

# Aminoglycoside antibiotics

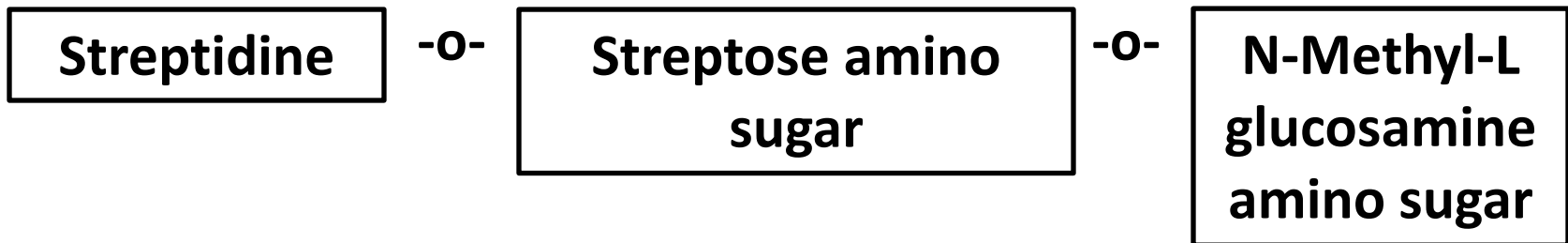
# Aminoglycosides

- Streptomycin – 1944
- Actinomycetes – *Streptomyces griseus*
- Bactericidal antibiotics
- Interfere with protein synthesis
- Used to treat aerobic Gram –ve bacteria
- Resemble each other in MOA, pharmacokinetic therapeutic and toxic properties
- Relatively low margin of safety
- Exhibit ototoxicity and nephrotoxicity

# Chemistry



## Aminoglycosides Structure



## Streptomycin structure

Streptobiosamine

# Aminoglycosides

- Systemic

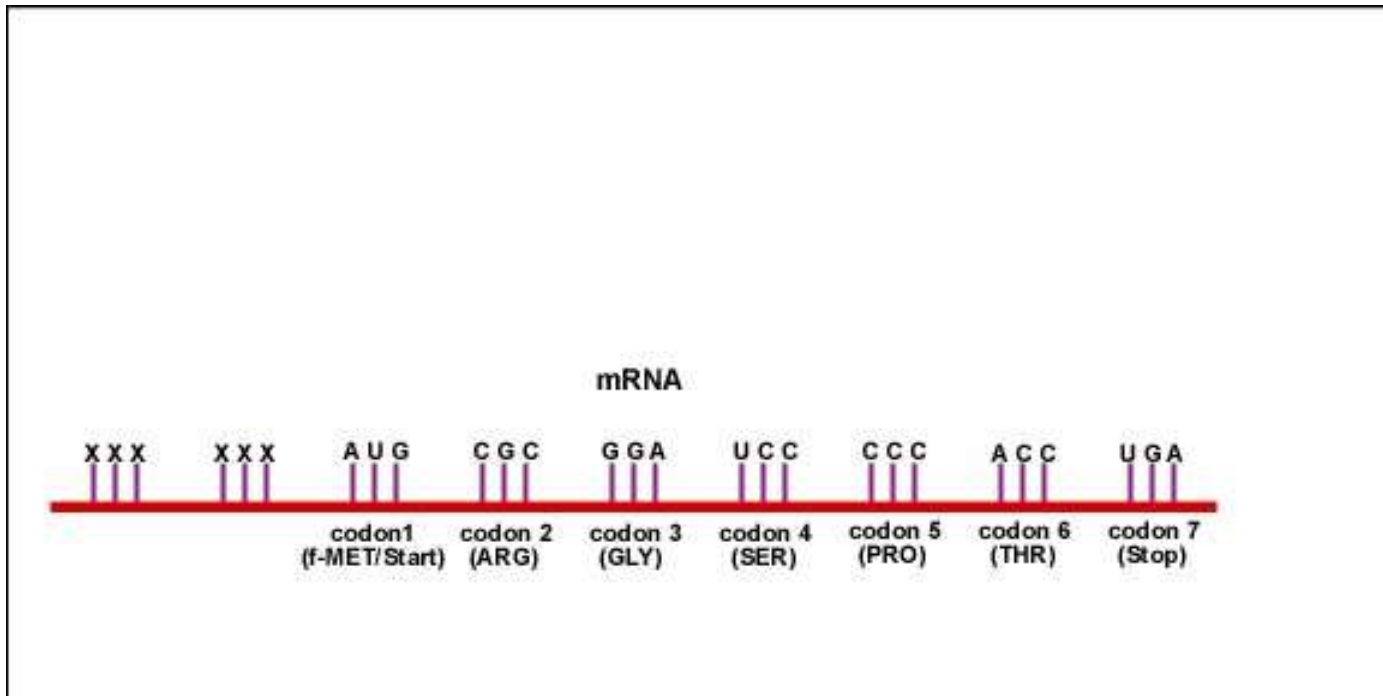
- Streptomycin
- Gentamicin
- Kanamycin
- Amikacin
- Sisomicin
- Tobramycin
- Netilmicin

