Anti-Microbial Drugs

Lecture 2
Inhibitors of Cell wall synthesis:

Some antimicrobial drugs interfere with synthesis of bacterial cell wall. The cell wall is a polymer called peptidoglycan that consists of glycan units joined to each other by peptide cross-links.
To be maximally effective, inhibitors of cell wall synthesis require actively proliferating microorganisms.

(1) Penicillins

- The penicillins are among the most widely effective antibiotics & also the least toxic drugs known, but increased resistance has limited their use.
  Members differ from one another in the R substituent attached to the 6-aminopenicillanic acid residue.
  The nature of this side chain affects¹ the antimicrobial spectrum,² stability to stomach acid, &³ susceptibility to bacterial degradative enzymes (β-lactamases).
Mechanism of action:
The penicillins interfere with **last step of bacterial cell wall synthesis** (transpeptidation or cross linkage), resulting in exposure of the osmotically less stable membrane. Cell lysis can then occur, either through osmotic pressure or through the activation of autolysis. These drugs are thus bactericidal. Penicillins are only effective against rapidly growing organisms that synthesize a peptidoglycan.

1. **Penicillin binding proteins (PBP's):** penicillins inactivate numerous proteins on the bacterial cell membrane. These PBP's are bacterial enzymes involved in the synthesis of the cell wall and in the maintenance of the morphologic features of the bacterium. Alterations in some of these target molecules provide the organism with resistance to the penicillins e.g. methicillin resistant staphylococcus aureus (MRSA).

2. **Inhibition of transpeptidase:** some PBP's catalyse formation of the cross-linkages between peptidoglycan chains. Penicillins inhibit this transpeptidase-catalyzed reaction, thus hindering the formation of cross links essential for cell wall integrity.

3. **Production of autolysins:** many bacteria particularly the gram +ve cocci produce degradative enzymes (autolysins) that participate in the normal remodeling of the bacterial cell wall. In the presence of penicillin, the degradative action of the autolysins proceeds in the absence of cell wall synthesis.
Antibacterial Spectrum

In general, gram +ve microorganisms have peptidoglycan cell walls that are easily traversed by penicillins to reach the PBP's in the periplasmic space. Gram -ve microorganisms have an outer lipoploysaccharide membrane surrounding the cell wall that presents a barrier to the water soluble penicillins. However, they've proteins inserted in the lipopolysaccharide layer that act as water filled channels (called porins) that permit transmembrane entry. (Note: Pseudomonas aeruginosa lacks porins).

1. Natural penicillins:
Penicillin G (benzyl penicillin) is the cornerstone of therapy for infections caused by a number of
Gram +ve cocci (Streptococcus pyogenes, Streptococcus viridans),
Gram +ve bacilli (Bacillus anthracis, Corynebacterium diphtheriae),
Gram -ve cocci (Neisseria gonorrhoeae, Neisseria meningitidis),
Anaerobic organisms (Clostridium perfringens), &
Spirochetes (Treponema pallidum).

- Penicillin G is susceptible to inactivation by β-lactamase (penicillinases).

- Penicillin V has a spectrum similar to that of penicillin G, but it's not used for treatment of bacteremia because of its higher MBC. It is more acid stable than penicillin G. It is often employed for the treatment of oral infections, where it is effective against some anaerobic organisms.
2. **Anti-staphylococcal penicillins**: Methicillin, nafcillin, oxacillin, cloxacillin & dicloxacillin are penicillinase-resistant penicillins. Their use is restricted to the treatment of infections caused by penicillinase-producing staphylococci. Because of its toxicity, methicillin is not used. A serious source of hospital-acquired infection, MRSA are usually susceptible to vancomycin and rarely to ciprofloxacin or rifampin.
3. Extended spectrum penicillins:
- Ampicillin and amoxicillin have an antimicrobial spectrum similar to that of penicillin G, but are more effective against gram-ve bacilli. They are therefore referred to as extended spectrum penicillins. The antimicrobial spectrum of ampicillin includes gram +ve bacilli (Listeria monocytogenes) and gram-ve rods (Proteus mirabilis & Salmonella typhi while Escherichia coli and Haemophilus influenzae are frequently resistant).

- Amoxicillin is employed prophylactically by dentists for patients with abnormal heart values who are to undergo extensive oral surgery. Resistance to these antibiotics is now a major clinical problem because of inactivation by plasmid-mediated penicillinase. Formulation with a β-lactamase inhibitor, such as clavulanic acid or sulbactam, protects amoxicillin or ampicillin, respectively, from enzymatic hydrolysis & extends their antimicrobial spectrum.
4. Anti-pseudomonal penicillins: Carbenicillin, ticarcillin, and piperacillin are called antipseudomonal penicillin because of their activity against Pseudomonas aeruginosa. Piperacillin is the most potent of these antibiotics. They're effective against many gram-ve bacilli including Enterobacter, Escherichia coli, Proteus, Haemophilus influenzae & Pseudomonas aeruginosa, but not against Klebsiella, because of its constitutive penicillinase.

