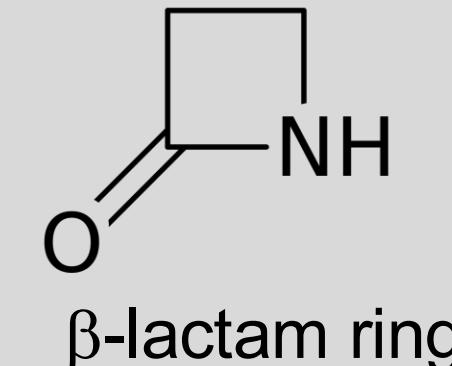
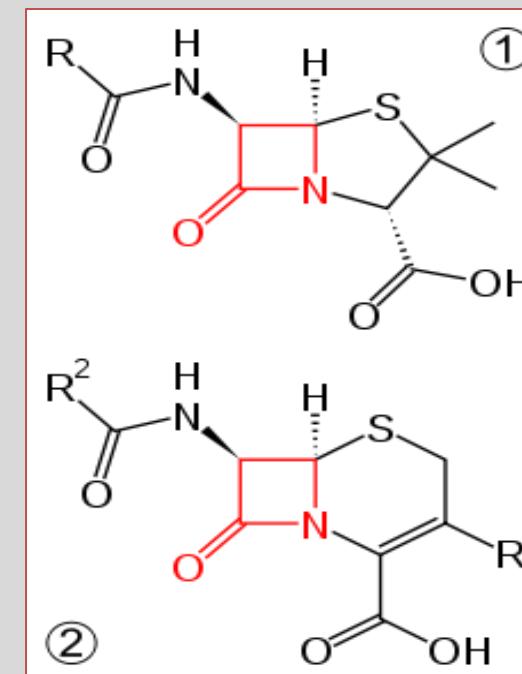
Penicillins

Cephalosporins

Carbapenems

Monobactam

D-alanyl-D-alanine

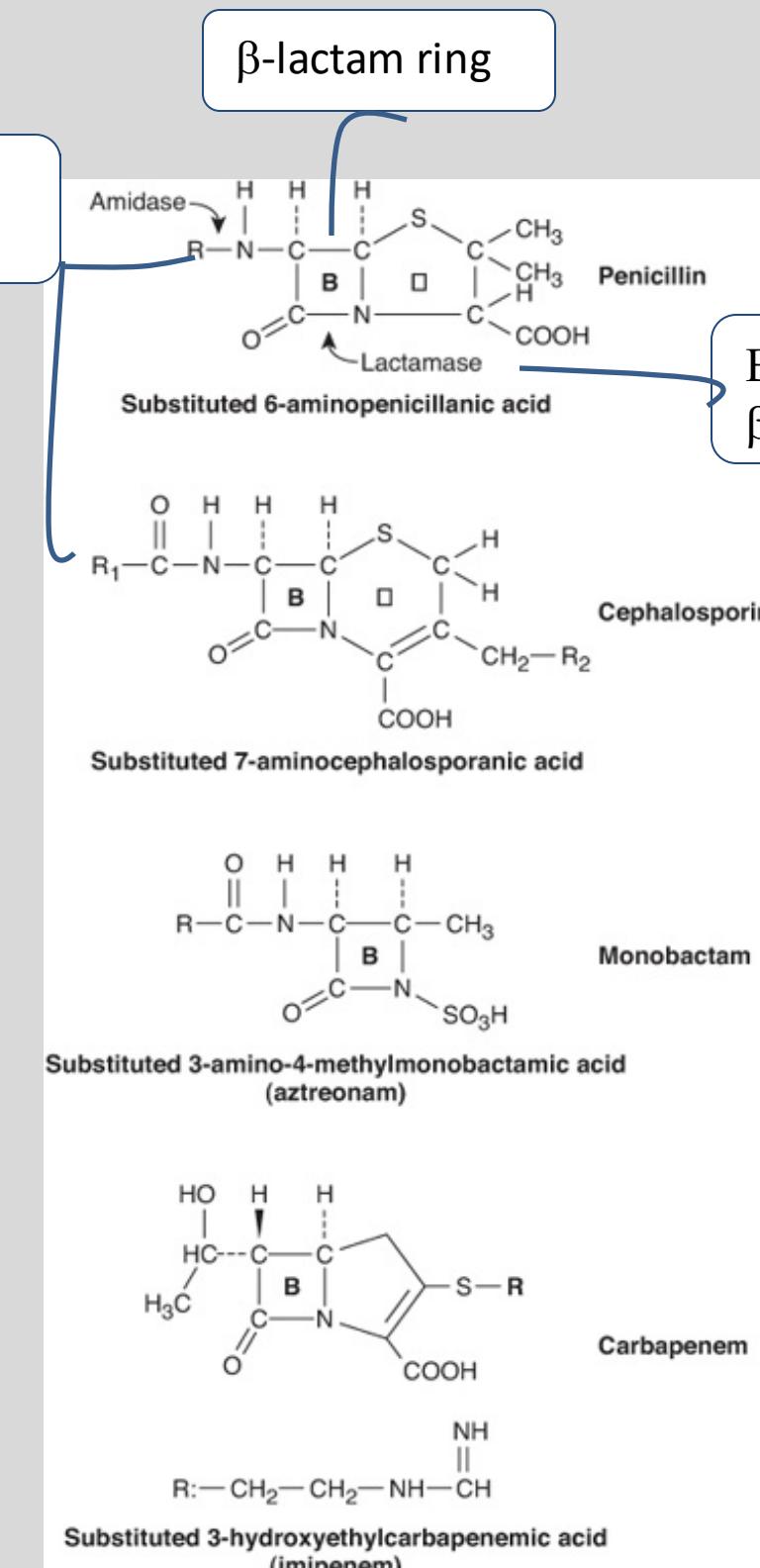


core structures of  
penicillin (1) and  
cephalosporins (2)

# 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.

R groups change the properties of drug.



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

# Pharmacokinetics: Beta-lactams class properties

PK properties are related  
antibacterial to efficacy.

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

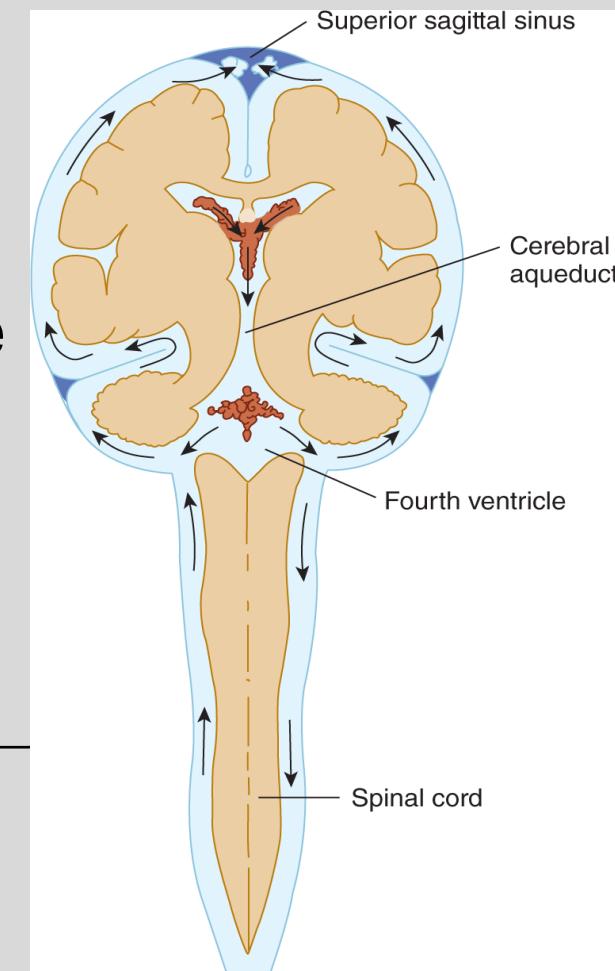
💡 Ceftriaxone, cefotaxime, cefuroxime, ceftazidime →

