

Beta-Lactam Antibiotics and Vancomycin

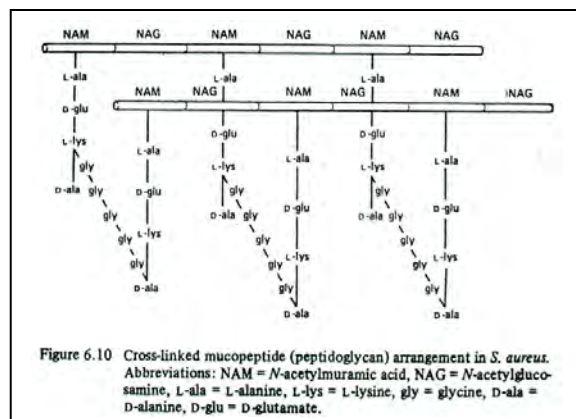
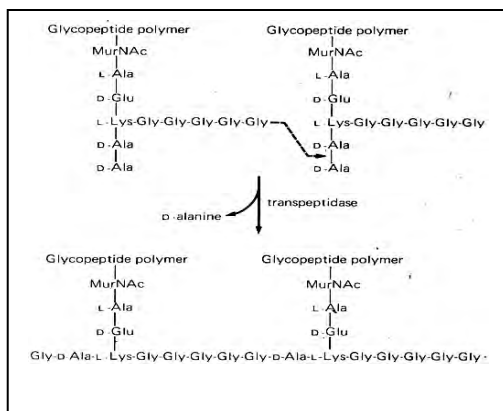
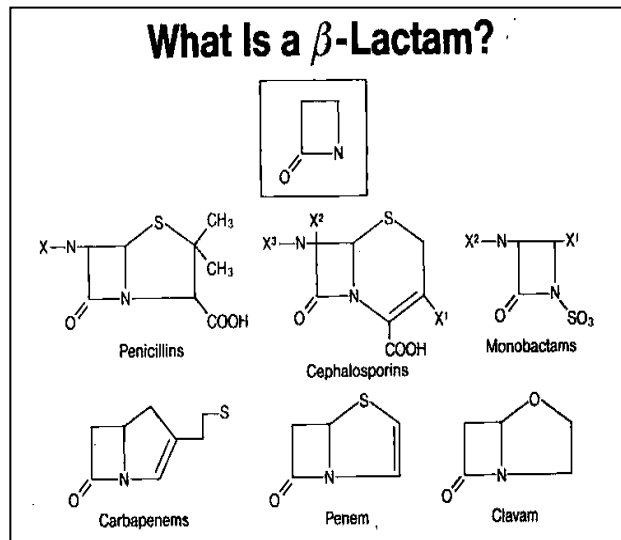
Beta-lactam antibiotics

Penicillins
Cephalosporins
Carbapenems
Monobactams

I. General principles of antibiotic activity:

Anti-bacterial drugs have “selective toxicity”, that is they interact with a target present on the bacterial cell, the prokaryote, that is not present in the mammalian host, the eukaryote. For the β -lactam drugs, this target is the cell wall. Mammalian cells lack cell walls, which for the bacteria are a critically important barrier protecting the organism from not only the vagaries of osmotic stresses, heat and viruses but also as a protection from anti-microbial peptides, and host defense mechanisms.

The major properties of an antibiotic that determine its activity against specific bacteria are then associated with the: **1- affinity of the drug for the target, 2- the permeability of the drug** - how well it can get to its target; and **3- stability to bacterial enzymes that inactivate or destroy the drug.**



1- What are the targets for the β -lactam antibiotics?

Although the discovery of penicillin by Alexander Fleming was serendipitous (he noticed a mold, the penicillium mold, killing the staphylococci he was growing on an agar plate), there has since been a tremendous effort to understand exactly how penicillins and related compounds actually **KILL** bacteria. These drugs are **CIDAL** to actively growing organisms. Strominger noted a structural resemblance between the backbone of penicillin G and the D-ala-D-ala portion of the pentapeptide side chain of the peptidoglycan that is cross linked to make bacterial cell walls. Spratt examined this association further and defined the **PENICILLIN BINDING PROTEINS** (PBP's), by radioactively labeling penicillin G and identifying the proteins that were directly bound. These PBP's are the enzymes needed for peptidoglycan (cell wall) synthesis and fall into two groups: the **carboxy-peptidases**, which cleave the terminal D-ala from the pentapeptide releasing ATP and exposing the amino acid to be cross linked and the **transpeptidases** which perform the cross-linking reaction.

Exactly how interfering with the cross-linking of the bacterial cell wall actually kills the organism remains unclear. However, β -lactam antibiotics are only CIDAL to actively growing organisms. There are autolytic enzymes that are necessary for cell division and growth and data to suggest that the activity of the penicillins also triggers this autolytic activity resulting in bacterial death.

