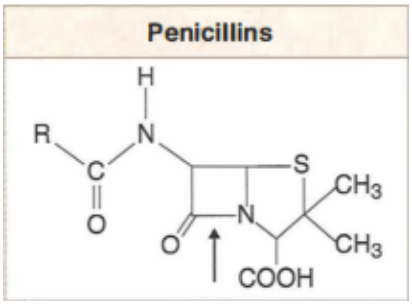
CELL WALL INHIBITORS

BETA-LACTAMS:
PENICILLINS:

The penicillins are among the most widely effective and the **least toxic** drugs known, but increased resistance has limited their use.

Members of this family differ from one another in the **R substituent** attached to the 6- aminopenicillanic acid residue.

The nature of this side chain affects the **antimicrobial spectrum**, **stability to stomach acid**, **cross hypersensitivity**, and **susceptibility to bacterial degradative enzymes** (**β-lactamases**).



Mechanism of action

The penicillins interfere with the **last step** of bacterial cell wall synthesis (**transpeptidation or cross-linkage**), resulting in exposure of the osmotically less stable membrane.

Penicillins are only effective against **rapidly growing organisms** that synthesize a peptidoglycan cell wall.

Consequently, they are **inactive against organisms devoid of this structure**, such as mycobacteria, protozoa, fungi, and viruses.

Penicillin-binding proteins

These **penicillin-binding proteins (PBPs)** are bacterial enzymes involved in the **synthesis of the cell wall** and in the **maintenance of the morphologic**

features of the bacterium. The number of PBPs varies with the type of organism.

Alterations in some of these PBPs provide the organism with resistance to the penicillins. [Note: **Methicillin-resistant Staphylococcus aureus (MRSA) arose because of such an alteration**.]

Inhibition of transpeptidase

Some PBPs catalyze formation of the cross-linkages between peptidoglycan chains

Production of autolysins

In the presence of a penicillin, **the degradative action** of the **autolysins** proceeds in the absence of cell wall synthesis. Thus, the antibacterial effect of a penicillin is the result of **both inhibition of cell wall synthesis** and **destruction of the existing cell wall** by autolysins.

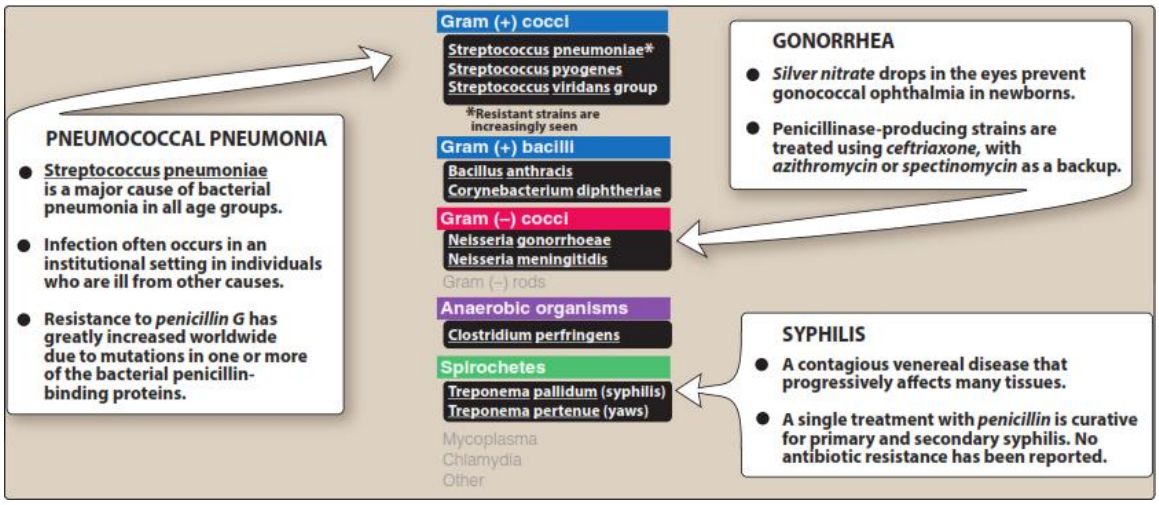
Antibacterial spectrum

The antibacterial spectrum of the various penicillins is determined, in part, by their **ability to cross** the bacterial peptidoglycan **cell wall** to reach the PBPs in the periplasmic space.

