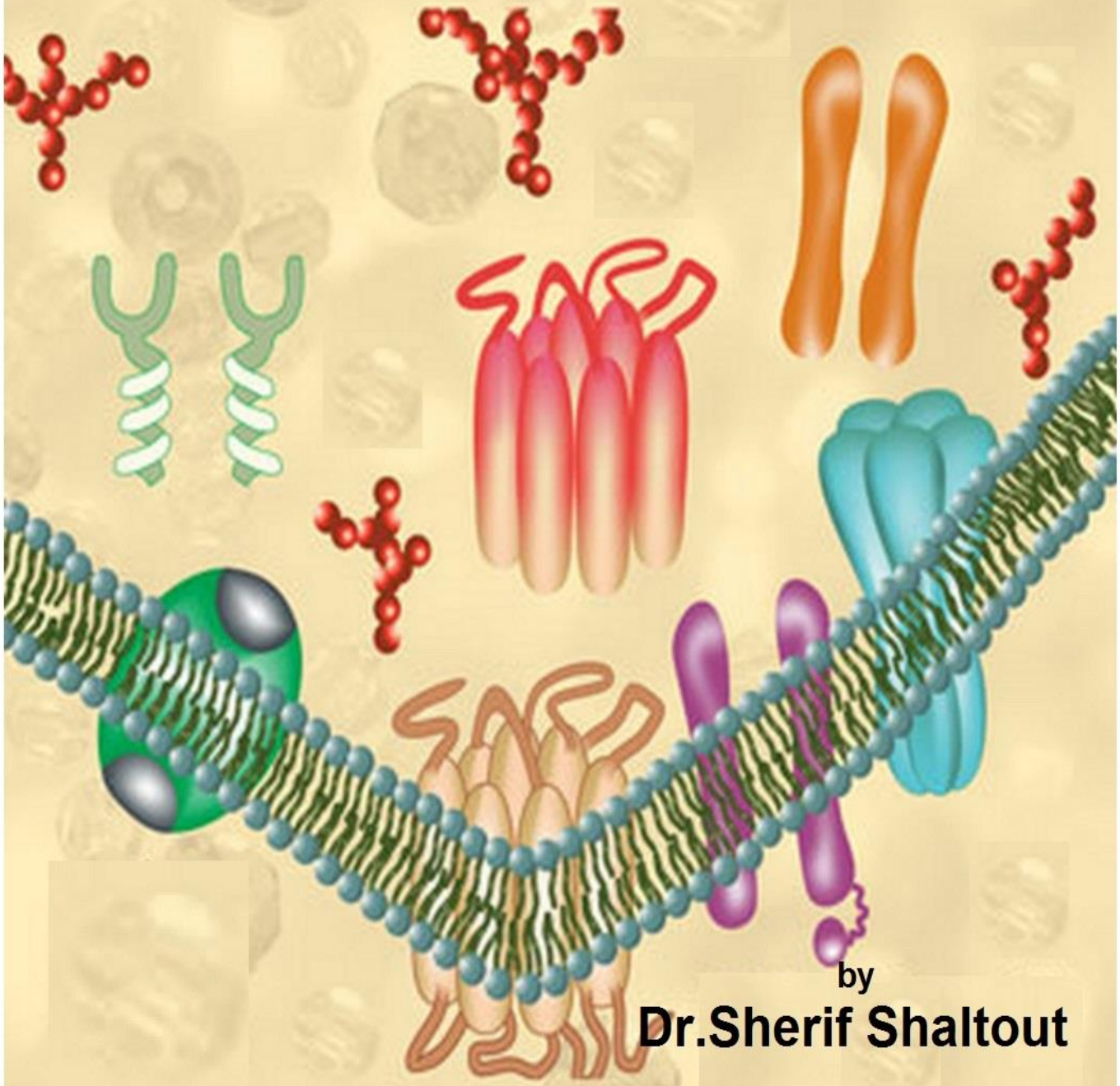
Pharmacology of Genitourinary System

2021



by

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RENAL PHARMACOLOGY

Basic Physiology of the Kidney

The kidney performs two major functions:

- Excretion of waste products such as urea, creatinine and uric acid.
- Control of blood volume, electrolytes and acid-base balance.

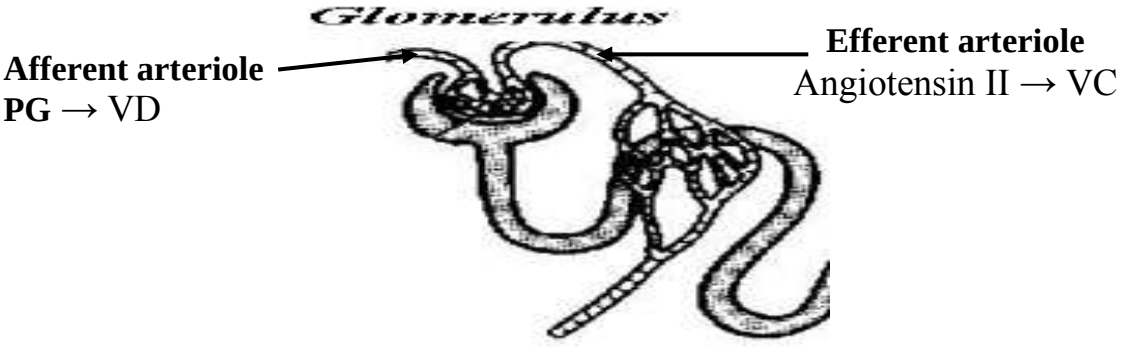
Structure of the Nephron

The functional unit of the kidney is the nephron, which is formed of a glomerulus, proximal tubule, loop of Henle, distal tubule and collecting duct.

Glomerular Filtration

- The higher hydrostatic pressure in the glomerular capillaries (60 mmHg) compared to the lower osmotic pressure (25 mmHg) allows filtration of all components of plasma except the plasma proteins.
- **Maintenance of glomerular filtration in hypoperfusion states**

In renal hypoperfusion states, glomerular pressure is increased to maintain GFR through: ↑ angiotensin II → VC of efferent arteriole & ↑ PG → VD of afferent arteriole→↑ blood flow



- In renal hypoperfusion states, administration of ACEIs (→ inhibit efferent VC) or administration of the PG synthesis inhibitors NSAIDs (→ inhibit afferent VD) causes marked reduction in glomerular filtration → acute renal failure.

Tubular Reabsorption

- Following glomerular filtration, the hydrostatic pressure in the peritubular capillaries falls (18 mmHg) and the osmotic pressure rises (32 mmHg) due to concentration of plasma proteins. This allows rapid tubular reabsorption.
- Na^+ is reabsorbed in the different segments of the nephron as follows:

Proximal Tubules

Site (1): 60% of filtered Na^+ is reabsorbed as NaCl (Na^+ is actively reabsorbed by Na^+-pump, Cl^- follows Na^+ passively).

Site (2): 5% of filtered Na^+ is reabsorbed as $NaHCO_3$ in exchange with H^+ under effect of carbonic anhydrase enzyme**.**

- Water is reabsorbed passively (proximal tubules, highly water permeable).
- Ca^{2+}, Mg^{2+} and K^+ reabsorption follows that of Na^+ to the same degree.
- Glucose & amino acids are reabsorbed by Na^+ cotransport mechanism.

Loop of Henle:

Site (3): Thick Ascending Loop of Henle

- 25% - 30% of filtered Na^+ is reabsorbed via active 2 $Cl^-/Na^+/K^+$ pump.
- This segment is impermeable to water rendering the tubular fluid hypotonic (diluting segment).

- **Medullary hypertonicity**: is created by active reabsorption of Na^+ coupled with passive transport of urea at this segment. It provides osmotic driving forces for water reabsorption from **descending loop of Henle & collecting tubules** under the effect of ADH

Distal Tubules:

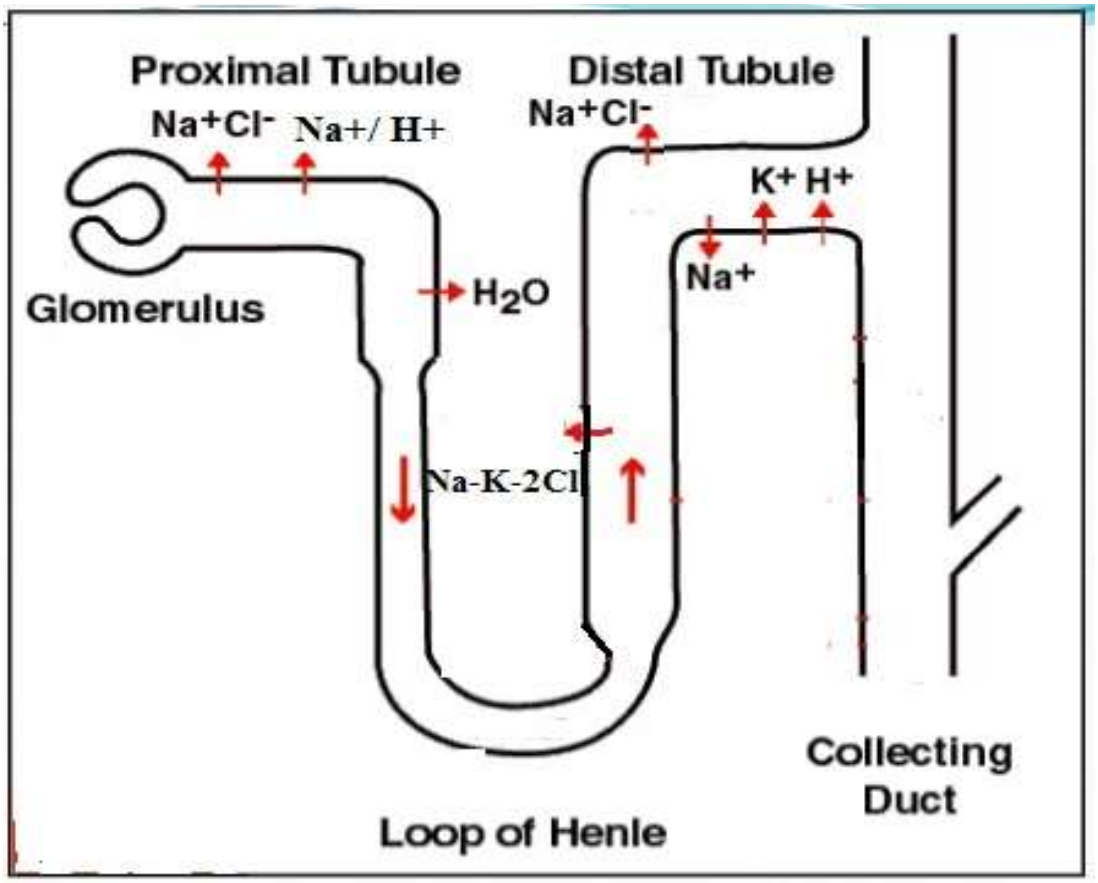
Site (4): Proximal (early) Part: There is active NaCl reabsorption (10%).

Site (5): Distal (late) Part:

- Na^+ is reabsorbed (5%) in exchange with K^+ or H^+ via $K^+/Na^+/ H^+$ pump.
- Na^+ reabsorption is aldosterone-dependent & aldosterone-nondependent.

