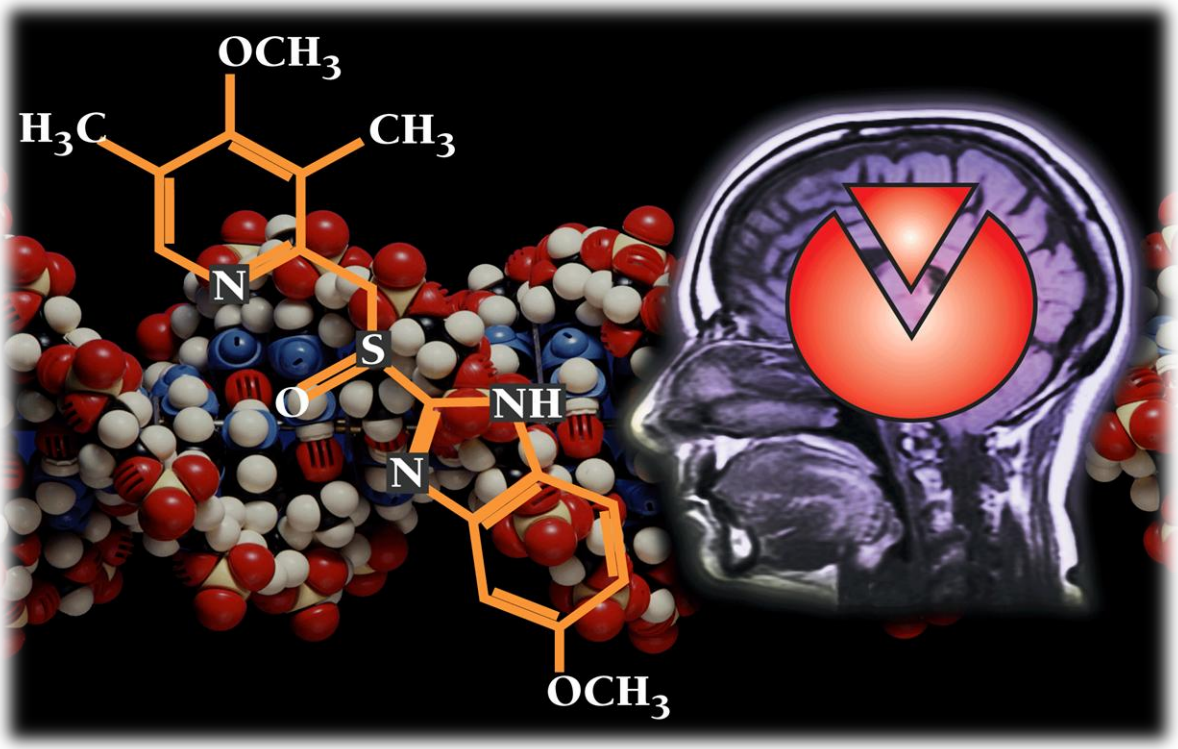
# Treatment of UTI

King Saud University
College Of Medicine
Pharmacology Team 430
Renal Block

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# Background:

- It is the 2nd most common infection (after respiratory tract infections).
- It is often associated with some obstruction of the flow of urine.
- It is more common in women more than men 30:1 ( Because of the shorter and wider urethra in women, and because of the proximity of the anal canal to the urethra )
- Incidence of UTI increases in old age (10% of men & 20% of women).
- Urinary Tract infection (UTI) divided into upper and lower urinary tract infection.
- Normally urine is sterile. Bacteria come from digestive tract to opening of the urethra.

## Classification of urinary tract infections:

**Symptomatic infections**

**Uncomplicated UTI (mainly in women)**

- Non-catheter associated (community-acquired).
- Do not spread to other parts of the body and go away readily with treatment (Due to E.coli in most cases).

**Complicated**:

- Catheter associated (nosocomial), immunosuppression, stones, renal disease, and diabetes)
- Spread to other parts of the body and resistant to many antibiotics and more difficult to treat.{Due to hospital- acquired bacteria(E.coli, Klebsiella,, Proteus, Pseudomonas, enterococci, staphylococci)}

Asymptomatic Infections

Present with significant bacteriuria (bacteria in Urine), but without symptoms of an infection.

