Pharmacology Team

Urinary Tract Infection

الدكتور الحميد نبه على عدم حفظ الأسماء التجارية !

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URINARY TRACT INFECTIONS

- **Upper Urinary Tract Infections** >> *Pyelonephritis* (Kidney & Ureters)
- **Lower Urinary Tract Infections** >> *Cystitis* (Bladder), Urethritis &Prostatitis

UPPER URINARY TRACT INFECTIONS	LOWER URINARY TRACT INFECTIONS
Clinical Picture Headache/Malaise – Nausea/Vomiting Fever/Chills – Muscular Pain Suprapubic pain (back pain at waist level) Hematuria – Proteinuria - Leukocytosis	**Clinical Picture** No fever – *Dysuria* (difficulty in urination) Frequency (urinate many times) lower abdominal pain – bacteruria *Hesitancy* (cant complete urination) - *Urgency* (can't hold urine) Cloudy urine (not pure) – Bloody Urine *Bad smell* (due to presence of bacteria, convert urea to ammonia)
Harder To Treat – more serious	Easy To Treat

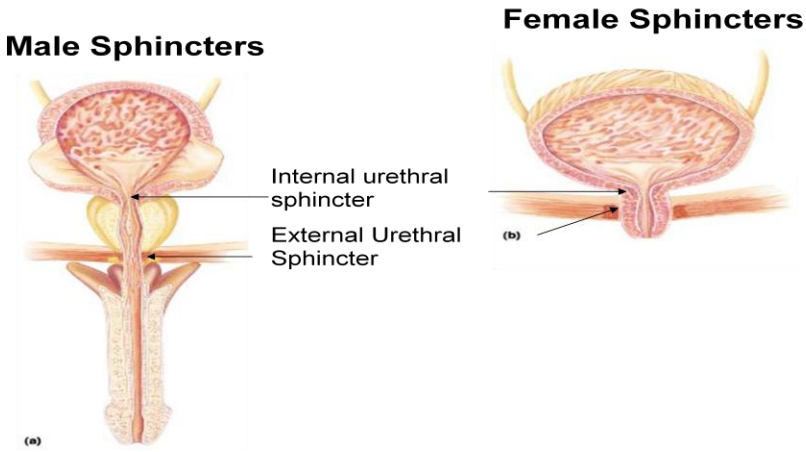
It's the 2nd most common infection (after Reproductive Tract Infections: RTI)

- **ASSOCIATED WITH:** obstruction of flow of urine

- **MORE COMMON IN FEMALES THAN IN MALES** (WHY IS?)
  Because
- -females have, shorter urethra
- – their urethral opening is near sources of normal flora (bacteria) e.g. vagina & anus
  Incidence increase with age

- **CAUSES OF UTIS:** normally, urine is *Sterile*. Bacteria comes from digestive tract to openings of the urethra

  - Obstruction of flow of urine (e.g. kidney stone)
  - Enlargement of *Prostate Gland* in men (common cause)
    prostatic hypertrophy → obstruct urethra → urine not properly expelled out
    → ↑residual volume → source of infections (high risk factors)
  - Catheters placed in urethra and bladder
  - Not drinking enough fluids
  - Holding urine (urinary bladder become weak) → then some urine remains in the bladder after micturation allowing bacteria to multiply
  - Large uterus (in pregnant women)
  - Poor toilet habits (wiping back to front – in women)
    (it changes PH in vagina → more growth of pathogenic organisms → goes to urethra)
  - Disorders that suppress the immune system (e.g. diabetes, cancer chemotherapy ..etc)



Risk Factors:

In Females	In Males
- Pregnancy - Spermicidal contraceptives (kills sperms) - Estrogen Deficiency (↓E → PH changes and this favors bacterial growth) - Diabetes, cancer (chemotherapy) → ↓immunity	- Lack of Circumcision التطهير او الختان (very important to complete excretion – left out urine triggers infection) - Prostatic Hypertrophy – Use of condom or catheter - Old age – obstruction of flow of urine (e.g. kidney stone) - Neurogenic bladder – renal transplantation

- **Pathogens of UTI**
  - Gram (-) bacteria (MOST COMMON)
    - E-coli - Proteus - Klebsiella - Psuedomonas
  - Gram (+) bacteria (LESS COMMON)
    - Staphylococcus species (s.aureus – saprophytocus)
    - Chlamydia trachomatis ,Mycoplasma & N.gonorrhea (limited to urethra, unlike E.coli **may be sexually transmitted**)

Why is chlamydia serious? It is sexually transmitted → you have to treat both, husband and wife.

