Lecture 2&3

Treatment of Urinary Tract Infections

Objectives:

1. Recognize different groups of antibiotics used in urinary tract.
2. Describe their mechanism of action, pharmacokinetic properties and adverse effects.
3. Describe the use of antibiotics and their rational of combination of different antibiotics.
4. Describe the spectrum of various antibiotics

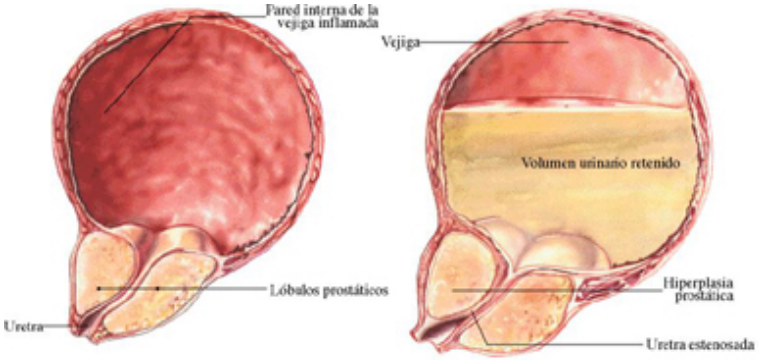
- Additional Notes
- Important
- Explanation –Extra-

Classification of urinary tract infections

- Symptomatic infections
  - Uncomplicated UTI (mainly in women)
    - acute cystitis
    - Acute urethritis
    - recurrent cystitis
    - Acute pyelonephritis
  - Complicated UTI
    - Acute **prostatitis** → usually due to gm- (E.coli or Klebsiella)
    - chronic **prostatitis** → due to (E.coli, Klebsiella & Proteus)
- Asymptomatic bacteriuria

Antibiotics used for treatment of prostatitis :

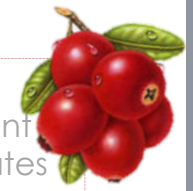
- **TMP/SMX**
- **3rd Generation cephalosporin** :Ceftriaxone
- **Quinolones** :Ciprofloxacin , levofloxacin
- **Tetracycline's** :Doxycycline in chronic prostatitis especially in trachomatis & chlamydia infections



Urinary tract infections (UTI's)

General information	– 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. – Incidence of UTI increases in old age (10% of men & 20% of women). – Normally urine is sterile. Bacteria comes from digestive tract to opening of the urethra.	
Causes	– Obstruction of the flow of urine (e.g. kidney stone) – Enlargement of prostate gland in men –**prostatitis**- (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 agents	(Gm-) bacteria **–common-**	E.coli (approx. 80% of cases), Proteus, Klebsiella, Pseudomonas.
	(Gm+)bacteria **-less common-**	Staphylococcus species , Chlamydia trachomatis , Mycoplasma and N. gonorrhea (common cause of STD)

Cranberry products may help prevent UTIs in some women especially those with recurrent infections it contain compounds called tannins (or proanthocyanadins). Tannins may prevent E. coli bacteria from adhering to cells in the urinary tract, thereby inhibiting infection, indicates a 2012 review of studies. Drinking several glasses of cranberry juice a day appeared to offer more protection than taking cranberry tablets. Researchers think that cranberries help prevent harmful bacteria from attaching and sticking to urinary tract cells.



