PHARMACOLOGY

Modified slides no.4 V2
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■ **Additional information**:mechanism of action (MOA) refers to the specific biochemical interaction through which a drug substance produces its pharmacological effect.

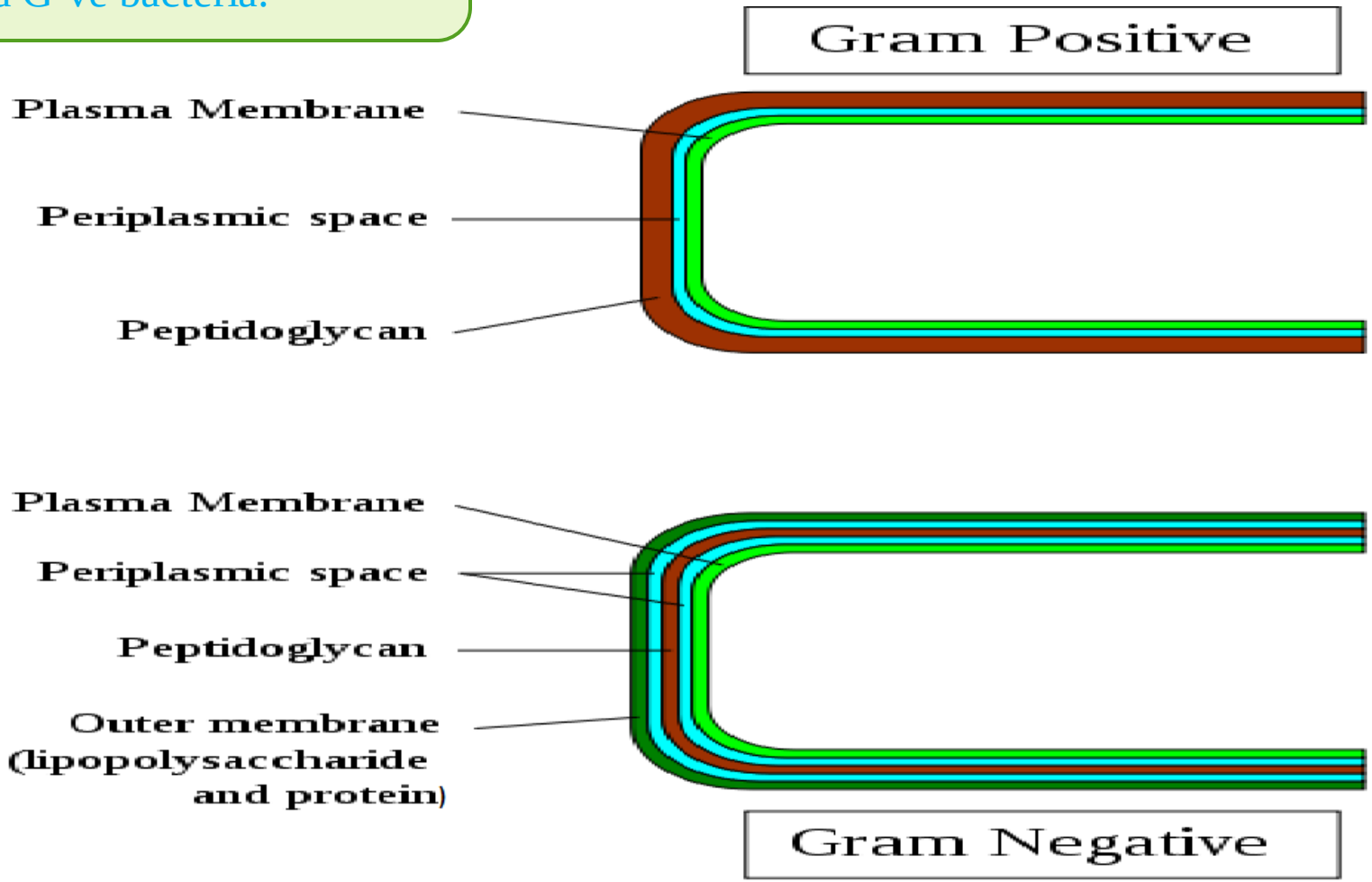
▶ MOA of Penicillins:

Most bacteria have rigid cell walls that are not found in host cells (selective toxicity)

PNC's act by inhibiting transpeptidases, the enzymes that catalyze the final cross-linking step in the synthesis of peptidoglycan, thus leading to the lysis of cell wall

Disruption of the cell wall causes death of the bacterial cell (Bactericidal effect)

■ **NOTE**:The figure demonstrating the difference between the structure of G+ve and G-ve bacteria.



■ **NOTE**: G-ve is more difficult to be effected by specific antibiotics because in addition of cell wall and plasma membrane, they have an outer membrane (lipopolysaccharide and protein).

- Pharmacokinetics of PNC's:

Bind plasma proteins, widely distributed, their concentrations in ocular fluid, joints and CSF are poor (do not cross BBB unless meninges are inflamed), do not cross the placenta

Metabolized by the liver and excreted by glomerular filtration and tubular secretion

Probenecid inhibits tubular secretion of PNC's (nafcillin & oxacillin are mainly excreted by the liver)

■ Information from lecture 3 : PNC's is Widely distributed except in CSF (except if inflammation is present) and in intraocular fluid.

■ Sereprospinal Fluid

■ **NOTE**: As I said before the best of use antimicrobs is identification the microorganism and then test the microorganism sensitivity.

- **Indications for Penicillin's:**

- More effective in treating G+ve infections
- Used to treat infections of the skin, GUS, GIT, respiratory tract and soft tissues
- Selection depends on the organism and severity of the infection e.g. anti-staph vs. anti-pseudomonal

** Combination of PNC's or a cephalosporin with a potent inhibitor of lactamases

■ **NOTE**: We have some substances that inhibit B-Lactamase and they are inactive antibiotics. They are added to penicillins (or cephalosporins) that are sensitive to B-Lactamase. So, combination of B-Lactamase inhibitor and antibiotic, make it more resistant to B-Lactamase and some of them make more potentcy and more spectrum antibiotic.

▶ β-lactemase inhibitors:

Have no antibacterial activity, increase potency and spectrum of activity of combined antibiotic

Clavulanic acid, Sulbactam, Tazobactam

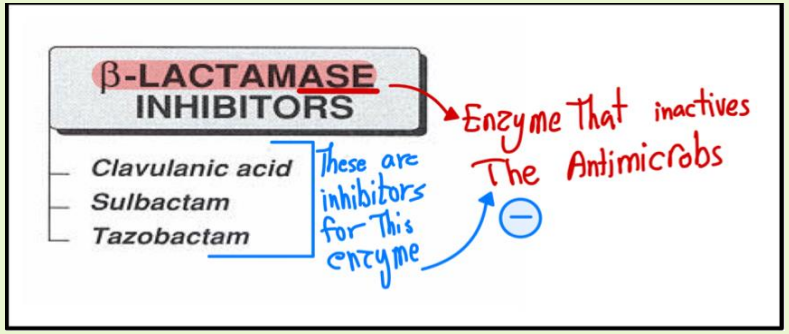
(Augmentin® =amoxicillin/clavulinate)

(Unasyn®=ampicillin/sulbactam)

