ANTIBIOTICS

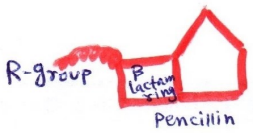
PENICILLIN

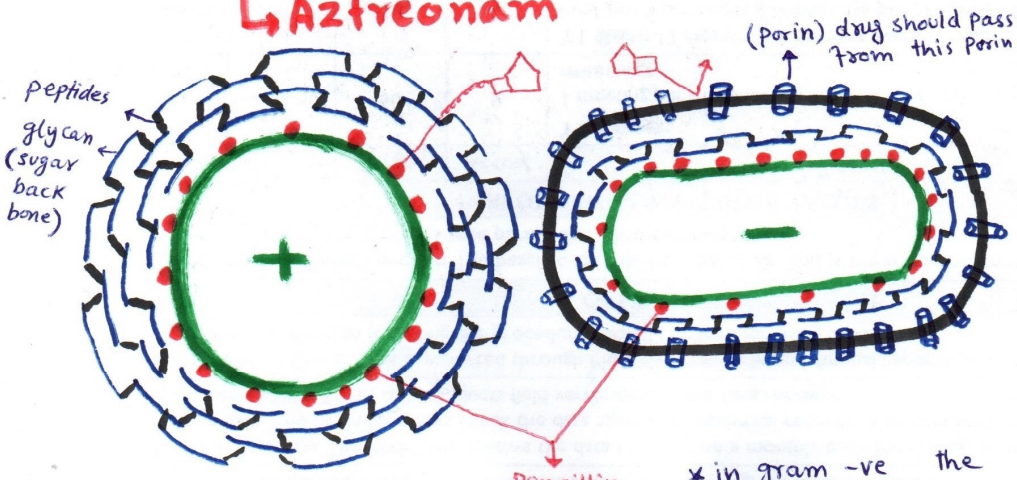
BY: ZAKIRULLAH YOUSUFZAI

1. cyclosporine
2. Bacitracin
3. Vancomycin
4. β-Lactam

Bacterial cell wall active agents or inhibitors

- penicillin
- cephalosporins
- carbapenems
- Aztreonam





* In gram +ve the peptidoglycan layre is thick but highly porus so Penicillin can easily pass through it

* Pencillin binding proteins are present on outer side of inner cytoplasmic membrane.

* in gram -ve the peptidoglycan layre is thin but an outer cytoplasmic membrane is also present which is not porus.

* special channels Perforins are present on outer cytoplasmic membrane, so the Penicillin should pass from this Porins

* Penicillin binding proteins present on the outer side of inner cytoplasmic membrane.

PENICILLINS
- *Amoxicillin** AMOXIL
- *Ampicillin*** GENERIC ONLY
- *Dicloxacillin** GENERIC ONLY
- *Nafcillin* GENERIC ONLY
- *Oxacillin* GENERIC ONLY
- *Penicillin G* PFIZERPEN
- *Penicillin G benzathine* BICILLIN L-A
- *Penicillin G benzathine and penicillin G procaine* BICILLIN C-R
- *Penicillin V** GENERIC ONLY

CEPHALOSPORINS
- *Cefaclor** GENERIC ONLY
- *Cefadroxil** GENERIC ONLY
- *Cefazolin* ANCEF, KEFZOL
- *Cefdinir** OMNICEF
- *Cefepime* MAXIPIME
- *Cefixime** SUPRAX
- *Cefotetan* CEFOTAN
- *Cefoxitin* MEFOXIN
- *Cefprozil** CEFZIL
- *Ceftaroline* TEFLARO
- *Ceftazidime* FORTAZ
- *Ceftriaxone* GENERIC ONLY
- *Cefuroxime*** CEFTIN, ZINACEF
- *Cephalexin** KEFLEX

CARBAPENEMS
- *Doripenem* DORIBAX
- *Ertapenem* INVANZ
- *Imipenem/cilastatin* PRIMAXIN
- *Meropenem* MERREM

MONOBACTAMS

β-LACTAMASE INHIBITOR + ANTIBIOTIC COMBINATIONS
- *Avibactam + ceftazidime* AVYCAZ
- *Clavulanic acid + amoxicillin* AUGMENTIN
- *Sulbactam + ampicillin* UNASYN
- *Tazobactam + ceftolozane* ZERBAXA
- *Tazobactam + piperacillin* ZOSYN
- *Vaborbactam + meropenem* VABOMERE

