Bacterial Resistance of β-Lactam Antibiotics

Inhibitors of peptidoglycan synthesis

β-Lactams

Acquired resistance to β-Lactam antibiotics can occur by three different mechanisms: **inactivation of the antibiotic, alteration of the target site and reduced permeability**.

A first mechanism: β-Lactams are inactivated by enzymes called β-lactamases which hydrolyze the cyclic amide bond in the antibiotic molecule. **Penicillins are converted to penicilloic acid which is unable to bind to penicillin-binding proteins (PBPs).** A similar reaction occurs with **cephalosporins**, *except that the cephalosporoic acid derivative is unstable and tends to break up*.

It is worth noting that in **Gram-negative** organisms, **β-lactamases are found in the periplasmic space where they inactivate β-lactams before the antibiotics can bind to their PBP targets on the cytoplasmic membrane**. In **Gram-positive** organisms, however, **β-lactamases are excreted extracellularly and therefore resistance is very much a characteristic of the population rather than individual β-lactamase-producing cells**. *If enough enzyme is synthesized, levels of β-lactam may be reduced sufficiently to permit growth of non-β-lactamase-producing strains.*

A second mechanism of resistance involves **alterations in PBPs which affect binding of β-lactams.** These changes have been found to occur by multiple substitutions through recombination rather than point mutations. Clinically, one of the most important examples of β-lactam resistance is that found in **methicillin-resistant *Staph. aureus* (MRSA)** strains. These are causing increasing concern in hospitals, especially because methicillin resistance is often accompanied by multiple resistance to unrelated antibiotics. Methicillin is resistant to β-lactamases and is a mainstay in the

treatment of *Staph. aureus* since over 90% of hospital strains produce β-lactamase. Methicillin resistance is due to a novel PBP with low affinity for β-lactams. It is capable of functioning when all other PBPs have been inhibited and is sufficient to catalyze all the reactions necessary for cell growth.

A third resistance mechanism is akin to that described for the AGAC antibiotics and chloramphenicol, **whereby changes in the outer membrane porins of Gram-negative bacteria reduce the penetration of β-lactams resulting in low levels of resistance.**

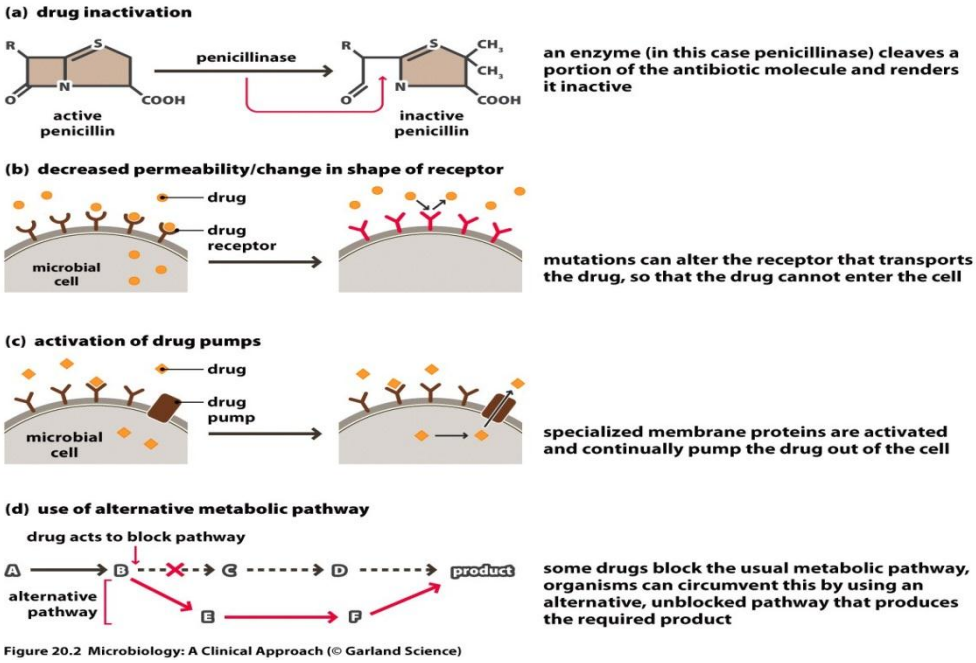
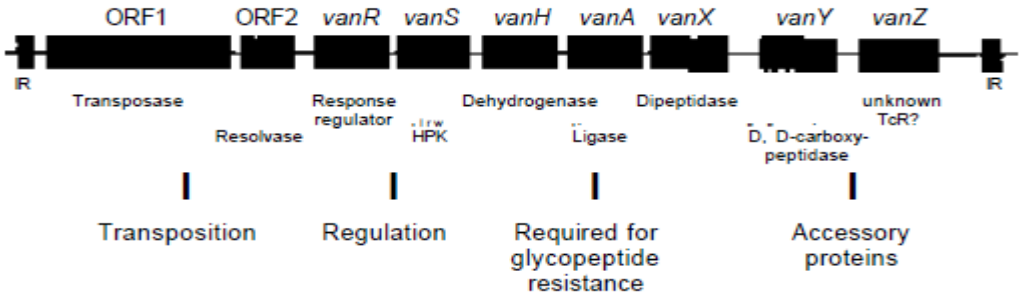


Figure 20.2 Microbiology: A Clinical Approach (© Garland Science)

Glycopeptides

Glycopeptide antibiotics interfere with **peptidoglycan synthesis** by binding to the D-alanyl - D-alanine terminus of peptidoglycan precursors. **Resistance to glycopeptides was thought unlikely** *because the changes in integral structures and functions of the cell wall and the enzymes involved in its synthesis would render bacteria non-viable*.



Organization of glycopeptide-resistance genes in transposon Tn1546. IR, invested repeats; HPK, histidine protein kinase; TcR, low level teicoplanin resistance.

Acquired resistance to the glycopeptides is transposon-mediated and has so far been largely confined to the enterococci. Two types of acquired glycopeptide resistance have been described: The **Van A phenotype** is resistant to vancomycin and teicoplanin, whereas **Van B** is resistant to vancomycin only. Van A and Van H are essential for the expression or resistance, which is due to a modification of the peptidoglycan pathway to produce precursors with reduced affinity for glycopeptides. Van A is a ligase which catalyzes the synthesis of D-alanyl-D-lactate depsipeptide instead of D-alanyl-D-alanine. Van H is a dehydrogenase which catalyzes the synthesis of D-lactate as the substrate for Van A.

Fosfomycin

Fosfomycin inhibits **pyruvil transferase**, which is an enzyme involved in peptidoglycan synthesis. Two mechanisms of acquired resistance have been described for fosfomycin .

Plasmid- or transposon-mediated resistance occurs by inactivation of the antibiotic. Fosfomycin is combined with glutathione intracellularly to produce a compound lacking in antibacterial activity.

A second mechanism of acquired resistance to fosfomycin involves chromosomal mutations in sugar phosphate uptake pathways which are responsible for transporting fosfomycin into the cell. The alterations decrease accumulation of the antibiotic to levels below those required for inhibition.