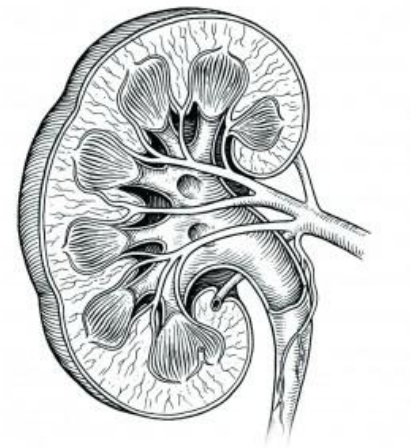
Pharmacology
Team 437

MED437
KING SAUD UNIVERSITY



Treatment of Urinary Tract Infection

Editing File

Objectives:

- Recognize different groups of antibiotics used in UTIs.
- Describe their mechanism of action, pharmacokinetics properties and adverse effects.
- Describe the use of antibiotics and their rational of combination of different antibiotics.
- Describe the spectrum of various antibiotics.

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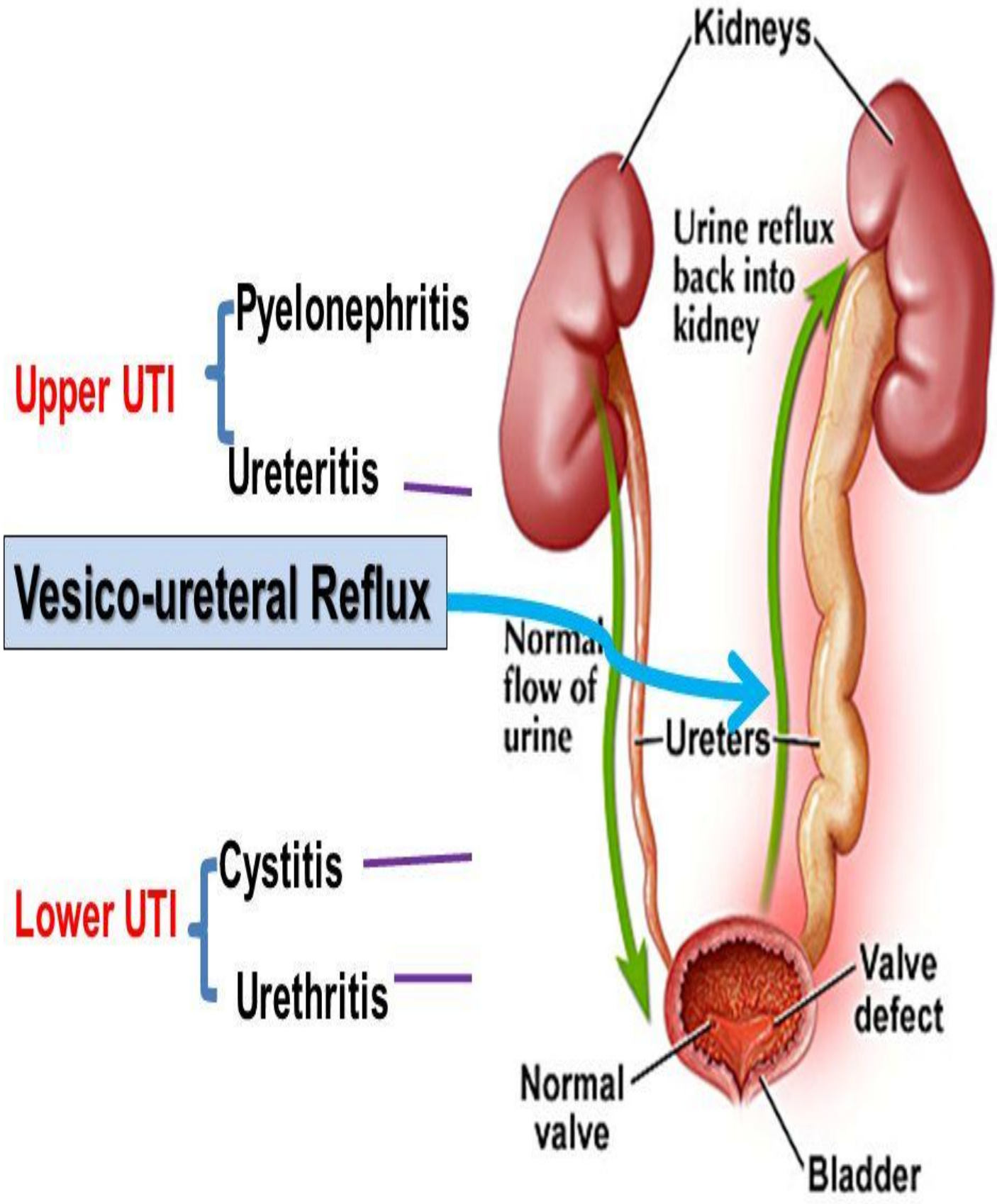
Important Notes Extra

