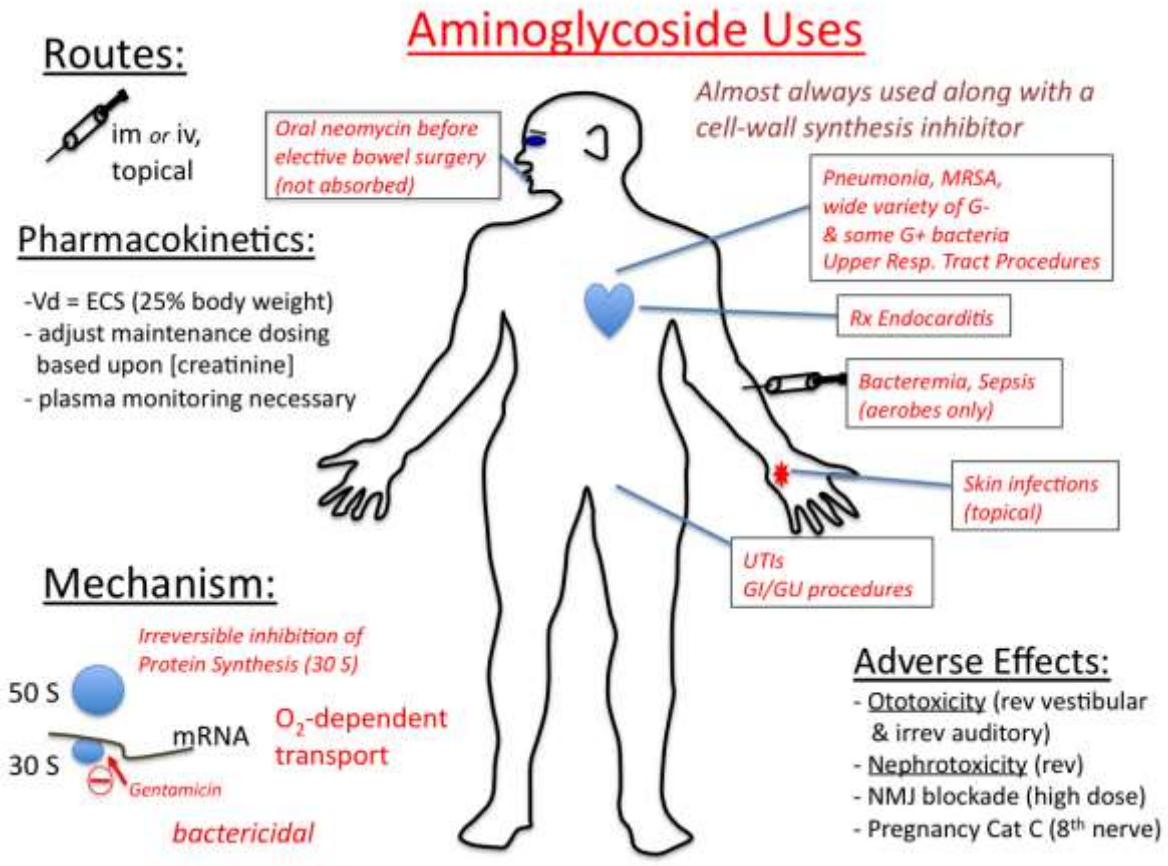
Aminoglycosides



- **Examples:**
  - **Streptomycin** (generic)
  - **Neomycin** (generic)
  - **Gentamicin** (generic, Garamycin ®)
  - **Tobramycin** (generic, Nebcin ®)
  - **Amikacin** (generic, Amikin ®)
  - **Netilmicin** (Netromycin ®)
- **Mechanism of Action:**
  - **Protein synthesis inhibitors:**
    - **Gram-negative bacteria**:
      - In gram-negative bacteria, positively charged aminoglycosides are electrostatically attracted to the negative surface charge of the outer membrane that contains abundant amounts of lipopolysaccharide (LPS)(Taber et al, 1987; Jackson et al, 1990).
      - Positively charged aminoglycosides displace divalent cations from binding sites that cross-link and stabilize lipopolysaccharide (LPS) chains that are critical for stabilization of the outer membrane (Hancock et al, 1991; causing permeabilization of the outer membrane, which promotes the uptake of antibiotic and other large molecules. This process is similar to the mechanism of action of polymyxins, and can be antagonized by elevated concentrations of Mg^{2+} that stabilize the outer membrane (Hancock et al, 1991).