good penetration even when meninges are not inflamed

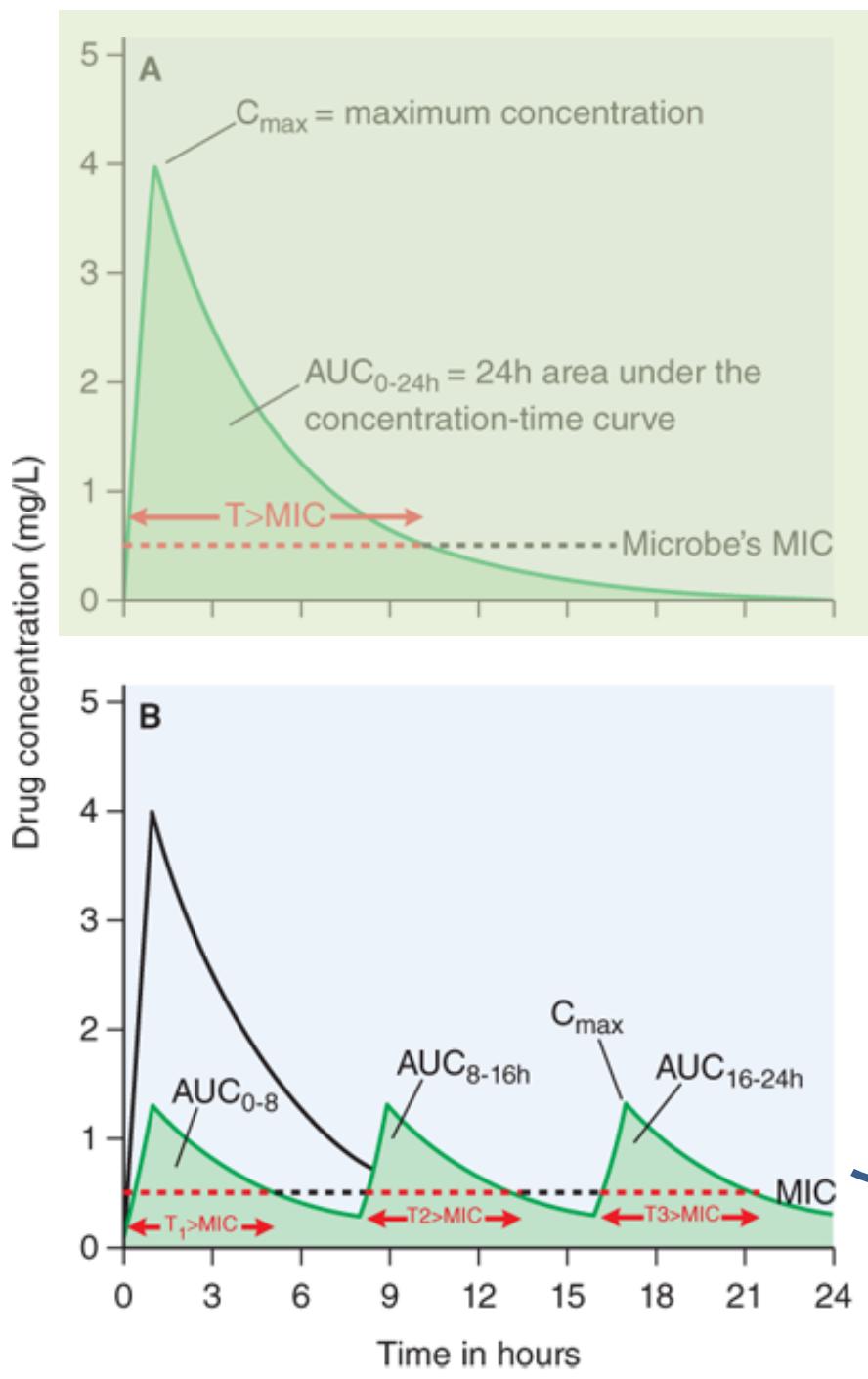
E Renal elimination (glomerular filtration / secretion)

Penicillinase-resistant (“antistaphylococcal”): hepatic metabolism

$t_{1/2}$  short ~30-60 minutes (ceftriaxone is an exception)



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



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.

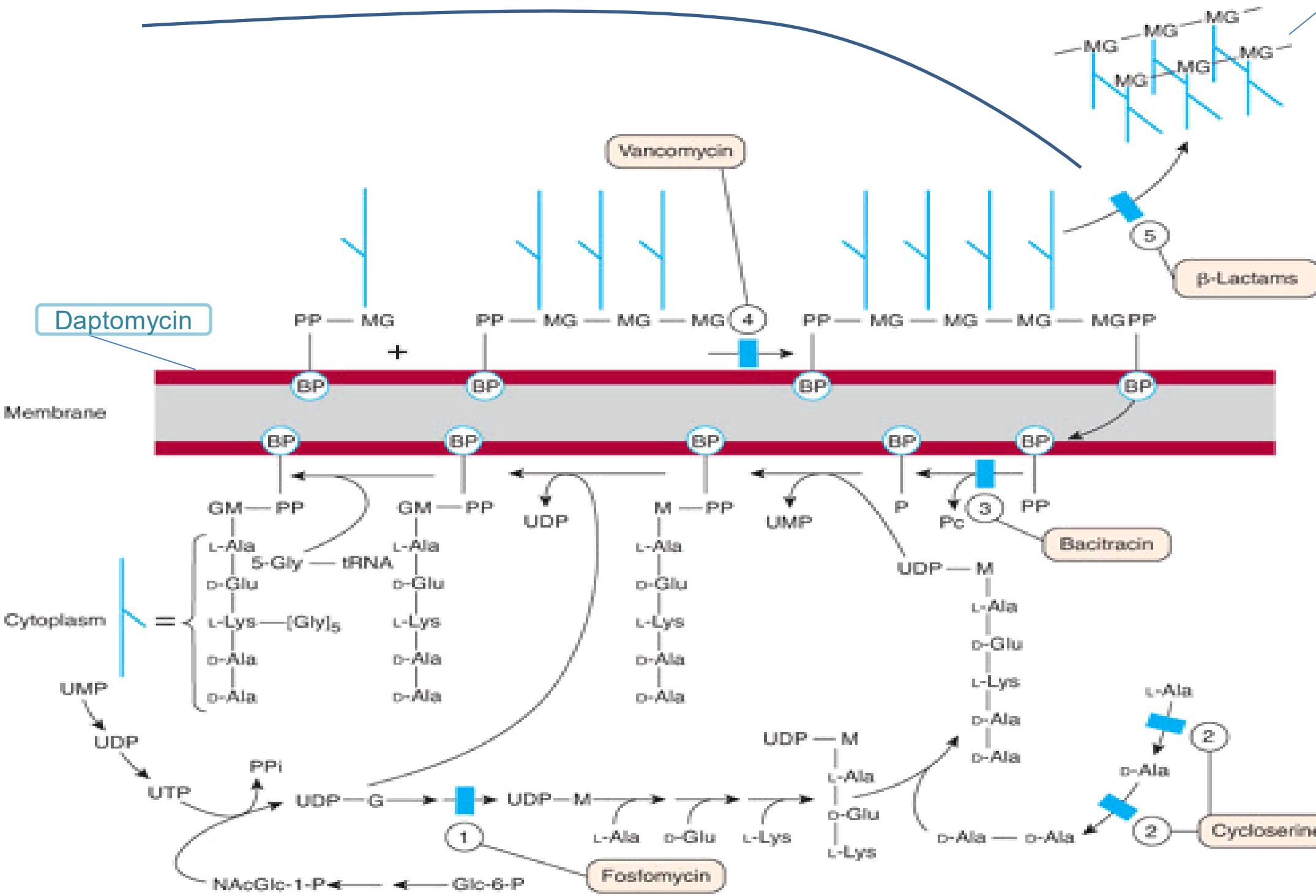
## Beta-Lactams PK-PD Profile: $T > \text{MIC}$

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  $T_1 > \text{MIC}$ ,  $T_2 > \text{MIC}$ , and  $T_3 > \text{MIC}$ , which results in a fraction greater than that for A.

# Target of Beta-Lactams: Peptidoglycan cell wall



## Cell wall cross-linking

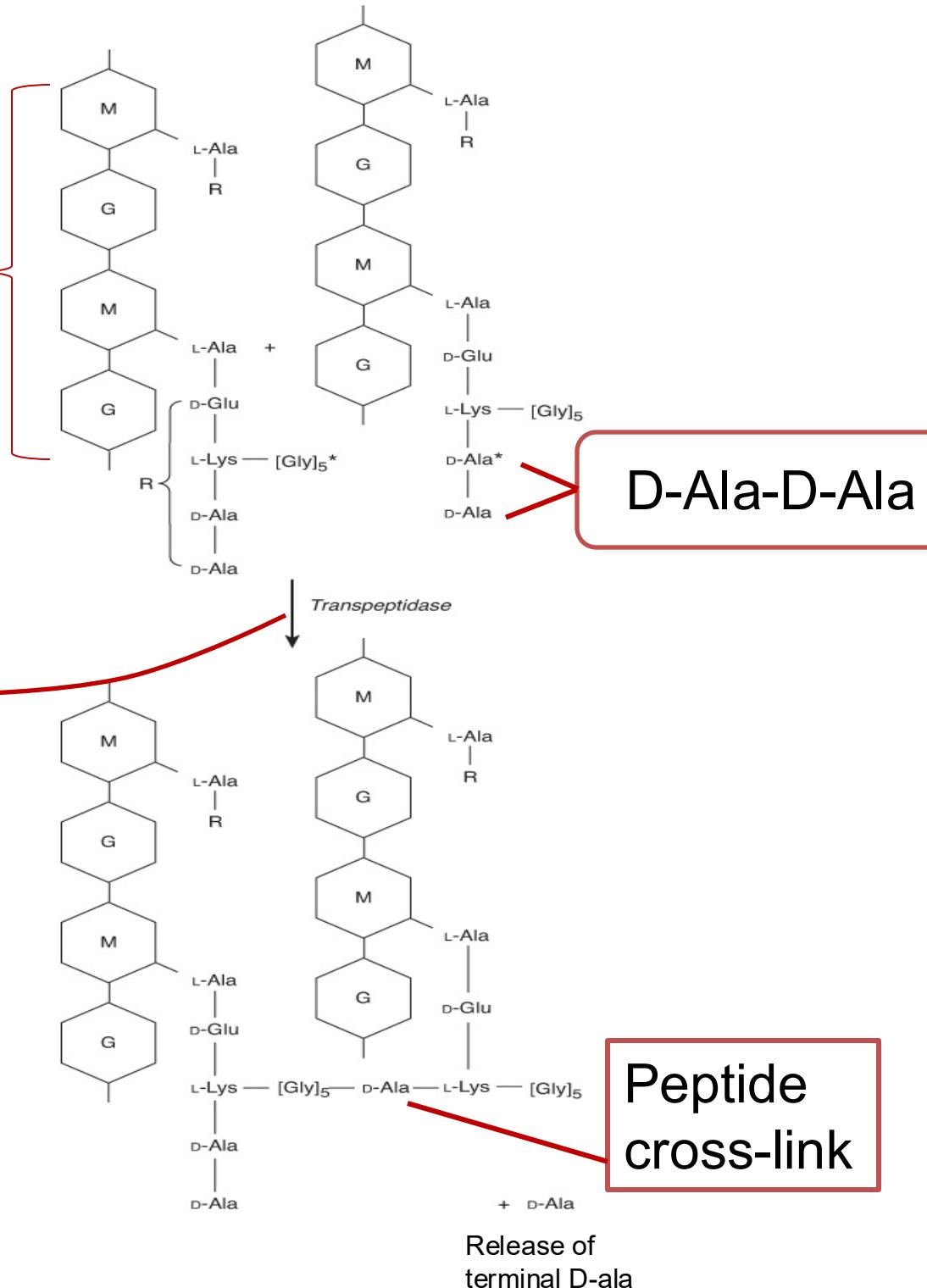
- The peptidoglycan cell wall is built molecule by molecule in the cytoplasm.
- The NAM/NAG-pentapeptide subunits are ferried across the plasma membrane by bactoprenol (BP).
- Cell wall construction is completed externally.

