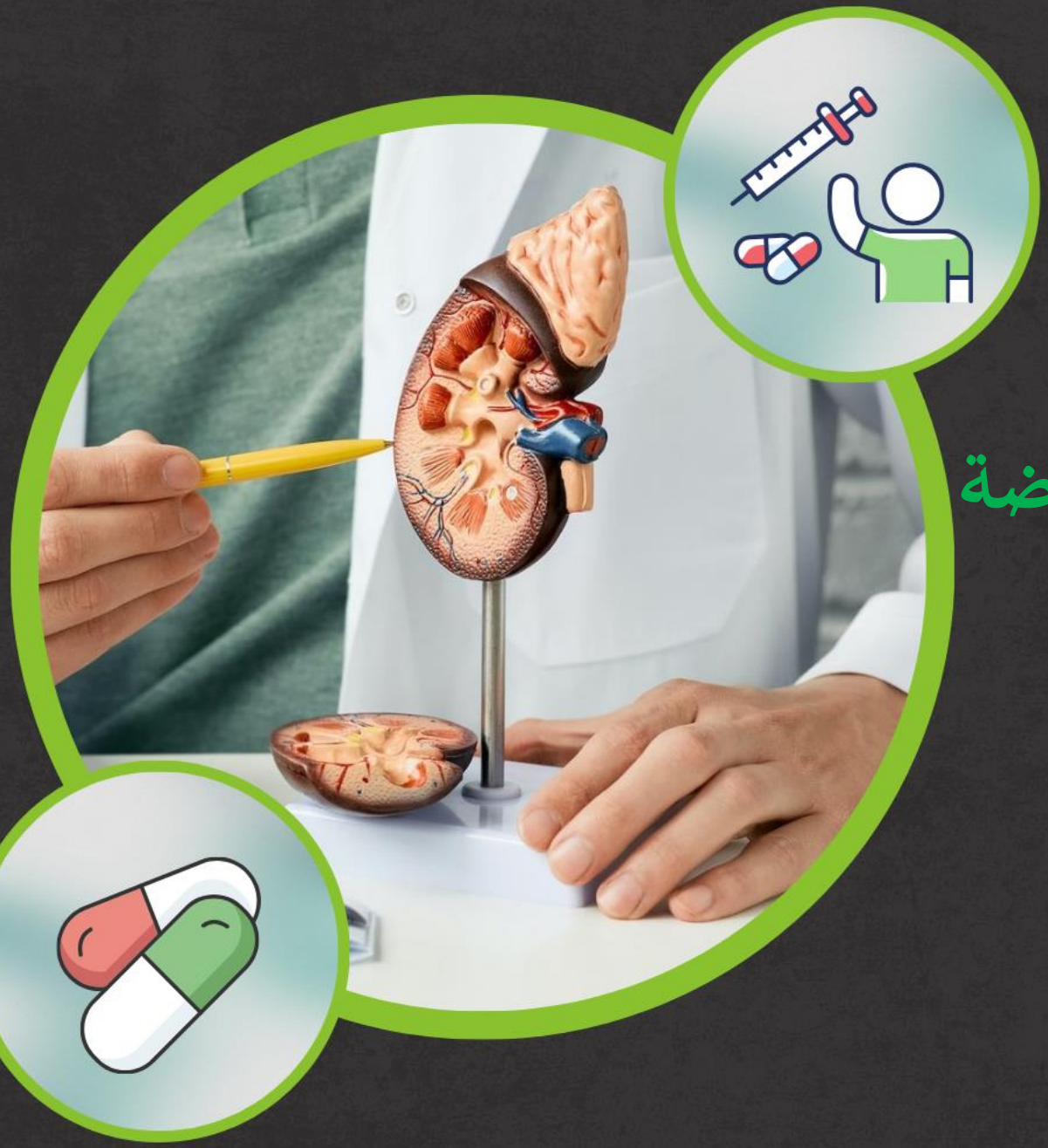

PHARMA

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الكُتّاب: سرى علي وإسماعيل العارضة

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Drugs Used for Urinary Tract Infections

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Color code

- Slides
- Doctor
- Additional info
- Important

Drugs Used in Urinary Tract Infetions

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

- We are going to talk about 3 drugs in this lecture:

