

Miscellaneous Antibiotics

This session will be held as a team-based learning session. Additional details regarding the organization of this session will be provided shortly before the session. It will however be held in the usual HHSC lecture hall room 401. In preparation for the session please read the syllabus below. The following references are also worth reviewing for additional information:

1. **Fluoroquinolones in UptoDate -**
http://www.uptodate.com/online/content/topic.do?topicKey=antibiot/8621&selectedTitle=1~150&source=search_result
2. **Trimethoprim-sulfamethoxazole in Upto Date –**
http://www.uptodate.com/online/content/topic.do?topicKey=antibiot/9295&selectedTitle=1~150&source=search_result
3. **Metronidazole in UptoDate -**
http://www.uptodate.com/online/content/topic.do?topicKey=antibiot/10108&selectedTitle=4~150&source=search_result
4. **Daptomycin – article by Carpenter and Chambers at the end of the syllabus**
<http://www.journals.uchicago.edu/doi/pdf/10.1086/383472>

Syllabus

Quinolones

Introduction: The quinolone family of antibiotics first came into use in the mid 1980's. They are an increasingly important family of antibiotics because they can be administered orally and parenterally, they are active against a broad spectrum of bacteria including a number of common nosocomial pathogens, and they have limited toxicity.

Chemical Structure: Quinolones have a bicyclic aromatic core with a nitrogen at position 1, a carbonyl at position 4 and a carboxyl group attached to carbon at C3. The ring structures vary depending on the compound however the derivatives are still referred to as quinolones. Alterations of both the basic ring structure and the side chains alter the activity and pharmacology of the agents.

Mechanism of Action: As a family, quinolones are bactericidal. They have several sites of action. 1) They bind DNA-DNA gyrase (topoisomerase II) complex and block further DNA replication. 2) They also block topoisomerase IV interfering with the separation of interlocked, replicated DNA molecules. 3) There appear to be other, as yet undefined, mechanisms of killing that may involve RNA and protein synthesis.

Mechanism of Resistance: Because of the widespread use of these drugs, the emergence of quinolone resistant strains has been a major problem. Resistance can emerge by mutations in either the topoisomerase II or IV genes. In addition, several active efflux pumps have also been demonstrated in both Gram positive and negative bacteria. Resistance can emerge during therapy.

Antibacterial spectrum: The different quinolones have varied antibacterial spectrums. The first generation drugs, *e.g.*, nalidixic acid, are active only against Gram negatives. The second generation drugs, such as the fluoroquinolones, have enhanced coverage against pseudomonas and they also have Gram positive activity including staphylococcus. The newer agents – third generation quinolones, have activity against the above agents as well as legionella, mycoplasma and some include the anaerobes.

Pharmacology: Quinolones are well absorbed orally and most can also be administered parenterally. The ability to switch from parenteral to oral therapy is an advantage. They are extremely well distributed achieving high concentrations in most tissues and fluids. CSF concentrations are lower than the serum. One additional advantage of these compounds is their ability to achieve high intracellular concentrations, thus enhancing their activity against intracellular pathogens. Most quinolones are eliminated by the kidneys.

Toxicity: Quinolones are well tolerated. Allergic reactions including fever and rash can occur. Photosensitivity can occur, especially with quinolones having a fluorine or chloride at the C8 position. Gastrointestinal and CNS effects as well as tendinitis are also described.

Indications for use: Quinolones are used for the empiric treatment of community-acquired pneumonia, infectious diarrhea and sexually transmitted diseases. They are also used for the treatment of serious infections caused by susceptible pathogens. Some of the quinolones have activity against *M. tuberculosis* and have been used in combination therapy to treat drug-resistant tuberculosis.

Trimethoprim-Sulfamethoxazole

Introduction: Trimethoprim-sulfamethoxazole is a fixed drug combination that combines two compounds that block folate synthesis. Originally developed in the 1960's, this combination has remained an important and useful antimicrobial preparation.

Chemical Structure: Trimethoprim-sulfamethoxazole combines two agents. Trimethoprim is a pyrimidine that was synthesized as a dihydrofolate reductase inhibitor with the goal of sequentially inhibiting folate synthesis by potentiating sulfa activity.

Sulfamethoxazole is a paraaminobenzoic acid (PABA) inhibitor. A sulfur atom must be directly linked to the benzene ring for the antimicrobial activity. A free amino group at the C4 position is associated with enhanced activity. Substitutions at the N1 position can change the pharmacological and antimicrobial properties of the compound.