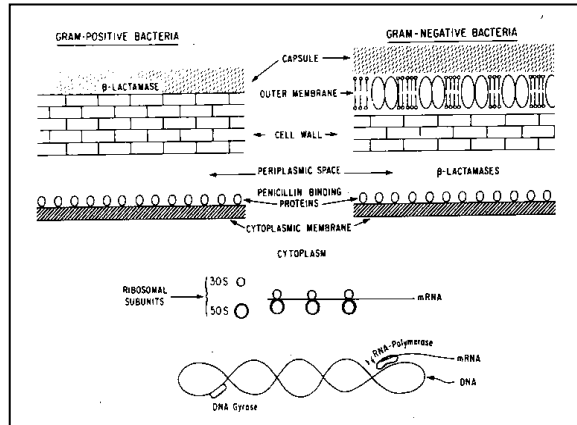
The affinity of a specific β -lactam drug for these PBP's will determine, to a major degree, its potency. The physiology of these PBP's in bacteria is important in determining the susceptibility to a specific β -lactam drug. The number of copies of a given PBP, whether they are essential, or whether they can be mutated will all contribute to overall susceptibility.

Clinical example: *Staphylococcus aureus* is a common pathogen which is often susceptible to β -lactam antibiotics, penicillin and cephalosporins. By mutating PBP2, the affinity of this essential PBP is substantially DECREASED and the organisms become resistant to this entire class of antibiotics. The clinical lab uses a gene probe to identify the mutant PBP2a - and if present, labels the isolate "MRSA" or methicillin resistant *Staphylococcus aureus*.

2- Permeability properties - How does the β -lactam drug get to its target, the penicillin binding proteins in the bacteria ?? The permeability properties of a given drug are critical to its activity and depend upon how they can gain access to PBP's in the organism as well as whether the organism is EXTRA-cellular, in the bloodstream for example, or sequestered within a macrophage. Complicating this more, the bacteria could be encased in a mucus plug in the airways or deep within an intra-abdominal mass.

Permeability issues in Gram positive versus Gram negative bacteria.

Starting at the level of the organism, there are inherent differences in the nature of the cell walls of Gram positive as opposed to Gram negative bacteria that determine susceptibility. Gram negative organisms have an outer cell wall, a lipoprotein barrier studded with protein channels or porins. Charged antibiotics, such as the β -lactams, must get through the porin proteins to reach their targets, the PBP's which are on the inside of the outer lipoprotein cell wall. A potential space, the periplasmic space occupies the region between the outer cell wall and the peptidoglycan. Bacteria actively regulate what goes through these porins: electrolytes, amino acids and various sugars.



For some organisms the porins must be large to enable the bacteria to take up pre-formed compounds that they need for growth. Since the porins are large, they do not pose a major barrier to the relatively small β -lactam antibiotics. Examples of these organisms with large porins which are relatively susceptible to β -lactam drugs are the Gram negative respiratory pathogens such as the *Hemophilus* and *Neisseria* species.

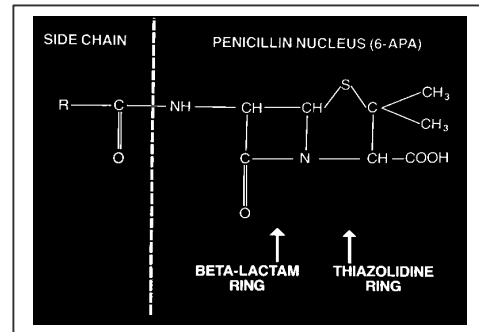
“Opportunist” Gram negative bacteria (*Pseudomonas*, *Enterobacter* and many others) can synthesize whatever they need from small sized components, a simple carbon source for example. Their porins are highly regulated, relatively small, and pose a **major barrier** for the entry of β -lactams to the periplasmic space and access to the PBP's. In addition, these organisms have EFFLUX PUMPS which can be activated to pump the antibiotics back out the porins, even if they do get to the site of peptidoglycan synthesis.

Thus, the β -lactam antibiotics with the best permeability properties for these Gram negatives are zwitterions, compact structures that are efficiently taken up by these porins.

Gram positive bacteria lack an outer cell wall, but instead have multiple layers of peptidoglycan. This peptidoglycan forms a loose mesh that does not pose a significant permeability barrier to the hydrophilic β -lactam compounds. β -lactams (and other classes of antibiotics) can have relatively bulky side chains and still gain access to their target PBP's in these gram positive organisms.

