بسم الله الرحمن الرحيم

Drugs used in UTIs

FINAL | Lecture 4

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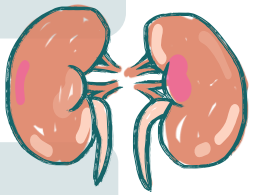
﴿قُلْ بِفَضْلِ ٱللَّهِ وَبِرَحْمَتِهِۦ فَبِذَٰلِكَ فَلْيَفْرَحُوا۟ هُوَ خَيْرٌ مِّمَّا يَجْمَعُونَ﴾



Drugs Used for Urinary Tract Infections

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Drugs Used in Urinary Tract Infetions

Include:

1. **Penicillins and 2nd and 3rd generation cephalosporins (cefuroxime and ceftriaxone), ampicillin + gentamicin, or ampicillin-sulbactam, amxicillin/clavulanate ……).**
2. **Trimethoprim/sulfamethoxazole (Co-trimoxazole).** Trimethoprim can be used alone, but its combination with sulfamethoxazole produces a more profound effect. **Sulfamethoxazole** is the only sulfonamide commonly used clinically because other sulfonamides can cause adverse effects such as precipitation in the kidneys, leading to kidney damage.
3. **Fluoroquinolones** such as levofloxacin and moxifloxacin.
4. **Nitrofurantoin.**

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.** When you inhibit it, bacterial division is inhibited.
- **Pyrimethamine is similar, but inhibit protozoal dihydrofolate reductase.**
- **In combination with sulfamethoxazole (co-trimoxazole)** inhibit the **sequential steps in folate synthesis are blocked → synergism of activity of both drugs.** Sulfamethoxazole inhibits dihydropteroate synthase, while trimethoprim inhibits dihydrofolate reductase, preventing the conversion of dihydrofolic acid to tetrahydrofolic acid.
- **The combination is bactericidal.**

Trimethoprim

Mechanisms of Resistance: We study mechanisms of resistance to understand how to deal with **similar** drugs.

1. **Reduced cell permeability.** By altering the bacterial cell membrane within the cell wall (the antibiotic will not reach its site of action).
2. **Overproduction of dihydrofolate reductase.** To bypass the inhibition.
3. **Altered reductase with low binding** affinity **to the drug (most important clinically).**

Trimethoprim

Pharmacokinetics:

- **Absorbed after oral administration.**
- **Can be given IV in combination with sulfamethoxazole.**
- Can be used orally or intravenously depending on the infection severity.
- **Distributed widely in body fluids and tissues.** Including renal tissues, prostatic tissues, and vaginal fluids.
- **Excreted in urine partially as metabolites.** It should be filtered into the urine to reach the site of infection within the urinary system.
- **Dose should be reduced in renal failure.**
- **It concentrates in prostatic and vaginal fluids, which are more acidic than plasma.** Chronic UTIs may lead to prostatitis, which is more difficult to treat; therefore, antibiotics that can penetrate the prostatic tissue are required, as not all drugs achieve adequate tissue concentrations. **Fluoroquinolones** and **trimethoprim** can reach these sites.

Trimethoprim

Therapeutic Uses:

1. **Acute UTI (oral), either alone or in combination with sulfamethoxazole (Co-trimoxazole).**
2. **Prostatitis.**
3. **Salmonellosis.** Salmonella typhi, and Salmonella enterica serovar Typhimurium that causes diarrhea.
4. **Shigellosis.** trimethoprim is NOT the drug of choice, but it may be used in some cases.
5. **Infections with *Pneumocystis jiroveci*. (IV infusion).**

   Causes pneumonia in immunocompromised patients.

Related to UT

Trimethoprim

Adverse Effects:

1. **Megaloplastic anemia,** bone marrow suppression **(leukopenia and granulocytopenia).** Due to possible inhibition of **human dihydrofolate reductase.**
2. **The combination with sulfonamides may cause all the side effects of sulfonamides.** "Sulfonamides adverse effects" *see the next slide*
3. **Patients with AIDS and pneumocystis *jiroveci* 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,** which mediate Na^+ reabsorption in exchange for K^+ secretion**).**

Sulfonamides commonly cause rash, so to remember adverse effects of sulfonamides, one must know ABC of RASH.

