Q10 Discuss the bacteriocidal activity, and toxicity, of gentamicin (March 2011)

Gentamicin →

- Covers a wide range of gram negative enterobacteria and has gram positive cover that includes staph and some streptococci.
- No anaerobic activity but is synergistic with beta lactams and vancomycin.
- Used for infections of the GUT, GIT, respiratory tract, skin and soft tissues, neutropaenic sepsis, CNS infections, and surgical prophylaxis

Mechanism →

- Bactericidal antibiotic, which inhibits the bacterial 30S ribosomal subunit
- This impairs transcription and/or induces misreading of the mRNA, impairing protein synthesis

Toxicity →

- Gentamicin is not metabolized in humans
- It is excreted in the urine unchanged
- The presence of transport molecules in the epithelial cells of the proximal and distal tubule and the cortical collecting ducts allows gentamicin to accumulate within the cytosol of these cells.
- In the cytosol, gentamicin acts on the endoplasmic reticulum, impairing protein synthesis, and on the mitochondria to impair ATP production, increasing oxidative stress via the production of free radicals and superoxides. It also acts on lysosomes to impair protease degradation, causing further cell damage
- Independent of the cellular damage, gentamicin also inhibits some of the epithelial cell transport processes. Tubular damage may then partially or totally obstruct the lumen, causing further disruption of the nephron resorptive processes → hence the rise in plasma creatinine and fall in eGFR
- The accumulation of drug within the cell means that the toxic effects can continue long after plasma drug levels have declined
- Ototoxicity may be caused through similar processes, via accumulation of the drug in the inner ear perilymph, where it is disrupts mitochondrial protein synthesis and promotes formation of free radicals within the hair cells
- Nephrotoxicity usually reverses with cessation of drug, however ototoxicity may be permanent
- Gentamicin may also cause muscle weakness due to impairment of prejunctional release of ACh, use with caution with NMDR and in myasthenia gravis.