PHARMACOLOGY

Modified slides no.3
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Bacterial resistance:

Occurs:

- When clinical condition of host is impaired
- When normal flora have been suppressed
- With interrupted or inadequate Rx
- More frequently in certain types of bacteria (Gram negatives possess an outer membrane and cytoplasmic membrane preventing passage of antibiotec through pores)
- With widespread use of broad spectrum antibiotics
- In poor environmental setting of host

■ **NOTE**: Rx: medical prescription

■ **Note** :**usually we start with a narrow spectrum antibiotics or we used what is called the first drug of choice for specific microorganisms**

Mechanisms of bacterial resistance

- Natural resistance

*Absence of a metabolic process or an enzyme or protein in the bacteria which is required for the action of the antimicrobial

*Absence or hard cell wall making the antimicrobial difficult to penetrate

■ **Additional information**: The antimicrobial failed to enter the cell in order to act , it will act in ,ex: protein, DNA,RNA synthesis." Antimicrobial activity "

Important slide

■ **Additional information**: In other words , lower concentration at target tissue as compared to plasma concentration is required or achieved by specific antibiotics this makes the bacteria naturally resistant to the action of the antibiotics

* The need of antimicrobial drug in large amounts at site of action above its concentration in the plasma

To overcome this type of resistance the drug has to be given in very large doses which leads to severe side effects

■ **Additional information**: In order to achieve a proper concentration we have to use a large dose of that particular antibiotic

■ **Additional information**: we need the drug in general, not with respect to antibiotics, what we really need of the drug is to have a travel concentration as cycle of action, so if the target tissue with this concentration is lower than it's plasma concentration, it naturally resistant to the antibiotics.

Acquired resistance

Development of resistance in a previously sensitive microorganism. This could occur in the following ways:

1. Mutation or genetic change

2. Adaptation

Production of enzymes breaking the antimicrobial e.g. ß-lactamases

- **Note**:misuse or abuse of certain antibiotic

- the bacteria adapts itself against the action of antibiotic

3. Infectious or multiple drug resistance

Through:

- **bacteriophage** :viral infection affect the bacteria

Transduction by bacteriophage which transfers chromosomal or extrach romosomal DNA (plasmid) to bacteria

Transformation, transfer of DNA responsible for resistance from environment to bacteria

Conjugation Passage of resistant genes from cell to cell by direct contact

** Most of resistance is acquired due to misuse or abuse of antibiotics e.g. improper dose & DOA, R_x of suppurative diseases, R_x of viral infections with antibacterial agents

■ **notice the difference:**

Misuse : use the drug in condition which is not indicated

Abuse : the drug is indicated but we use it improperly

Examples on mechanisms of resistance:

■ **Additional information**: point 2: When we come to penicillin, likewise many other antibiotics, they find the specific proteins on the bacterial or as penicillin binding proteins then they produce their effect.

- - Generating enzymes that inactivate the antibiotic (beta lactamase)
- - Changing structure of target site e.g. PBP's (beta lactams and aminoglycosides)
- - Preventing cellular accumulation of antibiotic by altering outer membrane proteins or using efflux pumps e.g. G-ve

■ **Additional information**: point 3: the antibiotic enters to the bacteria but it has pumps that will pump it outside the bacteria

- - Changing the metabolic pathway that is being blocked (sulfa drugs)
- - Overproducing the target enzyme or protein to overpower the effects of antibiotics
- - Mycoplasma lacks a cell wall making it resistant to penicillins
- - Sulfonamides have no impact on bacteria that obtain their folate from environment

■ **Additional information:** more protein need more antibiotics concentration inside the cell

■ **Additional information**:Sulfonamides they act by inhibiting the first step in folic acid synthesis by acting on it's synthetase enzyme Which converts Paraaminobezoic acid (PAPA) to dihydrofolic acid (DHFA)

Combined therapy:

■ **Additional information**:if we lower the dose —> no side affects but the drug become in sub therapeutic dose and this lead to resistance so the sol is : combined therapy

Indications:

- To obtain synergism or reduce the dose of a toxic drug

- To reduce emergence of resistance

- Treat mixed infections with microorganisms of different sensitivities

■ **TB is NEVER treated with a single drug, usually we start with three drugs**

- Treat infections at different anatomical sites (bile, CSF) And eye

- Treat infections of unknown etiology especially in patients at high risk of developing infections e.g. AIDS patients or patients with agranulocytosis Neutropenia

■ synergism happens to the desired effect and the side effect as well

Outcome of combined chemotherapy:

- Indifference — One drug doesn't have any effect on the second drug
- Antagonism Cidal + static
- Synergism (Penicillins+aminoglycosides)

■ **Additional information**: Whatever you decide to combine more than one antibiotic at the same time, try as much as possible to use drugs with different mechanism of action , use different antibiotics with no over lacking side effects

■ **Additional information**:Synerigm:one drug can enhance the effect of others.
Aminoglycosides inhibit protein synthesis.
Pencillins interfere with the permeability of the cell wall.
The synerigm occurs in aminoglycosides because when pencillin interfere with the function of the cell wall, they will increase it's permeability ,so aminoglycosides will enter one little bit more the bacterial cell increasing it's effect and toxicity.