LIPOGLYCOPEPTIDES
- *Dalbavancin* DALVANCE
- *Oritavancin* ORBACTIV
- *Telavancin* VIBATIV

OTHER ANTIBIOTICS
- *Colistin* COLY-MYCIN M
- *Daptomycin* CUBICIN
- *Fosfomycin* MONUROL
- *Polymyxin B* GENERIC ONLY
- *Vancomycin* VANCOCIN

Figure 29.1 Summary of antimicrobial agents affecting cell wall synthesis. (Figure continues on next page.) *Only available in oral formulation. **Available in oral and intravenous formulations.

PENICILLIN

- **Narrow Spectrum**
  - House wife Penicilline
  - **natural Penicillin**
    - PG
    - PV
  - **V.V.V narrow Penicilin** → obese Penicillin (antistaphylococcal penicillin)
    - These are so bulky (larger) so only specific for Staphylococcus hence called "Anti staphylococcus penicillin"
- **wide Spectrum**
  - **Semisynthetic Penicillin** (Smart penicillin) "lik model girl" OR (Extended spectrum penicillin)
  - **Anipseudomonal Penicilline** (V.V.V Smart penicillin) "super model girl"

P.G & P.V are moderately large:

P.G acts on Gram +ve bacilli & Gram -ve cocci but not on Gram -ve bacilli. ie

1. Gram +ve cocci
2. Gram -ve cocci
3. Gram +ve bacilli
4. **NOT** on Gram -ve baccilli
5. spirochetes (Treponema pallidum) → syphilis
   - ↳ normally present b/w gums & teeth

V.V.V narrow Penicillin (Antistaphylococcal)

1. Methacilline (clinically not used b/c it damage the kidney)
2. Nafacillin
3. Dicloxacite
4. fludoxine
5. cloxacillin

This "o" means these are available in Oral form

Nafcillin → There N is red colour (dangerous) b/c Nafcilline cause → Nephritis, Neutropenia

Many staphylococci are releasing penicillinases OR β-lactamases, which cut the β-lactam ring of penicillin

So, such penicillin which are modified they are specific for staphylococcus, destroyed by such a bacteria, e.g:

They have modified R-group, so penicillinase does not destroy base of β-lactam ring

In this molecule is made large to acts only on staphylococcus, so it belive to V.V.V narrow spectrum.

naRRow

This **RR** means v.narrow spectrum are very resistant to penicillinases.

P.G (benzyl Penicillin)	**P.V**
① Used parentrally b/c Not stable to stomach acid. → Penicillinase & stomach acid both destroy the base of β-lactam ring	① Used orally b/c Stable to Acid Given in → ⓐ Rheumatic fever ⓑ Dental infection (Aerobic + inaerobic)

NOTE Antisaphylococci acts on those staphylococci which are resistant to penicillinases, but doesn't work on those staphylococci bacteria which are resistant to **METhacillin**, & **MRSA** (methacilline resistant staph. Aureus).

SEMISYNTHETIC Penicillin

① Amoxicillin
② Ampicillin
} **HELPS to clear enterococci**

- ⊖ **H**emophilus influenzae
- ⊖ **E**. coli
- ⊕ **L**isteria monocytogenes (only G.+ve bacteria which produce endotoxin)
- ⊖ **P**roteus
- ⊖ **S**olmonella

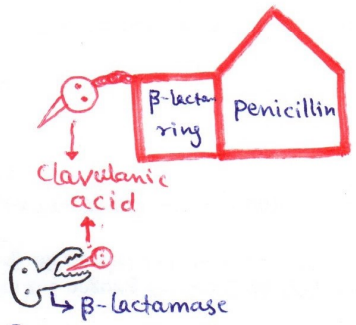
Amoxicillin & Ampicillin are smart, so their R-group does not protect base of β-lactam ring from penicillinases So with these drugs we add some other drugs (body guard & model) which neutralize the β-lactamases

Clavalunic acid is given along with Amoxicilline, here the Clavalunic acid acts as a β-lactamases drug.