Urinary Tract Infection



Urinary Tract Infection (UTI)

- It is the 2nd most common infection after RTI's. (respiratory tract infection)
- It is often associated with some obstruction of the flow of urine.
- Incidence of UTI increases in old age (10% of men & 20% of women).
- It is more common in women more than men 30:1 due to urethra in female shorter (4cm)

Causes of UTIs

Normally urine is sterile. Bacteria comes from digestive tract to opening of the urethra.

- Obstruction of the flow of urine(e.g. kidney stone)
- Enlargement of prostate gland in men(common cause)
- Catheters placed in urethra and bladder.
- Not drinking enough fluids.
- Waiting too long to urinate.
- Large uterus in pregnant women.
- Poor toilet habits(wiping back to front for women)
- Disorders that suppress the immune system (diabetes , cancer chemotherapy).

Bacteria Responsible of UTIs

Gm- bacteria (most common)	Gm+ bacteria	Bacteria that also cause UTI
• E.coli (approx. 80% of cases) • Proteus mirabilis • Klebsiella • Pseudomonas aeruginosa	Staphylococcus Saprophyticus (Approx. 20%) cause honeymoon cystitis	Mycoplasma, Chlamydia trachomatis & N. gonorrhea (limited to urethra, unlike E.coli may be sexually transmitted)

In general gram negative bacteria are more common causes of UTIs

UTIs can be

Simple (uncomplicated)

Infections do not spread to other parts of the body and go away readily with treatment (Due to E.coli in most cases).

Complicated

Infections Spread to other parts of the body and resistant to many antibiotics and more difficult to cure. {Due to hospital- acquired bacteria (E.coli, Klebsiella, Proteus, Pseudomonas, enterococci, staphylococci)

Treatment of UTIs

First we will do urine analysis to find the causative organism then choose the antibiotics according to it.

Antibiotics:

- Co-trimoxazole (SMX/TMP)), p.o. (combination of trimethoprim and sulfamethoxazole).
- Nitrofurantoin, p.o.
- Tetracyclines, e.g. Doxycycline, p.o.
- Aminoglycosides, e.g. Gentamicin IV/IM
- Cephalosporins, e.g. Ceftriaxone & Ceftazidime IV 3rd gen most used because of their efficacy against gram -ve organisms
- Quinolones, e.g. Ciprofloxacin, p.o.

p.o. = orally

Co-trimoxazole (Bactrim, Septra)
combination of Sulfamethoxazole (SMX) - Trimethoprim (TMP)

Overview

- Alone, each agent is bacteriostatic
- Together they are bactericidals (synergism) This is the reason we combine the two drugs.
- The optimal ratio of TMP to SMX in vivo is 1:20 (formulated 5(SMX):1(TMP)*; 800mg SMX+160mg TMP; 400 mg SMX+ 80 mg TMP; 40 mg SMX+8 mg TMP). *our FORMULATED dosage ratio is always giving sulfonamides 5 times more than Trimethoprim, our IN VIVO dosage is 1:20

