Antipseudomonal penicillins

- **Penicillins (penicillin G):**
  - Activity against Gram (+) organisms, Gram (-) cocci and non-β-lactamase producing anaerobes (because they are destroyed by β-lactamase).
  - Little activity against Gram (-) rods.
- **Antistaphylococcal penicillins (nafcillin):**
  - Active against staphylococci and streptococci.
  - Resistant to β-lactamase (not destroyed by it).
- **Extended-spectrum penicillins (aminpenicillins and antipesuomonal penicillins):**
  - Retain the antibacterial spectrum of penicillins.
  - Improved activity against Gram (-) organisms.
  - Susceptible to β-lactamase (destroyed by it).
- **Antipseudomonal penicillins include:**
  - **Ureidopenicillins**: example → piparacillin.
  - **Carboxypenicillins**: example → ticarcillin.
- Note that some bacteria have the ability to produce β-lactamase enzyme which interferes with susceptible penicillins and destroy them before they can bind to penicillin binding protein (PBP) in the cytoplasmic membrane of the bacteria.
- **Vancomycin is one of the drugs which act on the cell wall.**
- **Resistance to penicillins: by 4 general mechanisms:**
  - Inactivation of antibiotic by β-lactamase.
  - Modification of target PBPs.
  - Impaired penetration of drug to target PBPs.
  - Antibiotic efflux.
- **Penicillins are pregnancy category B (safe).**