- **Gram-positive bacteria**:
    - In gram-positive bacteria, negatively charged teichoic & lipoteichoic acids that extend through the peptidoglycan cell wall are initial sites of ionic attraction for positively charged aminoglycosides. (Taber et al, 1987).
- **All bacteria**:
    - **Synergism with Inhibitors of Cell Wall Synthesis.** Evidence from *in vitro* experiments indicates that transport across the cell wall can be enhanced by cell-wall inhibitors such as penicillin or vancomycin, resulting in a synergistic effect with aminoglycosides. However, synergism is not observed in every species of bacteria. Synergism is typically seen when the aminoglycoside is given in low concentrations (below its MIC), in combination with a cell wall synthesis inhibitor given above its MIC (Taber et al, 1987). Evidence for synergism has been confirmed in several animal studies. However there have been conflicting reports that such drug combinations produce a superior clinical response (Marcus et al, 2011; Tamma et al, 2012)(**see Box Discussion**).
    - **Oxygen dependent active transport** (this required step makes aminoglycosides ineffective against anaerobic bacteria).
        - a slow energy-dependent phase (EDP-I) that transports the drug into the bacterial cytosol
        - a second rapid energy-dependent phase (EDP-II) involving binding to the ribosomes
    - **Binds irreversibly to 30S ribosome**;
        - 3 mechanisms of action for inhibiting protein synthesis have been identified:
            1. **blocks protein synthesis at the initiation complex stage**
            2. **mis-coding of RNA** occurs, with production of nonfunctional or toxic proteins
            3. **break up of polysomes** into nonfunctional monosomes. (See animation of its mechanism of action at pharmacology corner [http://pharmacologycorner.com/protein-synthesis-inhibitors-aminoglycosides-mechanism-of-action-animation-classification-of-agents/]).
    - ***"Post-antibiotic effect":*** aminoglycosides can inhibit bacterial growth for some time after plasma levels have fallen to the point where little drug is detectable in the blood. This results from their strong, irreversible binding to the 30 S ribosome, causing them to remain intracellular and effective long after plasma levels fall. This allows for a prolonged dosage interval.
    - **Bactericidal at higher drug concentrations (this is unique for protein synthesis inhibitors)**.
- **Mechanisms of Resistance**:
    - **Most Common Mechanism**: **inactivation by bacterial-induced enzymatic modification of aminoglycosides** (phosphorylation, acetylation & adenylation of aminoglycodsides); plasmid mediated (Garneau-Tsodikova & Labby, 2016; Krause et al 2016)
    - Bacterial expression of **efflux pumps** (Fernandez & Hancock, 2012)
    - Rare: 16S rRNA methylation (decreases binding affinity)(Garneau-Tsodikova & Labby, 2016)

Synergy with Cell Wall Synthesis Inhibitors is Not Always Observed In the Clinical Setting

Under the right conditions, inhibitors of cell wall synthesis can increase the permeability of aminoglycosides through the peptidoglycan layer of the cell wall, resulting in increased cellular uptake of aminoglycosides, and synergistic killing of sensitive bacteria. However, such synergy has been found to be dependent upon drug concentration (it occurs with concentrations of cell wall synthesis inhibitors above their MIC, combined with aminoglycosides given below their MIC), and has also been found to be dependent on the bacterial strain, as well as the particular drugs used (Taber et al, 1987; Tamma et al, 2012; Hirzel et al, 2016). This variability may explain why evidence for synergy has not been consistently observed in different clinical settings. **A systematic review of randomized clinical trials has not shown an advantage to adding an aminoglycoside to a beta lactam antibiotic for treatment of most clinical infections (Marcus et al, 2011), especially when newer broad-spectrum antipseudomonal beta-lactam antibiotics are used** (Tamma et al, 2012). In what appears to be an exception to this rule, **gentamicin is recommended for combination therapy with cell wall synthesis inhibitors for the treatment of infective endocarditis**, based upon the available evidence that such drug combinations are synergistic in this clinical setting (Baddour et al, 2015; Sexton, 2016).

- **Indications:**
    - **Aerobic gram-negative & gram-positive bacteria**, e.g.

