PHARMACOLOGY
TEAM 439

MED439
KING SAUD UNIVERSITY

UTI

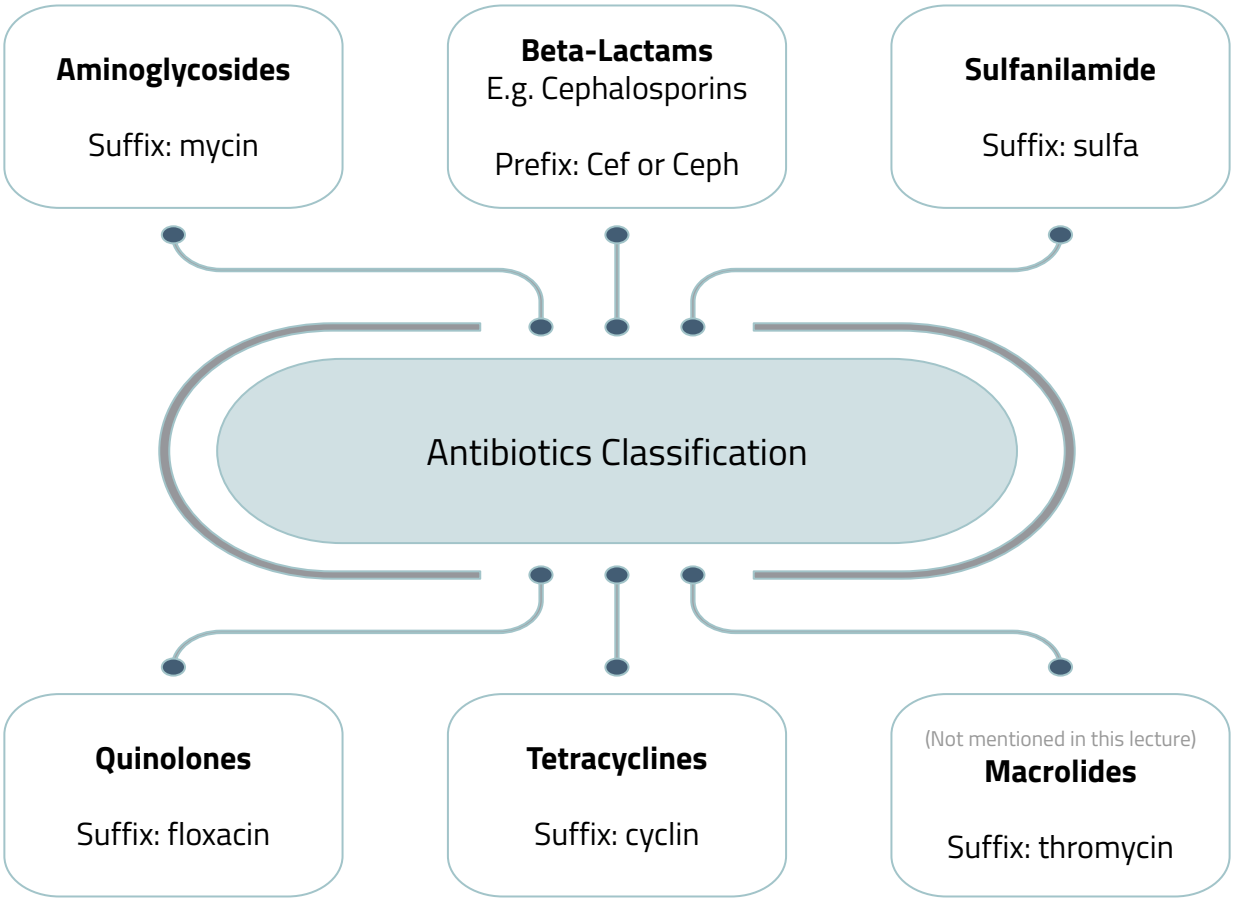
Objectives:

- Recognize different groups of antibiotics used urinary tract.
- Describe their mechanism of action,P.K and ADRS.
- Describe the use of antibiotics and their rationale of combination of different antibiotics.
- Describe the spectrum of various antibiotics.

