

Lecture 12: Penicillins and Cephalosporins

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Knowledge Objectives

1. Know the components of bacterial cell wall, and basic processes of cell wall synthesis and maintenance.
2. Know the mechanism of antimicrobial activity for penicillins, cephalosporins, bacitracin, vancomycin, aztreonam, imipenem, clavulanic acid, sulbactam
3. Know the classification of penicillins and cephalosporins according to their chemical structure and their antimicrobial spectrum. Know lactamase resistant/sensitive drugs.
4. Know the most common adverse effects of the these drugs.
5. Know the mechanisms of bacterial resistance for these drugs.
6. Know the most common applications of these antibiotics for the treatment of disease. Which drugs are broad spectrum, and which have specific or unique uses.

Drug List

Penicillins

penicillin G
penicillin V

nafcillin
methicillin
oxacillin
cloxacillin
dicloxacillin
flucloxacillin

ampicillin
amoxicillin

carbenicillin
ticarcillin

azocillin
mezlocillin
piperacillin

Cephalosporins

cephalothin
cefazolin
cefalexin

cefuroxime
cefamandole
cefoxitin
cefaclor

moxalactam
cefaperazone
ceftazidime

Other β -lactams

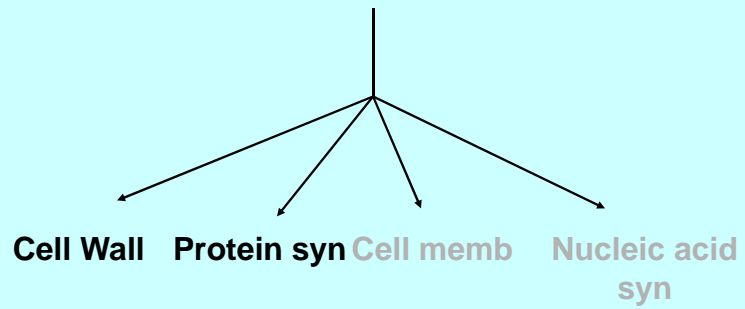
clavulanic acid
sulbactam
imipenem
aztreonam

Other Drugs

vancomycin
bacitracin

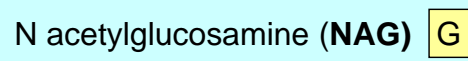
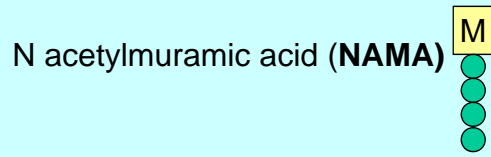
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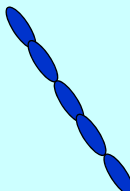
Antimicrobial Therapy



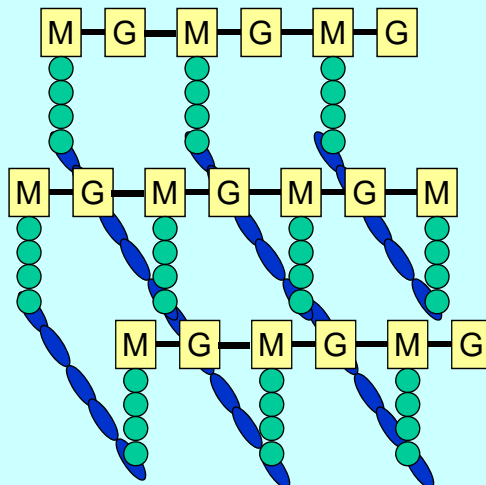
Bacterial Cell Wall Components

Peptidoglycan



Penta peptide Glycine 

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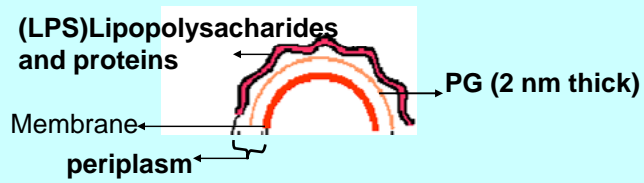


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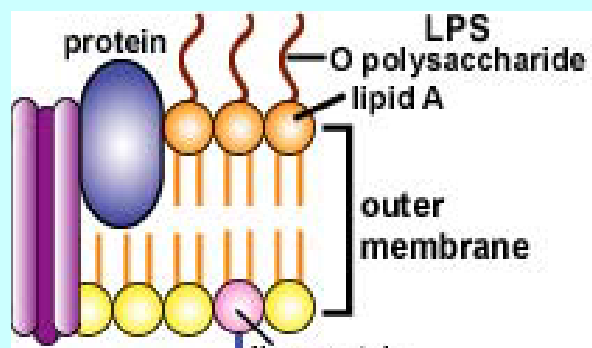
Gram +



