MED438
KING SAUD UNIVERSITY

pharmacology
Team 438

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Renal Block

Pharmacology Team 438

UTI

Editing File

Objectives:

By the end of this lecture, students should be able to:

- 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.

Color Index:

Red : important

Black :Main content

Pink : in female's slides only

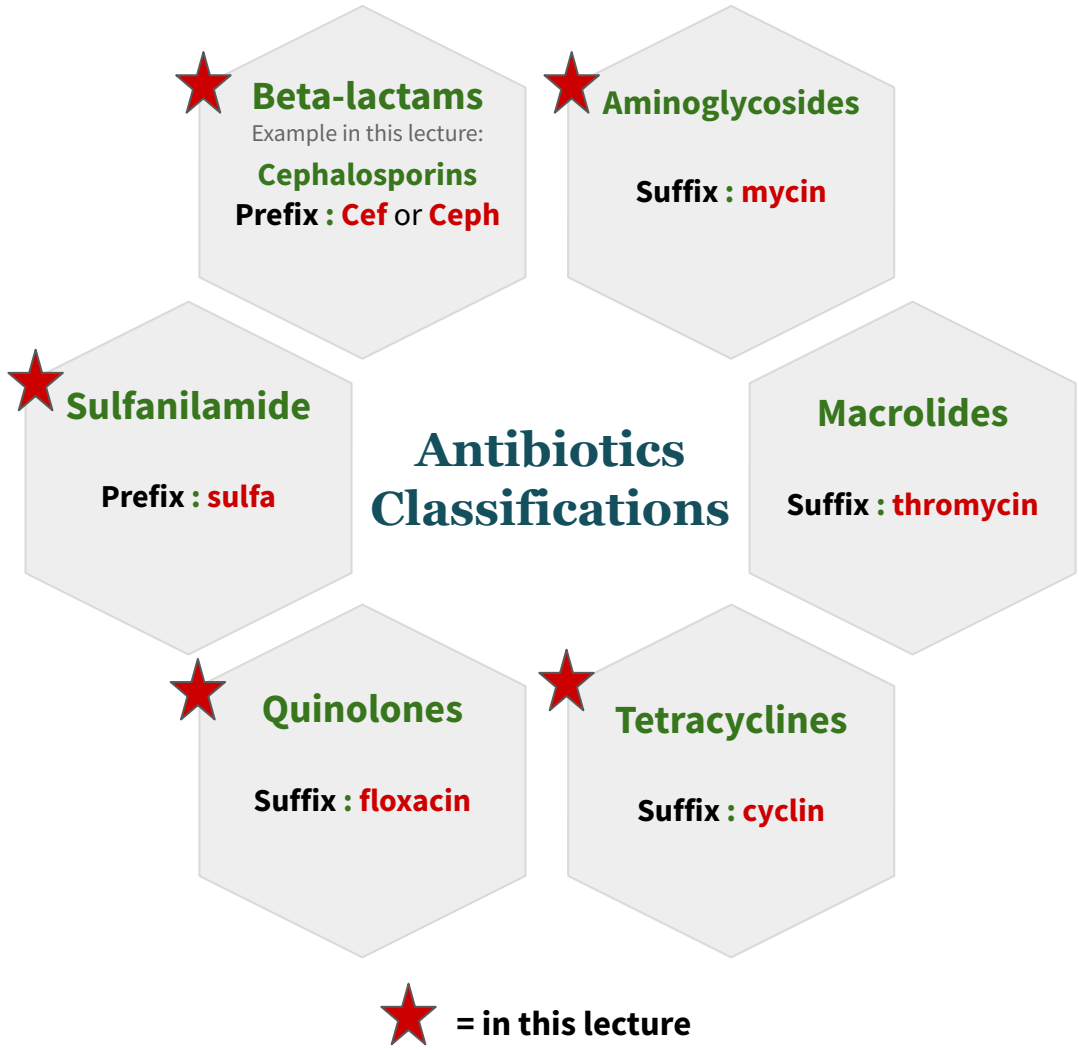
Blue : in male's slides only

Green : Dr's notes

Grey: Extra information , explanation

-Not important-

Recall from respiratory Block ...



