NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

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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Make.
Heal.
Innovate.
Reinvent the Future.

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):

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Scholar Rx Bricks: (required)

General Microbiology > Antimicrobial Agents > Antibacterial Drugs > Penicillins
https://exchange.scholarrx.com/brick/penicillins

Suggested supplemental resources:

Access Medicine Katzung's Basic & Clinical Pharmacology, 16e, 2024; Chapter 43: Beta-Lactams and Other Cell Wall- & Membrane-Active Agents
https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3382&sectionid=281754499

Access Medicine Katzung's Pharmacology: Examination & Board Review, 14e, 2024; Chapter 43: Beta-Lactams and Other Cell Wall- & Membrane-Active Agents
https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3461&sectionid=285597666

LWW Health Library, Premium Basic Sciences: Lippincott's Illustrated Reviews: Pharmacology, 8e, 2023; Chapter 29: Cell Wall Inhibitors
https://premiumbasicsciences-lwwhealthlibrary-com.nyit.idm.oclc.org/content.aspx?sectionid=253328533&bookid=3222

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

- Medical Microbiology textbooks are available on NYITCOM Library website

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.

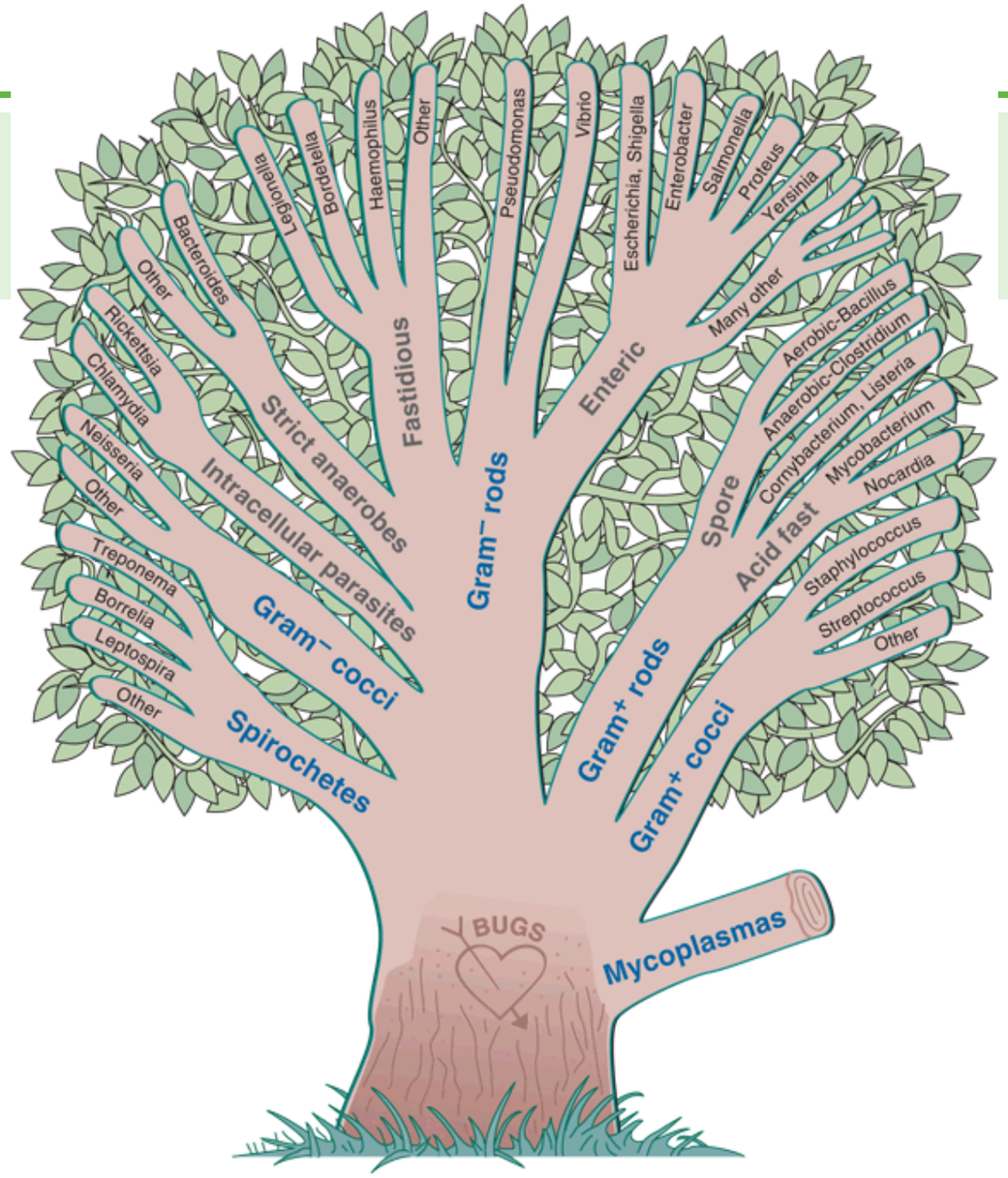
- Prokaryote structure and Gram stain | cocci (spheres), bacilli (rods), spirochetes (spiral)
- Gram-positive bacteria | Gram-negative bacteria including spirochetes | Atypical bacteria
- Some bacteria require an aerobic or anaerobic environment for growth. These are categorized as “obligate aerobes” 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.

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.

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.)

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

Nasopharynx (Know the bacteria bolded in red.)

Any amount of the following: diphtheroids, nonpathogenic ***Neisseria meningitidis*** and other *Neisseria* species, **α-hemolytic (viridens) 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.

Gastrointestinal tract – mainly colon: The highest microbial density of any human-associated microbial community. The species are far to 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 mirabilus, 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, microogranisms not killed by the antibiotic can proliferate and cause infection.

Know this

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.

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?

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

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?

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

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

Class PK Properties

- Not metabolized
- High concentrations excreted in urine.
- Unabsorbed oral ampicillin excreted in feces → disruption of microbiota
- Short half-life: Ampicillin IV may be administered by continuous infusion.

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

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*?