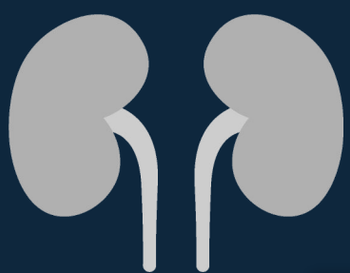
PHARMACOLOGY
TEAM 439

MED439
KING SAUD UNIVERSITY



# SUMMARY
# RENAL block

- Important
- In male and female slides
- Only in male slides
- Only in female slides
- Extra information
- notes

**Helpful flash cards**

**Editing file**

# Renal excretion (thx for 438)

## 1 GFR occurs to : Low molecular weight drugs, Free form of the drug (Unbound to plasma proteins) , Ionized drugs and drugs with low Vd

## 2 Active Tubular Secretion types of competition:

competition occurs when 2 drugs have **similar ionic charge & employing the same carrier** -transporter-

**Beneficial ✓:**

**Probenecid & penicillin G**
probenecid prolongs duration of action of penicillin G & ↑ its antibacterial action

**Harmful X:**

**Probenecid & nitrofurantoin**
probenecid ↓ nitrofurantoin efficacy in UTIs

## 3 Active / Passive Tubular Reabsorption:

1. **Passive Reabsorption:** occurs with **unionized, lipophilic** drugs so, urinary excretion will be low (Ionized drugs are poorly reabsorbed and their urinary excretion will be high).
2. **Active Reabsorption:** occurs with **endogenous substances** e.g. Uric Acid.
Probenecid inhibits active tubular reabsorption of uric acid thus increasing its excretion in the urine (used as a uricosuric agent for gout)

### Urinary pH trapping (Ion trapping):

Changing in urine PH can inhibit or enhance the passive tubular reabsorption of drugs

, **so it is used to enhance renal clearance of drugs during toxicity.**

**Urine acidification:** By ammonium chloride (NH4Cl) increases excretion of basic drugs (amphetamine, gentamicin)

**Urine alkalization:** By sodium bicarbonate (NaHCO3) increases excretion of acidic drugs (aspirin , barbiturates)

| Drug renal clearance | Creatinine clearance Rate (CrCl) |
|---|---|
| Important for:<br>→ Drugs with narrow therapeutic index E.g lithium , digoxin ,warfarin<br>→ Drugs excreted mainly by the kidney E.g NSAIDs , Antibiotics (penicillins) , Lithium , Anticancer (cisplatin) , immunosuppressant (cyclosporins)<br><br>$\frac{\text{Excretion rate (mg/min)}}{\text{Plasma concentration (mg/ml)}}$ | Used to estimate GFR<br>**Cockcroft-Gault equation:**<br><br>for female : $\frac{0.85(140-\text{age})\ BW}{SCr \times 72}$<br><br>for male : $\frac{(140-\text{age})\ BW}{SCr \times 72}$ |

→ Drugs that are primarily excreted by the kidney need dose adjustment when creatinine clearance is below 60 ml/min
→ Minor dose adjustment if CrCl = 30-60 mL/min
→ Major dose adjustment if CrCl < 15 mL/min

## Zero - Order:

Constant **AMOUNT** is lost per unit time

The rate of excretion is **independent** of the conc. of drugs in the plasma.

E.g. Ethanol(alcohol), phenytoin, aspirin

## First - Order:

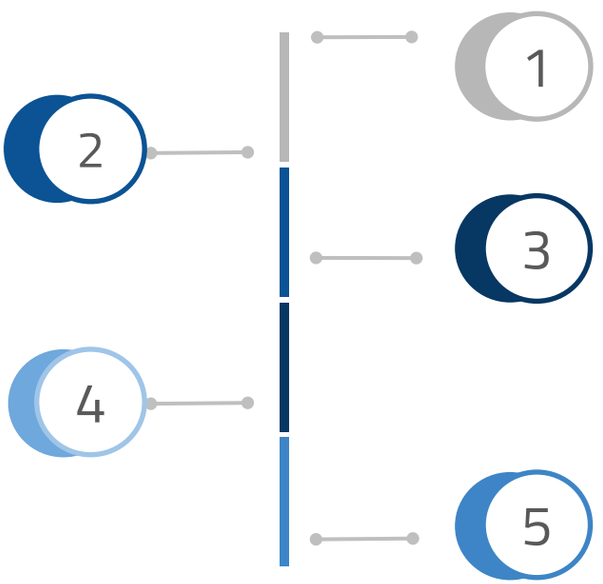
Constant **PERCENTAGE** is lost per unit time

The rate of excretion is **directly proportional** with conc. of drug in plasma.