3. Stability to bacterial enzymes - How do bacteria respond to these drugs ?
The third major principle of antimicrobial susceptibility is stability to bacterial

enzymes. The fungi (penicillium and cephalosporium molds) are the sources of many β -lactam antibiotics and are soil organisms which in nature grow in the same ecological niche as many bacteria. Thus, the bacteria evolved mechanisms to deal with the presence of these natural antimicrobial products, by the production of the β -lactamases. These enzymes cleave the β -lactam ring and destroy the ability of the β -lactam drug to bind to the target PBP. They were first classified as either penicillinases, such as the enzymes often produced by *S. aureus*, or cephalosporinases, the chromosomal enzyme produced by many Enterobacteriaceae. Enzymes were then characterized by their molecular weight, requirement for a metal in the active site, isoelectric point, and substrate profile. However, the consequences of mutation and genetic exchange blurred these distinctions. Thus, the nomenclature for the β -lactamases is complex, confusing, and often changes. The principles of β -lactamase expression, however, are relatively simple.



Properties of β -lactamases - The genes for β -lactamase expression co-evolved with the genes for the PBP's as both had similar targets. Thus, there are **chromosomal enzymes**, such as AmpC, which are subject to the same regulatory mechanisms as other bacterial operons: there is a two-component sensing system that responds to the presence of β -lactam structures; a response regulator that activates (or derepresses) the target gene, the β -lactamase etc. What this means is that many organisms, particularly the Gram negative opportunists, have **INDUCIBLE** β -lactamase expression, that is chromosomally mediated and turns on and off depending upon the presence of an inducer (i.e. an antibiotic in clinical use). Mutants can be selected that are **stably derepressed** - meaning that they are constitutively producing large amounts of these enzymes that inactivate and destroy the β -lactam drug. The chromosomal enzymes may prefer either the 5-membered penicillin nucleus or the 6-membered cephalosporin nucleus as a substrate. There are also metallo-based chromosomal enzymes with a zinc moiety in the active site which are exceptionally active against drugs in clinical use.

There are also **plasmid-encoded β -lactamases** that are constitutively expressed and can be readily transferred from one organism to another. The most famous is TEM-1, named after a little girl Temora, who had an E. coli urinary tract infection that turned out to be penicillin resistant - due to the presence of this "TEM" enzyme that destroyed the antibiotic. The TEM family has accrued many many point mutations and there are now >30 variants identified. With the acquisition of these mutations, these plasmid mediated enzymes have expanded their spectrum of activity to include not just simple penicillins, but the 6-membered cephalosporin ring as well. These are aptly named "extended spectrum β -lactamases," and since they are often plasmid mediated, are transferable in places that many bacteria co-mingle - such as the gut flora.

Often these β -lactamase genes are flanked by repeated sequences or transposable elements which enable them to move from the chromosome to a plasmid or vice versa. Thus, there are reports of plasmid encoded *ampC* that may lack the expected regulatory elements and be constitutively expressed.

Localization of β -lactamases - In Gram negative bacteria, enveloped by their outer cell wall, the β -lactamases are strategically placed in the potential “peri-plasmic space” where compounds entering the cell via the porins would be immediately detected. Thus, there is an economy of β -lactamase production and efficient use of the enzymes. There is a competition between the affinity of the incoming antibiotic and its target PBP's and the affinity of the β -lactamase for the drug. If two drugs were entering at the same time, one with substantial affinity for the β -lactamase and one with more affinity for the PBP, it would be possible to competitively inhibit the β -lactamase and let the penicillin kill the bacteria.

In Gram positive bacteria that lack this outer cell wall, β -lactamases are similarly synthesized and secreted into a “cloud” surrounding the organism. Thus, antibiotics that approach the organism must be stable to these enzymes once they reach the vicinity of the bacteria. However, since there are no porin protein channels to squeeze through, bulky side chains that sterically inhibit β -lactamase activity can be added to the penicillins which are targeting Gram positive organisms such as Staphylococci that produce β -lactamases.

Clinical example - Amoxicillin is a well absorbed oral penicillin that kills Gram positive and some Gram negative respiratory pathogens, most often used to treat respiratory tract infections and otitis media. It is susceptible to β -lactamase destruction. By adding clavulanic acid, a specific β -lactamase inhibitor, to the amoxicillin formulation, the combination “Augmentin” (amoxicillin + clavulanate) is active against β -lactamase producing organisms in the respiratory tract, such as Hemophilus or Neisseria. It is also active against staphylococci that are producing β -lactamases.

To target Gram positive organisms such as staphylococci, the anti-staphylococcal penicillins were developed that contain a large side chain (isoxazol or methoxy groups) making the β -lactam ring inaccessible to the bacterial enzymes. These bulky penicillins do not get through the Gram negative porins, thus these penicillins are narrow in spectrum, limited to the Gram positives.

