"Pharmacology"

Anti-Microbial Drugs

Lecture 3

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(2) Cephalosporins

They're $\beta$-lactam antibiotics that are closely related both structurally & functionally to penicillins. Most cephalosporins are produced semi-synthetically by the chemical attachment of side chains to 7-aminocephalosporanic acid. Cephalosporins have the same mode of action as penicillins & they are affected by the same resistance mechanisms. However, they tend to be more resistant than the penicillins to $\beta$-lactamases.

**Antibacterial spectrum:**

Cephalosporins have been classified as 1st, 2nd, 3rd or 4th generation, based largely on this bacterial susceptibility patterns & resistance to $\beta$-lactamases. They're ineffective against MRSA, *listeria monocytogenes*, *Clostridium difficile* & the enterococci.

I. First generation:

This group includes cephalexin, cefazolin, cephalothin & cefadroxil. These drugs are very active against gram +ve cocci, including staphylococci, streptococci & pneumococci. They're resistant to the staphylococcal penicillinase. Anaerobic streptococci are usually sensitive. They also have activity against gram –ve rods, mainly *Proteus mirabilis*, *E.coli* & *Klebsiella pneumoniae* (the acronym PEcK has been suggested). Cefazolin finds application as a single prophylaxis dose prior to surgery because of its 1.8hr half life and its activity against penicillinase producing *S.aureus*. Cefazolin is effective for most surgical procedures, including orthopedic surgery because of its ability to penetrate bone.
2. Second generation:
Members of this group include cefaclor, cefoxitin, cefuroxime, cefamandole & cefotetan. The 2\textsuperscript{nd} generation cephalosporins display greater activity against 3 additional grams –ve organisms: H.influenzae, enterobacter aerogenes & some Neisseria species (HENPEcK), whereas activity against gram +ve organisms is weaker.

\begin{itemize}
  \item The exception to this generalization is cefoxitin which has little activity against H.influenzae yet is effective against the anaerobe Bacteroides fragilis. Thus cefoxitin is useful in patients with intra abdominal sepsis & pelvic inflammatory disease. Cefuroxime has a longer half life & crosses the blood brain barrier. It can be used for community acquired pneumonia.
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3. Third generation:
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  \item These cephalosporins have assumed an important role in the treatment of infectious diseases. 3\textsuperscript{rd} generation agents include cefotaxime, ceftriaxone, ceftazidime, cefoperazone, ceftizoxime & cefixime. The major features of these drugs are their gram –ve coverage & the ability of some to cross the blood brain barrier. Although inferior to 1\textsuperscript{st} generation cephalosporins in regard to their activity against gram +ve cocci, the 3\textsuperscript{rd} generation cephalosporins have enhanced activity against gram –ve bacilli, including those mentioned above, as well as most other enteric organisms plus serratia.
\end{itemize}
Ceftazidime has activity against *Pseudomonas aeruginosa*. Ceftriaxone or cefotaxime have become agents of choice in the treatment of meningitis. Ceftriaxone has the largest half life of any cephalosporin (6-8hrs), which permits once a day dosing. It is effective against penicillin resistant *Neisseria gonorrhoeae*. The drug is excreted in bile & is frequently employed in patients with renal insufficiency. It has a good penetration into bone. Cefixime is administered orally once daily.

4. **Fourth generation**: cefepime is classified as a 4th generation cephalosporin & must be administered parenterally. Cefepime has a wide antibacterial spectrum, being active against streptococci & staphylococci. Cefepime is also effective against aerobic gram –ve organisms, such as *Enterobacter*, *P.mirabilis*, *E.coli*, *K.pneumoniae* and *P.aeruginosa*.
**Resistance:** Mechanisms of bacterial resistance to the cephalosporins are essentially the same as those described for the penicillins. Although they're not susceptible to hydrolysis by the staphylococcal penicillinas; cephalosporins maybe susceptible to extended-spectrum β-lactamases.

**Pharmacokinetics:**
1. **Administration:** most of the cephalosporins must be administered I.V or I.M because of their poor oral absorption. Cephalexin, cefadroxil, cefaclor, & cefixime are administered orally.
2. **Distribution:** Adequate therapeutic levels in the CSF, regardless of inflammation are achieved only with 3rd generation cephalosporins. For example, ceftriaxone or cefotaxime are effective in the treatment of neonatal and childhood meningitis caused by H. influenzae. All cephalosporins cross the placenta.
3. **Fate:** elimination of cephalosporins occurs through tubular secretion &/or glomerular filtration. Therefore doses must be adjusted in cases of severe renal failure. Ceftriaxone is excreted through the bile into the feces.

**Adverse effect:**
1. **Allergic manifestation:** the cephalosporins should be avoided or used with caution in individuals who are allergic to penicillins (5–15% show cross sensitivity). In contrast, the incidence of allergic reactions to cephalosporin is 1–2% in patients without history of an allergy to penicillins.

2. **Disulfiram-like effect:** when cefamandole, cefotetan or cefoperazone is ingested with alcohol, a disulfiram-like effect is seen. This occurs because they
block the second step in alcohol oxidation, which results in the accumulation of acetaldehyde. The toxicity is due to the presence of the methyl thio tetrazol (MTT) group.