Mechanism of action

see next slide ^_^

Enzymes requiring folate-derived cofactors are essential for the synthesis of purines and pyrimidines (precursors of RNA and DNA) and other compounds necessary for cellular growth and replication. Therefore, in the absence of folate, cells cannot grow or divide. And that is the mechanism of THE FOLATE ANTAGONISTS (Sulfamethoxazole + trimethoprim). The synergistic antimicrobial activity of cotrimoxazole results from its inhibition of two sequential steps in the synthesis of tetrahydrofolic acid. Sulfamethoxazole inhibits the incorporation of PABA into dihydrofolic acid precursors, and trimethoprim prevents reduction of dihydrofolate to tetrahydrofolate

Adverse effects

- Gastrointestinal- Nausea, vomiting
- Allergy
- Hematologic

  a) Acute hemolytic anemia Sulfonamide especially

  a) hypersensitivity b) G6PD deficiency

  b) Megaloblastic anemia due to TMP.
- Drug interactions:

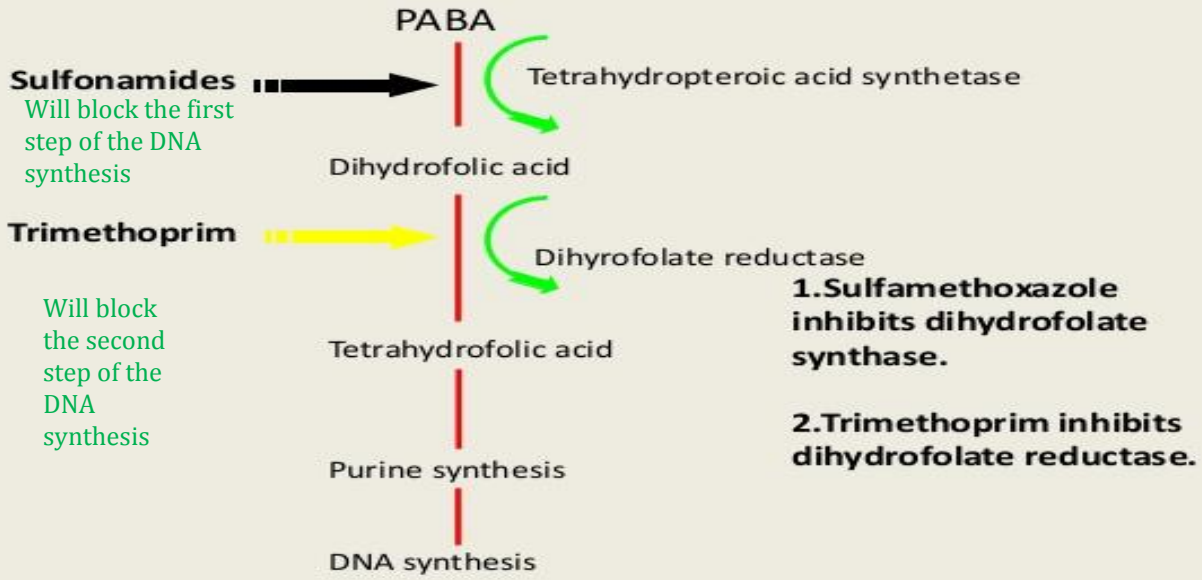
  Displace bilirubin- if severe – kernicterus condition in which bilirubin accumulates in brain

  Potentiate warfarin causes bleeding, oral sulfonylurea hypoglycemics oral antidiabetic.

Contra-indication

- Pregnancy
- Nursing mother
- Infants under 6 weeks because it will cause displacement of bilirubin leading to jaundice
- Renal or hepatic failure
- Blood disorders eg Haemophilia because of risk of hemolytic anemia