Gram -



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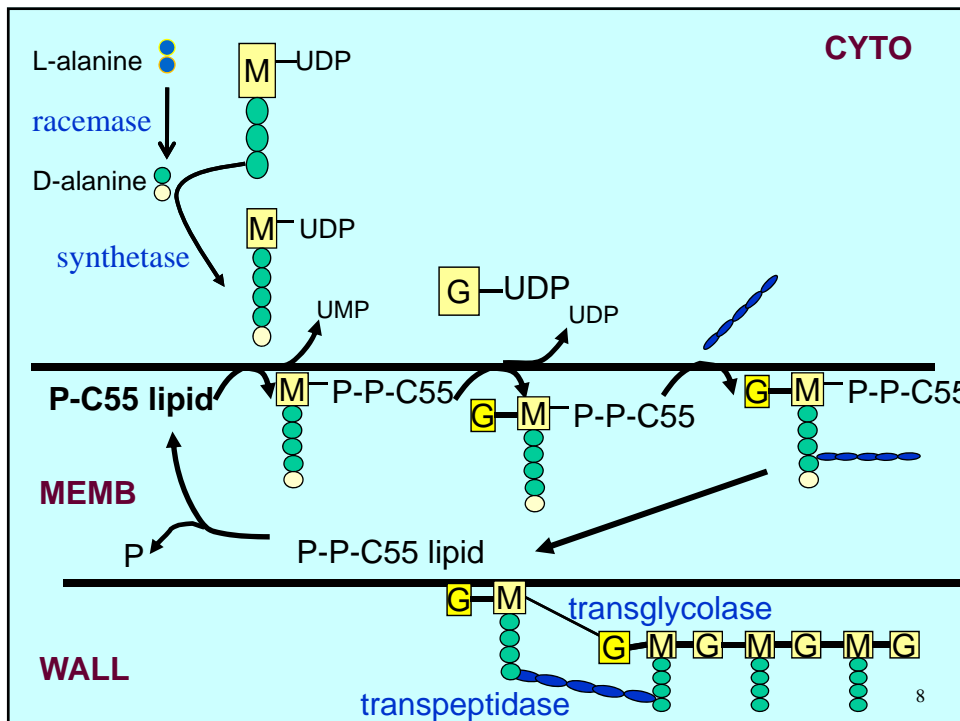
Biosynthesis of Peptidoglycan

30 enzymes

Three stages:

- 1) Precursor formation: Cytoplasm
- 2) Binding with phospho-C55 lipid carrier to form long polymer: Cell membrane
- 3) Cross-linking in cell wall

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β -Lactam antibiotics

Penicillin G and V
Nafcillin
Ampicillin
Extended-spectrum penicillin
Cephalosporins
Clavulanate
Carbapenems

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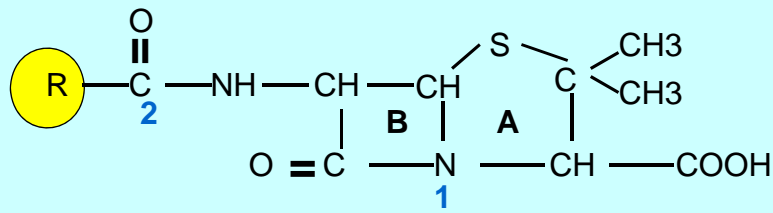
Penicillin: β -Lactam antibiotics

Drug of choice for a large number of diseases

Discovered by Alexander Flemming 1928.

Produced by penicillium

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R decides:

Penicillin subtype
 Antibacterial activity
 resistance to β -lactamase
 stability for stomach acids

A Thiazolidine ring

B β -lactum ring

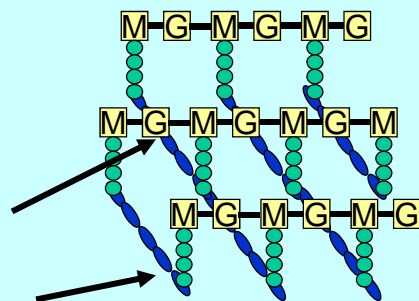
1 penicillinase

2 amidase

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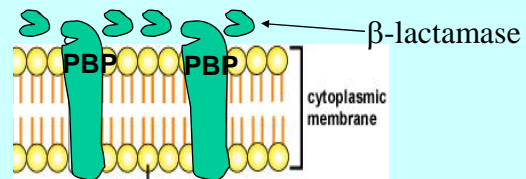
Mechanism:

Inhibits cross linking of peptidoglycan (transpeptidase)

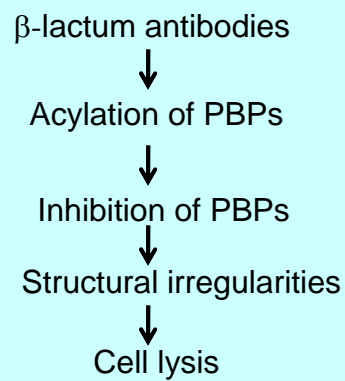


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β -lactum moiety of penicillins binds covalently (irreversibly) with penicillin-binding proteins (PBPs) at serine residue



