Resistance Mechanisms

- **Efflux pumps** - low level aminoglycosides resistance attributed to impaired cell wall permeability may be due to the result of drug efflux mechanisms e.g activation of the efflux pumps in *P. aeruginosa*. The pumps are named Mex XY or AmrAB

- **Enzymatic modification of the drug** may occur as result of aminoglycosides- modifying enzymes (AMEs) that phosphorylate, acetylate, or adenylate exposed amino or hydroxyl groups. The enzymatically modified drugs bind poorly to ribosomes, resulting in high levels of resistance.

- **Modifying enzyme genes** are spread by plasmids or transposon or both; Some are chromosomal. The plasmid-transposon genes can result in rapid spread of drug resistant phenotypes both within and between bacterial species

- **Aminoglycosides resistance in enterococci**- all enterococci have intrinsic resistance to aminoglycoside which attributed to the facultative anaerobic metabolism of enterococci, which reduce the trans-membrane potential and thereby limits the drug uptake. Concomitant exposure of enterococci to a cell wall – active drug such as ampicillin or vancomycin facilitate access of aminoglycoside to their ribosomal target site and classic synergistic bactericidal activity

- **Acquisition of genes that encode aminoglycoside-modifying enzymes** leads to high level aminoglycoside resistance and loss of synergistic activity with penicillin or vancomycin. Nine genes have been described that mediate resistance to aminoglycosides synergism in eneterococci. The most important gene is the bifunctional gene aa(6")-Ie-aph(2")-Ia, which encodes bifunctional enzyme AaC(6')-Ie-Aph (2")Ia. Presence of the enzyme results in high level resistance of gram positive cocci to all aminoglycosides except streptomycin.

- The current threshold for detection of high- level resistance to gentamicin in vitro is an MIC of 500 µg/ml or greater. These levels of resistance are surrogate markers for predicating synergism on the basis of the presence or absence of the aac(6')-Ie-aph(2")- Ia bifunctional gene.