Aminoglycosides & Quinolones

Aminoglycosides are a group of bactericidal antibiotics
- obtained from various streptomyces species
- The group includes streptomycin, neomycin, kanamycin, amikacin, gentamicin, tobramycin, sisomycin, netilmicin, and others

Chemistry
- have a hexose ring, either streptidine (in streptomycin) or 2-deoxystreptamine (other AMG) to which various amino sugar are attached by glycosidic linkage
  - water-soluble
  - more active at alkaline than at acid pH

Gentamicin, tobramycin, amikacin: the most widely employed

Neomycin, kanamycin: limited to topical or oral use

Antimicrobial activity
- against gram-negative enteric bacteria
- bactericidal

Mechanism of action
- irreversible inhibitors of protein synthesis (30S ribosomal subunit)
- penetration cell envelope:
  - passive diffusion
  - active transport (oxygen-dependent process)

Mechanisms of resistance
plasmid-mediated formation of inactivating enzyme (group transferases)
Pharmacokinetics
- are polar compounds and are not absorbed after oral administration
- must be given parenterally for systemic effect and have limited tissue penetration
- largely excluded from CNS and the eye
- glomerular filtration is the major mode of excretion
- excretion of AMG is directly proportionate to creatinine clearance
- T½ in serum : 2-3 hrs

- Treatment of antimicrobial infections with antibiotics : multiple daily dosage regimens maintain serum concentration above MIC

- Beta- lactam antibiotics : time-dependent killing : antibacterial activity is directly related to time above MIC and becomes independent of concentration once the MIC has been exceed

Aminoglycosides : concentration-dependent killing : increase concentrations kill an increasing proportion of bacteria and at a more rapid rate

- Aminoglycosides : capable of exerting a postantibiotic effect (PAE) [antibacterial activity persists beyond the time that measurable drug is present]

Adverse Reactions
- all aminoglycosides are ototoxic and nephrotoxic (more likely to encountered when therapy is continued for more than 5 days)
- concurrent use with loop diuretics (furosemide) or other nephrotoxic antimicrobial agents (vancomycin) can potentiate nephrotoxicity
- can produce a curare-like effect with neuromuscular blockade (in very high doses)
  respiratory paralysis (reversible by calcium gluconate or neostigmine)
Clinical Uses

- are mostly used against gram-negative enteric bacteria
- almost always used in combination with a beta-lactam antibiotic (penicillin + aminoglycosides: enterococcal endocarditis)

Streptomycin

- Streptomyces griseus 1944
- Clinical uses
  1. Mycobacterial infections (only in combination with other agents to prevent emergence of resistance)
  2. Nontuberculous infections: plague, tularemia

Gentamicin

- Micromonospora purpurea
- Gentamicin 2-10 μg/mL, inhibits in vitro many strains of staphylococci and coliforms and other gram-negative bacteria
- it is active alone, but also as synergistic companion with beta-lactam antibiotics against pseudomonas, proteus

Kanamycin & Neomycin

- are active against gram-negative bacteria and some mycobacteria, not significantly absorbed from the GIT, excreted in the feces (excretion of any absorbed drug is mainly through glomerular filtration)
- Clinical Uses
  - neomycin is too toxic for parenteral
  - topical: ointment: apply to infected skin lesions
  - PO: in preparation for elective bowel surgery (reduce the aerobic bowel flora with little effect on anaerobes)

Spectinomycin

- Aminocyclitol antibiotic that structurally related to AMG
- active in vitro against gram-positive and gram-negative organisms
- Rapidly absorbed after IM
- alternative treatment for gonorrhoea in patients who are allergic to penicillin or whose gonococci are resistant to other drugs

Quinolones

- Synthetic fluorinated analogs of nalidixic acid
- Earlier quinolones: nalidixic acid
- Newer fluorinated derivatives: norfloxacin, ciprofloxacin, ofloxacin, levofloxacin, lomefloxacin, sparfloxacin
**Mechanism of action**
Block bacterial DNA synthesis by inhibiting bacterial topoisomerase II (DNA gyrase) and topoisomerase IV

**Antimicrobial activity**
Fluoroquinolones
- Usually bactericidal against susceptible organisms
- Gram-negative rods, gram-positive organisms
- Intracellular pathogen

**Resistance**
- Due to one or more point mutations in the quinolone binding region of the target enzyme or to change in the permeability of the organisms

**Pharmacokinetics**
- PO: well absorbed (bioavailability 80-95%)
- Distributed widely in body fluids and tissues
- Serum half-life: range from 3 hrs (norfloxacin, ciprofloxacin) up to 10 hrs (pefloxacin, fleroxacin) or longer (sparfloxacin)

**Pharmacokinetic properties of fluoroquinolones**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life (h)</th>
<th>Primary route of excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>3-5</td>
<td>Renal</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>5-7</td>
<td>Renal</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>3.5-5</td>
<td>Renal</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>5-7</td>
<td>Renal</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>18</td>
<td>50% renal, 50% fecal</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>9-10</td>
<td>Nonrenal</td>
</tr>
<tr>
<td>Trovafloxacin</td>
<td>11</td>
<td>Nonrenal</td>
</tr>
</tbody>
</table>

**Clinical Uses**
1. Urinary tract infections: even when caused by multidrug-resistant bacteria
2. Bacterial diarrhea caused by shigella, salmonella, toxigenic E coli
3. Infections of soft tissues, bones, joints, intra-abdominal and respiratory tract infections (except norfloxacin: does not achieve adequate systemic blood level)
4. Gonococcal infection: ciprofloxacin and ofloxacin
5. Chlamydial urethritis or cervicitis: ofloxacin
Adverse Reactions

Fluoroquinolones are extremely well tolerated
- Most common effects: nausea, vomiting, and diarrhea
- Occasionally: headache, dizziness, abnormal liver function test, skin rashes
- Not routinely recommended: < 18 y (may damage growing cartilage and cause an arthropathy)