- Topical

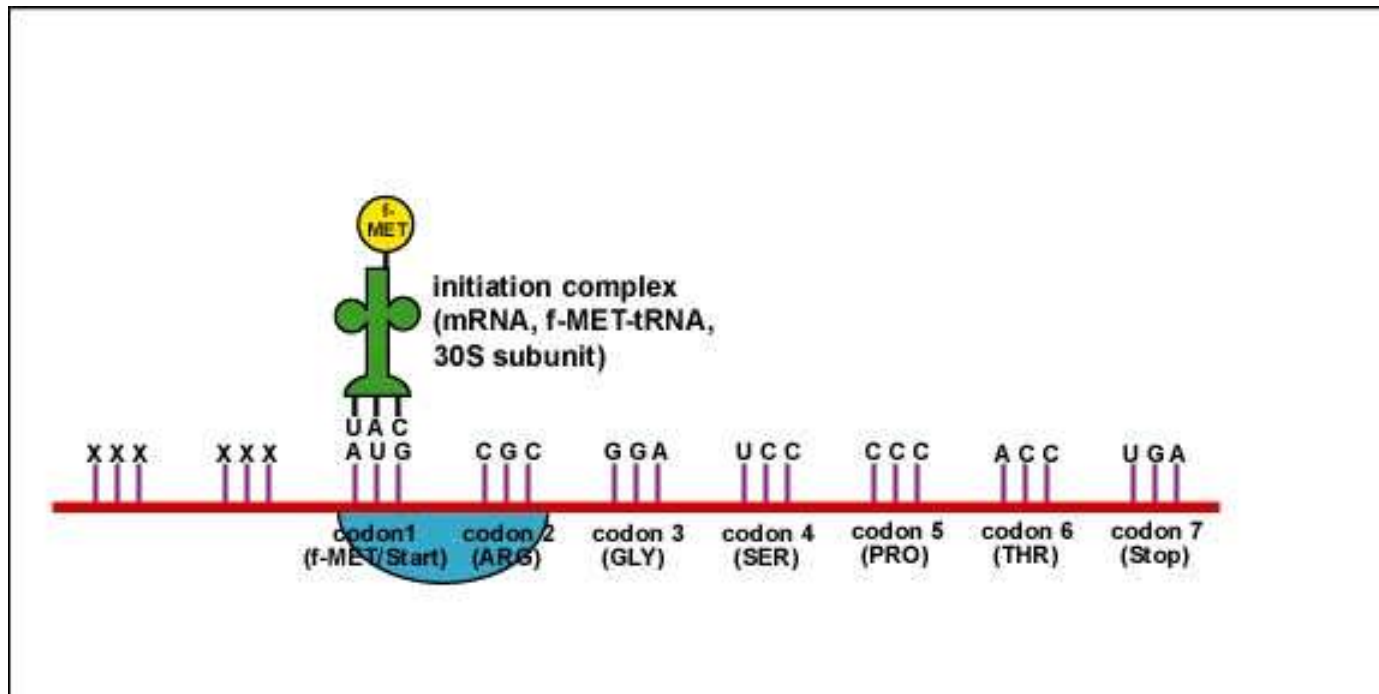
- Neomycin
- Framycetin

# Mechanism of Protein synthesis

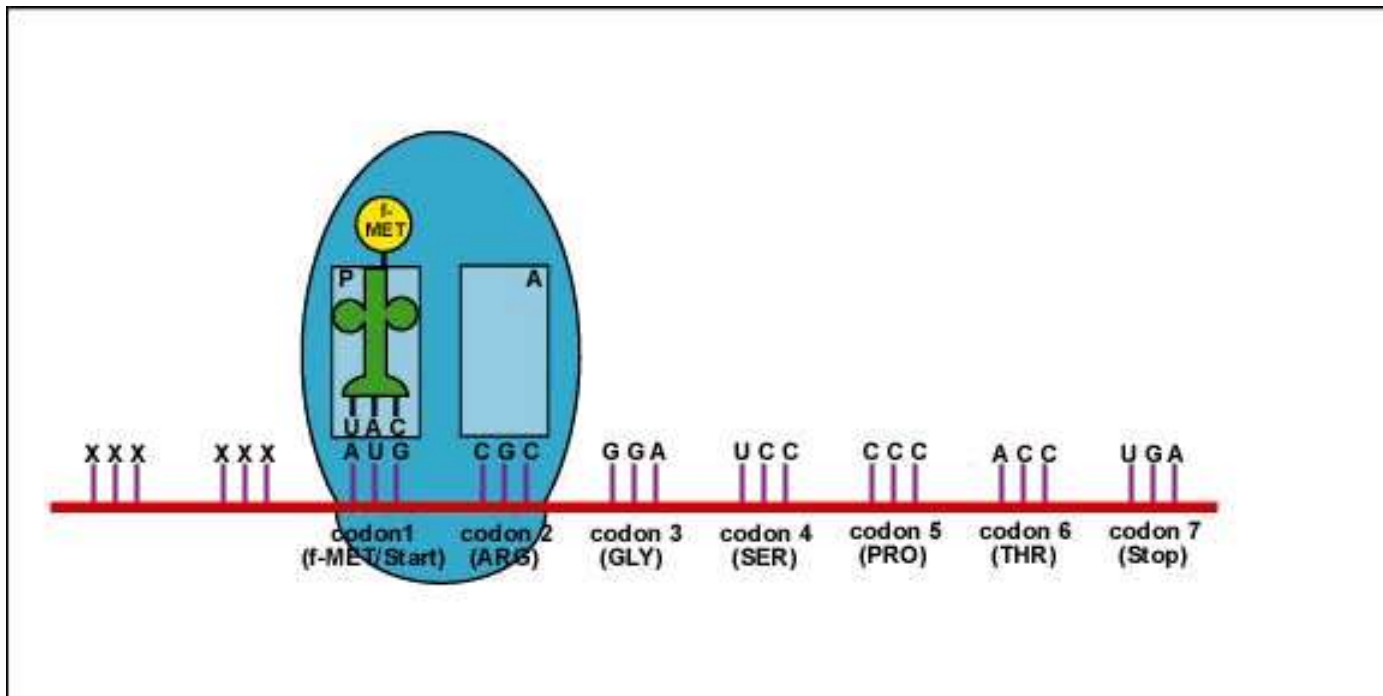
# Formation of the Initiation Complex



# Joining of 50S Ribosomal Subunit

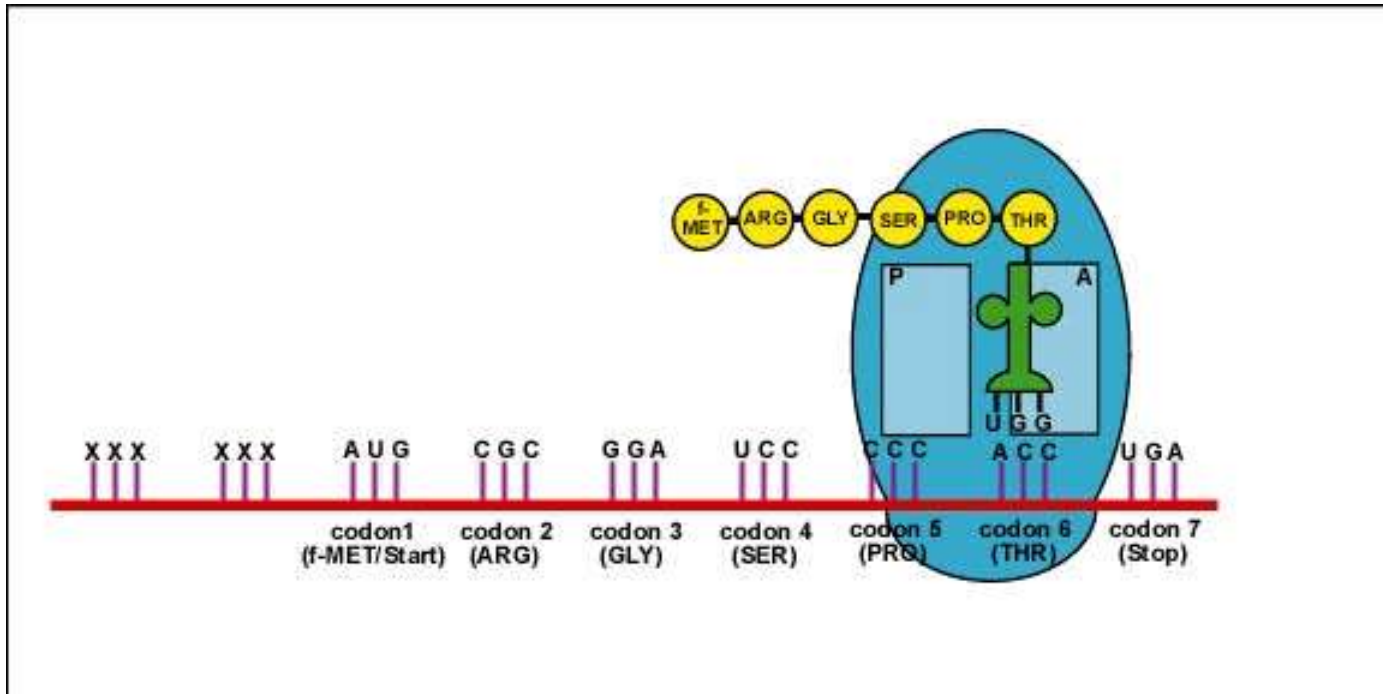


# Protein Elongation



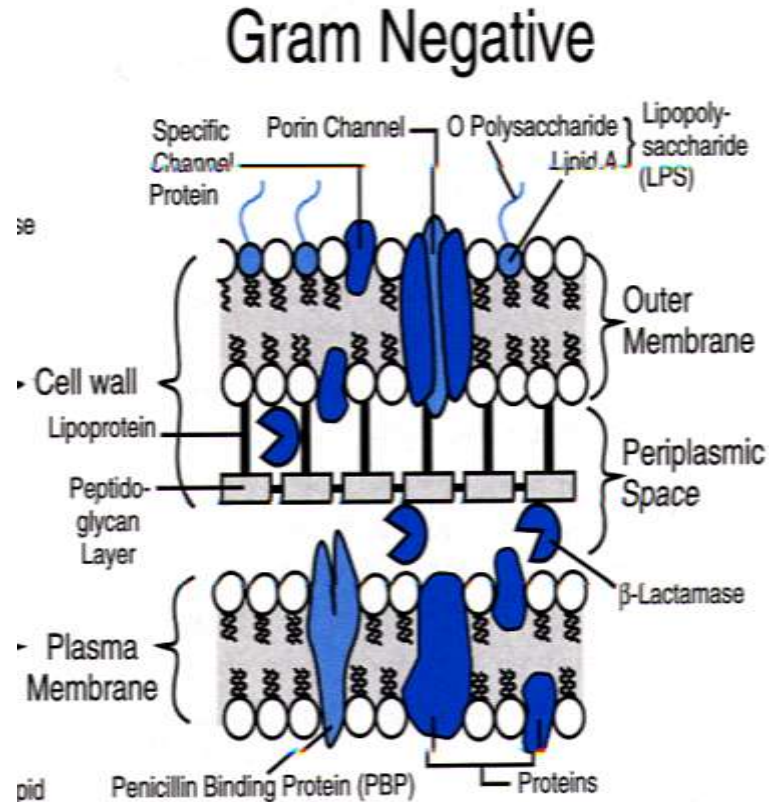


