

# Pharmacology Team 431

Lecture :

## Treatment of Urinary Tract Infection

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 IMPORTANT

 Female Notes

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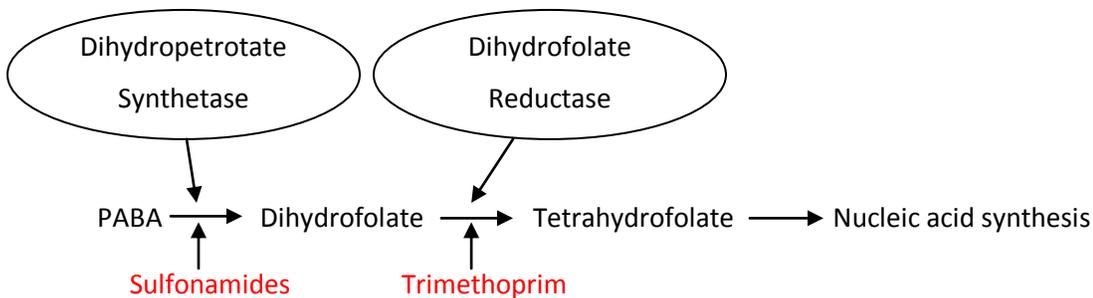
## Antibiotics we use in UTI :

1. **TMP, TMP/SMX ( co-trimoxazole) p.o.**
2. **Nitrofurantoin p.o. ( only used in UTI )**
3. **Tetracyclines, e.g. Doxycycline p.o.**
4. **Aminoglycosides, e.g. gentamicin**
5. **B-lactam antibiotics : extended – spectrum penicillins (e.g.piperacillin)**
6. **3<sup>rd</sup> generation cephalosporins -e.g.ceftriaxone & ceftazidime**
7. **Quinolones, e.g. ciprofloxacin,p.o**

### 1- (Sulfamethoxazole – Trimethoprim ) co-trimoxazole (SMX) (TMP)

- Known as Co-trimoxazole ( Bactrim, Septra )
- 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) < **for your info**

#### ❖ Mechanism of Action :



شرح لـ MOA :

البكتيريا لكي تصنع الحمض النووي تحتاج PABA والذي يتحول لـ Folic acids عن طريق الـ pathway المذكور ، جزء sulfonamide من العلاج الكلي هذا عبارة عن Structural analogue لـ PABA يعني مطابق إلى حد ما لـ تركيبة الـ PABA .. بالتالي sulfonamides تتنافس مع الـ PABA على اخذ الـ pathway ، النتيجة هي أن البكتيريا بتطلع مركبات ليست ... folates الـ Trimethoprim يعمل inhibition للإنزيم الآخر في الخطوة الي بعدها بحيث يكون داعم لـ sulfonamides

So we can say **Sulfamethoxazole** - which is sulfonamide - acts as a "**false-substrate**" inhibitor of DHP synthetase

PABA = para-aminobenzoic acid

DHF = Dihydrofolate

DHP = dihydropyrotate

## ❖ Pharmacokinetics :

### A ) 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.

### B) 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 % ) **less than Sulfonamides**
- 60% of TMP or its metabolite is excreted in the urine
- TMP concentrates in the prostatic fluid. ( **Because it's more lipid soluble, it will penetrate the prostatic membrane** )

## ❖ Clinical uses:

- Acute urinary tract infections
- Complicated urinary tract infections
- Recurrent urinary tract infections
- Upper respiratory tract infections
- *Pneumocystis carinii pneumonia*
- Prostatitis ( acute/ chronic )

## ❖ Adverse Effects :

- Gastrointestinal- Nausea, vomiting
- Allergy
- Hematologic
  - **Acute hemolytic anemia**
    - A)hypersensitivity B) G6PD deficiency
  - **Megaloblastic anemia** due to TMP.
- Drug interactions
  - Displace bilirubin- if severe – **kernicterus ( jaundice)** < severe elevation of bilirubin , it can cause damage to nerve cells. It's not used in case of **(children and pregnancy)** because their enzymes are not mature enough to handle the drug.
  - **Potentiate warfarin, oral hypoglycemics.**

G6PD deficient individuals are at high risk of hemolytic anemia in states of oxidative stress. Oxidative stress can result from oxidative drugs such as TMP/SMX . These oxidative drugs can result in rupture due to interfere with Glutathione system of RBCs and therefore causing Haemolytic anaemia

يعني يزيد من سيولة الدم بشكل خطير في حالة استخدامه مع الوارفارين ، او تسبب انخفاض شديد في السكر مع أدوية خفض السكر

### ❖ Contraindications :

- **Pregnancy** ( b/c it can cross the placenta and affect the fetus)
  - Nursing mother ( the drug is excreted with milk )
  - **Infants** under 6 weeks
  - **Renal or hepatic failure**
  - **Blood disorders (E.g: patient with hemolytic anemia)**
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## 2- Nitrofurantoin

### ❖ Antibacterial Spectrum :

**Effective against E. coli** or Staph saprophyticus, but other common UT Gm- bacteria may be resistant. Gm+ cocci are susceptible.

### ❖ Mechanism of action :

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

شرح للـ MOA :

الدواء هذا عندما يدخل إلى البكتيريا الحساسة من هذا الدواء ، تقوم البكتيريا بعملية reduction له بإنزيم اسمه nitrofurantoin reductase وبعدها يكون مركبات نشطة ويدمر الـ DNA الخاص بالبكتيريا ويمنع بعض الإنزيمات الهامة للنمو.