NAG-NAM-pentapeptide subunits

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

This figure shows *Staphylococcus aureus* cell wall synthesis.

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



Beta-lactams bind transpeptidase (PBP)

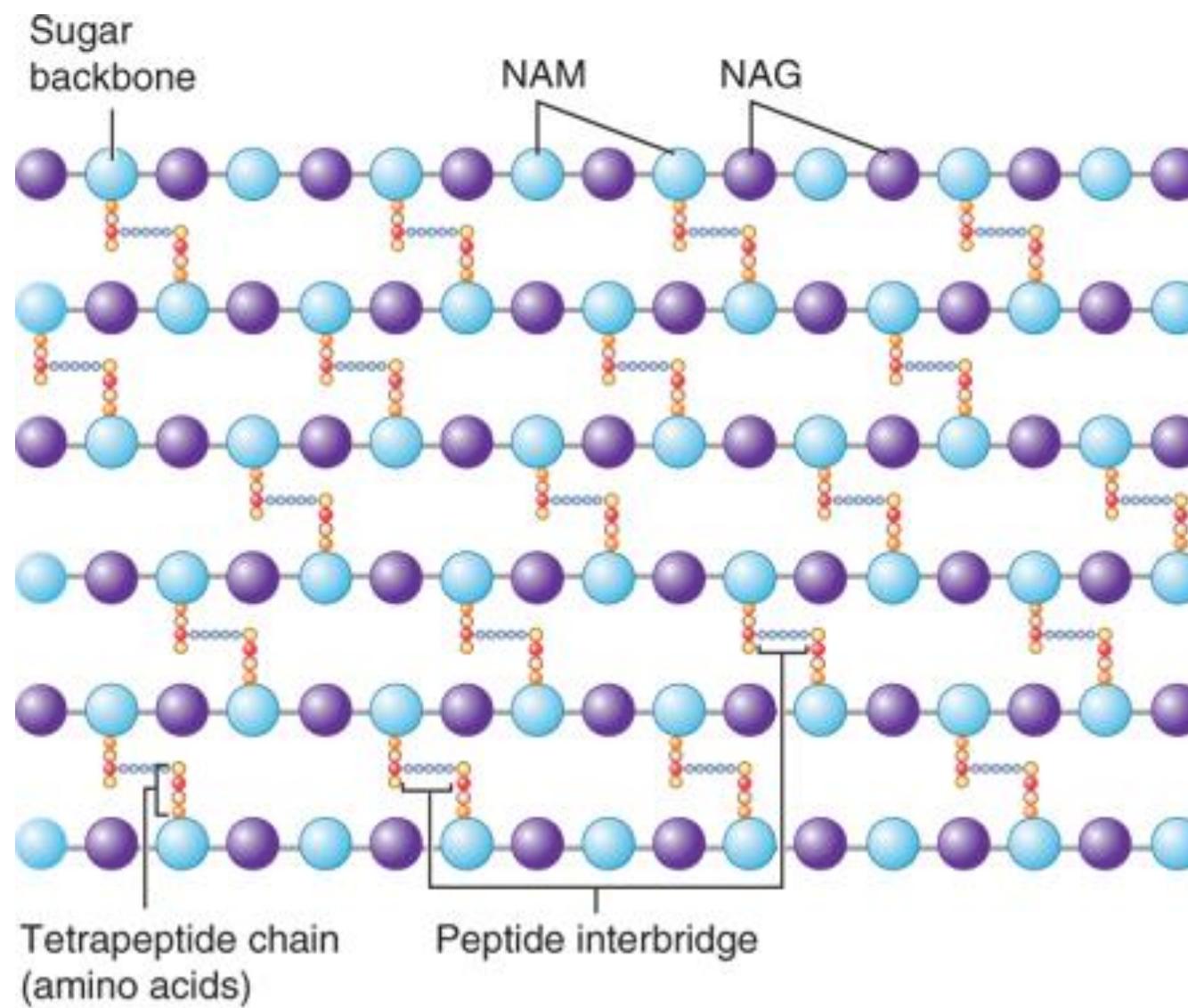
blocks peptide cross-linking

blocks cell wall synthesis

triggers bacterial autolysins

Osmotic rupture

plus, probable non-lytic mechanisms



**B**

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.

- $\beta$ -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

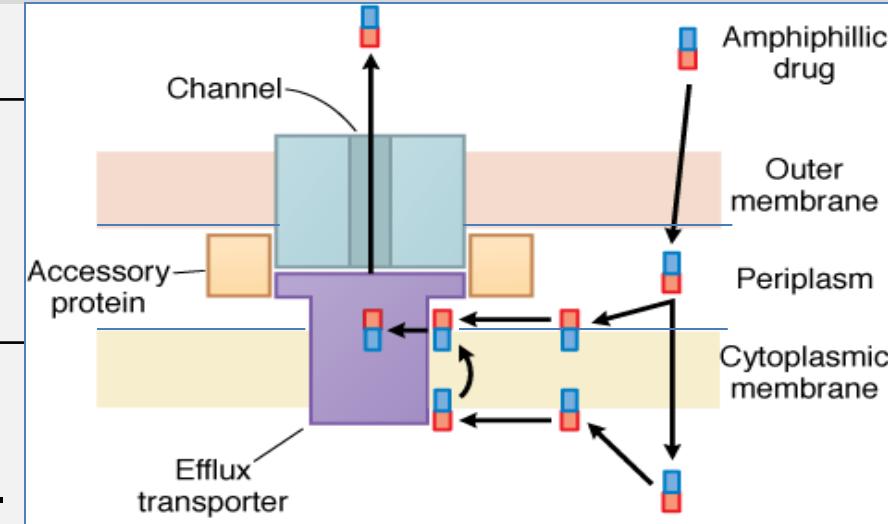
## Intrinsic resistance

Obligate intracellular bacteria

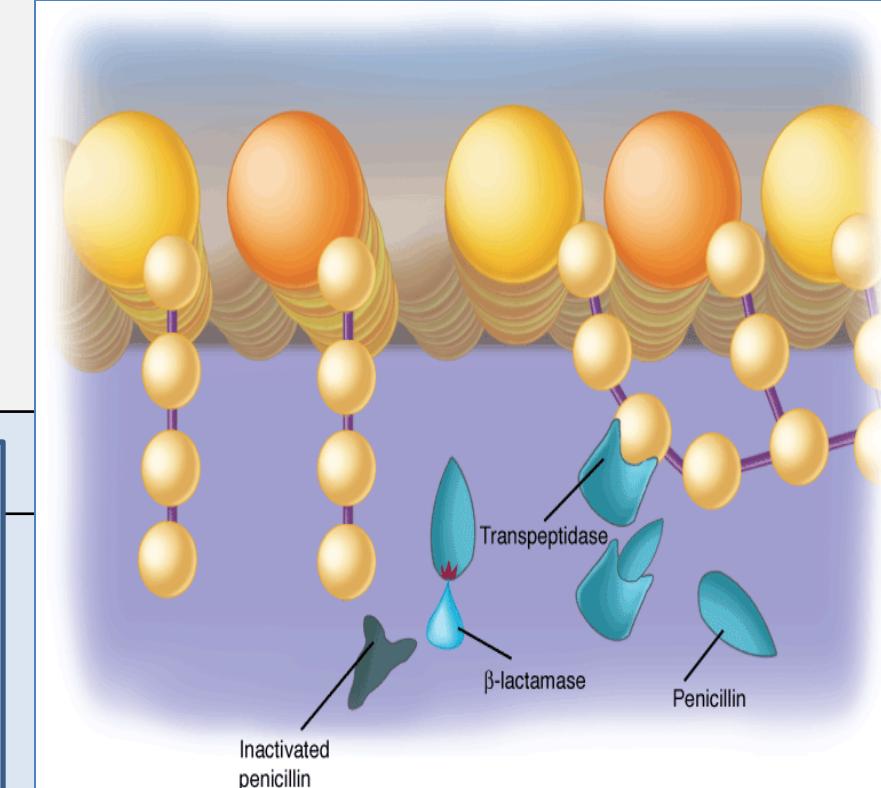
- Beta-lactams do not penetrate into host cells.
- “Atypicals”: Chlamydiaceae, Legionella, Rickettsia

Bacteria that lack peptidoglycan cell wall: *Mycoplasma*

Mnemonic: 6 Ps  
Penicillinases  
(=  $\beta$ -lactamases)  
PBPs  
Porins  
Pumps  
Penetration  
Peptidoglycan



Source: Brunton LL, Chabner BA, Knollmann BC: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition: www.accessmedicine.com  
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Source: Ryan KJ, Ray CG: Sherri's Medical Microbiology, 5th Edition: www.accessmedicine.com  
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🔑 Beta-lactam antibiotics kill bacterial cells only when they are **actively growing and synthesizing cell wall.**

**Bacteria in biofilms formed on prosthetic devices are much less sensitive to antibiotics.**

The density of the bacterial population and the age of an infection influence the activity of beta-lactam antibiotics:

- 1) Microorganisms in biofilms have decreased rates of growth.
- 2) A greater number of relatively resistant microorganisms occur in a large population.