Collecting Duct

- ADH increases the permeability of the collecting duct to water which is reabsorbed by the driving osmotic force of the hypertonic medulla



DIURETICS

- Diuretics are drugs that cause a net loss of sodium and water from the body through the kidney resulting in contraction of the extracellular fluid.

They include:

1- Extrarenal:

- H_2O & Alcohol
- Digitalis in HF
- Dobutamine
- Methylxanthines

2- Renal

A.K^+-losing diuretics

- Thiazides.
- Loop diuretics.
- Carbonic anhydrase inhibitors.
- Osmotic diuretics.

B. K^+-sparing diuretics

- Spironolactone - amiloride - triamterene.

General Principles in Diuretic Therapy

1. **Diuretics act by different mechanisms** and at different sites along the nephron. Thus, they have a **synergistic effect if they are combined** together.
2. **All diuretics (except spironolactone**) have to **reach their site of action in the lumen of the nephron**, by organic acid or organic base secretory systems. Therefore, any defect in delivery of diuretics to their sites of action (e.g. in renal impairment) will result in diminished diuretic response.
3. **Carbonic anhydrase inhibitors, thiazides and loop diuretics are organic acids** secreted by organic acid secretory systems and, therefore, **compete** with secretion of other organic acids such as uric acid resulting in **hyperuricemia.**
4. **Diuretics interfering with reabsorption of Na^+ at any site lead to enhanced Na^+ reabsorption in exchange with K^+& H^+** at distal tubule (aldosterone-dependent $Na^+/K^+/H^+$ exchange site) → **hypokalemia and alkalosis.**
5. **Diuretics inhibiting Na^+ reabsorption** at a certain site **interfere with other renal functions related to Na^+ reabsorption** at that site, for example:
   a. Loop diuretics inhibit Ca^{2+} & Mg^{2+} reabsorption at thick ascending loop.
   b. K^+-retaining diuretics inhibit excretion of K^+ and Mg^{2+} ions in distal tubule.

Diuretic	Route of access to site of action	Site of action
•Carbonic anhydrase Inhibitors	Organic acid secretion	Proximal tubule (2)
•Osmotic diuretics	Glomerular filtration	Proximal tubule & loop of Henle (1,2,3)
•Loop diuretics	Organic acid secretion	Loop of Henle (3)
•Thiazides	Organic acid secretion	Early Distal tubule(4)
•Amiloride •Triamterene •Spironolactone	Organic base secretion Organic base secretion Peritubular circulation	Late Distal tubule and collecting duct (5)

EDEMA

- **Edema:** Increased fluid in interstitial spaces
- **Factors** that govern movement of water between vascular and interstitial spaces:
  1. **Vascular hydrostatic pressure**: ↑ hydrostatic pressure → ↑ interstitial fluid
  2. **Plasma osmotic (oncotic) pressure:** ↓ osmotic pressure → ↑ interstitial fluid
  3. **Lymphatic drainage**: excess interstitial fluid is drained away by lymphatics, so lymphatic obstruction → edema
  4. **Capillary permeability**: ↑ capillary permeability → edema e.g. immune reactions- inflammations- Burns

- **Types of edema:**

  1. **Localized:**

     1. LYMPHATIC OBSTRUCTION: can result from:

     - Inflammation - Neoplastic obstruction
     - Parasitic infection: filariases
     - Cancer of breast: removal/irradiation of breast & axillary lymph nodes → severe edema of the arm

     2. INFLAMMATIONS (Inflammatory edema is a protein-rich exudate while in other types, fluid is usually a protein-poor transudate)

  2. **Generalized:**

     1. CARDIAC: CHF affects Rt.ventricular function → stagnation of blood in veins & ↓CO → ↓ renal perfusion → ↑RAA → ↑Na, H_2O retention→ ↑vascular hydrostatic pressure

     2. RENAL: Nephrotic Syndrome: leaky glomerular capillary wall → excessive loss of serum albumin→↓ plasma osmotic pressure

     3. Hepatic: Liver cirrhosis: ↓ production of albumin→↓ plasma osmotic pressure & portal hypertension → ↑vascular hydrostatic pressure

- **Pulmonary edema: -** Most often in left ventricular failure
  - Can cause death by interfering blood/gas exchange
  - Fluid in alveoli create favorable place for bacterial infection

- **Brain edema: -** May be localized (abscess, neoplasm, trauma), or generalized (encephalitis, hypertensive crises, trauma)
  - Generalized brain edema can be rapidly fatal (as brain herniation or brain stem vascular supply can be compressed → injure vital centers)

THIAZIDE DIURETICS

(Moderately powerful diuretics)

Mechanism of Action

1- **Diuretic:** Inhibit active NaCl reabsorption in the early part of distal tubule (diluting segment) causing excretion of 5-10 % of filtered Na^+.

2- **Vasodilator action:**

1- Depletion of Na^+ from arterial wall→↓ sensetivity to noradrenaline and angiotensin

2- K^+ channel opener → hyperpolarization → relaxation of vascular smooth muscle

3- May increase vasodilator PGs

4- May direct effect

Action:

Urine	Blood
Excess Na+	Hyponatremia
Excess Cl-	Hypochloremia
Excess H_2O	Hypovolemia
Excess K+	Hypokalemia
Excess H+	Alkalosis
Excess Mg++	Hypomagnesemia
↓ Ca++ excretion	Hypercalcemia

Therapeutic Uses:

1. All types of salt & water retention: (mild to moderate)

a. Generalized edema b. Ascites c. pleural & pericardial effusion

2. Hypertension: mild and moderate HTN

- Initially: diuresis → ↓ blood volume.
- Persistent effect: due to vasodilation

N.B.: Patients on thiazides have a reduced risk of osteoporosis and hip fractures as they ↓ Ca^{2+} excretion. So, **thiazides are preferred in elderly hypertensives**.

3. Idiopathic hypercalciuria & recurrent Ca^{2+} stones

- Chronic therapy → ↓ GFR & ↑ tubular Ca^{2+} reabsorption → ↓ Ca^{2+} excretion.

4. Nephrogenic diabetes insipidus

- Chronic therapy paradoxically↓ urine output in nephrogenic diabetes insipidus (may be due to ↓ GFR → ↓ urine volume or ↑ sensitivity of ADH receptors in tubular cells).

Adverse Effects

1.**Hypo**volemia

2. **Hypo**tension

3.**Hypo**natremia

4.**Hypo**kalemia & 5. Metabolic **alkalosis**

6.**Hypo**chloremia

7. **Hypo**magnesemia

6.**Hyper**calcemia.

7. **Hyper**glycemia:

* ↓ Insulin release: thiazide-induced hypokalemia →↑ K^+ outflux from pancreatic islet cells → membrane hyperpolarization →⊖Ca^{2+} influx →⊖insulin release.
* ↓ peripheral glucose utilization

8. **Hyper**lipidemia: (↑ blood cholesterol &LDL)

9. **Hyper**uricemia. (↓tubular secretion of uric acid)

10. **Hyper**sensitivity.

11. **Impotence**.

Pharmacokinetics:

- The drugs are effective orally.
- All thiazides are secreted by the organic acid secretory system of the kidney
- Onset: 1 hr and duration: variable 8-24 hr
- Most thiazides take 1 to 3 weeks to produce a stable reduction in blood pressure

Doses and Preparations

- **Hydrochlorthiazide& chlorthiazide**
- **Drugs related to Thiazides**
  - **Chlorthalidone**: very long acting (it is given once/d)
  - **Indapamide**:Vasodilator properities - less metabolic side effects – can be used in patient with renal failure
  - **Metolazone**: more potent than thiazide – effective in cases of advanced renalfailure

LOOP DIURETICS

(High ceiling - most effective diuretics)

Mechanism of action:

1. **Diuretic:** block the 2 $Cl^-/Na^+/K^+$ reabsorption pump in the thick ascending loop of Henle resulting in:
   - Excretion of 20% of filtered Na^+.
   - Interference with medullary hypertonicity → failure of water reabsorption by medulla under effect of ADH → excretion of water in excess of Na^+.
2. **Vasodilator:** release vasodilator **PGs** & ↓ of Na^+ from arterial wall:
   - VD of afferent arteriole → ↑ glomerular filtration.
   - Increase renal blood flow→ useful in acute renal failure.
   - **IV → Venodilator** → useful in acute pulmonary oedema.

Loop diuretics are **high ceiling diuretics** as they block nearly all reabsorption sites → excretion of 20% of filtered Na^+ (maximum capacity of the ascending loop).

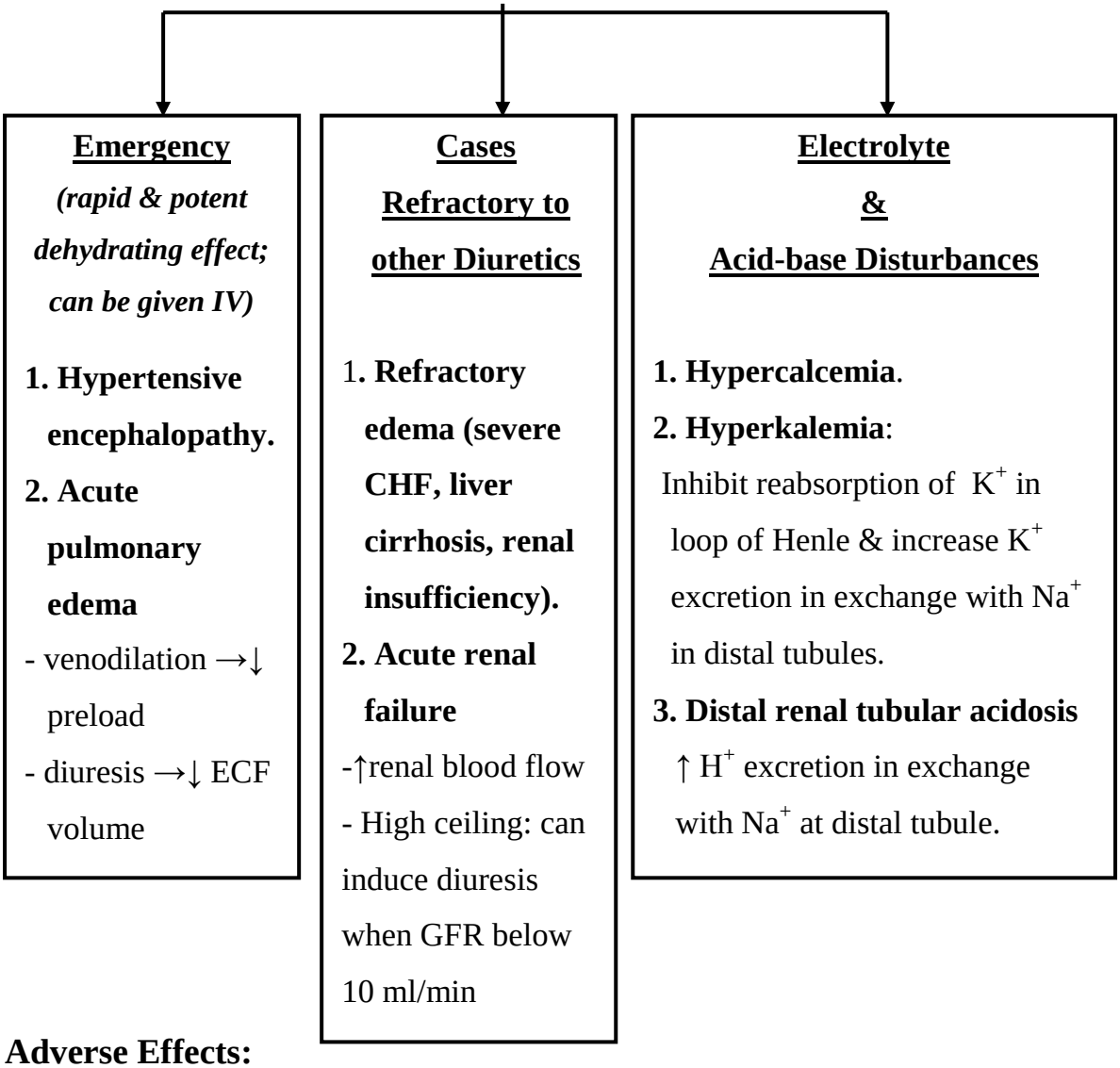
Pharmacokinetics

- Loop diuretics are **highly protein bound (90%)**.
- Good absorbed orally
- Onset: 30 min. and Duration: 4 hrs
- IV: onset within 5 min.