    - Gram-negative bacilli: *Kliebsiella, Serratia, Proteus, Pseudomonas,*, *Mycobacteria* (TB), *N. gonorrhoeae*, tularemia, plague, brucellosis….
    - Gram positive cocci: *Staphylococcus*, Group B *Streptococcus*, *viridans streptococci*, *Enterococcus*
  - Treatment of **severe Gram negative infections including sepsis, pneumonia, endocarditis, intra-abdominal infections, kidney infections, UTIs, skin infections**
  - **Aminoglycosides are not recommended as monotherapy for severe infections, but must be combined with another agent**
  - **Used in combination with vancomycin or a penicillin for enterococcal endocarditis, *and for treatment of* tuberculosis**.
  - Oral administration to eliminate gut bacteria (it isn't absorbed systemically)
  - **Not effective against anaerobes** (anaerobes lack the oxygen-dependent transport mechanism required for cellular uptake of aminoglycosides).
  - Streptomycin is used for tuberculosis, brucellosis, plague & tularemia.
  - Neomycin is used only for alteration in bowel flora & topically with other antibiotics (e.g. Neosporin ®).
- **Contraindications:**
  - other drugs (e.g. anticancer drugs, cisplatin) that are nephrotoxic or cause auditory toxicity.
- **Side Effects:**
  - **NEPHROTOXICITY** (~10-20% incidence)
    - injures renal proximal convoluted tubule, causing a decrease in GFR, elevated BUN & plasma creatinine, elevated protein in urine (usually reversible)
    - aminoglycosides are positively charged compounds that bind avidly to anionic phospholipids of cell membranes in the proximal tubule. Endocytosis results in a dose-dependent intracellular accumulation, resulting in free radical production, disruption of mitochondrial function and cellular toxicity (Decker & Molitoris, 2015).
  - **Ototoxicity** (~10% incidence)
    - **vestibular toxicity is typically reversible**, while **auditory toxicity is irreversible**
    - damages hair cells (cochlear & vestibular); discontinuing aminoglycoside therapy at the earliest recognition of ototoxicity may reduce the extent of impairment (Leis et al, 2015).
    - after administration, aminoglycosides are cleared from the plasma with a half life of 2-3 hours, but persist for weeks to months in tissues of the inner ear where they cause the death of hair cells (Forge & Schacht, 2000). Two mechanisms have been identified: a) excitotoxic effects by stimulating NMDA receptors present in the synapse between cochlear hair cells and neural afferents (Basile et al, 1996; Decker & Molitoris, 2015); b) increased production of oxygen free radicals, resulting in mitochondrial damage and cell toxicity (Selimoglu 2007; Decker & Molitoris, 2015).
  - **Neuromuscular blockade** (rare)
    - manifests as skeletal muscle weakness or respiratory depression
    - most commonly seen in patients with Mysthenia Gravis
    - in non-myasthenic patients, it has usually been associated with the use of large doses, or concomitant use of other neuromuscular blocking agents, or general anesthesia.
    - aminoglycosides block voltage-dependent calcium channels in the presynaptic membrane of motorneurons, which inhibits the release of acetylcholine. This effect can be managed by intravenous infusion of calcium (Paradelis et al, 1988; Parsons et al, 1992).

Black Box Warnings:

Patients treated with aminoglycosides should be under close clinical observation because of the potential toxicity associated with their use. Aminoglycosides are potentially **NEPHROTOXIC**. The risk of toxicity is greater in patients with reduced renal function and in those receiving prolonged therapy or high dosage. Neurotoxicity is manifested by **OTOTOXICITY** (both vestibular & auditory); which may be irreversible. Renal & 8th cranial nerve function should be closely monitored. Urine should be examined for changes in specific gravity, and the presence of cells or protein. BUN and serum creatinine should be checked periodically. When feasible, serial audiograms should be performed in patients old enough for the procedure. When feasible, serum concentrations of aminoglycosides should be monitored to insure adequate levels (e.g. trough levels of gentamicin above 2 µg/ml) and to avoid prolonged toxic levels (e.g. above 12 µg/ml for gentamicin). Hemodialysis may aid in reducing blood

levels of gentamicin. In newborn infants, exchange transfusion may also be considered. Concurrent systemic or topic use of other potentially neurotoxic or nephrotoxic drugs should be avoided (e.g. polymyxin B, colistin, cisplatin). The concurrent use of potent diuretics that also produce ototoxicity (furosemide, ethacrynic acid) and alter serum concentrations of aminoglycosides should be avoided. Aminoglycosides can cause fetal harm when administered to a pregnant woman.

- **Pharmacokinetics:**
  - **Minimal oral absorption; given i.v. or i.m.**
  - Minimal metabolism
  - **Extracellular distribution (Vd (L) = 25% of body weight)**
  - Renal excretion (glomerular filtration)
  - Three phases of clearance: distribution, renal elimination & slow elimination from deep tissue sites
  - Poor penetration into the CSF & bronchial secretions
  - **Maintenance doses must be adjusted if creatinine clearance is not normal**. (For example, if serum creatinine increases from 1 to 2, you need to decrease the maintenance dose by half, or double the dosing interval. The loading dose is not changed.)

Don't Mix Aminoglycosides with Beta Lactams in the Same IV Line

If an aminoglycoside and a beta lactam antibiotic are inadvertently mixed in the same bottle of parenteral solution (e.g. for slow iv infusion) **penicillins have the capacity to inactivate aminoglycosides** (e.g. gentamicin) via nucleophilic opening of the beta lactam ring, by the methylamino group of aminoglycosides. The interaction does not occur in vivo if the drugs are given by different routes (Ervin et al, 1976).

- **Notes:**
  - Gentamicin, tobramycin and amikacin are the most widely used
  - Neomycin is limited to topical use
  - Streptomycin is primarily used in drug combinations for resistant tuberculosis as a fourth or fifth drug in regimens containing isoniazid (INH), rifampin, pyrazinamide and ethambutol (RESPI). It is not typically added to TB drug regimens if the likelihood of INH or rifampin resistance is very low.
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- rxlist.com (netilmicin) [http://www.medicinenet.com/netilmicin_sulfate-injection/article.htm]

Keywords

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