Factors that determine the susceptibility of PBPs to these antibiotics include the **size**, **charge**, and **hydrophobicity** of the particular β-lactam antibiotic.

Natural penicillins

Natural penicillins (**penicillin G** and **penicillin V**) are obtained from fermentations of the fungus **Penicillium chrysogenum**. Penicillins are susceptible to inactivation by **β-lactamases** (**penicillinases**) that are produced by the resistant bacteria.



Antistaphylococcal penicillins

Methicillin, nafcillin, oxacillin, and dicloxacillin are **β-lactamase (penicillinase)-resistant** penicillins. Their use is restricted to the treatment of infections caused by **penicillinase-producing staphylococci**, including methicillin sensitive Staphylococcus aureus (**MSSA**). The penicillinase-resistant penicillins have **minimal to no activity** against **gram-negative** infections.

Extended-spectrum penicillins

Ampicillin and **amoxicillin** have an antibacterial spectrum similar to that of **penicillin G** but are **more effective** against **gram negative bacilli.** **Ampicillin** (with or without the addition of gentamicin) is the **drug of choice** for the **gram- positive bacillus Listeria monocytogenes** and susceptible **enterococcal** species. These extended-spectrum agents are also widely used in the treatment of **respiratory infections**, and **amoxicillin** is employed **prophylactically** by dentists in high-risk patients for the prevention of **bacterial endocarditis**.

Resistance to these antibiotics is now a major clinical problem because of inactivation by plasmid-mediated **penicillinases**. [Note: **Escherichia coli** and **Haemophilus influenzae** are frequently resistant.]

Antipseudomonal penicillins

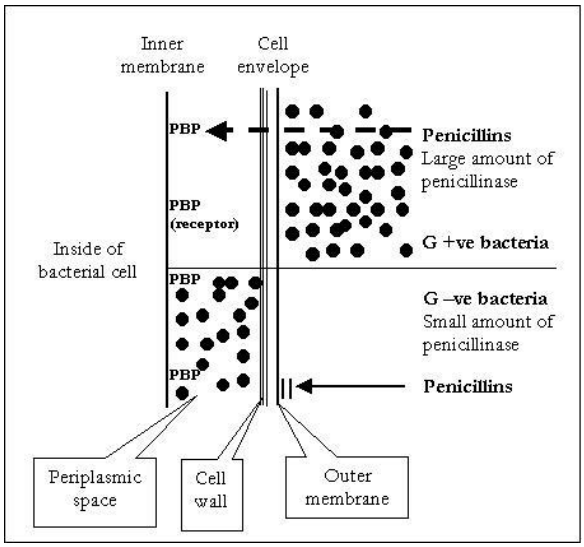
Piperacillin and **ticarcillin** are called **antipseudomonal** penicillins because of their activity against **Pseudomonas aeruginosa. Piperacillin** is the **most potent** of these antibiotics. They are effective against many **gram-negative bacilli**, but **not against Klebsiella** because of its **constitutive penicillinase**.

Resistance

Natural resistance to the penicillins occurs in organisms that either **lack a peptidoglycan** cell wall (for example, **Mycoplasma pneumoniae**) or have **cell walls** that are **impermeable** to the drugs. **Acquired resistance** to the penicillins by plasmid-mediated **β-lactamases** has become a significant clinical problem. By obtaining resistance plasmids, bacteria may **acquire one or more** of the following properties, thus allowing survival in the presence of β-lactam antibiotics.

1- β-Lactamase activity

This family of enzymes **hydrolyzes** the cyclic amide bond of **the β-lactam ring**, which results in loss of bactericidal activity. β-Lactamases either are **constitutive**, mostly produced by the bacterial **chromosome** or, more commonly, are **acquired** by the transfer of **plasmids**. Certain organisms may have chromosome-associated **β-lactamases** that are inducible by β-lactam antibiotics (for example, second and third generation cephalosporins).