E.g. penicillin, aminoglycoside, quinolones

Orders Of Eliminations:

## Risk Factors for NSAIDs-Associated Acute Renal Failure:




Prostaglandins (PGs) have **major role** in the preservation of renal function

PGI2 and PGE2 **antagonize the local effects** of circulating angiotensin II

angiotensin II , endothelin,vasopressin, and catecholamines that **reduce** renal circulation

**Prostaglandins** preserve GFR by antagonizing arteriolar vaso**constriction**.

A significant **reduction** in **GFR** can occur following administration of a **NSAID**
(NSAIDs inhibit production of PGs)

## Physicochemical factors affecting renal excretion of drug:

| | Increase excretion | Decrease excretion |
|---|---|---|
| **Molecular size** | Smaller size drugs | Larger size drugs |
| **Degree of ionization** | Water soluble | Lipid soluble |
| **Vd** | Low Vd | Large Vd |
| **Plasma Protein binding** | – | ✓ |
| **Renal blood flow** | When increased perfusion | When decreased perfusion |
| **Biological factors** | | Neonates and Elderly |
| **Plasma Conc.** **"Depends on Vd"** | Low Vd →↑drug conc. in the blood | Large Vd→↓drug conc. in the blood |

# Antibiotics in UTI

| | Co-trimoxazole (TMP-SMX)<br>Trade names: Bactrim and Septra | | Nitrofurantoins | Tetracyclines |
|---|---|---|---|---|
| **Drug** | **Sulfamethoxazole** | **Trimethoprim** | **Nitrofurantoins** | **Doxycycline**<br>**(long acting tetracycline)** |
| **Antibacterial spectrum** | - Inhibit gram-ve & gram+ve bacteria<br>- Alone, each drug is **bacteriostatic** but together they are **bactericidals** (synergism). | | **- Bactericidal for gram -ve & gram +ve bacteria.**<br>- Effective against E.coli & Staph. Saprophyticus.<br>- Other common UT gram -ve bacteria may be resistant. | -**Bacteriostatic** Against gram +ve & gram -ve bacteria. |
| **MOA** | - Both drugs **stop folic acid production in microorganisms.**<br>- In microorganisms: PABA PABA: para aminobenzoic acid is turned into dihydrofolic acid by dihydropteroate synthetase **(SMX disturbs this step).**<br>- Dihydrofolic acid is turned into tetrahydrofolic acid by dihydrofolate reductase<br>**(TMP inhibits this enzyme).** | | Sensitive bacteria reduce (Converts)the drug to an active agent action (by bacterial reductase) that inhibits various enzymes and damages DNA. | -inhibits protein synthesis by binding **reversibly** to 30s ribosomal subunit. |
| **Uses** | - Useful in UTI and prostatitis | | - Used as urinary antiseptic. **Its usefulness is limited to lower uncomplicated UTI's & cannot be used for upper UT or systemic infections.** | - Treatment of UTIs due to gram -ve & gram +ve bacteria including Mycoplasma & Chlamydia<br><br>- Prostatitis |
| **ADRs** | **1- GIT: Nausea, vomiting**<br><br>**2- Skin Rash ( Allergy)**<br><br>**3- Hematologic :**<br>3a.Acute hemolytic anemia. (caused by: G6PD deficiency).<br>3b.Megaloblastic anemia. | | - **GI disturbances** are common :<br>(Must be taken with food)<br>1. Bleeding of the stomach<br>2. Nausea<br>3. Vomiting<br>4. Diarrhea<br>-Headache & Nystagmus<br>- Hemolytic anemia ( G6PD Deficiency ) | **- Nausea, vomiting ,diarrhea & epigastric pain (give with food)**<br>- Thrombophlebitis – I.V.<br>- Hepatic toxicity (prolonged therapy with high dose)<br>**- Brown discolouration of teeth + deformity or growth inhibition of bones (in children)**<br>**- Phototoxicity**<br>- Vertigo.<br>- Superinfections (alter the intestinal flora due to broad spectrum activity) |
| **Drug Interactions** | - Displace bilirubin ( from plasma protein) if severe; leads to kernicterus ( bilirubin encephalopathy ).<br>- potentiate warfarin, oral sulfonylurea hypoglycemics. | | - | - |
| **Contraindi-cation** | - Pregnancy, nursing mother, infants under 6 weeks,<br>- Renal or hepatic failure<br>- blood disorders. | | - Patients with G6PD deficiency → Anemia.<br>- Neonates<br>- Pregnant women. (after 38 weeks of pregnancy) | - Pregnancy<br>- Breast feeding<br>- Children ( below 10 yrs ), Because it binds to Calcium in bones and teeth. |