TCS

- **T**azobactam
- **C**lavalunic acid
- **S**ulbactam

} anti β-lactam drugs These are the body guard of Penicillin



* **Amoxicillin + clavalunic acid = AUGMENTIN**
* **Ampicillin + Sulbactum = unasen**

Pseudomonas Aerogenosa (Gram -ve) (produce green pus) have very very thight porins, so it is belived that, it have no porins. So such wide sprectum antibiotics doesn't reach to such a wound caused by P. Aerogenosa.

ANTIPSEUDOMONAL Penicillin

Piper Azlo Mezlo Ti Car

- **Piperacillin** → (most powerful)
- **Azlocillin**
- **Mezlocillin**
- **Ticarcillin**
- **Carbanicillin**

Ticarcillin + clavalunic acid = TIMENTIN
piperacillin + Tazobactum = Zosyn

HOW ANTIBIOTICS INHIBIT BACTERIAL CELL WALL

Transpeptidase is blocked by β-lactam ring, so no peptidation rtn occur.

The BPP take peptide molecule & transfer it to the outer surface of bacterial membrane (cell wall) on this way cell wall keep growing

e.g: Penicillin, Trans peptidase

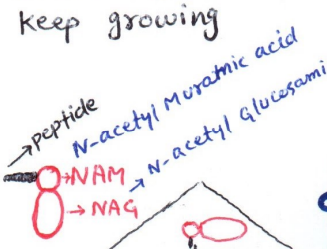
BPP

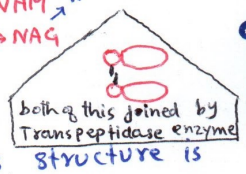
glycosylation = on this way the one peptide chain attached to other chain

Transpeptidase enzyme

Transpeptidation = on this way the peptide of one raw attached to the another raw peptides.

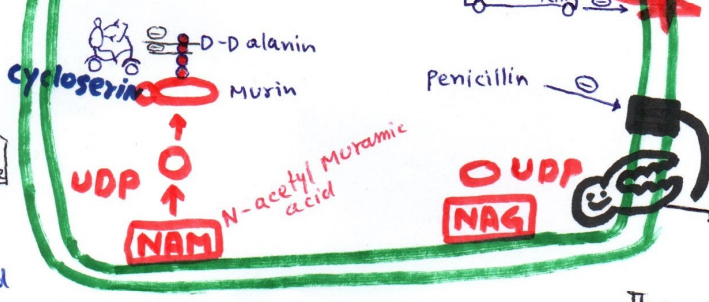
Glycosylate enzyme: This enzyme is responsible for normal glycation rtn.





All this structure is formed by NAM–NAG units, which are called peptidoglycan back bone

* which is highly porus, it give shape to bacteria b/c
  1. in Gram +ve 80–90 peptidoglycan molecules makes the layre
  2. in Gram -ve 2-3 molecules makes the layre
* cell wall prevent the osmotic burst of bacteria



The autolysine breakdown the old peptides, instead of that new peptide come & the cell wall keeps healthy.

* The Autolysin is normally slightly inhibited by Autolysin inhibitor & prevent from over activity.

cycloserine does not allow the formation of peptide, so Transpeptidation does not occur, so the bacteria undergo osmotic burst.

Bacitracin does not allow BPP (bacto prenol phosphate) to cycle again & again, so no peptide goes to cell wall.

Vancomycin inhibit the enzyme which cause glycosyalation.

* **penicillin bind with transpeptidase, so no transpeptidation occurs.**
* **penicicillin also inhibit Autolysine inhibitor, so the Autolysine become free & overactive, so destroy the cell wall.**

Autolysin normally present in bacterial cell wall, & cause remodeling of cell wall. ie removal of old peptides & adding of new peptides

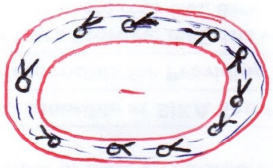
* Autolysine is controlled by Autolysine inhibitor

For penicillin to do its action

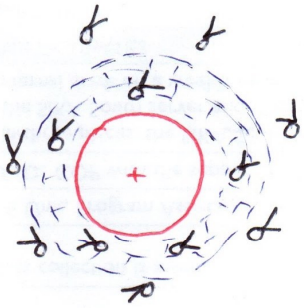
① Penicillin must reach to penicillin binding proteins.