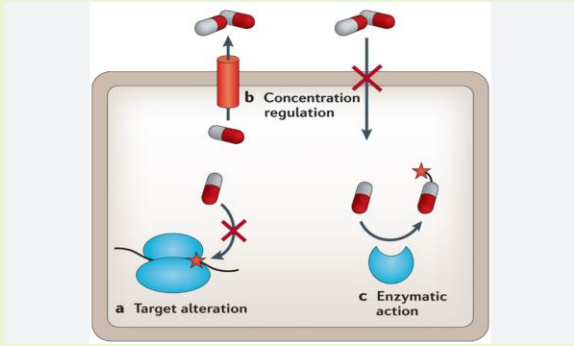
(Zosyn®=piperacillin/tazobactam)…etc

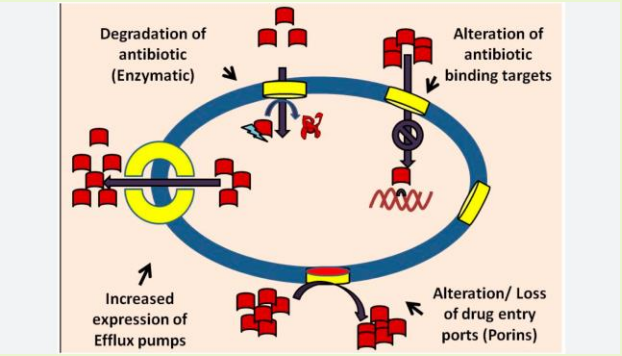
■ **NOTE**: A combination of penicillin and B-Lactamase inhibitor.

■ **Attachment**:



■ **Attachment**: figures to imagine the mechanisms 😁 :





▶ Mechanisms of resistance to PNC's:

- Altered penicillin binding proteins (PBPs)
- Production of beta-lactamase (penicillinases)
- Decreased penetration*decrease the permeability /increased efflux *efflux pump to flow out the drug (pseudomonas is an example of bacteria that use this machanism)

▶ Preparations to PNC's :

Oral, parenteral, intrathecal, topical, intra-articular…

■ **Additional information**: Remember the parenteral route defined as medications placed into the tissues and the circulatory system by injection.

- **Side effects to PNC's:**

- Allergy (Most frequent and dangerous)

Type I allergic reactions. Early onset (immune IgE mediated) occur (5-6) after administration.

Type II allergic reactions. Late onset (2-10 days). May manifest as eosinophilia, hemolytic anemia, interstitial nephritis or serum sickness (fever; arthralgia; malaise…)

- Nonallergic ampicillin rash, occurs only once (more common in pts with acute leukemias; mononucleosis, lymphomas, cytomegaloviral infections…)
- Neurotoxicity (more common with oxacillin)
- Hepatotoxicity (more common with IV oxacillin)
- Bone marrow depression (reversible) (more common with IV nafcillin)
- Nephrotoxicity (more common with Methicillin)

■ **NOTE**: Methicillin is a semi-synthetic penicillinase resistance penicillin, in other word is the first one was synthesised can be resistance to B-lactamase enzyme

■ **NOTE**: Na+ and K+ are used in penicillin for pharmaceutical purposes , they are added to the R group of drug structure .

■ **NOTE**: So we can use penicillin that doesn't contain Na+ or K+ for these patients.

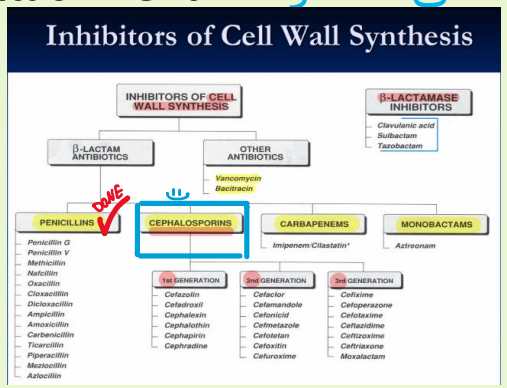
- **Other restrictions in the use of PNC's:**

- Na+ penicillins → restricted use in pts with hypertension or heart failure
- K+ Penicillins → restricted use in pts with renal failure (Hyper or hypokalemia both are dangerous)
- Absolute contraindications to all PNC's in pts with history of allergy

Cephalosporins

■ **NOTE**: cephalosporinase = B-Lactamase.
But cephalosporin = type of B-lactam drug