MOA OF TRIMETHOPRIM-SULFAMETHOXAZOLE



Drug	Trimethoprim (TMP)	Sulfamethoxazole (Sulfonamides) (SMX)
Absorption, metabolism & Excretion	❖ Usually given orally/IV, alone or in combination with SMX. ❖ Well absorbed from the gut. ❖ Widely distributed in body fluids & tissues (including CSF). ❖ More lipid soluble than SMX. ❖ Protein bound (approx.40 %) ❖ 60% of TMP or its metabolite is excreted in the urine ❖ TMP concentrates in the prostatic fluid & vaginal fluids (> acidity than plasma).	❖ Mainly given orally (can be given IV in some cases) ❖ Rapidly absorbed from stomach and small intestine. ❖ Widely distributed to tissues and body fluids (including CNS, CSF), placenta and fetus. ❖ Absorbed sulfonamides bind to serum protein (approx. 70%). ❖ Metabolized in the liver by the process of acetylation. ❖ Eliminated in the urine, partly as such and partly as acetylated derivative.

Nitrofurantoins

Antibacterial Spectrum	❖ Bactericidal for gm-ve & gm+ve bacteria ❖ Nitrofurantoin is effective against E.coli & Staph. Saprophyticus. ❖ Other common UT gram -ve bacteria may be resistant. So if we're sure one of the 2 organisms mentioned above is the causative organism of the UTI, we will use nitrofurantoin
Mechanism of Action	Sensitive bacteria reduce the drug to an active agent that inhibits various enzymes and damages DNA.
Pharmaco-kinetics	❖ Complete and rapid oral absorption. ❖ 75% metabolized & is excreted so rapidly that no systemic antibacterial action can be achieved. So that means nitrofurantoin is a poor choice in sytemic spreading infections because it does not stay long enough in the body to spread to the other infected areas. ❖ Concentrated in urine. (25% is excreted unchanged) ❖ Urine turns to dark orange-brown (harmless).
Adverse Effects	❖ GI disturbances: ◇ Bleeding of the stomach ◇ Nausea ◇ Vomiting ◇ Diarrhea (Must be taken with food) ❖ Headache & Nystagmus (involuntary eye movements). ❖ Hemolytic anemia (G6PD Deficiency)
Contra-indications	❖ Patients with G6PD deficiency. ❖ Neonates. ❖ Pregnant women. (after 38 weeks of pregnancy)
Uses	❖ Used as urinary antiseptic. It's usefulness is limited to lower UTI's & cannot be used for upper UT or systemic infections. Because it has bad distribution in body. ❖ Dose: 50-100mg, orally, 6h/7 days. ❖ Long acting: 100mg twice daily.

Tetracyclines

E.g.	Doxycycline (Long acting tetracycline)
Mechanism of action	Inhibit protein synthesis by binding reversibly to 30s subunit Against gm+ve & gm-ve bacteria.
Pharmaco-kinetics	❖ Usually given orally. ❖ Absorption is 90-100% so given 3 hrs after or 2 hrs before food ❖ Absorbed in upper small intestines, best on an empty stomach. ❖ Food with these di & tri cations (Ca, Mg, Fe, Al) impair absorption. ❖ Protein binding 40-80%. ❖ Well distributed, including CSF. ❖ Cross placenta, excreted in milk. ❖ Largely metabolized in liver.
Adverse effects	❖ Nausea, vomiting, diarrhea, & epigastric pain (when give with food containing the mentioned impairing substances) ❖ Thrombophlebitis - I.V ❖ Hepatic toxicity (Prolonged therapy with high dose) ❖ Brown discolouration of teeth in children ❖ Deformity/growth inhibition of bones in children ❖ Phototoxicity ❖ Vertigo ❖ Superinfections (because they alter the intestinal flora due to broad spectrum activity).
Contra-indications	❖ Pregnancy ❖ Breast feeding ❖ Children below 10 years
Uses	❖ Treatment of UTI's due to Mycoplasma & Chlamydia. ❖ 100mg orally, bid (twice a day) for 7 days. ❖ Prostatitis.