## Causes:

- 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).

## Causative Bacteria:

| Gm-ve bacteria (most common): | Gm+ve bacteria (less common): | Other: |
|---|---|---|
| • E.coli (approx. 80% of cases)<br>• Proteus<br>• Klebsiella<br>• Pseudomonas | •Staphylococcus species (S.aureus and Saprophyticus) | • Chlamydia trachomatis, Mycoplasma & N. gonorrhea (limited to urethra, and may be sexually transmitted) |

# Drugs for Treatment of UTI

## 1-Co-trimoxazole ( Bactrim, Septra ):

A combination of two drugs {Sulfamethoxazole (SMX) &Trimethoprim (TMP)}

- Alone, each agent is bacteriostatic ( Inhibits the growth of bacteria)
- Together they are bactericidal (sequential Synergism)

**Note:** The synergistic antimicrobial activity of cotrimoxazole results from its inhibition of two sequential steps in the synthesis of tetrahydrofolic acid. This leads to a greater inhibition of bacterial growth, which then may lead to a bactericidal (killing the bacteria) activity.

- The optimal ratio of TMP to SMX in vivo (within systemic circulation) is 1:20 , so the dose is formulated to 5(SMX):1(TMP); 800mg SMX+160mg TMP; 400 mg SMX+ 80 mg TMP; 40 mg SMX+8 mg TMP).

**Note:** To kill the bacteria, SMX concentration must 20 times higher than TMP concentration in the systemic circulation. To reach such a ratio, the dose of SMX should be five times higher than TMP. (800mg SMX + 160mg TMP)

### MOA:

**Note:** Enzymes requiring folate-derived cofactors are essential for the synthesis of purines and pyrimidine (precursors of RNA and DNA) and other compounds necessary for cellular growth and replication. To synthesize the critical folate derivative, tetrahydrofolic acid, humans must first obtain preformed folate in the form of folic acid as a vitamin from the diet. Therefore, in the absence of folate, cells cannot grow or divide. In contrast, many bacteria are impermeable to folic acid and other folates and, therefore, must rely on their ability to synthesize folate de novo.

"Lippincott's Illustrated Reviews 4th edition p.391"