Action:

Urine	Blood
Excess Na+	Hyponatremia
Excess Cl-	Hypochloremia
Excess H2O (due to ↓ medullary hypertonicity)	Hypovolemia
Excess K+	Hypokalemia
Excess H+	Alkalosis
Excess Mg++	Hypomagnesemia
Excess Ca++	(No hypocalcemia as Ca is reabsorbed again in DCT under the control of PTH)

Indications of Loop Diuretics



Adverse Effects:

The same as thiazide diuretics **(Hypo….. & Hyper……) but** it causes:

1. **Oto**toxicity.
2. **NephrO**toxicity.
3. **RefractO**riness (see below).

Drug interactions:

1. NSAIDs inhibit PGs synthesis → interfere with action of loop diuretics.
2. With aminoglycosides → ↑ ototoxicity
3. With cephalosporines→ ↑ ototoxicity

Causes & management of refractoriness to loop diuretics

A. Pharmacokinetic Causes

I. Defective intestinal absorption in decompensated HF: Give the diuretic **IV.**

II. Defective plasma protein binding in hypoalbuminemic states (liver cirrhosis & nephrotic syndrome) → extravascular diffusion of diuretic →↓ renal excretion**:**

Mix the diuretic **with albumin** prior to infusion**.**

III. Defective excretion of diuretics by acid secretory system in renal impairment due to accumulation of acids: ↑ Dose of diuretics

B. Pharmacodynamic Causes

I. Hypertrophy of distal tubular cells (on chronic use →↑ Na^+ reabsorption →blunts the action of the diuretic**):Add thiazides**

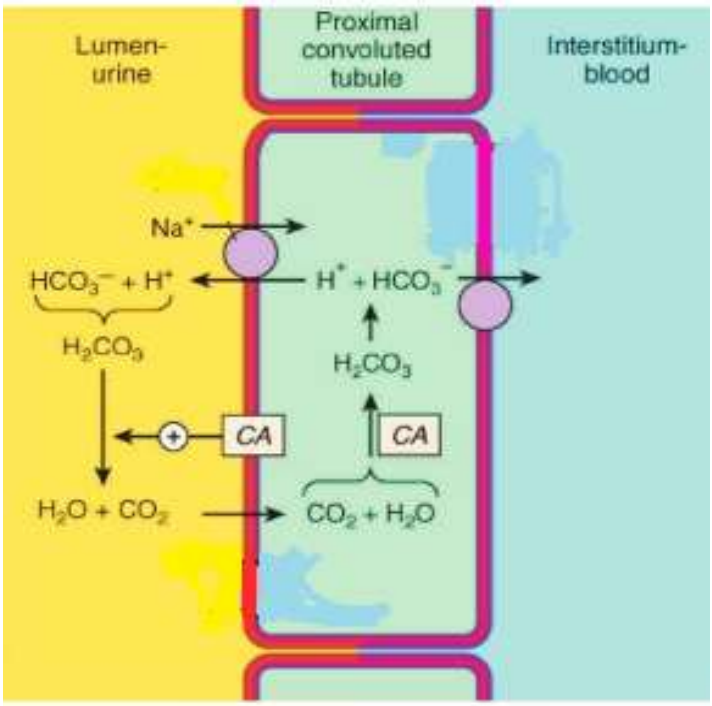
II. Na^+ lost by loop diureticis reabsorbed in exchange with K^+ in distal tubules (under the effect of aldosterone)**:Add** the aldosterone antagonist **spironolactone.**

Doses and Preparations (all are sulfonamide-like **except ethacrynic acid)**

- **Frusemide:***oral dose 80 mg (40 - 120); IV dose 40 mg (20 - 60 mg).*
- **Bumetanide**(**40 times more potent**): *oral and IV dose 1 - 5 mg.*
- **Ethacrynic acid**.
- **Torsemide**
- **Endocrinone**

CARBONIC ANHYDRASE INHIBITORS (CAIS)

Mechanism of Action:



Inhibit carbonic anhydrase enzyme responsible for H^+ production:

- <u>In the Kidney:</u> inhibition of Na^+/H^+ exchange at the proximal tubules → inhibition of $NaHCO_3$ reabsorption → loss of $NaHCO_3$ in urine leading to: a. Diuresis with alkaline urine.
  b. Decreased blood bicarbonate with metabolic acidosis.

- <u>In the brain:</u> Decrease formation of CSF.

- <u>In the eye:</u> Decrease formation of aqueous humor.

<u>N.B.</u>: CAIs are weak diuretics as most of the fluid & Na^+ lost are reabsorbed at more distal nephron sites.

Indications:

1. **H**igh altitude (mountain) sickness: [Weakness, dizziness, insomnia, headache, and nausea in rapid ascend above 3000 m; (to correct alkalosis)].

3. **H**ydrocephalus (to decrease ICT)

2. **E**pilepsy: suppress the irritable focus directly or by inducing acidosis.

3. **E**ye: treatment of **glaucoma** by decreasing formation of aqueous humor

4. **E**xcretion of acidic drugs in cases of toxicity as salicylates & barbiturates (alkalinize urine).

Adverse Reactions

- **Metabolic acidosis** → drowsiness & refractoriness to the diuretic effect (The body preserves $NaHCO_3$ to buffer acidosis).
- **Calcium and phosphate stones** due to alkaline urine.
- **Hypersensitivity** reactions as they are sulfonamide derivatives.

Preparations:

- **Aceta**zolamide
- **Metha**zolamide **(orally: preferred in glucoma due to less adverse effects)**
- **Brin**zolamide **& Dor**zolamide **(topically: eye drops)**

OSMOTIC DIURETICS

(Mannitol)

(Powerful diuretic action)

Mechanism of Action:

Mannitol is freely filtrated at the glomerulus with limited reabsorption by renal tubules → ***increase in osmotic pressure of tubular filtrate*** resulting in:

- **Retention of water and increased urine volume** (main effect → useful as DEHYDRATING agent).
- Opposing plasma osmotic pressure → **inhibition of Na^+ reabsorption** throughout the nephron (but to a much lesser extent than water; so, they are INEFFECTIVE in edematous states with Na^+ overload).

Indications:

1. **Dehydrating agents for:**
   a. **Cerebral edema** (caused by head injury or brain surgery) to produce rapid reduction of intracranial tension.
   b. **Acute congestive glaucoma** to produce rapid of reduction of intraocular tension.
2. **Prophylaxis against acute renal failure**:
   - Mannitol prevents acute renal failure following surgery, trauma or hemolytic transfusion reactions by maintaining high rate of urine flow, preventing concentration of toxic agents which cause renal damage.

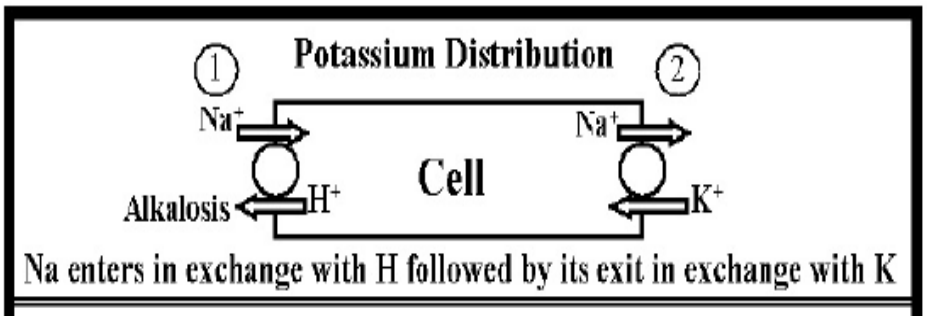
Adverse Effects & Contraindications:

- **In impaired renal function** (e.g. acute renal failure), mannitol is not filtered & persists in plasma → ↑ **intravascular volume** → **heart failure & dilutional hyponatremia**
- CI in acute renal failure & congestive heart failure**.**

POTASSIUM-RETAINING DIURETICS

(Weak diuretics; excrete only 5% of Na+ filtrate)

Mechanism:



Inhibit Na+/K+/H+ exchange at the distal tubule by two different mechanisms:

I. Indirect: Spironolactone& eplerenone (delayed onset of action)

- Antagonize aldosterone receptor-binding decreasing synthesis of a specific protein that stimulates the Na^+ pump (requires 3 - 4 days).

II. Direct: Triamterene & amiloride (rapid onset of action).

- Act independent of aldosterone → block Na^+ channels directly.

Indications:

1. Edema of hyperaldosteronism

- **Spironolactone is the drug of choice (more effective):**

1. 1^{ry} hyperaldosteronism (Conn's syndrome)
2. 2^{ry} hyperaldosteronism (liver cirrhosis, nephrotic syndrome & CHF)

More effective*: as edema of hyperaldosteronism is resistant to other diuretics because Na^+ lost by other diuretics is reabsorbed again by excess aldosterone at $Na^+/K^+/H^+$ exchange site in distal tubule*

(directly acting K^+-retaining diuretics are less effective than spironolactone in hyperaldosteronism).

2. Hypokalemia and hypomagnesemia

- **Triamterene and amiloride, are preferable** to spironolactone **(more rapid & shorter acting** → daily dosage adjustment possible).