Aminoglycosides

E.g.	Gentamicin
Pharmaco-kinetics	❖ Bactericidal antibiotics. ❖ Given I.M or I.V . ❖ poorly absorbed orally (highly charged). ❖ Active against **gm-ve aerobic** organisms ❖ Excreted unchanged in urine . ❖ More active in alkaline medium . ❖ Cross placenta.
Mechanism of action	❖ Inhibit protein synthesis by binding to 30S ribosomal subunits . ***Similar to tetracyclines***
Adverse effects	❖ Ototoxicity. ❖ Nephrotoxicity. ❖ Nerve damage ❖ Neuromuscular blocking effect.
Uses	❖ Only active against gram negative aerobic organism. ❖ Severe infections caused by gram negative organism (pseudomonas or enterobacter).

Cephalosporins

Generation	1st	2nd	3rd
Drugs	Cephalexin	Cefuroxime, Cefaclor	Ceftriaxone, Cefotaxime, Cefixime, Ceftazidime
Route of Administration	Orally	Orally Well absorbed	I.V
Spectrum	Gram-positive bacteria	Gram-negative bacteria (Active against β-lactamase -producing bacteria)	Gram-negative bacilli
Mechanism of Action	❖ Inhibit bacterial cell wall synthesis ❖ Bactericidal (similar to Penicillins) ❖ Classified into 3 generations:		
Pharmaco-kinetics	❖ Cephalosporins are given parenterally ❖ Relatively lipid insoluble (like penicillins). ❖ Don't penetrate cells or the CNS, except for third generations. ❖ Mostly excreted unchanged by the kidney (glomerular & tubular secretion). ❖ Probenecid slows their elimination & prolong their half lives (Half-life: 30-90 min; except ceftriaxone 4-7 hr).		
Adverse Effects	❖ Hypersensitivity reactions. ❖ Thrombophilibitis. Inflammation of the wall of vein ❖ Superinfections. Because of killing of normal flora ❖ Diarrhea. *Dr. Aliah said: Local irritation can produce pain after IM injection & thrombophlebitis after IV injection.		
Uses	Effective in URTIs	Upper & lower RTIs	severe/complicated UTIs & acute prostatitis Effective in treatment

Fluoroquinolones

Drugs	Ciprofloxacin	Moxifloxacin	Gatifloxacin
Antibacterial spectrum	G–ve aerobic organism highly active against Pseudomonas species	G –ve & G+ve highly active against Pseudomonas species	
Mechanism of action	Block bacterial DNA synthesis by inhibiting DNA Gyrase enzyme (an enzyme involved in DNA supercoiling).		
Dose	twice-daily	once daily	
Pharmaco-kinetics	❖ Given po or parenterally ❖ Concentrates in many tissues (kidney, prostate, lung & bones/ joints) it means it can treat infections in these organs. ❖ Excreted mainly through the kidney ❖ long Half-life		
Adverse effects	❖ Nausea, vomiting and diarrhea ❖ CNS effects (confusion, insomnia, headache and anxiety) ❖ Damage of growing cartilage (arthropathy) inflammation of joint ❖ Phototoxicity (avoid excessive sunlight) cause skin irritation		
Contra-indications	❖ Not recommended for patients younger than 18 years ❖ Pregnancy ❖ Breastfeeding women		
Clinical Uses	❖ UTIs caused by multidrug resistance organism as pseudomonas ❖ Prostatitis (acute/chronic)		

Questions

MCQs:

1. …….is when the sum of two drugs effect is greater than the individual drug effect?
   a-combination
   b-co-administration
   c-synergism
   d-drug interaction

2. Managment of UTI mainly depends on…...?
   a-NSAIDs
   b-Diuretics
   c-chemotherapy
   d-antibiotics

3. A patient with UTI was given co-trimoxazole drugs (sulfamethoxazole SMX/Trimethoprim TMP) if the doctor prescribed 40 mg of SMX then the formulated dose of TMP should be equal to….?
   a-200 mg
   b-8mg
   c-4mg
   d-800mg

4. Using the same data in question for if the SMX level in vivo is 20mg than TMP level should be….?
   a-40ml
   b-4mg
   c-1mg
   d-400mg