Antibiotics mechanism of action

Bactericidal
(Kills the bacteria) either by :

1-destroying the Cell wall .
Ex : Cephalosporins

2-destroying the Nucleic acid (DNA or RNA) .
Ex :
*Quinolones **(DNA)**
*Rifampin **(RNA)**
*TMP-SMX **(Folate)**

Bacteriostatic
(Stops the growth) by :

Affecting protein synthesis

Ex :
- Tetracyclines
- Macrolides
- Aminoglycosides

EXCEPTION: Aminoglycoside affects the protein synthesis but is considered Bactericidal

Urinary Tract Infections

- Normally urine is sterile. Bacteria comes from digestive tract to opening of the urethra.
- It's the 2nd most common infection after Respiratory Tract Infections (RTIs).
- It's often associated with some obstruction of the flow of urine.
- It's more common in **women** than men 30:1 (why? shorter urethra in females).
- The incidence of UTIs increase in **Old age** (10% of men & 20% of women).

Classification

Upper urinary tract infections (Kidney & ureters):

- E.g. Pyelonephritis
- More serious & difficult to treat.

Lower urinary tract infections (Bladder, urethra & prostate):

- E.g. Cystitis, Urethritis, Prostatitis, more common & easier to treat.

Causes of UTI

- Enlargement of prostate gland in men (common cause).

- Not drinking enough fluids.

- Large uterus in pregnant women.

- Disorders that suppress the immune system (diabetes & cancer chemotherapy).

- Obstruction of the flow of urine (e.g. Kidney stone)

- Catheters placed in urethra & bladder.

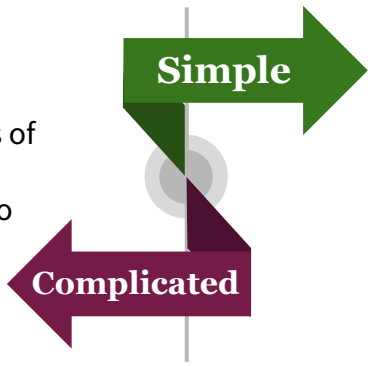
- Waiting too long to urinate.

- Poor toilet habits (wiping back to front for women).

UTI can be

Complicated UTIs

- 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 UTIs

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

Bacterial responsible of UTI

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

Treatment of UTIs

1. **Co-trimoxazole** (SMX/TMP). P.o.
2. **Nitrofurantoin** P.o.
3. **Tetracyclines** E.g. Doxycycline P.o.
4. **Aminoglycosides** E.g. Gentamicin I.M , I.V
5. **Cephalosporins** E.g. Ceftriaxone & Ceftazidime. I.V
6. **Quinolones** E.g. ciprofloxacin P.o.

P.o. = Taken orally.

Co-trimoxazole (TMP-SMX)

Trade names: Bactrim and Septra

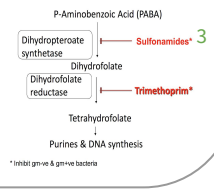
overview

-Trimethoprim -Sulfamethoxazole
- Alone, each drug is **bacteriostatic** but together they are **bactericidals** (synergism)
- They are given orally in 5(SMX):1(TMP) ratio
Ex: 400mg SMX + 80mg TMP
So when they reach the plasma their concentration will be 20 (SMX) : 1 (TMP) which is the optimal ratio for killing bacteria.

Mechanism of action

- Both drugs stop folic acid[1] 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



Drugs		Sulfamethoxazole (Sulfonamides)	Trimethoprim
General information		—	-More lipid soluble -**A weak base, concentrates in prostatic and vaginal fluid**[4] **(> acidic than plasma)**
Pharmacokinetics	**Absorption and Distribution**	- Mainly given orally or IV - Rapidly absorbed from stomach and intestine - Widely distributed to tissues and body fluids including (CNS,CSF) - cross placenta and reaches the fetus	
	Protein binding	70% of absorbed SMX is bound to serum proteins	40% protein bound
	Metabolism and excretion	- Metabolized by acetylation in the liver - Eliminated in urine partially unchanged and partially acetylated	60% eliminated in urine unchanged or metabolized
Adverse effects		**1-** GIT: Nausea, vomiting **2-** Allergy [5] **3-** Hematologic: -Acute hemolytic anemia (caused by: hypersensitivity, G6PD deficiency [6]) -Megaloblastic anemia [2] **(in TMP)**	
Drug interaction		- Displace bilirubin (from plasma proteins) if severe; leads to kernicterus (bilirubin encephalopathy) - potentiate warfarin, oral sulfonylurea hypoglycemics	
Contraindications		Pregnancy[7], nursing mother, infants under 6 weeks, Renal or hepatic failure, blood disorders	

1) 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

2)For people with reduced Folic acid.
3)sulfamethoxazole is a sulfonamide drug.
4)useful in UTI especially in females.
5)famous ADR of sulfonamides
6)which is important to protect RBCs
7) any drug that interfere with blood is contraindicated in pregnancy.