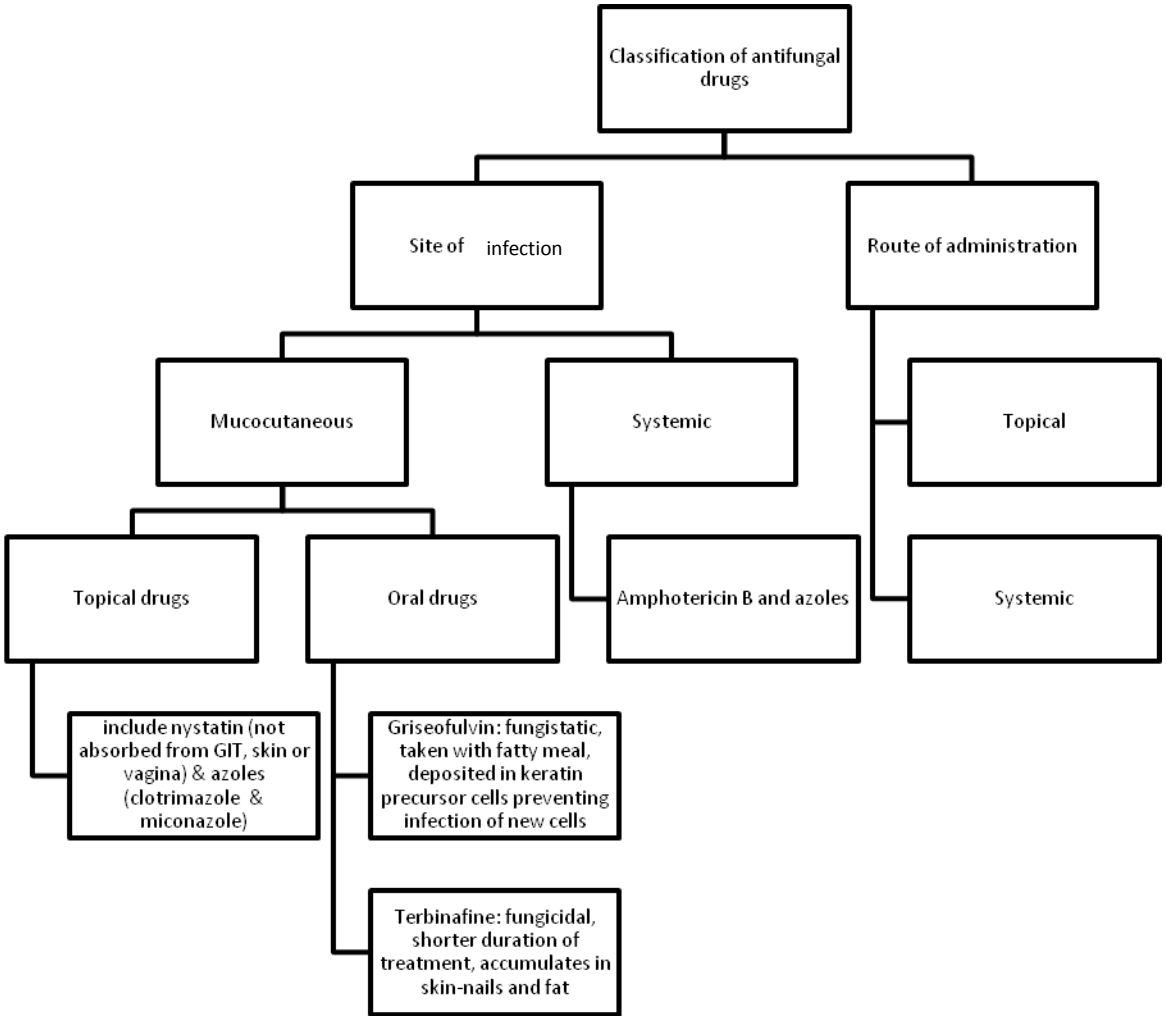
Aminoglycosides

- **Examples:**
  - Streptomycin & amikacin (both used for the treatment of multi-drug-resistant tuberculosis).
  - Neomycin, gentamycin & tobramycin.
- **Aminoglycosides are used most widely in combination:**
  - With a β-lactam antibiotic in serious infections with Gram (-) bacteria.
  - With vancomycin or β-lactam antibiotic for Gram (+) endocarditis.
- **Mechanism of action:**
  - Binding to specific 30S-subunit ribosomal proteins which will lead to irreversible inhibition of protein synthesis by:
    - ✓ Interference with initiation complex (blocking it).
    - ✓ Misreading of mRNA (which will result in miscoded peptide chain).
    - ✓ Breakup of polysomes into non-functional monosomes (block of translocation).
- **Resistance: by three principle mechanisms:**
  - Production of a transferase enzyme (most common).
  - Impaired entry of aminoglycoside into the cell.
  - Receptor protein on the 30S ribosomal subunit may be deleted or altered.
- **Pharmacokinetics:**
  - Aminoglycosides are polar compounds which are very poorly absorbed from the GIT.
  - They are largely excluded from the CNS (cannot cross the blood-brain barrier as it is polar) and the eye.
  - It is excreted by the kidneys.
- **Administration:**
  - Traditionally, aminoglycosides are given in divided doses but entire daily dose in a single injection is preferred for two reasons:
    - ✓ Higher concentrations kill more and faster.

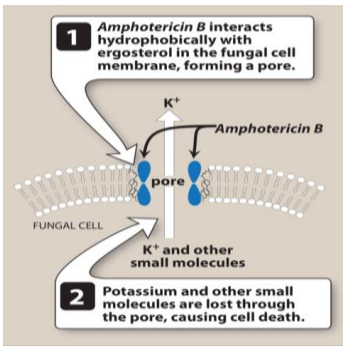
- ✓ Antibacterial activity lasts several hours beyond the time during which measurable drug is present.

- **Toxicity:**
  - All aminoglycosides are ototoxic and nephrotoxic.
  - **Factors resulting in toxicity include:**
    - ✓ Therapy for more than 5 days.
    - ✓ Higher doses.
    - ✓ Elderly.
    - ✓ Renal insufficiency.
    - ✓ Drug interactions with loop diuretics (furosamide) & nephrotoxic antibiotics (vancomycin or amphotericin B).
  - **In very high doses (curare-like effect):**
    - ✓ Neuromuscular blockade resulting in respiratory paralysis. This is reversible by neostigmine or calcium gluconate.
- **They are pregnancy category D (positive fetal risk but benefits might outweigh the risks).**

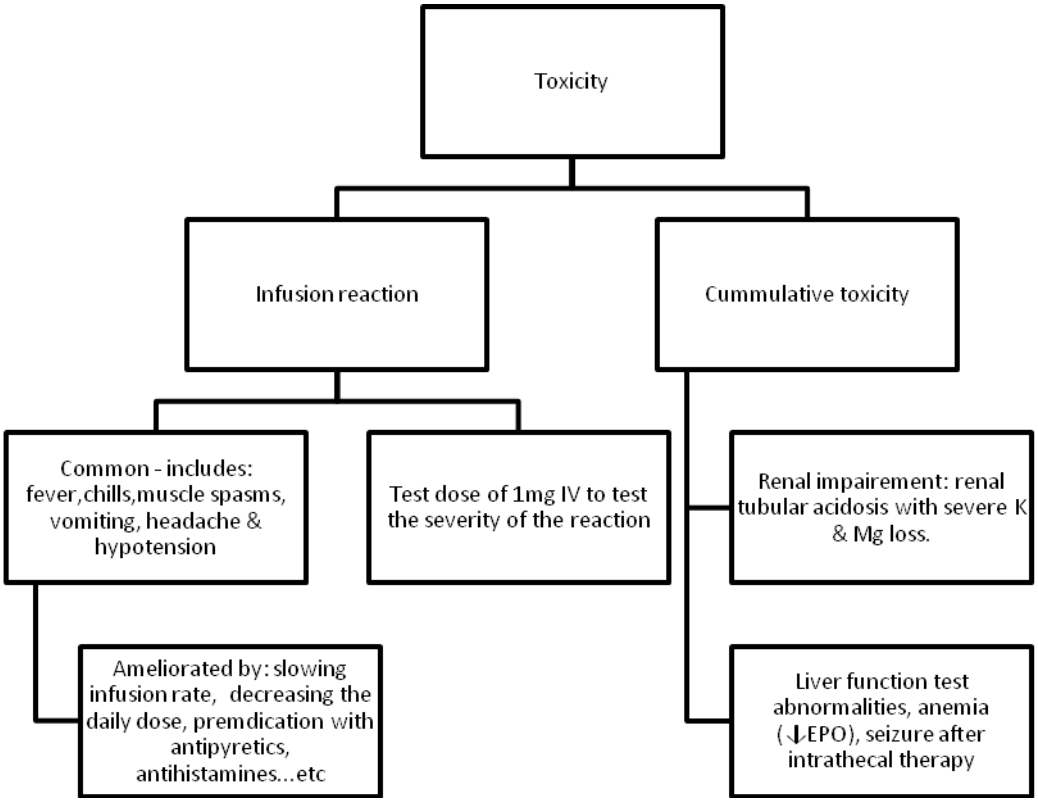
Amphotericin B



- Amphotericin B is produced from streptomyces nodosus and it is an amphoteric polyene macrolide.
- It is poorly absorbed that's why it given IV (it will be distributed widely except in the CSF). It is given intrathecal for fungal meningitis and topical for ocular and bladder infections.
- **Mechanism of action**: it bounds to ergosterol and alters the permeability of the cell by forming amphotericin B-associated pores.



- **Liposomal amphotericin B preparation**: shows lower toxicity.



- **Pregnancy category B: safe.**