β-LACTAMASE INHIBITORS

clavulanic acid, **sulbactam**, and **tazobactam**, contain a β-lactam ring but, by themselves, do not have significant antibacterial activity or cause any significant adverse effects. The β-lactamase inhibitors are therefore formulated in combination with β-lactamase–sensitive antibiotics. **coamoxiclav (augmentin**).

2- Decreased permeability to the drug

Decreased penetration of the antibiotic through the outer cell membrane of the bacteria prevents the drug from reaching the target PBPs. The presence of an **efflux pump** can also reduce the amount of intracellular drug (for example, **Klebsiella pneumoniae**).

3- Altered PBPs

Modified PBPs have a **lower affinity for β-lactam** antibiotics, requiring clinically unattainable concentrations of the drug to effect inhibition of bacterial growth. This explains **MRSA** resistance to most commercially available β-lactams.

Pharmacokinetics

Administration

The combination of **ampicillin with sulbactam**, **ticarcillin with clavulanic acid**, and **piperacillin with tazobactam**, and the antistaphylococcal penicillins **nafcillin** and **oxacillin** must be administered intravenously (**IV**) or intramuscularly (**IM**).

Procaine penicillin G and **benzathine penicillin G** are administered **IM** and serve as depot forms. They are slowly absorbed into the circulation and persist at low levels over a long time period.

Absorption

Most of the **penicillins** are **incompletely absorbed** after **oral** administration, and they reach the intestine in sufficient amounts to affect the composition of the intestinal flora.

Food **decreases the absorption** of all the penicillinase-resistant penicillins because as gastric emptying time increases, the drugs are destroyed by stomach acid. Therefore, they should be taken on an empty stomach.

Distribution

The β-lactam antibiotics **distribute well** throughout the body. **All** the penicillins **cross the placental barrier**, but **none** have been shown to have **teratogenic** effects. penetration into **bone** or cerebrospinal fluid (**CSF**) is **insufficient** for therapy unless these sites are **inflamed.** Penicillin levels in the **prostate** are **insufficient** to be effective against infections.

Metabolism

Host metabolism of the β-lactam antibiotics is usually insignificant, but some metabolism of penicillin G may occur in patients with impaired renal function.

Excretion

The primary route of excretion is through the organic acid (**tubular) secretory system** of the kidney as well as by **glomerular filtration**. **Nafcillin** and **oxacillin** are primarily metabolized in the **liver** and do not require dose adjustment for renal insufficiency. **Probenecid** inhibits the secretion of penicillins by competing for active tubular secretion via the organic acid transporter and, thus, can increase blood levels. The penicillins are also excreted in **breast milk**.

Adverse reactions

1. Hypersensitivity (5%) !!! Cross allergy!!!

2. Diarrhea (Extended spectrum)

3. Nephritis (methicillin)

4. Neurotoxicity: The penicillins are irritating to neuronal tissue, and they can provoke seizures if injected intrathecally or if very high blood levels are reached. Epileptic patients are particularly at risk due to the ability of penicillins to cause GABAergic inhibition.

5. Hematologic toxicities : high doses of piperacillin, ticarcillin, and nafcillin. Cytopenias have been associated with therapy of greater than 2 weeks, and therefore, blood counts should be monitored weekly for such patients.

CEPHALOSPORINS

The **cephalosporins** are **β-lactam** antibiotics that are closely related both structurally and functionally to the **penicillins**. Most cephalosporins are produced **semisynthetically** by the chemical attachment of **side chains** to 7-aminocephalosporanic acid.

- same mode of action as penicillins
- same resistance mechanisms.
- more resistant than the penicillins to certain β-lactamases.

Antibacterial spectrum

classified as first, second, third, fourth, and advanced generation, based largely on their bacterial susceptibility patterns and resistance to β-lactamases.

Commercially available cephalosporins are **ineffective against MRSA**, **L. monocytogenes**, **C. difficile**, and the **enterococci**.

First generation

- act as **penicillin G** substitutes.
- resistant to the **staphylococcal penicillinase** (that is, they cover MSSA)

- have activity against **Proteus mirabilis**, **E. coli**, and **K. pneumoniae**.