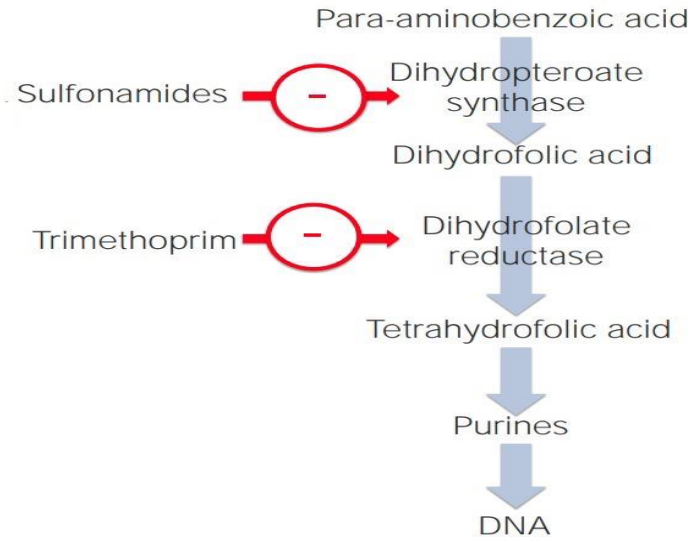
1) Trimethoprim (with or without sulfamethoxazole).
2) Fluoroquinolones.
3) Nitrofurantoin.

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** (for cell division)**.**
- **Pyrimethamine is similar** (in the pharmacology and mechanism of action)**, but inhibit protozoal dihydrofolate reductase** (more selective).
- **In combination with sulfamethoxazole (co-trimoxazole) sequential steps in folate synthesis are blocked → synergism of activity of both drugs.**
- **The combination is bactericidal.**

- Co-trimoxazole= trimethoprim+sulfamethoxazole in one dosage form.

- Co-trimoxazole is responsible for inhibition of the synthesis of dihydrofolic acid by inhibiting the dihydropetroate synthase enzyme which originally responsible for the synthesis of dihydrofolic acid,so by giving a combination, we will have a synergistic effect because we attack tetrahydrofolic acid formation which is the active form of folic acid at different steps.
- Trimethoprim is a bacteriostatic, also sulfamethoxazole is a bacteriostatic ,but the combination is a bactericidial.
- So, we give trimethoprim in a combination with sulfamethoxazole except if the patient has a contraindication to sulfa drugs in general, we give trimethoprim alone.



- Extra picture

- We attack tetrahydrofolic acid synthesis at two different levels.

Trimethoprim

- In antibiotics, when we talk about mechanism of action and therapeutic uses ,we have to talk about mechanisms of resistance because almost all antibiotics have a bacterial resistance to them.

Mechanisms of Resistance:

1. **Reduced cell permeability.** The bacteria cell wall won't be permeable for the drug ,so there isn't enough drug reach to produce it's action.
2. **Overproduction of dihydrofolate reductase.** The overproduction kinetically will lead to formation of tetrahydrofolate reductase either by the same mechanism or different mechanisms ,so there is a tetrahydrofolate reductase despite the inhibition of dihydrofolate reductase because of excess of dihydrofolate reductase.
3. **Altered reductase with low binding to drug (most important clinically).** Changes in dihydrofolate reductase biochemical structure which will have low affinity for binding of the drug (trimethoprim) strongly ,so the action will be impaired.

Trimethoprim

Pharmacokinetics:

- **Absorbed after oral administration.**
- **Can be given IV in combination with sulfamethoxazole** (We can give it alone or in combination).
- **Distributed widely in body fluids and tissues** to reach the site of action **.** (Very important)
- **Excreted in urine partially as metabolites.**
- **Dose should be reduced in renal failure.**
- **It concentrates** means that it reaches the site of action **in prostatic and vaginal fluids, which are more acidic than plasma.**

- When we talk about UTI, chronic or repetitive UTI mainly to prostatitis and prostate gland is one of the organs that have a poor penetration of antibiotics ,so infection of prostate are difficult to treat and require long duration of treatment.

Trimethoprim

Therapeutic Uses:

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

- It is active against salmonellosis and shigellosis ,but we have another drugs for these.

