المجلس الطلابي

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كلية الطب
College of Medicine

RENAL SYSTEM

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Introduction to The Upper Urinary Tract

Embryology

Development of the Kidneys:

Three systems of kidney develops from the nephrogenic ridge pronephros, mesonephros, and metanephros.

	Appearance time	Function
Pronephros (fish)	Week 3 of development; then degenerates.	Nonfunctional.
Mesonephros (amphibians)	Week 4 of development.	As interim kidney for 1st trimester; Function temporarily. persists in the male genital system as Wolffian duct, forming ductus deferens and epididymis.
Metanephros	Week 5 of development.	Permanent kidney.

Metanephros:

- Ureteric bud (metanephric diverticulum): derived from mesonephric duct; gives rise to ureter, pelvises, calyces, collecting ducts; fully canalized by week 10 of development. Starts to function at the 9th week.
- Metanephric mesenchyme (metanephric blastema): ureteric bud interacts with this tissue; which induces the formation of glomerulus through to distal convoluted tubule (DCT).

The fetal kidney:

- The kidney, initially in the pelvic region, later shifts to a more cranial position in the abdomen.
- In the pelvis, the metanephros receives its arterial supply from a pelvic branch of the aorta.

Embryology

Congenital anomalies:

	Description	Cause
Horseshoe kidney	Inferior poles of both kidneys fuse abnormally. Functional.	As they ascend from pelvis, horseshoe kidneys get trapped under inferior mesenteric artery and remain low in the abdomen.
Unilateral renal agenesis	Complete absence of kidney and ureter.	Ureteric bud fails to develop.
Pelvic Kidney	Failure of ascent of one kidney. Ureter is short.	
Duplex collecting System + malrotation of kidney	Bifurcation of ureteric bud before it enters the metanephric blastema creates a Y-shaped bifid ureter.	Two ureteric buds reaching and interacting with metanephric blastema. Strongly associated with vesicoureteral reflux and/or ureteral obstruction.
Multicystic dysplastic kidney	Nonfunctional kidney consisting of cysts and connective tissue.	Ureteric bud fails to induce differentiation of metanephric mesenchyme.

Anatomy

Kidneys:

- They are bean-shaped and lie in the extraperitoneal connective tissue immediately lateral to the vertebral column.
- The right kidney somewhat lower than the left because of its relationship with the liver.
- The left kidney is longer and more slender organ than the right kidney, and nearer to the midline.

Relations:

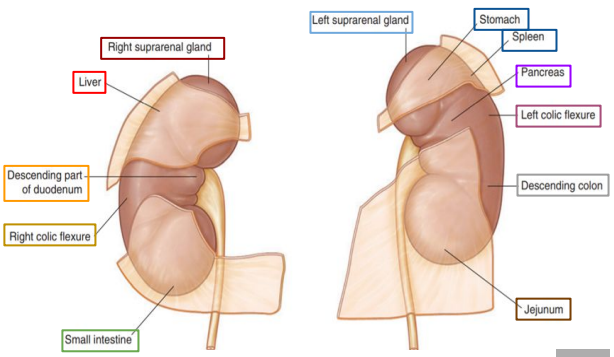
1 Anteriorly

Right kidney:

- Right suprarenal gland.
- Liver.
- Descending part of the duodenum.
- Right colic flexure.
- Segment of the intraperitoneal small intestine.

Left kidney:

- Left suprarenal gland.
- Stomach and spleen.
- Pancreas.
- Left colic flexure.
- Descending colon.
- Jejunum.



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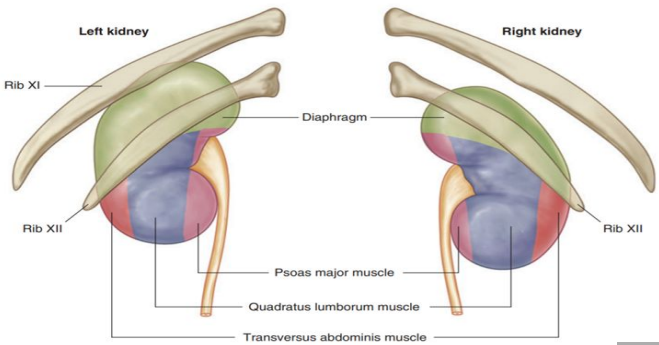
2 Posteriorly

- Diaphragm.
- Psoas major muscle.
- Quadratus lumborum muscle.
- Transversus abdominis muscle.
- Right kidney is anterior to rib XII.
- **Left kidney is anterior to ribs XI and XII.**
- The costodiaphragmatic recesses.
- Subcostal vessels and nerves.
- Iliohypogastric and ilioinguinal nerves.



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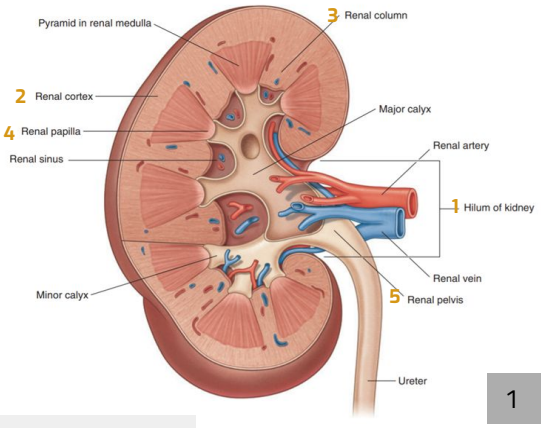
Anatomy



Kidney structure:

1 A deep vertical slit through which renal vessels, lymphatics, and nerves enter and leave the substance of the kidney. It is continuous with the renal sinus.

Hilum

2 A continuous band of pale tissue that completely surrounds the renal **medulla**.

Cortex

3 Extensions of the renal cortex, project into the inner aspect of the kidney, dividing the renal medulla into discontinuous aggregations of triangular shaped tissue (**renal pyramids**).

Renal columns

4 Contains the openings of the papillary ducts draining the renal tubules and is surrounded by a **minor calyx**.

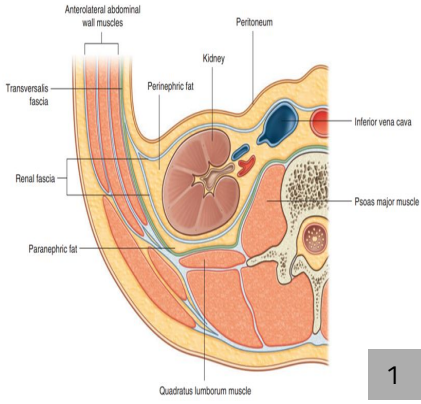
Renal papilla

5 The funnel-shaped superior end of the ureters, it is formed by two or three **major calyces**.

Renal pelvis

Anatomy

Renal fat and fascia: All support the kidney in position



- **Perinephric fat** (perirenal fat), completely surrounds the kidney.
- **Renal fascia** (extraperitoneal fascia) is a membranous condensation enclosing the perinephric fat. The suprarenal glands are also enclosed.
- **Paranephric fat** (pararenal fat) accumulates posterior and posterolateral to each kidney.

1

Arterial supply of kidney	The renal artery, and a lateral branch of the abdominal aorta at the level of 2nd lumbar vertebra. When the renal artery approaches the renal hilum, it divides into anterior and posterior branches, which supply the renal parenchyma. The extrahilar arteries originate from the lateral aspect of the abdominal aorta, and enter the hilum with the primary arteries or pass directly into the kidney at some other level.
Venous drainage of kidney	Left and right renal veins, both of which are anterior to the renal arteries. The left renal vein: is three times longer than the right. Receives the left gonadal and left suprarenal veins. It crosses the midline anterior to the abdominal aorta and posterior to the superior mesenteric artery and can be compressed by an aneurysm.
Lymphatic drainage of kidney	To the lateral aortic (lumbar) nodes around the origin of the renal artery.
Nerve supply of kidney	By the renal plexus, 10th, 11th, and 12th thoracic nerves.

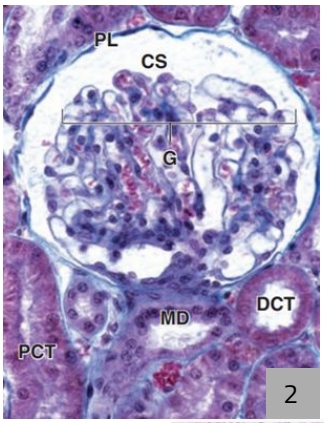
Histology

Renal cortex and medulla:

The kidney's parenchyma consist of:

- Renal **cortex**, a darker stained region with many round corpuscles and tubule cross sections.
- Renal **medulla** consisting mostly of aligned linear tubules and ducts. The renal medulla in humans consists of 8-15 conical structures called renal pyramids.

Renal corpuscle	An initial dilated part enclosing a tuft of capillary loops and the site of blood filtration, always located in the cortex. Consists of a small mass of capillaries called the **glomerulus**, The visceral layer composed of podocytes.
Proximal tubule (PCT)	A long convoluted part, located entirely in the cortex, with a shorter straight part that enters the medulla. Thick wall and brushy lumen.
Loop of Henle	in the medulla, with a thin descending and a thin ascending limb.
Distal tubule (DCT)	Consisting of a thick straight part ascending from the loop of Henle back into the cortex and a convoluted part completely in the cortex. Thin wall clear lumen.
Connecting tubules	Consists of merged connecting tubules from several nephrons.
Collecting duct	Consists of merged collecting tubules.



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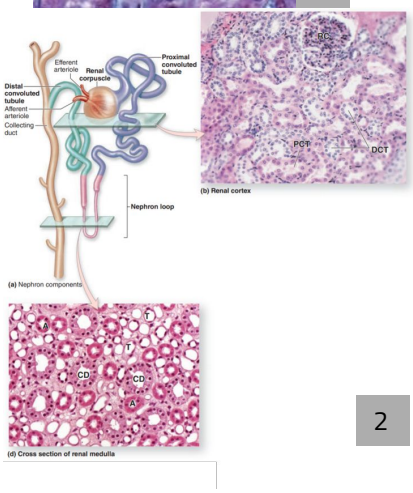

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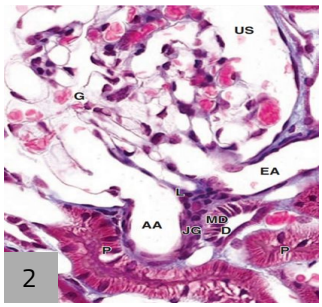
Histology

Histologic features of renal tubules:

Region of Tubule	Histologic Features
PCT	Simple cuboidal epithelium - long microvilli - lumens often occluded.
Loop of Henle	(TDL): Simple squamous epithelium; few mitochondria (TAL): Simple cuboidal epithelium; no microvilli, but many mitochondria.
DCT	Simple cuboidal epithelium; short microvilli and basolateral folds.
Collecting system	**Principal cells:** Most abundant, cuboidal to columnar; pale-staining, distinct cell membranes. **Intercalated cells:** Few and scattered; slightly darker staining.

Juxtaglomerular apparatus:



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- Forms at the point of contact between a nephron's distal tubule and the vascular pole of its glomerulus.
- Then the cells of the distal tubule become columnar as a thickened region called the **macula densa** with tall cells with centrally-placed nuclei
- Tunica media are converted from a contractile to a secretory morphology as **juxtaglomerular granule cells** with round nuclei and granular cytoplasm (Secrete renin).
- At the vascular pole are **extraglomerular mesangial cells** that have many of the same supportive, contractile, and defensive functions.
- Basic functions of the JGA in the autoregulation of the GFR and in controlling blood pressure include the following activities.

Tubular Processing

Objectives

Glomerular Filtration Regulation:

- Describe that the mechanism of urine formation includes three basic processes; glomerular filtration, tubular reabsorption and tubular secretion.
- Define GFR and quote normal value.
- Identify and describe the factors controlling GFR in terms of starling forces, permeability with respect to size, shape and electrical charges and ultrafiltration coefficient.
- Describe Intrinsic and extrinsic mechanism that regulate GFR.
- Describe autoregulation of GFR & tubuloglomerular feedback mechanism.

Tubular Reabsorption:

- Define tubular reabsorption, tubular secretion, transcellular and paracellular transport.
- Identify and describe mechanisms of tubular transport.
- Describe tubular reabsorption of sodium and water.
- Revise tubuloglomerular feedback and describe its physiological importance.
- Identify and describe mechanism involved in Glucose reabsorption.
- Study glucose titration curve in terms of renal threshold, tubular transport maximum, splay, excretion and filtration.
- Identify the tubular site and describe how Amino Acids, HCO3-, P04- and Urea are reabsorbed.
- List and explain the factors that control aldosterone and ADH release
- Identify and describe the juxtamedullary apparatus and its role in checking the filtrate.

Tubular Secretion:

- Describe tubular secretion with PAH transport and K^+.
- Identify and describe the characteristic of loop of Henle, distal convoluted tubule and collecting ducts for reabsorption and secretion.
- Identify the site and describe the influence of aldosterone on reabsorption of Na^+ in the late distal tubules.

Functional Anatomy

Nephron

The functional units of the kidney are nephrons. Each kidney contains approximately 1 million nephrons.

1-**Glomerulus**: A capillary tuft associated with a renal tubule, In which large amount of fluid is filtered from blood.

2-Bowman's Capsule: Blind end of the tubules, completely surrounds the glomerulus and receives the filtrate.

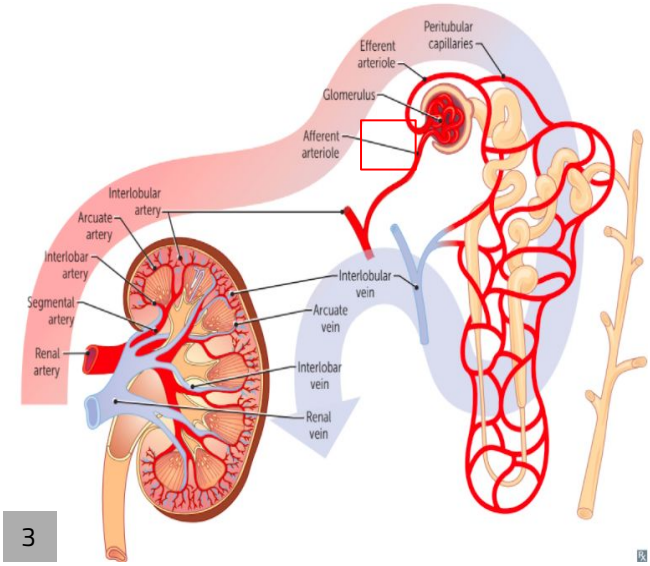
3-**Tubules**: Here filtered fluid eventually is converted into urine. Contains: PCT, Loop of henle, DCT and Connecting ducts.

There are two types of nephrons:

A. Superficial cortical nephrons: their glomeruli is in the outer cortex with short loops of Henle descend only into the outer medulla.
B. Juxtamedullary nephrons: : their glomeruli is near the corticomedullary border with long loops of Henle descend only into the outer medulla.