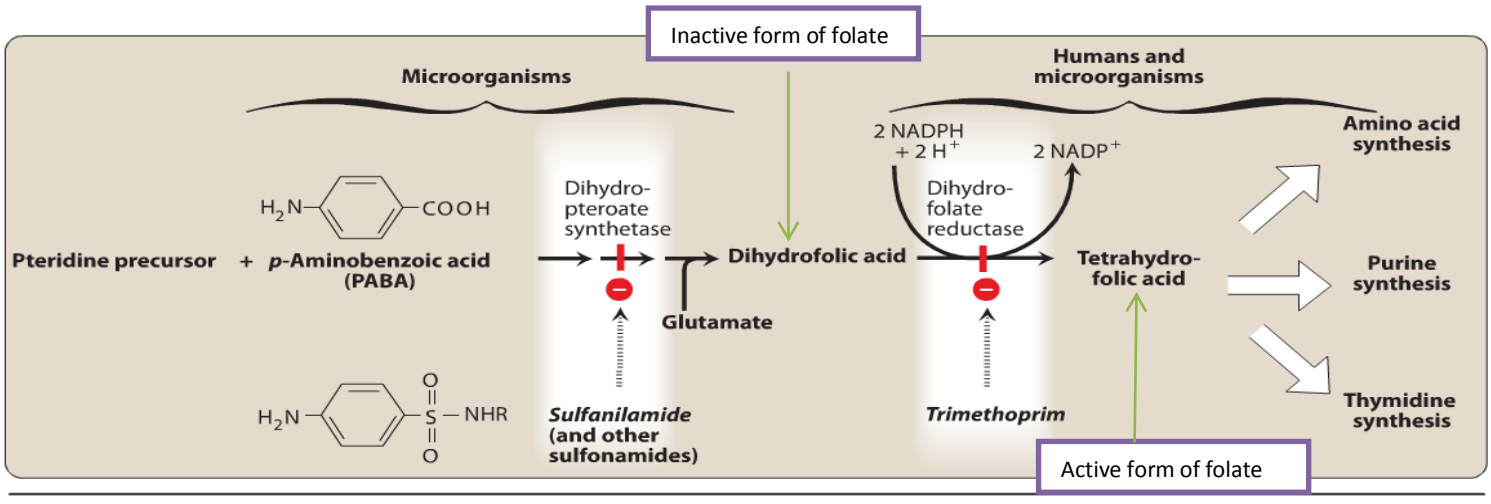


**Figure 33.9**
Inhibition of tetrahydrofolate synthesis by sulfonamides and *trimethoprim*.

**The sulfonamides (sulfa drugs):** inhibit the enzyme Dihydropteroate synthase, thus inhibiting the synthesis of bacterial dihydrofolic acid (de novo synthesis of folate).

**Trimethoprim:** Inhibits the enzyme Dihydrofolate reductase (Trimethoprim prevents microorganisms from converting dihydrofolic acid to tetrahydrofolic acid, with minimal effect on a human cell's ability to make this conversion).

## PHARMACOKINETICS

| Sulfonamides(SMX) | Trimehoprim ( TMP ) |
|---|---|
| • Mainly given orally<br>• Rapidly absorbed from stomach and small intestine.<br>• Widely distributed to tissues and body fluids (including CNS, CSF), placenta and fetus.<br>• Absorbed sulfonamides bind to serum protein (approx. 70%)<br>• Metabolized in the liver by the process of acetylation. (Where it's converted to sulfonamide acetylate)<br>• Eliminated in the urine, partly as such and partly as acetylated derivative. | • Usually given orally, alone or in combination with SMX<br>• Well absorbed from the **gut(intestine).**<br>• Widely distributed in body fluids & tissues<br>• More lipid soluble than SMX **( crosses membranes more easily)**<br>• Protein bound ( approx.40 % )<br>• 60% of TMP or its metabolite is excreted in the urine<br>• TMP concentrates in the prostatic fluid.**(excellent drug to treat prostatitis because it's can easily cross the membrane barrier, and 60% of the drug is free-bound)** |

Note: When the drug is highly protein bound, the amount of free-bound drug **(That preform the drug effect)** is low.

## Adverse Effects:

1-**Gastrointestinal**: Nausea, vomiting

2-Hypersenstivity **( Due to sulpha drug that causes rashes, angioedema, Steven Johnson syndrome ).**

Note: Stevens - Johnson syndrome is a potentially deadly skin disease

**3-Hematologic:**

A) **Acute hemolytic anemia with patients suffering from**

1- Hypersensitivity due to sulpha 2-G6PD deficiency

**Note:** Sulfa drugs are oxidizing agents they can cause hemolysis in patients suffering from G6PD deficiency**.**

**B) Megaloblastic anemia** due to Trimethoprim

**Note:** Since Trimethoprim has minimal effect on human cells, it can produce the effects of folic acid deficiency which leads to megaloblastic anemia, especially, in pregnant patients and those having very poor diets of folic acids. These blood disorders can be treated by the simultaneous administration of folic acid supplements, which does not enter bacteria.

3- Kernicterus (is a form of brain damage caused by excessive jaundice that usually occur in newborns & infants)

**Note:** The baby's blood brain barrier is not fully developed. Sulfa drugs displace bilirubin from binding sites on serum albumin. Bilirubin is then free to pass to CNS that then causes brain damage leading to kernicterus (If only few amount of bilirubin is free, jaundice occurs. If an excessive amount of bilirubin is free, kernicterus occurs)

4- **Crystaluria:** found in urine when performing a urine test. This leads to formation of kidney stones. (Any patient using sulpha drugs are recommended to drink a lot of fluids to avoid this adverse effect)

## Drug interactions:

1. Displace bilirubin.
2. Potentiate warfarin and oral hypoglycemic e.g (talbutamide).

**Note**: A percentage of warfarin and oral hypoglycemics are bound to serum albumin. Sulpha drug displaces them; leading to more free-bound warfarin and oral hypoglycemics (drug potentiation)

## CONTRAINDICATIONS:

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

# 2- Nitrofurantoin: (specific for lower UTIs)

## Antibacterial Spectrum:

- Effective against E. coli or Staphylo saprophyticus.
- Other common urinary tract gram-ve bacteria may be resistant. (P- Aeruginosa).
- Gram +ve cocci are susceptible.