Adverse Effects:

1. **Megaloplastic anemia**(due to inhibition of folic acid synthesis.) **, leukopenia and granulocytopenia .**
2. **The combination with sulfonamides may cause all the sidebar 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.** (Pneumocystis pneumonia is caused in immunocompromised patients like AIDS patient ,who take immunosuppressant drugs ,diabetes and malnourished.)
4. **Hyperkalemia and hyponatremia (by blocking amiloride-sensitive sodium channels in the cortical collecting duct** so there is loss of Na+ and retention of K+.)

Fluoroquinolones

- Fluoroquinolones are a quinolones with florine groups.
- In the past, there is a drug used for UTI called nalidixic acid which is a quinolone not a fluoroquinolone.
- Fluoroquinolones inhibit bacterial cells at 2 sites.

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** (so the bacterial cells won't grow).

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.**

- They aren't only used for UTI and they are uses for other purposes.

Fluoroquinolones

2. Ciprofloxacin, levofloxacin, and ofloxacin have:

- Could be used for osteomyelitis.

- **Excellent gram negative activity** (they are among the first line drugs for that infection)**(Enterobacteriaceae, Pseudomonas, Neisseria, Haemophilus and Campylobacter).**
- **Moderate to good activity against gram positive bacteria.**
- But not strongly as in gram –ve bacteria.
- **Active against staphylococci but not methicillin-resistant strains.**
- **Streptococci and enterococci are less susceptible.**
- "Less" Not no susceptible.
- **Ciprofloxacin is the most active against *Pseudomonas aeruginosa*.**
- **Levofloxacin has superior activity against *Streptococcus pneumoniae*** Which cause pneumonia..

- You need to know all these informations.
- A possible question:
- What is the best Fluoroquinolones for pseudomonas aerginosa (which won’t cause UTI)?
- Answer: Fluoroquinolones.

Fluoroquinolones

- A newer Fluoroquinolones they come after ciprofloxacin, levofloxancin and ofloxacin.

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

- They are called respiratory fluoroquinolones because they are used in respiratory tract infection and the most common cause is streptococcus pneumoniae.

- **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*** which cause tuberculosis.

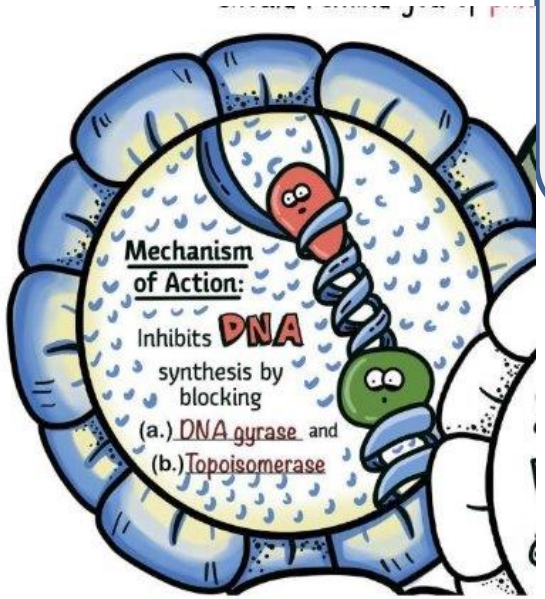
- Mycoplasma ,chlamydia and legiomella don't have a cell wall.

Fluoroquinolones

Pharmacokinetics:

- Well absorbed after oral administration.
- Oral absorption is impaired by divalent cations including those in antacids, and dairy products. ➡ Divalent cations such as calcium and magnesium. These cations are commonly found in antacids (e.g. calcium carbonate) and dairy products
- Distributed widely in body fluids and tissues. → which means they can effectively reach the sites of infection.
- 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

- Most fluoroquinolones are eliminated by the renal system.Therefore, dose adjustment is required in patients with renal dysfunction. An exception is moxifloxacin, which is eliminated by hepatic metabolism rather than by the kidneys. This means that moxifloxacin generally does not require dose adjustment in cases of renal impairment.



- The half-life of fluoroquinolones ranges from 3 to 10 hours, depending on the specific drug. A longer half-life (up to 10 hours) allows for once or twice-daily dosing.. In contrast, fluoroquinolones with shorter half-lives need to be administered more frequently.