A – **A**plastic anemia
B – **B**ilirubin displacement (kernicterus)
C – **C**rystalluria
R – **R**ash (MC side effect)
A – **A**cetylation
S – **S**LE
H – **H**emolysis in G-6-PD deficiency

Extra figure

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

Mode of Resistance:

- **One or more point mutation in the quinolone binding region of the target enzyme** (topoisomerase II or topoisomerase IV) **or change in the permeability of bacterial cell** that prevents antibiotic entry.

Antibacterial Spectrum:

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

Fluoroquinolones

The most common causative organism of urinary tract infection (UTI) is Escherichia coli. Other Gram-negative bacteria are more commonly seen in hospitalized patients, complicated UTIs, or in patients with urinary tract obstruction.

2. Ciprofloxacin, levofloxacin, and ofloxacin have:

- Initially, ciprofloxacin was the drug for gram-negative infections.
- **Excellent gram negative activity (Enterobacteriaceae** (E.coli, klebsiella)**, Pseudomonas, Neisseria, Haemophilus and Campylobacter).**
- **Less active against gram positive bacteria** except **levofloxacin**.
- **Active against staphylococci but NOT methicillin-resistant strains;** these require **Linezolid or Vancomycin**.
- **Streptococci and enterococci are less susceptible.**
- **Ciprofloxacin is the most active against *Pseudomonas aeruginosa*** (among the fluroquinolones)
- **Levofloxacin has superior activity against *Streptococcus pneumoniae*** that's why it is considered a respiratory fluroquinolones.

Fluoroquinolones

3. **Gemifloxacin and Moxifloxacin make up the second and third group of respiratory 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*.**
  - ✓ Because they can enter the cells (not all drugs reach them).

Fluoroquinolones

Pharmacokinetics:

- **Well absorbed after oral administration.**
- **Oral absorption is impaired by divalent cations** (Mg++ , Ca++) **including those in antacids, and dairy products.**
  - Fluoroquinolones should not be taken with milk, dairy products, because they can become chelated.
  - **Chelation** means that the drug binds to metal ions and forms a complex that cannot be absorbed from the intestine. As a result, the absorption of the antibiotic decreases significantly, and the drug may be lost in the stool instead of entering the bloodstream. Therefore, the effectiveness of the medication is reduced.
- **Distributed widely in body fluids and tissues.**
- **Most are eliminated by renal mechanisms (tubular secretion or glomerular filtration).**
  - Drug interactions can occur between medications that are actively secreted into the urine because they compete with each other for the same active transport mechanism in the renal tubules. As a result, the secretion of one or both drugs may be reduced, leading to decreased elimination and increased drug levels in the body.

Next slide..

Fluoroquinolones

Pharmacokinetics:

- **Dose reduction is required in renal failure, except for moxifloxacin (hepatic elimination).**
  - considered a respiratory and anaerobic fluoroquinolone, because it is primarily metabolized in the liver rather than being excreted unchanged by the kidneys.
- **t½ ~ 3-10 hours.** Given once or twice daily

Fluoroquinolones

Therapeutic Uses:

1. **Urinary tract infection (except moxifloxacin) caused by multidrug-resistant gram negative bacteria.**
   - Urinary tract infections are mainly caused by gram-negative bacteria, especially E. coli, although other gram-negative organisms may also be involved. Gram-positive bacteria can also cause UTIs, particularly Group B Streptococcus, especially during pregnancy. Fluoroquinolones are active against Streptococcus pneumoniae, but they are NOT reliably active against GBS. They are commonly used for gram-negative infections such as UTIs
2. **Bacterial diarrhea caused by *Shigella*, *Salmonella* and toxigenic *E. coli* and *Campylobacter*.** Single or two doses treat the infection
3. **Soft tissue, bone** (Few drugs) **and joint, intraabdominal, and respiratory tract infections (except norfloxacin), including those caused by multidrug-resistant organisms such as *Pseudomonas* and *Enterobacter*.**

**Not all drugs identical

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** in females. If the infection occurs in a married woman, the husband should also be treated to prevent reinfection.
    - Other drugs are commonly used for gonococcal infections, like Ceftriaxone.
6. **Ciprofloxacin, levofloxacin or moxifloxacin are among second- line agents for tuberculosis.**