Renal Blood Vessels

1. Afferent arteriole:
   Delivers blood into the glomeruli.
2. Glomeruli:
   Capillary network that produces filtrate that enters the urinary tubules.
3. Efferent arteriole:
   Delivers blood from glomerulus to peritubular capillaries.
4. Peritubular capillaries:
   Vasa recta



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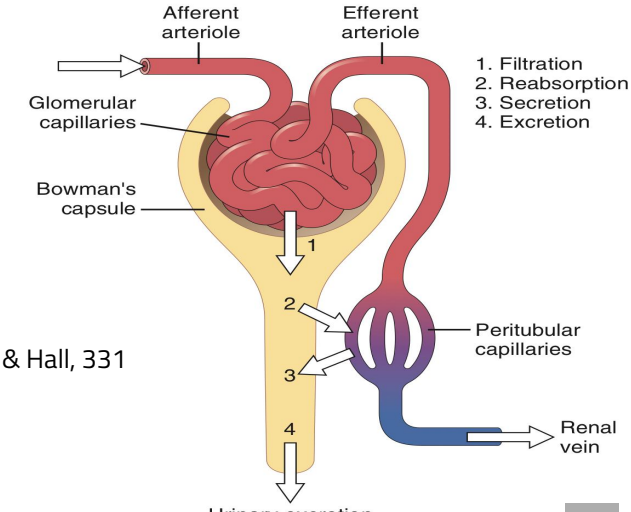
First Aid for the USMLE Step 1

Regulation of glomerular filtration



Guyton & Hall, 331

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Mechanism of urine formation

1.Glomerular filtration

- Is the first step of urine formation, 1200 ml of blood reach kidney per minute, containing about 625 ml plasma and these are called "renal plasma flow".
- These 625 ml plasma **about 125 ml of protein free plasma are filtered from the glomerular membrane then reach renal tubules** and they are called the glomerular filtration rate **(GFR).**
- The rest of the plasma (625-125= 500ml) return back to the efferent arterioles and runs through the Peritubular capillaries (around tubules).
- Large amounts of fluid is filtered through the glomerular capillaries into Bowman's capsule almost 180 liters per day.

2.Tubular reabsorption

- Is the movement of substances from lumen of renal tubules crossing tubular cells back to the blood.
- Some type of substances undergo complete reabsorption such as as amino acids & glucose, while other substance undergoes partial reabsorption such as Na^+ , K^+ , & HCO^3.
- Almost 99% of the Glomerular filtrate is reabsorbed, leaving only about 1 liter of fluid to be excreted each day.

3.Tubular secretion

- Is the movement of substances from blood surrounding the tubules to the tubular lumen to be excreted with urine.
- Secretion can be active or passive.

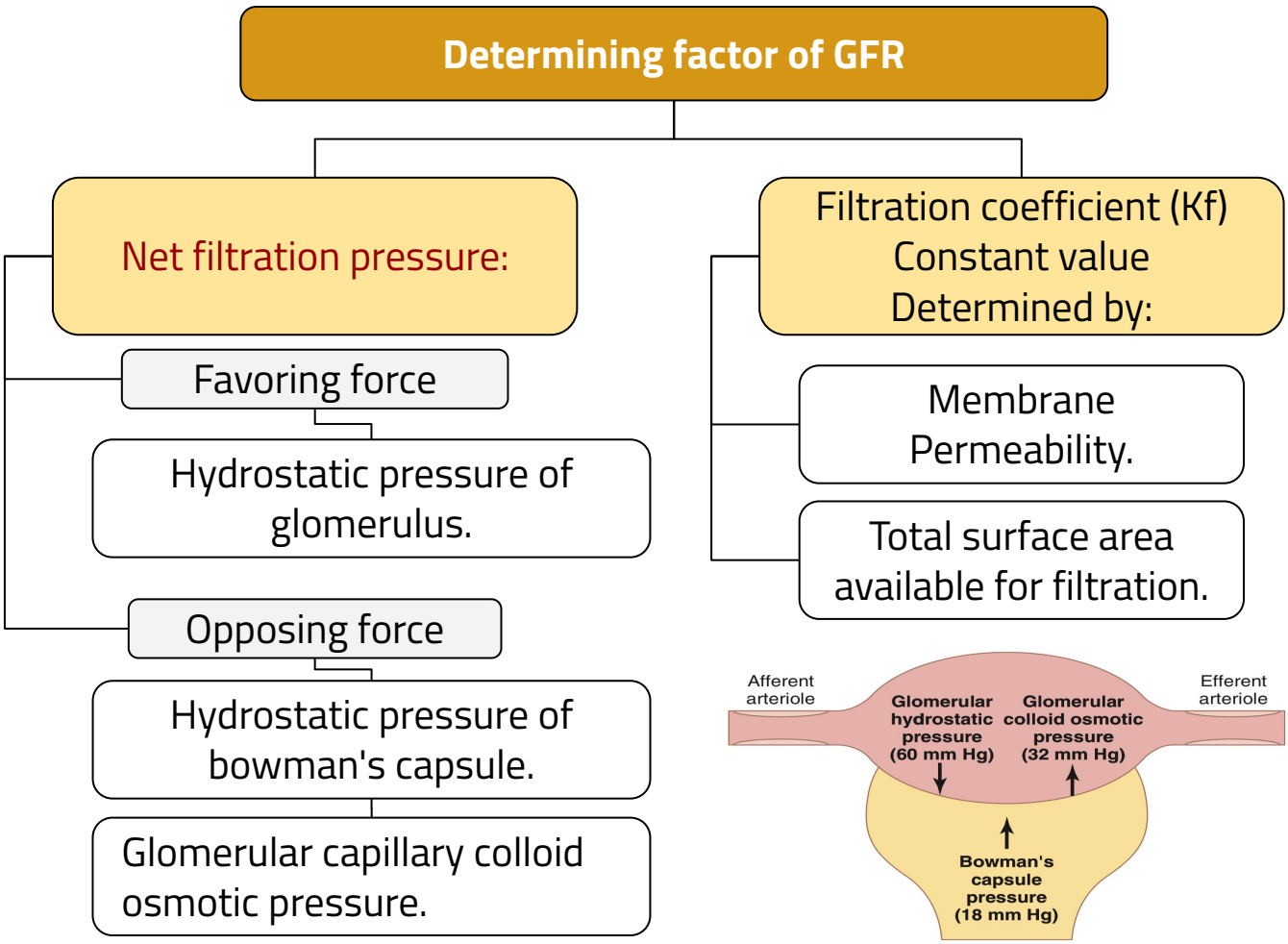
Regulation of glomerular filtration

Glomerular filtration rate (GFR)

- It's the amount of protein free plasma, that is filtered in both kidneys per minute across the glomerular membrane.
- Changes in GFR normally result from changes in glomerular blood pressure.
- GFR = 125 ml/min, Totals about 180 L/day.

Determining factor of GFR

- **GFR** = Kf x Net filtration pressure.
- GFR= Kf × (PG –PB –πG +πB)
- **Net filtration pressure across the glomerular capillaries (NFP):** is sum of the forces acting across the membrane (starling forces).
- **Factors related to the membrane:** glomerular capillary filtration coefficient **(Kf).**



Net filtration pressure (10 mm Hg) = Glomerular hydrostatic pressure (60 mm Hg) – Bowman's capsule pressure (18 mm Hg) – Glomerular oncotic pressure (32 mm Hg)

Guyton & Hall, 337

Regulation of glomerular filtration

Control of GFR

GFR is controlled by adjusting of glomerular blood pressure through the following mechanisms:

Intrinsic factor	Extrinsic factors	
Autoregulation. (by two mechanisms)	Sympathetic control.	**Hormonal mechanism**: Renin and Angiotensin.

Tubuloglomerular feedback mechanism:	
Decrease ABP lead to decrease the amount of NaCl. The **Macula Densa cells** are capable of sensing these ABP changes, this will lead two effects:	
1- **Vasodilatation of the afferent arterioles**: by decreasing its resistance, so that will lead to increase in the glomerular hydrostatic pressure and GFR to normal levels.	2- **Vasoconstriction of the efferent arteriole**: by increasing the Renin release from Juxtaglomerular cells, therefore glomerular hydrostatic pressure will increase.

Myogenic mechanism:
Increased ABP leads to stretching of the vascular wall, then the elevation of the renal blood flow. However, that will lead to increase in the movement of calcium ions from the extracellular fluid into the cells causing them to contract, therefore that will help to prevent the excessive increases in renal blood flow and GFR when arterial pressure increases.

Regulation of glomerular filtration

<table>
<tr><th colspan="2">Extrinsic factors</th></tr>
<tr><th>Sympathetic control</th><th>Hormonal mechanism: Renin and Angiotensin.</th></tr>
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Activation of sympathetic nervous system:

- Extreme drop in blood pressure, leads to increase in sympathetic output (Norepinephrine - Epinephrine).
- This will lead to constriction in the afferent arterioles so GFR decreases.
- The net result: Increased sympathetic stimulation is reduction of blood flow to the glomerular capillary, that eventually will lead to reduced urine output.
- **Note**: during fight or flight blood is shunted away from kidneys.
-

The sympathetic nervous system also stimulates the renin -angiotensin mechanism this induces vasoconstriction of efferent arteriole. There's no parasympathetic effect on the kidney.

</td><td>

1. **Decrease in ABP** causes juxtaglomerular cells to release Renin.
2. Renin promote formation of angiotensin II.
3. That will promote vasoconstriction of afferent arterioles, so the blood flow to the glomerular capillary will be reduced.
4. Result: GFR decreases.

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1. **Increase in ABP** will lead to stretch the atria of the heart.
2. ANP is released from the atria to bloodstream.
3. Causing relaxation of mesangial cells.
4. Increase in surface area of capillary.
5. Result: GFR increases.

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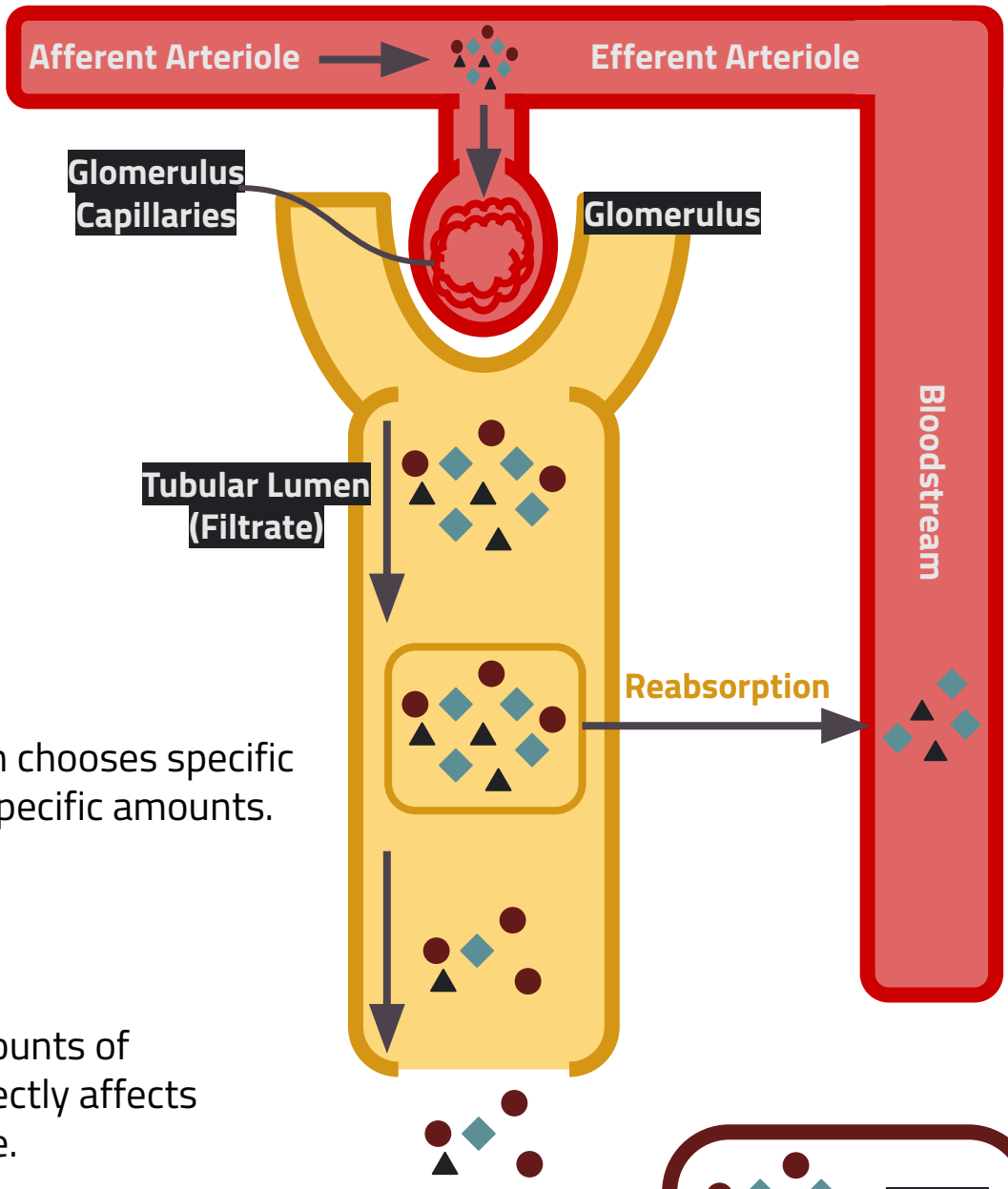
Tubular Reabsorption

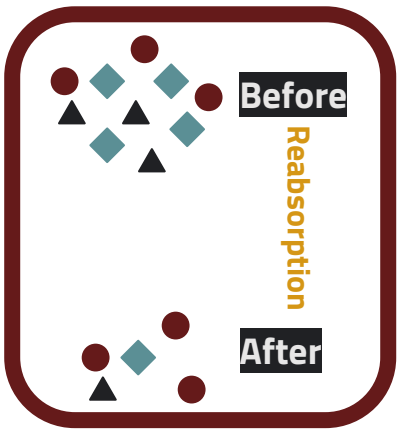
- Tubular reabsorption is the process that moves solutes and water from tubular Lumen back into the bloodstream.



1- Reabsorption chooses specific substances at specific amounts.

2- The large amounts of reabsorption directly affects excretion volume.

3- Therefore, more reabsorption —> Less substances at tubular lumen —> Less excretion volume.



Tubular Reabsorption

Features of tubular reabsorption compared to other tubular functions

	Amount Filtered	Amount Reabsorbed	Amount Excreted	% of Filtered Load Reabsorbed
Glucose (g/day)	180	180	0	100
Bicarbonate (mEq/day)	4,320	4,318	2	>99.9
Sodium (mEq/day)	25,560	25,410	150	99.4
Chloride (mEq/day)	19,440	19,260	180	99.1
Potassium (mEq/day)	756	664	92	87.8
Urea (g/day)	46.8	23.4	23.4	50
Creatinine (g/day)	1.8	0	1.8	0

4

01 Tubular reabsorption is **quantitatively** large

- A small change in tubular reabsorption can potentially cause a large change in urinary excretion.