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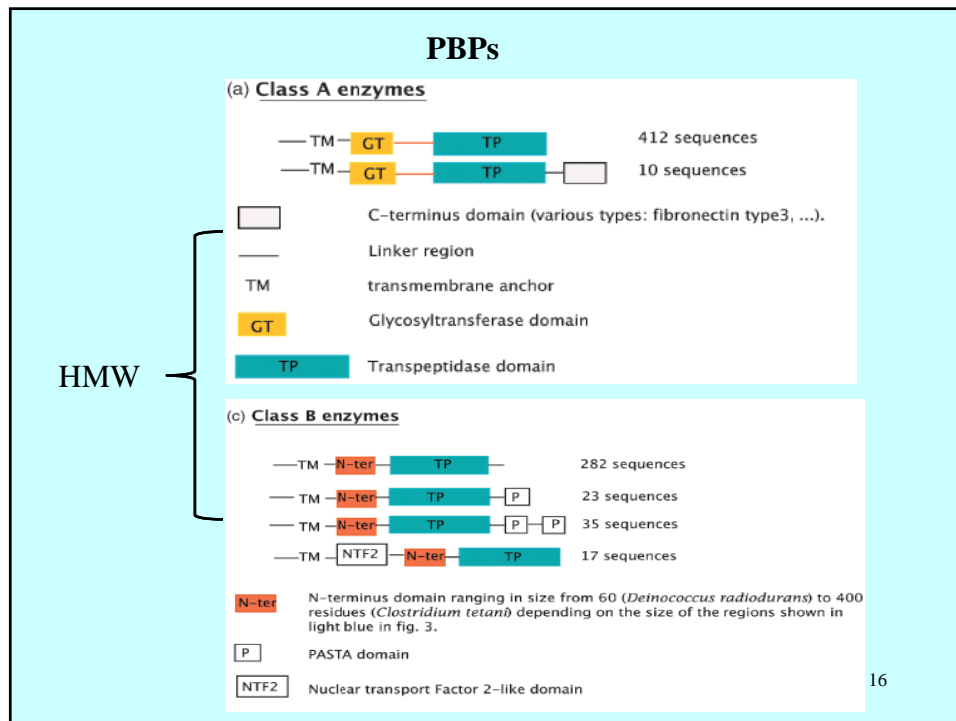
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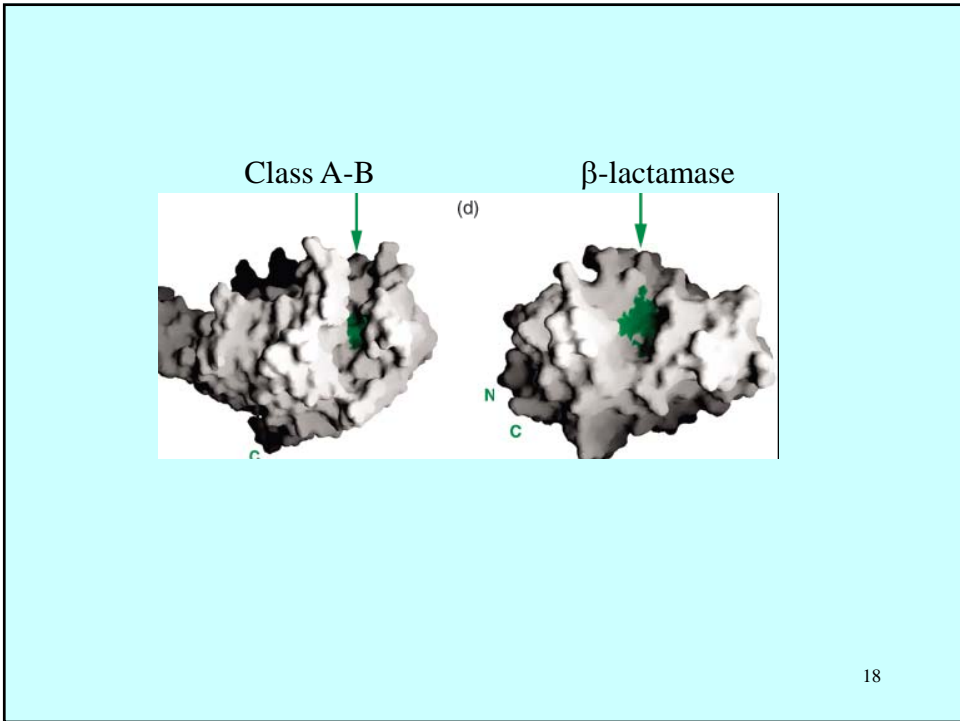
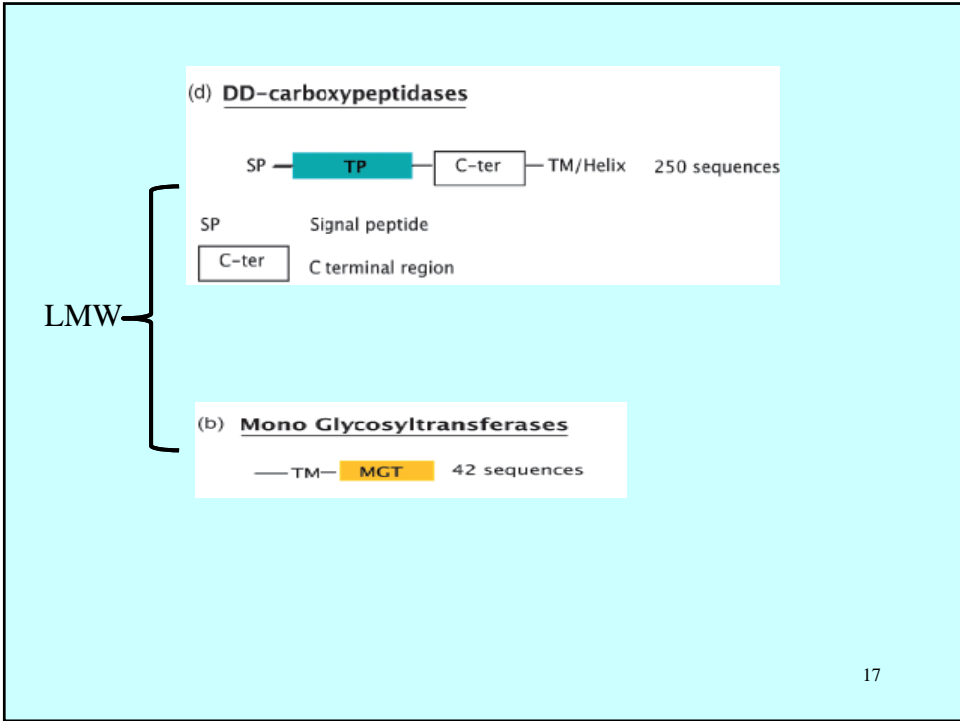
PBPs:

belong to the family of **acyl serine transferases**

- high-molecular-weight (HMW) PBPs
- low-molecular-weight (LMW) PBPs
- β -lactamases

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PBP's (40kD-91kD):

Number of PBPs varies within bacterial strain. i.e.