Formulation of ticarcillin or piperacillin with clavulanic acid or tazobactam, respectively, extends their antimicrobial spectrum to include penicillinase producing organisms.

Penicillins & aminoglycosides: The antibacterial effects of all β-lactam antibiotics are synergistic with the aminoglycosides. Because cell wall synthesis inhibitors alter the permeability of bacterial cells, these drugs can facilitate the entry of aminoglycosides that might not ordinarily gain access to intracellular target sites.

Resistance

Natural resistance to the penicillins occurs in organisms that either lack a peptidoglycan cell wall e.g. mycoplasma or have cell wall that are impermeable to the drugs.

Acquired resistance to the penicillins by plasmid transfer has become a significant clinical problem because an organism may become resistant to several antibiotics at the same time.

1. β-lactamase activity: this family of enzymes hydrolyzes the cyclic amide bond of the β-lactam ring, which results in loss of bactericidal activity.

β-lactamases are either constitutive, or more commonly, are acquired by the transfer of plasmids. Some of the β-lactam antibiotics are poor substrates for β-lactamases & resist cleavage. Gram +ve organisms secrete β-lactamases
extracellularly, whereas gram –ve bacteria have the enzymes in the periplasmic space between the inner & outer membranes.

2. Decreased permeability to the drug: decreased penetration of the antibiotic through the outer cell membrane prevents the drug from reaching the target PBP_s. The presence of an efflux pump can also reduce the amount of intracellular drug.

3. Altered PBP_s: modified PBP have lower affinity for β-lactam antibiotics, requiring clinically unattainable concentrations of the drug to effect inhibition of bacterial growth. This mechanism may explain MRSA.

**Pharmacokinetics**

1. Administration: the route of administration of a β-lactam antibiotic is determined by the stability of the drug to gastric acid and by the severity of the infection. Ticarcillin, piperacillin, ampicillin + sulbactam, ticarcillin + clavulanic acid and piperacillin + tazobactam must be administrated IV or IM. Penicillin V, amoxicillin and amoxicillin + clavulanic acid are available as oral preparations. Others are effective by the oral, IV or IM routes. Procaine penicillin G & benzathine penicillin G are administrated IM and serve as depot forms. They're slowly absorbed into the circulation and persist at low levels over a long period of time.

2. Absorption: most of the penicillins are incompletely absorbed after oral administration & they reach the intestine in sufficient amount to affect the composition of the intestinal flora. However, amoxicillin is almost completely absorbed. Consequently is not appropriate therapy for the treatment of shigella & salmonella derived enteritis, because therapeutically effective levels don't reach the organisms in the intestinal crypts. Oral penicillins, except for amoxicillin,
shouldn't be given at meal times, to minimize binding to food proteins & acid inactivation.

3. Distribution: distribution of the β-lactam antibiotics throughout the body is good. All the penicillins cross the placental barrier, but none has been shown to be teratogenic. However, penetration into certain sites, such as bone or CSF, is insufficient in therapy unless these sites are inflamed.

4. Excretion: the primary route of excretion is through the organic acid (tubular) secretory system of the kidney as well as by glomerular filtration. Patients with impaired renal function must have dosage regimens adjusted. Probenecid inhibits the secretion of penicillins and thus, can increase blood levels.

**Adverse Reactions**

1. Hypersensitivity: This is most important adverse effect. The major antigenic determinants of penicillin hypersensitivity are its metabolite, penicilloic acid, which reacts with proteins and serve as a hapten to cause an immune reaction. Approximately 5% of patients have some kinds of reactions, ranging from maculo-papular rash (the most common rash seen with ampicillin hypersensitivity) to angioedema (marked swelling of the lips, tongue and periorbital area) and anaphylaxis. Among patients with infectious mononucleosis who are treated with ampicillins, the incidence of maculopapular rash approaches 100%. Cross allergic reactions do occur among the β-lactam antibiotics.

2. Diarrhoea: this effect which is caused by disruption of the normal balance of intestinal microorganisms is a common problem. It occurs to a greater extent with those agents that are incompletely absorbed & have an extended antibacterial spectrum. Diarrhea appears to be less frequent with amoxicillin than ampicillin. As with some other antibiotics, pseudomembranous colitis may occur.
3. **Nephritis**: all penicillins, but particularly methicillin, have the potential to cause acute interstitial nephritis.

4. **Neurotoxicity**: the penicillins are irritating to neuronal tissue, & they can provoke seizures if injected intrathecally or if very high blood levels are reached. Epileptic patients are particularly at risk.

5. **Hematologic toxicities**: decreased agglutination maybe observed with the antipseudomonal penicillins (ticarcillin & carbenicillin) & to some extent, with penicillin G. Additional toxicities include eosinophilia.

6. **Cation toxicity**: Penicillins are generally administered as the sodium or potassium salts. Toxicities maybe caused by the large quantities of sodium or potassium that accompany the penicillin.