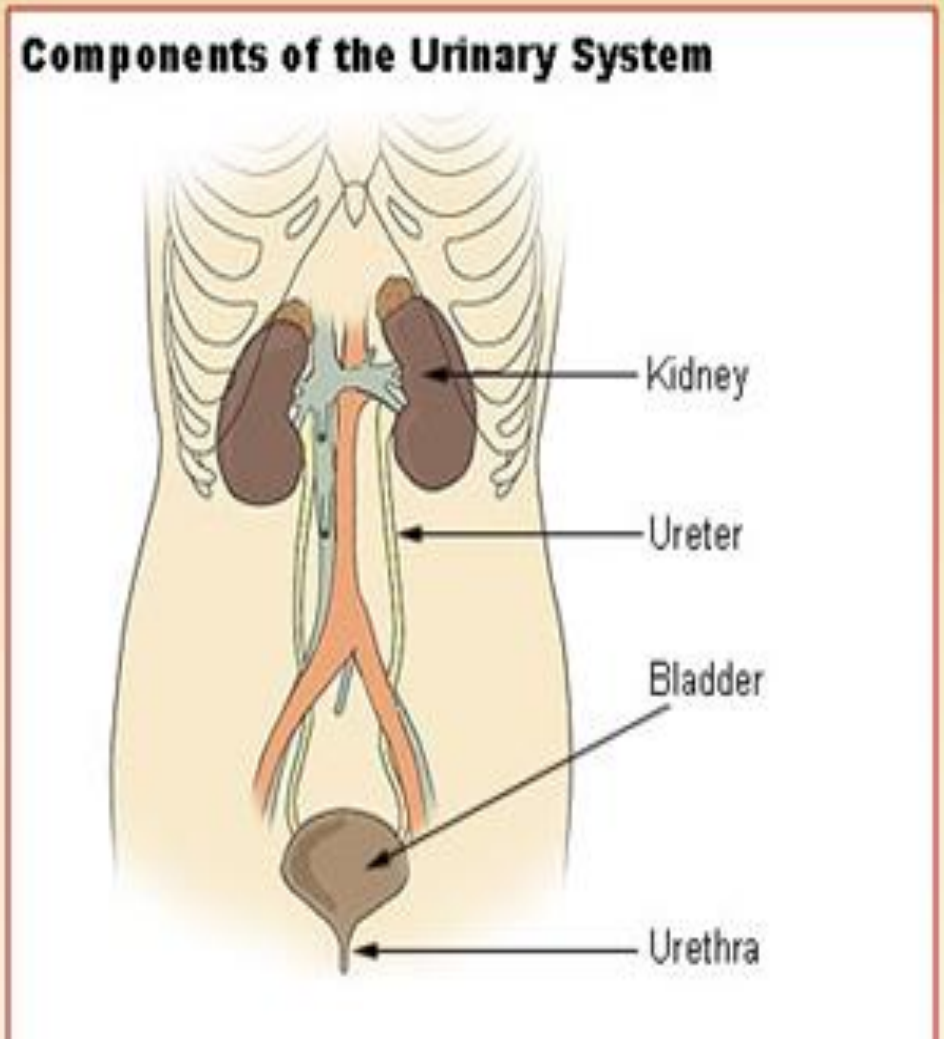
Prof. Mohammad Alhumayyd
Dr. Ishfaq Bukhari
Department of Pharmacology

Urinary Tract System



Urinary tract infections(UTI's)

1. **Upper urinary tract (kidney &ureters) infections: pyelonephritis**

1. **Lower urinary tract (bladder, urethra & prostate): cystitis , urethritis & prostatitis.**

** **Upper urinary tract infections are more serious.**

Urinary tract infections(UTI's)

- **It is the 2nd most common infection (after RTI's).**
- **It is often associated with some obstruction of the flow of urine.**
- **It is more common in women more than men**
- **30:1 (Why?).** (**pathogens responsible for UTI are found in the colonic fl ora. Subsequent UTI is usually ascending, i.e. after perivaginal, perineal, and transurethral colonization, also immunity and other changes …**)
- **Incidence of UTI increases in old age(10% of men & 20% of women).**

What are the causes of UTI's

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 urinary tract infections

Gm- bacteria (most common):

- **E.coli (approx. 80% of cases)**
- **Proteus mirabilis**
- **Klebsiella**
- **Pseudomonas aeruginosa**

Gm+ bacteria :

- **Staphylococcus Saprophyticus(Approx. 20%)**

- **Mycoplasma, Chlamydia trachomatis & N. gonorrhea**

(limited to urethra, unlike E.coli may be sexually transmitted)

Urinary tract infections can be:

- **Simple:**

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 UTI's

Antibiotics:

Co-trimoxazole(SMX/TMP)),p.o.

Nitrofurantoin,p.o.

Tetracyclines, e.g. Doxycycline,p.o.

Aminoglycosides, e.g. gentamicin i.v/i.m

cephalosporins(e.g.ceftriaxone&ceftazidime IV

Quinolones, e.g. ciprofloxacin,p.o.