3. Heart failure: ↓ mortality & hospitalization and ↑ survival rate

4. Combined with loop & thiazide diuretics to:

* Synergize their diuretic effects in refractory (resistant) edema

* ↓ risk of electrolyte imbalance:

  Loop & thiazide diuretics → hypokalemia

  K^+-sparing diuretics → hyperkalemia

* ↓ risk of acid-base imbalance:

  Loop & thiazide diuretics → metabolic alkalosis

  K^+-sparing diuretics → metabolic acidosis

5. Treatment of hirsutism & acne in female

Spironolactone has antiandrogenic effect

Adverse Effects:

1. **Hyperkalemia & metabolic acidosis.**
2. **Nausea, abdominal pain, drowsiness & mental confusion**
3. **Spironolactone antagonizes other steroid hormones:**
   - Androgens → gynecomastia, loss of libido & impotence in males.
   - Estrogen → menstrual irregularities female.
   - **Eplerenone → NO** antiandrogenic effect
4. **Triamterene may precipitate in urine → stone formation.**

	Spironolactone	**Triamterene & Amiloride**
Structure	Synthetic steroid	Synthetic non-steroid
Metabolism	Extensive metabolism in liver	- Triametrene is metabolized in liver - Amiloride is excreted unchanged
Mechanism	Competitive antagonism with aldosterone at its receptors in DCT	Direct block of $Na^+/K^+/H^+$ exchange in DCT
Antiandrogenic effects	Gynecomastia & impotence	Not present

CLINICAL APPLICATIONS OF DIURETICS:

CONGESTIVE HEART FAILURE		
Pathology	**Advantage of diuretics**	**Disadvantage of diuretics**
• Na & H_2O retention • Weak cardiac ms. • Lung congestion	1. ↓ Na & H_2O retention 2. ↓ preload (due to ↓ ECF volume) and ↓ afterload (due to VD) → improve cardiac function 3. ↓ lung congestion	1. Marked ↓↓ ECF volume → ↓↓ COP. 2. Metabolic alkalosis → impair cardiac function 3. Hypokalemia → ↑ digitalis toxicity & arrhythmia

CHRONIC RENAL DISORDERS		
Pathology	**Advantage of diuretics**	**Disadvantage of diuretics**
• Na & H_2O retention • Hypertension. • Hyperkalemia	1. ↓ Na & H_2O retention 2. Reduction of hypertension 3. Correction of hyperkalemia	1. Thiazides are ineffective if GFR < 30 ml/min 2. K^+-sparing are contraindicated due to hyperkalemia • **Loop diuretics are the best choice**

LIVER CIRRHOSIS		
Pathology	**Advantage of diuretics**	**Disadvantage of diuretics**
• Edema & ascites • Hypotension. • ↑↑ NH_3 level • ↑↑ aldosterone level	1. Correction of edema 2. Correction of ascitis	1. Thiazides & loop diuretics are generally ineffective due to ↑ aldosterone level 2. Aggravation of hypotension 3. Hypokalemia → intracellular acidosis → ↑↑ NH_3 formation → hepatic coma 4. Vigorous diuresis → hepatorenal syndrome • **The best choice is Spironolactone + Frusemide (in ratio 100:40 mg)**

FORCED DIURESIS

Definition: Increased urine formation by **diuretics and fluid** to enhance the excretion of certain drugs or compounds in urine.

Aim: 1. Treat drug toxicity or overdose

2. Treat some pathological conditions as hemorrhagic cystitis and rhabdomyolysis

Types:

1. Forced alkaline diuresis:

- sodium bicarbonate is added to the infusion fluid to make blood and, in turn, urine alkaline.
- Potassium replacement because hypokalemia → bicarbonate ion retention → prevents bicarbonate excretion → interfering with alkalinization of the urine.
- Used to increase the excretion of acidic drugs e.g. salicylates and phenobarbitone.

2. Forced acid diuresis:

- Ascorbic acid (vitamin C) is added.
- Used to increase the excretion of basic drugs e.g. cocaine, amphetamine, quinine.

DRUGS THAT CHANGE URINE pH

Urine alkalization is required to:

1- Relief **dysuria**.

2- Prevent **urate renal stones** because urates are soluble in alkaline medium.

1- Increase urinary **excretion of acidic drugs** in cases of intoxication e.g. barbiturates and salicylates.

4- Prevent growth of certain **microorganisms** e.g. E.coli

5- Prevent precipitation and **crystallization of sulfonamides**

Examples:

Sodium bicarbonate - sodium citrate - carbonic anhydrase inhibitors

Toxicity:

Excessive use of urine alkalizing agents may result in:

* Hypernatremia

*Aggravation of congestive heart failure and renal failure

<u>Urine acidification</u> (urine pH should be less than 5.5) **is required to:**

1. Prevent **phosphate renal stones**.

2. Increase urinary **excretion of basic drugs** in cases of intoxication. e.g. amphetamine, ephedrine, methadone.

3. As a **renal function test** to investigate the ability of the renal tubules to acidify urine.

Examples:

-Vitamin C - ammonium chloride - arginine HCL - calcium chloride.

NEPHROGENIC DIABETES ISIPIDUS (DI)

Causes: <u>1. Congenital:</u>

<u>2. Acquired:</u> * Hypercalcemia, hypokalemia

* <u>drug-induced</u>: lithium, clozapine, demeclocycline, and others

Treatment:

1. **Adequate intake of water**
2. **Amiloride** in lithium-induced nephrogenic DI *(blocks the uptake of lithium by the Na^+ channel in the collecting-duct system)*
3. **Thiazide diuretics** in non-lithium-induced with **moderate restriction of Na^+ intake**
4. **May *Indomethacin*** *(→ salt & water retention, ↓ decrease GFR and ↓ PGs → ↑ ADH effect on renal tubules)*

TREATMENT OF IDIOPATHIC HYPERCALCIURIA

Diet:

1. Low dietary Na^+: ↓ blood volume → ↓ GFR & ↑ tubular Ca^{2+} reabsorption

2. Avoid high protein diet:

Proteins produce acidosis which increases Ca^{2+} stones *by the following:*

1. Acids mobilize calcium from bone to blood and then to urine.

2. Intracellular acidosis consumes citrate decreasing its concentration in blood & urine (urinary citrate normally prevents crystallization of Ca^{2+} stone).

3. Avoid restriction of dietary Ca^{2+}:

Oral Ca^{2+} binds with oxalate in the intestine *decreasing oxalate absorption* → ↓ *urine oxalate. The low oxalate in urine prevents the formation of Ca^{2+} oxalate stones.*

Drug therapy:

1. Thiazides (chronic use): ↓ *blood volume* →↓ *GFR & ↑ tubular Ca2+ reabsorption or ↑ sensitivity of renal tubules to ADH*

2. K^+ citrate: to avoid hypokalemia as it is associated with increased intracellular acidosis *which decreases citrate excretion in urine.*

URINARY ANTISEPTICS

- They disinfect the urine without systemic antibacterial effect.
- **Uses:** for prophylaxis and long term suppressive therapy of UTI.
- They include: **2N, 2M**

1- Nitrofurantoin:

- It is a synthetic antimicrobial.
- Active against the majority of urinary pathogens **except pseudomonas**.
- Well absorbed orally and concentrated in urine.
- **Uses:** prophylaxis against lower UTI.

N.B.: Could be used **safely during pregnancy except near term** to avoid neonatal hemolysis.

- **Adverse effects:**
  1. Nausea & vomiting
  2. Diarrhea
  3. Peripheral neuritis (in renal impairment)
  4. Allergic reactions.
- **Contraindication:**
  - Renal impairment as it renders the drug more toxic and less effective.
  - G-6P-D deficiency.

2-Nalidixic acid:

a quinolone derivative. **Not used with nitrofurantoin**. It may cause hemolysis in G-6P-D deficiency.

3-Methenamine: it releases the antiseptic formaldehyde in acidic urine

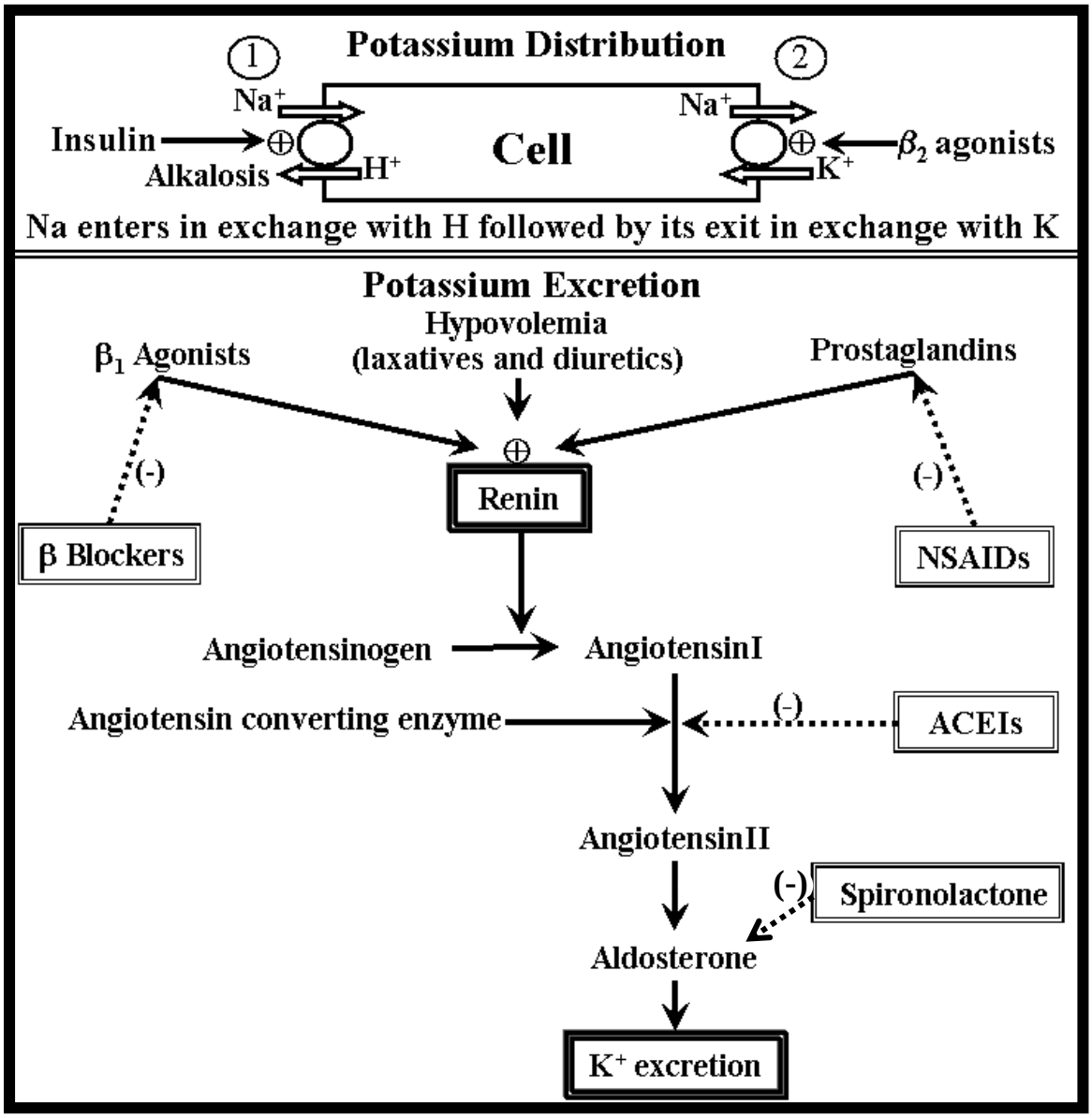
4-Mandelic acid: it is a urinary antiseptic and acidifying agent **potentiates methenamine**.

DRUGS AND POTASSIUM HOMEOSTASIS

- Potassium is the major intracellular cation with low concentration in the extracellular fluids (3.5 - 5 mEq/L). The body maintains this low plasma K^+ level through:

  i. Promoting entry of K^+ into the cell by the Na^+-K^+ ATPase pump. Insulin & β_2 adrenergic receptor stimulation activate this pump.

  ii. Excretion of K^+ through the kidney (mainly) & colon (limited amount). Both processes are stimulated by aldosterone through the renin-angiotensin system.