# Termination of Translation



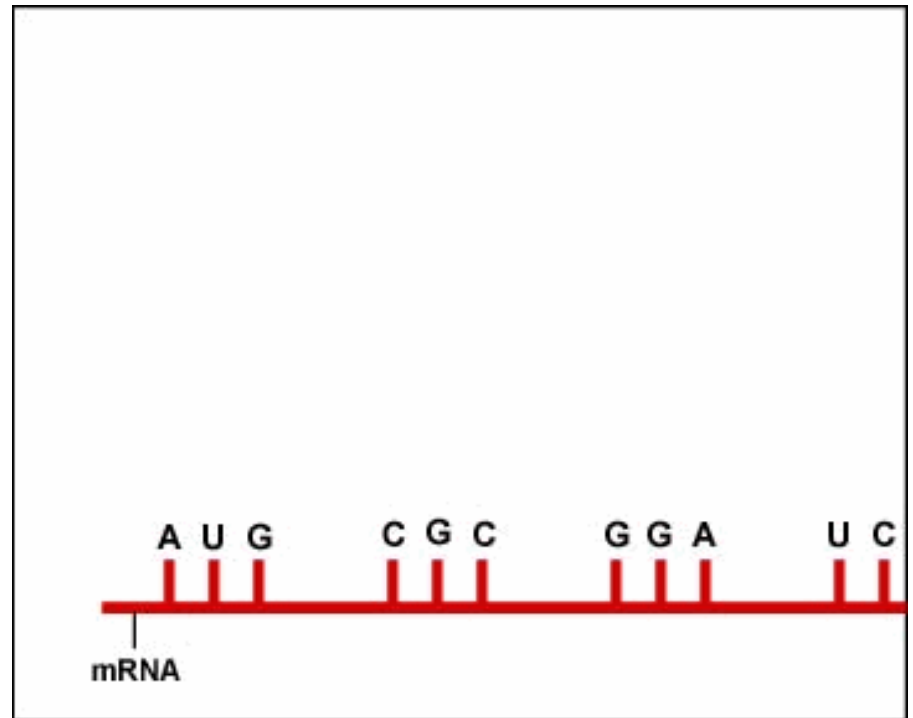
# Mechanism of action

- Initially they penetrate bacterial cell wall, to reach periplasmic space through porin channels (passive diffusion)
- Further transport across cytoplasmic membrane takes place by active transport by proton pump; an oxygen-dependent process



# Mechanism of Action

- Bind 30S ribosomal subunits and interfere the initiation complex
- Induce misreading of genetic code on mRNA
- Breakup of polysomes into monosomes



# Post antibiotic effect

- Aminoglycosides exhibit concentration dependent killing.
- They also possess significant Post-antibiotic effect.
- Single daily dosing at least as effective as and no more toxic than multiple dosing.

# Mechanism of resistance

- Synthesis of plasmid mediated bacterial transferase enzyme: Inactivate aminoglycosides
- ↓ transport into bacterial cytosol
- Deletion/alteration of receptor protein on 30 S ribosomal unit by mutation: prevents attachment