Drugs	Co-trimoxazole (Bactrim, Septra) = trimethoprim + sulfamethoxazole	
Spectrum	- each drug alone is **bacteriostatic** - Together they are **bactericidal** (synergism → تعاون تتابعي واحد يسوي شي و الثاني يكمل)	
Pharmacokinetics	**Sulfonamides (SMX)**	**Trimethoprim (TMP)**
	Orally - rapidly absorbed in stomach + s. intestine - widely distributed - bind to serum proteins	
	- cross placenta - metabolized by liver (acylation). - eliminated in urine (unchanged or as acylated derivative)	- more lipid soluble than SMX - protein bound - 60% of TMP or its metabolite is excreted in the urine - TMP concentrates in the prostatic fluid **(used in prostatitis)**
MOA	P - Aminobenzoic Acid ↓ Dihydropetroate synthetase ✖ **SMX** Dihydrofolate — Inhibits growth ↓ Dihydrofolate reductase ✖ **TMP** Tetrahydrofolate — Inhibits nucleic acid synthesis ↓ Nucleic acid synthesis	
Clinical uses	– Acute, Complicated and **Recurrent** urinary tract infections – Prostatitis (acute/ chronic)	
ADRs	- GIT - Hematologic: 1. Acute **hemolytic anemia** can happen due to : (sulfa) → a) hypersensitivity b) G-6-PD deficiency (SMX) 2. **Megaloblastic anemia** due to TMP. (folic acid deficiency) (TMP) → **can be avoided by giving folic acid** - Kernicterus (bilirubin –induced brain dysfunction) → Jaundice in neonates due to ↑ bilirubin in blood and it's because of sulfa. - Crystalluria: **(crystals in urine due to precipitation of drug – avoided by ↑ water intake)** - Hypersensitivity reactions → urticarial or fever	
Contraindicated	- Pregnancy (cross placenta) - Nursing mother (secreted in milk) - Newborn Infants (encephalopathy) → Jaundice that might cause abnormalities in brain. - Renal or hepatic failure (caused by metabolism & secretion). - Blood disorders (give supplements).	

drugs	Nitrofurantoin	Tetracycline (Doxycycline – Minocycline)
Organism	• effective on E-coli • suscebtable: Gram +ve • not effective: P-aeruginoa	This substance likes to combine with milk products (Ca), so it can't be taken with them, neither given to children because it will affect their bones (bones are formed from Ca).
MOA	Changed by bacteria to an active agent that inhibits various enzymes and damages bacterial DNA	Inhibit protein synthesis by binding **reversibly** to 30 s ribosomal subunit
Spectrum	(bactericidal)	Broad spectrum (Bacteriostatic) Cause it's reversible.

Pharmacokinetics	• orally → Absorbed rapidly and completely from GIT (Because of that it causes gastric irritations, so it should be given with food).
	• Well concentrated in the urine
	• Rapidly metabolized by the liver
	• 40 % is excreted unchanged into the urine
	→ Turns urine to a **dark orange- brown**.
	• Given with food
	• higher activity in acidic urine
		• Long acting → given orally once per day.
		• 90 – 100% Absorbed in the s. intestine.
		• Protein binding 40-80 %.
		• Distributed well, including prostatic tissues
		• Cross placenta and excreted in milk.
		• Metabolized in liver.
		• **Excretion:**
		  • Doxycycline → in bile
		  • Minocycline → in urine
		• **Absorption is impaired by:**
		1. divalent cations (Ca, Mg, Fe)
		2. milk and its products
		3. antacids (aluminium hydroxide gel, sodium bicarbonate)

Clinical uses	• urinary antiseptics . • Prophylaxis: for recurrent UTI • Not effective in systemic UTI as **pyelonephritis** • Dose: 50-100 mg (orally four times daily) for 7 days	UTI's & **chronic prostatitis** due to Mycoplasma Chlamydia.
ADRs	• GIT • Headache and nystagmus. • Hemolytic anemia (G-6-PD deficiency) • Pulmonary fibrosis (on chronic use)	• GIT • Thrombophlebitis (i.v route) • Hepatic toxicity (prolonged therapy with high dose). • Brown discoloration & deformity of teeth (children) • Deformity or growth inhibition of bones (children) • Vertigo (minocycline) • Super-infections (because it's broad spectrum so it kills normal flora & allows other organisms to enter the body).
Contra-indications	• Patients with G-6PD deficiency • Neonates (babies up the age of one month) • ↓ renal function • Pregnant women (after 38 weeks of pregnancy) [even at late pregnancy]	• Pregnancy • Breast feeding • Children (up to 12 years)