Second generation

- display **greater activity** against three additional **gram-negative** organisms: **H. influenzae**, **Enterobacter aerogenes**, and some **Neisseria species**,
- activity against **gram-positive** organisms is **weaker**.
- Antimicrobial coverage of the **cephamycins** (**cefotetan** and **cefoxitin**) also includes **anaerobes** (for example, **Bacteroides fragilis**).

Third generation

- **less potent** against **MSSA**,
- have **enhanced activity** against **gram-negative** bacilli as well as most other **enteric** organisms plus **Serratia marcescens**.
- **Ceftriaxone** and **cefotaxime** have become agents of choice in the treatment of **meningitis**.
- **Ceftazidime** has activity against **P. aeruginosa**; however, resistance is increasing and use should be evaluated on a case-by-case basis.

Fourth generation

Cefepime has a wide antibacterial spectrum, with activity against streptococci and staphylococci (but only those that are methicillin susceptible). Cefepime is also effective against aerobic gram-negative organisms, such as Enterobacter species, E. coli, K. pneumoniae, P. mirabilis, and P. aeruginosa.

Advanced generation

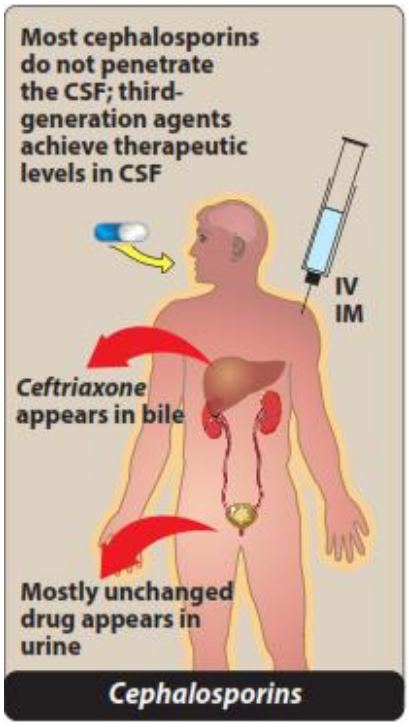
Ceftaroline [sef-TAR-oh-leen] is a broadspectrum, advanced-generation cephalosporin that is administered IV as a prodrug, ceftaroline fosamil. It has activity against MRSA and is indicated for the treatment of complicated skin and skin structure infections and community-acquired pneumonia.

In addition to its broad gram-positive activity, it also has similar gram-negative activity to the third-generation cephalosporin ceftriaxone.

Resistance

Mechanisms of bacterial resistance to the cephalosporins are essentially the same as those described for the penicillins. Although they are not susceptible to hydrolysis by the staphylococcal penicillinase, cephalosporins may be susceptible to ESBLs. Organisms such as E. coli and K. pneumoniae are particularly associated with ESBLs.

Pharmacokinetics (Adminsteration & Elimination)



Distribution

ceftriaxone and cefotaxime are effective in the treatment of neonatal and childhood meningitis caused by H. influenzae. Cefazolin is effective for most surgical procedures, including orthopedic surgery because of its ability to penetrate bone. All cephalosporins cross the placenta.

Adverse effects

Like the penicillins, the cephalosporins are generally well tolerated. Current data suggest that the cross-reactivity between penicillin and cephalosporins is around 3% to 5% and is determined by the similarity in the side chain, not the β-lactam structure. The highest rate of allergic cross-sensitivity is between penicillin and first-generation cephalosporins.

OTHER β-LACTAM ANTIBIOTICS

Carbapenems

Imipenem, meropenem, doripenem, and ertapenem are the drugs of this group currently available. Imipenem is compounded with cilastatin to protect it from metabolism by renal dehydropeptidase.

Antibacterial spectrum

Imipenem resists hydrolysis by most β-lactamases, but not the metallo-β-lactamases. This drug plays a role in empiric therapy because it is active against β-lactamase–producing gram-positive and gram-negative organisms, anaerobes, and P. aeruginosa . Meropenem and doripenem have antibacterial activity similar to that of imipenem. Unlike other carbapenems, ertapenem lacks coverage against P. aeruginosa, Enterococcus species, and Acinetobacter species.