Important
In male and female slides
Only in male slides
Only in female slides
Extra information
Notes

Editing file

EXTRA (Respiratory Block, team438)



Antibiotics Mechanism of Action

Bactericidal
Kills the bacteria by destroying:

- 1- Cell wall
  e.g. Cephalosporins
- 2- Nucleic acid (DNA or RNA)
  e.g.
  - Quinolones (DNA)
  - Rifampin (RNA)
  - TMP-SMX (Folate)

Bacteriostatic
Stops the growth by:

- Affecting Protein Synthesis e.g.
  - Tetracyclines
  - Macrolides
  - Aminoglycosides

  EXCEPTION:
  Aminoglycosides affects the protein synthesis but is considered bactericidal

Urinary Tract Infections

01 ▪ 2nd most common infection (after RTIs)

02 ▪ Often associated with some obstruction of the flow of urine

03 ▪ More common in women more than men 30:1 (Why?) short urethra in women

04 ▪ Incidence of UTI increases in old age (10% of men & 20% of women).

05 ▪ Normally urine is sterile. Bacteria comes from digestive tract to opening of the urethra.

Classification

Upper UTIs (Kidney & Ureters)

- ❖ Pyelonephritis
- ❖ More serious & difficult to treat

Lower UTIs (Bladder, Urethra & Prostate)

- ❖ Cystitis, Urethritis & Prostatitis
- ❖ More common & easier to treat

Causes of UTI

- Obstruction of the flow of urine (e.g. kidney stone)
- Enlargement of prostate gland in men (common cause)
- Catheters placed in urethra & 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).

UTI can be

- Infections spread to other parts of the body and resistant to many antibiotics. Thus more difficult to cure, due to hospital-acquired bacteria (E.coli , Klebsiella , Proteus , Pseudomonas , Enterococci , Staphylococci)

Simple

Complicated

- Infections do not spread to other parts of the body and go away readily with treatment (due to E.coli in most cases).

Bacteria responsible of UTIs

Gram -ve (Most common)	• **E.coli** (approx. 80% of cases) • Proteus mirabilis • Klebsiella • Pseudomonas aeruginosa
Gram +ve (less common)	• **Staphylococcus Saprophyticus** (approx. 20%)
Others	• Mycoplasma, Chlamydia trachomatis, & N.gonorrhea. ○ Limited to urethra, unlike E.coli may be sexually transmitted.

Treatment of UTIs

P.o.= taken orally

Cephalosporins
E.g. Ceftriaxone & Ceftazidime.
(I.V)

Co-trimoxazole
(SMX/TMP). P.o.

Quinolones
E.g. Ciprofloxacin
(P.o.)

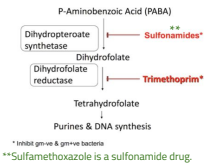
Nitrofurantoin
P.o.

Aminoglycosides
E.g. Gentamicin
(I.M , I.V)

Tetracyclines
E.g. Doxycycline
(P.o.)

Co-trimoxazole (TMP-SMX)