■ **Attachment**: حتى ما نتوه



- Derivatives of 7-aminocephalosporanic acid
- ß- lactam antibiotics, Cidal
- Semisynthetic
- Broad spectrum *even 1st generation
- Inhibitors of microbial cell wall synthesis
- Differ in pharmacokinetic properties and spectrum of activity
- Classified into 1st 2nd 3rd 4th and 5th generations

* First generation	*Second generation	* Third generation	* Fourth generation	* Fifth generation
• Cefadroxil • Cefalexin Oral • Cefazolin IM, IV • Cephapirin • Cephradine • Cephaloridine	• Cefaclor Oral • Cephamandole IM, IV • Cephmetazole • Cefonicid • Cefotetan • Cefoxitin • Cefprozil • Cefuroxime • Cefuroxime axetil • Loracarbef *we will talk about it later	• Cefixime Oral • Cefoperazone IM, IV • Cefdinir Cefpodoxime • Cefotaxims Ceftazidime • Ceftriaxone Ceftibuten Ceftizoxime	• Cefepime IM, IV	• Ceftaroline IV *has the widest spectrum of activity.

1st generation cephalosporins

- have the best activity against G+ve microorganisms,
- less resistant to ß- lactamases,
- and do NOT cross readily the BBB as compared to 2nd, 3rd and4th generations

- **Cephalosporins** never considered drugs of choice for any infection, however they are highly effective in [1] upper and lower respiratory infection, [2] H. influenza, [3] UTI's, [4] dental infections, [5]severe systemic infection…**(very Wide use)**

Comparison between cephalosporin generations

■ **The complement in this slide**:
1st generation cephalosporins has a spectrum of activity
But, 2nd ,3rd and 4th generations have a broad spectrum.

■ **The complement in this slide**: Many of 1st generation cephalosporins are sensitive to B-Lactamase (less resistant)
But, 2nd ,3rd and 4th generations are resistant to B-Lactamase.

■ **The complement in this slide**: 1st generation cephalosporins do not cross BBB same as penicillin so, they do not enter the CNS.
But, 2nd ,3rd and 4th generations can cross BBB and enter CNS.

** Among cephalosporins:

- - Cefoxitin (2^{nd}) has the best activity against Bacteroides fragilis
- - Cefamandole (2^{nd}) has the best activity against H. influenza
- - Cefoperazone (3^{rd}), Ceftazidine (3^{rd}) and Cefepime (4^{th}) have the best activity against P.aeruginosa infections
- - Ceftaroline (5^{th}) has a broader G+ve spectrum of activity than all other cephalosporins due to its activity against MRSA(Methicillin-resistant Staphylococcus aureus); also has some activity against G-ve bacteria

▶ Side effects to cephalosporins:

- **Allergy**

  Cross allergy with penicillins (10%)

- **Hepatotoxicity**

- **Nephrotoxicity**

  Mostly seen with Cephaloridine (1st)

  ↑ with concomitant aminoglycosides use

- **disulfiram-like reaction (cefamandole, cefoperazone, ceftriaxone, cefmetazole…)**

- **Hemolytic anemia**

All cephalosporins are excreted by the kidney except Ceftriaxone (3rd) which is excreted by the liver

■ **NOTE**: If one has allergy to penicillin there is a chance to be allergic to cephalosporin.

■ **Additional information**: Disulfaram-like reaction: a process in the body that produces symptoms similar to those that occur when alcohol is consumed after taking disulfaram (Antabuse). Disulfiram is an oral drug used for treating alcoholism that causes unpleasant symptoms when alcohol is consumed.