S aureus has 4 PBPs whereas *E coli* has 7

Protein	Apparent molecular weight	Binding of penicillin(% total)	Molecules/cell
1	91000	8.1	230
2	66000	0.7	20
3	60000	1.9	50
4	49000	4.0	110
5	42000	64.7	1800
6	40000	20.6	570

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Affinity of PBPs to antibiotics is variable

Penicillin (lytic as well as non-lytic)



Lytic PBP1; Non-lytic (PBP2/3)
(affect holin-like proteins in bacterial cell memb
which alter membrane potential)

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Mechanisms of Resistance:

A. Elaboration of altered PBPs

- a) decreased affinity for β -lactams
 - a1. formed by homologous recombination between PBPs of different bact sp.
 - a2. by transposans from unknown org
- b) structural differences in PBPs

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B. Inability of agent to penetrate to site of action

- b1. Gram (-) bact outer layer of LPS

Small hydrophilic antibiotics can pass through channels
porins

i.e. amoxicillin, ampicillin > Penicillin G

P *aeruginosa* resistant to most antibiotics lacks
porins

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C. Increased expression of efflux pumps i.e *E. coli*

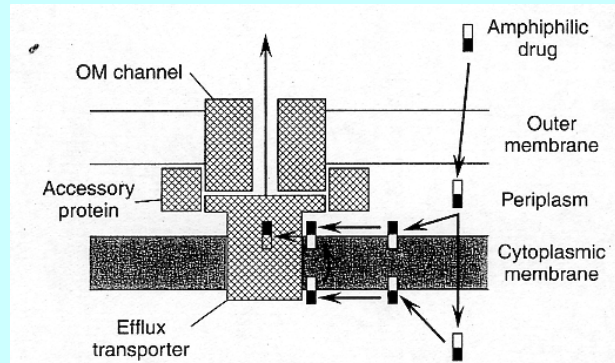


Figure 44-5. Antibiotic efflux pumps of gram-negative bacteria. Multidrug efflux pumps traverse both the inner and outer membranes of gram-negative bacteria. The pumps are composed of a minimum of three proteins and are energized by the proton motive force. Increased expression of these pumps is an important cause of antibiotic resistance. (Reprinted from Nikaido, 1998, with permission.)

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D. Production of β -lactamase

Hydrolyse β lactam ring of penicillin's

d1. β -lactamases class A-D:

Class A (extended spectrum β -lactamase): degrade penicillin, some cephalosporin's and carbapenems

Class B (Zn-dependent): destroy all β -lactams except aztreonam

Class C: cephalosporin's

Class D: cloxacillin

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d2. Site of liberation

Gram (+), β lactamase is secreted extracellularly in large amounts

Gram (-), β lactamase is located in the periplasmic space, small amounts.

Primary mechanism of acquired resistance!

d3. Other factors:

surviving bacterial cell,
biofilms produce bacteria in prosthetics

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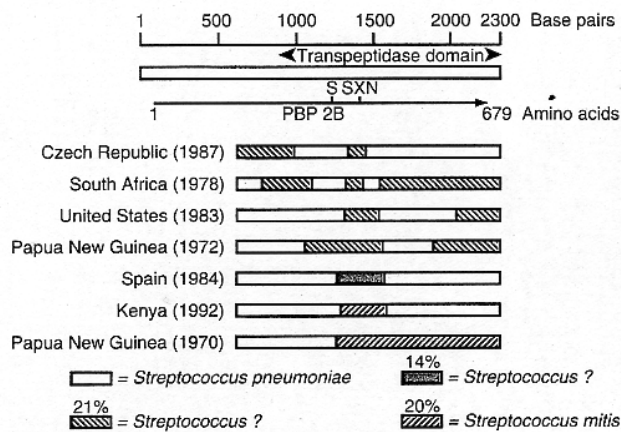
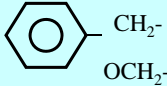
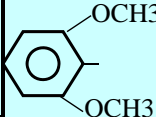
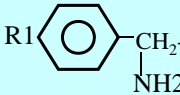
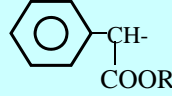


Figure 44-4. Mosaic PBP 2B genes in penicillin-resistant pneumococci. The divergent regions in the PBP 2B genes of seven resistant pneumococci from different countries are shown. These regions have been introduced from at least three sources; one of which appears to be *Streptococcus mitis*. The approximate percent sequence divergence of the divergent regions from the PBP 2B genes of susceptible pneumococci is shown. (Reprinted from Spratt, 1994, with permission.)

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Classification	Spectrum	
Natural Penicillins Penicillin V and G (phenoxymethyl penicillin)	Gram (+) cocci, hydrolyzed by penicillinase so ineffective against most strains of S. aureus	
β-lactamase resistant Penicillin; methicillin (discontinued in US), nafcillin, isoxazoyl penicillin	Less active agnst bacteria sensitive to Penicillin G First choice for S aureus and S epidermidis	
Aminopenicillins (or modern spectrum) Ampicillin, amoxicillin	Gram (-) e.g Hemophilus influenzae, E.Coli, Neissaria sp. <i>Administered with b-lactamase inhibitor such as clavunate to prevent hydrolysis</i>	
Carboxypenicillin Cabbenicillin (discontinued in US) Ticarcillin	Gram (-) e.g. pseudomonas sp, enterobacter sp. Inferior to ampicillin against Gram + cocci	
Ureidopenicillins (extended penicillin) Mezlocillin, Azliocillin (discontinued in US), Piperacillin	Pseudomonas sp, 10 times more effective than carboxypenicillin	

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General features of the Penicillins

Distribution

widely distributed throughout body fluids but conc varies in diff tissues.