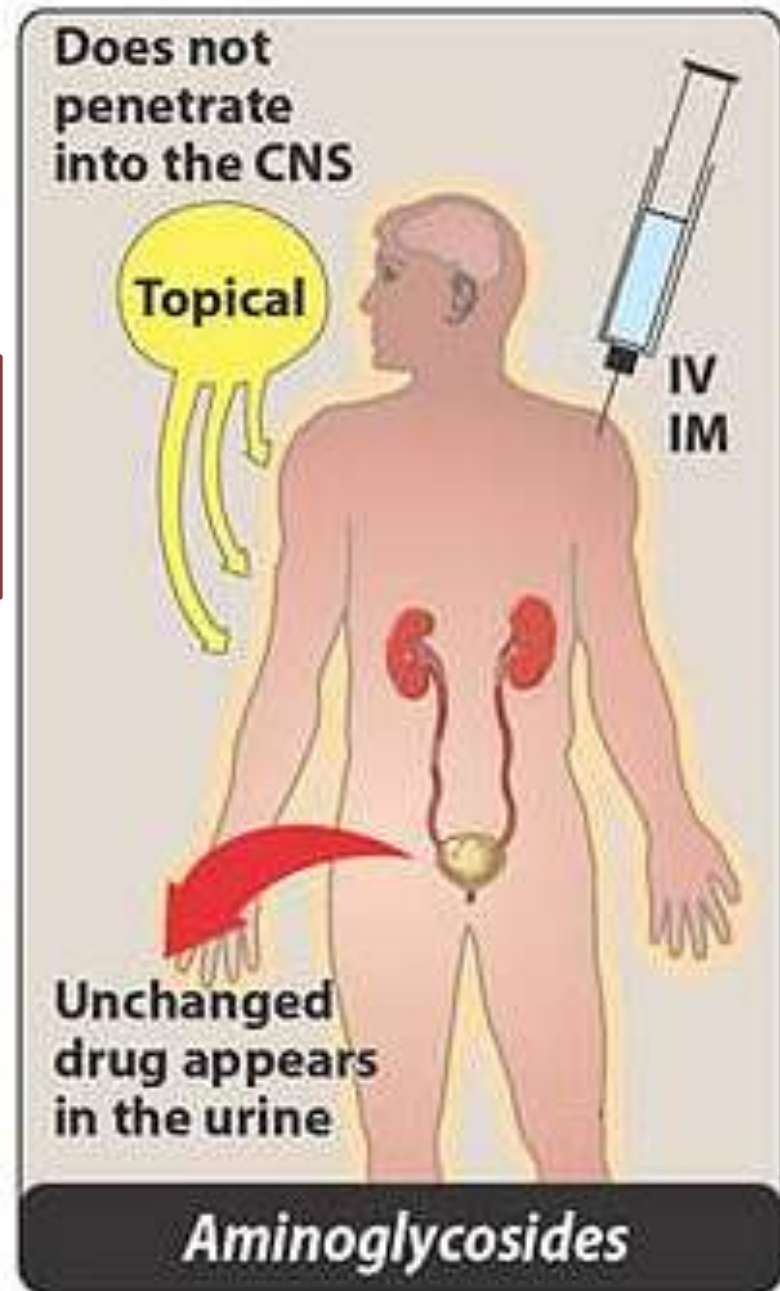
# Antibacterial spectrum

- Primarily against Gm –ve aerobic bacilli
  - Proteus, pseudomonas
  - E.Coli, enterobacter
  - Klebsiella
  - Shigella
- Only few Gm +ve cocci:
  - staph aureus, strepto viridans
- Not effective against Gm +ve bacilli, Gm-ve cocci and anaerobes

# Pharmacokinetics

- Highly polar basic drugs: poor oral BA
- Administered parenterally or applied locally
- Poorly distributed and poorly protein bound
- Do not undergo any significant metabolism
- Nearly all IV dose is excreted unchanged in urine
- Dose adjustment is needed in renal insufficiency

# Pharmacokinetics





# Dose for a case of renal insufficiency

= Normal therapeutic dose

Sr creatinine value (mg/dl)

# Dose for a case of renal insufficiency

- Cockcroft gault formula:

$$\text{CrCl} = \frac{(140 - \text{age}) \times \text{weight [kg]}}{(\text{sCr} \times 72)}$$

– For females multiply above value by 0.85

- Corrected dose =  $\frac{\text{Normal dose} \times \text{pt CrCl}}{\text{Normal CrCl}}$

# Clinical uses

- Gram –ve bacillary infection
  - Septicaemia, pelvic & abdominal sepsis
- Bacterial endocarditis –
  - enterococcal, streptococcal or staphylococcal infection of heart valves
- Pneumonias, Tuberculosis
- Tularemia
- Plague, Brucellosis
- Topical – Neomycin, Framycetin.
- Infections of conjunctiva or external ear
- To sterilize the bowel of patients who receive immunosuppressive therapy, before surgery & in hepatic coma

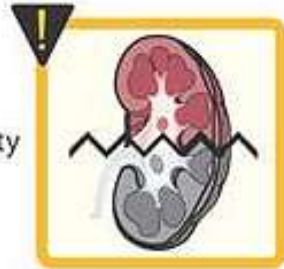
# Shared toxicities

- Ototoxicity
  - Vestibular damage
  - Cochlear damage
- Nephrotoxicity
- Neuromuscular blockade

Ototoxicity



Nephrotoxicity



Paralysis



Skin rash



# Ototoxicity

- Impairment of VIII cranial nerve function
- May be irreversible
- Cochlear damage
  - Hearing loss and tinnitus
  - More with neomycin , amikacin and kanamycin
- Vestibular damage
  - Vertigo, ataxia, loss of balance
  - More with Streptomycin, gentamycin
- Tobramycin has both types of toxicity
- Netilmycin claimed to have low ototoxicity