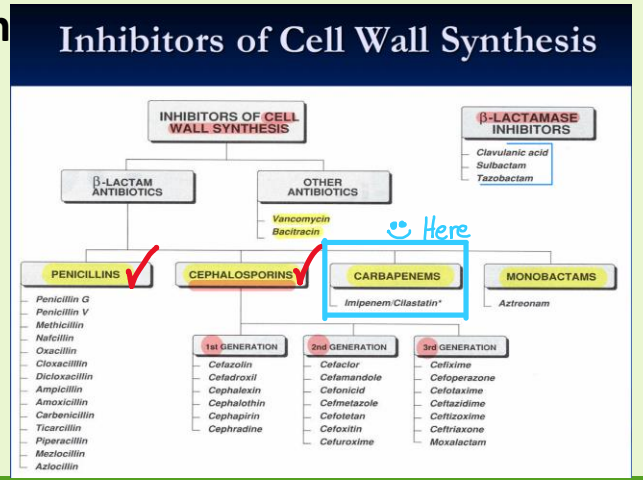
حتى تغني المريض عن شرب الكحول

لتغني المدخن عن الدخان nicotine patches مثل وظيفة

Other β- lactam antibiotics

-Carbapenems e.g. Imipenem, Meropenem

■ Attachm



* Imipenem

- Has the broadest spectrum of activity of all β-lactam antibiotics, effective against most G+ve & - ve bacteria and anaerobes,
- given IM, IV;
- β-lactamase resistant
- More potent against E. faecalis(Enterococcus faecalis), B. fragilis (Bacteroides fragilis) and pseudomonas aeroginosa as compared to 3rd generation cephalosporin

■ **NOTE**:If the question: what is the broadest of activity of all cephalosporins ?
The Answer is : Ceftaroline (5th)
But, if the question: what is the broadest of activity of all B-lactams antibiotics?
The Answer is: Imipenem

- Some consider imipenem the drug of choice in the management of polymicrobial pulmonary, intra-abdominal and tissue infections
- Imipenem is metabolized and excreted by the kidney. It is metabolized in kidney by the enzyme dehydropeptidase I; so it is combined with Cilastatin (inhibitor to dehydrpeptidase I) to decrease rapid metabolic clearance of imipenem
- Seizures are major side effect to imipenem

■ **NOTE**

Additional information for understanding:

Imipenem, a broad-spectrum antibiotic, exerts its mechanism of action (MOA) by inhibiting bacterial cell wall synthesis. Specifically, imipenem inhibits the activity of enzymes called penicillin-binding proteins (PBPs), which are crucial for the cross-linking of peptidoglycan chains in bacterial cell walls. By interfering with this process, imipenem disrupts the integrity of the bacterial cell wall, leading to cell lysis and death. This antibiotic is effective against a wide range of bacteria, including both Gram-positive and Gram-negative organisms.

Imipenem is often used in combination with cilastatin to prevent its rapid breakdown in the kidneys and enhance its therapeutic efficacy

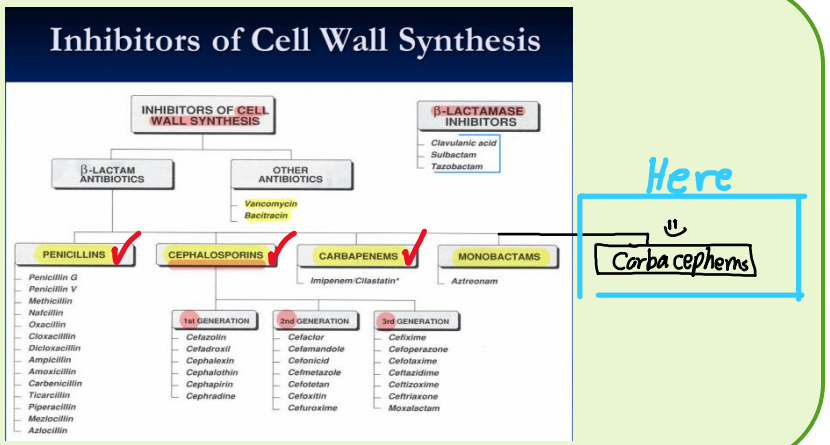
*Meropenem;