Biofilm (bacterial and fungal): Colonies of slowly growing cells enclosed within a negatively charged exopolysaccharide matrix.

## Therapeutic uses

- Antibiotics should *only* be prescribed when there is a reasonable suspicion of, or documented infection with, susceptible organisms.

**Antibiotics should *never* be used  
to treat viral infections  
— they are not effective —**

- Antibiotic selection is based on:
  - ◊ Site of infection
  - ◊ Spectrums of activity
  - ◊ Microbial resistance
  - ◊ Patient factors
  - ◊ Drug toxicity
  - ◊ Cost

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

- ④ **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.

- ④ **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.

- ④ 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.**

# Hypersensitivity reactions may be characterized by:

- **Anaphylaxis: Rapidly progressive, life-threatening**
  - Hypotension, bronchoconstriction, death (in a few minutes)
  - Treatment:
    - Airway, respiratory, cardiovascular support
    - Epinephrine, antihistamines, glucocorticoids
- Angioedema (vasculitis of deeper vessels): Can be life-threatening when it involves the larynx, upper airway, and tongue and causes airway obstruction.
- Serum sickness: delayed type III reaction (fever, rash, arthralgia, other features)
- Immune hemolysis ⇒ hemolytic anemia
- Rash; Stevens-Johnson syndrome / toxic epidermal necrolysis
- Fever; interstitial nephritis; vasculitis; neutropenia and thrombocytopenia can also occur



### Angioedema

The deeper tissues are affected  
with swelling and pressure on airways

### Urticaria

### Stevens-Johnson syndrome

- <http://www.cram.com/flashcards/usmle-step-3-random-deck-2-2457583>
- <http://www.allergy-clinic.co.uk/skin-allergy/urticaria/>
- <http://www.dermnet.com/images/Stevens-Johnson-Syndrome>

## Non-immunogenic side effects of beta-lactams

GI: mild to severe diarrhea; nausea; vomiting

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*Clostridioides difficile* secondary infection: may cause significant morbidity or mortality (active drug excreted in feces increases risk)

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Candidiasis (yeast) secondary infection: oral thrush, vaginal yeast infection

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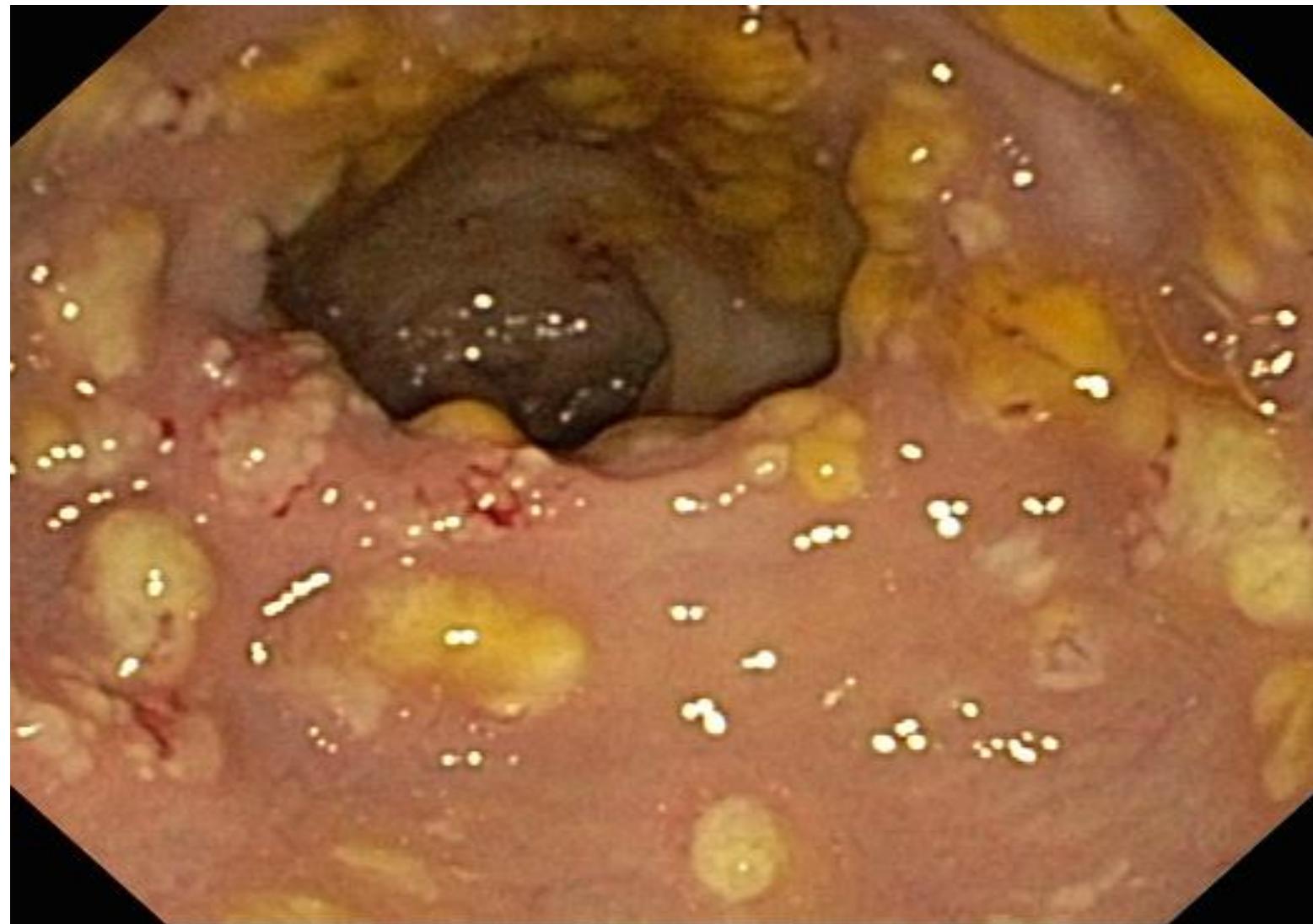
I.M. injection → pain; sterile inflammatory reaction may occur at injection site

---

I.V. injection → phlebitis or thrombophlebitis can occur

---

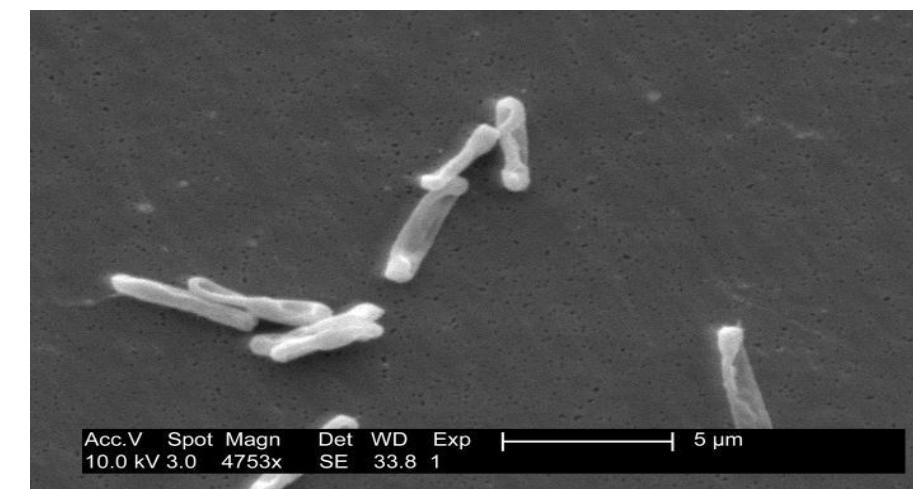
**Intrathecal use is NOT RECOMMENDED.** CNS irritants. High exposure may cause seizures, myoclonus, arachnoiditis or severe, fatal encephalopathy.