Pharmacokinetics

Imipenem/cilastatin and meropenem are administered IV and penetrate well into body tissues and fluids, including the CSF when the meninges are inflamed (except merop.). They are excreted by glomerular filtration. Imipenem undergoes cleavage by a dehydropeptidase found in the brush border of the proximal renal tubule.

Adverse effects

Imipenem/cilastatin can cause nausea, vomiting, and diarrhea. Eosinophilia and neutropenia are less common than with other β-lactams. High levels of imipenem may provoke seizures.

Monobactams

Aztreonam [az-TREE-oh-nam], which is the only commercially available monobactam, has antimicrobial activity directed primarily against gram-negative pathogens, including the Enterobacteriaceae and P. aeruginosa. Aztreonam is resistant to the action of most β-lactamases, with the exception of the ESBLs. It is administered either IV or IM and can accumulate in patients with renal failure.

Adverse effects

Aztreonam is relatively nontoxic, but it may cause phlebitis, skin rash and, occasionally, abnormal liver function tests. This drug may offer a safe alternative for treating patients who are allergic to other penicillins, cephalosporins, or carbapenems.

	VANCOMYCIN	DAPTOMYCIN	TELAVANCIN
Mechanism of Action	Inhibits synthesis of bacterial cell wall phospholipids as well as peptidoglycan polymerization	Causes rapid depolarization of the cell membrane, inhibits intracellular synthesis of DNA, RNA, and protein	Inhibits bacterial cell wall synthesis; disrupts cell membrane
Pharmacodynamics	Time dependent Bactericidal	Concentration dependent Bactericidal	Concentration dependent Bactericidal
Common Antibacterial Spectrum	Activity limited to gram-positive organisms: Staphylococcus aureus (including MRSA), Streptococcus pyogenes, S. agalactiae, penicillin-resistant S. pneumoniae, Corynebacterium jeikeium, *vancomycin*-susceptible Enterococcus faecalis, and E. faecium		
Unique Antibacterial Spectrum	Clostridium difficile (oral only)	*Vancomycin*-resistant E. faecalis and E. faecium (VRE)	Some isolates of *vancomycin*-resistant enterococci (VRE)
Route	IV/PO	IV	IV
Typical Administration Time	60- to 90-minute IV infusion	2-minute IV push 30-minute IV infusion	60-minute IV infusion
Pharmacokinetics	Renal elimination Normal half-life: 6–10 hours Dose is adjusted based on renal function and serum trough levels	Renal elimination Normal half-life: 7–8 hours Dose is adjusted based on renal function	Renal elimination Normal half-life: 7–9 hours Dose is adjusted based on renal function
Unique Adverse Effects	Infusion related reactions due to histamine release: Fever, chills, phlebitis, flushing (red man syndrome); dose-related ototoxicity and nephrotoxicity	Myalgias, elevated hepatic transaminases and creatine phosphokinases (check weekly), and rhabdomyolysis (consider holding HMG-CoA reductase inhibitors [statins] while on therapy)	Taste disturbances, foamy urine, QTc prolongation, interferes with coagulation labs (PT/INR, aPTT, ACT), not recommended in pregnancy (box warning recommends pregnancy test prior to initiation)
Key Learning Points	Drug of choice for severe MRSA infections; oral form only used for C. difficile infection; resistance can be caused by plasmid-mediated changes in permeability to the drug or by decreased binding of *vancomycin* to receptor molecules; monitor serum trough concentrations for safety and efficacy	*Daptomycin* is inactivated by pulmonary surfactants and should never be used in the treatment of pneumonia	Use with caution in patients with baseline renal dysfunction (CrCl < 30 mL/min) due to higher rates of treatment failure and mortality in clinical studies; any necessary coagulation labs should be drawn just prior to the *telavancin* dose to avoid interaction

POLYMYXINS

The polymyxins are cation polypeptides that bind to phospholipids on the bacterial cell membrane of gram-negative bacteria. Polymyxins are concentration-dependent bactericidal agents with activity against most clinically important gram-negative bacteria, including P. aeruginosa, E. coli, K. pneumoniae, Acinetobacter species, and Enterobacter species. The use of these drugs has been limited for a long time, due to the increased risk of nephrotoxicity and neurotoxicity (for example, slurred speech, muscle weakness) when used systemically.