Nitrofurantoins

Antibacterial spectrum	• Bactericidal for **gm-ve & gm+ve** bacteria. • Effective against **E.coli** & **Staph. Saprophyticus**. • **Other common UT gram -ve bacteria may be resistant**.
Mechanism Of action	• Sensitive bacteria reduce the drug to an active agent (by bacterial reductase) [1] that inhibits various enzymes and damages DNA.
Pharmaco -kinetics	• Complete and rapid oral absorption. • 75% metabolized & is excreted so rapidly that no systemic antibacterial action can be achieved. • Concentrated in urine (25% excreted unchanged) • Urine pH is kept <5.5 (acidic) to enhance drug activity. • Urine turns to dark orange-brown (harmless). • Patient shouldn't eat food that increase the PH
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. • Dose: 50-100mg, orally, 6h/7 days. • Long acting: 100mg twice daily.
Adverse effects	• GI disturbances: (Must be taken with food) - Bleeding of the stomach - Nausea - Vomiting - Diarrhea • Headache & Nystagmus [2] • Hemolytic anemia (G6PD Deficiency)
Contraindications	• Patients with G6PD deficiency → Anemia. • Neonates • Pregnant women. (after 38 weeks of pregnancy)

1) bacteria lack this enzyme resistant to this drug.
2)involuntary eye movements

Tetracyclines

Drug	**Doxycycline** (long acting tetracycline)
Mechanism Of action	• Bacteriostatic, inhibits protein synthesis by binding reversibly to 30s ribosomal subunit. • Against **gm+ve & gm-ve** bacteria.
Pharmaco -kinetics	• Usually given orally. • Absorption is 90-100%. • Absorbed in the upper s. intestine & best in absence of food. • Food & di & tri-valent cations (Ca, Mg, Fe, AL) impair absorption and reduce effectiveness [1] avoid dairy products. • Protein binding 40-80 % . • Distributed well, including CSF. • Cross placenta and excreted in milk. • Largely metabolized in the liver.
Therapeutic uses	• Treatment of UTI's due to gm-ve & gm+ve bacteria including **Mycoplasma** & **Chlamydia**, 100mg orally for 7 days. • Prostatitis .
Adverse effects	1. nausea, vomiting ,diarrhea & epigastric pain (give with food if these side effects are present but avoid dairy products). 2. Thrombophlebitis – i.v . 3. Hepatic toxicity (prolonged therapy with high dose) . 4. Brown discolouration of teeth – children [2] . 5. Deformity or growth inhibition of bones – children . 6. Phototoxicity. 7. Vertigo. 8. Superinfections (alter the intestinal flora due to broad spectrum activity)
Contraindications	• Pregnancy • Breast feeding • Children(below 10 yrs)

1)they bind with tetracyclines and make an insoluble complex that's not absorbed.
2) they combine with Calcium in the teeth and bones

Aminoglycoside

Drug	Gentamicin
Mechanism Of action	• Inhibit protein synthesis by binding to 30S ribosomal subunits. • Bactericidal [1] , only effective against **gm-ve aerobic** bacteria.
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).
Adverse effects	• Ototoxicity. [2] • Nephrotoxicity. • Nerve damage • Neuromuscular blocking effect.

Cephalosporins

Drugs	3rd generation cephalosporins : Ceftriaxone & Ceftazidime
Mechanism Of action	• Acts by inhibition of cell wall synthesis. • Bactericidal.
Pharmaco -kinetics	• They are given parenterally .
Therapeutic uses	• Mainly effective against **gm-ve** bacteria. • Given in severe / complicated UTIs . • Given in acute prostatitis.