Treatment strategy

- ***Uncomplicated lower UTI (cystitis)***
- **For empirical therapy:**
- **Trimethoprim 200mg bd (or co-trimoxazole 960mg bd). short-course (3 days)**
- **• *Or* Nitrofurantoin 100mg bd (not in renal impairment). longer-course (7 – 10 days)**

Uncomplicated lower UTI (cystitis)

- If second-line treatment is necessary, e.g. hypersensitivity, side effects, failure of first-line treatment, then urine culture with sensitivity testing is recommended.

Options:

Fluoroquinolones, ciprofloxacin 500mg bd or levofloxacin 250mg od.

Oral cephalosporins (cefixime) often offer a useful alternative.

- Encourage high fluid intake, e.g. >2L/day.

Complicated UTIs e.g pyelonephritis

- Select the antibiotics as per culture sensitivity results
- Empiric therapy include ciprofloxacin or levofloxacin, third generation cephalosporin e.g ceftriaxone,
- use additional single dose of aminoglycosides (Gentamycin) if needed
- Rehydration is very useful

Treatment option in pregnancy

- Ampicillin or amoxacillin
- Nitrofurantoin (caution in neonatal jaundice)
- Ceftriaxone
- Trimethoprim (use folate supplementation, avoid in folate deficiency)
- Short term aminoglycosides can also be used in complicated UTIs.

Co-trimoxazole (Bactrim, Septra)

Sulfamethoxazole- Trimethoprim

(SMX) (TMP)

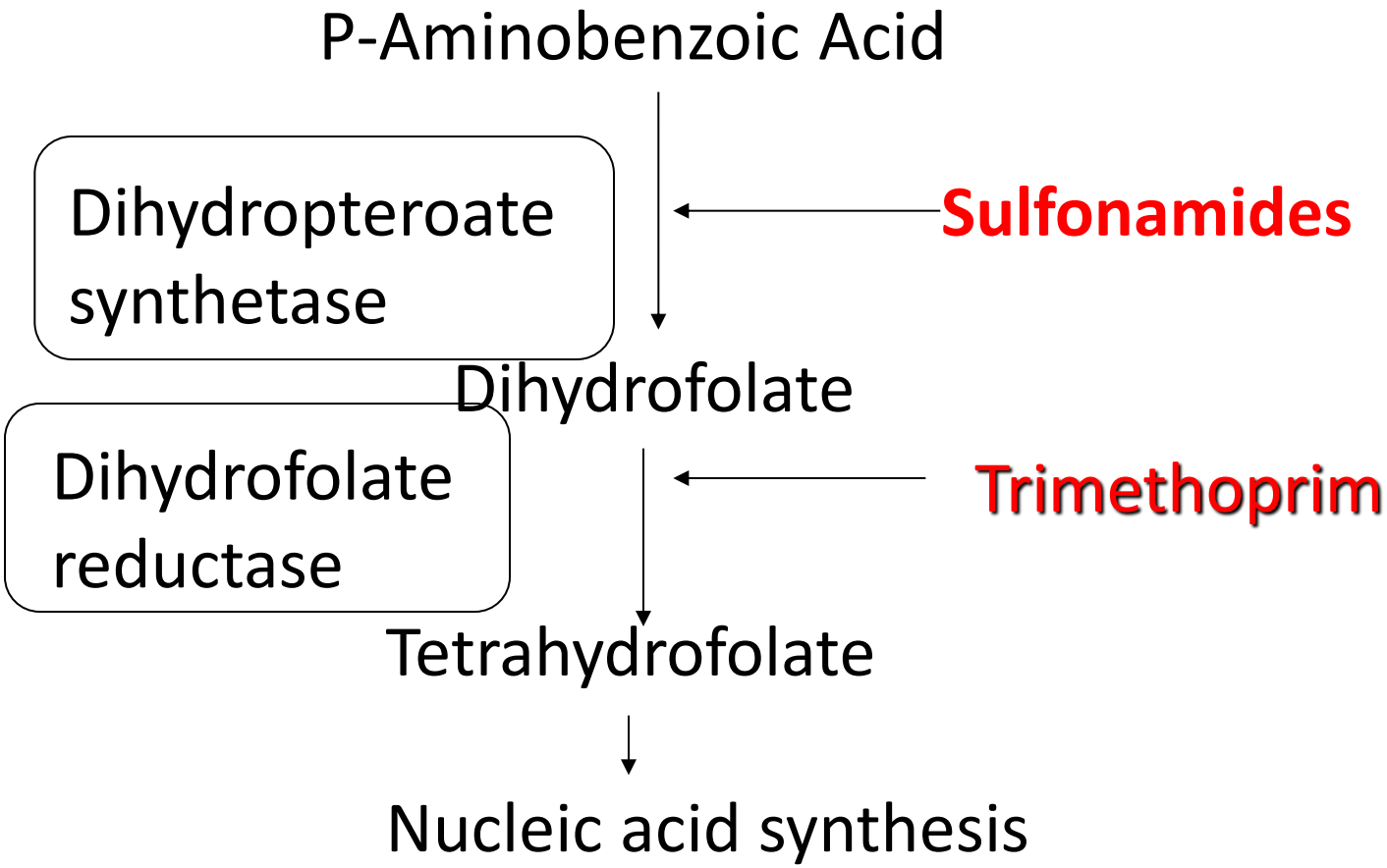
Alone, each agent is bacteriostatic

Together they are bactericidals(synergism)

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).