# Nephrotoxicity

- Gentamicin, amikacin and tobramycin are more toxic than streptomycin
- Responsible for 10-15% of all renal failure cases
- Reversible if drug promptly discontinued
- ↓ GFR, ↑ sr creatinine
- ↓ clearance of antibiotic → ↑ ototoxicity

# Neuromuscular blockade

- Cause N-M junction blockade by
  - Displacing  $\text{Ca}^{2+}$  from NM junction
  - By blocking post synaptic  $\text{N}_M$  receptors
  - Inhibiting Ach release from motor nerve
- Neomycin & streptomycin: more propensity
- Tobramycin least likely to produce it
- Myasthenic weakness ↑ by these drugs

# Precautions / Contraindications

- Pregnancy: foetal ototoxicity
- With other ototoxic drugs: furosemide, minocycline
- With nephrotoxic drugs: vancomycin ,cisplatin
- Elderly patients
- Those with kidney disease
- Cautious use of muscle relaxants
- Do not mix with any other drug in same syringe



# Streptomycin

- Ribosomal resistance develops fast
- Limited usefulness as single agent
- Plague, tularemia and brucellosis
  - In combination with tetracycline
- SABC: due to Streptococcus Viridans & faecalis
  - With penicillin but gentamicin preferred
- Reserve first line drug for tuberculosis used only in combination

# Gentamicin

- Obtained from *Micromonospora purpurea*
- Most commonly used aminoglycoside
  - More potent than Streptomycin
  - Broader spectrum: pseudomonas, proteus, E.coli, klebsiella, enterobacter, serratia
  - Low cost, reliability of use, long experience
  - Acts synergistically with ampicillin, penicillin G, Ticarcillin, ceftriaxone, Vancomycin
- Ineffective against *M.tuberculosis*
- Relatively more nephrotoxic

# Gentamicin (Uses)

- Use restricted to serious Gm-ve bacillary infections
- Septicaemia, sepsis, fever in immunocompromised patients
  - Used with penicillins
- Pelvic infections : with metronidazole
- SABE: with Penicillin G or ampicillin or vancomycin
- Coliform infection: with ampicillin or ceftriaxone
- Pseudomonal infections: with ticarcillin
- Meningitis by Gm-ve bacilli : III generation cephalosporin alone or with gentamicin

# Guideline for adjustment of dose in renal insufficiency

Creatinine clear. ( ml/min)	% Maximal daily dosing	Frequency of dosing
100	100	Every 24 hr
75	75	”
50	50	”
25	25	”
20	80	Every 48 hr
10	60	”
◁ 10	40	”

# Tobramycin

- Identical to gentamicin
- Used in pseudomonas and proteus infections
- Ototoxicity and nephrotoxicity probably lower

# Sisomicin

- Identical to gentamicin
- More potent on pseudomonas and  $\beta$ -hemolytic streptococci
- Used interchangeably with gentamicin

# Amikacin

- Less toxic semisynthetic derivative of kanamycin
- **Resistant to enzymes** that inactivate gentamicin and tobramycin
- **Widest** spectrum of activity
- Uses:
  - Same as gentamicin
  - Reserve drug for hospital acquired Gm-ve bacillary infections
  - **Multidrug resistant TB** along with other drugs
- Dose : 15mg/kg/day in 1-3 doses

# Netilimicin

- Semisynthetic derivative of sisomicin
- Relatively **resistant to aminoglycoside inactivating enzymes**
- More active against klebsiella, enterobacter & staphylococci
- Less active against pseudomonas aeruginosa
- Doses and pharmacokinetics similar to gentamicin

# Neomycin

- wide spectrum active against Gm-ve bacilli and some gm+ve cocci
- Pseudomonas and strep.pyogenes not sensitive
- Too toxic for parenteral use , limited to topical use



# Neomycin (uses)

- Topically used in **skin, eye and external ear infections** combined with bacitracin or polymyxin-B to widen antibacterial spectrum and to prevent emergence of resistant strains
- Orally
  - **Preparation of bowel** before surgery 1 gm TDS
  - **Hepatic coma**: Suppresses ammonia forming coliforms prevents encephalopathy (**Lactulose more preferred**)
- Bladder irrigation along with polymyxin B

# Framycetin

- Very similar to neomycin
- Too toxic for systemic administration
- Used topically on skin, eye ear