② β-lactam ring of penicillin should be intact.

③ For all

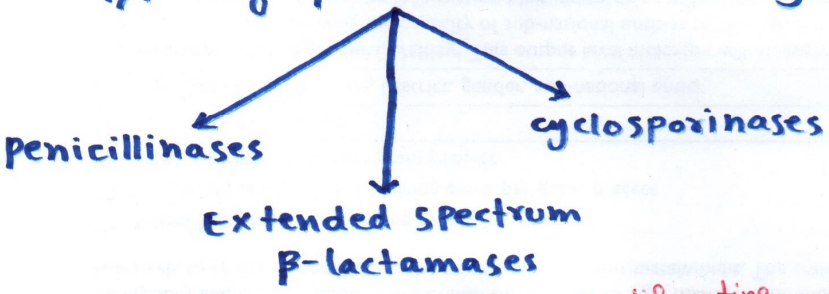


The β-lactamase are not spread here b/c of outer cytoplasmic membrane, so Gram -ve bacteria are much resistan b/c destroy the antibiotic by β-lactamases



The β-lactamases are spread b/c of lack of outer cytoplasmic membrane, antibiotic work well on Gram +ve b/c of less β-lactamases in the cytoplasm of bacteria

types of β-lactamases accrding to the action on antibiotic



If bacteria are rapidly proliferating and produce alot of new cell wall, if penicillin is given at that time bacteria will die.

So β-lactam antibiotic are most effective on those bacteria which are rapidly dividing & proliferating

If There are bacteria which are not proliferating, their cell wall will be remain strong, so such bacteria are not very affected by β-lactam antibiotic.

Penicillin & Cephalosporin kill the bacteria, so they are called Bactericidal drugs

Bacterocidal: Can eradicate bacteria in the prescence of inappropriate immune system.

Bacteriostatic: only stop the growth of bacteria & the host defence eradicate (eleminate) the bacteria.

Penicillin & **C**ephalosporin **A**re **V**ery cidal **F**or **M**icrobes

- * Penicillin
- * Cephalosporin
- * Aminoglycosides
- * Vancomycine
- * Fluroquinolone
- * Metronidazole

] Bacteriocidal Drugs

RESISTANCE TO PENICILLIN

Natural Resistance

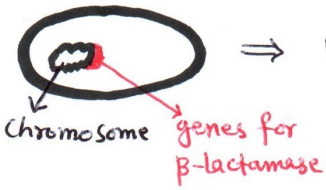
① all Those cells which don't have peptidoglycans are resistant to penicillin.
e.g → virus
→ Fungi
→ Mycoplasma
→ Mycobacteria
→ claymedia (this replicate within human cell so Penicilline can't enter to human cell)
→ Human cells

② There are some bacteria which have peptidoglycan but does show natural resistance to penicillin
e.g: pseudomonas → which is resistant to → PG, PV

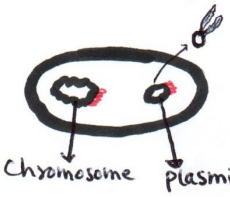
Acquired Resistance

* ① β-lactamase production
② ↓ Permeability (due to thight poins)
③ ↑ Efflux Pump
* ④ Alteration of penicillin binding proteins.
↓
These microbes are called MRSA

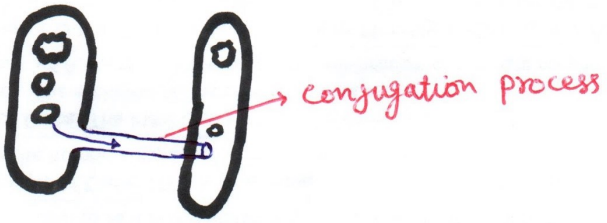
normally bacteria have one chromosome, & genes for β-lactamases are present on that chromosomes.
sometime bacteria have additional chromosome (plasmid) which also produce β-lactamases.



⇒ if such bacteria divide it give this gene to only its own doughter cell



If such bacteria divided it give gene of β-lactamase to many other classes of bacteria by the process of conjugation, it form many plasmids.



β-lactamase production

- **Chromosome mediated** → Spread slowely
- **Plasmid mediated** → Spread Rapidly

In β-lactamase productive bacteria we give V.V.V narrow spectrum Antibiotics.