Causes of Hypokalemia & Hyperkalemia

Hypokalemia (<3.5 mEq/L)	Hyperkalemia (>5 mEq/L)
A. Increased K^+ entry into cells: **1. Insulin**. **2. β_2 agonists** **3. Alkalosis (** due to K^+-losing diuretics or vomiting**).** • H^+ diffuses out of cell to buffer the alkalosis → K^+ diffusion into cells to maintain cell electronegativity.	**A. Increased K^+ exit out of cells:** **1. Digitalis** (⊖ Na^+-K^+ ATPase) **2. β blockers** (β_2- blockade) **3. Acidosis (**due to K^+-retaining diuretics & salicylates**)** • H^+ diffuses into cell to buffer the acidosis→ K^+ diffusion out of cell to maintain cell electronegativity .
B. Increased K^+ loss: **1. Renal loss:** • Hyperaldosteronism • K^+-losing diuretics as loop diuretics & thiazides. • ***Hypomagnesemia*** **2. GIT loss:** • Laxatives – severe diarrhea. • Sever vomiting	**B. Decreased renal K^+ excretion:** **1.** Impaired renal function**.** **2.** Hypoaldosteronism: Addison's disease **3.** K^+-retaining diuretics **4.** β_1Bs – NSAIDs: ⊖ renin release. **5.** ACEIs: ↓ Ag II & aldosterone.

Manifestations & treatment

Hypokalemia	Hyperkalemia
• **Arrhythmia (mainly tachyarrhythmia)** • **Muscle weakness** • **Alkalosis (**due to ↑ renal absorption → ↑ H^+ excretion**)**	• **Bradyarrhythmia up to cardiac arrest in diastol (if > 6.5 mEq/L)** • **Muscle weakness up to paralysis** • **Acidosis (**due to ↑ renal excretion → ↑ H^+ reabsorption**)**
1. ↑ K^+ supplementation: • Mild (2.5-3.5 mEq/L): **- K^+- rich diet** as banana, orange & lemon. **- Oral KCl** administration (has gastric & esophageal irritant effect and should be given with plenty of fluids while sitting upright) • Sever (<2.5 mEq/L): **IV infusion** (may cause phlebitis and should be given in large veins) **2. Combine K^+-sparing diuretics with K^+-losing diuretics**. **3. Mg^{++} supplementation** if hypokalemia due to hypomagnesemia	**1. Removal of K+ from body:** It is useful in mild (5-5.5 mEq/L) or asymptomatic cases. a- Loop or thiazide diuretics. b- Cation-exchange resins → inhibit intestinal absorption of K^+. **2. Increasing K+ movement into the cells:** **a- Insulin:** • Small dose of insulin 6 - 8 units plus 20 g IV glucose (as hypoglycemia is liable to occur). **b- IV sodium bicarbonate**. Bicarbonates induce alkalosis which increases influx of K^+ **3. Sever case (> 6.5 mEq/L)** **1. IV Ca^{++}:** It is the most rapid treatment used in severe cases. It ***stabilizes myocardial*** membrane by opposing the effect of hyperkalemia on membrane potential **2- Dialysis** in severe resistant cases

Drug therapy of urinary tract infections (UTIs)

General considerations:

1- Most UTIs are caused by gram-negative bacteria especially coliforms.
2- Majority of acute infections involve a single organism (commonest is E. coli). Chronic and recurrent infections may be mixed infections.
3- Acute infections are largely self-limiting: high urine flow rates with frequent bladder voiding may suffice.
4- 3 days regimen is considered optimal for lower UTIs. Upper UTIs require more aggressive and longer treatment.
5- In any case, treatment for more than 2 weeks is warranted
6- Overuse and misuse have contributed to the growing problem of resistance amongst uropathogenic bacteria, which is a serious threat to public health
7- Use of Antimicrobial aims to:
   a- optimize clinical outcomes
   b- ensure cost-effective therapy
   c- minimizing unintended consequences of antimicrobial use such as healthcare associated infections including Clostridium difficile, toxicity and emergence of resistant bacterial strains

Asymptomatic bacteriuria in adults:

A- Occurs in **-** healthy pre-menopausal females
- healthy elderly females and men
- patients with diabetes
- pregnant women
- patients with spinal cord injuries
- Asymptomatic bacteriuria in younger men is uncommon but, when detected, chronic bacterial prostatitis must be considered.

B- ***Diagnostic evaluation***

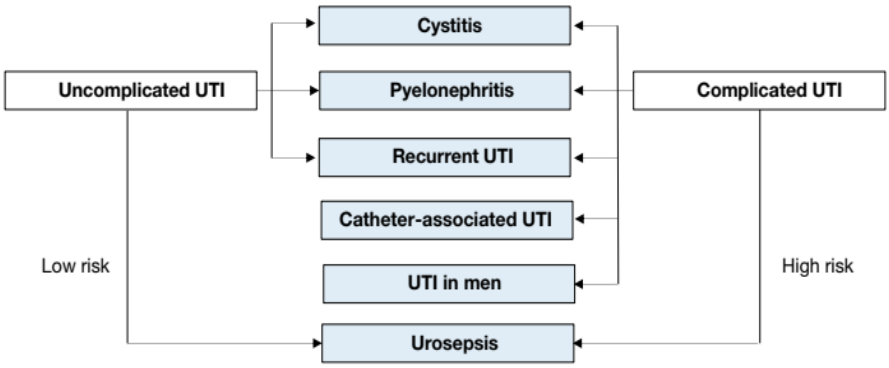
An individual **without urinary tract symptoms** with a mid-stream sample of urine showing:
- Bacterial growth **> 10^5 cfu/mL**
  - in <u>two</u> consecutive samples <u>in women</u>
  - in <u>one</u> single sample <u>in men</u>
- Bacterial growth **10^2 cfu/mL** <u>in a single catheterized</u> sample in both men and women

C- Management:

1- Screen for and treat asymptomatic bacteriuria:
   - Prior to urological procedures breaching the mucosa.
   - In pregnant women with standard short course treatment (2-7 days)

2- Do Not screen or treat in the following conditions:
- women without risk factors
- patients with well-regulated diabetes mellitus
- post-menopausal women;
- elderly institutionalized patients;
- patients with dysfunctional and/or reconstructed lower UT
- patients with renal transplants
- patients with recurrent urinary tract infections.

Classification of UTIs (EAU Urological Infections Guidelines):



Classification of UTIs	Diagnostic evaluation:	Management
Uncomplicated UTIs	• Acute, sporadic or recurrent, • lower (uncomplicated cystitis) and/or upper (uncomplicated pyelonephritis) UTI, • limited to non-pregnant women, • with no known relevant anatomical and functional abnormalities within the urinary tract or comorbidities.	• **Uncomplicated cystitis:** - 1st line in women: ***fosfomycin***, ***pivmecillinam*** *or* ***nitrofurantoin*** - Do **Not** use ***aminopenicillins or fluoroquinolones*** due to high resistance rates. • **Uncomplicated pyelonephritis:** - ***Fluoroquinolones and cephalosporines*** are the only agents recommended for oral empirical - IV regimens may include in addition an ***aminoglycoside (with or without ampicillin),*** - ***Carbapenems*** should only be considered in patients with early culture results indicating the presence of multi-drug resistant organisms - Do **Not** use ***nitrofurantoin, fosfomycin, and pivmecillinam***

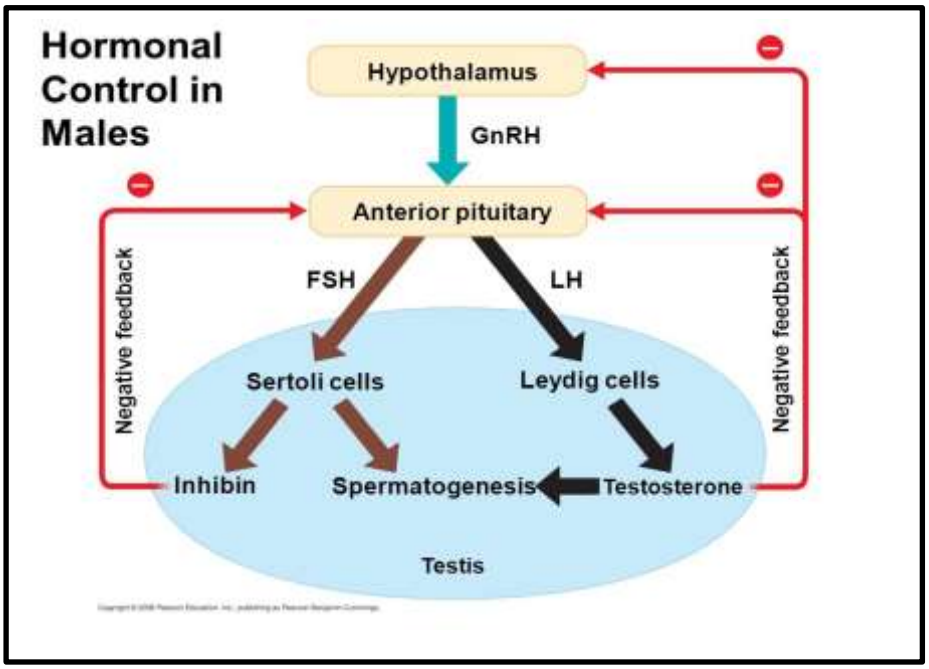
Complicated UTIs	All UTIs which are not defined as uncomplicated: •All men •Pregnant women •Patients with relevant anatomical or functional abnormalities of the UT, indwelling urinary catheters, renal diseases, and/or immunocompromising diseases e.g. DM.	•Use: - the combination of: • ***amoxicillin or 2nd generation cephalosporin + an aminoglycoside;*** - a ***3rd generation cephalosporin*** **IV** as empirical treatment of complicated UTI with systemic symptoms •**Only use *ciprofloxacin*** provided that the local resistance are < 10% when; • the entire treatment is given orally; • patients do not require hospitalisation; • patient has an anaphylaxis for beta-lactam antimicrobials
Recurrent UTIs	•Recurrences of uncomplicated and/or complicated UTIs, • with a frequency of at least 3 UTIs/year or 2 UTIs/the last 6 months.	•For prophylaxis of rUTIs: - Use vaginal oestrogen replacement in post-menopausal women - continuous or post-coital antimicrobial prophylaxis
Catheter-associated UTIs (CA-UTI)	UTIs occurring in a person whose urinary tract is: •currently catheterized or •has had a catheter in place within the past 48 hours.	•For treatment: - ***nitrofurantoin , fosfomycin, trimethoprim*** - during pregnancy ***cephalexin or cefaclor***
Urosepsis	•life threatening organ dysfunction caused by a dysregulated host response to infection originating from the urinary tract and/or male genital organs •Alerting symptoms (inflammatory response): - fever or hypothermia, - leukocytosis or leukopenia, - tachycardia and tachypnea	•General considerations: 1. adequate life-supporting care 2. Initial empiric antimicrobial therapy should provide broad antimicrobial coverage against all likely causative pathogens and should be adapted on the basis of culture results, once available. 3. The dosage of the antimicrobial agents should generally be high, with appropriate adjustment for renal function. 4. Antimicrobials must be administered no later than one hour after clinical assumption of sepsis 5. Duration of antimicrobial therapy : 7-10 days (Longer courses in patients with slow clinical response) •***3rd generation cephalosporines, Piperacillin/tazobactam, carbapenems, aminoglycosides (Not as monotherapy)***

MALE SEX HORMONES = ANDROGENS

- The androgens are a group of steroid hormones that have anabolic and androgenic effects → the development and maintenance of the male sex organs and secondary sex characteristics.