- For example:
  - 178.5 liters are reabsorbed daily, and 1.5 liters are excreted daily. If the reabsorption is decreased by 10% to 160.7 L/day, the excretion would increase to 19.3 L/day (13 Folds!).

02 Tubular Reabsorption is Highly **Selective**

- Glomerular filtration accepts all solutes in plasma (except plasma proteins or substances bounded to them. They cannot pass through GF Due to their large size) making it non-selective tubular function.

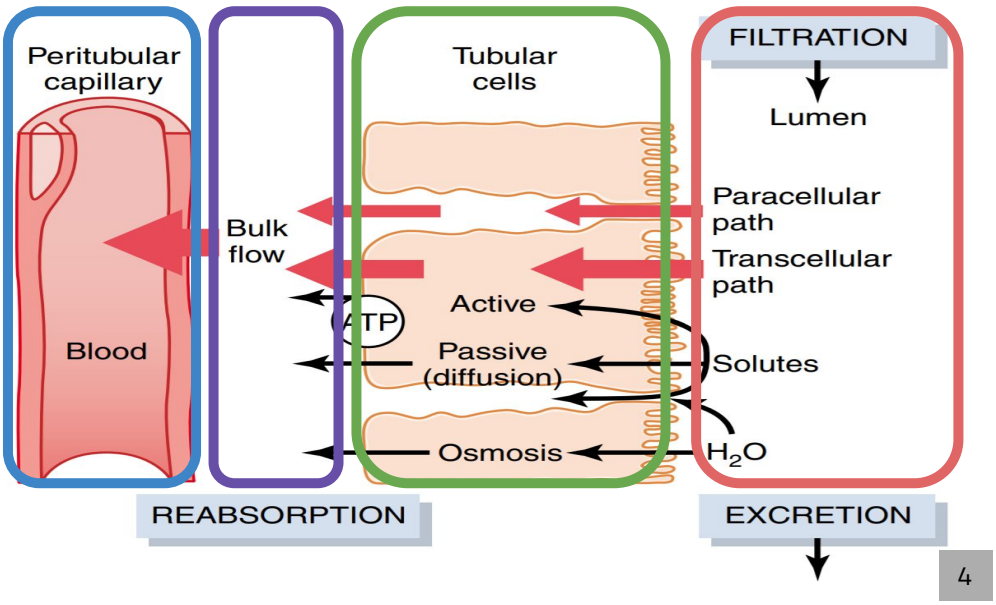
- Whereas the tubular reabsorption only accepts specific substances such as: Glucose, Amino Acids, Na^+, Cl^-, HCO.

Tubular Reabsorption

Transport pathways of tubular reabsorption

- For a substance to be reabsorbed it must be transported.

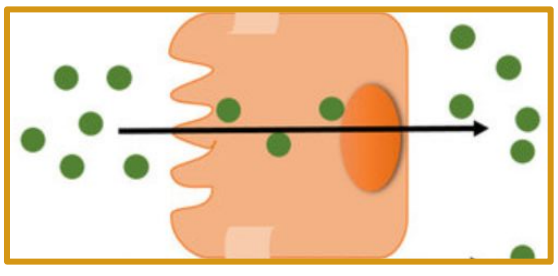
1. Initially, moving solutes from the tubular lumen across the tubular epithelial membranes into the renal interstitium (space between cells).
2. Then moving solutes from the renal interstitium through the peritubular capillary membrane (blood vessels around the renal tubules) back into the blood.



- The First Step occurs in **two** Pathways:

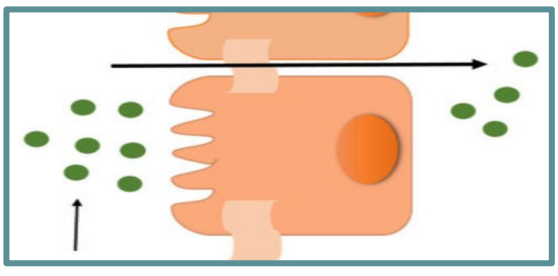
01 **Transcellular Path**

Transport of Solutes **Through** Cells.



02 **Paracellular Path**

Transport of Solutes **Between** Cells.



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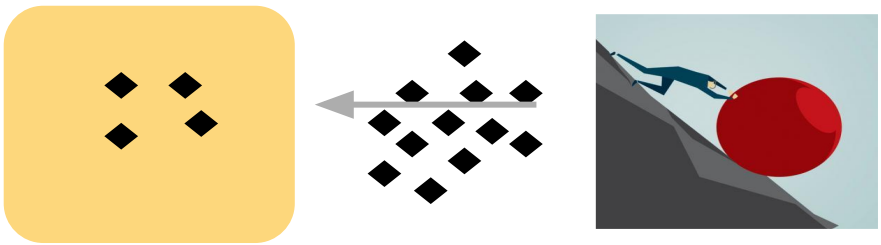
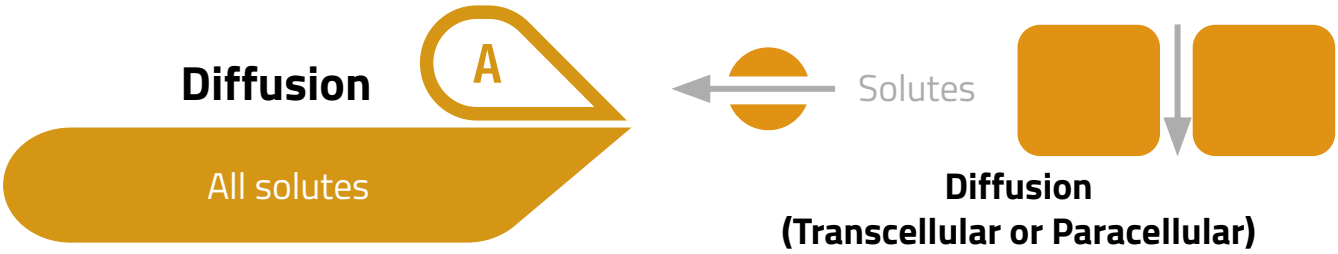
Tubular Reabsorption

Transport Mechanisms 1 (Passive Transport)

Which is the movement of solutes **down** their electrochemical gradient, with **no** energy (the many follows the few).

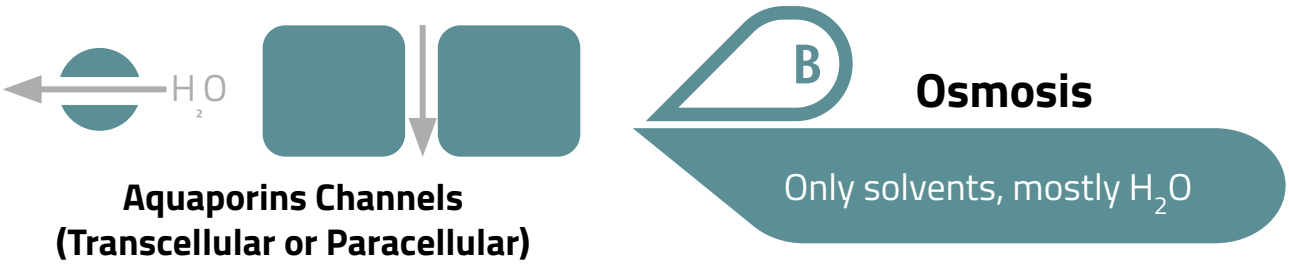




Diffusion: Movement of solutes area with:

High solute concentration	⟶	**Low solute** concentration

Examples: Na^+ , Ca^{2+} , Mg^{2+} , Urea , Cl^-, and GLUT2 (Glucose Transporter).



Osmosis: Movement of water (transcellular or paracellular) from area with:

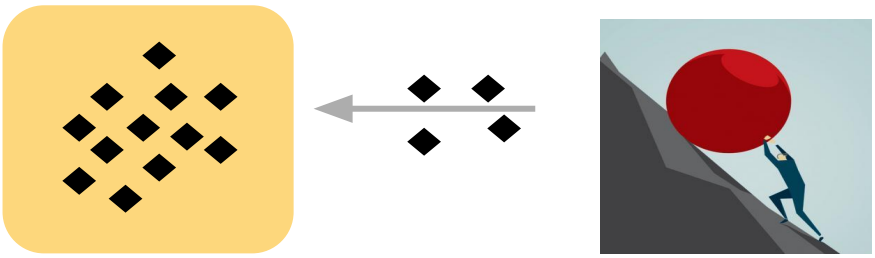
High water concentration OR **Low solute** concentration (low salts)	⟶	**Low water** concentration OR **High solute** concentration

Examples: Aquaporins.

Tubular Reabsorption

Transport Mechanisms 2 (Active Transport)

Which is the movement of solutes **against** their electrochemical gradient, while **using energy** (the few follow the many).



Primary (1st A.T)

A

Coupled directly to energy Source

Primary A.T: Uses energy directly from hydrolysis of ATP (ATPase Family).

Examples: Na^+/K^+ ATPase - H ATPase - H/K ATPase - Ca^{2+} ATPase.

Secondary A.T: Uses energy **in**directly from Primary A.T, mediated by protein carrier, and it has two unique subtypes:

1. Co-Transporters: Transports solutes at the **same direction**.
   - **Examples:** Na^+/Glucose Transporter, Na^+/Amino Acids Transporter.
2. Counter-Transporters: Transports solutes at the **opposite direction**.
   - **Examples:** Na^+/H_2 Transporter.

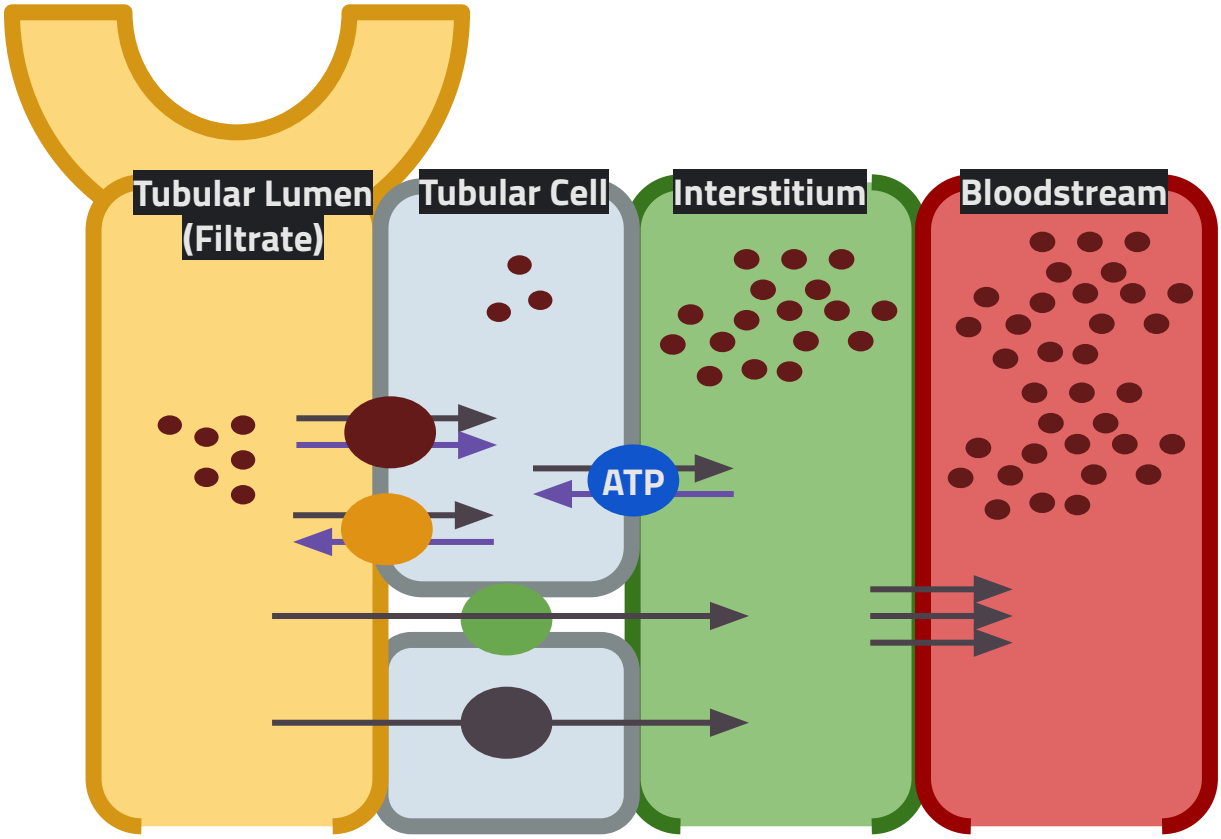
B

Secondary (2nd A.T)

Coupled Indirectly to Energy Source.

Co-Transport **Counter-Transport**

Tubular Reabsorption



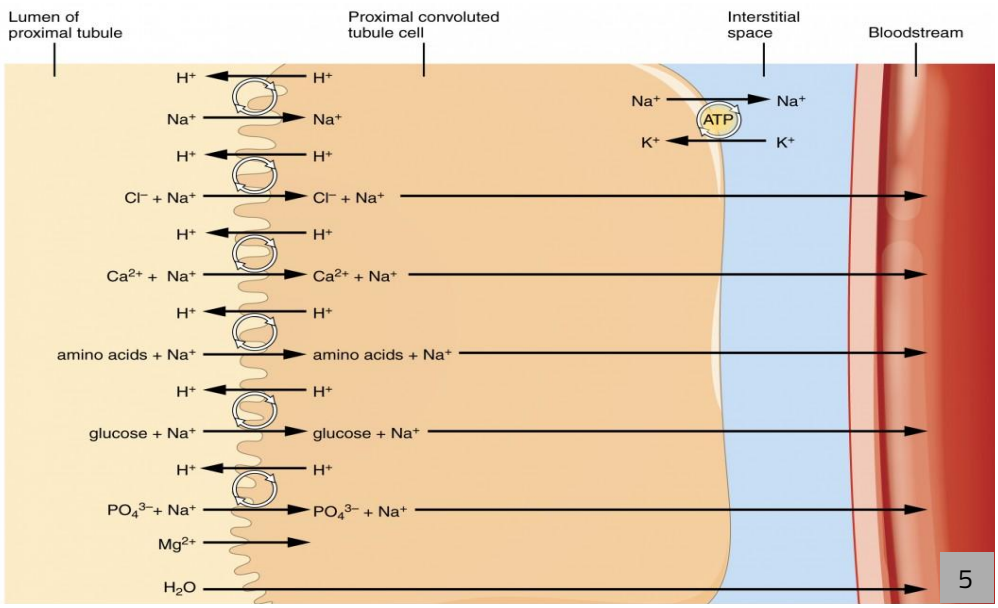
ATP Primary Active Transport

Secondary Active Transport (Co Transport)

Secondary Active Transport (Counter Transport)

Diffusion or Osmosis (**Paracellularly**)

Diffusion or Osmosis (**Transcellular**)