Disadvantages of combined chemotherapy:

- Toxicity

- ↑ cost

Prophylactic use of antibacterial agents:

- **Indications:**

- Protection of healthy individuals againsthighly contagious disease or infections e.g.syphilis, gonorrhea, T.B, meningococcalmeningitis

- Prevent 2° infection in very ill patients

  e.g. AIDS, before major surgeries, delivery, organ transplantation, recurrent UTI's…etc

- **Prophylaxis is successful if:**

- A single antibiotic is used
- The dose required for prophylaxis is less than the therapeutic dose
- The drug is needed or used for a brief period

  (chronic therapy or prophylaxis is not advised → bacterial resistance)

Complications of antibiotic therapy:

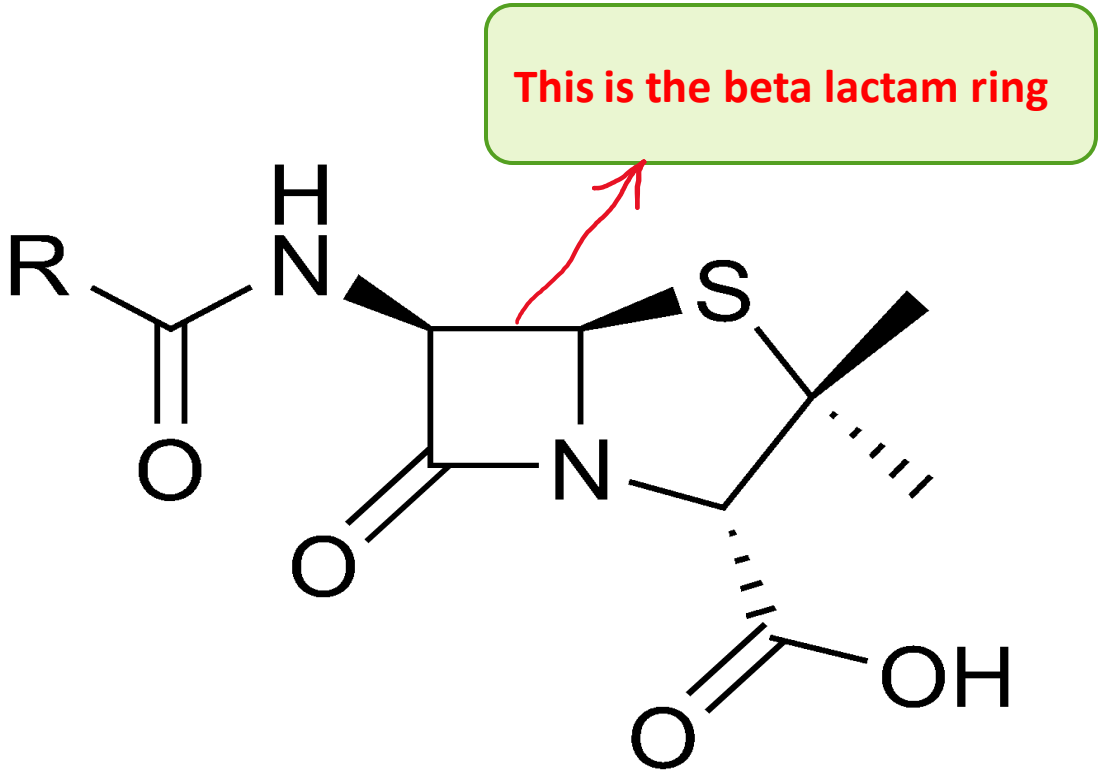
1. - Hypersensitivity
2. - Direct toxicity (toxic to certain site) There are some antibiotics that are toxic to the kidneys
3. - Super infection When we use broad spectrum of antibiotic

Alterations of the normal microbial flora of the upper respiratory, intestinal, and genitourinary tracts, permitting the overgrowth of opportunistic organisms, especially fungi or resistant bacteria

Inhibitors of Microbial Cell Wall

β-lactam antibiotics

- Contain a beta-lactam ring that is part of their chemical structure
- An intact beta-lactam ring is essential for antibacterial activity
- Include: Penicillins, Cephalosporins, Carbapenems, Carbacephems & Monobactams