Alteration of penicillin binding proteins are 1st time done in staphylococcus Aeurus.
Now it is also discovered in staphylococcus pneumonia
Penicillin G → Kills stap. pneumonia previously, b/c they don't produce β-lactamases

PENICILLIN WHICH ARE given ONLY ORALLY

(1) Penicillin V
(2) Amoxicillin
(3) Amoxicillin + Clavlunic Acid = AUGMENTIN
(4) INDANYL CARBINCILLIN

PENICILLIN WHICH ARE GIVEN PARENTRALLY

(1) CARbencillin
(2) PIPERACILLIN
(3) TICARCILLIN
(4) AMPICILLIN + sulbactum = UNASEN

PENICILLIN WHICH ARE PRESENT IN DEPOT FORM

(1) PROCAIN PENICILLIN
(2) BENZATHINE PENICILLIN

Benzathine penicillin are given deep intramuscularly in Rheumatic fever.

* Depot form work for longer time (about 3W)

Amoxicillin have absorbed from GIT very easily, so it has good & bad both effects:

* **Good Effects**: if bacteria is present somewhere in blood So drug is absorb rapidly from GIT to blood & work good.

* **Bad effects**: If bacteria is present in GIT, & Amoxicillin is given, it is absorb rapidly from GIT, so Amoxicillin fail in GIT infections.

Ampicillin is poorly absorbed from GIT, there for used in GIT infections (shegella, salmonella---)

Drugs belong to V·V·V narrow spectrum are orally absorbed, so therfor they depend on food, so they must be given 1 hour before or 2-hr after meal.

Penicillin are not good lipid soluble therefor they don't work well on bacteria present intracellecularly they present abundantly in Extracellecular fluid

normally penicillin doesn't cross BBB, but in inflamation (Meningitis, Encephalitis) the BBB Epithelial cells shrink, so gap increases & penicillin enter to brain.

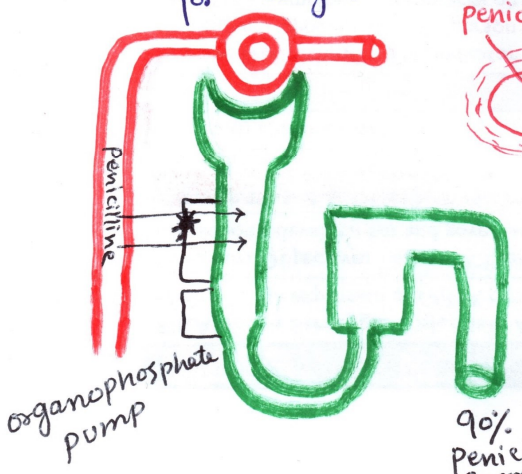
It is good that penicillin enters to brain when needed.

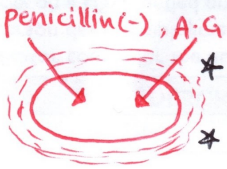
* similarly penicillin acts on bone in osteomyelitis

Excretion of Penicillin

Penicillins are filtered through glomeruli & most of them are secreted through Peritubular capillary by organophosphat pump.

when probenacid are given along with penicilline, the probenacid are more strongly bind with organophospate, so no chance available for penicillin to bind with organophospate, on this way penicillin remain for longer time in the blood.





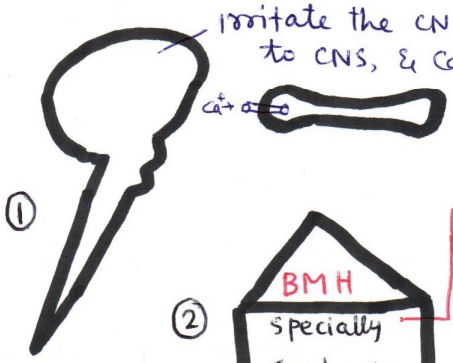
90% Penicillin excreted in Urin

* Penicillin also cross placental barier
* penicillin also come out in milk.
* penicillin also come out in saliva.

Penicillin + Aminoglycoside

penicillin are –ve & A·G are +vely charged so, they are not put in a container to gather, b/c make insoluble noneffective complex.