Tubular Reabsorption

Tubular Reabsorption of Na^+ & H_2O

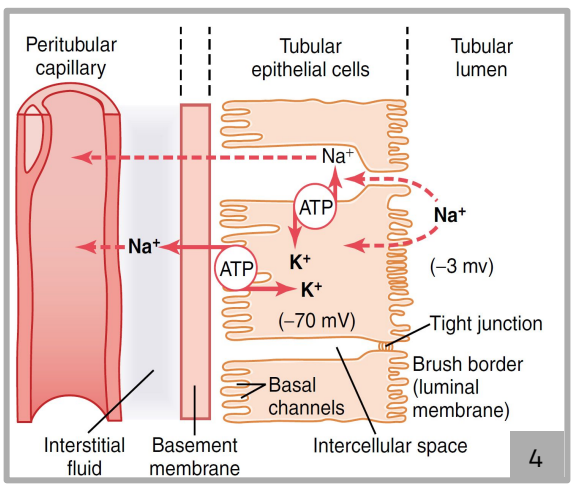
1 Na^+

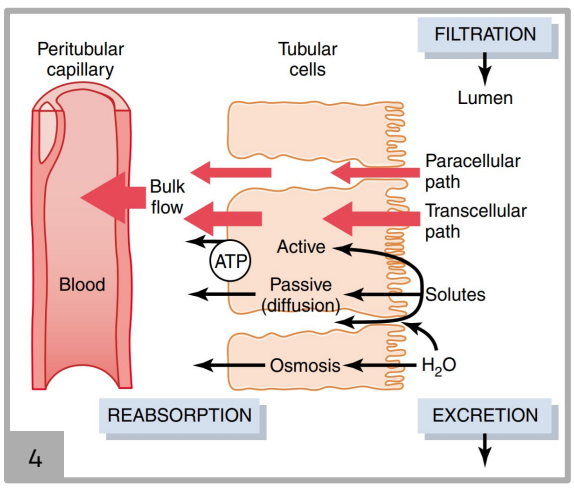
1. Sodium **diffuses** across the luminal/ apical membrane **down** an electrochemical gradient established by Na^+-K^+ ATPase on the basolateral membrane (step 2).
2. It is transported across the basolateral membrane **against** an electrochemical gradient by the **Na+-K+ ATPase pump.**
3. Sodium, water, and other substances are reabsorbed into the bloodstream by ultrafiltration/**bulk flow**, a passive process driven by the hydrostatic and colloid osmotic pressure gradients.

2 H_2O

After solutes reabsorption, their concentrations decreases. This phenomenon creates a concentration difference, causing **osmosis** of water in the same direction.
Solutes will be dragged with it (solvent drag).

- Proximal tubule and descending loop of Henle: water **permeability is high** due to abundant expression of the water channel aquaporin-1 (AQP-1).
- Ascending loop of Henle: **impermeable** to water.
-The distal tubules, collecting tubules, and collecting ducts: permeability be high or low, depending on the presence or absence of ADH.





Tubular Reabsorption

Tubuloglomerular Feedback

- Tubuloglomerular Feedback ensures there is a constant delivery of NaCl to the distal tubule and helps prevent Changes in GFR & renal excretion.
- Tubuloglomerular Feedback involves two components which are:

01 **A**fferent Arteriolar Feedback

02 **E**fferent Arteriolar Feedback

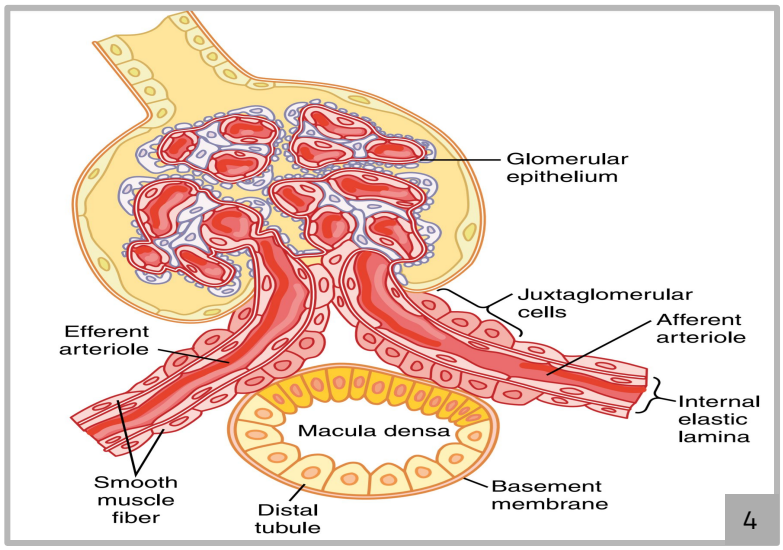
- And both of them depend on one specific anatomical site:

01 Juxtaglomerular complex

Cells involved in the Tubuloglomerular Feedback

01 ***Macula Densa Cells*** Contacts with the Afferent & Efferent arterioles to detect NaCl levels.

02 ***Juxtaglomerular Cells*** Release Renin in response to Macula Densa functioning.



Tubular Reabsorption

Tubuloglomerular feedback mechanism

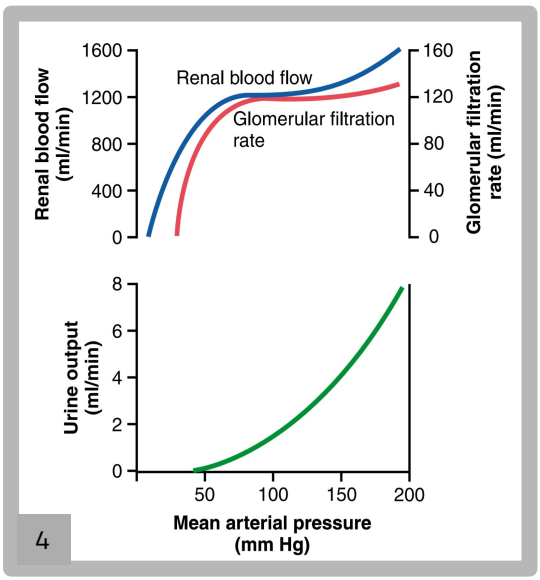
- Decreasing blood pressure of the body, causes drop in the Afferent arteriolar pressure.
- This results in low blood supply to the kidneys, which means Low NaCl content in the blood.
- Macula Densa cells detects that change and starts functioning by:
    - Decreasing the resistance of Afferent arterioles (vasodilatation) by releasing Nitric Oxide, which then leads to the increase in the Glomerular Hydrostatic pressure & GFR to normal levels.
    - Increasing the resistance of Efferent arterioles (vasoconstriction) by activating Juxtaglomerular cells to release renin.
- Final result: ↑in solutes entering the nephron → ↑ Reabsorption of NaCl → BP Restored.

The importance of the Tubuloglomerular feedback

Refers to feedback mechanisms intrinsic to the kidney that keep the renal blood flow and GFR relatively constant despite fluctuations in ABP.

- These mechanisms operate over an ABP ranging between 75-160 mmHg.

1. Regulates GFR & Glomerular Hydrostatic pressure.
2. Stabilizing NaCl delivery to the Nephron.
3. Functions on it's own, no need for neural or hormonal agents.
4. Regulates blood pressure.



Tubular Reabsorption

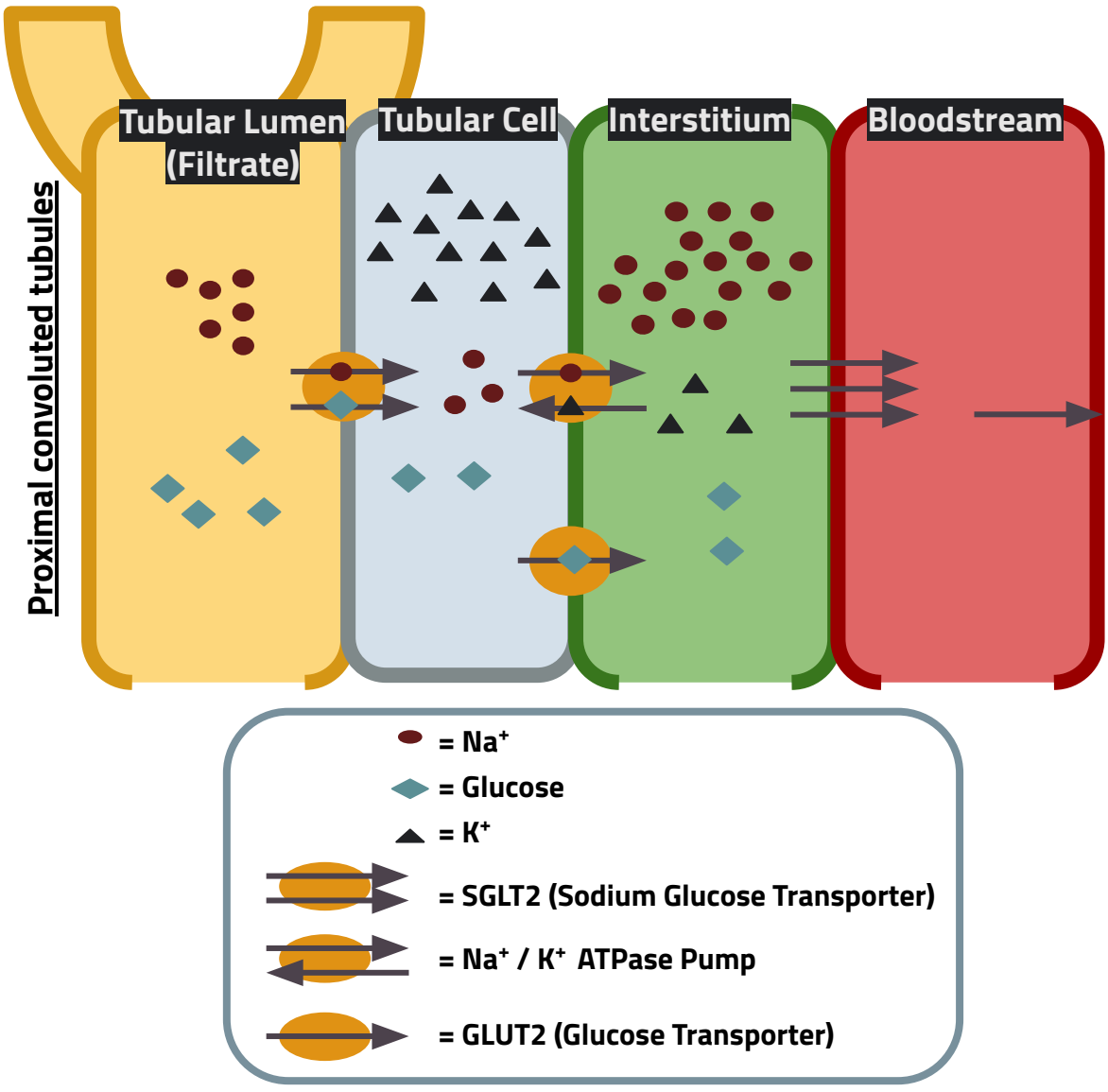
Glucose Reabsorption and Titration Curve

1. Glucose is transported from tubular lumen into tubular cell couple with Na^+ through SGLT2.

2. Glucose is then transported to interstitium alone through GLUT2.

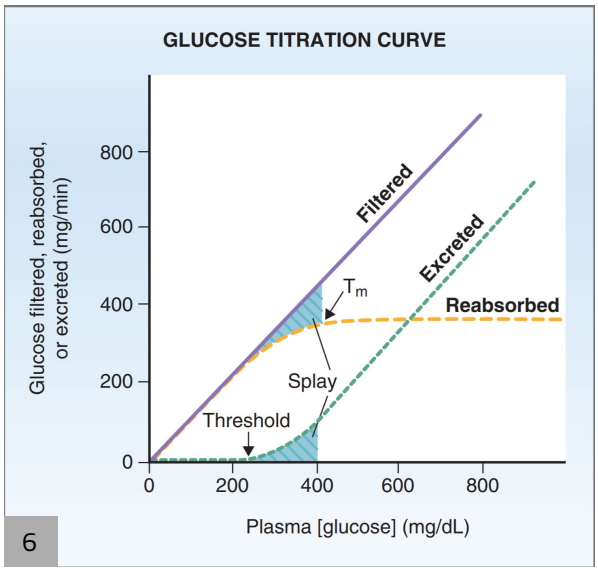
3. After that it's reabsorbed to bloodstream by bulk flow.

- Glucose is 100% reabsorbed At PCT.
- Na^+ / K^+ ATPase pump is the **first step** at all reabsorption processes, to create the gradient.



Tubular Reabsorption

Glucose Reabsorption and Titration Curve



Note:
Excretion appears before reaching **Tm**, because when Glucose exceeds the threshold, transporters get saturated gradually (**partially**), leading the remnant Glucose to be excreted.

01

Renal Threshold (160 - 180 mg/dL)

The normal amount of Glucose that can be 100% reabsorbed **without** appearing in urine.

02

Tubular Transport Maximum (Tm) (380 mg/dL)

The state when all Glucose transporters are saturated.

03

Splay

The difference between Glucose reabsorption and excretion.

04

Excretion

The appearance of Glucose in urine due to partial or complete saturation of Glucose transporters.

05

Filtration

The response of the nephron to Glucose filtration.

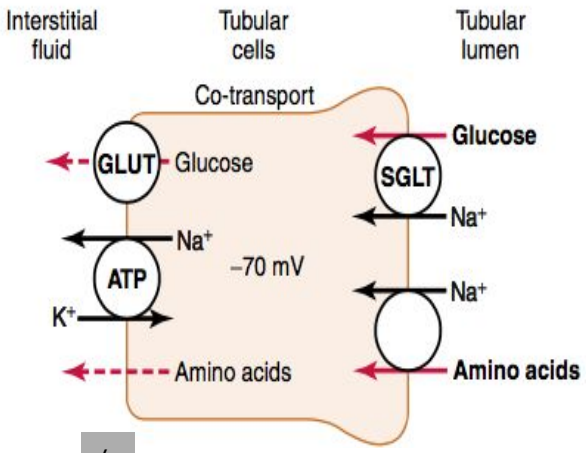
Tubular Reabsorption

Amino Acids Reabsorption

- 100% of amino acid is reabsorbed in the first half of proximal tubules by secondary active transport.

- The epithelial brush border is loaded with protein carrier molecules that transport a large fraction of Na^+ across the luminal membrane linked via the co-transport mechanism along with amino acids.(Symporters)

- Then it enters the interstitial fluid by facilitated diffusion through basolateral membrane.