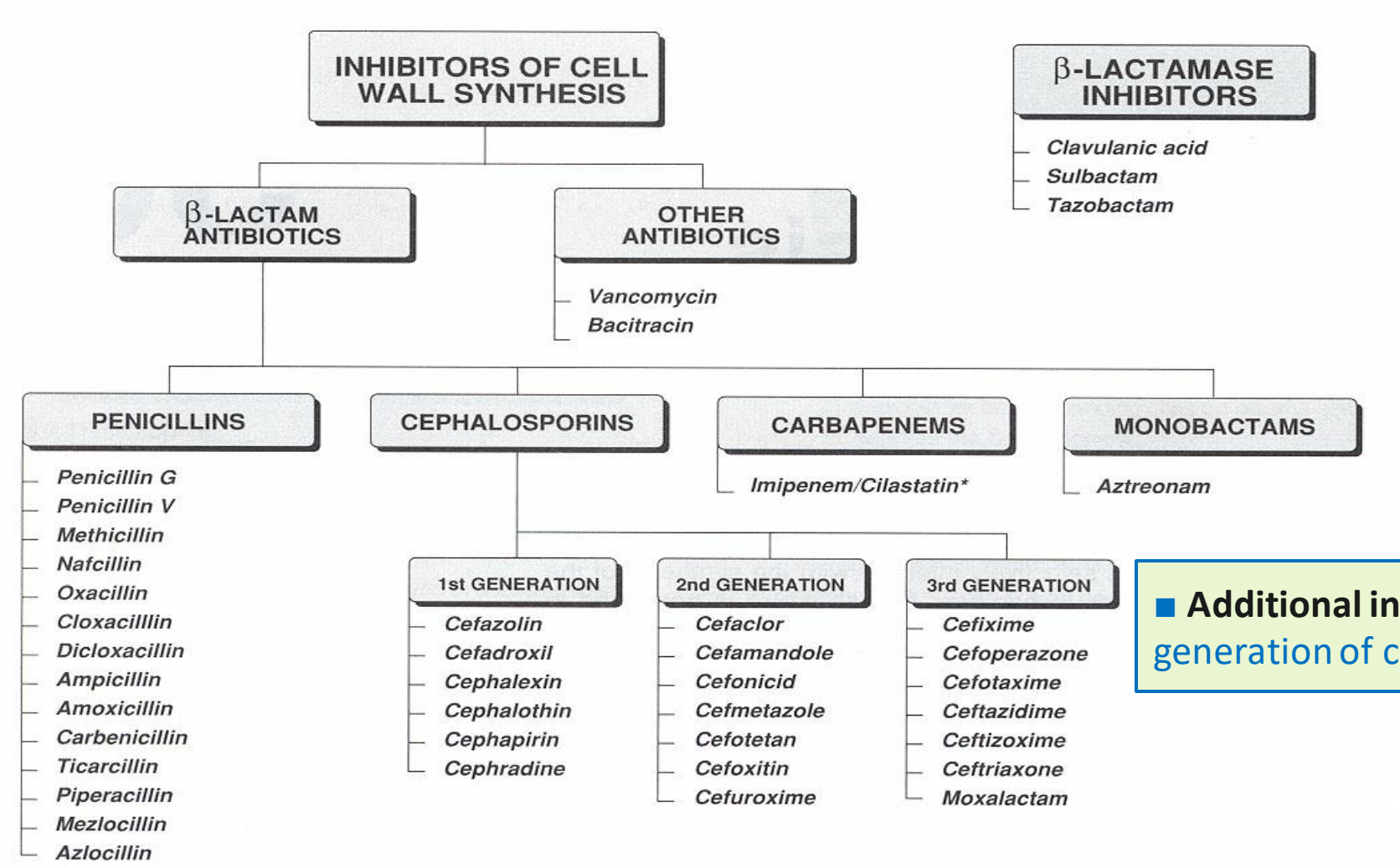

This is the beta lactam ring
R
H
N
O
O
N
S
O
OH

- The R in the structure of ß-lactam antibiotic determines the characteristic of antimicrobial agent e.g. narrow or broad spectrum; oral vs parenteral administration; sensitivity vs resistance to ß lactamases..etc
- The ß-lactam ring is the site of attack by gastric acidity and lactamases

Beta Lactams Mechanism of Action:

1. Inhibit synthesis of bacterial cell walls by binding to proteins in bacterial cell membranes e.g. PBP's (Pencillin binding proteins)
2. Binding produces a defective cell wall that allows intracellular contents to leak out (lysis of the bacteria and death)
3. Most effective when bacterial cells are dividing

Inhibitors of Cell Wall Synthesis



■ **Additional information**:We also have 4th and 5th generation of cephalosporins

Bacteria that produce ß-lactamase (hydrolyze ß-lactam ring and hence inactivation of antimicrobial activity):

- Staph aureus
- Moraxella catarrhlis
- Neisseria gonorrhoeae
- Enterobacteriaceae
- Hemophilus influenzae
- Bacteroides species