Adverse effects of Penicillin



irritate the CNS, b/c allot of Ca^{+} enter to CNS, & cause seizure specilly in Epiliptic Patients

① Ca^{+}

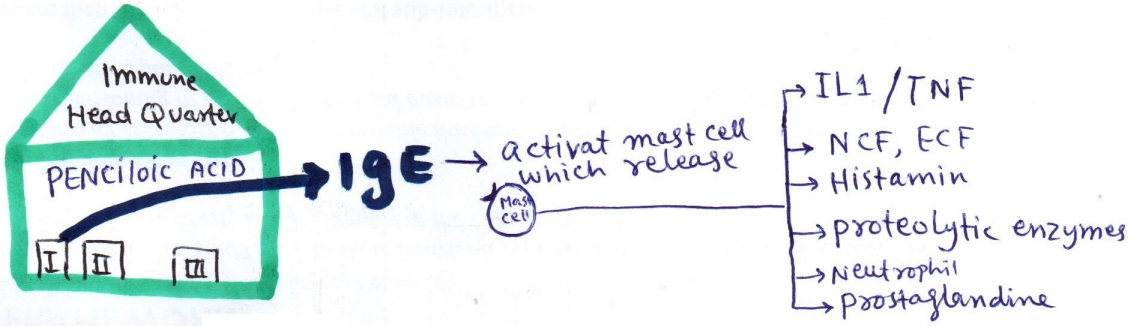
② BMH
Specially
→ Carbacillin
→ Ticarcillin

→ alter platlet membrane so platlet aggregation can't occur

→ also disturp the surface protein of Neutrophil So, Neutropenia occur

nephritis caused by
→ Methacillin (mostly) → not used nowadays
→ Nafcillin

Extended spectrum penicillin specially (Ampicillin) when used for long time It kills the most bacteria & colustrium deficile overgrow & caus diarrhea & sometime pseudomembraneous collitis.



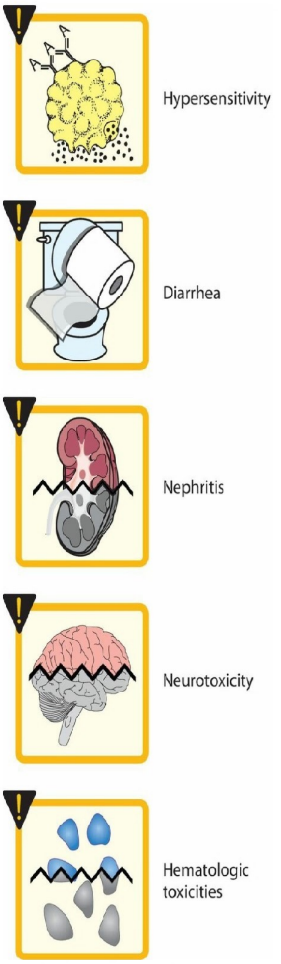
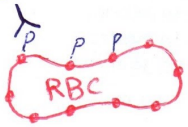


Figure 29.9 Summary of the adverse effects of penicillins.

Type I Penicillin & its Metabolic products e.g: mostly penciloic acid is so small, that normally it can't cause stimulation of our immune system.

The most serious of Type I Reaction is ANAPHYLITIC SHOCK, But it is rare

TYPE II



Penicillin bind with RBCs intrisic proteins & altered its structure, so immune system can't recognize such cell, & Immune system make Antibodies against these proteins, so this is called penicillin mediated hemolytic anemia

Type III Ag–Ab complex formed in the blood & deposited into many areas like:

1. Vasculitis with skin rash
2. Glumerolonephritis
3. polyarthritis
4. pleuritis / pericarditis
5. Generalized lymphadenopathy
6. Angeoedema in → lips, → tongue, → periorbital area

Maculopapular skin rash also occur due to penicillin but that is not hypersensitivity reaction, but it is the direct action of penicillin on skin.

* If someone has Epsten bar virus, & we give penicilline that person 100% develop Maculopapular skin rash.

Type I hypersensitivity reaction occur immediately, while Type III occur 7–12 days later of penicillin injection.

* If someone has penicilline IgE mediated sensitivity, cephalosporin should be avoided.

penicillin also loaded body with Catoins like Na^+ & loss of K^+