5. Sulfamethoxazole alone is considered….?
   a-bacteriostatic
   b-bactericidal
   c-both
   d-no effect

6. A patient with megaloblastic anemia should avoid……..?
   a-gentamycin
   b-amoxicillin
   c-nitrofurantoin
   d-TMP

7. Patient with upper UTI should avoid using …?
   a-nitrofurantoin
   b-gentamycin
   c-amoxicillin
   d-quinolones

8. Doxycycline mechanism of action is inhibiting protein synthesis by binding ……to…….S subunit?
   a-irreversibly /60
   b-reversibly /60
   c-irreversibly/30
   d-reversibly/30

9. If Doxycycline given by IV it might cause ……?
   a-heart burn
   b-thrombophlebitis
   c-Sydenham corrhea
   d - urine retention

10. Aminoglycoside are not active against?
    a-gram – bacteria
    b-gram + bacteria
    c-viruses
    d- both b and c

Answers:
1. C
2. D
3. B*
4. C**
5. A
6. C***
7. A****
8. D
9. B
10. D

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*remember: for each 5 mg of SMX: 1mg of TMP.

**in vivo 1mg TMP:20mg SMX.

***c: cause hemolytic anémia.

****WORK ON LOWER UTI ONLY

Questions

SAQ:

Case: A 20 year old male patient came to clinic with spontaneous urethral discharge, incomplete voiding, fever and prostatic pain biopsy showed gram- diplococci.

1. what is the causing organism?
2. what is the name of this disease ?
3. what is the best drug for this case?
4. what is the route of administration for this drug?
5. what is the mechanism of action for this drug?
6. name 2 contraindications for this drug?

1. neisseria gonorrhea.
2. acute prostatitis.
3. cephalosporin(ceftriaxone or ceftazidime).
4. parental (I.V.).
5. inhibition of cell wall synthesis (bactericidal).
6. hypersensitivity and GIT problems.

Questions

SAQ:

Case: 58 year old lady told you that she have UTI and that her previous doctor prescribed an antibiotic for her but she says the drug worked at first but the problem returned you did some lab test than you found out that her urine contained +Leukocytosis,culture showed aerobic, nonfermentative, non enterobacterial gram-negative bacilli and her ultrasound tests showed no anatomical problems.

clinical presentation results : no signs of TB or pneumonia

1. causative organism ?
2. what is the name of the antibiotic that was given by her old doctor?
3. why didn't the drug work ?
4. what drug should you use in this case?
5. what is the mechanism of this drug?
6. name 2 side effect associated with this drug ?

1. pseudomonas.
2. might be amoxicillin.
3. because it is a multi drug resistance bacteria.
4. ciprofloxacin.
5. it inhibit DNA gyrase enzyme.
6. phototoxicity and arthropathy (damage cartilage).

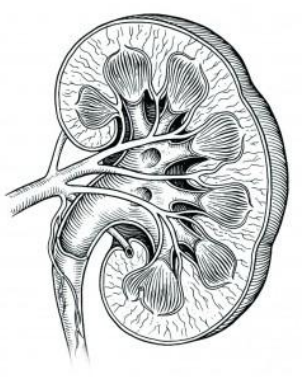
Questions

SAQ:

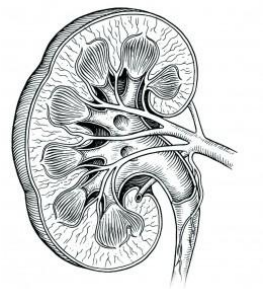
Case: Pregnant women complaining from the following problems:
burning sensation when voiding urine, urgency for peeing.
lab test showed cloudy urine ,leukocytes + , bacteria count more than 100000 per ml and urine culture showed Gram-negative, facultatively anaerobic, rod-shaped bacteria.

1. what is the problem ?
2. what is the causative organism ?
3. what is the best drug for this case ?
4. what drugs should you avoid ?
5. to prevent future infections should we use prophylaxis in this case ?

1. cystitis .
2. E.coli.
3. amoxicillin ,penicillin and erythromycin.
4. tetracyclines , SMX,TMP and Nitrofurantoin.
5. yes we should continue with antibiotic one daily dose throughout the pregnancy period.



"It is not hard, you just made it to the end!"



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