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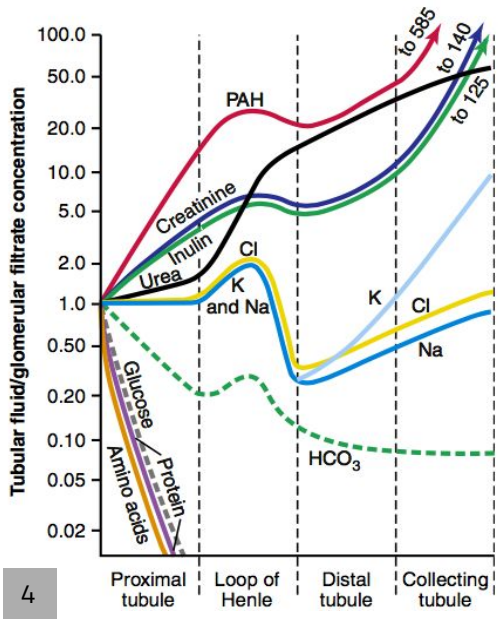
Urea Reabsorption



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- Urea is passively reabsorbed from the tubule.

- H_2O reabsorption leads to urea concentration in the tubular fluid creating a gradient for its absorption.

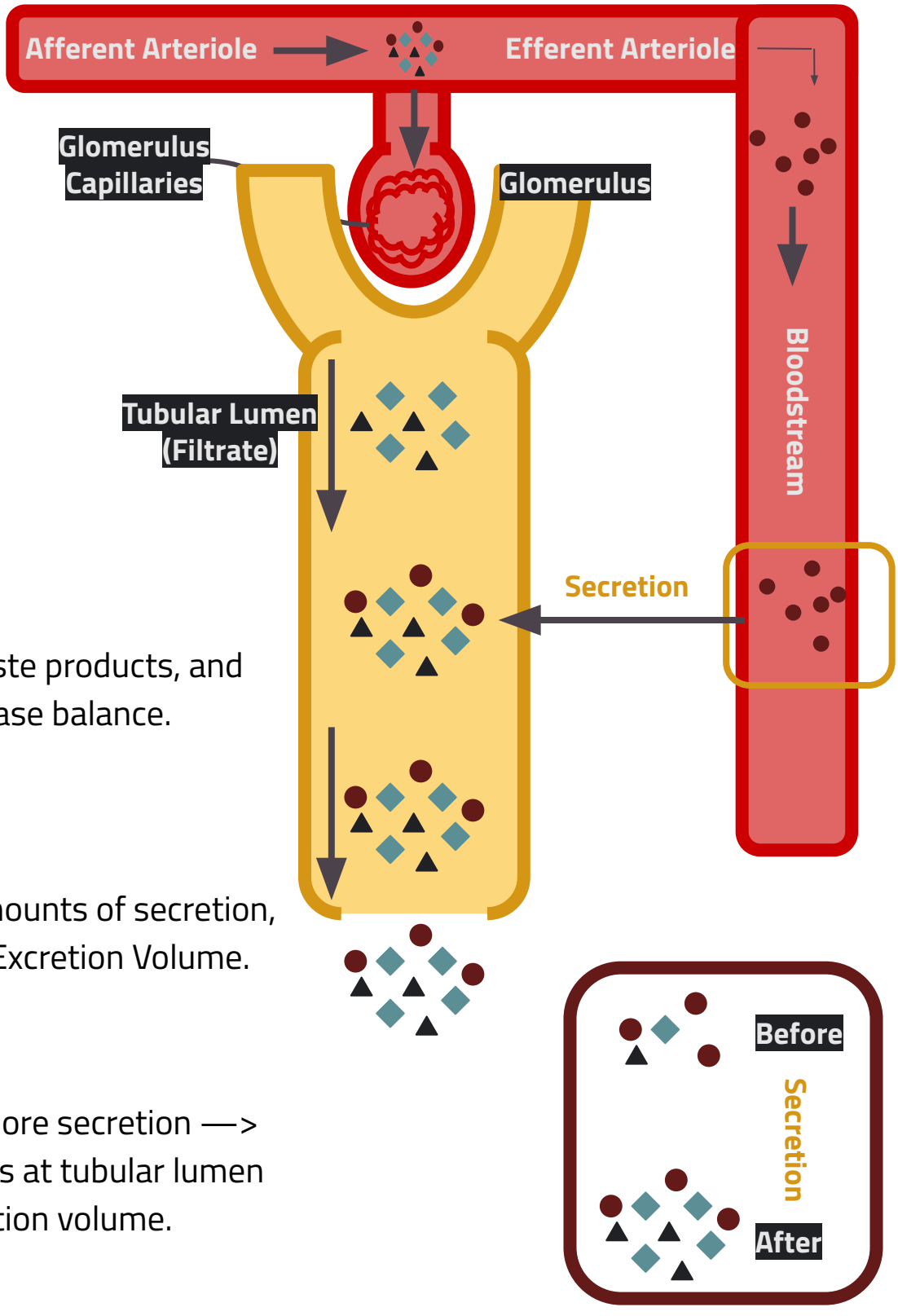
-In the inner medullary collecting duct, passive urea reabsorption is facilitated by specific urea transporters.

- The distal tubules are impermeable to urea.

- Only 50% of the urea is reabsorbed, the remaining passes into the urine to excrete this waste product.

Tubular Secretion

- Tubular secretion is the process that moves solutes out of the bloodstream and back into your filtrate.



1- Disposes waste products, and maintain acid-base balance.

2- The Large amounts of secretion, directly affects Excretion Volume.

3- Therefore, more secretion —> more substances at tubular lumen —> more excretion volume.

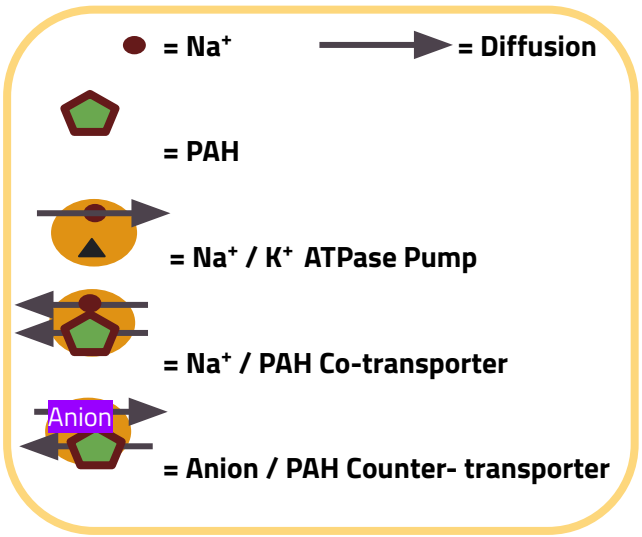
Tubular Secretion

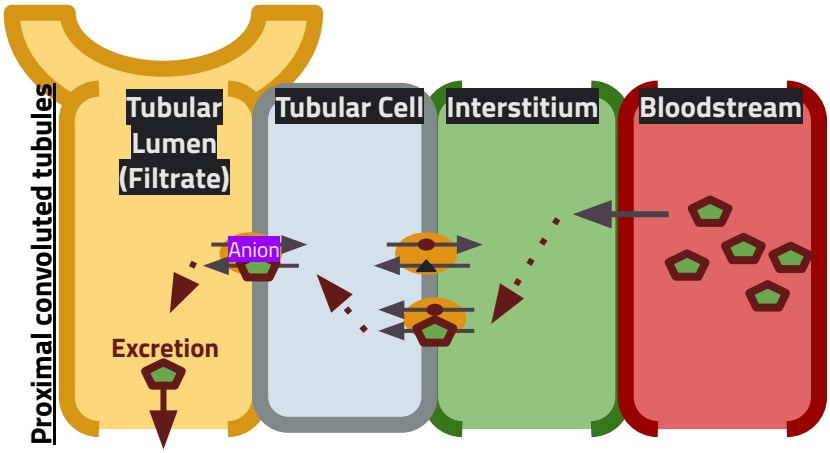
PAH Secretion

PAH: sx909**P**ara**A**mino**H**ippuric acid, a compound that is rapidly secreted by 90% from bloodstream and excrete it in the urine (Given by Injection).

01 **PAH**
Due the Rapid secretion, it's used to determine kidney function.

1. PAH Diffuses from Bloodstream to Interstitium.
2. PAH is transported to Tubular cell coupled with Na^+, through Na^+ / PAH Co Transporter.
3. PAH is transported to Tubular lumen in exchange with Anion through Anion / PAH Transporter.





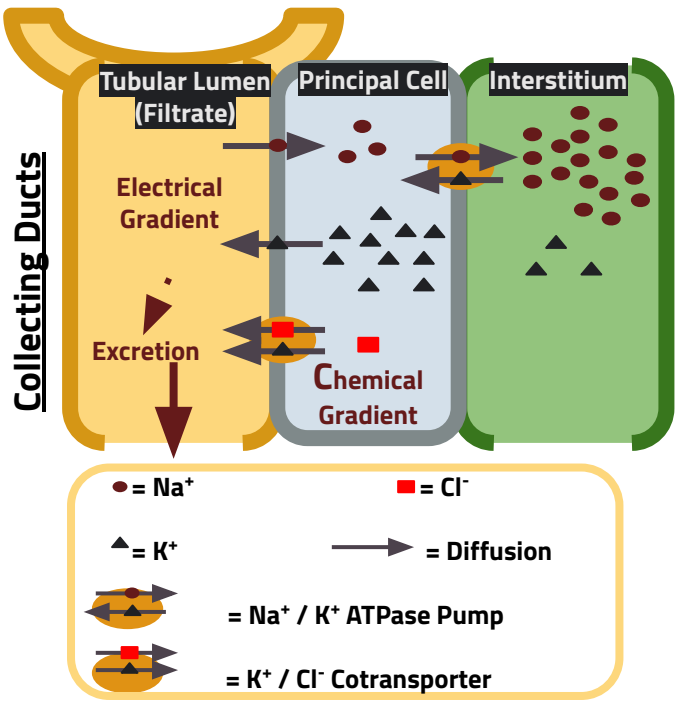
K^+ Secretion

K^+ Secretion is a process that involves regulating acid–base balance and maintenance of electrochemical gradients across cell membranes.

01 **Principal Cell**
Mediates the process at collecting ducts & Distal tubules.

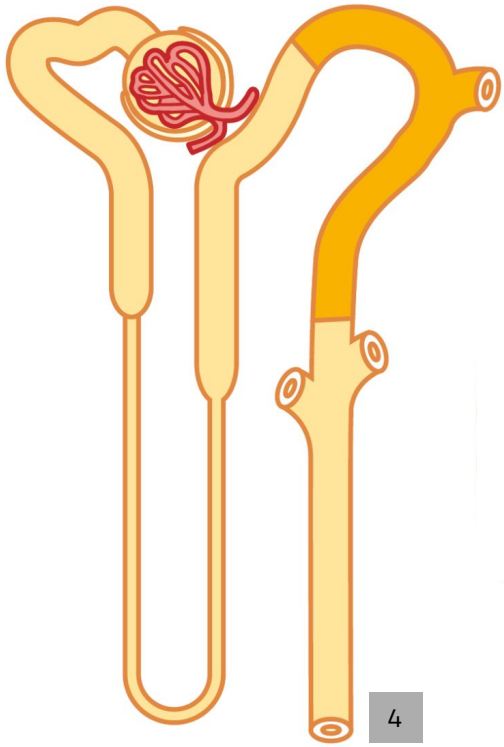
02 **K^+ / Cl^- CoT**
Functions as well at the process, by secreting K^+ & Cl^- into tubular.

1. Na^+ / K^+ ATPase Pump creates chemical gradient, by↓ Na^+ conc & ↑ K^+ conc at principal cells.
2. Na^+ diffuses from tubular lumen into principal cells, by the down gradient rule, and causes an electrical gradient by↓ Electrical potential (Less +Ions).
3. High conc of K^+ in cell will respond to the electrical gradient and quickly diffuse into tubular lumen, achieving K^+ secretion.



Tubular Secretion

Aldosteron Influence On Na^+ Reabsorption at DCT (Late)



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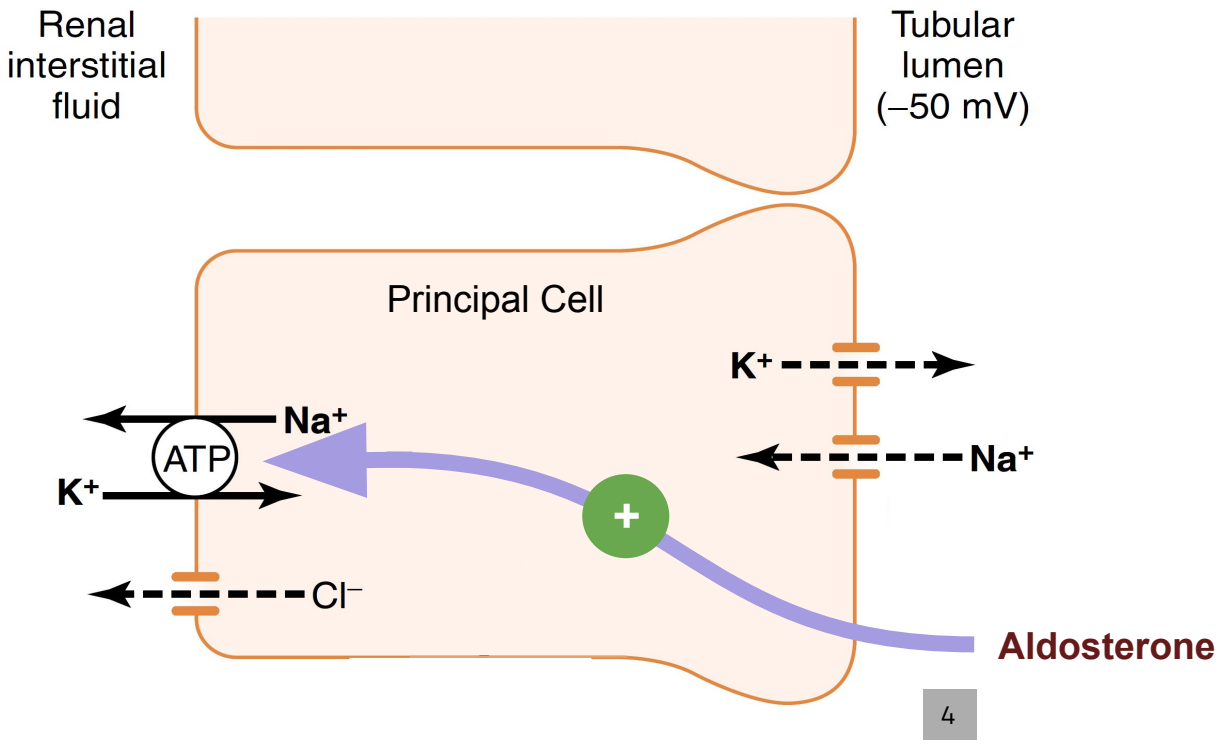
Aldosterone **regulates** Na^+ Reabsorption & K^+ Secretion by stimulating Na^+ / K^+ ATPase pump at Distal Convoluted Tubule & Cortical Collecting Ducts.



4

Regulation of Potassium

Control of potassium distribution between the extra-cellular and intracellular compartments

It plays an important role in potassium homeostasis. Because more than 98% of the total body potassium is contained in the cells, they can serve as an overflow site for excess extracellular fluid potassium during hyperkalemia or as a source of potassium during hypokalemia. Thus, redistribution of potassium between the intracellular and extracellular fluid compartments provides a first line of defense against changes in extracellular fluid potassium concentration.