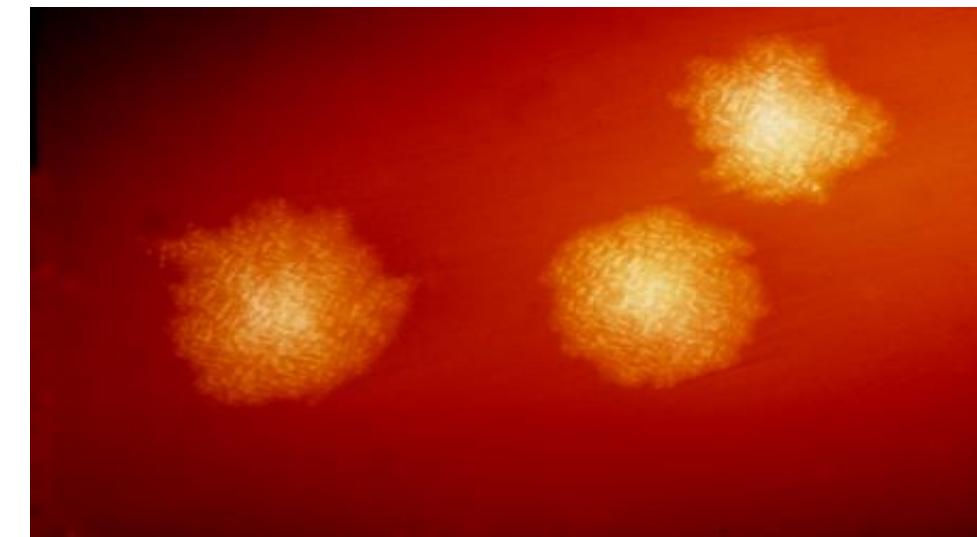
Endoscopic image of pseudomembranous colitis,  
with yellow pseudomembranes seen on the wall of  
the sigmoid colon **Caused by Toxin A and Toxin B**

Jawetz, Melnick, & Adelberg's Medical Microbiology, 28e, 2019; Chapter 11  
Figures: [http://en.wikipedia.org/wiki/Clostridium\\_difficile](http://en.wikipedia.org/wiki/Clostridium_difficile)

*Clostridioides difficile*: Gram-positive,  
spore-forming, anaerobic bacillus



Individual, drumstick-shaped *C. difficile* bacilli seen  
through scanning electron microscopy



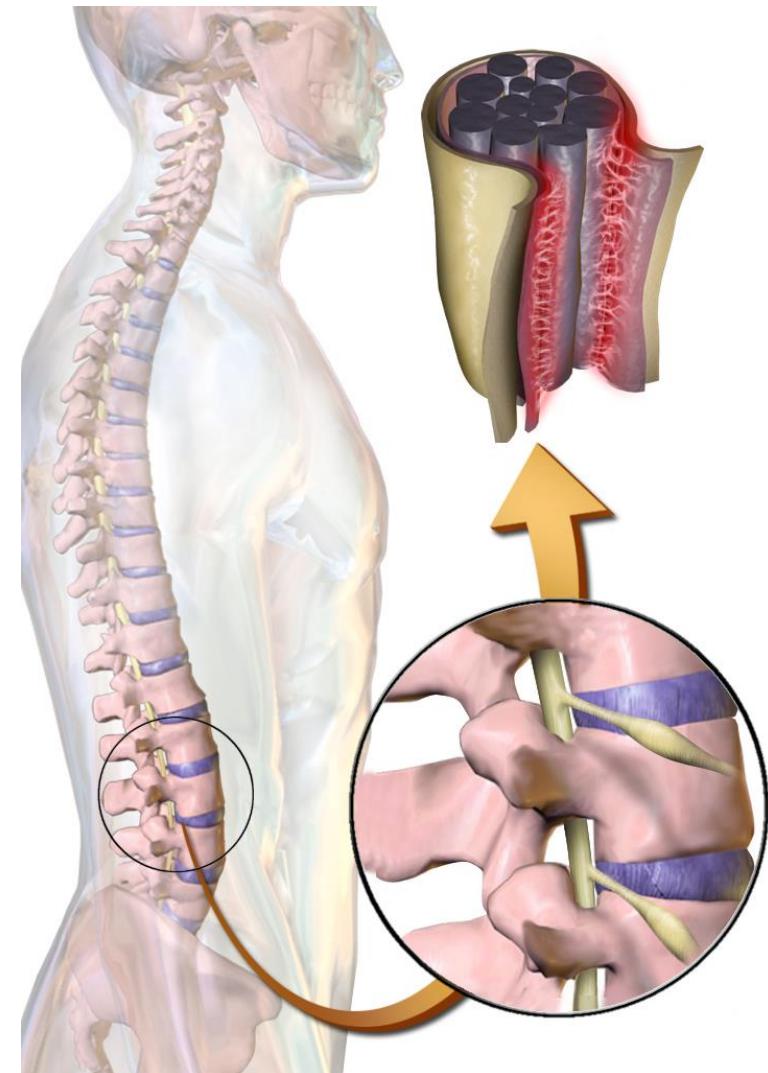
*C. difficile* colonies after 48hrs growth  
on a blood agar plate



Oral candidiasis



Phlebitis: inflammation of vein wall  
Complication of I.V. insertion or administration



Arachnoiditis

[https://en.wikipedia.org/wiki/Candidiasis#/media/File:Human\\_tongue\\_infected\\_with\\_oral\\_candidiasis.jpg](https://en.wikipedia.org/wiki/Candidiasis#/media/File:Human_tongue_infected_with_oral_candidiasis.jpg)

<https://nursingug.wordpress.com/2015/12/13/iv-insertionadministration-complications/>

[https://en.wikipedia.org/wiki/Arachnoiditis#/media/File:Blausen\\_0044\\_Arachnoiditis.png](https://en.wikipedia.org/wiki/Arachnoiditis#/media/File:Blausen_0044_Arachnoiditis.png)

# Special populations

- Pregnancy: Generally compatible with pregnancy
  - No evidence of impaired fertility or fetal harm
  - Maternal use of penicillins has generally not resulted in an increased risk of adverse fetal effects
- Lactation:
  - May be excreted in breast milk
  - may cause non-dose-related modifications of bowel flora
- Pediatrics:
  - PK information and evidence for use is available for infants and children.
  - Many beta-lactams are considered safe in neonates.
- Neonates' have immature renal function → ↑  $t_{1/2}$ .

# Drug interactions, mechanisms, and effects

Drug	Mechanism	Effect
Probenecid	Inhibition of renal OAT	↑ beta-lactam level/duration
Methotrexate	Inhibition of renal OAT	↑ MTX level/toxicity
Warfarin	Disruption of microbiome may ↓vitamin K production → ↓clotting factors → hypoprothrombinemia	↑ bleeding risk
Estrogen / progestin oral contraceptives	Disruption of microbiome may decrease estrogen recycling	↓ OC efficacy pregnancy risk?
Gastric acid suppressors (independent risk factor)	PPIs increase risk of <i>C. difficile</i> infection	↑ <i>C. difficile</i> risk
Tetracyclines	TCNs are bacteriostatic → may reduce beta-lactam efficacy	↓ PCN efficacy
Typhoid vaccine, oral (live attenuated)	Antibiotic may inactivate the vaccine (the bacterium)	↓ vaccine efficacy

Students: What to know? The mechanisms and effects. You do not need to memorize the drug names at this time.

## 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 $\beta$ -Lactamases and Pharmacology of Beta-Lactamase Inhibitors

Thousands of  $\beta$ -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 $\beta$ -Lactamases

**ESBLs** (extended spectrum  $\beta$ -lactamases):

Class A      TEM, SHV, CTX-M: Resistance to most  $\beta$ -lactams

**KPC: Carbapenemase**

*Beta-lactamase inhibitors usually block Class A  $\beta$ -lactamases.*

Class C      AmpC, CMY: Resistance to broad and extended-spectrum beta-lactam antibiotics

Class D      OXA-type: ESBLs and Carbapenemases

Serine  
 $\beta$ -lactamases

Class B      IMP, VIM, GIM, SPM, SIM: Carbapenemases  
New Delhi (NDM-1): Carbapenemases  
***Not inhibited by any of the beta-lactamase inhibitors.***

Metallo-  
 $\beta$ -lactamases

# Beta-Lactamase Inhibitors

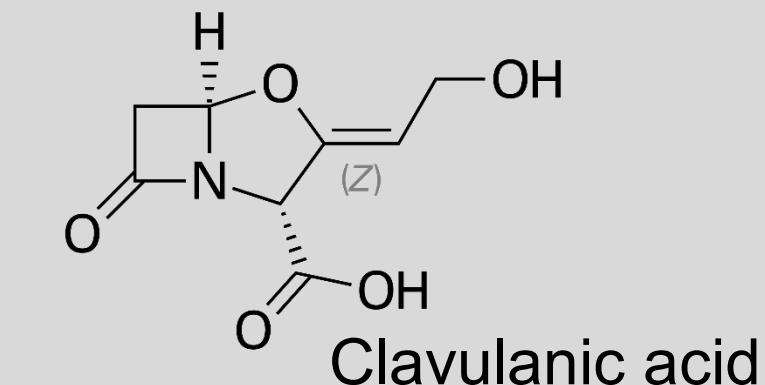
(formulated only in fixed combinations with  $\beta$ -Lactam antibiotics)

1. \*Clavulanic acid

2. \*Sulbactam

3. \*Tazobactam

Beta-lactam structure



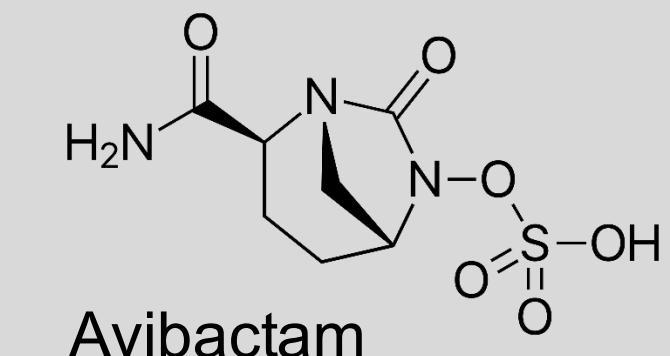
4. \*Avibactam

5. \*Vaborbactam

6. \*Relebactam

7. \*Durlobactam

Non-beta-lactam structure



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  $\beta$ -lactamases

### Potent, reversible inhibitors:

Avibactam, Vaborbactam, Relebactam, Durlobactam

- Inhibit Ambler class A, and C  $\beta$ -lactamases

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

\*Sulbactam is bactericidal against *A. baumannii*. Sulbactam binds *A. baumannii* 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.