II - Specific Drugs -

How are the activities of different antibiotics compared ? How does a clinician know which drug to choose - what is “best” for a given infection in a specific patient? Easiest choices are based simply upon in vitro activity - what is the least amount of a drug that will kill a given organism. Various assays are

used, some of which can be automated to determine the rate of growth in the presence of various concentrations of antibiotics:

Kirby - Bauer Disc diffusion - a filter paper disc is soaked in a standardized concentration of an antibiotic and placed on a plate that has been inoculated (in a lawn) with a known concentration of bacteria. Following incubation at 37 degrees C overnight, the size of the zones surrounding the discs are measured and compared to standards for each drug that reflect the amount of the drug expected to be achieved in a patient. If the zone is large enough (i.e. more bacterial killing at lower concentrations as the drug diffuses out of the disc) the bacteria is considered susceptible; if the bacteria grow across the disc, they are obviously resistant; if colonies pop up in the zones of inhibition, it suggests that there is a mixed population or that mutants are arising at a high frequency.

E-strips - Are based on the same principle - filter paper soaked in graded amounts of the drug - enabling the technician to directly read the concentration of an antibiotic that kills the organism.

Minimum inhibitory concentrations (MIC) - More commonly, bacteria are inoculated into 96 well microtiter plates with decreasing concentrations of antibiotics. After overnight incubation turbidity is read spectrophotometrically and the well without turbidity is considered the MIC.

MBC - Minimum bactericidal concentration - In liquid culture a small number of organisms does not result in turbidity - but if the liquid were placed on solid media, colonies could arise if there were still a few bacteria present. The MBC is measured by plating out the apparently “clear” liquid media and establishing the concentration where there is >99.9% killing.

Penicillins

First described by the abbess Hildegard von Bingen in the 15th century (she also wrote madrigals) as the “good things that grow on trees” - who identified the penicillium mold as having anti-infective properties.

Penicillin G is the prototype - β -lactam ring + a thiazolidine ring + R-groups - which are side chains that influence pharmacologic properties. It is not β -lactamase stable but nonetheless is highly active against streptococci, spirochetes (cause syphilis and Lyme disease) and meningococci. Pen G is not acid stable so it is given parenterally: either intravenously or in a repository form (procaine pen G or benzathine pen G) which is given intramuscularly.

Ampicillin - Amoxicillin - The addition of a charged NH_3 group improves the penetration of the penicillin nucleus through Gram negative porins in organisms

such as *E. coli* while retaining excellent activity against *Streptococci*; the OH-group in amoxicillin provides stability to stomach acid. Neither ampicillin nor amoxicillin is β -lactamase stable so they are often given in combination with a β -lactamase inhibitor:

Ampicillin + sulbactam = Unasyn - used parenterally for a wide variety of infections including those caused by anaerobic bacteria, Gram positive and Gram negative organisms.

Amoxicillin + clavulanic acid = augmentin - Oral drug that is commonly used for

respiratory infections; it covers *S. aureus* also since the clavulanate inhibits the staphylococcal β -lactamase, as well as β -lactamase-producing *Haemophilus* and *Moraxellae*.

Anti-staphylococcal penicillins -

Oxacillin

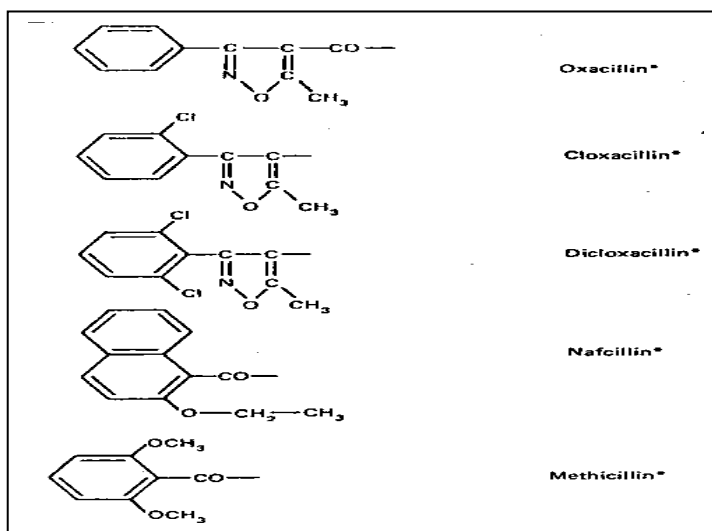
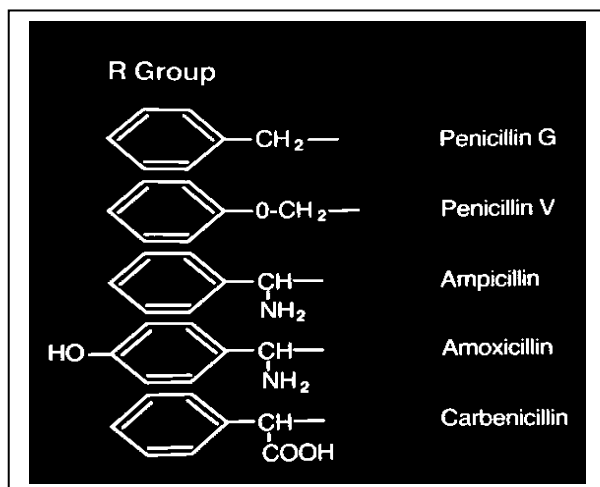
Methicillin