	β -Lactam antibiotics		Fluroquinolones	
Drug	Extended spectrum penicillins **piperacillin**	**Cephalosporin's** **3rd generation: Ceftriaxone & Ceftazidime**	**Ciprofloxacin**	**Levofloxacin**
MOA	Inhibit bacterial cell wall synthesis		Inhibits DNA gyrase enzyme	
Spectrum	Broad spectrum **(Bactericidal)**			
Organism	Effective against **pseudomonas aeruginosa** & Enterobacter.	Mainly effective against gm- bacteria.	Effective against **pseudomonas aeruginosa**	
Pharmacokinetics and other notes	**Penicillinase** sensitive can be given in combination with β -lactamase inhibitors as **clavulanic acid , sulbactam, tazobactam.**	Given parentally (I.V.)	**Contraindicated in:** - Adolescent under 18 yrs. - Pregnancy. - Breast feeding mothers.	
Uses	Given in severe / complicated UTIs & acute prostatitis		-prostatitis -UTIs caused by multidrug resistance organisms as **pseudomonas**	
Side effect	**Hypersensitivity reaction up to anaphylactic shock**	**Hypersensitivity reaction**	**Damage grown cartilage that's why it is contraindicated in children < 18 yrs.**	

You can give cephalosporin in penicillin allergic patients but if the allergy is anaphylactic shock then it is contraindicated.

Extended- spectrum penicillin's:
We can combine:

- Amoxicillin with clavulanic acid
- piperacillin with tazobactam.

Pseudomonas Aeruginosa

EXTRA INFO

You are going to hear so much about this bug while working in the hospital. It's VERY resistant to many antibiotic & infect patients with weak immune system. It doesn't affect healthy people! It produces GREEN color in the nutrient agar & It causes so many diseases such as: UTI's pneumonia, endocarditis.

Drugs	Aminoglycosides (gentamycin – tobramycin)
MOA	Inhibits protein synthesis by binding **irreversibly** to 30S ribosomal subunits.
spectrum	**narrow spectrum (Bactericidal)** (Because it's irreversible).
Organism	Active against gram negative aerobic organisms.
Pharmacokinetics	1. Poorly absorbed orally → not used orally except in GIT infection 2. Given I.M, I.V. 3. cross placenta 4. Excreted unchanged in urine 5. More active in **alkaline** medium.
Clinical uses	Severe UTIs caused by gram negative aerobic organisms , **gentamicin** is **effective in treating pseudomonal infections**
ADRs	TRIAD: • Ototoxicity → up to deafness • Nephrotoxicity • Neuromuscular blocking effect → **curari** like action. It shouldn't be given before surgery with anesthesia or it will paralyze the diaphragm muscle & patient will die.
Contraindications	– Renal dysfunction – Pregnancy – Patients with hearing problem (Diminished hearing) – Myasthenia gravis → due to muscular relaxant.

What does each drug look like?

Nitrofurantoin

Doxycycline

Minocycline

Gentamicin I.V. & I.M.

Sulfamethoxazole (SMX) Trimethoprim (TMP)

Ceftriaxone

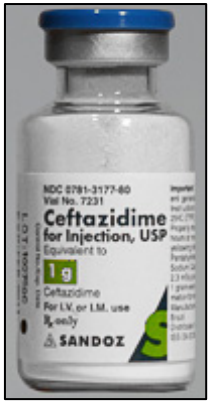
Piperacillin (tazobactam)