# 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	✓			
	Sulbactam	✓			
	Tazobactam	✓			
potent reversible	Avibactam	✓	✓ (some)	✓ (some)	✓
	Vaborbactam	✓	✓ (some)		✓
	Relebactam	✓	✓ (some)		✓
	Durlobactam	✓	✓ (some)	✓ (some)	✓

None of the beta-lactamase inhibitors is effective.

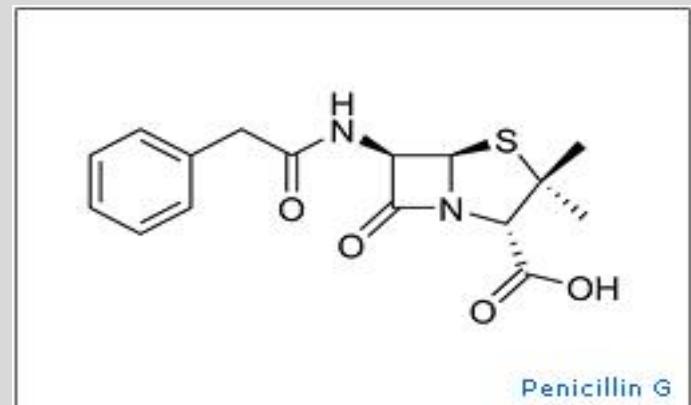
Gram-negative bacteria that express inducible chromosomal AmpC  $\beta$ -lactamases include:  
*Serratia, Pseudomonas, indole-positive Proteus, Citrobacter, Enterobacter* (S.P.I.C.E.)

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  $\beta$ -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)  $\beta$ -lactamases?
8. Which beta-lactamase inhibitors are active against the Ambler class B metallo- $\beta$ -lactamases?

## Penicillins Class

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



Structural modifications enhance affinity for PBPs and increase the spectrums of activity against gram-negative bacteria



### **Natural penicillins:** Highly active (when no resistance)

- Gram-positive aerobic, anaerobic
- *N. meningitidis*; spirochetes

### **Penicillinase-resistant penicillins:**

- Tx of methicillin-sensitive *S. aureus* (MSSA) and *S. epidermidis* (MSSE, coagulase-negative *Staphylococcus*)

### **Aminopenicillins:**

- Activity of Penicillin G plus
- Extended spectrum: Some Gram-negative bacteria

### **Antipseudomonal penicillins:**

- Activity of Ampicillin plus
- activity against *Pseudomonas*

**NOTE:** The activity of the drugs in the subclasses represents the ideal world of no resistance.  $\beta$ -lactamases and altered PBPs reduce the effectiveness of the antibacterial agents.

## Natural Penicillins

- \* Penicillin G (benzylpenicillin)
- \* Penicillin V (phenoxyethylpenicillin)

# 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)

## Gram-negative aerobes

- Pseudomonas aeruginosa
- Enterobacteriales (rods) (facultative anaerobes)
  - *Escherichia coli*
  - *Proteus mirabilis*
  - *Klebsiella spp*
- Respiratory
  - *Haemophilus influenzae*
  - *Moraxella catarrhalis*
  - *Neisseria meningitidis*
- STD
  - *Neisseria gonorrhoea*

## STD

- *Neisseria gonorrhoea*

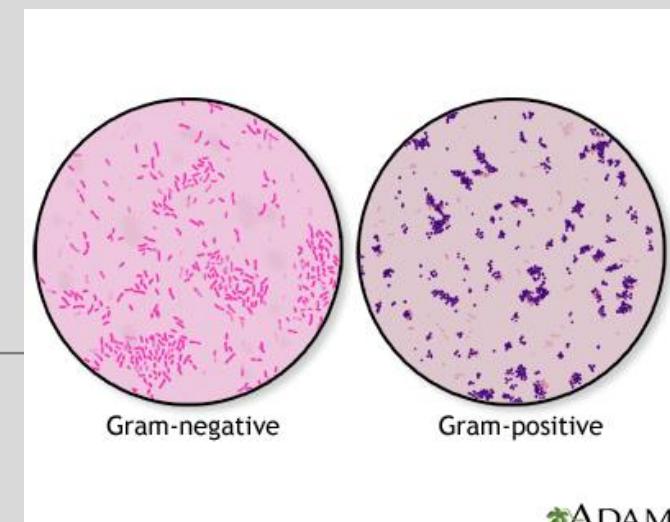
## Obligate G- Anaerobic

- *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

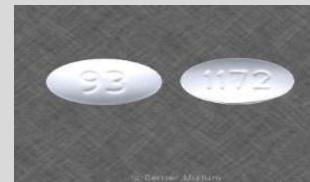
**Beta-lactams are ineffective in the treatment of infection caused by the atypicals.**

# Penicillin G and Penicillin V



**Penicillin G, aqueous**  
(sodium and potassium salts)  
I.V. and I.M.

rapidly achieves  
high therapeutic concentrations



**Penicillin V**  
Oral only

more acid stable than penicillin G  
lower plasma concentrations ⇒ for mild to  
moderate *susceptible* bacterial infections

**Repository Penicillin G**  
I.M. injection only

Penicillin G benzathine (right)  
Penicillin G procaine  
Penicillin G benzathine/procaine combo



**IV administration** of repository formulations is **CONTRAINDICATED**.  
Cardiopulmonary arrest and death have occurred with inadvertent IV  
administration.

## Natural Penicillins:

### Resistance mechanisms

β-lactamases	<p><i>Staphylococcus aureus</i> expresses penicillinase. Gram-negative bacilli express various β-lactamases.</p>
PBP alterations with low affinity for beta-lactams	<p><i>Streptococcus pneumoniae</i> MRSA (methicillin-resistant <i>S. aureus</i>) <i>Enterococcus faecium</i></p>
Intrinsic resistance	<p>Gram-negative bacilli Penicillin G cannot penetrate porins of most gram-negative bacteria.</p>

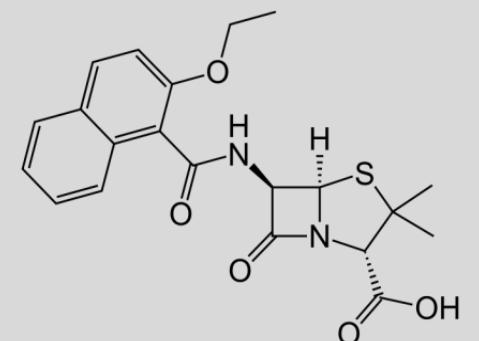
## Natural Penicillins: Adverse Effects

### Hypersensitivity reactions, anaphylaxis

Seizures	High dose penicillin
Electrolyte disturbances	<p>Drugs are formulated as <math>\text{Na}^+</math> and <math>\text{K}^+</math> salts.</p> <p>Penicillin G aqueous has a short <math>t\frac{1}{2}</math> and <math>T &gt; \text{MIC}</math> with minimal persistent effects.</p> <p>I.V. administration 6 times daily or by continuous infusion.</p>
Jarisch-Herxheimer reaction	<p>Syphilis: Acute, self-limited, febrile reaction to antibiotic treatment, which often resolves 12-24 hours without intervention.</p> <p>Proposed mechanism: Immune reaction in response to lipoproteins released by dying <i>Treponema pallidum</i> spirochetes with subsequent proinflammatory cascade</p> <p>Management: Symptomatic, NSAIDs or acetaminophen</p>

## Penicillinase-Resistant Penicillins

- \* Nafcillin (IM, IV)
  - \* Oxacillin (IM, IV)
  - \* Dicloxacillin (oral)
  - Cloxacillin (oral)
- Isoxazolyl penicillins