Nafcillin

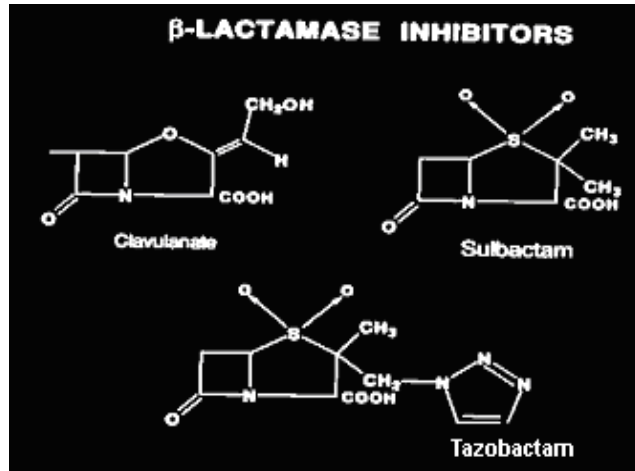
The anti-staphylococcal penicillins, also referred to as "semi-synthetic" (which is true for most of the penicillins - as they are partially produced by molds with chemical modifications) were developed in the 1950's to deal with the growing problem of Staphylococcal infections due to penicillin-resistant organisms. These

S. aureus strains produced β -lactamases with primarily penicillinase activity. Adding a large bulky side chain (methoxy or isoxazoyl groups) protected the β -lactam bond and did not interfere with penetration to the target PBP's since these Gram positive bacteria have no outer cell walls. Cloxacillin and di-cloxacillin are oral forms of these drugs, used for staphylococcal infections.

Anti-pseudomonas penicillins - Piperacillin (carbenicillin and ticarcillin are older drugs no longer in use) - To kill the opportunists, the Gram negative bacteria with tightly regulated porin channels and multiple efflux systems, "semi-



synthetic” or “broad spectrum” penicillins were developed that have charged R- side chains to improve permeability through the porins and with structural properties that increase affinity for the PBP3 target. Piperacillin has a piperazine ring - a compact charged group that significantly increases the activity of the drug against *P. aeruginosa*, a common Gram negative opportunist.



Piperacillin is formulated with a β -lactamase inhibitor - tazobactam = Zosyn - which provides protection against the plasmid mediated β -lactamases, particularly those of the TEM type. Unfortunately the tazobactam does not provide protection against the derepressed chromosomal β -lactamase of *P. aeruginosa* (*ampC*) which has predominantly cephalosporinase activity. However, the combination of piperacillin+ tazobactam does provide broad spectrum activity against Gram positive bacteria (streptococci and staphylococci) as well as many of the enteric Gram negative (*E. coli*, *Klebsiellae*, *Proteus* species) and opportunistic pathogens (*P. aeruginosa*).

Mechanisms of resistance to penicillins

Mutations in PBP's - Bacteria spontaneously undergo mutation at a frequency of approximately 10^{-6-7} . In the presence of an antibiotic, mutations that enhance survival are selected and eventually organisms with these mutations can predominate. *Streptococcus pneumoniae*, a very common Gram positive respiratory pathogen, can accumulate mutations in the PBP's and become relatively or absolutely resistant to penicillin. When these organisms die and lyse, their DNA is taken up by other streptococci (they are naturally transformable) and in the presence of antibiotic selective pressure, the now transformed penicillin-resistant organisms are maintained in the population.

A DNA cassette which encodes a mutant PBP2 in *S. aureus* is also a common clinical problem and causes methicillin resistant *S. aureus* (MRSA).

β -lactamase production - Both Gram positive and Gram negative organisms can produce β -lactamases that cause clinically significant antibiotic resistance. In Gram positives, this is a major problem with *S. aureus* which classically produces a penicillinase. In some recent outbreaks, staphylococci were found to be producing β -lactamases with cephalosporinase activity as well. Again, there can be mutations in the β -lactamase genes that alter the activity of the enzyme, and in the presence of selective pressure, these mutants flourish. Gram negative bacteria can express both chromosomal β -lactamases as well as plasmid mediated enzymes with a wide variety of activities.

Permeability - The expression of efflux pumps in both Gram negative and in Gram positive bacteria is a major cause of antibiotic resistance. The drugs are rapidly removed from the cell by an inducible pump system. In Gram negative organisms, such as *P. aeruginosa*, there are >20 different efflux systems that have been identified.