Testosterone

- It is the most important androgen
- It is synthesized by Leydig cells in the testes
    - Smaller amounts are synthesized by the ovary of the female and by the adrenal gland in both sexes.
- Its secretion by is controlled by gonadotropin-releasing hormone from the hypothalamus → stimulates the anterior pituitary gland → secrete:
    1. FSH→ necessary for spermatogenesis
    2. LH → stimulates steroidogenesis **(testosterone)** in the Leydig cells
        - Testosterone or its active metabolite dihydrotestosterone **(DHT)** → a negative feedback on trophic hormones → regulates testosterone production.



- **Mechanism of action:**

- It binds to a specific intracellular androgen receptors in a target cell → The hormone-receptor complex → binds to DNA and affects gene expression
- In muscle and liver: testosterone is the active ligand.
- In the prostate, seminal vesicles, epididymis, and skin: testosterone is converted by **5-α reductase** enzyme to dihydrotestosterone **(DHT)**, which binds to the receptor.
- In the brain, liver, and adipose tissue: testosterone is biotransformed by **cytochrome P450 aromatase** enzyme to **estradiol**.

- **Actions:**

A. Androgenic:

1. Male sex organs development (penile & scrotal development) } **Puberty**
2. 2ry sex characters (hair growth, thickening of vocal cords) }
3. Testosterone + FSH → ⊕ spermatogenesis → **Fertility**
4. ↑ libido in males & females
5. Large doses for prolonged time → feedback inhibition of Gns → testicular atrophy.

B. Anabolic:

1. ↑ protein synthesis
2. ↑ bone density and closure of epiphyseal ends of long bone
3. ↑ muscle development. 4. ↑ Erythropoiesis and coagulation

- **Uses:**

A. For its Androgenic effects:

1. **Replacement therapy in Male hypogonadism:**

- **1ry hypogonadism** due to testicular dysfunction→ give testosterone
- **2ry hypogonadism** (due to failure of the hypothalamus or pituitary) → L.H + F.S.H if normal and functioning testes

2. **Adjuvant in the treatment of Cancer breast**: ↓release of gonadotropins (+ anti-estrogen)

B. For its anabolic effect

1. **Growth stimulant** in debilitating conditions e.g. after major surgery.
2. **Senile osteoporosis**: ↑ protein formation and calcium deposition in bones.
3. **Aplastic anemia**: ↑erythropoietin synthesis

- **Preparations:**

1. Natural: Androsterone and **Testosterone** (more active) are **INeffective orally** due to the **extensive 1st pass metabolism** in the liver.

- are given **IM**. , **S.C**.

2. Synthetic: including

- Esterified preparations: **testosterone propionate** (**IM)**
- Conjugated preparations : **methyl-testosterone (sublingual- oral)**

3. Semisynthetic**: Fluoxymesterone (oral)**

- **Adverse Effects:**

1. In female: Virilization: masculinization – acne - growth of facial hair deepening of the voice - menstrual irregularities - clitorial enlargement.
   CI: pregnant women → virilization of the female fetus
2. In males: Azospermia - ↑ libido – priapism (painful erection for more than 4 hours treated by aspiration of the corpora cavernosa and injection of alpha agonist).
   - Behavioral effects: increased aggressiveness, and psychotic symptoms.
3. In children: Short stature due to premature closure of epiphysis
4. Methyl-testosterone causes reversible cholestatic jaundice.
5. Increase incidence of cancer prostate **CI: cancer prostate**

ANTIANDROGENS

A. Inhibitors of testosterone secretion:

- Analogs of GnRH as **Leuprolide** when are given continuously → inhibit LH secretion → inhibit testosterone production
- Used to - suppress **precocious puberty**
  - treat **prostate cancer**

B. Inhibitors of testosterone synthesis:

- Some antifungal drugs such as **ketoconazole** inhibit CYPs → block the synthesis of steroid hormones, including testosterone and cortisol.
- They are **not used to inhibit androgen synthesis** because they may induce adrenal insufficiency and are associated with hepatotoxicity
- May used in cases of glucocorticoid excess

C. Inhibitors of androgen action:

1) 5-α reductase inhibitors: Finasteride & Dutasteride:

- block the conversion of testosterone to dihydrotestosterone, especially in the male external genitalia.
- Used in **Benign Prostatic Hyperplasia (BPH)**.

2) Androgen receptor (AR) antagonists:

Flutamide - Bicalutamide & Cyproterone:

- **Competitive antagonist** at androgen receptors.
- Used in **- Cancer prostate - Acne & hirsutism in females**.

Spironolactone: aldosterone antagonist that also is a weak AR antagonist and a weak inhibitor of testosterone synthesis (by inhibiting CYP)

**** Common adverse effects** of antiandrogens:

1. Gynecomastia
2. ↓ libido (sexual desire)
3. Erectile dysfunction (impotence): inability to obtain or maintain erection of penis for sexual intercourse.

ANABOLIC STEROIDS

(Stanozolol - Nandrolone)

- Synthetic androgens with high anabolic and low androgenic activities.

Indications

1. Chronic debilitating diseases, e.g. cancer.
2. Bodybuilding & athletes
3. Osteoporosis
4. Prolonged immobilization.

Adverse effects: as androgens

ERECTILE DYSFUNCTION (ED)

Causes of ED:

1- Cardiovascular diseases.

2- DM.

3- Psychological (14%).

4- Drugs: e.g. antidepressants, H_2-blockers and thiazide diuretics.

Management:

1. Sildenafil (Viagra):

Mechanism of action:

It **inhibits phosphodiesterase type-5 (PDE5)** → ↑ levels of cGMP → vasodilatation → engorgement of the sinusoids and expansion of the corpora cavernosa → erection of the penis.

Side effects*:* headache, flushing, nasal congestion & transient color vision disturbance. **Priapism** may occur.

Contraindications:

- With nitrates → severe acute hypotension.
- Recent stroke, acute myocardial infarction
- blood pressure < 90/50 mmHg.

2-Alprostadil : PGE_1→ powerful vasodilator injected in the corpora.

3- Androgens: effective only if ED due to testosterone deficiency

4-papaverine + phentolamine: were used by injection in the corpora.

- Painful - priapism - penile fibrosis may occur on repeated injections.

BENIGN PROSTATIC HYPERPLASIA (BPH)

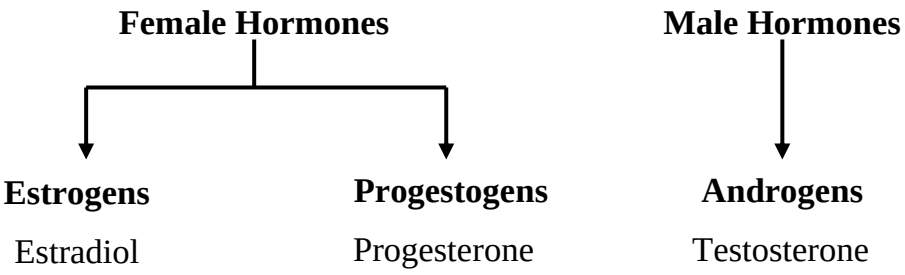
The prostate gland is formed of:

- Capsular & stromal tissue rich in alpha adrenoreceptors.
- Glandular tissue under the influence of androgens.

Both alpha adrenoreceptors and androgens are targets for drug therapy.

1. $Alpha_1$-adrenoceptors blockers e.g. **prozosin, terazosin**
    - ↓ prostatic congestion → ↑ the maximal urine flow rate.
    - Additional effect → ↓ BP in hypertensive patients.
    - Major adverse effect: 1st dose hypotension & postural hypotension
    - **Tamsulosin** doesn't block vascular α1-adrenoceptors → avoid undesirable side effects of other alpha-blockers.
2. Antiandrogen: **Finasteride - Dutasteride**
3. Phosphodiestrase type-5 inhibitor: if ED developed due to antiandrogen

REPRODUCTIVE PHARMACOLOGY



Estrogens

Classification:

1. **Natural estrogens**:
   - **Estradiol** is the **major** estrogen secreted by the ovary.
   - They are synthesized from the precursor, cholesterol, in a series of steps. Aromatization is the last step in estrogen synthesis.
   - In liver: Estradiol →oxidation→ Estrone →hydroxylation→ Estriol.
   - **All three are active**, but **estradiol is the most potent** estrogen
   - in Males: Small quantity of estradiol is derived from aromatization of testosterone in the testes and extraglandular tissues
   - **Oral** natural estrogens are **inactive** and have a **short duration** of action due to hepatic 1st pass metabolism.

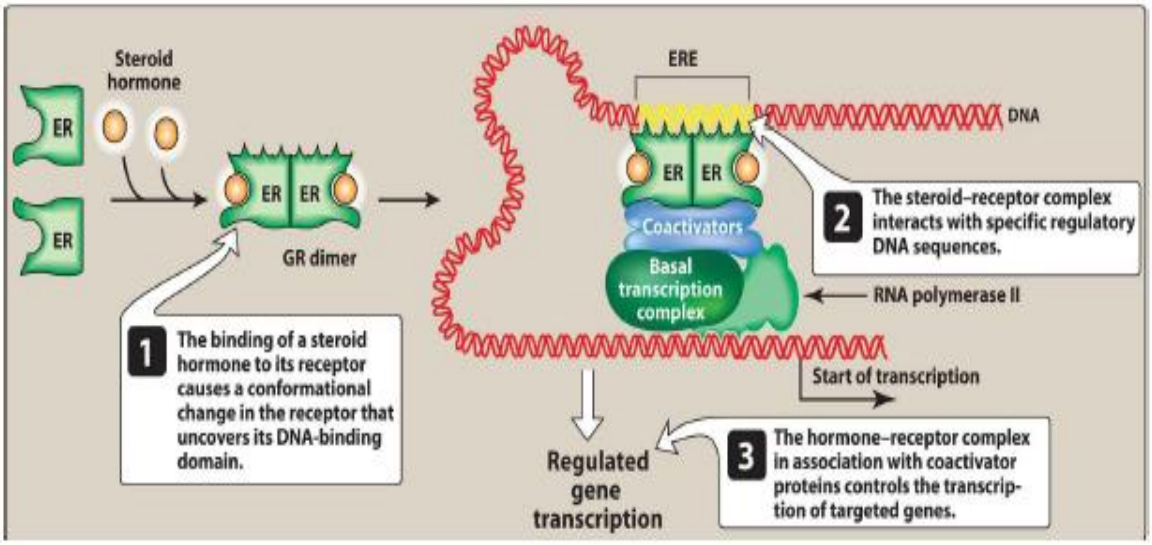
   - Regulation of secretion:
     - Its secretion starts from the ovary under the effect of FSH → blood level ↑ gradually → feedback inhibition of FSH (also of LH at higher concentration) by direct action on hypothalamus-pituitary pathway.
2. **Synthetic estrogens:**
   - Steroidal: **Ethinylestradiol**, Mestranol
   - Nonsteroidal: **Diethylstilbestrol (stilbestrol)**