→ **therapeutic concentrations** is achieved readily in tissues and in secretions such as joint fluid, pleural fluid, pericardial fluid, and bile

→ **Do not** penetrate phagocytic cells, very low conc in prostatic fluids, brain tissue, and intracular fluid

→ <1% in CSF when meninges are normal; ~5% when inflamed meningis

Active transport process pumps penicillin's from CSF to the bloodstream. This mechanism is blocked by **Probenecid**

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Excretion

Predominantly eliminated rapidly by glomerular filtration. Short half life (30-90 min) in body. So higher urine concentrations.

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Specific Agents

	Penicillin G	Penicillin V
Stability	Low acid stability; gastric juices at pH<2 degrades it rapidly. Food interference (30 min before meal)	More acid stable
Absorption	Oral dose: Rapidly absorbed and max conc 30-60 min in blood; should be used only when proven efficacious Peak value 0.3ug/ml after an oral dose of 250 mg in adult	Yield 2-5 fold more plasma level than G Peak value 3ug/ml after an oral dose of 500 mg in adult

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Parenteral administration of Penicillin G

peak conc in plasma reached within 15-30 min
but decline due to 30 min half life

Repository Forms of Penicillin G:

Penicillin G procaine (Wycillin) (benzyl penicillin with local anesthetic agent procaine)

slowly absorbed after IM injection but an injection of 300,000 units will maintain adequate plasma levels for 24 hours.

→ Syphilis, RTI, anthrax

Penicillin G benzathine (Bicillin L-A, Permapen) has the slowest rate of absorption even after IM absorption. An injection of 1.2 million units will maintain adequate plasma levels for 10 days.

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Distribution

0.35L/kg

60% is reversibly bound with albumin
significant amount appear in liver, bile,
kidney, semen, lymph, intestine

Excretion

Pen G → rapidly eliminated from the body by kidney
10% by glomerular filtration; 90% by tubular secretion

60-90% urine within 1st hr after injection
rest metabolized to penicilloic acid

Renal clearance ~ total renal plasma flow
(3 million u (1.8 g)/hr)

lower in neonates and infants (3hrs in 1wk old baby)³²

Renal dysfunction:

i.e Anuria → increases the half life of Pencillin G from 0.5 hr → 10hr
impairment of renal function

7-10% antibiotic may be inactivated by liver/hr

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Therapeutic uses

Penicillin G: cellulitis, bacterial endocarditis, gonorrhea
Pneumonia, Steptococcal infections, syphilis,
meningococcal infections

Penicillin V: tonsillitis, pharyngitis, skin infection,
odontogenic infection

Prophylactic uses:

Affords protection agnst

Steptococcal infections

Rheumatic fever

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β -lactamase resistant Penicillin (narrow spectrum)
(anti-staphylococcal aureus penicillin)

Isoxazolyl penicillin (oxacillin, cloxacillin, dicloxacillin)

Inhibits the growth of penicillin producing bact
s. aureus (dicloxacillin most active 0.05 ug/ml of than
1-3 ug/ml of others)

Relatively stable in an acid medium
Absorbed rapidly but incompletely (30-80%)
increases after empty stomach

Peak conc in plasma 5-10 ug/ml after an oral
dose of 250 mg in adult

Eliminated rapidly by kidney. Also hepatic

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Nafcillin

Very effective agnst S aureus (0.06 to 2 ug/ml)

Inactivated in the acidic medium

Peak plasma conc is ~ 8ug/ml after 1-g IM injection;
bile has more; CSF adequate

β -lactamase resistant Penicillin (narrow spectrum)
(anti-pseudomonas aeruginosa or acinetobacter spp)

Temocillin

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Aminopenicillins (Moderate spectrum)

	Ampicillin (Principen)	Amoxicillin
β -lactamase sensitive	Yes	Yes
Acid stable	No	Yes
Absorption	Well; oral dose of 500 mg \rightarrow peak plasma conc of about 3 ug/ml at 2hrs Food diminishes absorption	Quick and complete Peak plasma conc is 2-3 fold higher than Ampicillin Food has no effect
half life	80 min Renal dysfunction prolongs half life	= Ampicillin but avl longer in plasma (~x2)

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Ampicillin (Principen)

Amoxicillin

Excretion	Appears in bile, undergo enterohepatic circulation and is excreted in feces	Eliminated in urine; probenecid delays excretion of drug;
Use	Upper respiratory infections, UTI, Meningitis, salmonella infections Amoxicillin less effective than ampicillin for shigellosis	

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**Antipseudomonal penicillins: (extended spectrum)
Carboxypenicillin and Ureidopenicillin**

β-lactamase sensitive

Carbenicillin Indanyl sodium (Geocillin)
only used for managing UTI caused by Proteus