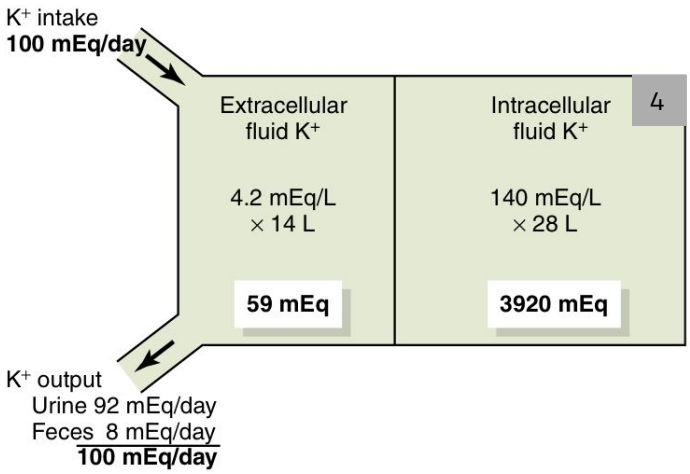
Regulation of internal potassium distribution

ingestion of a potassium- rich meal

↑ [K+] in ECF

All the potassium remained in the extracellular compartment. Fortunately, most of the ingested potassium rapidly moves into the cells until the kidneys can eliminate the excess.

Between meals, plasma potassium concentration also remains nearly constant as potassium is released by the cells to balance the extracellular fluid potassium excreted by the kidneys.



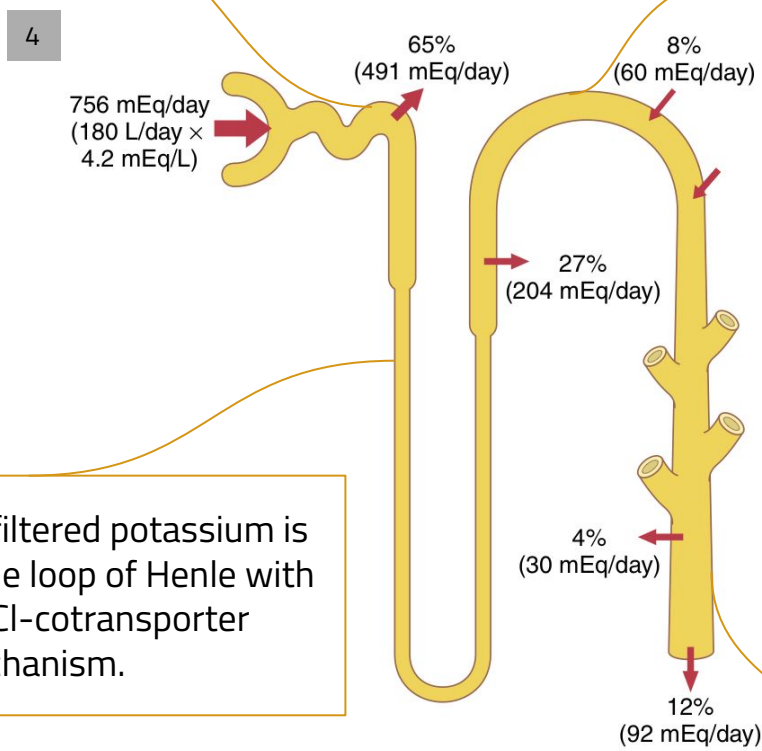
Factors That Shift K⁺ Into Cells (Decrease Extracellular [K⁺])	Factors That Shift K⁺ Out of Cells (Increase Extracellular [K⁺])
Insulin	Insulin deficiency (diabetes mellitus)
Aldosterone	Aldosterone deficiency (Addison disease)
β-Adrenergic stimulation	β-Adrenergic blockade
Alkalosis	Acidosis Cell lysis Strenuous exercise Increased extracellular fluid osmolarity

4

Regulation of Potassium

60–70% of the filtered potassium (K+) is reabsorbed in the proximal tubule. There are no specific K-transporter, reabsorption is managed with the absorption of water (Solvent drag).

Potassium handling by the thick ascending loop is by secondary active transport using the apical triple transporter (NKCC2).



25–35% of the filtered potassium is reabsorbed in the loop of Henle with the Na-K-2Cl-cotransporter mechanism.

5–15% of the filtered potassium reaches the distal nephron Depending on the metabolism there are now possibilities of potassium reabsorption or excretion (controlled by aldosterone).

Tubular Reabsorption & Secretion

	PCT	Loop of Henle	DCT	Collecting duct
Na^+	**65%** actively reabsorbed.	25% reabsorbed in thick ascending limb; active transport.	5% reabsorbed; active.	5% reabsorbed, stimulated by aldosterone; active.
Cl^-	Reabsorbed, symport with Na^+, diffusion.	Reabsorbed in thin and thick ascending limb; diffusion in ascending limb.	Reabsorbed; diffusion.	Reabsorbed; symport.
H_2O	**67%** reabsorbed osmotically with solutes.	15% reabsorbed in descending limb; osmosis.	8% reabsorbed if ADH; osmosis.	Variable amounts reabsorbed, controlled by ADH, osmosis.
H^+	Secreted; diffusion.		Secreted; active.	Secreted; active.
$NH4^+$	Secreted; diffusion.		Secreted; diffusion.	Secreted; diffusion.
HCO^{3-}	Reabsorbed; diffusion.	Reabsorbed; diffusion in ascending limb.	Reabsorbed; diffusion.	Reabsorbed; antiport with Na^+.
K^+	65% reabsorbed; diffusion.	20% reabsorbed in thick ascending limb; symport.	Secreted; active.	Secretion controlled by aldosterone; active.
PO_4	85% reabsorbed, inhibited by PTH, diffusion.		Reabsorbed; diffusion.	
Urea	50% reabsorbed by diffusion; also secreted.	Secretion, diffusion in descending limb.		Reabsorption in medullary collecting ducts; diffusion.

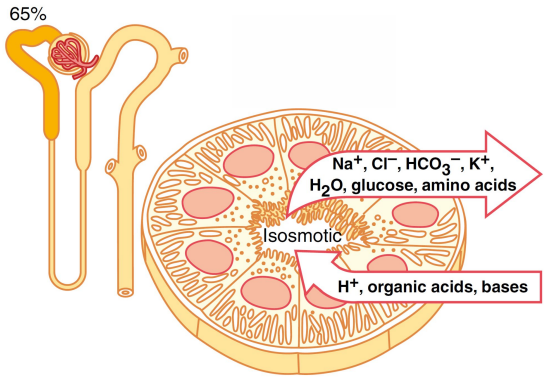
Tubular Reabsorption & Secretion

	Major Functions	Cellular Mechanisms
Early Proximal Tubule	-Isosmotic reabsorption of solute and water. -Creatinine secretion. -**100%** Amino acid and glucose reabsorption.	Na^+-glucose, Na^+-amino acid, Na^+-phosphate cotransport and Na^+-H^+ exchange.
Late Proximal Tubule	-Isosmotic reabsorption of solute and water.	-NaCl reabsorption driven by Cl^-gradient.
Thick Ascending Limb of the Loop of Henle	-Reabsorption of NaCl without water -Dilution of tubular fluid Single effect of countercurrent multiplication. -Reabsorption of Ca^{2+} and Mg^{2+} driven by lumen-positive potential.	-Na^+-K^+-$2Cl^-$ cotransport.
Early Distal Tubule	-Reabsorption of NaCl without water. -Dilution of tubular fluid.	-Na^+-Cl^- cotransport.
Late Distal Tubule and Collecting Ducts (principal cells)	-Reabsorption of NaCl -K^+ secretion -Variable water reabsorption.	-Na^+ channels (ENaC). -K^+ channels. -AQP2 water channels.
Late Distal Tubule and Collecting Ducts (α-intercalated cells)	Reabsorption of K^+. Secretion of H^+.	-H^+-K^+ ATPase. -H^+ ATPase.

Tubular Reabsorption & Secretion

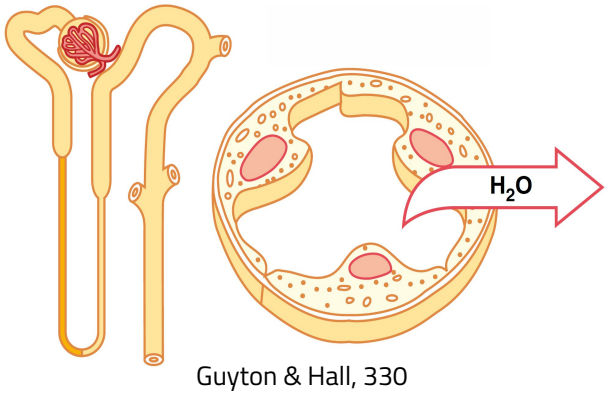
Characteristics of Nephron tubules

Proximal Convoluted Tubule



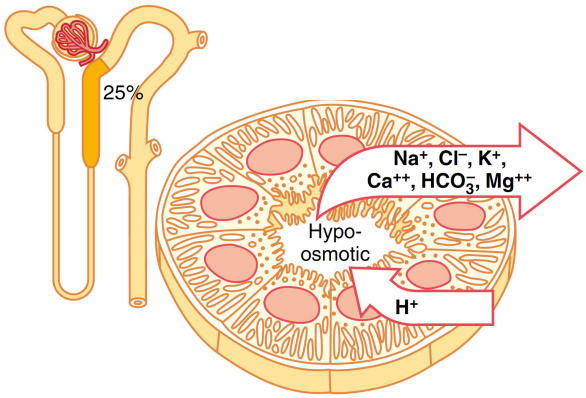
Guyton & Hall, 329

Thin descending loop of Henle



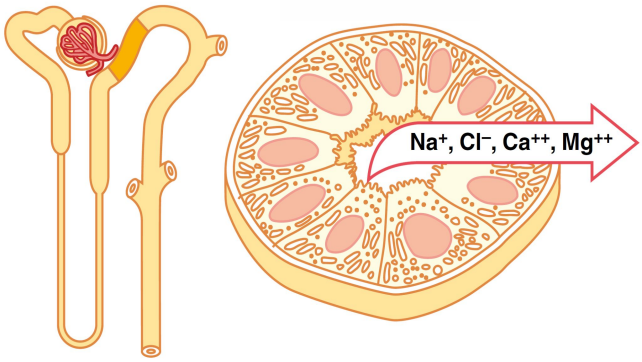
Guyton & Hall, 330

Thick Ascending loop of Henle



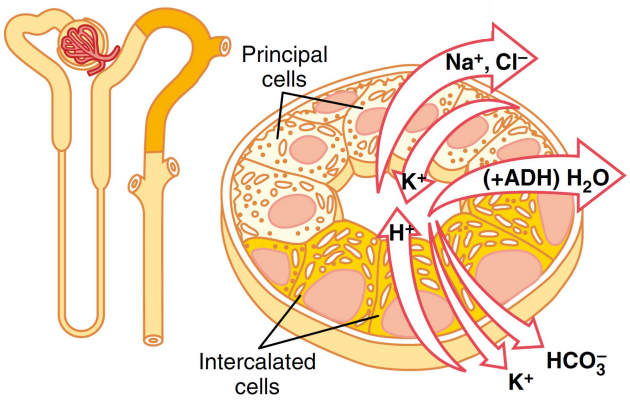
Guyton & Hall, 330

Distal Convoluted Tubule (Early)



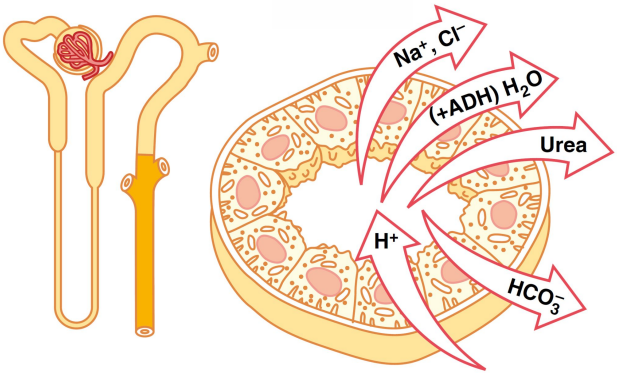
Guyton & Hall, 332

Distal Convoluted Tubule (Late)



Guyton & Hall, 332

Medullary Collecting Ducts



Guyton & Hall, 333

Clinical Integration - Tubular Reabsorption

Diabetes insipidus	Central (Low ADH secretion)	Nephrogenic (unresponsiveness of renal tubules to ADH)
Etiology	• Idiopathic (most common). • Traumatic. • Infiltration.	• Chronic lithium use is the most common cause. • Side effect of demeclocycline. • May be congenital.
Clinical features	• Polyuria (very large volume of diluted and colourless urine). • Polydipsia and thirst. • Hypernatremia may be mild.	
Diagnosis	• Water deprivation test/Dehydration test is a must for diagnosis. • Urine has low osmolality and low specific gravity.	
Management	• Treat the underlying cause. • DDAVP is the treatment of choice. • Chlorpropamide maybe used.	Sodium restriction and thiazides.

Water deprivation test:

- Patient is deprived from fluids and urine osmolality is measured hourly and when it's stable, patient gets desmopressin them we measure urine osmolality one hour later and ADH is measured as well.
- The response as shown in the table gives us the diagnosis:

Response	Raised osmolality above 280 mOsm/kg.	Further response to ADH
Psychogenic/Normal	+	-
Central	-	+
Nephrogenic	-	-

Clinical Integration - Tubular Secretion

	SIADH **(S**yndrome of **i**nappropriate **s**ecretion of **a**ntidiuretic **h**ormone**)**
Pathophysiology	Overproduction of ADH from posterior pituitary gland leads to increased Reabsorption of water and sodium and water causing diluted plasma (ECF expansion and hyponatremia).
Etiology	• Small cell carcinoma of the lung. • CNS disorders. • Medications (e.g. Desmopressin,SSRIs, Oxytocin and Morphine). • Anaesthesia.
Clinical features	• **Acutely**: Lethargy, weakness and may lead to seizure, coma or death if left untreated. • **Chronicall**: asymptomatic or nausea, vomiting and anorexia but CNS symptoms are less commonly seen.
Diagnosis	Diagnosis of exclusion, so you've to rule out other causes of hyponatremia. • Hyponatremia. • Concentrated urine. • volume expansion without edema. • Low BUN and normal/low creatinine. • Hypouricemia. • Normal thyroid and adrenal functions.
Management	• Treat the underlying cause. • Water restriction and Lithium carbonate/Desmocycline for asymptomatic patients. • Water restriction and isotonic saline if symptoms are present. **Note**: Central pontine myelinolysis may result from rapid raise in serum sodium, so sodium replacement rate shouldn't exceed 0.5 mEq/L per hour.