### ❖ Pharmacokinetics :

- Absorption is complete after oral use
- Metabolized (75%) & excreted rapidly that has 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 brown.** ( so you have to tell the patient )
- **Must be given with food or milk**, not given with empty stomach (b/c it causes severe gastric ulcer up to gastric bleeding)

### ❖ Adverse effect :

- **GI disturbances:** bleeding of the stomach, nausea, vomiting and **diarrhea** (must be taken with food). **Used with food to increase its absorption and decrease GI irritation**
- Headache and nystagmus ( زغلة في البصر )
- **Hemolytic anemia**
- **Pulmonary toxicity on chronic use (Pulmonary fibrosis).**

### ❖ Contraindications:

- Pts with **G6PD deficiency ( haemolytic anaemia )** as in TMP/SMX
- **Neonates** (cause their enzymes are not mature enough to handle the drug as in TMP/SMX )
- **Pregnant women** ( after 38 wks of pregnancy ) as in TMP/SMX

### ❖ 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, po q 6h/7 days.

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## 3- **Tetracyclines:** ( it is a group which has a large number of drugs )

in General they are :

- Broad spectrum antibiotic.
- Bacteriostatic .

E.g ( **Doxycycline** )

### ❖ Mechanism of action :

- **Inhibit protein synthesis** by binding **reversibly (Bacteriostatic )** to **30S** subunit.

### ❖ Pharmacokinetics

- Given orally
- **Absorption is 90-100%(completely absorbed from GIT)**  
**BUT**
- **di & tri-valent cations ( Ca, Mg, Fe, AL) impair absorption**
- Protein binding 40-80 %
- Distributed well, including , **prostatic tissues**  
(so it can be used with patient who has **Prostatitis** )
- **Cross placenta** and **excreted in milk**
- Excreted through **non-renal route**(we can use it with patient who has **renal impairment** )

( **Doxycycline** ) must be not given with **milk or milk products** b/c there is a grade affinity between **Tetyacyclines** and **Ca**.

When they meet each other, they rapidly make an **insoluble complex** which excreted in stool.

The end result is that the patient does not get any benefit from the Ca, nor from the drug.

❖ **Adverse effects:**

- Nausea, vomiting and diarrhea
- Thrombophlebitis. (inflammation of veins )
- Hepatic toxicity
- **Brown discoloration & deformity of teeth ( children)..( b/c they has grad affinity with Ca)**
- **Deformity of bones ( children).. ( b/c they has grad affinity with Ca)**
- Vertigo
- Superinfections.

❖ **Therapeutic Uses:**

- **UTI's** due to Mycoplasma & Chlamydia.
- **Prostatitis.**

❖ **Contraindications**

- Pregnancy
- Breast feeding
- Children

b/c it can cause

1- **Brown discoloration & deformity of teeth**

2- **Deformity of bones**

with (children)

## 4-Aminoglycosides

In general, they are:

- **Bactericidal**

### ❖ Mechanism of action

- **Inhibits protein synthesis** by binding to **30S** ribosomal subunits.

### ❖ Pharmacokinetics

- **Active only against gram negative + aerobic organisms.**
- Poorly absorbed orally
- **Given I.M, I.V.**
- **cross placenta**
- Excreted unchanged in urine
- More active in **alkaline medium**

the drug needs Oxygen dependent active transport to enter the bacterial cytosol and binds to the ribosomes. As we all know anaerobes live in the absence of Oxygen, so anaerobic bacteria are resistant to aminoglycosides

### ❖ Adverse effects:

- **Ototoxicity** (lead to loss of hearing-Deafness-,so you have to use the audiogram (Hearing Test) for your patient during the course)
- **Nephrotoxicity**
- **Neuromuscular blocking effect**  
(when the patient is in the operation, and the doctor does not know that his patient already took one of the **Aminoglycosides**. Then he give the pt  $\beta$ -blocker for the operation)  
-Aminoglycosides cause relaxation of the muscles }  
- $\beta$ -blocker causes relaxation of the muscles } Together may cause paralysis → death

### **E.g: Gentamicin**

### ❖ Clinical uses:

In severe infections caused by gram negative organisms as pseudomonas enterobacter

### ❖ Contraindications:

- **Renal dysfunction** (excreted in kidney)
  - **Pregnancy** (b/c it can cross placenta)
  - **Diminished hearing**
  - **Myasthenia gravis** (weakness of the muscles)
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## 5-β-Lactam antibiotics:

A-Extended- spectrum penicillins



(piperacillin)

- Effective against **pseudomonas aeruginosa.**
- Penicillinase sensitive.
- Given in combination with β-lactamase inhibitors as tazobactam.

B-3<sup>rd</sup> generation cephalosporins



(Ceftriaxone & Ceftazidime)

- Effective against **Gm-ve bacteria.**
- Inhibit bacterial **cell wall synthesis**
- Bactericidal
- Given parenterally
- Given in severe /- **complicated UTIs**  
**-acute prostatitis**

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## 6-Fluroquinolones:

- E.g: **Levofloxacin & Ciprofloxacin**

### ❖ Mechanism of action:

- Inhibits DNA gyrase enzyme (Not important)

This class of antibiotics can damage the cartilage causing arthropathy & can cause abortion and birth defects in case of pregnancy, so it's **contraindicated in children as well as pregnant women**

### ❖ Clinical uses:

- **UTI<sup>s</sup>** caused by **multidrug resistance organisms as pseudomonas.**
  - **Prostatitis** ( acute / chronic )
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❖ **Antibiotics used for treatment of prostatitis :**

1-TMP/SMX complex (co-trimoxazole )

2-Tetracyclines (Doxycycline)

3-Gentamicin

4-Piperacillin

5-Fluroquinolones(Ciprofloxacin)

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