Fluoroquinolones

Drugs	ciprofloxacin
MOA	• Inhibits DNA gyrase enzyme [3] and cell division.
Therapeutic uses	• Active against **gm-ve aerobic** organisms. • UTIs caused by multidrug resistance organisms as pseudomonas. • Prostatitis (acute / chronic)
Adverse effects	• Nausea , vomiting , diarrhea. • CNS effects (confusion, insomnia, headache, anxiety). • Damage of growing cartilage **(reversible arthropathy)** . • Phototoxicity (avoid excessive sunlight)

1)tetracyclines are bacteriostatic, and aminoglycosides are bactericidal. WHY ? That is because tetracyclines bind reversibly, while aminoglycosides bind irreversibly.(From 435)
2) damage in vestibular nerve
3) Which is important for gene transcription and DNA replication

Summary

Each Class with its important points …

Classes of Antibiotics	Important points
Co-trimoxazole (SMX/TMP)	• **MOA :** stop *folic acid production in microorganisms . • -SMX/TMP are bacteriostatic drugs , but together they are **bactericides** (synergism) . • **Contraindicated** in people with hematologic disorders (anemia) . • **Contraindicated** in pregnancy (cross the placenta)
Nitrofurantoin	• **MOA :** inhibits various enzymes and damages DNA. • 25% excreted unchanged in the urine , which is the portion that produce the local effect in the urinary tract . • No systemic effects is produced (only limited in UTI)
Tetracyclines (Doxycycline)	• **MOA :** inhibits protein synthesis , Bacteriostatic . • Food & di & tri-valent cations (Ca, Mg, Fe, AL) impair absorption. • Most important **ADR** : Brown discolouration of teeth and Deformity or growth inhibition of bones in children , so it is **Contraindicated** in children and pregnancy.
Aminoglycosides (Gentamicin)	• **MOA :** inhibits protein synthesis , Bactericidal . • **only effective** against **gm-ve aerobic** bacteria. • **ADR** : Ototoxicity , Nephrotoxicity , Neuromuscular blocking effect.
Cephalosporins (Ceftriaxone & Ceftazidime)	• **MOA :** inhibition of cell wall synthesis. • 3rd generation is used in UTI **(Ceftriaxone & Ceftazidime)**
Quinolones (Ciprofloxacin)	• **MOA :** Inhibits DNA gyrase enzyme and cell division. • Most important **ADR** : Damage of growing cartilage **(arthropathy)** .

Quiz

MCQ

Q1 : A 22-year-old female presents with a 2-day history of dysuria with increased urinary frequency and urgency. A urine culture and urinalysis are done. She is diagnosed with a lower urinary tract infection (UTI) caused by *Staphylococcus Saprophyticus*

All of the following would be considered appropriate therapy for this patient except:

A- Co-trimoxazole. **B-Gentamicin.** **C-Nitrofurantoins.**

Q2 : Which of the following drugs is correctly matched with the appropriate adverse effect?

A- Sulfamethoxazole; megaloblastic anemia. **B- Cephalosporins;Neuromuscular blocking effect .**

C- Tetracycline ;brown discoloration of the teeth .

Q3: Which of the following drugs that is only used for treating urinary tract infections?

A-Nitrofurantoins. **B-Ciprofloxacin.** **C-ceftriaxone.**

Q4: Which one of the following drugs is bactericidal ?

A-Trimethoprim . **B-Tetracyclines.** **C- Ceftazidime.**

Q5: Which one of the following Antibiotics enhance the efficacy of Warfarin ?

A- Co-trimoxazole. **B-Gentamicin.** **C-Nitrofurantoins.**

SAQ

32 years old pregnant woman developed urethritis caused by infection by gram negative bacteria, Her doctor prescribed for her an Antimicrobial drug for 10 days , later on there was a significant defects in the growing cartilage of the fetus (arthropathy) .

Q1: What is the drug was prescribed to the patient that can produce the mentioned defects in the fetus ?

Q2: what is the mechanism of action of this drug .

Q3: give one example of an antibiotic that considered safe during pregnancy .

Answers

MCQ's

Q1: **B** ; Gentamicin is effective only against Gram -ve Bacteria .

Q2: **C**

Q3: **A** ; 75% metabolized & is excreted so rapidly that no systemic action is produced.

Q4: **C**

Q5: **A**

SAQ

Q1: fluoroquinolone (for example ciprofloxacin) .

Q2: Inhibits DNA gyrase enzyme and cell division.

Q3:

- Cephalosporins (for example: ceftriaxone)
- Penicillins

pharmacology

Team 438

Good Luck

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Share with us your ideas !