Fluoroquinolones

Therapeutic Uses:

1. **Urinary tract infection (except moxifloxacin) caused by multidrug-resistant gram negative bacteria.**

Fluoroquinolones are commonly used to treat UTIs caused by multi-drug resistant gram-negative bacteria, primarily E. coli and Proteus species. Moxifloxacin, however, is not effective for UTIs because it achieves poor urinary concentrations and does not cover typical UTI pathogens effectively, especially since anaerobes are not the main causative agents of UTIs.

2. **Bacterial diarrhea caused by *Shigella*, *Salmonella* and toxigenic *E. coli* and *Campylobacter*.**

Toxigenic E. coli causes watery diarrhea, which can be severe. This strain becomes more virulent than typical E. coli by acquiring a toxin-producing gene, making it more dangerous.

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*.**

➡ Norfloxacin has weak activity.

➡ Bone infections are most commonly caused by Staphylococcus aureus.

➡ Infection often occurs following injury or fracture, allowing skin flora to enter and infect the bone, although other organisms can be involved.

Fluoroquinolones

4. Ciprofloxacin is the drug of choice for prophylaxis and treatment of anthrax.
5. Gonococcal infections, including disseminated disease (ciprofloxacin and levofloxacin), and atypical chlamydial urethritis and cervicitis.

Fluoroquinolones can penetrate vaginal fluid, which is essential for treating female genital tract infections

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 can be used for eradication of Neisseria meningitidis carriers, especially in close-contact groups such as Students in classrooms or soldiers sleeping in the same room . In such cases, a single prophylactic dose may be sufficient to eradicate the carrier state and prevent outbreaks.

Fluoroquinolones may be used for prophylaxis in neutropenic patients to prevent bacterial infections.

- prophylaxis involves long-term therapy which may come with consequences
  ➡️ This is different from empirical therapy, where antibiotics are started based on likely pathogens before a confirmed diagnosis. In prophylaxis, the goal is prevention, not treatment, and it's typically used in high-risk patients .

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.

should be avoided in patients with congenital long QT syndrome ‼️ ‼️ ‼️

Fluoroquinolones can cause photosensitivity, which is an increased sensitivity to UV light of the sun.

- What does this mean for patients?
  Patients should avoid direct sun exposure during treatment.

- What is QTC?
  The QT interval varies with heart rate, so clinicians use a corrected QT (QTC) to standardize it. Prolonged QTC can lead to serious arrhythmias(can be also caused by macrolide)

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.**

-Gatifloxacin has been specifically associated with hyperglycemia, even in patients receiving antidiabetic agents .