Trade names: Bactrim and Septra

Drug	Sulfamethoxazole	Trimethoprim
Overview	- Inhibit gram-ve & gram+ve bacteria -Alone, each drug is **bacteriostatic** but together they are **bactericidals** (synergism). - They are given orally in 5(SMX):1(TMP) ratio. - The optimal ratio of SMX to TMP in vivo is 20:1. - formulated 1(TMP): 5(SMX) Ex: 160 mg TMP + 800 mg SMX; 80 mg TMP + 400 mg SMX; 8 mg TMP + 40 mg SMX)..	
MOA	- Both drugs stop folic acid* production in microorganisms. - in microorganisms: PABA is turned into dihydrofolic acid by dihydropteroate synthetase (**SMX disturbs this step**). - dihydrofolic acid is turned into tetrahydro folic acid by dihydrofolate reductase (**TMP inhibits this enzyme**). PABA: para aminobenzoic acid *MOA: folic acid is required for synthesis of coenzymes important for enzymes that catalyze purines and pyrimidines synthesis and cell cannot divide in their absence.	
General Information	–	-More lipid soluble **-A weak base, concentrates in prostatic and vaginal fluid* (> acidic than plasma).** *Useful in UTI especially in females.
Pharmacokinetics — **Absorption and Distribution**	- Mainly given orally or IV Distribution. - SMX Rapidly absorbed from stomach and small intestine. -TMP absorbed from gut - Widely distributed to tissues and body fluids including (**CNS**,CSF). - cross placenta and reaches the fetus.	
Pharmacokinetics — **Protein binding**	70% of absorbed SMX is bound to serum proteins.	40% protein bound.
Pharmacokinetics — **Metabolism and excretion**	- Metabolized by acetylation in the liver. - Eliminated in urine partially unchanged and partially acetylated.	60% eliminated in urine unchanged or metabolized.
ADRs	**1-** GIT: Nausea, vomiting **2-** Allergy* **3-** Hematologic: -Acute hemolytic anemia. (caused by:hypersensitivity, G6PD deficiency**). -Megaloblastic anemia*** (in TMP). حاول مثل ما قالوا (Tri \ Meth \ megalo) *Famous ADR of sulfonamides **Which is important to protect RBCs. ***For people with reduced folic acid.	
Drug Interactions	- Displace bilirubin (from plasma proteins) if severe; leads to kernicterus (bilirubin encephalopathy). من كتر ما سولفو!(Sulfonamude) فوق راسي فقعوا مراريتي (Displace bilirubin) حتى وصلت لمخي (Kernicterus) - potentiate warfarin, oral sulfonylurea hypoglycemics.	
Contraindication	Pregnancy*, nursing mother, infants under 6 weeks, Renal or hepatic failure, blood disorders. *Any drug the interfere with blood is contraindicated in pregnancy.	

Drug	Nitrofurantoins
Antibacterial spectrum	• Bactericidal for gram -ve & gram +ve bacteria. • Effective against **E.coli** & Staph. Saprophyticus. • Other common UT gram -ve bacteria may be resistant.
Mechanism of action	• Sensitive bacteria reduce (Converts) the drug to an active agent (by bacterial reductase) that inhibits various enzymes and damages DNA.
Pharmacokinetics	• Complete and rapid oral absorption. • 75% metabolized & is excreted so rapidly that no systemic antibacterial action can be achieved. ممكن نقرا اول مقطع من اسم الدرق No travel to systemic = Ni trof ممكن نقرأ اسم الدرق نيتروجين في اليورن فايركت وجهته هناك ما يروح للجسم كله Nitro f uran • Concentrated in urine (25% excreted unchanged) • Urine pH is kept <5.5 (acidic) to enhance drug activity. • **Urine turns to dark orange-brown (harmless).** نقدر نقول (nitro) نظروا (انتظروا) فوران (furan) المويهٔ على النار , النار يجي لونها (orange)
Therapeutic uses	• Used as urinary antiseptic. It's usefulness is limited to lower uncomplicated UTI's & cannot be used for upper UT or systemic infections. Nitro f uran which is stored in bladder in the lower UT
Dose	• Long acting: 100mg twice daily. • 50-100mg, orally, 6h/7 days.
Adverse effects	• GI disturbances: (Must be taken with food)* 1. Bleeding of the stomach 2. Nausea 3. Vomiting 4. Diarrhea • Headache & Nystagmus نظرتهم حتى طلعت عيوني من مكانها • **Hemolytic anemia (G6PD Deficiency)** *We advise the patient to not consume any Dairy foods and drinks because they make the urine more alkaline. Also,the Nitrofurantoin activity might be affected if the patient was on anti-acids.
Contraindications	• Patients with G6PD deficiency → Anemia. • Neonates • Pregnant women. (after 38 weeks of pregnancy)