Actions:

1. **Sex organs**: pubertal changes in the female including:
   - Growth of uterus, fallopian tubes and vagina.
   - Vaginal epithelium → thickened, stratified.
   - The proliferation of endometrium
   - The cervix → a watery alkaline secretion → help sperm penetration.
   - Sensitize the uterus to oxytocin.
   - Deficiency of estrogens is responsible for atrophic changes in the female reproductive tract that occur after menopause.
2. **Secondary sex characters**
   - Growth of breasts, proliferation of ducts and stroma, accumulation of fat.
   - Appear of the pubic and axillary hair
   - Feminization of body contours and behavior.
   - Acne is common in girls at puberty (probably due to small amount of androgens produced simultaneously), so administration of estrogens → suppress pituitary-gonadal axis → ↓acne.
3. **Metabolic effects**: Estrogens are **anabolic** (similar to than testosterone but weaker).
   - Promotes fusion of epiphyses both in girls and boys.
   - Maintaining bone mass by ↓ bone resorption (↓ osteoclast formation →↑ expression of bone matrix proteins such as osteocalcin, collagen and alkaline phosphatase).
   - ↓ plasma LDL and ↑ HDL & TGs levels
   - Impair glucose tolerance → affects diabetic patients
4. **Blood, body fluids and electrolytes:**
   - ↑ synthesis of clotting factors (II, VII, IX and X) →↑ blood coagulability
   - ↑ nitric oxide and PGI_2 production. → vasodilatation.
   - ↑ cholesterol secretion & ↓ bile salt secretion →↑lithogenicity
   - Salt and water retention → edema and ↑ BP after prolonged use.

Mechanism of action:

- Estrogens bind to specific nuclear receptors in target cells → interaction with 'estrogen response elements' (EREs) of target genes in association with coactivator proteins → gene transcription → regulating protein synthesis.
- On binding an estrogen antagonist with the receptor → a different conformational changes in receptor and interacts with corepressor proteins → inhibiting gene transcription.
- Two subtypes of ERs: **ERα & ERβ**
  - Most tissues express both subtypes, but:
  - ERα predominates in uterus, vagina, breast, bone, hypothalamus and blood vessels
  - ERβ predominates in prostate gland of males and ovaries in females.



Pharmacokinetics:

- Estrogens are well absorbed orally and transdermally
- Natural estrogens orally → inactive due hepatic 1st pass metabolism.
  - Estradiol, Estrone and Estriol are conjugated with glucuronic acid and sulfate → excreted in urine and bile.

- Synthetic estrogens:
  - IM preparations: slow absorption → prolonged action.
  - Ethinylestradiol: orally → active and more potent - is metabolism → very slow → prolonged action
- Enterohepatic circulation occurs due to deconjugation in intestine → reabsorption.

Uses of synthetic estrogens:

✓ **1. Oral contraceptive pills.**

2. Replacement therapy:

✓ ***a. Postmenopausal hormonal replacement therapy (HRT).***

- **↓ Vasomotor Symptoms:** hot flushes, sweating, paresthesias, pains
- **↓ Psychological disturbances**: irritability, depressed mood, loss of libido & self-confidence, anxiety
- **↓ Urogenital atrophy**: vaginal dryness, vulval shrinkage, vaginitis, itching, urinary urgency, predisposition to urinary tract infection
- **↓ Osteoporosis**: thinning and weakening of bone → minimal trauma → fractures especially of femur, hip, radius, vertebrae
- **↓ Dermatological changes** Thinning, dryness and loss of elasticity of skin, wrinkles, thin and listless hairs.

b. Delayed puberty in girls: due to ovarian agenesis (Turner's syndrome) or hypopituitarism. (growth hormone and/or a small dose of androgen may be added for the rapid gain in height)

c. Senile vaginitis: atrophic vaginitis that occurs in elderly women. (Topical therapy is commonly used. Oral can be used)

4. Dysmenorrhea:

- **NSAIDs** (PGs synthesis inhibitors) are the **first line** drugs,

- **Cyclic estrogen therapy + progestogen** → inhibiting ovulation (anovular cycles are painless) → for **severe cases**.

5. Acne in girls: (It occurs at puberty due to ↑ androgen secretion).

- Estrogens → inhibit Gn release from pituitary → ↓ ovarian androgen.
- Topical therapy with antimicrobials, tretinoin and other drugs is preferred.

6. Dysfunctional uterine bleeding: Estrogens have adjuvant value

- Cyclic Progestogen is the effective therapy.

7. Cancer prostate: Estrogens → ↓ androgen production → produce relief in primary & metastatic cancer prostate

- GnRH agonists with or without androgen antagonist are preferred.

Adverse Effects

1. Nausea
2. Breast tenderness
3. Weight gain.
4. Endometrial hyperplasia
5. ↑ risk of endometrial & breast cancer.
6. Hypertension & thromboembolim (↑ blood coagulation).
7. In male: feminization - impotence - ↓ libido - gynecomastia.

Antiestrogens

1. Clomiphene

Mechanism:

Partial-agonist estrogen that acts **centrally**:

Blocks **central estrogen receptors** in hypothalamus ➔ prevents normal feedback inhibition of FSHRH & LHRH in hypothalamus ➔ ↑ amount of LH/FSH ➔ ↑ stimulation of ovulation.

Ph.kinetics:

- Well absorbed orally
- Deposited in adipose tissue
- Long t½ of ~6 days.
- It is largely metabolized and excreted in bile.

Uses (oral)

1. **Female infertility due to disorders of ovulation** (ovulation-inducing agent): **50** mg once/day for **5** days starting from **5th** day of cycle.
   - Treatment is given monthly → If no conception for 1–2 months → duplication of the daily dose for 2–3 cycles.
   - No more than 6 treatment cycles should be tried
2. **"*in-vitro*" fertilization [+ Gonadotropins**] → maturation of several ova → improves their harvesting for in vitro fertilization.

Adverse Effects

1. Polycystic ovaries
2. Multiple pregnancy
3. Hot flushes
4. Gastric upset
5. ↑Risk of ovarian tumor

2. Tamoxifen

Mechanism:

Selective estrogen receptor modulators (SERMs); acting **peripherally:**

[These drugs exert estrogenic & anti-estrogenic actions in a tissue selective manner]

- **Antagonistic** action: preventing endogenous estrogen from activating receptors in **estrogen-sensitive tumors (breast cancer),** blood vessels and other peripheral sites
- **Partial agonistic** action: in - **Bone** → ↑ bone density → prevent osteoporosis in women taking the drug for breast cancer.
  - **Uterus** → ↑ endometrial proliferation
  - **Pituitary** → ↓Gonadotropins and prolactin levels
  - ↑ **Blood coagulability** → ↑ risk of venous thromboembolism
  - **Liver** → ↓total cholesterol & LDL (No change in HDL or TGs level)

Use: treatment of hormone-sensitive breast cancer**.**

Adverse Effects: Hot flushes - vaginal bleeding, menstrual irregularities - venous thromboembolism - ↑ **risk of endometrial carcinoma**

3. Raloxifene

- **Mechanism: Selective estrogen receptor modulator** (SERM):
  - **Antagonistic** action: on **breast cancer & endometrium**
  - **Partial agonistic** action: on **Bone & CVS**
- **Use** : treatment of osteoporosis in postmenopausal women (2nd line)
- **Adverse effects**: Hot flushes – vaginal bleeding (occasional)- DVT

	Bone	**Breast**	**Endometrium**
Tamoxifen	P-agonist	Antagonist	**P-agonist**
Raloxifen	P-agonist	Antagonist	**Antagonist**

4. Letrozole

- **Aromatase inhibitor (AIs):** reversible inhibitor of aromatization (the final and key step in the production of estrogens) → ↓ estrogen production all over the body, including the breast cancer cells
- **Uses:** treatment of hormone-sensitive breast cancer **(1st line)**
- **Adverse effects**: Hot flushes, GIT upset, joint pain and ↓ bone mass

Tamoxifen	**Letrozole**
1. SERMs: estrogen antagonist in breast and blood vessels but agonist in uterus, bone, liver and pituitary	1. AIs: inhibits production of estrogens in all tissues
2. Used for breast Cancer in premenopausal	2. Not to be used in premenopausal women
3. Causes endometrial hyperplasia → endometrial carcinoma	3. No endometrial hyperplasia/cancer predisposition
4. No bone mass loss → No ↑fractures	4. ↑ bone mass loss → ↑ fractures
5. ↑ risk of venous thromboembolism	5. No ↑ in thromboembolic risk
6. Improves lipid profile (↓ LDL)	6. No effect on lipid profile

Progestogens

Classification:

1. **Natural progestogens**:
   - **Progesterone** is the natural progestogen
   - Synthesis: is derived from cholesterol.
   - Regulation of Secretion:
     - It is secreted from the ovary in the later half of menstrual cycle under the influence of LH.
     - Its production declines a few days before the next menstrual flow.
     - If the ovum gets fertilized and implanted→ immediate production of chorionic gonadotropin → sustains the corpus luteum in early pregnancy.
     - Placenta secrets lots of estrogens and progesterone from 2nd trimester till term.
2. **Synthetic progestogens (progestins)**
   - Progesterone derivatives (21 C): **Medroxyprogesterone**
   - 19-nortestosterone derivatives (18 C): **Norethindrone -Norgestrel**

Actions:

- The main function of progesterone is preparation of the uterus for the pregnancy.

1. Uterus: Progesterone → secretory changes in the endometrium:

- Tortuocity of glands and increased secretion
- ↓ Sensitivity of myometrium to oxytocin is decreased.

2. Cervix: Progesterone converts the watery cervical secretion → viscid scanty and cellular secretion → hostile to sperm penetration.

3. Vagina: Progesterone → leukocyte infiltration of epithelium.

4. Breast: Progesterone causes proliferation of the mammary glands.

- with estrogens → prepare breast for lactation.

5. CNS:

- Sedative effect
- ↓ mood.

6. Body temperature: A slight ↑in body temperature

7. Metabolism:

- Impairs glucose tolerance: progestogens induce insulin resistance
- ↑ LDL and ↓ HDL levels.

9. Pituitary:

- It exerts negative feedback → ↓ frequency of GnRH pulses.
- Progesterone → weak inhibition of Gn secretion from pituitary.

Mechanism of action: (As estrogens)

- Progestins bind the intracellular progesterone receptors (PR) → attaches to progesterone response element (PRE) of target genes → regulates transcription through coactivators.
- The antiprogestins bind to PR → opposite effects by interaction with corepressors

Pharmacokinetics

- Progesterone: is inactive orally due to high 1st pass metabolism in liver.
  - It is mostly injected IM.
  - Has a short t½ (5–7 min) [However, effects of progesterone last longer than the hormone itself]
  - Nearly complete degradation in the liver → glucuronide and sulfate conjugates → excreted in urine.
- A micronized formulation of progesterone → oral administration.
- Most of the progestins
  - are orally active and are metabolized slowly → longer duration plasma (t½ 8–24 hours)

Uses

- ✓ **1. Hormonal contraception (major use).**

2. Hormone replacement therapy (HRT): In postmenopausal women: progestin is given with estrogen for 10–12 days/month →↓risk of endometrial carcinoma

3. Dysmenorrhea (inhibit ovulation).

4. Endometriosis: (presence of endometrium at ectopic sites → dysmenorrhea, painful pelvic swellings and infertility)

- Continuous administration of progestin → long-lasting ovarian suppression → prevents bleeding in the ectopic sites and atrophy of the ectopic masses

5. Endometrial carcinoma

Adverse Effects

1. Breast engorgement
2. Headache, ↑body temperature
3. Irregular bleeding or amenorrhea if continuous administration
4. Depression.
5. Edema - hypertension - weight gain.
6. ↓ HDL - ↑ blood sugar 7. Hirsutism, acne (androgenic).