Amoxicillin / clavulanic acid = Augmentin

Amoxicillin

ciprofloxacin

levofloxacin



Ceftazidime

tobramycin

Summary

Drug	Kind	Notes	Side Effects
TMP/SMX	Together are bactericidal (Each 1 alone is bacteriostatic)	• TMP concentrates in prostate fluid crosses prostate membrane used in prostatitis • Used in Acute / complicated / recurrent UTI and prostatitis	• Hypersensitivity Reactions • Acute Hemolytic Anemia (SMX) • Megaloblastic Anemia due to folinic acid def. (TMP)
Nitrofurantoin	• Effective against E.coli and Gram +ve cocci • Inhibits bacterial enzymes + damages DNA	• Antibacterial activity higher in acidic urine • Given with food • Well concentrated in urine • Used as urinary antiseptic , prophylaxis and treatment of recurrent UTI	• Severe GIT upset. • Hemolytic anemia (G6PD deficiency) • Pulmonary fibrosis
Tetracyclines	• Broad-spectrum bacteriostatic antibiotics. • Inhibits protein synthesis. • Used in UTI due to mycoplasma + chlamydia and in prostatitis.	• Absorption is impaired by divalent cations, milk and its products and antacids • Distribution include prostate tissues • Doxycycline excreted by non-renal routs while minocycline • kidneys	• Discoloration and deformity of teeth • Deformity or growth inhibition of bones (both in children) • Vertigo • Hepatotoxicity • Superinfections
Aminoglycosides	• Bactericidal , inhibits protein synthesis. • Effective against Gram –ve aerobics.	• Crosses placenta. • More effective in alkaline medium. • Used in sever UTI due to gram –ve aerobics • Gentamicin is effective in pseudomonal infections.	• Ototoxicity • Nephrotoxicity • Neuromuscular blocking effect.

Guidelines recommend using nitrofurantoin or trimethoprin-sulfamethoxazole as first-line antibiotic treatments for UTIs. Fluoroquinolones (such as ciprofloxacin) are now only recommended when other antibiotics are not appropriate.

✸ Summary

Drug	1) Extended Spectrum Penicillins	2) Cephalosporins
B-Lactam Antibiotics	Ex.(piperacillin/tazobactam) • Bactericidal, inhibits cell wall synthesis. • Effective against pseudomonas aeruginosa + Enterobacter • Can be given with β -Lactamase inhibitors.	(3rd Generation) • Effective against Gram –ve bacteria. • Given in complicated UTI and acute prostatitis .

Fluroquinolones	**Ex.** (Ciprofloxacin , Levofloxacin) • Inhibits DNA gyrase enzyme	**Used in** • UTI due to multidrug resistance organisms (ex. Pseudomonas aeruginosa) • Prostatitis	**Side effect:** • CNS manifestations • Damage cartilage growing. • Phototoxicity

Antibiotics used for recurrent cases for prophylaxis:
- Nitrofurantoin
- TRM-SMX

Antibiotics NOT recommended in children or pregnant women :
- Tetracycline
- Quinolones :Ciprofloxacin , levofloxacin

Antibiotics recommended in pregnant women :
- Amoxicillin
- Cephalosporins

Antibiotics recommended in children :
- TRM-SMX
- Gentamicin – with precaution -
- Cephalosporins
- Penicillins

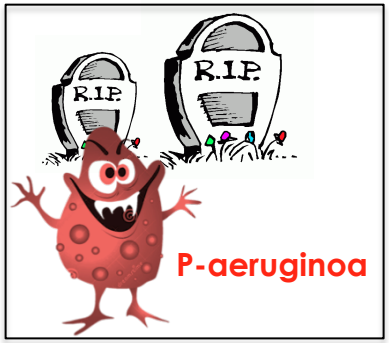
سوبر نايترو بيقضي على الأعداء !

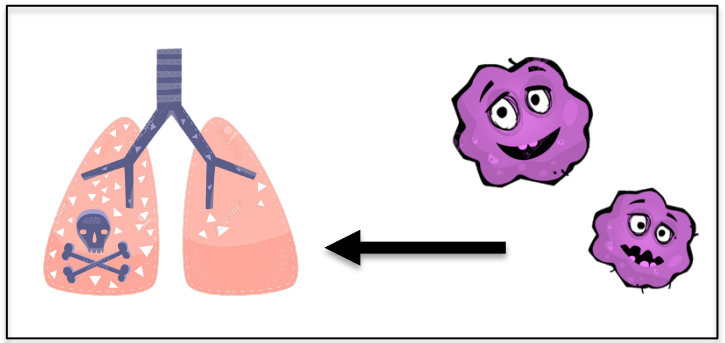
نايتروفيرنتوين شخص طبيعي جدا، ولكن عندما يرى **الإي كولاي** عدوه اللدود يتحول إلى أكتف إيجنت ويصبح اسمه **سوبر نايتروفيرنتوين**، فيصبح قويا جدا ويعصر الإي كولاي مثل العصير ويقضي على ***الدي ان اي*** تبعه فيصبح لون الإي كولاي غامق عندما ينخنق (Dark urine)!