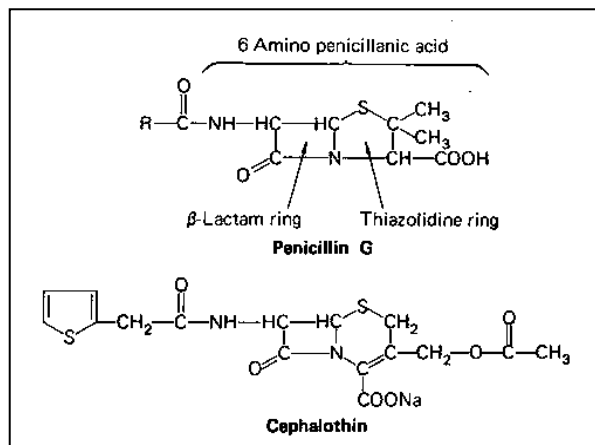
Pharmacology - In general, the penicillins are charged molecules with distribution limited to the extracellular space. With inflammation, they can achieve bactericidal levels in the CSF and are used to treat meningitis. The penicillins are handled by the kidneys, primarily by **tubular secretion** and achieve high levels in the urine in patients with normal renal function. Each drug has somewhat different pharmacokinetic properties. There is some biliary excretion (significant for nafcillin) and therapeutic levels are achieved in bile. Adverse effects that are most important include allergy, both immediate IgE-mediated hypersensitivity reactions that include anaphylaxis, and delayed responses such as rash.

Cephalosporins

The cephalosporins look and act much like the penicillins. Their basic structure consists of a 6 membered dihydrothiazine ring with substitutions at the #3 position generally affecting their pharmacological properties and changes at the #7 position

affecting antimicrobial activity (more or less). As this dihydrothiazine backbone was more amenable to chemical manipulation, there was a great deal of drug development centered upon new and improved cephalosporins during the 1970's and 1980's. This was in direct response to the increasing sophistication of medical practice, ICU's, neonatal medicine and the associated problems of hospital -associated infection and the selection of multiply antibiotic resistant bacteria.

In the late 1940's Giuseppe Brodtzu identified the antimicrobial activity associated with the cephalosporium mold while he was vacationing in Sardinia. Cephalosporin C was found to have broad activity against both Gram positive and Gram negative bacteria, and was resistant to degradation by staphylococcal penicillinases (β -lactamases). Unfortunately, it did not cross the blood brain barrier and was ineffective for meningococcal meningitis and was not further developed until the clinical need for more potent, β -lactamase stable drugs developed. As the cephalosporin nucleus was inherently stable to the penicillinases made by staphylococci, the drugs came into wide use during the S.



aureus outbreaks in hospitals that were problematic in the 1950's, and derivatives were synthesized with more desirable properties - less painful to inject intra-muscularly, longer half life (Cephalothin).

Properties of the cephalosporins - As members of the β -lactam class of antimicrobials, the activity of the cephalosporins is a function of their affinity for PBP's, their permeability properties, and their stability to β -lactamases. A few salient features are worth remembering. The cephalosporins, as a group DO NOT bind well to the PBP's of Enterococci - which are, accordingly, entirely resistant to cephalosporins. It is also important to understand that the cephalosporins, as a group, are much more potent inducers of the Gram negative chromosomal β -lactamases, the members of the *ampC* family, which (ironically) have cephalosporin activity. Thus, if there are sizable populations of bacteria present, sub-inhibitory levels of cephalosporins may well select out mutants with derepressed chromosomal β -lactamase activity resulting in clinical failures of therapy.

First generation cephalosporins - "house cephalosporins"

Cefazolin - parenteral

Cephalexin - oral

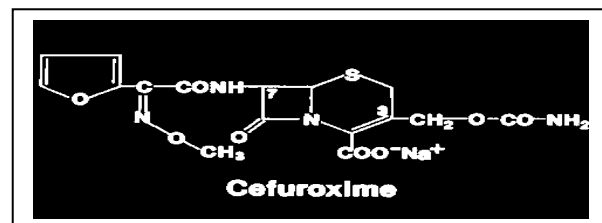
The development of the cephalosporins is conveniently divided into "generations" These initial broad spectrum agents have excellent activity against community acquired bacteria; streptococci, many *S. aureus*, *Enterobacteriaceae*, *E. coli*, *Klebsiellae*, and *Proteus mirabilis*. While rarely considered the drug of choice for a specific indication, they are often used for surgical prophylaxis, given immediately at the time of surgery, or for skin and soft tissue infections (but not bites). As more resistant Gram negative infections became common, and the importance of β -lactamase producing anaerobes in the bowel was appreciated, the use of second generation cephalosporins increased.

Second generation cephalosporins -

Cefoxitin, cefotetan and cefuroxime

Cefoxitin and cefotetan are very β -lactamase stable - and active against many aerobic and anaerobic Gram negative rods, but they have somewhat less activity against Gram positive organisms than the first generation cephalosporins. Thus, they are used primarily to treat infections arising from the bowel flora. (Note as cephalosporins they do not have activity against enterococci, also common in the gut flora.)