•Fluoroquinolones can cause damage to growing cartilage, leading to arthropathy

CONTRAINDICATIONS

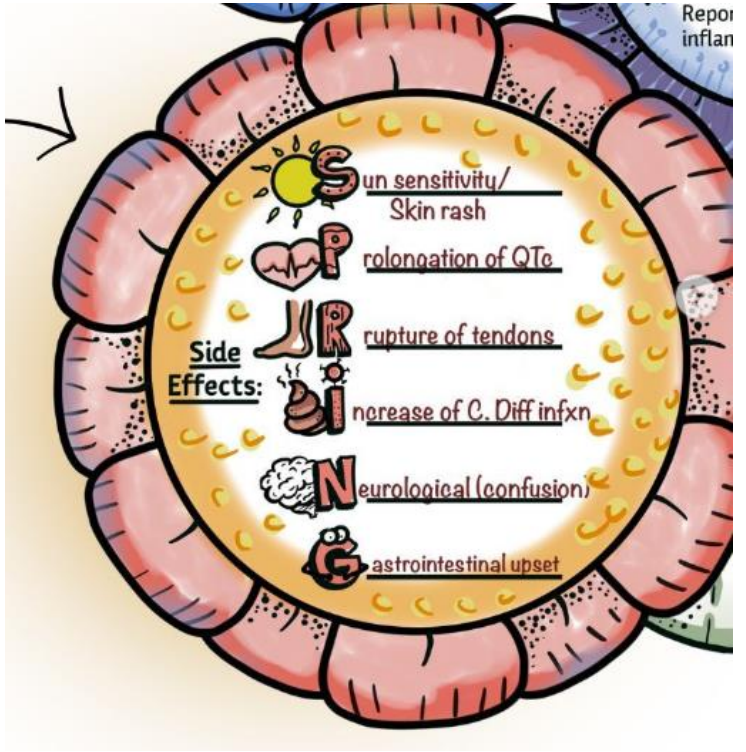
•Should not be used in pregnant women

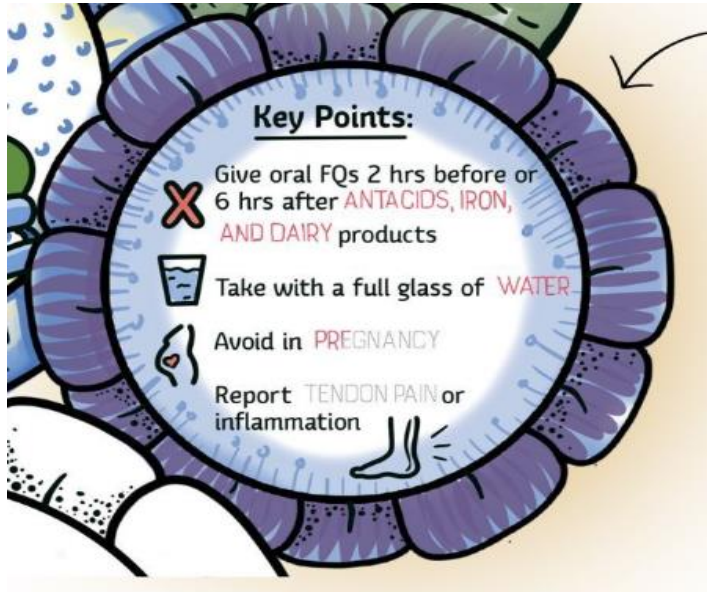
•Not recommended in children or adolescents (under 18 years old)

➡️ **May be considered only when growth is complete** (e.g. if growth ceases at age 16, treatment may begin thereafter)

•Cartilage damage interferes with normal bone development, since bones grow through cartilage plates.

•Though rare, fluoroquinolones have been linked to tendinitis and tendon rupture, especially involving the Achilles tendon.





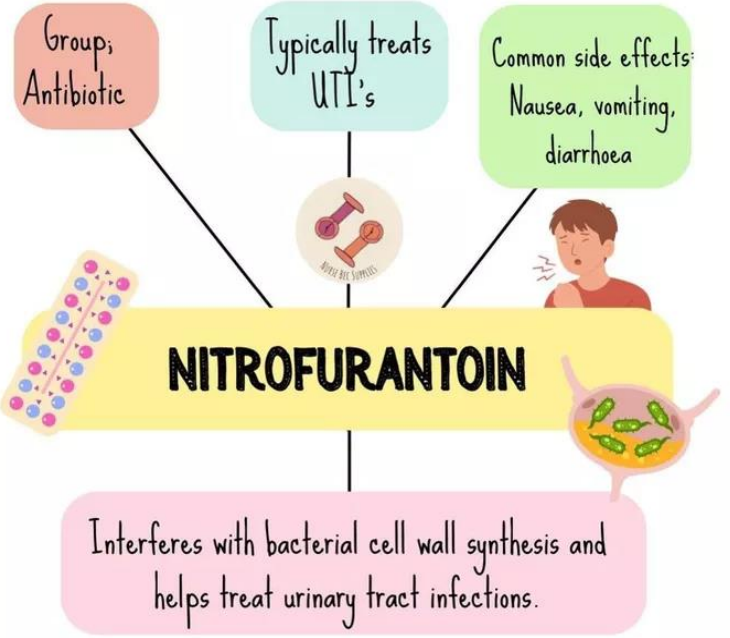
Nitrofurantoin

- Is a prodrug, activated to metabolites that damage bacterial DNA.
- Bacteriostatic.
- Active against *E. coli* and enterococci (from feces)→ UTIs
- *Pseudomonas, Proteus, Enterobacter* and *Klebsiella* are resistant.
  →RARE causes of UTIs
- Should not be used in patients with impaired renal function or below 1 month of age.→ The kidney is not well developed during this time
- It should be avoided in pyelonephritis because it does not achieve therapeutic levels outside urine.