سوبر نايتروفيرنتوين لديه أعداء آخرون أيضًا !

فهو يقضي على **قرام (−)** جميعهم ما عدا رئيسهم **سودوموناس أرجينوسا**، ويخافوا منه **قرام (+)**، فعندما يجي سوبر نايترو في المكان يخافوا منه وينكتم نفسهم فيسبب لهم pulmonary fibrosis.

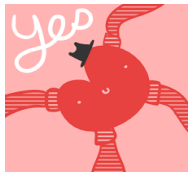
الناس دائما يستعينون بسوبر نايترو لكي يقيهم من الأعداء (prophylaxis) ولكي يطهر بيوتهم (anti-septic).





Mind maps

Doxy



Mino

USES

UTI
-mycoplasma
-chlamydia

30 s
- reversible
- bacteriostatic

Tetracyclines

Long acting

absorbed
prostatic tissue

not absorbed
- ca++
- Milk
- antacid

---

30 S
-irraRevisable
-Bactericidal

Aminoglycosides

Favors
Alkaline
Medium

Genta..

Tobra..

Ototoxicity

NOT GIVEN ORALLY

Mycin

GIVEN I.V or I.M

USES:

UTI: Gram (-) → Pseudomonal

Nephrotoxicity

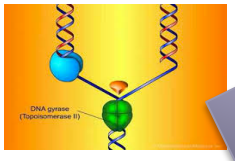
Neuromuscular blocking

Mind maps

B- Lactam

-Inhibit cell wall
-Bactericidal

- Penicillin
  - Pepracillin
    - -Pseudomona aeruginosa
    - -enterobacter
  - amoxacillin
- Cephalosporin
  - 1st
    - Cephalaxin
    - Ceftrazidine
  - 3nd
    - Ciftriaxone
    - -Prostatitis
    - -Gram (-)



-DNA Gyrase

FLuroquinolones

-pseudomonas
-prostitis

- Cipro
- Levo

FLOXACIN

MCQs

1-MCQs Pharma 2 and 3 What are the clinical uses of Co-trimoxazole?

a) Acute UTI
b) Complicated
c) Angina
d) Both a and b

2-Which one of the following adverse effects is NOT due to Sulfamethoxazole?

a) Acute hemolytic anemia
b) Megaloblastic anemia
c) Kernicterus (Jaundice)

(Explanation: It's due to Trimethoprim)

3-Nitrofuranton is effective against which of the following organism?

a) E-coli
b) P-aeroginosa
c) Klebsia

4-Which drug of the following causes Pulmonary Fibrosis?

a) Co-trimoxazole
b) Nitrofurantoin
c) Doxycycline

5-A patient came to a follow up appointment due to his UTI condition, complaining that he took Tetracyclines as prescribed daily with milk and the infection still didn't go. Which of the following statements is correct?

a) He should've taken folic acid with it
b) The absorption is impaired when it's combined with dairy products
c) Tertracycline is not the right drug for his condition

6-True or false. Doxycylcine is excreted through renal route and Minocycline excreted through non renal route.

a) True
b) False

7-All of the following drugs are Bactericidal except for?

a) Gentamycin
b) Tetracyclines
c) Co-trimoxazole

8-Which of the following drugs is more effective in Alkaline medium?

a) Aminoglycosides
b) Nitrofurantoin
c) Trimethoprim

Answers:
1-d
2-b
3-a
4-b
5-b
6-b
7-b
8-a

Good luck!

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