Fluoroquinolones

7. **Eradication of meninigococci from carriers.** Also rifampin and ceftriaxone may be used
8. **Prophylaxis of infection in neutropenic patients.**
   - Very severe immunosuppressed ,they may have infection without fever, so diagnosis will be affected.
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.** After oral administration
2. **Headache, dizziness, insomnia, skin rash or abnormal liver function tests** (Doesn't always mean liver toxicity) **.**
3. **Photosensitivity.**
   - Exposure to UV light from the sun can trigger histamine release and produce skin reactions that resemble allergy; however, this is not a true allergic reaction. It is called **photosensitivity**. Some drugs, such as Morphine and certain muscle relaxants, can also cause direct histamine release and produce allergy-like signs and symptoms without involving an actual immune allergy. In photosensitivity reactions, UV light induces histamine release in the skin, leading to redness, irritation, and increased sensitivity to sunlight.
4. **QTc prolongation can occur with gatifloxacin, levofloxacin, gemifloxacin and moxifloxacin → arrhythmogenic.**
   - This may lead to polymorphic ventricular tachycardia and serious cardiac arrhythmias.
   - ✓ **Levofloxacin** is especially important because it is active against both gram-negative and gram-positive bacteria.
   - Before prescribing these drugs, it is important to evaluate whether the patient has any underlying cardiac problems or risk factors for QT prolongation.

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 (?!).** (Before closure of epiphysis, because it will affect growth)
7. **Tendonitis and tendon rupture have been reported in adults.** (Rare)
8. **Contraindicated in pregnancy.**

Nitrofurantoin

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

Because the concentration in kidney will be very low and not sufficient to eradicate the microorganism.

Nitrofurantoin

Adverse Effects:

1. **Nausea, vomiting and diarrhea are the most common.**
   - Although any medication can potentially cause these symptoms in certain patients, they are considered genuine and significant adverse reactions when they occur in a noticeable percentage of patients. When a drug is given orally, nausea and vomiting may cause the patient to expel the medication, while diarrhea can increase intestinal motility and may lead to loss of the drug from the body before adequate absorption occurs.
2. **Hypersensitivity reactions.**
3. **Acute pneumonitis.**
4. **Interstitial pulmonary fibrosis.**
   - Nitrofurantoin is not considered an ideal choice for treating infections in many situations, but it may still be used when there is contraindication or resistance to other known antibiotics.
5. **Hemolysis in G6PD deficient patients and megaloblastic anemia.**
6. **Polyneuropathies.** Which means abnormalities in the nerve sensation or motor activity can be affected
7. **Colors urine brown.** Not dangerous ,it is a stain from the same drug. But it is important to tell patient about this.

PHARMACOLOGY QUIZ

LECTURE 4

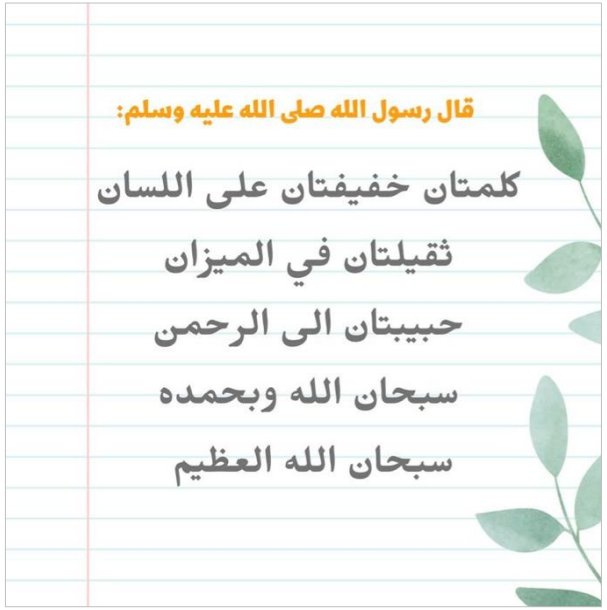
External Resources

رسالة من الفريق العلمي

Additional sources:

1. Dr. Fouda

اللهم إن عمر عطية في ذمتك وحبل جوارك، فقِه من فتنة القبر وعذاب النار، أنت أهل الوفاء والحق، فاغفر له وارحمه إنك أنت الغفور الرحيم.



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Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
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