Clinical Integration - Tubular Secretion

	Hypokalemia	Hyperkalemia
Etiology	Normal potassium level is 3.5-5 mEq/L, It can be lower than normal level due to: ● GI loss: Diarrhoea, vomiting, NG drainage and malabsorption. ● Renal loss: Diuretics, 1ry or 2ry hyperaldosteronism, Bartter syndrome (Autosomal recessive defects in ascending limb of loop of Henle leads to increased renin level and 2ry hyperaldosteronism) , Mg deficiency, and excessive steroids intake. ● Others: hyperhidrosis, insulin, drugs like (bactrim, amphotericin B, Beta 2 agonists like epinephrine) and poor dietary intake.	-Increased total body potassium: ACEis, spironolactone, renal failure, Addison's disease and maybe iatrogenic. -Redistribution: Hypoinsulinemia, Acidosis, Rapid Beta blockers administration, tussle breakdown and GI bleeding. -Pseudohyperkalemia: due to prolonged use of a tourniquet with or without repeated fist clenching, and others like leukocytosis or thrombocytosis.
Clinical features	**-Cardiac**: Arrhythmia, flattened T wave, U wave maybe seen, digoxin (digitalis) toxicity. **-Musculoskeletal**: Muscle weakness and cramps and decreased deep tendon reflexes. **-Others**: Nausea and vomiting, Paralytic ileus, and polyuria/polydipsia. **Note**: Arrhythmia is the most fatal cause in hypokalemia conditions.	**-Cardiac**: Arrhythmia, prolonged PR interval, tall & peaked T wave, loss of P wave, QRS widening, and sine-wave pattern. **-Musculoskeletal**: muscle weakness and flaccid paralysis, and decreased deep tendon reflexes. **-Others**: respiratory failure, intestinal colic.
Management	-Treat underlying cause. -Remove any offending agent, e.g. drugs. -Oral KCl. -Retest Potassium level after oral KCl. -Every 10 mEq/L of oral KCl increases potassium level by 0.1 mEq/L. -IV KCl can be given in severe hypokalemia (K<2.5) or in case of arrhythmia 2ry to low K level. In this case it's transfused slowly to prevent hyperkalemia. -ALWAYS monitor K level and perform and EKG.	-Stabilise heart cells by giving **IV calcium** in the presence of ECG changes. -Shift potassium into cells by giving **glucose & insulin**. -Lower total body potassium by giving **Kayexalate** or **furosemide**. -**Hemodialysis** is the most effective way to reduce total body potassium. (reserved for renal failure)

Clinical Integration - Tubular Secretion

	Primary Adrenal insufficiency (Addison's disease)	Primary Hyperaldosteronism (Conn's syndrome)
Etiology	• Idiopathic. • Infection: The most common worldwide is TB. • Iatrogenic such in bilateral adrenalectomy. • Metastatic disease.	Aldosterone-producing adrenal adenoma.
Clinical features	• Symptoms of low cortisol such as: Hypoglycemia & Hyperpigmentation. • Symptoms of low aldosterone: Hyperkalemia and Hyponatremia.	• Symptoms of low aldosterone: Hypokalemia and Hypernatremia. • HTN is the most common clinical feature (Due to sodium and water retention). • Polydipsia and nocturnal polyuria (due to hypokalemia). • Absence of peripheral edema.
Diagnosis	• Low serum cortisol. • High ACTH. • Low aldosterone. • High renin.	• High aldosterone, low renin and Aldosterone: Renin > 30. • Confirm with saline infusion test or oral sodium loading. • Find the cause with MRI/CT scan go adrenal glands.
Management	Daily oral glucocorticoid (hydrocortisone or prednisone) and daily fludrocortisone (mineralocorticoid).	Surgical resection.

Function, Test, Clearance, and Excretion of Glomerular Filtration

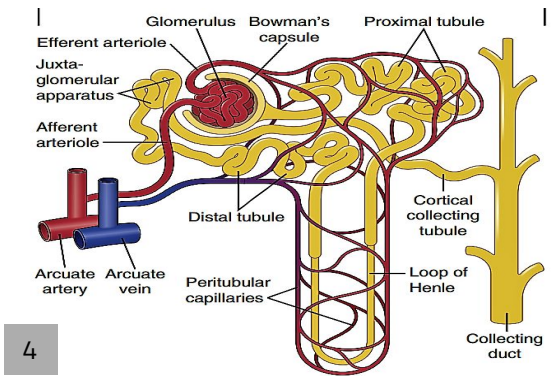
Renal Function

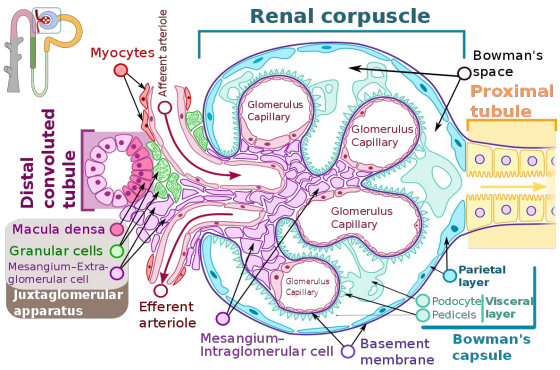
Nephron

- cortical
  - Renal corpuscle
  - Glomerulus
  - Bowman's capsule
  - Renal tubule
  - PCT
  - Loop of henle
  - DCT
- juxtamedullary
  - JG cells
  - Macula densa
  - Mesangial cells

Kidney function

- Regulation
  - Water & Electrolytes
  - Blood pressure
  - Acid base balance
- Excerection
  - Metabolic waste products
  - Foreign chemicals eg, Drugs
- Production
  - Erythropoietin
  - Glucose
  - Active Vit D





https://en.wikipedia.org/wiki/Renal_corpuscle

Physiology of Renal Clearance

Renal clearance

The rates at which different substances are cleared from the plasma provide a useful way of quantitating the effectiveness with which the kidneys excrete various substances (Table 28-4).

By definition, the **renal clearance** of a substance is the volume of plasma that is completely cleared of the substance by the kidneys per unit of time.

Although there is no single volume of plasma that is completely cleared of a substance, renal clearance provides a useful way of quantifying excretory function of the kidneys. We can use renal clearance to quantify **renal blood flow**, **GFR**, **tubular reabsorption**, and **tubular secretion**.

For example, if the plasma passing through the kidneys contains 1 mg of a substance in each milliliter, and if 1 mg of this substance is also excreted into the urine each minute, then 1 ml/min of the plasma is cleared of the substance. **Clearance** refers to the volume of plasma that would be necessary to supply the amount of substance excreted in the urine per unit of time. Stated mathematically: $Cs \times Ps = Us \times V$

where **Cs** is the clearance rate of a substance s, **Ps** is the plasma concentration of the substance, **Us** is the urine concentration of that substance, and **V** is the urine low rate. In this equation, clearance can be expressed as: $Cs = (Us \times V)/Ps$

Thus, renal clearance of a substance is calculated from the **urinary excretion rate** (Us × V) of that substance divided by its plasma concentration.

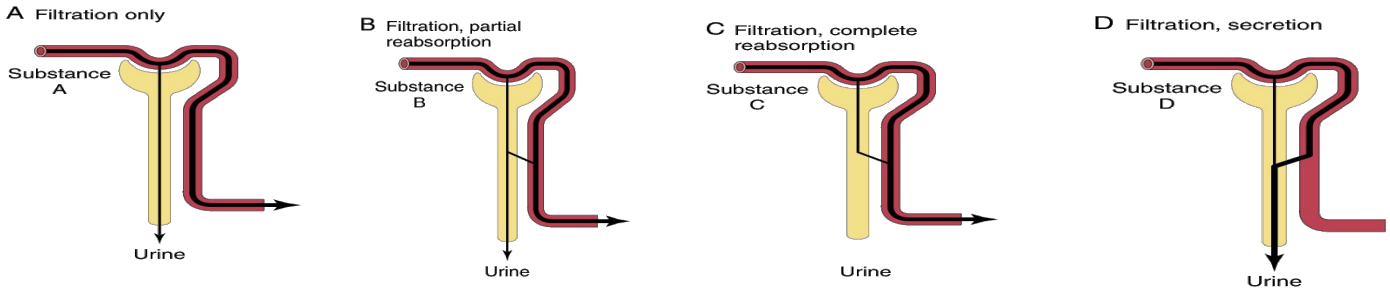
Table 28-4 Use of Clearance to Quantify Kidney Function

Term	Equation	Units
Clearance rate	$C_s = \frac{U_s \times \dot{V}}{P_s}$	ml/min
Glomerular filtration rate	$GFR = \frac{U_{inulin} \times \dot{V}}{P_{inulin}}$	
Clearance ratio	Clearance ratio $= \frac{C_s}{C_{inulin}}$	None
Effective renal plasma flow	$ERPF = C_{PAH} = \frac{U_{PAH} \times \dot{V}}{P_{PAH}}$	ml/min
Renal plasma flow	$RPF = \frac{C_{PAH}}{E_{PAH}} = \frac{(U_{PAH} \times \dot{V}/P_{PAH})}{(P_{PAH} - V_{PAH})/P_{PAH}} = \frac{U_{PAH} \times \dot{V}}{P_{PAH} - V_{PAH}}$	ml/min
Renal blood flow	$RBF = \frac{RPF}{1 - \text{Hematocrit}}$	ml/min
Excretion rate	Excretion rate $= U_s \times \dot{V}$	mg/min, mmol/min, or mEq/min
Reabsorption rate	Reabsorption rate = Filtered load − Excretion rate $= (GFR \times P_s) - (\dot{U} \times \dot{V})$	mg/min, mmol/min, or mEq/min
Secretion rate	Secretion rate = Excretion rate − Filtered load	mg/min, mmol/min, or mEq/min

C_s, Clearance rate of substance s; E_{PAH}, PAH extraction ratio; ERPF, effective renal plasma flow; GFR, glomerular filtration rate; P, plasma concentration; PAH, para-aminohippuric acid; P_{PAH}, renal arterial PAH concentration; RBF, renal blood flow; RPF, renal plasma flow; S, a substance; U, urine concentration; V, urine flow rate; V_{PAH}, renal venous PAH concentration.

Physiology of Renal Clearance

Renal handling of four hypothetical substances			
A: Freely filtered by the glomerular capillaries but is **neither reabsorbed nor secreted**.	B: Freely filtered but is also **partly reabsorbed** from the tubules back into the blood.	C: Freely filtered but is not excreted into the urine because all the filtrate is **reabsorbed.**	D: Freely filtered and is not reabsorbed but additional quantities are **secreted** from the peritubular capillary into the renal tubules.
Excretion rate = filtration rate. **E.g.**creatinine and inulin.	Excretion rate = filtration rate - reabsorption rate. **E.g.** Na^+ and urea.	Amount excreted=0 **E.g.** amino acids and glucose.	Excretion rate = filtration rate + secretion rate. **E.g.** PAHA.



Criteria of a substance used for GFR measurement

1. Freely filtered.
2. Not secreted by tubular cells.
3. Should not be metabolized.
4. Should not be toxic.
5. Not reabsorbed by tubular cells.
6. easily measurable.

Inulin clearance can be used to estimate GFR

If a substance is **freely filtered** and is **not reabsorbed or secreted by the renal tubules**, then the rate at which that substance is excreted in the urine (Us × V) is **equal** to the filtration rate of the substance by the kidneys (GFR × Ps). Thus:

$$GFR \times Ps = Us \times V$$

- Therefore, the GFR can be calculated as the clearance of the substance as follows:

$$GFR = \frac{Us \times V}{Ps} = C2$$

- A substance that fits these criteria is **inulin**, a polysaccharide molecule with a molecular weight of about 5200.

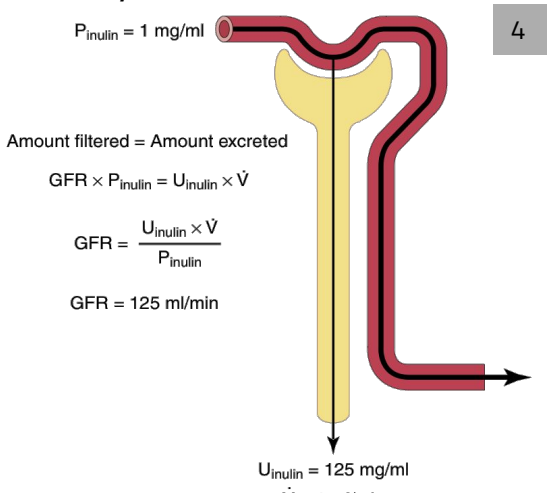


Figure 28-20 Measurement of glomerular filtration rate (*GFR*) from the renal clearance of inulin. Inulin is freely filtered by the glomerular capillaries but is not reabsorbed by the renal tubules. P_{inulin}, Plasma inulin concentration; U_{inulin}, urine inulin concentration; $\dot{V}$, urine flow rate.

Physiology of Renal Clearance

Renal blood flow

Substances used for measurement of GFR are not suitable for the measurement of Renal Blood Flow. Why?

Because Inulin clearance only reflects the volume of plasma that is filtered and not that remains unfiltered (RBF) and yet passes through the kidney.
It is known that only 1/5 of the plasma that enters the kidneys gets filtered.
Therefore other substances to be used with special criteria.

1. The substance we will be using for RBF is **PAHA** (Para aminohippuric acid).

2. To measure renal blood flow we will have to measure renal plasma flow first and then from the **hematocrit** value we calculate the actual blood flow.

Measurement of renal plasma flow then using it to get RBF

$$RPF = \frac{(UPAH \times V)}{P_{PAH}}$$

$$RBF = \frac{RPF}{(1 - Hct\%)}$$

Comparisons of Inulin Clearance with Clearances of Different Solutes. The following generalizations can be made by comparing the clearance of a substance with the clearance of inulin, the gold standard for measuring GFR: (1) if the clearance rate of the substance equals that of inulin, the substance is only filtered and not reabsorbed or secreted; (2) if the clearance rate of a substance is less than inulin clearance, the substance must have been reabsorbed by the nephron tubules; and (3) if the clearance rate of a substance is greater than that of inulin, the substance must be secreted by the nephron tubules. Listed below are the approximate clearance rates for some of the substances normally handled by the kidneys:

Substance	Clearance Rate (ml/min)
Glucose	0
Sodium	0.9
Chloride	1.3
Potassium	12.0
Phosphate	25.0
Inulin	125.0
Creatinine	140.0

4

Biochemistry of Renal Function Test

RFT are group of tests that measure the renal function ability. The tests measure levels of various substances including creatinine , electrolytes, glucose, etc.

- **Why is it important?**

Destruction of nephrons occur in many disease, however symptoms of renal impairment appear at late stages. So renal function tests are the only way to detect early renal impairment.

1. Measurements:

- Serum creatinine.
- Creatinine clearance.
- Urea.
- Electrolytes.

2. Glomerular filtration rate (GFR):

GFR is the volume of blood that filters from the glomerular capillaries into the bowman's capsule per minute.

- GFR used as index of numbers of functioning nephrons.
- Creatinine clearance used as estimation of GFR.