- has similar activity to imipenem; but resistant to metabolism by dehydropeptidase I (no need to combine it with cilastatin)
- and incidence of seizures is less than imipenem

- Carbacephems e.g. Loracarbef Oral

- Spectrum of activity similar to 2nd generation cephalosporin particularly cefaclor and cefprozil even some list it under 2nd generation cephalosporins; effective orally; excreted renally

■ **Attachment**:



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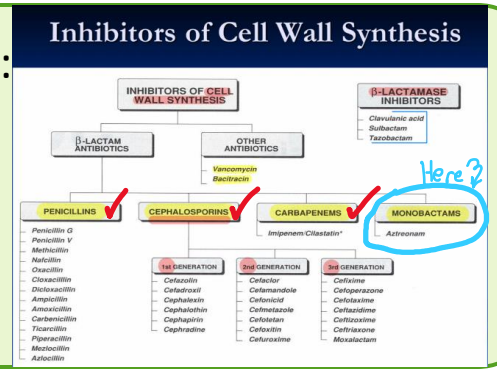
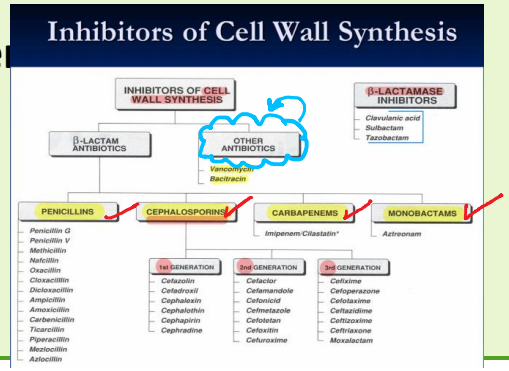


- Monobactams e.g. Aztreonam IM, IV

- Has excellent activity against G-ve bacteria
- little if any effect against G+ve MO's
- β-lactamase resistant
- Considered a substitute to aminoglycosides to treat G-ve infections (less toxic compared to aminoglycosides)
- Rarely, causes allergic reactions in pts with type I allergy to other β-lactam antibiotics mainly penicillin

Vancomycin & Teicoplanin

- Attachme



- Glycopeptides (Large molecules)
- Prevent crosslinking of peptidoglycans
- Bactericidal in nature but vancomycin has a static action to certain bacteria specially Enterococcus bacteria.
- Narrow spectrum of activity, effective against G+ve bacteria especially methicillin resistant Staph aureus (MRSA)
- Alternatives (Not second line therapy)to PNC's to treat G+ve Strep & Staph infections in pts allergic to PNC's
- Given IV (oral absorption is poor)

- Considered drug of choice ± metronidazole to treat pseudomembranous colitis=antibiotic associated colitis (Clostridium difficille colitis; Staph enterocolitis) and in this case vancomycin could be given orally (IV in life threatening cases)
- Teicoplanin is given IM

- **Side effects:**

- Rapid IV → flushing, tachycardia, ↓ BP, skin rashes… (Red man syndrome)
- Thrombophlebitis, ototoxicity, circumoral parasthesia…

Inhibitors of Microbial Protein Synthesis

■ **NOTE**: we finished the inhibitors of microbial cell wall synthesis and we will start inhibitors of microbial protein synthesis

Aminoglycosides

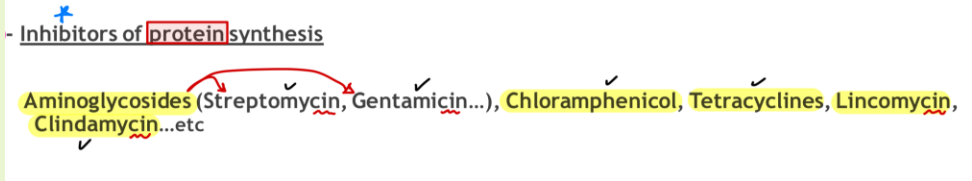
- Aminosugars
- Highly toxic
- Polar substances (water soluble=Hydrophilic) never absorbed by intestine .
- Include:

Streptomycin Gentamicin Netilmicin

Kanamycin Tobramycin Amikacin

Neomycin Paromomycin

■ **Attachment**: Remember from lecture 1:



Common properties:

- Have similar structure (group of antibiotics which contain amino sugars and a cyclohexane ring)
- Differ in pharmacokinetic properties ($t_{½}$) Biological half life
- Have similar spectrum of activity; highly effective against G-ve bacteria (some are broad spectrum but mostly used against gram-ve bacteria)

- **- Bactericidal**
- **- Ineffective orally**
- **- Interfere with the integrity of bacterial membrane and inhibit bacterial protein synthesis (30S inhibitors) (bind irreversibly to the 30S subunit of ribosome inhibiting protein synthesis and cause misreading of mRNA)**
- **- Do not bind plasma or tissue proteins**

■ **NOTE**: They are available in orally capsule or tablet dosage form but they are mainly for local infection in GIT, because they are polar and the intestines can not absorb them.

- - Have small AVD (25% of lean body wt), do not penetrate the BBB & eye
- - Rapid excretion as free form (unchanged) by the kidney (no secretion or re-absorption)
- - Toxic (have narrow therapeutic window)

  Ototoxic

  Nephrotoxic

  Curare-like effect (muscular relaxent effect or muscular weakness)

  Allergy

** Neomycin the most nephrotoxic used only topically and orally (local GIT infection)

** Gentamicin the drug of choice to treat neonatal G-ve meningitis

** Streptomycin is effective in Brucellosis & T.B

- **Dose adjustment to aminoglycosides is necessary in:**

- Children & old pts

- Pts with renal disease

- Pts with hypotension

- Pts on diuretics

All such conditions could have high incidence of nephrotoxicity

Aminoglycosides clinical uses:

- - Gentamicin, netilmicin, tobramycin, amikacin

1. Very potent against G-ve bacilli (E. coli, Klebsiella, Proteus, Pseudomonas…)
2. Synergistic with antipseudomonal PNC's
3. Strains resistant to gentamicin could be sensitive to amikacin and vice versa **(important sentence)**
4. Gentamicin is considered the drug of choice to treat neonatal G-ve bacilli meningitis

- **- Netilmicin**

Similar to gentamicin but less ototoxic and could be effective in infections resistant to gentamicin

- **- Kanamycin**

Same as above but has no activity against Pseudomonas

- **- Neomycin**

Most nephrotoxic (not given systemically), used to sterilize bowel before abdominal surgeries (along with erythromycin as prophylactic agents)

Also used locally on skin and eye

- **- Streptomycin**

Highly effective against TB, used with PNC's to treat Strep endocarditis

Highly effective against brucellosis (Malta fever)

- **- Paromomycin**

Effective only to treat tape worm infestation and intestinal amoebiasis.

It is a first-line treatment for amebiasis or giardiasis during pregnancy

- **Aminoglycosides toxicity:**
- **- Neuromuscular blockade (curare-like effect)**
- **- Ototoxicity (toxic to 8th cranial nerve), reversible but severe toxicity could lead to deafness**

Kana (most Ottoxin)>Amikacin >> Genta=Tobra

↑ risk with renal failure or concomitant use of other ototoxic drugs

- **- Nephrotoxicity**

Neo (most sever nephrotoxicity)>>> Genta=Amikacin > Tobra

They lead to acute tubular necrosis; more in pts with renal disease or with concomitant use of other nephrotoxic drugs

فرُّبما كنتَ نائمًا أو تتناول طعامك أو منهمكًا في عمل...

لكنَّ عدَّادَ الأجرِ يعمل عند الله 🤍بسبب وقتٍ بذلته او علمٍ كتبته لغيرك

فقط إعادة تنسيق : V2