## MOA:

Sensitive bacteria reduce the drug to an active agent that inhibits various enzymes and damages bacterial DNA (Nitrofurantoin is a prodrug that has bactericidal effect)

## Pharmacokinetics:

- Absorption is complete after oral use
- Metabolized in liver (75%) & excreted so rapidly that no systemic antibacterial action is achieved.
- Concentrated in the urine (25% of the dose excreted unchanged), so it's specific for treating the lower UTIs
- Urinary pH is kept <5.5(acidic) to enhance drug activity .( To keep the urine in acidic state **Ammonium chloride** is administrated, because **nitrofurantoin is highly active in acidic media)**
- It turns urine to a dark orange-brown. **( which is a normal thing)**
- Given with food.

## Adverse effects:

1. **GIT disturbances:** nausea, vomiting, diarrhea & gastric bleeding ( must be taken with food)
2. **Headache and nystagmus** (rapid involuntary movement of the eye).
3. **Hemolytic anemia** (especially in patients with G6PD deficiency because Nitrofurantoin is an oxidizing agent)
4. **Pulmonary fibrosis** ( patients usually complain of dry cough, chest pain, dyspnea which are usually seen in old patients or prolonged use of Nitrofurantoin)

## Contraindications:

- Patients with G6PD deficiency(hemolytic anemia)

**Note:** Nitrofurantoin is an oxidizing agent

- Neonates ( Because neonates have immature enzyme system in RBCs. Administering nitrofurantoin may lead to hemolytic anemia)
- Pregnant women (after 38 weeks of pregnancy).

**Note:** Nitrofurantoin can be used in early stages of pregnancy, but not in late stages.

## Therapeutic Uses

- It is used as urinary antiseptics but has little or no systemic antibacterial effect.
- Its usefulness is limited to lower UTI's.
- Dose: 50-100 mg ( orally four times daily every 6 hours ) for 7 days

## 3- Tetracyclines: (e.g. Doxycycline)

- Broad spectrum antibiotic
- Bacteriostatic
- It is a long acting tetracycline.

## MOA:

Inhibits protein synthesis by binding reversibly to 30 s ribosomal subunit.

## Pharmacokinetics

- Usually given orally
- Absorption is 90-100%
- Absorbed in the upper small intestine & best in absence of food
- It's absorption is impaired by: 1-divalent & trivalent cations ( Ca, Mg, Fe,Al )
  2-milk and its products,
  3-antacids (aluminium hydroxide gel, sodium bicarbonate)
- Protein binding 40-80 %
- Distributed well throughout the body, including prostatic tissues, CSF ( cerebral spinal fluid)
- Cross placenta and **excreted in milk**
- Largely metabolized in the liver
- Excreted through non-renal route

## Adverse effects:

1. Nausea, vomiting, diarrhea & epigastric pain (given with food, even if it interfered with the absorption)

2. Thrombophlebitis (if given i.v)

3. Hepatic toxicity (prolonged therapy with high dose)

4. Brown discoloration of teeth – children

5. Deformity or growth inhibition of bones – children

**Note:** During development of teeth (bone formation), tetracycline becomes calcified in the tooth to produce tetracycline calcium-ortho-phosphate (a yellow fluorescent) once exposed to light is converted to a brown permanent color (tetracycline tooth stains).

This binding of tetracycline to calcium leads to hypoplasia of teeth& bones.

6. Vertigo (is a type of dizziness where there is a feeling of motion when one is stationary)

7. Superinfections. (Tetracycline may kill bacteria that are beneficial to our bodies, this promotes the overgrowth of other more serious infectious organisms (e.g. Candida overgrowth).