nafcillin



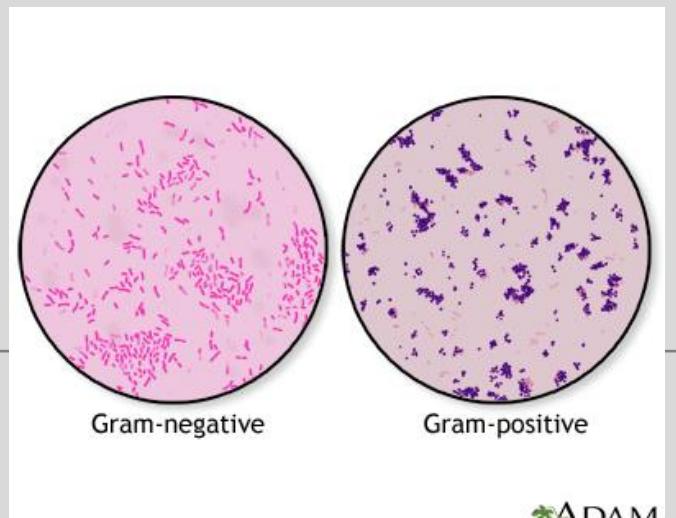
isoxazole



dicloxacillin

# Penicillinase-Resistant Penicillins' Narrow Spectrum of Activity

Strike through = once susceptible but now significant resistance to penicillin

Gram-positive	Gram-negative aerobes	Spirochetes	Atypicals*
<b>Cocci</b> <ul style="list-style-type: none"> <li>• <i>Streptococcus pneumoniae</i></li> <li>• Group A strep (GAS)</li> <li>• MSSA: <i>S. aureus</i></li> <li>• MSSE: <i>S. epidermidis</i></li> <li>• <i>Enterococcus faecalis</i></li> <li>• <i>Enterococcus faecium</i></li> </ul> <b>Bacillus (rod)</b> <ul style="list-style-type: none"> <li>• <i>C. diphtheriae</i></li> <li>• <i>Listeria monocytogenes</i></li> </ul>	<b>Pseudomonas aeruginosa</b> <b>Enterobacteriales (rods)</b> (facultative anaerobes) <ul style="list-style-type: none"> <li>• <i>Escherichia coli</i></li> <li>• <i>Proteus mirabilis</i></li> <li>• <i>Klebsiella spp</i></li> </ul> <b>Respiratory</b> <ul style="list-style-type: none"> <li>• <i>Haemophilus influenzae</i></li> <li>• <i>Moraxella catarrhalis</i></li> <li>• <i>Neisseria meningitidis</i></li> </ul> <b>STD</b> <ul style="list-style-type: none"> <li>• <i>Neisseria gonorrhoea</i></li> </ul>	Gram-negative, thin-walled spiral-shaped flexible organisms <ul style="list-style-type: none"> <li>• <i>Treponema pallidum</i></li> <li>• <i>Leptospira</i></li> <li>• <i>Borrelia burgdorferi</i></li> </ul>	Bacteria remain colorless when gram-stained <ul style="list-style-type: none"> <li>• <i>Mycoplasma</i></li> <li>• <i>Chlamydiaceae</i></li> <li>• <i>Legionella</i></li> <li>• <i>Rickettsia</i></li> </ul> <b>STD</b> <ul style="list-style-type: none"> <li>• <i>Chlamydia trachomatis</i></li> </ul>
<b>Obligate Anaerobic</b> <ul style="list-style-type: none"> <li>• <i>Clostridia spp</i></li> <li>• <i>Clostridioides difficile</i></li> </ul>	<b>Obligate Anaerobic</b> <ul style="list-style-type: none"> <li>• <i>Bacteroides fragilis</i></li> </ul>		<b>Beta-lactams are ineffective in the treatment of infection caused by the atypicals.</b> <p>*Not visible on Gram stain</p> <p>52</p>

# 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 <i>S. aureus</i> , <i>S. epidermidis</i>
Resistance (common)	MRSA / MRSE: Modification of staphylococcal PBPs <b>PBP2a (<i>MecA</i> gene)</b> → 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. epidermidis*  
MRSA / MRSE: Methicillin resistant *S. aureus*, *S. epidermidis*

# Extended-spectrum penicillins

Better activity against gram-negative organisms:

They are semisynthetic derivatives of penicillin that have higher affinity for PBPs and greater penetration through the gram-negative outer membrane.

## Aminopenicillins

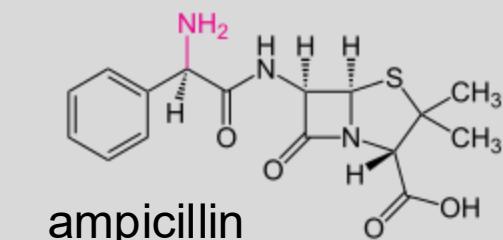
\* Ampicillin

\* Amoxicillin

**Combinations with  $\beta$ -lactamase inhibitors expand the activity by increasing stability against bacterial  $\beta$ -lactamases.**

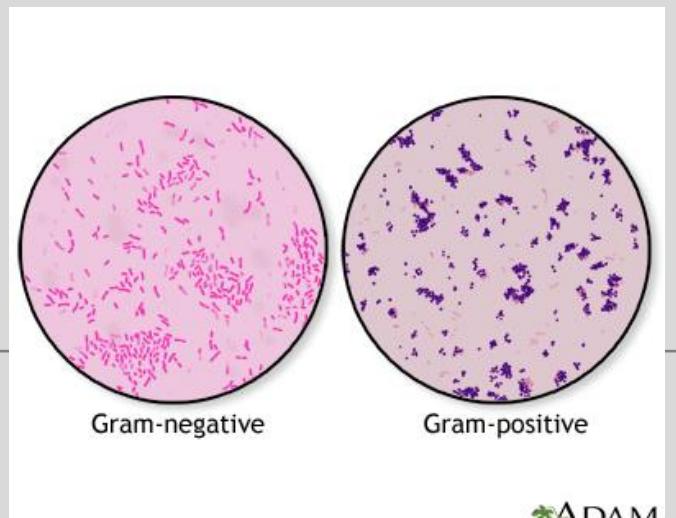
\* Ampicillin-sulbactam

\* Amoxicillin-clavulanate



# Aminopenicillin's Spectrum of Activity

(without beta-lactamase inhibitor combination)

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

## Spectrum

(ideal world of no resistance)

### Amoxicillin and Ampicillin:

- Same as penicillin
- plus
- Some respiratory pathogens
- and
- Some aerobic GNBs\*, enteric

### Amoxicillin-clavulanate

### Ampicillin-sulbactam

Beta-lactamase inhibitor expands spectrum of activity.

## Resistance

### Modified PBPs:

MRSA, *S. pneumoniae*, *Enterococcus*

### Class A ESBLs:

Resistance can be overcome with the addition of beta-lactamase inhibitor.

### *Bacteroides fragilis*: (obligate anaerobic GNB\*)

Resistance can be overcome with the addition of beta-lactamase inhibitor.

### Intrinsic resistance:

*Pseudomonas aeruginosa*

\*GNB: Gram-negative bacteria

# Aminopenicillins

## Adverse Effects

### Non-allergic rash:

Maculopapular rash on trunk and may spread to face; usually appears 5-7 days from the start of therapy; may occur earlier or as late as day 16

Incidence is higher in patients with:

- **Viral infection** such as Roseola or mononucleosis
- **Allopurinol + ampicillin or amoxicillin**

### 🔑 Differentiate allergic reaction:

Onset of pruritic urticarial rash within hours of first dose, cough, fever, and wheezing / difficulty breathing.

## PK Properties

Ampicillin	Amoxicillin
IM, IV, oral 50% bioavailability	Oral only 100% bioavailability Detectable in plasma for twice as long as ampicillin
<b>Class PK Properties</b>	
<ul style="list-style-type: none"><li>• Not metabolized</li><li>• High concentrations excreted in urine.</li><li>• Unabsorbed oral ampicillin excreted in feces → disruption of microbiota</li><li>• Short half-life: Ampicillin IV may be administered by continuous infusion.</li></ul>	

**A true allergic reaction is a contraindication** to future administration drugs in the penicillins class.

## Extended-spectrum penicillins

### Antipseudomonal Penicillins

#### Piperacillin-tazobactam (parenteral only)

Piperacillin

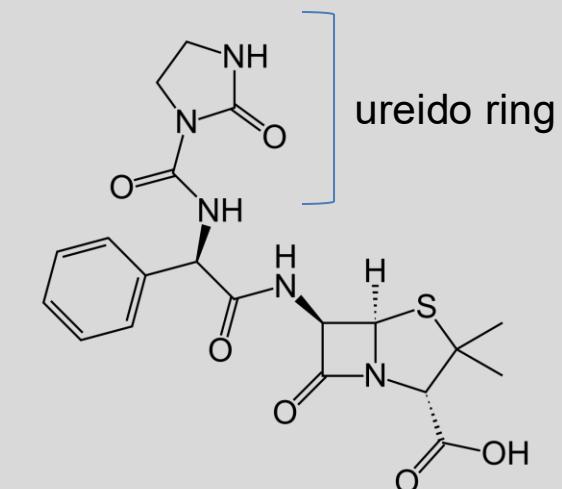
Ticarcillin-clavulanate

} No longer available

Structure: Piperacillin is a ureidopenicillin.

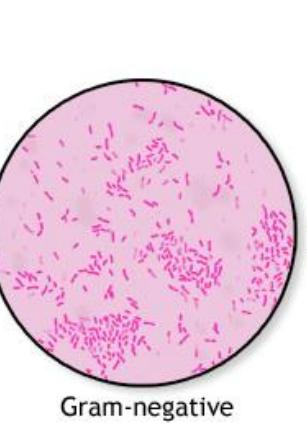
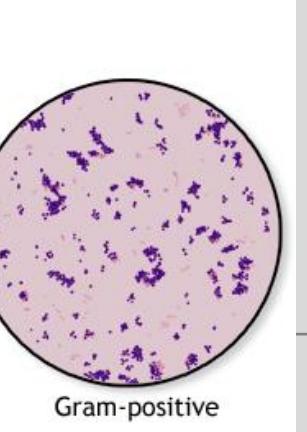
Class PK properties

- 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)