Nitrofurantoin is almost completely filtered by the kidneys and concentrates in the urine, particularly in the bladder. This makes it effective for treating cystitis, but not pyelonephritis, because it does not reach high enough concentrations in the kidney tissue.

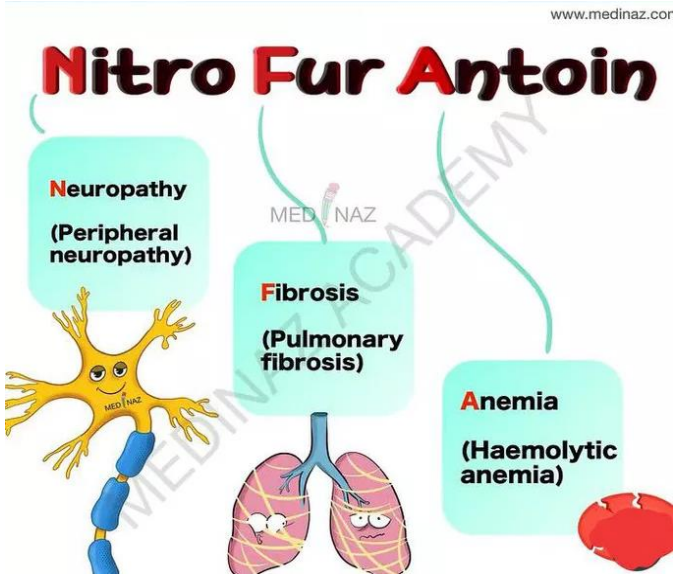
This differentiates it from other drugs like Penicillins, Cephalosporins, Fluoroquinolones and Trimethoprim (± sulfamethoxazole)

Nitrofurantoin



Adverse Effects:

1. Nausea, vomiting and diarrhea are the most comm
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.



NOTES ABOUT NITROFURANTOIN

•Nitrofurantoin causes Acute pneumonitis (a type of chemical pneumonitis)
➡ This pneumonitis is not an infection and not bacterial pneumonia. It is a chemical-induced inflammation of the lungs. Over time, it may heal with fibrosis, leading to interstitial pulmonary fibrosis, which is a very serious and often fatal complication.

Nitrofurantoin can cause hemolysis in individuals with G6PD deficiency.
➡Similarly, sulfonamides, such as sulfamethoxazole (especially when combined with trimethoprim), can also cause hemolysis in these patients.

Nitrofurantoin may turn the urine brown ➡ This is not dangerous, but it is important to warn the patient in advance. Otherwise, it might scare them.

➡This is similar to:
Metronidazole, which may darken the urine.
Rifampicin, which can color not only the urine but also saliva, tears, and sweat orange.
➡ This orange color is due to the drug itself and appears in all secretions.
In contrast, nitrofurantoin mainly affects the urine, causing it to turn brown.

Additional sources

1. Book pages
2. Youtube videos
3. Webpages…etc

كان النبي صلى الله عليه وسلم يُقسِّم غنائم الحرب بين المقاتلين بالسوية، الفارس شديد البأس، ككبير السن، لا فرق.
ورأى سعد بن أبي وقاص أنه يجب أن تكون حصته أكبر لشجاعته، فقال للنبي صلى الله عليه وسلم: حامية القوم أيكون سهمه وسهم غيره سواء؟ فقال له النبي صلى الله عليه وسلم: ثكلتك أمك يا ابن أم سعد، وهل تُرزقون أو تُنصرون الا بضعفائكم؟
لعل رزقك بسبب أبوين كبيرين تنفق عليها، أراد الله تعالى أن يعطيهما ولكنك لست أكثر من باب يدخل منه الرزق.
ولعل رزقك بسبب ابن لك فيه عاهة فصبرت وحمدت، وقد أراد الله تعالى أن يرزقه وما أنت الا سبب.
ولعل رزقك بسبب يتيم كفلته أو مريض تتعهد دواءه كل شهر، او راتب شهري جعلته لأختٍ أرملة، وأخ مسكين، لعل الرزق بالأساس لهم وإنما تُرزق انت بسببهم، لعلك لست أكثر من سبب وباب، فلا تقطع السبب وتغلق الباب.

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V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!