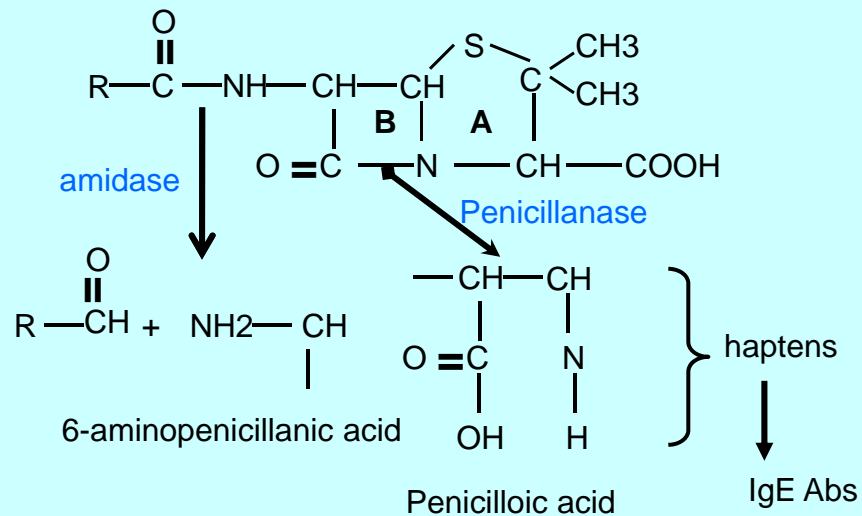
Ticarcillin
2-4 times effective for P aeruginosa than
Carbenicillin, which is toxic

Piperacillin (Pipracil)
extends the spectrum of ampicillin to include
most strains of P aeruginosa

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VIII. Untoward Effects:

•**Hypersensitivity: MOST common** side effect (0.7%-4%)
Allergy to one penicillin → greater risk to other penicillins



- Serious hypersensitive reaction:
 - angiodema** (swelling of lips, tongue etc
asthmatic breathing, giant hives)
 - anaphylaxis** (severe hypotension, death)

- Convulsions and encephalopathy can occur, especially at higher doses if administered intrathecally (NOT advised).

- Coombs' positive hemolytic anemia during prolonged therapy with Penn/Cephalo

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- Decreased platelet aggregation (carbenicillin and ticarcillin)
- Neutropenia (especially the β -lactamase-resistant penicillins)
- Hyponatremia and hypokalemia (carbenicillin)
- Pseudomembranous colitis: due to effect on microflora

Management of patient potentially allergic to penicillin:

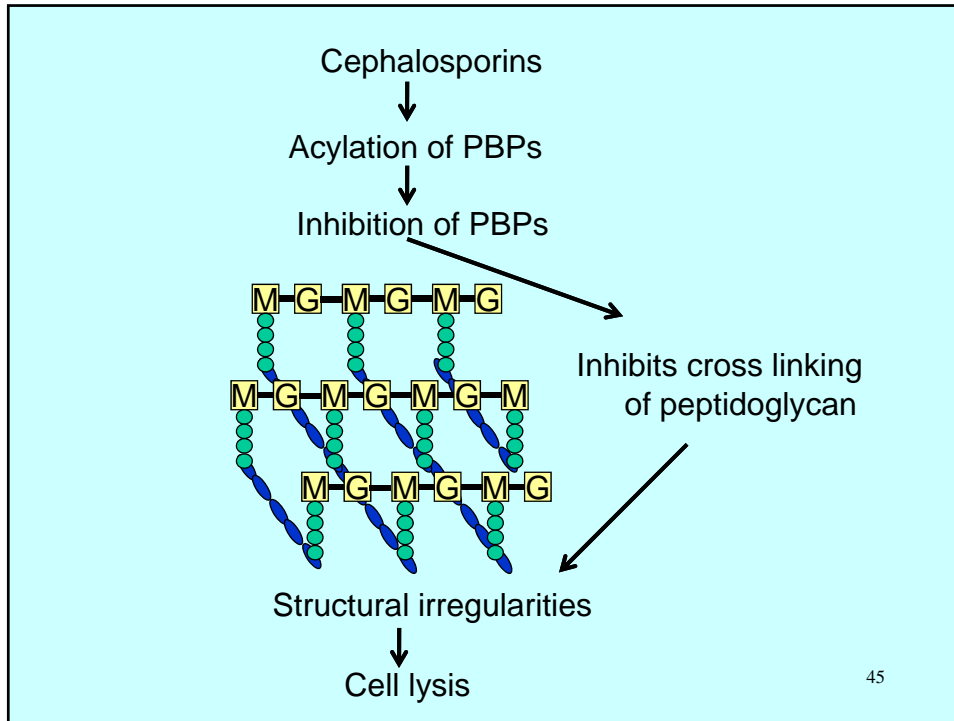
history

skin tests (not confirmatory)

desensitization

achieved by administering gradually increasing dose of penicillin

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Classification: Best indicated by *generation*
based on antimicrobial activity

Ist -IVth generation

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Ist generation	Useful spectrum
Cefazolin (ANCEF, ZOLICEF, others) Cefadroxyl (DURACEF) Cefalexin monohydrate (KEFTAB) Cefradine (VELOSEF)	good against Gram (+); modest against Gram (-) <i>Streptococci (except penncillin-resistant strains); Staphylococcus aureus (except Methicillin-resistant strain)</i>
IInd generation	Increased activity against Gram (-) but much less active than IIIrd generation
Cefuroxime (ZINACEF) Cefuroxime axetil (CEFTIN) Cefprozil (CEFZIL) Cefmatazole (ZEFAZONE) Loracarbef (LORABID)	<i>Gram (-) e.g., Enterobacter sp, Klebsiella sp., haemophilus influenza; Not active against gram + as Ist generation</i>

