

**Q1 Explain the mechanisms by which a bacterium may become resistant to an antimicrobial agent and provide an example (organism and antimicrobial) of each mechanism. (60% of marks) How is antimicrobial resistance spread? (40% of marks) (Sept 2009)**

Mechanisms of resistance:

- Alteration in target site
  - Production of an alternative enzyme for that which the antibiotic inhibits (Eg, MRSA synthesizes an additional penicillin binding protein that enables it to continue cell wall synthesis in the presence of a beta lactam drug)
  - Overproduction of the target of the antibiotic
- Alteration in access to target site
  - Reduced binding of the antibiotic (eg, VanA and VanB vancomycin resistance involves a gene mutation leading to decreased affinity of vancomycin for the binding sites of peptidoglycan precursors; changes to the DNA-binding surface of DNA supergyrase infers resistance against ciprofloxacin)
  - Reduced uptake of the antibiotic (eg, transport defect or membrane impermeability to gentamicin, alteration of porins through which beta lactams must diffuse in gram negative outer membranes)
  - Active efflux of the antibiotic (eg, active transport of ciprofloxacin out of the bacterial cell)
- Enzymes produced against the antibiotic
  - Beta lactamases and cephalosporinases which hydrolyse and inactivate beta lactam antibiotics
  - Multiple enzymes have been identified that block aminoglycosides, including acetyltransferase, adenylyltransferase, and phosphotransferase)

Methods of spread of resistance:

- By transfer of resistant bacteria between people
- By transfer of resistance genes between bacteria (horizontal gene transfer), by:
  - Conjugation → Plasmids are extrachromosomal genetic elements that can carry genes coding for resistance. The resistant bacteria forms a connecting tube with other bacteria through which the plasmid can pass (most common method of spread)
  - Transduction → plasmid DNA is enclosed in a bacterial virus ('phage') and transferred to another bacterium (important in staph and strep resistance)
  - Transformation → bacteria take up DNA from the environment and incorporate it into the genome
- By transfer of resistance genes between genetic elements within bacteria, on transposons (stretches of DNA that can be readily transposed from one plasmid to another plasmid or chromosome)