Antiprogestins

Mifepristone

Mechanism

- Recently is **"Progesterone receptor modulator"**: has a partial agonist and competitive antagonist at progesterone and glucocorticoid receptors.
- **Uses: 1. Major use**: **Therapeutic abortion** (e.g. termination of pregnancy in intrauterine fetal death): by blocking the relaxant action of progesterone on uterus in combination with prostaglandins
  2. Cushing's syndrome: May be used for inoperable cases.

Adverse effects: abdominal pain, uterine bleeding, and the possibility of an incomplete abortion

Hormonal Contraceptives

1. Combined oral contraceptives

Mechanism of Action

1. Suppression of ovulation: inhibit FSH & LH.

2. Change cervical mucosa (thick & more acidic) ➔ inhibit sperm penetration.

3. ↓ Endometrial glycogen deposition ➔ inhibit implantation.

Preparations: Combined contraceptive Pills

- They contain estrogen and progestin .
- They are taken for 21 days starting from the 5th day of the cycle and are omitted for 7days.

- Monophastic pills contain constant dose.
- Biphasic pills: change of dose once
- Triphasic change of dose twice:

6 days: 0.03 mg estrogen + 0.05 mg progestin.

5 days :0.04 mg estrogen + 0.075 mg progestin.

10 days:0.03 mg estrogen +0.125 mg progestin.

Indications

1. Contraception.
2. Regulation of menstrual cycle.
3. To postpone menstruation e.g. during pilgrimage.
4. Dysfunctional uterine bleeding

Adverse Effects & Contraindications (CI) of Combined Pills

I. Minor Risks

1. Nausea, vomiting, headache.
2. Breast tenderness.
3. Edema.

II. Intermediate Risks

1. Bleeding (low dose), amenorrhea (large dose).
2. Acne, hirsutism, skin pigmentation.

III. Major Risks: mostly from estrogen. Modern preparations contain low-dose estrogen→↓ risks.

1. Cardiovascular: ↑ in females over 35 & smokers:
   a. Thromboembolism - pulmonary embolism.
   b. Hypertension - stroke - myocardial infarction.

CI: myocardial infarction and cerebrovascular disorders.

2. Carcinogenic

   ↑ Risk of endometrial & breast cancer (estrogen): ↓ by adding progestins.

CI:	1. Estrogen-dependent tumors of breast & uterus. 2. Undiagnosed vaginal bleeding.

3. Cholecystitis - gall stones – jaundice → **CI** in liver disease.
4. Hyperglycemia
5. Depression: by progesterone.

2. Progestin-Only Preparations

A. Oral preparations (Minipills)

B. Parenteral Preparations

a. Implants → 5 years.

- Biodegradable: do not need to be removed on expiry.
- Non-biodegradable: be removed on expiry

b. Depot injections (medroxyprogesterone acetate) →3 months.

Mechanism of action:

1- Inhibition of ovulation

2- Inhibition of sperm penetration in the uterus due to increase viscosity of cervical mucous.

Advantages:

1. Useful in patients with hepatic disease, hypertension, thromboembolism
2. They do not suppress lactation. → used in lactating women

Disadvantages:

1. Less effective than combined preparations
2. Long term progestin injections are not desirable for women planning a pregnancy soon after cessation of therapy because ovulation suppression can sometimes persist for as long as 18 months after the last injection
3. Unpredictable spotting and bleeding, particularly during the first year of use.

3. Other hormonal preparations:

A. Transdermal patch

- contains synthetic estrogens and the progestins.

B. Vaginal ring

- contains synthetic estrogens and the progestins.
- The ring is inserted into the vagina and left in place for 3 weeks

C. Progestin intrauterine device

- levonorgestrel-releasing intrauterine devices → highly effective method of contraception for 3 to 5 years.

D. Postcoital contraception

- Postcoital or emergency contraception reduces the probability of pregnancy after intercourse without effective contraception
- The most common method: a single high dose of **levonorgestrel** → should be taken as soon as possible after unprotected intercourse and preferably within 72 hours.
- An alternative: **ulipristal**: progesterone agonist/antagonist → within 5 days of unprotected intercourse

MALE CONTRACEPTIVE

- The only way to suppress male fertility by drugs is to inhibit spermatogenesis
- No acceptable solution is yet available due to:
  1. Complete suppression of spermatogenesis is relatively difficult (millions of spermatozoa are released at each ejaculation versus a single ovum per month in women).
  2. Spermatogenesis takes 64 days. A drug which even completely inhibited spermatogenesis will take a long latent period to produce infertility. Accordingly, return of fertility will be slow.
  3. Gonadotropin suppression inhibits testosterone secretion as well, → loss of libido and impotence
  4. Risk of adverse effects.
- Drugs tried are:

  1. Antiandrogens →↓ spermatogenesis & unacceptable loss of libido.

  2. Estrogens and progestins: → ↓Gns → unacceptable feminization.

  3. Androgens → ↓Gns but have poor efficacy.

4. Gn RH analogues → ↓Gn release by continuous action → ↓testosterone & impotence, loss of libido.

5. Cytotoxic drugs: Cadmium, nitrofurans → spermatogenesis, but are toxic.

6. Gossypol: It is obtained from cotton seed; → ↓ of spermatogenesis and sperm motility. Libido and potency are not affected. The mechanism probably involves direct toxicity on seminiferous epithelium.

Most important adverse effect is hypokalaemia, muscular weakness edema, diarrhea, breathlessness and neuritis

UTERINE STIMULANTS

(Oxytocics, Abortifacients)

- These drugs increase uterine contraction, especially at term.

1. Posterior pituitary hormone*:* **Oxytocin**, **Desamino-oxytocin, Carbetocin**

2. Ergot alkaloids: **Ergometrine**, **Methylergometrine**

3. Prostaglandins (E2, F2α) analogues: **Dinoprostone, Dinoprost, Misoprostol**

1. OXYTOCIN

- Secretion by the posterior pituitary (↑ coitus, parturition, suckling)
- Actions:

  1. Uterus: - ↑ force and frequency of uterine contractions.

  - Estrogens sensitize the uterus to oxytocin by ↑its receptors while progestins ↓ the sensitivity,

  - *Mechanism of action:* a- G-protein coupled oxytocin receptors → ↑ DAG, IP3 → ↑ intracellular Ca^{2+} & depolarization of muscle fibres

  b. Oxytocin ↑PGs synthesis and release → contractile response.

  2. Breast: contracts the myoepithelium of mammary alveoli and forces milk into the bigger milk sinusoids → 'milk ejection reflex' is initiated by suckling so that it may be easily sucked by the infant.

  3. Kidney: high doses exerts → ADH-like action → ↓ urine output: [pulmonary edema can occur if large amounts of IV fluids and oxytocin are infused together].

- Pharmacokinetics: inactive orally (peptide)- by IM or IV routes,
- Uses:

  1. Induction of labor*:* in case of toxemia of pregnancy, diabetic mother, ruptured membranes or placental insufficiency.

  2. Uterine inertia uterine contractions are feeble and labour is not progressing satisfactorily

  3. After **Caesarean section** to prevent uterine atony

  4. Postpartum hemorrhage

- Adverse effects:

  1. Too strong uterine contractions → force the presenting part through incompletely dilated birth canal → maternal & fetal soft tissue injury, rupture of uterus, fetal asphyxia and death.

  2. Water intoxication: if large doses given along with IV fluids, especially in toxemia of pregnancy and renal insufficiency.

Desamino-oxytocin buccal formulation; action is similar to injected oxytocin, but less consistent and used for → Induction of labor- Uterine inertia (buccal tablet repeated every 30 min)- Breast engorgement (before breast feeding)

Carbetocin: long-acting analogue of oxytocin used for → prevention of uterine atony after caesarean section - control PPH.

2. Ergometrine, methylergometrine

- Actions:

  1. Uterus: ↑ force, frequency and duration of uterine contractions. Mechanism of action: partial agonist on serotonin (5-HT2) and α-adrenergic receptors.

  2. GIT: High doses ↑ peristalsis.

- Methylergometrine is **more potent** than ergometrine on the uterus
- Pharmacokinetics:rapid and nearly complete absorption from the oral route.
- **Adverse effects :-** Nausea, vomiting and ↑BP occur occasionally.
  - High doses for many days → ↓ milk secretion (due to inhibition of prolactin release).
- Uses:

  1. The main indication: control and prevent **postpartum hemorrhage (PPH)** only in those expected to bleed more e.g. grand multipara, uterine inertia. A combination of ergometrine with oxytocin may be used in **severe bleeding**.

  2. After **caesarean section** to prevent uterine atony.

3. Diagnosis of variant angina: A small dose of ergometrine injected IV during coronary angiography → prompt constriction of reactive segments of coronary artery that are responsible for variant angina.

3. Prostaglandins

- PGE2, PGF2α are potent uterine stimulants, & cause ripening of cervix.
- **Dinoprostone & Dinoprost** and **Misoprostol** are PGs analogues used in:
  1. Induction of labor (especially in toxemic and renal failure patients as an alternative to oxytocin because PGs do not cause fluid retention)
  2. Therapeutic abortion (proceeded 2 days by Mifepristone)
  3. Postpartum hemorrhage

UTERINE RELAXANTS

(Tocolytics)

- These drugs ↓ uterine contractions.
- Uses: 1. Delay or postpone labor,
  2. Arrest threatened abortion
  3. Dysmenorrhea.
  4. Prevention of premature labour (to allow the foetus to mature, to allow time for initiating glucocorticoid therapy for foetal lung maturation or to transfer the mother in labour to a centre with proper facilities)

1. Adrenergic agonists: **Ritodrine, Terbutaline**

- They are β2-selective agonists
- **Adverse effects**:

1. **T**remors of skeletal muscle, **T**achycardia.
2. **H**ypokalemia and muscle cramps, **H**ypoxemia, **H**yperglycemia

2. Calcium channel blockers Nifedipine →↓influx of Ca^{2+} ions →
↓ uterine contractions,

- can postpone labour if used early enough.
- Adverse effects: Tachycardia, hypotension

3. Oxytocin antagonist: Atosiban acts as antagonist at the oxytocin receptors.

- postpone preterm labor with fewer cardiovascular and metabolic complications than β2 adrenergic agonists.

4. Magnesium sulfate IV infusion → **first line** drug for prevention & treatment of seizures in **preeclampsia and eclampsia**.

- It acts as a tocolytic by competing with Ca^{2+} ions for entry into myometrium at Ca^{2+} channels (both voltage gated & ligand gated).