Drugs Used for Urinary Tract Infections

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Drugs Used in Urinary Tract Infetions

- **Include penicillins and 2nd and 3rd generation cephalosporins (cefuroxime and ceftriaxone), ampicillin + gentamicin, or ampicillin-sulbactam, amxicillin/clavulanate ……**

Trimethoprim

- **It inhibits bacterial dihydrofolate reductase which converts dihydrofolic acid to tetrahydrofolic acid (the active form of folic acid) which is needed for synthesis of purines and DNA.**
- **Pyrimethamine is similar, but inhibit protozoal dihydrofolate reductase.**
- **In combination with sulfamethoxazole (co-trimoxazole) sequential steps in folate synthesis are blocked → synergism of activity of both drugs.**
- **The combination is bactericidal.**

Trimethoprim

Mechanisms of Resistance:

1. **Reduced cell permeability.**
2. **Overproduction of dihydrofolate reductase.**
3. **Altered reductase with low binding to drug (most important clinically).**

Trimethoprim

Pharmacokinetics:

- Absorbed after oral administration.
- Can be given IV in combination with sulfamethoxazole.
- Distributed widely in body fluids and tissues.
- Excreted in urine partially as metabolites.
- Dose should be reduced in renal failure.
- It concentrates in prostatic and vaginal fluids, which are more acidic than plasma.

Trimethoprim

Therapeutic Uses:

1. **Acute UTI (oral), either alone or in combination with sulfamethoxazole (Co-trimoxazole).**
2. **Prostatitis.**
3. **Salmonellosis.**
4. **Shigellosis.**
5. **Infections with *Pneumocystis jiroveci*. (IV infusion).**

Trimethoprim

Adverse Effects:

1. **Megaloplastic anemia, leukopenia and granulocytopenia.**
2. **The combination with sulfonamides may cause all the side effects of sulfonamides.**
3. **Patients with AIDS and pneumocystis pneumonia have high frequency of adverse reactions to trimethoprim-sulfamethoxazole, especially fever, rash, leukopenia, diarrhea, elevation of liver enzymes.**
4. **Hyperkalemia and hyponatremia (by blocking amiloride-sensitive sodium channels in the cortical collecting duct)**

Fluoroquinolones

Mechanism of Action:

- They block bacterial DNA synthesis by inhibiting bacterial topoisomerase II (DNA gyrase) and topoisomerase IV.
- Inhibition of DNA gyrase prevents the relaxation of positively supercoiled DNA that is required for transcription and replication.
- Inhibition of topoisomerase IV interferes with separation of replicated chromosomal DNA into daughter cells during cell division.

Fluoroquinolones

Mechanisms of Resistance:

- One or more point mutations in the quinolone binding region of the target enzyme or change in the permeability of bacterial cell.

Antibacterial Spectrum:

1. Norfloxacin is the least active against both gram negative and gram positive bacteria.

Fluoroquinolones

2. Ciprofloxacin, levofloxacin, and ofloxacin have:

- **Excellent gram negative activity (Enterobacteriaceae, Pseudomonas, Neisseria, Haemophilus and Campylobacter).**
- **Moderate to good activity against gram positive bacteria.**
- **Active against staphylococci but not methicillin-resistant strains.**
- **Streptococci and enterococci are less susceptible.**
- **Ciprofloxacin is the most active against *Pseudomonas aeruginosa*.**
- **Levofloxacin has superior activity against *Streptococcus pneumoniae*.**

Fluoroquinolones

3. **Gemifloxacin and Moxifloxacin make up a third group of fluoroquinolones with improved activity against gram positive bacteria, particularly *Streptococcus pneumoniae* and some staphylococci.**

- **Moxifloxacin has good activity against anaerobic bacteria also.**
- **Fluoroquinolones are also active against agents of atypical pneumonia (*Mycoplasma* and *Chlamydia*) and against intracellular pathogens such as *Legionella* and *Mycobacteria*.**

Fluoroquinolones

Pharmacokinetics:

- Well absorbed after oral administration.
- Oral absorption is impaired by divalent cations including those in antacids, and dairy products.
- Distributed widely in body fluids and tissues.
- Most are eliminated by renal mechanisms (tubular secretion or glomerular filtration).
- Dose reduction is required in renal failure, except for moxifloxacin (hepatic elimination). t½ ~ 3-10 hours

Fluoroquinolones

Therapeutic Uses:

1. **Urinary tract infection (except moxifloxacin) caused by multidrug-resistant gram negative bacteria.**
2. **Bacterial diarrhea caused by *Shigella*, *Salmonella* and toxigenic *E. coli* and *Campylobacter*.**
3. **Soft tissue, bone and joint, intraabdominal, and respiratory tract infections (except norfloxacin), including those caused by multidrug-resistant organisms such as *Pseudomonas* and *Enterobacter*.**

Fluoroquinolones

4. **Ciprofloxacin is the drug of choice for prophylaxis and treatment of anthrax.**
5. **Gonococcal infections, including disseminated disease (ciprofloxacin and levofloxacin), and chlamydial urethritis and cervicitis.**
6. **Ciprofloxacin, levofloxacin or moxifloxacin are among second-line agents for tuberculosis.**

Fluoroquinolones

7. Eradication of meninigococci from carriers.
8. Prophylaxis of infection in neutropenic patients.
9. Upper and lower respiratory tract infections (levofloxacin, gatifloxacin, gemifloxacin, and moxifloxacin because of gram positive and atypical bacteria activity).

Fluoroquinolones

Adverse Effects:

1. **Nausea, vomiting and diarrhea.**
2. **Headache, dizziness, insomnia, skin rash or abnormal liver function tests.**
3. **Photosensitivity.**
4. **QTc prolongation can occur with gatifloxacin, levofloxacin, gemifloxacin and moxifloxacin → arrhythmogenic.**

Fluoroquinolones

5. **Hyperglycemia has been associated with gatifloxacin even in patients receiving oral hypoglycemic agents.**
6. **Damage of growing cartilage and development of arthropathy. Should not be used in patients under 18 years of age. Arthropathy is reversible (?!).**
7. **Tendonitis and tendon rupture have been reported in adults.**
8. **Contraindicated in pregnancy.**

Nitrofurantoin

- **Is a prodrug, activated to metabolites that damage bacterial DNA.**
- **Bacteriostatic.**
- **Active against *E. coli* and enterococci.**
- ***Pseudomonas, Proteus, Enterobacter* and *Klebsiella* are resistant.**
- **Should not be used in patients with impaired renal function or below 1 month of age.**
- **It should be avoided in pyelonephritis because it does not achieve therapeutic levels outside urine.**

Nitrofurantoin

Adverse Effects:

1. **Nausea, vomiting and diarrhea are the most common.**
2. **Hypersensitivity reactions.**
3. **Acute pneumonitis.**
4. **Interstitial pulmonary fibrosis.**
5. **Hemolysis in G6PD deficient patients and megaloblastic anemia.**
6. **Polyneuropathies.**
7. **Colors urine brown.**