## Contraindications:

1. Pregnancy
2. Breast feeding ( since it's excreted during breast feeding to the infant)
3. Children(below 10 years)

**Note:** Children are susceptible to tetracycline tooth stains from the time they are in utero until the age of 8-10. Since teeth start to develop before we're even born, pregnant women should not take tetracycline to prevent the possibility of the drug affecting the unborn baby's oral and bone growth health

## Therapeutic Uses:

- Treatment of UTI's due to Mycoplasma & Chlamydia which are sexually transmitted diseases.
- Prostatitis (because Tetracyclines are distributed in prostatic tissues).
- Also may be used in traveler diarrhea.

# 4- Aminoglycosides

- e.g Gentamicin
- Bactericidal antibiotics
- Active against gram negative aerobic organisms.
- Active against gram positive if given with penicillin

## MOA:

Inhibits protein synthesis by binding to 30S ribosomal subunits

## Pharmacokinetics

- Poorly absorbed orally so it's given I.M or I.V ‹.
- Crosses placenta.
- Excreted unchanged in urine ( not metabolized in the liver)
- More active in alkaline medium

**Note:** It is important to monitor plasma levels of gentamicin to avoid concentrations that are toxic to the body. Because it's excreted unchanged in urine these concentrations can easily be measured in plasma.

## Adverse effects

- Ototoxicity
- Nephrotoxicity( gentamicin accumulates in renal cortex causing toxicity)
- Neuromuscular blocking effect (In high doses)

**Note:** Gentamicin accumulates in the endolymph and perilymph of the inner ear, and toxicity correlates with the number of destroyed hair cells in the organ of Corti found in the ear. It may cause irreversible deafness.

## Contraindications:

- Renal dysfunction
- Pregnancy
- Diminished hearing
- Myasthenia gravis

## Therapeutic uses

Severe UTIs caused by gram negative aerobic organisms (pseudomonas or enterobacteria).

# 5- β-Lactam antibiotics (Both are bactericidal)

1-Extended- spectrum penicillin (piperacillin)

2-Cephalosporins

MOA: both inhibit bacterial cell wall synthesis. (Bactericidal)

## Piperacillin: (is a safer drug than gentamycin)

- Effective against pseudomonas aeruginosa & Enterobacteria.
- Penicillinase sensitive
- Can be given in combination with β-lactamase inhibitors as clavulanic acid, sulbactam, tazobactam.

**Note:** Penicillinase (beta-**lactamase)** is an enzyme produce by bacteria to resist penicillin activity making the drug nonfunctional.

## 3rd generation cephalosporins

Ceftriaxone & Ceftazidime (safe and effective)

- Mainly effective against gram-ve bacteria.
- Effective on N.Ghonorhea
- They are given parenterally (I.M or I.V)
- Given in severe / complicated UTIs & acute prostatitis

# 6- Fluroquinolones

e.g. ciprofloxacin

## MOA:

Inhibits DNA gyrase enzyme.

## Therapeutic uses

- UTI'S caused by multidrug resistance organisms as pseudomonas.
- Prostatitis ( acute / chronic )
- Also used for traveler diarrhea

# Prostatitis

## Acute prostatitis:

### Non- catheter- usually due to gram-ve(E.coli or Klebsiella)

Antibiotics used:

1. TMP/SMX (Co-trimoxazole),
2. IV cephalosporin
3. ciprofloxacin.

### Catheter associated due to gram-ve or enterococci.

Antibiotics used:

1. ciprofloxacin
2. ceftriaxone.

## Chronic prostatitis due to E.coli, Klebsiella & Proteus

Antibiotics used:

ciprofloxacin (fluroquinlones), 500mg bid for at least 12 weeks

## Antibiotics used for treatment of prostatitis in general:

1. **TMP/SMX** ( Co-trimoxazole)
2. **3rd Generation cephalosporins (ceftriaxone)**
3. **Flurquinolones ( ciprofloxacin , levofloxacin )**
4. **Tetracyclines ( Doxycycline)**