# Antibiotics in UTI

| | Aminoglycoside | Cephalosporins | Fluoroquinolones |
|---|---|---|---|
| **Drug** | **Gentamicin** | **Ceftriaxone & Ceftazidime**<br>**3rd generation cephalosporins** | **ciprofloxacin** |
| **Anti-bacterial Spectrum** | - Bactericidal, **only effective against gm-ve** aerobic bacteria. | - Bactericidal., Mainly effective **against gm-ve bacteria.** | - Active against **gm-ve aerobic organisms.** |
| **MOA** | - Inhibit protein synthesis by binding to 30S ribosomal subunits **irreversibly**. | - Acts by inhibition of cell wall synthesis. | - Inhibits DNA gyrase enzyme and cell division, resulting in bacterial cell death. |
| **Therapeutic uses** | - Severe infections caused by **gram negative** organism (pseudomonas or enterobacter). Also combined with other antibiotics. | - Given in severe / complicated UTIs .<br><br>- Given in acute prostatitis | - UTIs caused by multidrug resistance organisms as **pseudomonas**.<br><br>- Prostatitis ( acute / chronic ) |
| **Adverse effects** | - Ototoxicity.<br>damage in vestibular nerve<br><br>- Nephrotoxicity.<br><br>- Neuromuscular blocking effect.<br><br>- Nerve damage | - | - GIT :<br>Nausea, vomiting, diarrhea.<br><br>- CNS effects :<br>( confusion, insomnia, headache, anxiety).<br><br>- Damage of growing cartilage (reversible arthropathy).<br><br>- Phototoxicity<br>(avoid excessive sunlight) |

# Diuretics

| Class | Drug | MOA | Pharmacokinetics | Uses | Adverse Effect | Contraindication |
|---|---|---|---|---|---|---|
| Carbonic Anhydrase Inhibitors | **Acetazolamide** | Inhibits carbonic anhydrase (CA) enzyme in **proximal convoluted tubules** PCT.<br>(↑ excretion of bicarbonate with accompanying Na+, K +and water) | - Given orally 1/day.<br>- Onset of action is rapid (30 min).<br>- Duration of action (9-12 h).<br>- Excreted by active secretion in PCT.<br>- Produces alkaline urine. | - Diuretic (mainly acetazolamide).<br>- Open angle glaucoma (mainly dorzolamide).<br>- Prophylactic therapy, in acute mountain sickness.<br>- Benign intracranial hypertension.<br>- Urinary alkalinization.<br>- Hyperphosphatemia.<br>- Adjunct for treatment of epilepsy.<br>- Metabolic alkalosis. | - Hypokalemia (potassium loss).<br>- Metabolic acidosis.<br>- Renal stone formation (calcium phosphate stones).<br>- Hypersensitivity reaction.<br>-Drowsiness<br>-Numbness<br>-Disturbance of vision<br>-Tingling sensation of the face & extremities | - |
| | **Dorzolamide** | | - Topically.<br>- No diuretic or systemic side effects. | | | |
| Osmotic Diuretics | **Mannitol** | Increases urine output by osmosis, drawing water out of cells and into the bloodstream. | - Given I.V.<br>- Excreted by glomerular filtration without being reabsorbed or secreted within 30-60 min. | - Acute renal failure due to shock or trauma.<br>- Haemolysis, Rhabdomyolysis.<br>- In acute drug poisoning.<br>- Cerebral edema. | - Headache, nausea, vomiting.<br>- Extracellular volume expansion.<br>- Excessive use= dehydration & hypernatraemia. | - Chronic heart failure.<br>- Pulmonary oedema. |
| Loop Diuretics<br>( high ceiling diuretic ) | **Bumetanide**<br>( most potent ) | - Inhibit $Na^+$/ $K^+$/ 2Cl cotransporter in the luminal membrane of the **thick ascending loop of Henle** (TAL).<br>- Inhibit $Ca^{++}$, $Mg^{++}$ reabsorption. | - Given orally or I. V.<br>- Have fast onset of Action (suitable for emergency).<br>- Have short duration of action.<br>- Excreted by active tubular secretion of weak acids into urine.<br>- Interfere with uric acid secretion (**hyperuricemia**) | **Are drug of choice for emergency situations as:**<br>- Edema associated with congestive heart failure, nephrotic syndrome.<br>- Acute pulmonary edema (drug of choice).<br>- Acute hyperkalaemia.<br>- Acute hypercalcemia.<br>- Hypertension in presence of renal failure.<br>- Edema in case with impaired renal function.<br>- Congestive Heart failure in severe cases. | - Hypovolemia.<br>- Hyponatraemia.<br>- Hypokalemia.<br>- Hypomagnesaemia.<br>- Hypocalcaemia.<br>- Metabolic alkalosis.<br>- Postural hypotension.<br>- Hyperuricemia (gout).<br>- Ototoxicity (risk increased if combined with aminoglycosides).<br>- Allergic reactions. | - Gout.<br>- Diabetes.<br>- patients using NSAIDS (decrease Diuretic Response).<br>-Patients using digitalis (arrhythmia). |
| | **Torsemide** | | | | | |
| | **Furosemide** | | | | | |
| | **Ethacrynic acid** | | | | | |