Cefuroxime retains excellent activity against many Gram positive bacteria, but has improved β -lactamase stability and is active against the Gram negatives in the respiratory



tract, such as *Moraxellae* and *Hemophilus*. It is often used to treat some respiratory tract infections - but has been supplanted by more active drugs.

Third generation cephalosporins

Cefotaxime
Ceftriaxone
Ceftazidime

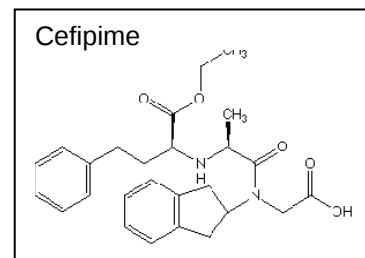
Cefotaxime and ceftriaxone - These drugs were developed to treat the increasingly resistant Gram negative rods that were seen in hospitalized patients. However, due to their enhanced activity, high blood levels, and pharmacokinetic properties, they have enjoyed widespread use against a number of common infections. Both are highly active agents against pneumococci (penicillin-susceptible and most penicillin-resistant), *Hemophilus*, *Meningococci*, *Gonococci*, and many enteric Gram negative bacteria. Both get into the CSF and with their intrinsic activity against the common causes of bacterial meningitis (*S. pneumoniae* and *N. meningitidis*) are the agents of choice for presumed meningitis.

Ceftriaxone is exceptionally active and is highly protein bound with a long half life. It can be given once (or twice) a day intramuscularly or intravenously for serious infections, making it ideal for many indications in an outpatient setting, where compliance may be an issue or when prolonged therapy may be needed, as in CNS Lyme disease.

Ceftazidime - This is the cephalosporin that is used for *P. aeruginosa* infection. Ceftazidime has the piperazine side chain also present in piperacillin. It is also active against many other Gram negative enteric and opportunistic pathogens, but has limited Gram positive activity (as compared with the first generation cephalosporins or cefotaxime). As a cephalosporin, it can induce chromosomal β -lactamases and thus should be used selectively.

Fourth generation

Cefipime has increased Gram positive as well as Gram negative activity and is used in settings where broad spectrum coverage is needed. It is also very active against *P. aeruginosa* and many of the opportunistic Gram negative pathogens that are found in hospitalized patients.

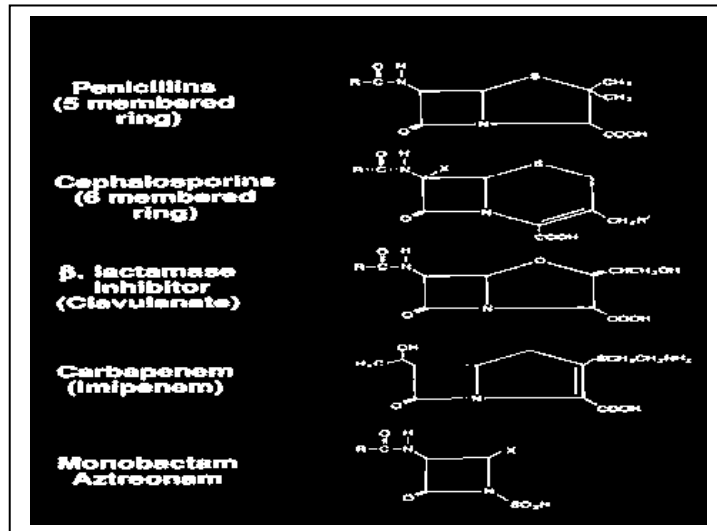


Carbapenems -

Imipenem
Meropenem
Ertapenem

This family of β -lactam-like agents has lost the β -lactam ring itself, while still acting much like a penicillin or cephalosporin. They have very high affinity for PBP2, which is present in low copy number and is accordingly an excellent target

for the antibiotic. In general, they have improved permeability properties and can selectively use OprD, a porin channel that is not usually activated by the more common efflux pumps. While they lack a β -lactam ring and were initially thought to be entirely β -lactamase stable, there have been organisms that have developed enzymes to break down these agents as well.



These are very very broadly active drugs and it is easier to remember the organisms that are not killed: *Stenotrophomonas* and *Burkholderia* (opportunistic Gram negatives) and *Enterococci*. They penetrate into the CSF and, in fact, imipenem is associated with CNS toxicity in patients with renal failure, meropenem perhaps less so.

Monobactams

Aztreonam - During the search for potent antimicrobials against Gram negative organisms, this monobactam was found as a microbial product in New Jersey sewage (in the Meadowlands !). It has a single ring and thus is stable to most β -lactamases but only binds to the PBP's of Gram negative bacteria. Aztreonam can be used in penicillin allergic patients (since it has a different structure) and has the excellent safety profile of a β -lactam type antibiotic. Unfortunately, it can be removed by efflux pumps that are expressed by some of the multi-resistant Gram negative pathogens.