Tetracyclines

Drug	**Doxycycline** (long acting tetracycline)
Mechanism of action	• Bacteriostatic, inhibits protein synthesis by binding reversibly to 30s ribosomal subunit. • Against gram +ve & gram -ve bacteria.
Pharmacokinetics	• Long acting • Usually given orally. • Absorption is 90-100%. • Absorbed in the upper s. intestine & best in absence of food. • Food, divalent & trivalent cations (Ca, Mg, Fe, AL) impair absorption and reduce effectiveness (avoid dairy products) • Protein binding 40-80 % . • Distributed well, including CSF. • Cross placenta and excreted in milk. • Largely metabolized in the liver. • Excreted by the kidney
Therapeutic uses	• Treatment of UTIs due to gram -ve & gram +ve bacteria including Mycoplasma & Chlamydia • Prostatitis
Dose	• 100mg orally ,Twice a day for 7 days.
Adverse effects	• Nausea, vomiting ,diarrhea & epigastric pain (give with food) • Thrombophlebitis – I.V. • Hepatic toxicity (prolonged therapy with high dose) . • Brown discolouration of teeth – children طاح الطفل من السيكل (cycline) وتوسخت أسنانه بالتراب (brown teeth) وتكسرت عظامه (deformity of bone) , وبعدين مع الجرح جته التفكشن (superinfection) • Deformity or growth inhibition of bones – children . • Phototoxicity.sensitivity to sunlight • Vertigo. • Superinfections (alter the intestinal flora due to broad spectrum activity) ليش طاح الطفل من السيكل (cycline) ؟ عشان ضوء الشمس كان قوي عليه (phototoxicity) فجته دوخة ودارت فيه الدنيا (vertigo) وطاح
Contraindications	• Pregnancy • Breast feeding • Children (below 10 yrs), Because it binds to Calcium in bones and teeth.

Aminoglycoside

Drug	mnemonic: **AMINO** -Against aerobic gram negatives -Mainly bactericidal -Inhibit protein synthesis at 30s subunit -Nephrotoxic -Ototoxic **Gentamicin**
Mechanism of action (MOA)	• Inhibit protein synthesis by binding to 30S ribosomal subunits irreversibly. • Bactericidal, only effective against **gm-ve** aerobic bacteria. (Bactericidal) معه اكتاب وقرر ينتحر (Gentamicin) جنتا
Pharmaco -kinetics	• poorly absorbed orally (highly charged). • Given I.M or I.V. • Excreted unchanged in urine. • More active in alkaline medium. • Cross placenta. (Contraindicated in Pregnancy)
Therapeutic uses	• Severe infections caused by gram negative organism (pseudomonas or enterobacter). Also combined with other antibiotics. جنتل مان (Gentamicin) زوجته اسمها منى (psudoMONAs)
Adverse effects	لما الواحد ما يسمع زين و تقول له سالفة يقول ها مين هو قلي (A min o gly) • Ototoxicity. damage in vestibular nerve • Nerve damage • Nephrotoxicity. • Neuromuscular blocking effect.

Cephalosporins

Drug	3rd generation cephalosporins: **Ceftriaxone** & **Ceftazidime**
Mechanism of action (MOA)	• Acts by inhibition of cell wall synthesis. • Bactericidal. • Mainly effective against **gm-ve** bacteria.
Pharmaco-kinetics	• They are given parenterally .
Therapeutic uses	• Given in severe / complicated UTIs . ما صفا (cepha) لنا الا هالدرق اخر شيء • Given in acute prostatitis. صفا (cepha) زوجها عنده بروستات)

Fluoroquinolones

Drug	**ciprofloxacin**
MOA	• Inhibits DNA gyrase enzyme and cell division resulting in bacterial cell death. • Active against **gm-ve** aerobic organisms.
Therapeutic uses	• UTIs caused by multidrug resistance organisms as pseudomonas. • Prostatitis (acute / chronic) باصبر على زوجها عنده بروستات منى (ModusANOps) بيغى لها صبر (cipro)
Adverse effects	• GIT : Nausea , vomiting , diarrhea. • CNS effects : (confusion, insomnia, headache, anxiety). • Damage of growing cartilage (reversible arthropathy) .• Phototoxicity (avoid excessive sunlight)