Gram-positive	Gram-negative aerobes	Spirochetes	Atypicals*
Cocci <ul style="list-style-type: none"> <li>• <i>Streptococcus pneumoniae</i></li> <li>• Group A strep (GAS)</li> <li>• <i>Staphylococcus aureus</i></li> <li>• Staph. epidermidis</li> <li>• <i>Enterococcus faecalis</i></li> <li>• <del><i>Enterococcus faecium</i></del></li> </ul> Bacillus (rod) <ul style="list-style-type: none"> <li>• <i>C. diphtheriae</i> (PCN preferred)</li> <li>• <i>Listeria monocytogenes</i></li> </ul>	Pseudomonas aeruginosa Enterobacteriaceae (rods) (facultative anaerobes) <ul style="list-style-type: none"> <li>• <i>Escherichia coli</i> and many others</li> <li>• <i>Proteus mirabilis</i></li> <li>• <i>Klebsiella spp</i></li> </ul> Respiratory <ul style="list-style-type: none"> <li>• <i>Haemophilus influenzae</i></li> <li>• <i>Moraxella catarrhalis</i></li> <li>• <i>Neisseria meningitidis</i></li> </ul> STD <ul style="list-style-type: none"> <li>• <i>Neisseria gonorrhoea</i></li> </ul>	Gram-negative, thin-walled spiral-shaped flexible organisms <ul style="list-style-type: none"> <li>• <i>Treponema pallidum</i></li> <li>• <i>Leptospira</i></li> <li>• <i>Borrelia burgdorferi</i></li> </ul>	Bacteria remain colorless when gram-stained <ul style="list-style-type: none"> <li>• Mycoplasma</li> <li>• Chlamydiaceae</li> <li>• Legionella</li> <li>• Rickettsia</li> </ul> STD <ul style="list-style-type: none"> <li>• Chlamydia trachomatis</li> </ul>
Obligate G+ Anaerobic <ul style="list-style-type: none"> <li>• <i>Clostridia spp</i></li> <li>• <i>Clostridioides difficile</i></li> </ul>	Obligate G- Anaerobic <ul style="list-style-type: none"> <li>• <i>Bacteroides fragilis</i></li> </ul>	 Gram-negative	 Gram-positive
			<b>Beta-lactams are ineffective in the treatment of infection caused by the atypicals.</b>
			59

# Piperacillin-Tazobactam

## The broadest antibacterial spectrum of the penicillins class

Activity	<p>The same activity as the aminopenicillins <i>plus</i> <i>Pseudomonas aeruginosa</i></p> <ul style="list-style-type: none"><li>• Polar side chains allow the drug to pass through the porins of <i>P. aeruginosa</i> and many GNBs (gram-negative bacilli).</li></ul>
Therapeutic uses	Bacteremia, pneumonias, burns, appendicitis, gynecologic infections, urinary tract infections

### Adverse effects

Congestive heart failure exacerbation: Na<sup>+</sup> salts, frequent administration

Abnormal platelet aggregation, thrombocytopenia → 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  $\beta$ -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 stable 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 Enterobacteriales (enteric GNPs), such as *E. coli*, *P. mirabilis*, 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  $\beta$ -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)  $\beta$ -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  $\beta$ -lactamases.

## Check your knowledge Answers to Slide 37

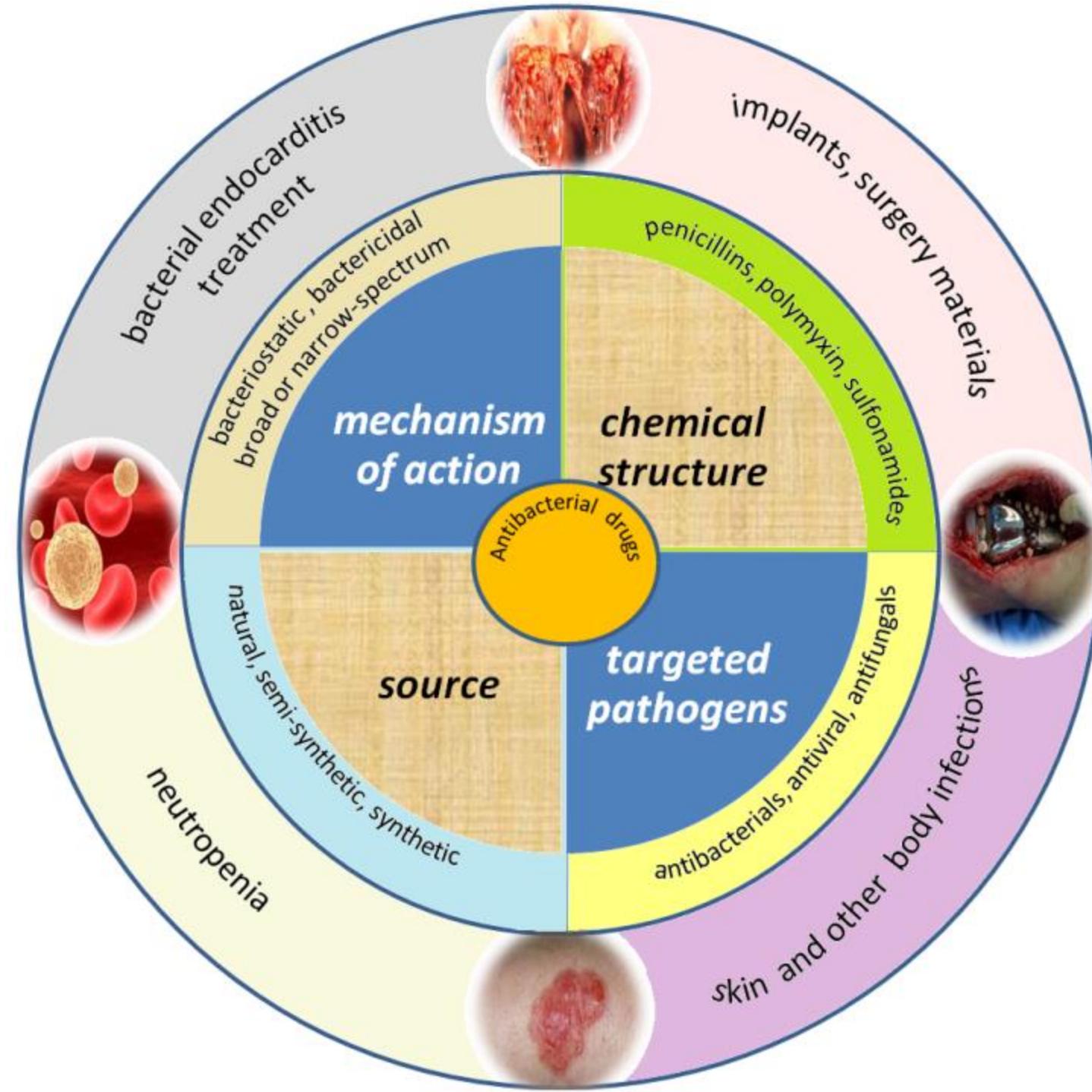
1. Drug inactivation by beta-lactamases, low-affinity PBPs, reduced penetration to target by alterations of porin proteins or expression of efflux pumps. Intrinsic resistance by organisms without cell wall and obligate intracellular bacteria. (6 Ps: Penicillinases ( $\beta$ -lactamases), PBPs, Porins, Pumps, Penetration, Peptidoglycan)
2. Hypersensitivity reactions, anaphylaxis, anaphylactic shock
3. *C. difficile*-associated diarrhea, pseudomembranous colitis, toxic megacolon; yeast infections (thrush, vaginal infection) caused by *Candida albicans* fungus.
4. Probenecid inhibits organic anion transporter in the proximal tubule, which reduces penicillin's rate of excretion and increases plasma levels and duration of penicillin action.
5. Antibiotics potentially eradicate gut organisms that cleave beta-lactamase from estrogen, thus reducing enterohepatic circulation and overall plasma levels of the hormone potentially reducing efficacy.
6. Beta-lactams are CNS irritants with high exposure. Intrathecal administration may cause seizures, myoclonus, arachnoiditis, or encephalopathy. Also, adequate levels are achievable with intravenous administration.
7. Commensal organisms may be pathogenic when outside their normal body site, which can occur when the natural anatomic barriers are penetrated.
8. Knowing the morphology (Gram stain) and growth requirements can guide empiric therapy decisions.
9. Viruses are not eradicated by antibiotics. Unnecessary antibiotic use puts the patient at risk of side effects, promotes development of resistance, and is an unnecessary expense for the patient.

## 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.

## Answers to questions on slide 61.

1. Piperacillin-tazobactam
2. Antipseudomonal activity
3. Amoxicillin
4. Penicillin G – long-acting benzathine penicillin G 2.4 million units as a single dose for primary and secondary syphilis; 2.4 million units once weekly x3 doses for late syphilis
5. *Neisseria meningitidis* = meningococcus (vaccines are available)
6. Extended-spectrum penicillins are semisynthetic derivatives of penicillin that have better activity against gram-negative organisms because of a higher affinity for PBPs and greater penetration through the gram-negative outer membrane. Piperacillin is also active against *Pseudomonas*, whereas ampicillin and amoxicillin are not.
7. None. Atypical pathogens *Mycoplasma*, *Chlamydiaceae*, and *Legionella* cause “atypical” community-acquired pneumonia. *Mycoplasma* lacks peptidoglycan so does not Gram stain and does not have PBPs. *Chlamydiaceae* are obligate intracellular bacteria and have a very thin peptidoglycan layer that does not Gram stain. *Legionella* is gram-negative obligate intracellular microbe.
8. Hypersensitivity reaction, type 1, with anaphylaxis
9. The penicillinase-resistant penicillins, nafcillin, oxacillin, dicloxacillin, and cloxacillin



<https://www.intechopen.com/chapters/48837>

From Concepts, Compounds, and the Alternatives of Antibacterials, 2015

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- Clinical Key Murray, Rosenthal, and Pfaller Medical Microbiology 9e, 2021 Chapters 12 through 35 microbiology of bacteria
- The Sanford Guide to Antimicrobial Therapy 52e, 2022
- Figures on Slide 25:
  - Upper: Goodman & Gilman 12e Figure 53-5 *Antibiotic efflux pumps of gram-negative bacteria.*
  - Lower:Sherris Medical Microbiology, 5e Figure 23-10:  $\beta$ -lactamase cleaves  $\beta$ -lactam ring

## Lecture Feedback Form:

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