Mechanism of Action: The two agents are sequential inhibitors of folic acid synthesis. Sulfamethoxazole is a structural analogue of PABA and competes for the enzyme dihydropteroate synthetase. This results in a reduced amount of dihydropteroic acid that is available for the second step in the folic acid synthesis pathway. Trimethoprim is a competitive inhibitor of the enzyme dihydrofolate reductase, the next step in the biosynthetic pathway. Of note mammalian cells do not synthesize folate, they require preformed folate and this accounts for the relatively targeted activity of the combination for bacteria.

Mechanism of Resistance: The frequency of resistance to the combination was initially low because of the need for more than one mutation, however resistance has increased over the years. For sulfamethoxazole, resistance occurs as the result of decreased permeability (most common) or increased production of PABA. For trimethoprim, resistance develops due to the synthesis of an enzyme with altered affinity for TMP or by the overproduction of dihydrofolate reductase.

Antibacterial spectrum: TMP-SMZ is a broad-spectrum antimicrobial agent. It has activity against Gram negatives including *E. coli*, klebsiella, vibrio, shigella, neisseria and *H. influenzae*. It is also active against Gram positives including staphylococci, streptococci, listeria, but not enterococci. TMP-SMZ also has activity against pneumocystis, nocardia, malaria and chlamydia.

Pharmacology: TMP-SMZ is combined in a 1:5 ratio that achieves a serum ratio of 1:20. This is the optimal ratio for synergistic activity. The agent is available both orally and parenterally and achieves excellent tissue distribution including the lungs, kidneys, prostate, biliary tree and the central nervous system.

Toxicity: There is a long list of potential side effects. The most common toxicity (~5%) is hypersensitivity reactions including fever and rash. The rash can be severe in rare cases progressing to the life-threatening Stevens Johnson syndrome. Other side effects include gi symptoms, and rarely megaloblastic anemia or renal insufficiency.

Indications for use: TMP-SMZ is used for the treatment of urinary tract infections, prostatitis, and diarrheal diseases. There has unfortunately been an increase in the amount of resistance to TMP-SMZ in the past 10 years. TMP-SMZ is the drug of choice for the treatment of *Pneumocystis carinii* pneumonia in HIV-infected subjects. It is also useful in selected miscellaneous infections caused by nocardia and *B. cepacia*.

Metronidazole

Introduction: Introduced in 1959 this agent has a broad range of activity that includes anaerobic bacteria as well as a variety of parasites.

Chemical Structure: Low molecular weight nitroimidazole

Mechanism of Action: Reduction of metronidazole following uptake by the bacteria results in the release of intermediate products. These products or free radicals damage DNA as well as other cellular macromolecules. Bactericidal against susceptible bacteria.

Mechanism of Resistance: Resistance is rare in part due to the need for multiple steps to be altered for resistance to emerge. Resistance is conferred through a reduction in pyruvate:ferredoxin oxidoreductase activity, which limits cellular uptake of metronidazole and subsequent activation.

Antibacterial spectrum: Most Gram negative anaerobes including bacteroides. Some Gram positive anaerobes - clostridia (including *C. difficile*). Also *Gardnerella vaginalis*, *Helicobacter pylori*, *Trichomonas vaginalis*, giardia.

Pharmacology: Can be administered orally, parenterally, vaginally and rectally. Extremely well distributed including CNS. T_{1/2} 8h. Metronidazole and most metabolites are excreted in the urine.

Toxicity: Generally well tolerated. Can cause nausea and vomiting, rarely CNS symptoms. There is a disulfiram effect with alcohol. It also interferes with metabolism of warfarin (anticoagulant). Generally not used in pregnancy due to concern for mutagenicity (not proven).

Indications for use: Used for parasitic infections such as trichomonas, giardia, also for anaerobic infections such as bacteroides infections, *C. difficile* associated diarrhea, and peptic ulcer disease associated with *H. pylori*.

Daptomycin

Introduction: Drug that was redeveloped in part due to increasing need for new drugs with activity against antimicrobial resistant Gram positive bacteria.

Chemical Structure: A new class of antibiotic – 13-member amino acid cyclic lipopeptide with a decanoyl tail.

Mechanism of Action: Bactericidal antibiotic inserts into the bacterial cell membrane, causing membrane depolarization and potassium efflux. Results in loss of cell viability.

Mechanism of Resistance: Clinical isolates with reduced susceptibility to daptomycin have been reported. The mechanism of resistance is uncertain.

Antibacterial spectrum: Active against Gram positive bacteria including staphylococci, pneumococci, enterococci.

Pharmacology: Only available parenterally. T_{1/2} 9h. Cleared via the kidney. Does not achieve adequate levels in the lung to treat pneumonia.

Toxicity: Gastrointestinal problems, concern about muscle discomfort, increased CPK.

Indications for use: resistant Gram positive bacterial infections such as MRSA or VRE. Used for skin/soft tissue infections, endocarditis, bacteremias.