The dr talked about s.aureus and said that the rest of them is for your information

Penicillins (PNC's)

- Most widely used antibiotics, most effective, least toxic and cheap
- Derivatives of 6-aminopenicillanic acid (ß-lactam ring is important structure for antibacterial activity, breaking down such B-lactam inactivate the antibiotic whether by gastric acidity or by specific enzyme lactamase)
- Derived from a fungus
- Prototype is Penicillin G (It's not good for CNS)(will be discussed later)
- Widely distributed except in CSF (except if inflammation is present) and in intraocular fluid
- Most serious complication is hypersensitivity (most serious side effect are allergic reactions)
- Can cause seizures and nephropathy

■ **Additional information**:The pentration of different pencillin to blood brain barrier (BBB) is only 1% of the dose.
With inflammation, it increases into 2%. but you can give it intrathecally or intraspinally
When we start treatment, there is healing in meninges.
From google: meninges is a three layers of membrane which they protect the brain and spinal cord

- **Natural penicillins:**

■ **Additional information**:We do modification for pensillin G such of change in the chemical structure of it to end up with many other pencillins.
In this case, it become semisynthetic.
If we manufactor the pencillin from the beginning, it become synthetic.

Benzylpenicillin=Penicillin G:

it should be given IM(Intramuscular), IV(intravenous)

Acid labile(the B-lactan will be broken down by the acidity), short acting, given 4-6 times/day

Depo IM forms to penicillin G

■ **NOTE**:Depo=Deep

Procaine penicillin given IM twice/day, IV injection contraindicated (could lead to ↓ BP & convulsions)

Benzathine penicillin given IM mainly used for rheumatic fever prophylaxis(treatment Given or action taken to prevent disease)

■ **Additional information**:RF isn't common after an age of 15 years old.
Tonsillitis,B-hemolytic type A, infection in the thorat and go to the joints, heart and affected valves of the heart.
It is caused by streptococcus bacteria.
It show high fever.
It can be treated by aspirin .
After treatment acute condition, the patient kept on benzylpencillin every month up to 15 years.

Phenoxy methylpenicillin= Penicillin V Oral

■ **NOTE**: it doesn't work with bacteria produce lactamase

Natural penicillins are narrow spectrum and penicillinase sensitive

Considered drugs of choice to treat infections with G+ve Strep., ß-hemolytic type A (most common microbe in tonsillitis)

Have little effect if any against G-ve bacteria

■ **NOTE**: if the patient has an allergy to penicillin we use erythromycin

- Narrow spectrum penicillinase resistant penicillins (anti Staph penicillins):

  Nafcillin IM, IV

  Oxacillin IM, IV

  Cloxacillin Oral

  Dicloxacillin Oral

  Flucloxacillin Oral & parenteral

- **Broad spectrum penicillinase sensitive PNC's (amino PNC's):**

  Ampicillin(absorption affected by food) IM, IV, Oral

  Amoxicillin (absorption is not affected by food) Oral More potent, has better bioavailability, longer DOA

These PNC's have very little effect, if any, against PNC ase producing bacteria e.g. H. influenza and against G-ve bacteria e.g. E. coli, Proteus. No effect against Pseudomonas

■ **NOTE**:PNC=pencillin

■ **NOTE**: ampicillin is given four times per day , amoxicillin is given three times per day so amoxicillin has longer DOA(duration of action)

Amino PNC's are widely used in tonsillitis, otitis media, gonorrhea, respiratory infections, shigella infections, UTI's (urinary tract infections)…etc

Amoxicillin has good activity against Helicobacter pylori (causes peptic ulcer) (+ PPI's (proton pump inhibitors) ± Clarithromycin ± Metronidazole)

■ **Additional information**:Amoxicillin is very widely used as antibiotics for peptic ulcer disease.
One drug isn't effective in peptic ulcer, you have to use at least 2
PPI: they inhibit the last step secretion in the stomach

- **Antipseudomonal PNC's:**

Piperacillin(the most potent) > Mezlocillin=Ticarcillin > Carbenicillin(the least potent)

All are synergistic with aminoglycosides against Pseudomonas

- **Amidinopenicillins:**

Mecillinam (IM; IV) Pivmicillinam (oral)

Most potent PNC's against enterobacteria (Salmonella, E. coli, Klebsiella, Shigella…), have little or no activity against G+ve cocci or pseudomonas; synergistic with other β-lactams but not with aminoglycosides

■ **Additional information**:Synergism:applied whenever two drugs producing similar response given together result in a final response greater than the sum of the response of individual drugs(1+1=3)

قال عليه الصلاة والسلام:

مثل المسلمين في توادهم وتراحمهم وتعاطفهم كمثل الجسد إذا اشتكى منه عضو تداعى له سائر الجسد بالسهر والحمى