3. Bleeding: bleeding also associated with agents that contain the MTT group because of anti-vitamin K effects.

(3) Carbapenems:
Carbapenems are synthetic β-lactam antibiotics. Imipenem, meropenem and ertapenem are the only drugs of this group currently available. Imipenem is compounded with cilastatin to protect it from metabolism by renal dehydropeptidase.

**Antibacterial spectrum:**
Imipenem/cilastatin & meropenem are the broadest-spectrum β-lactam antibiotics preparations currently available. Imipenem resists hydrolysis by most β-lactamases, but not the metallo-β-lactamases. The drug plays a role in empiric therapy, because it is active against penicillinase-producing gram +ve & -ve organisms, anaerobes & P. aeruginosa. Meropenem has antibacterial activity similar to that of imipenem. Ertapenem is not an alternative for P. aeruginosa.
**Pharmacokinetics:**

- Imipenem & meropenem are administered I.V & penetrate well into body tissue & fluids, including the CSF when the meninges are inflamed. They're excreted by glomerular filtration.

- Imipenem undergoes cleavage by a dehydropeptidase found in the brush border of the proximal renal tubule. This enzyme forms an inactive metabolite that is potentially nephrotoxic. Compounding the imipenem with cilastatin protects the parent drug & thus prevents the formation of the toxic metabolite. This allows the drug to be used in the treatment of UTIs. Meropenem doesn't undergo metabolism.

**Adverse effects:** imipenem/cilastatin can cause vomiting & diarrhea. Eosinophilia & neutropenia are less common. High levels of imipenem may provoke seizures.

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(4) **Monobactams:**

- These drugs are with a monocyclic \(\beta\)-lactam ring. Aztreonam, which is the only commercially available monobactam, is resistant to the action of \(\beta\)-lactamases. Aztreonam is active against gram -ve rods primarily the enterobacteriaceae. It has no activity against gram +ve bacteria or anaerobes. This narrow antimicrobial spectrum precludes its use alone in empiric therapy.

- Aztreonam is administered either I.V or I.M & is excreted in the urine. This drug is relatively nontoxic & has a low immunogenic potential. Thus, it may offer a safe alternative for treating patients who are allergic to penicillins &/or cephalosporins.
**ß-lactamase inhibitors:**

- ß-lactamase inhibitors such as clavulanic acid, sulbactam & tazobactam contain a ß-lactam ring, but by themselves don't have significant antibacterial activity. Instead, they bind to & inactivate ß-lactamases, thereby protecting the antibiotics that are normally substrates for these enzymes.
- They're potent inhibitors of many but not all bacterial ß-lactamases. ß-lactamase inhibitors are most active against ß-lactamases produced by staph., H.influenzae, gonococci, salmonella, shigella, E.coli & K.pneumoniae. They're not good inhibitors of ß-lactamases produced by pseudomonas & enterobacter.

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**VANCOMYCIN**

Vancomycin is a tricyclic glycopeptides that has become increasingly important. Bacitracin is a mixture of glycopeptides that also inhibits bacterial cell wall synthesis; however, its use is limited to topical application because of its potential for nephrotoxicity. Vancomycin inhibits synthesis of bacterial cell wall phospholipids as well as peptidoglycan polymerization.

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**Antibacterial spectrum:**

- Vancomycin is effective primarily against gram +ve organisms. It's been life saving in the treatment of methicillin-resistant staph aureus (MRSA) & methicillin-resistant staph epidermidis (MRSE) infections, as well as enterococcal infections. Vancomycin is used in the treatment of serious infections caused by ß-lactam resistant gram +ve microorganisms & in patients with gram +ve infections who have a serious allergy to the ß-lactams.
Oral vancomycin is limited to treatment for potentially life threatening antibiotic associated colitis due to C. difficile or staph. Vancomycin is used in individuals with prosthetic heart valves & in patients undergoing implantation with prosthetic devices. Vancomycin acts synergistically with aminoglycosides & this combination can be used in the treatment of enterococcal endocarditis.

**Resistance**: vancomycin resistance can be caused by plasmid-mediated changes in the permeability to the drug or by decreased binding of vancomycin to receptor molecules.

**Pharmacokinetics**: Slow I.V infusion is employed for treatment of systemic infections or prophylaxis. Because vancomycin is not absorbed after oral administration, this route is only employed for the treatment of antibiotic induced colitis due to c. difficile when metronidazole has proven ineffective. Inflammation allows penetration into the meninges. However, it is often necessary to combine vancomycin with other antibiotics, such as ceftriaxone. Metabolism of the drug is minimal & 90-100% is excreted by glomerular filtration.

**Adverse effect**: Side effects are a serious problem & include fever, chills & phlebitis at the infusion site. Flushing (red man syndrome) & shock results from histamine release. Dose related hearing loss has occurred in patients with renal failure. Ototoxicity & nephrotoxicity are more common when vancomycin is administered with another drug that can also produce these effects.

**Daptomycin**
Is a cyclic lipopeptide antibiotic that is an alternative to other agents such as linezolid and quinupristin – dalfopristin, for treating infections caused by resistant gram-positive organisms, including MRSA and vancomycin-resistant enterococci (VRE).