# Diuretics

| Class | Drug | MOA | Pharmacokinetics | Uses | Adverse Effect | Contra-indication |
|---|---|---|---|---|---|---|
| Thiazide diuretics | Chlorothiazide<br>Hydrochlorothiazide<br>Chlorthalidone<br>Metolazone<br>Indapamide | Acts via inhibition of Na/Cl co-transporter on the luminal membrane of **distal convoluted tubules** (DCT). | - Given orally.<br>- Slow onset of action.<br>- Long duration of action (40 h).<br>- Secreted by active tubular secretory system of the kidney.<br>- May interfere with uric acid secretion and cause **hyperuricemia**. | - Treatment of essential hypertension (First drug of choice).<br>- Treatment of **mild** heart failure.<br>- Treatment of osteoporosis.<br>- Calcium nephrolithiasis due to hypercalciuria.<br>- Nephrogenic diabetes insipidus.<br>- Mild edema with normal renal function. | - Hyponatremia.<br>- Hypovolemia.<br>- Hypokalemia.<br>- Metabolic alkalosis.<br>- Hyperuricemia (gout).<br>- Hypercalcemia,.<br>- Hyperglycaemia.<br>-Hyperlipidemia. | **Drug-drug interactions:**<br>- Thiazides diminish effect of uricosurics.<br>- Thiazides increase effect of digitalis.<br>- NSAIDs reduce thiazides effect. |
| Potassium-sparing diuretics | Steroids: Spironolactone | **Competitive aldosterone antagonist.**<br><br>Act at the **collecting duct** by competitive inhibition of cytoplasmic aldosterone receptors →<br><br>↑Excretion of Na+ & Cl-<br><br>↓ Excretion of K+ & H+ | - Delayed onset of Action (because it acts on nuclear receptors), maximum diuretic action 4 days.<br>- Well absorbed from GIT.<br>- Highly protein bound.<br>- Undergoes enterohepatic recycling.<br>- Converted in the gut & liver to active metabolite. | - Treatment of hypertension.<br>- Enhances natriuresis caused by other diuretics.<br>- Correct for hypokalemia (caused by other diuretics).<br>- Treatment of primary hyperaldosteronism (Conn's syndrome).<br>- Treatment of secondary hyperaldosteronism in diseases as:<br>• CHF.<br>• Edema of hepatic cirrhosis (Spironolactone is the drug of choice).<br>• Nephrotic syndrome.<br>- Treatment of hirsutism, acne (in case of female), due to the antiandrogenic effects. | - Hyperkalaemia.<br>- Metabolic acidosis.<br>- Gynecomastia (male).<br>- Impotence (male).<br>- Menstrual irregularities (female).<br>- GIT upset and peptic ulcer. | - Hyperkalaemia:<br>• chronic renal failure.<br>• K+ supplement use.<br>• b-blockers.<br>• ACE inhibitors.<br>- Liver disease (dose adjustment is needed).<br>**Drug-drug interactions:**<br>- ACEI<br>- B-blockers<br>-K supplements<br><br>K-sparing diuretics should be used in caution w/ these drugs that can induce **hyperkalemia** |
| | Non- steroids: Amiloride | $Na^+$ channels inhibitors: Block Na transport channels, result in ↓ Na/K exchange in the **collecting tubule**. | - | - Used in Combination with Loop & Thiazide Diuretics.<br>- Treatment for lithium Induced Diabetes Insipidus. | - Hyperkalemia. | **Drug-drug interactions:**<br>**hyperkalemia may develop :**<br>• ACE inhibitors.<br>• Angiotensin II receptor antagonists.<br>• Potassium-sparing diuretics.<br>• Potassium-containing supplements. |
| | Non- steroids: Triamterene | | | | - Hyperkalemia.<br>- Renal stones. | |

# GOOD LUCK!

## Team Leaders

Tarfa alsharidi

Khaled Alsubaie

## Team Members

Hamad almousa
Raghad Albarrak
Shuaa khdary
Nada Babelli

TeamPharma439@gmail.com

Pharmacology439

شكرا لكل من تحمل هذا الفلم حتى النهاية
See you in the CNS