- **Routes of infection:** it can be either:
  - ***Simple*** *:* non catheter associations (community acquired)
    do not spread to other organs and go away directly after treatment (mainly **due to** e-coli).
  - ***Complicated*** **:** Catheter associations (nosocomial), immunosuppression, stones, renal disease, diabetes
    spread to other organs, and is resistant to many antibiotics (more difficult to treat)
    (**due to** hospital acquired bacteria – e-coli, klebsiella, proteus, pseudomonas, enterococci, staphylococci)

- **Treatment: Antibiotics:**
  - **Trimethoprim** (TMP) ***AND*** **Sulfamethoxazole** (SMX) ***OR*** their combination (**co-trimoxazole)**
  - **Nitrofurantoin**
  - **Quinolones** (e.g. ciprofloxacin)
  - **Ceftriaxone**
  - **Ceftazidime**
  - **Doxycycline (C.trachomatis and mycoplasma)**

  Each Antibiotic is **selected** depending upon three, ***Patient History*** – ***Urine Test*** – ***Culture Sensitivity Test***

ANTIBIOTICS

Sulfamethoxazole (SMX) - Trimethoprim (TMP)

Co-trimoxazole

(Bactrium, Septra)

Alone, each agent is ***Bacteriostatic***

Together (synergism) they are ***Bactericidal***

2) SULPHONAMIDES (SMX)

- **Chemistry**

Structural analogue of *Para–Aminobenzoic Acid* (PABA)

PABA= precursor for folic acid synthesis in bacteria

- **Mechanism of Action**

Bacteriostatic,
suppress bacterial growth by
inhibiting synthesis of ***Folic Acid***
by inhibiting ***Dihydropteroate Synthetase***

- **Absorption, metabolism & Excretion**

Given orally, USUALLY in combination form
Absorption from stomach and small intestine.
Distribution widely distributed to tissues & body fluids
(including CNS, CSF), placenta and fetus.

- **Less lipid soluble than TMP**
- Bind to serum protein (approx. 70%).

Metabolism in the liver by the process of *Acetylation.*
Excretion in the urine
as its main form AND as acetylated derivative.

1) TRIMETHOPRIM (TMP)

- **Mechanism of Action**

Bacteriostatic, (given alone or in combination with SMX) It inhibits ***Dihydrofolate Reductase*** & inhibits conversion of ***Folate*** into ***Tetrahydro-folate***

*TMP acts 10000 times effective against bacteria than human but if the patient is deficient in folic acid , TMP can cause megaloblastic anemia

- **Absorption, metabolism & Excretion**

given orally, alone or in combination with SMX
Absorption from the gut
Distribution
Widely distributed in tissues & body fluids
(including CSF)
More lipid soluble than SMX
- Protein bound (approx.40 %)

Excretion
60% of TMP/its metabolite is excreted in the urine

- **TMP concentrates in the prostatic fluid.**

Prostatitis >> TMP is the drug of choice because, it can reach its fluid in high concentration

- **ADVERSE EFFECTS:**
  1. **Gastrointestinal** - Nausea, vomiting.
  2. **Allergy.**
  3. **Hematologic.**
     - ***A) Acute hemolytic anemia***
       - hypersensitvity .
       - G6PD deficiency.
     - ***B) Megaloblastic anemia due to TMP.***

- **CONTRAINDICATIONS:**
  - Pregnancy → because pregnant women are defieicent in folic acid
  - Nursing mother
  - Infants under 6 weeks →due to the immaturity of the liver
  - Renal or Hepatic Failure
  - Blood Disorders

4. **Drug interactions**

- **People with "Severe-Kernicterus"** (disorder in the newborn → accumulation of bilirubin). with these drugs → it displace ***Bilirubin → death.***
- **Potentiate warfarin** ((Drug-drug interaction → ↑ effect of warfarin)) .
- **Oral hypoglycemics** ((Renal damage → sulfonamide accumulate in urine →obstruction in the flow of urine)).