Resistance mechanisms are basically the same as for the penicillins. Some species, notably the *Enterococci*, are inherently resistant to the cephalosporins due to structural differences in their PBP's.

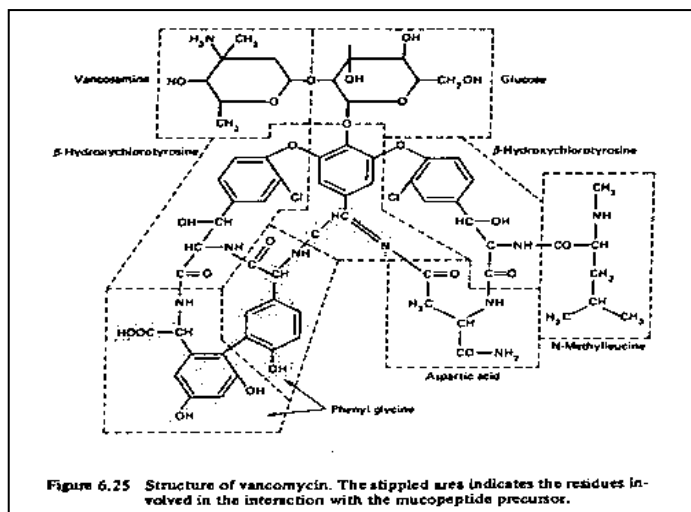
Pharmacology

The cephalosporins and related compounds, like the penicillins, are hydrophilic and well distributed into extracellular compartments. They are variably protein bound - with ceftriaxone being exceptionally highly protein bound, and have drug-specific half lives. Cefotaxime is metabolized and des-acetyl cefotaxime is excreted into the gut. Otherwise they are handled primarily by the kidney by tubular secretion and some glomerular filtration.

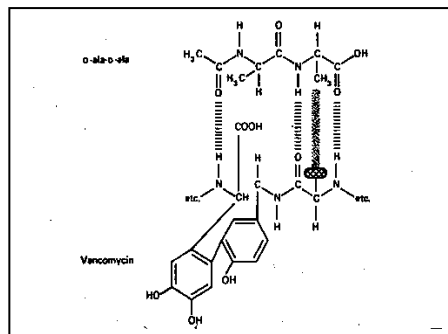
Other cell wall active antibiotics

Vancomycin -

Much of antimicrobial development has been driven by a specific clinical need (and market). In the 1950's with major outbreaks of staphylococcal infection, another fungal product, vancomycin was identified as having excellent activity against Gram positive bacteria, particularly *S. aureus*. However, the drug was not as "good" -- neither as active nor as readily purified -- as the anti-staphylococcal penicillins, and fell into disuse. However, with the emergence of methicillin resistant *S. aureus* and the common occurrence of infection associated with indwelling intravenous catheters caused by coagulase-negative staphylococci (not especially virulent skin flora that are inherently β -lactam resistant due to altered PBP's) vancomycin has become an exceptionally widely used drug.



Vancomycin targets the cell wall, interacting with the D-ala-D-ala portion of the pentapeptide side chain of staphylococci. It blocks both the carboxypeptidase activity as well as the transpeptidase. Thus, while it took awhile for organisms to become resistant, once vancomycin resistance is established it can be a significant problem in a given setting. Vancomycin does not get into Gram negative bacteria. Since it is only active against Gram positives, permeability is not an issue and there are no known bacterial enzymes (to date....) that destroy the drug.



The spectrum of vancomycin is limited to Gram positives, Streptococci, Clostridia, Listeria, and Bacillus species as well as the Staphylococci. It is active against the highly penicillin resistant *S. pneumoniae*, and is used for pneumococcal meningitis until the susceptibilities of the infecting organism are known.

Resistance - Resistance to vancomycin first developed in the enterococci, and was first reported in hospitals that used the drug orally thus exposing large populations of these commensal flora to selective pressure. There are several

genes that mediate vancomycin resistance. The most common enables the bacteria to produce a D-ala-D-lactate dipsideptide which thwarts vancomycin binding. These genes are most often found in *Enterococcus faecium* (VRE) and other enterococci. A major concern has been the spread of these genes to staphylococci. *S. aureus* resistant to vancomycin have been reported but are rare, and their prevalence is likely to increase.

Pharmacology - Since its initial isolation in the 1950's, vancomycin has been highly purified and initial reports of nephrotoxicity were likely due to impurities. The drug is eliminated by the kidneys and doses must be adjusted in renal failure. It is 55% protein bound with a half life of approximately 7 hours (with normal renal function). Although vancomycin allergy is uncommon, rapid infusion of the drug is associated with "RED MAN" syndrome, a histamine mediated flushing of the head and neck which may be associated with hypotension.