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IIIrd generation	Useful spectrum
Cefotaxime (CLAFORAN) Ceftriaxone (ROCEPHIN) Cefdinir (OMNICEF) Cefditoren pivoxil (SPECTRACEF) Ceftizoxime (CEFIZOX) Ceftibuten (CEDAX) Cefpodoxime proxetil (VANTIN) Cefoperazone (CEFOBID) Ceftazidime (FORTAZ, others) }	Less active than Ist generation against Gram (+) but more active against <i>Enterobacteriaceae</i> including β-lactamase producing bacteria Active agnst Pseudomonas
IV generation	Extended spectrum of activity than IIIrd generation and have increased stability against hydrolysis by β-lactamase
Cefepime (MAXIPINE)	

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Mechanism of Resistance:

Same as penicillin's. i.e. → Altered PBPs or lactamase function

First generation cefazolin is more susceptible to β -lactamase from *S aureaus* than is Cephalothin

Third generation: susceptible to hydrolysis by inducible chromosomally encoded (Class 1 β -lactamase)

Fourth generation: less susceptible

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General features of the Cephalosporins

Distribution

- Most of Cephalosporins such as cephalexin, cefadroxil etc are absorbed readily after oral administration
- Several cephalosporins can penetrate into CSF → meningitis
- Can also cross placenta
- High concentrations also seen in synovial, bile and pericardial fluids
- Penetration in aqueous humor of eye is high

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Excretion

Primarily excreted by kidney
dosage should be adjusted in patients with
renal insufficiency

Cefoperazone (excreted in bile)

cefotaxime is deacetylated in vivo; the metabolite
less active

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Specific Agents:

1st generation:

Cefazolin

Well-tolerated after either IM or IV

Conc in plasma after 1g IM administration reach to 64 ug/ml

Excreted by glomerular filtration and is bound to plasma
proteins (85%)

Preferred among 1st generation as can be administered less
frequently due to **longer half-life**

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IInd generation:

Cefoxitin

Resistant to β -lactamase produced by Gram (-) rods
For Gram (+) < active than Ist generation cephalosporins
More active than Ist or IInd generation agents agnst β -fragalis

Conc in plasma after 1g IM administration reach to 22 ug/ml;
half life **40 min**

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Cefotetan

More active than Cefoxitin agnst Gram (-)

Conc in plasma after 1-g IM administration reach to 70 ug/ml;
half life **3.3 hrs**

IIIrd generation:

Cefotaxime

Resistant to many β -lactamase and has a good activity
agnst most Gram (+) and (-) bacteria except *B. fragilis*

Half life in plasma **1 hr**
Metabolized \rightarrow desacetylcefotaxime

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IIIrd generation:

Ceftazidime

Active agnst Gram (+) excellent for Pseudomonas and Other Gram (-) bacteria

half life **1.5 hrs**; not metabolized

IVth generation:

Cefepime

Active agnst many enterobact which are resistant to other Cephalo

Excellent penetration in CSF;

Conc in plasma after 2-g IV administration reach to 126-193 ug/ml; half life **2 hrs**

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Therapeutic Uses:

First generation: skin and soft tissue infections, surgical prophylaxis of wound infection.

Third generation:

infections caused by Klebsiella, Enterobacter, Proteus etc,
ceftriaxone: all forms of gonorrhea, severe lyme diseases
cefotaxime or ceftriaxone: used to treat meningitis due to pneumococci, meningococci, and Haemophilus influenza

Fourth generation noscomal infections where resistance to β -lactum antibiotics is expected.

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Untoward Reaction:

Hypersensitivity: The frequency of cross-reactivity with penicillin-sensitive individuals is 5 to 15%.
CONTRAINDICATED in patients with a history of anaphylaxis to a penicillin.

Nephrotoxic

Renal tubular necrosis i.e. cephaloridine (4g/day)

**Hyperprothrombinemia,, Platelet dysfunction
Thrombocytopenia**

Disulfiram-like Effect: cefamandole, cefotetan, moxalactam, cefoperazone.

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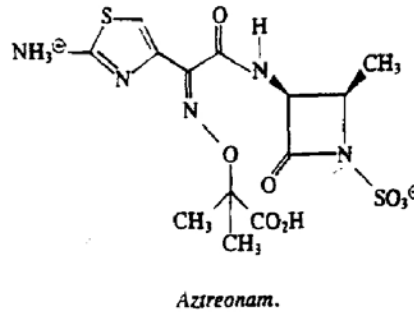
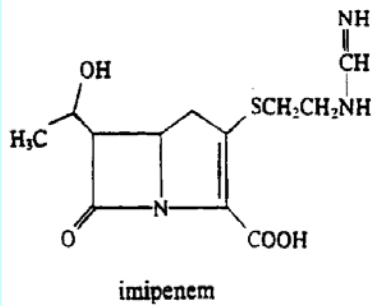
Drug-drug Interactions:

Concurrent administration of Cephalosporins or gentamicin cause nephrotoxicity (in >60 yr old patients)

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OTHER β -LACTAM Antibiotics

Carbapenems (fused β -lactum ring and a 5-membered ring sys)



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Imipenem:

i. Mechanism of action: Binds to PBPs, disrupting cell wall synthesis and is bactericidal.

ii. Spectrum: Broad-spectrum covers Gram (+) & Gram (-)
e.g. Streptococci, Enterococci.

Resistant to most forms of β -lactamase, including that produced by staphylococcus.

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iii. Metabolism:

not absorbed orally.

Rapidly hydrolyzed by **dipeptidase**, so always administered with **cilastatin**, an inhibitor of dipeptidase

500 mg IV produces 33 ug/ml in plasma, half life **1hr**

70% recovered in urine as the active drug; →renal insufficiency

iv. Side effects:

patients allergic to the penicillins may demonstrate cross-reactivity with imipenem.

nausea and vomiting.