Summary

Antibiotic	Important
Co-trimoxazole (TMP-SMX) **Sulfamethoxazole** **Trimethoprim**	• Inhibit folic acid synthesis in microorganism. • Alone, each drug is **bacteriostatic** but together they are **bactericidals** (synergism). • GIT: Nausea, vomiting **-**Allergy **-**Megaloblastic anemia • Contraindicated in Pregnancy*, nursing mother, infants under 6 weeks, • Renal or hepatic failure, blood disorders.
Nitrofurantoins	• Bactericidal for gram -ve & gram +ve bacteria. • Effective against **E.coli** • Sensitive bacteria reduce the drug to an active agent that inhibits various enzymes and damages DNA. • It's usefulness is limited to lower uncomplicated UTI's & cannot be used for upper UT or systemic infections. • Contraindicated to: Patients with G6PD deficiency, Neonates, Pregnant women
Tetracyclines: Doxycycline	• Bacteriostatic, inhibits protein synthesis by binding reversibly to 30s ribosomal subunit. g-ve and g+ve • Food, divalent & trivalent cations (Ca, Mg, Fe, AL) impair absorption. • ADRs: Brown discolouration of teeth and Deformity or growth inhibition of bones in children , Phototoxicity. • Contraindicated to children & pregnancy .
Aminoglycoside: Gentamicin	• Inhibit protein synthesis by binding to 30S ribosomal subunits irreversibly. Only against gram-ve • ADRs: Ototoxicity, Nephrotoxicity, Neuromuscular blocking effect.
3rd gen Cephalosporins: Ceftriaxone & **Ceftazidime**	• Acts by inhibition of cell wall synthesis, • Bactericidal gram-ve. • Used in complicated UTIs, acute prostatitis.
Fluoroquinolones: ciprofloxacin	• Inhibits DNA gyrase enzyme and cell division resulting in bacterial cell death. Active against g-ve • Used in: multidrug resistance UTIs, Prostatitis. • ADRs: Damage of growing cartilage (reversible arthropathy) Phototoxicity.

MCQ

1-: Which of the following drugs is contraindicated in children under 10 years?			
A- Sulfamethoxazole	B- Gentamicin	C- Doxycycline	D- Ceftriaxone

2-: one of the following is an ADRs of Nitrofurantoins			
A- Hemolytic anemia	B-Thrombophlebitis	C- Brown discolouration of teeth	D- Phototoxicity

3-What is the ratio between SMX and TMP when given orally			
A- 5:1	B- 2:1	C- 4:1	D- 3:1

4-: Which one of the following drugs is bactericidal ?			
A-Trimethoprim	B-Ceftazidime	C-Tetracyclines	D-chloramphen

5-Which of the following is true about SMX and TMP			
A- Given orally only	B-Slowly absorbed	C-Do Not cross BBB	D-Do cross placenta

6-The M.O.A of Gentamicin is			
A-inhibition of cell wall synthesis	B-Inhibit protein synthesis by binding to 30S ribosomal subunits	C-Inhibits DNA gyrase enzyme and cell division	D-stop folic acid production in microorganisms

Answers

1	2	3	4	5	6
C	A	A	B	D	B

SAQ

Q1) What is the mechanism of action of Nitrofurantoin?

Q2) A patient came to the hospital with UTI caused by Chlamydia. He was prescribed a drug for 7 days. 3 days after starting the treatment he came to the hospital complaining of vertigo, phototoxicity & nausea . What is the most likely drug that he was given?

Q3) What is the difference between Complicated UTIs and Simple UTIs

Q4) Give 3 ADRs of SMX and TMP

Q5) What are the therapeutic uses of ciprofloxacin

Q6) what is the M.O.A and therapeutic uses of cephalosporins

Answers

A1) Sensitive bacteria reduce the drug to an active agent (by bacterial reductase) 1 that inhibits various enzymes and damages DNA.

A2) Tetracycline (Doxycycline)

A3) complicated:Infections spread to other parts of the body and resistant to many antibiotics &more difficult to cure

Simple: Infections do not spread to other parts of the body and go away readily with treatment

A4) Nausea,Vomiting,Allergy,Acute hemolytic anemia

A5) 1-UTIs caused by multidrug resistance organisms as pseudomonas.2-Prostatitis (acute / chronic)

A6) Acts by inhibition of cell wall synthesis, Bactericidal, Mainly effective against gm-ve bacteria.

GOOD LUCK!

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SPECIAL THANKS TO
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