MECHANISM OF ACTION



Absorption,metabolism&Excetion

Sulfonamides

Mainly given orally

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.

Trimethoprim (TMP)

Usually given orally, 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.

ADVERSE EFFECTS

1.Gastrointestinal- Nausea, vomiting

2. Allergy

3. Hematologic

    a) Acute hemolytic anemia

        a) hypersensitvity b) G6PD deficiency

    b) Megaloblastic anemia due to TMP.

4. Drug interactions

    Displace bilirubin- if severe – kernicterus

    Potentiate warfarin, oral hypoglycemics.

CONTRAINDICATIONS

1. Pregnancy
2. Nursing mother
3. Infants under 6 weeks
4. Renal or hepatic failure
5. Blood disorders

Nitrofurantoin

Antibacterial Spectrum:

Effective against E. coli and Staph. saprophyticus, but other common UT gm- bacteria may be resistant.

Mechanism of action of nitrofurantoin

Sensitive bacteria reduce the drug to an active agent that inhibits various enzymes and damages DNA.

Pharmacokinetics of nitrofurantoin

- **Absorption is complete after oral use**
- **Metabolized (75%)& excreted so rapidly that no systemic antibacterial action is achieved.**
- **Concentrated in the urine(25% of the dose excreted unchanged)**
- **Urinary pH is kept <5.5(acidic) to enhance drug activity.**
- **It turns urine to a dark orange-brown.**

Adverse effects of nitrofurantoin

GI disturbances: bleeding of the stomach,nausea, vomiting and diarrhea(must be taken with food).

Headache and nystagmus.

Hemolytic anaemia(G6PD deficiency)

Containdications:

Pts with G6PD deficiency

Neonates

Pregnant women(after 38 wks of pregnancy)

Therapeutic Uses of nitrofurantoin

It is used as urinary antiseptics . Its usefulness is limited to lower UTI's & cannot be used for upper UT or systemic infections.

Dose: 50-100 mg, po q 6h/7 days.

Long acting: 100mg twice daily.

Tetracyclines
(e.g. Doxycycline)

It is a long acting tetracycline

Mechanism of action

Inhibit protein synthesis by binding reversibly to 30 s subunit

Doxycycline (Cont.)

Pharmacokinetics

Usually given orally

Absorption is 90-100%

Absorbed in the upper s. intestine & best in absence of food

Food & di & tri-valent cations (Ca, Mg, Fe, AL) impair absorption

Protein binding 40-80 %

Distributed well, including CSF

Cross placenta and excreted in milk

Largely metabolized in the liver

Doxycycline (Cont.)

Side effects

1. nausea, vomiting ,diarrhea & epigastric pain(give with food)
2. Thrombophlebitis – i.v
3. Hepatic toxicity (prolonged therapy with high dose)
4. Brown discolouration of teeth – children
5. Deformity or growth inhibition of bones – children
6. Phototoxicity
7. Vertigo
8. Superinfections.

Contraindications of doxycycline

- **Pregnancy**
- **Breast feeding**
- **Children(below 10 yrs)**

Therapeutic Uses of Doxycycline

- Treatment of UTI's due to Mycoplasma & Chlamydia, 100 mg p.o bid for 7 days.
- Prostatitis

Aminoglycosides

e.g. GENTAMICIN,i.m,i.v.

- **Bactericidal antibiotics**
- **Inhibits protein synthesis by binding to 30S ribosomal subunits.**
- **Active against gram negative aerobic organisms.**
- **Poorly absorbed orally(highly charged).**
- **cross placenta.**

Gentamicin(CONT)

- Excreted unchanged in urine
- More active in alkaline medium
- **Adverse effects** :
- Ototoxicity
- Nephrotoxicity
- Neuromuscular blocking effect

Therapeutic uses of Gentamicin in UTI's

- Severe infections caused by gram negative organisms (pseudomonas or enterobacter).

Cephalosporins

(Detail was explained in respiratory lec.)

3rd generation cephalosporins

Ceftriaxone & Ceftazidime

Mainly effective against gm- bacteria.

Acts by inhibition of cell wall synthesis

Bactericidal

They are given parenterally

Given in severe / complicated UTIs

& acute prostatitis

Fluroquinolones

(Detail was explained in respiratory lec.)

e.g. ciprofloxacin

Active against gram negative aerobic organisms.

Mechanism of action

- Inhibits DNA gyrase enzyme

Clinical use

- UTIs caused by multidrug resistance organisms as pseudomonas.
- Prostatitis (acute / chronic)

Adverse effects

- Nausea , vomiting , diarrhea
- CNS effects (confusion, insomnia, headache, anxiety).
- Damage of growing cartilage(arthropathy)
- Phototoxicity(avoid excessive sunlight)