Seizures have been reported with high doses.

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iv. Therapeutic Use:

urinary tract and lower respiratory infections
intraabdominal and gynecological infections

effective agnst cephalosporin resistant bacteria

prudent to use imipenem for empirical treatment of serious infections in hospitalized patients who have recvd other β -lactams

should **NOT** be used as monotherapy against pseudomonas due to risk of resistance during therapy

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Meropenem (MERREM IV):

does not require cilastatin

toxicity~imipenem

Therapeutics equivalent to Imipenem but less likely to cause seizures

Ertapenem (INVANZ):

long serum half life than imipenem or meropenem thus once daily dose

Gram (+) bacteria

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Aztreonam (AZACTAM)

A monocyclic β -lactam (a **monobactam**).

i. **Mechanism of action:** Interacts with PBPs and induces the formation of long filamentous bacteria

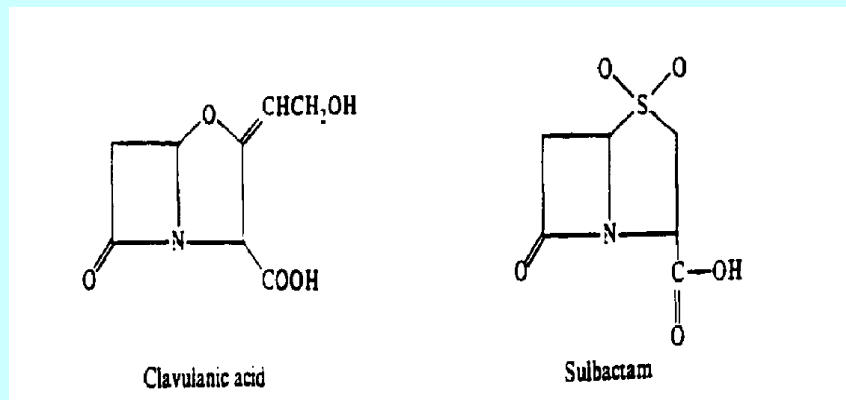
ii. **Spectrum:** It more closely resembles the spectrum of the **aminoglycosides**. No activity against **Gram (+) and anaerobic bacteria are resistant**.

Aztreonam is resistant to the β -lactamase produced by Gram (-) organisms.

iii. **Side effects:** well tolerated. Penicillin allergic patients do not exhibit **cross-reactions** with aztreonam.

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β -Lactamase Inhibitors:



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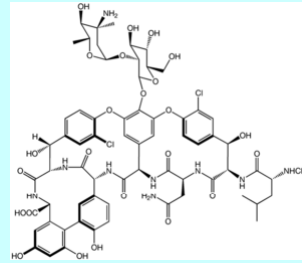
Mechanism of action:

- i. Inhibits β -lactamase \rightarrow prevent the destruction of β -lactam sensitive antibiotics.
- ii. Very efficient against plasmid encoded β -lactamase (the enzymes that degrade ceftazidime/cefotaxime).
However, inactive against β -lactamase produced by treatment with IInd and IIIrd generation cephalosporins.
- iii. Poor antimicrobial activity, but binds irreversibly with β -lactamase from both gram (+) or gram (-) bacteria so known as "**SUICIDE**" inhibitor of β -lactamase
- iii. well absorbed; included in combination with amoxicillin (Augmentum) or with ticarcillin (TIMENTIN)

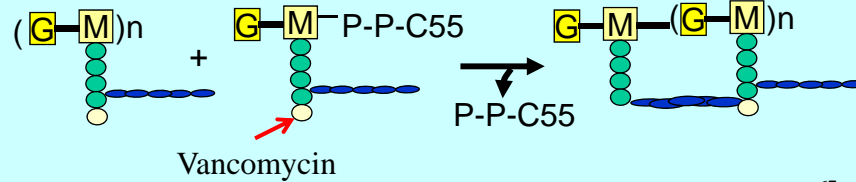
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Vancomycin

Complex tricyclic glycopeptide antibiotic



Mechanism: Inhibits cell wall polymerization by binding to terminal D-Ala-D-Ala terminus of incoming complex attached to carrier



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Antibacterial activity:

Gram (+)

Gram(-) are resistant because **D-ala-D-ala (target) is substituted with D-ala-D-ser or D-ala-D-lactate**

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Absorption, Distribution and excretion:

Oral absorption poor; slow IV is preferred, NEVER IM
A single 1 g IV → 15-30 ug/ml in plasma after 1-2 hr;
half life~ 6 hrs (dose should be adjusted to maintain
desirable trough levels)

appears in body fluids and CSF

90% excreted by glomerular filtration;
accumulates if renal function is impaired
(can be cleared by hemodialysis)

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Untoward Effects:

Hypersensitive Reacns (macular skin rashes, anaphylaxis,
Chills)

Rapid administration → flushing, tachycardia,
hypotension, erythematous or urticarial reacn

flushing → “red-neck” or “red-man” syndrome by
directly inducing toxicity in mast cells

auditory impairment (**ototoxicity**) and **nephrotoxicity**;
→ caution with the use of aminoglycosides

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Summary

Vancomycin	}	Inhibits enzymes inducing cell wall synthesis
bacitracin		
* Penn/cepha		
Carbapenems	}	Affects bact. growth by binding PBP's and/or β -lactamase
Aztreonam		
β -lactamase inhibitors		

Common Side effect: **Hypersensitivity**

Resistance is developed

PBPs, efflux pumps, cell wall, location of β -lactamase

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