Generally it is safe and used in resistance bacteria

Nitrofurantoin

- **Antibacterial Spectrum**
  Effective against "E.COLI". -- **Resisted in** common Gram (-) organisms. -- **Susceptible against** Gram (+) cocci.
- **Mechanism of Action**
  It is prodrug
  Not clearly known, mainly is:
  Drug + Sensitive bacteria → Drug becomes active → it inhibits various enzymes and damages DNA.
  Activity of drug is increased when the PH of urine is 5.5.

- **Therapeutic Uses**
  Used as urinary anti-septic but has little or no "systemic bacterial effect".
  Useful in lower urinary tract infections.

Anti-septics:
usually not used as drugs
they are agents that are used as supporting to inhibit the growth of microorganism in urine to help in the treatment of UTI

- **Adverse Effects**
  - GIT disturbances (nausea, vomiting and diarrhea).
  - Headache and nystagmus (involuntary eye movements).
- **Contraindications:**
  - Patients with G6PD (hemolytic anemia)
  - Neonates
  - Pregnant women
  - Severe renal insufficiency

Doxycycline

A long-acting Tetracycline

- **Mechanism of Action**
  - **Inhibits** protein synthesis by binding reversibly to 30 s subunit of ribosome
  - Bacteriostatic for Gram +ve & Gram -ve bacteria
  - Drug of choice for ***Chlamydia*** & ***Mycoplasma*** infections "we know that by **Culture Sensitivity Test**"
    Why it is the drug of choice in case of Chlamydia ?
    Because Chlamydia does not have cell wall → beta lactam antibiotics are not effective
- **Pharmacokinetics**
  - **Usually given orally**
  - **Absorption** is 90-100%
    Absorbed in the upper small intestine & is 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
    ((b\c it can easily bound to Ca → You can't give it to pregnant ladies or children
    Largely **metabolized** in the liver

- **Therapeutic Uses:**
  Treatment of UTI due to Chlamydia or Mycoplasma (100mg. po for 7 days) & hospital acquired UTI
  Traveler diarrhea

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- **Side Effects**
    1) Nausea, vomiting and diarrhea
    2) Thrombophelbitis (vein inflammation due to I.V)
    3) Hepatic toxicity (especially when prolonged therapy with high dose)
    4) Brown discoloration of teeth (× children – because it makes complexes with ca in children's teeth ×)
    5) Deformity or growth inhibition of bones (×children)
    6) Vertigo (feeling that your environment is spinning – differs from dizziness)
    7) **Superinfections**
       when you give Antibiotics for long time (especially tetracycline) → normal flora alters
       → there's a chance of development of other infections "superinfections"
       (Dr. prescribes vitamins to avoid them)

3rd Generation Cephalosporins (β-Lactam)

Ceftriaxone (Rocephin) & Ceftazidime (Fortum)

Effective Against Gram -ve bacteria.

- **Mechanism of Action:** inhibition of cell wall synthesis ((Bactericidal))
- **Pharmacokinetics:** They are given parenterally
- **Therapeutic Uses**
    - UTI during pregnancy
    - UTI unresponsive to other drugs
    - Complicated UTI – recurrent UTI
    - Severe UTI
      * it is expensive

Fluoroquinolones

Effective Against Gram –ve Aerobic Bacteria and Some Gram +ve
(e.g. Ciproflaxin, norflaxin, Levoflaxin)

- **Therapeutic Uses**
    - for complicated UTI
    - multidrug resistant UTI caused by Gram-ve

Pencillins

(e.g. Ampicillin & amoxicillin)

- **Therapeutic uses:** UTI caused by E.coli

Prostatitis:

Inflammation of the prostate gland → no proper flow of urine → residual urine → UTI

ETIOLOGY

A) Acute Prostatitis:

- Non-catheter associated - usually due to gram -ve (E.coli or Klebsiella)
  Antibiotics used : TMP/SMX - IV(160/800mg bid), cephalosporin or ciprofloxacin.
- Catheter associated - due to gram -ve or Enterococci.
  Antibiotics used: ciprofloxacin or ceftriaxone.

B) Chronic Prostatitis: due to E.coli, Klebsiella & Proteus
Antibiotics used: ciprofloxacin,500mg bid for at least 12 wks