- Optimal Substances clearance tests criteria:

Criteria	Creatinine
Freely filtered	Freely filtered
Not reabsorbed	Not reabsorbed
Not secreted	10% secreted
Constant concentration	Constant concentration
Present endogenously	Present endogenously
Easily measured	Easily measured

❖ Creatinine clearance can be calculated by two methods:

Only for: early renal disease, assessment of kidney donation, renal toxicity in drugs.

Measuring serum & urine Cr through 24h.

Clearance (ml/min)= $\frac{U \times V}{P}$

Measuring only serum Cr with sex, age, and weight. **(Cockcroft-Gault Formula)**

GFR= $\frac{K\,(140-age) \times \text{Body weight}}{\text{Serum creatinine (µmol/L)}}$

3. Serum creatinine:

Creatinine is a byproduct of muscle metabolism and it's cleared from the body almost entirely by glomerular filtration which make measurement for GFR, but its not perfect because a small amount of creatinine is **secreted in renal tubules.** Serum creatinine is more accurate than creatine clearance.

4. Serum urea:

Urea is a waste product produced in the liver from ammonia, normally a healthy kidney remove urea almost completely leaving a small amount in the bloodstream, BUN blood test can be used to check kidney function but its inferior to serum creatinine because its affected by:

1- Diet.
2- Any condition of increased protein catabolism.
3- Renal reabsorption (>50%).
4- Dehydration.

7

Substances	Measurement	Range of Good Values
SODIUM	mmol/L	135 ⟷ 145
POTASSIUM	mmol/L	3.5 ⟷ 5.1
CHLORIDE	mmol/L	98 ⟷ 107
BICARBONATE	mmol/l	22 ⟷ 29
UREA	mmol/L	1.7 ⟷ 8.3
CREATININE	umol/L	66 ⟷ 112

London Doctor Clinic

Pharmacology of Renal Excretion of Drugs

Clearance By The Kidney

Unlike absorption of drugs, eliminating them requires them to be polar. Drugs are excreted mainly by the kidney into urine, or by bile into feces. Renal dysfunction can affect a drug's elimination which may lead to its accumulation and subsequent adverse effects.

Before renal excretion, a drug undergoes 3 processes: glomerular filtration, proximal tubular secretion, and distal tubular reabsorption.

1 Glomerular filtration

Free drugs, that are not bound to albumin, enter through renal arteries and get filtered into the Bowman space as glomerular filtrate. In this process, lipid solubility and pH play no role. However, GFR, renal blood flow, and protein binding do.

2 Proximal tubular secretion

Unfiltered drugs proceed through the efferent arteriole and get secreted mainly into the proximal convoluted tubules where their concentration is higher. There, secretion occurs by two active transporters:

- an acid (anion) transporter.
- base (cation) transporter.

These transporters are saturable and nonspecific, which might potentiate competition between drugs.

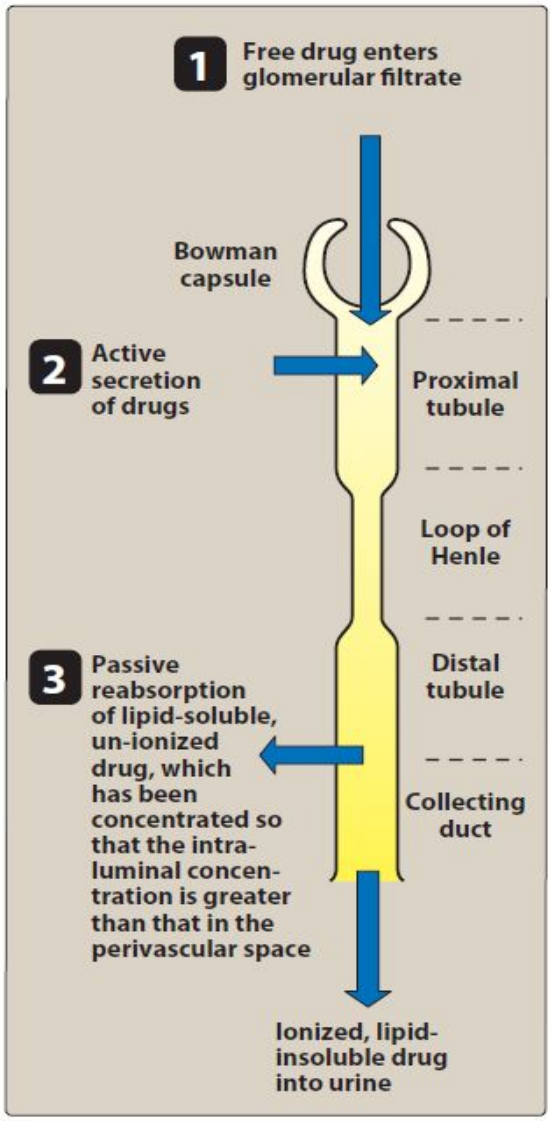


Figure 1.35
Drug elimination by the kidney.

Pharmacology of Renal Excretion of Drugs

Tubular secretion is important for:

1- Excretion of drugs that are **protein bound** and can't be filtered: NSAIDs, penicillins, cephalosporins, and glucuronic acid conjugates.

2- Delivering drugs to their site of action (e.g. Diuretics).

3- Manipulating the duration of action of some drugs that use the same carrier by **competition:**

Beneficial competition	Probenecid blocks **penicillin** secretion which prolongs its half-life.
Harmful competition	Probenecid blocks **nitrofurantoin** secretion which prevents it from reaching its active site.

3 Distal tubular reabsorption

At the distal convoluted tubules, the drug concentration increases such that nonpolar drugs may diffuse back into the systemic circulation.

Ion Trapping

Ion trapping is a process that alters the urine pH in order to ionize the drug and **prevent its reabsorption** across the renal membranes. It is used to enhance renal clearance of drugs during toxicity.

- Urine alkalization: A weak acid, such as phenobarbital, can be eliminated with bicarbonate.
- **Urine acidification**: Elimination of a weak base such as amphetamine increases by using ammonium chloride.

Pharmacology of Renal Excretion of Drugs

Factors Affecting Renal Excretion

- **Blood flow** to the kidney.
- **Physicochemical properties** of drugs: Molecular weight, lipid solubility, degree of ionization, volume of distribution, and protein binding.
- **Biological factors** (Age: neonates and elderly).
- **Urine pH.**
- **Plasma concentration** of drug: affects both glomerular filtration and reabsorption.
- **Disease states.** Impairs the elimination of drugs thus may increase half-life (t ½) of drugs:
  1. Reduced renal blood flow: Congestive heart failure, hemorrhage, cardiogenic shock.
  2. Decreased renal excretion: Renal disease that prevent drug extraction from plasma (e.g glomerulonephritis)

Pharmacology of Renal Excretion of Drugs

Excretion By Other Routes

Excretion can occur via the intestines, bile, lungs and breast milk.

- Unabsorbed oral drugs and polar drugs secreted into the intestines or bile are excreted through feces.
- Anesthetic gases, such as desflurane, are eliminated through the lungs.
- Drugs excreted through breast milk can potentiate undesirable side effects on the infant.
- Sweat, saliva, tears, hair, and skin are considered minor routes of excretion.

Orders of Elimination

	First-order Kinetics	Zero-order Kinetics
Half-Life	Constant.	Not Constant.
Rate of Elimination	Proportional to concentration; a constant **percentage** is eliminated per unit time.	A constant **amount** is eliminated regardless of concentration.
Examples	Most drugs in clinical use, e.g. Penicillin, Aminoglycoside, and Quinolones.	Ethanol, Phenytoin, and Aspirin.

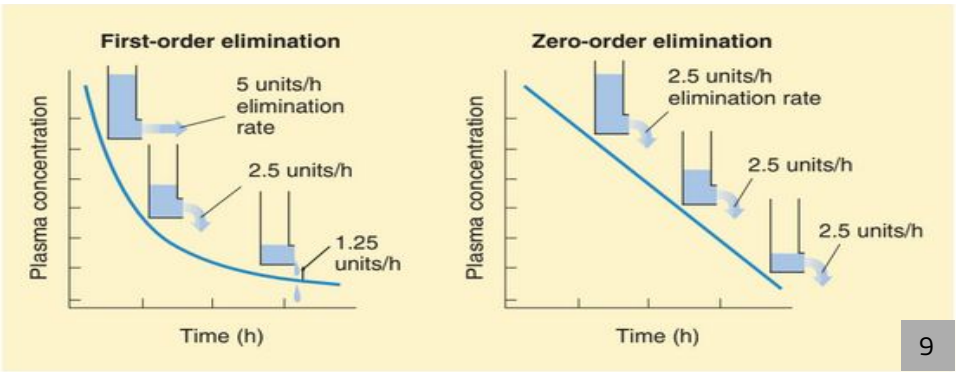


FIGURE 1–3 Comparison of first-order and zero-order elimination. For drugs with first-order kinetics (left), rate of elimination (units per hour) is proportional to concentration; this is the more common process. In the case of zero-order elimination (right), the rate is constant and independent of concentration.

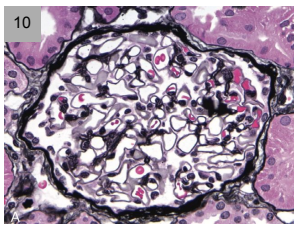
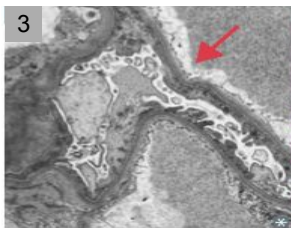
Kidney Injury

Nephrotic Syndrome

Epidemiology	In **children** the most common cause of nephrotic syndrome is minimal-change disease. In **adults** the most common primary nephrotic syndrome is Membranous glomerulopathy.
Etiology	**Primary Causes**: Minimal change disease, Membranous, Focal segmental glomerulosclerosis, and Membranoproliferative (can present as nephritic syndrome). **Secondary causes**:Diabetes mellitus (most common systemic causes), Amyloidosis, SLE (can present as nephritic syndrome), and Drugs.
Pathogenesis	Derangement in the capillary walls of the glomeruli that results in increased permeability to plasma proteins. Increased permeability of the glomerular basement membrane (GBM) may result from structural or physicochemical alterations in the GBM. With long-standing or heavy proteinuria, serum albumin is decreased, giving rise to hypoalbuminemia and a drop in plasma colloid osmotic pressure, which in turn leads to leakage of fluid from the blood into extravascular spaces.
Clinical features	heavy proteinuria (excretion of more than 3.5 g of protein/day in urine), hypoalbuminemia, severe edema, hyperlipidemia, and lipiduria.

Nephrotic Syndrome

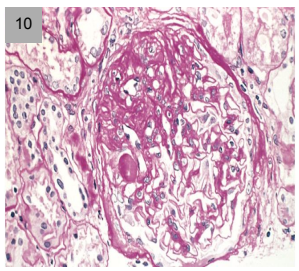
1 Minimal change disease

Epidemiology	Young children <7.		
Pathogenesis	Unknown usually idiopathic.		
Morphology	**LM**	- Glomeruli look normal. - The PCT cells are heavily laden with protein droplets and lipids.	
	IF	Negative.	
	EM	- Characterized by diffuse fusion or effacement of the epithelial cell (podocyte) foot processes.	
Clinical Course	- Abrupt. - Renal function is normal with no HTN. **-Selective proteinuria** (albumin).		
Prognosis	- Good, especially in children. - Some patients become steroid dependent i.e. relapse when it's stopped.		

Nephrotic Syndrome

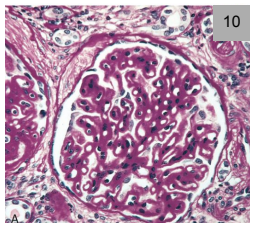
2 Focal Segmental Glomerulosclerosis

Epidemiology	Occurs in older children and adults.	
Etiology	1- Primary/ idiopathic. 2-secondary to: HIV, Heroin, other GN, and inherited.	
Clinical Course	Important to distinguish from minimal change disease: ● Incidence of hematuria and hypertension is higher. ● Proteinuria is nonselective.	
Morphology	**LM**	- Initially> affects juxtamedullary glomeruli. - Increased mesangial matrix, obliterated capillary lumina, hyalinosis, and foamy (lipid-laden) macrophages. - Severe disease> collapsing glomerulopathy.
	IF	Negative. Sometimes IgM is positive.
	EM	patchy/focal effacement of podocyte foot processes.
Prognosis	- Response to steroids is poor. - 50% develop end-stage renal disease within 10 years.	



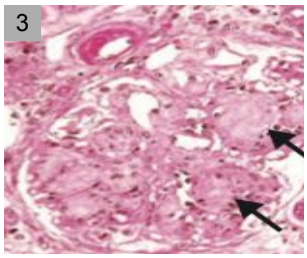
Nephrotic Syndrome

3 Membranous glomerulopathy/ nephropathy/ GN

Epidemiology	Adults (commonly 30-60 years).	
Etiology	1- Primary 80%: autoantibodies against phospholipase A2 receptor 1 (PLA2R1) antigen. 2- Secondary: • Infection (chronic hepatitis B, syphilis, schistosomiasis, and malaria). • Malignancy (Lung, colon, and melanoma) • Drugs (penicillamine, captopril, NSAIDs)	
Pathogenesis	Chronic immune complex disease. Immune complexes are formed either in-situ in the glomeruli or are pre-formed in circulation and then deposited in the glomeruli. It is characterized by immunoglobulin-containing deposits along the GBM.	
Morphology	**LM**	The capillary walls are diffusely thickened. 
	IF	**Granular** positivity for immunoglobulin IgG and complement C3 along the GBM.
	EM	Immune complexes appear in capillary walls as electron-dense deposits in the subepithelial space (spike and dome pattern).
Prognosis	- It is a slowly progressive disease. - If not treated some cases progress to fibrosis of the kidneys and end stage disease/ renal failure. - 10% to 30% have a more benign course.	

Nephrotic Syndrome

4 Diabetic Nephropathy

Pathogenesis	Long standing poorly controlled DM leads to kidney disease. Is a common cause of secondary nephrotic syndrome. Shows 2 types of glomerular lesion: **1. Diffuse mesangial sclerosis**: all the glomeruli show increase in mesangial matrix associated with mesangial proliferation and basement membrane thickening, ending in sclerosis. **2. Nodular glomerulosclerosis** (Kimmelstiel Wilson nodules): characterized by ball-like deposits in the periphery of the glomerulus. These nodules are PAS-positive, containing trapped mesangial cells.		
Morphology	**LM**	Diffuse thickening of the glomerular basement membrane.	
	IF	Negative	
	EM	Diffuse increase in the thickness of the glomerular basement membrane.	
Prognosis	If not treated can progress to end stage renal disease.		

Nephritic Syndrome

Etiology:

- Nephritic syndrome = inflammatory process.

1. Glomerular inflammation.
2. GBM damage.
3. Loss of RBCs into urine.
4. Dysmorphic RBCs, hematuria.

Clinical presentation:

- Hematuria.
- RBC casts in urine ↓GFR → oliguria.
- azotemia ↑renin release.
- Hypertension.
- Proteinuria often in the subnephrotic range (<3.5g/day) but in severe cases may be in nephrotic range.

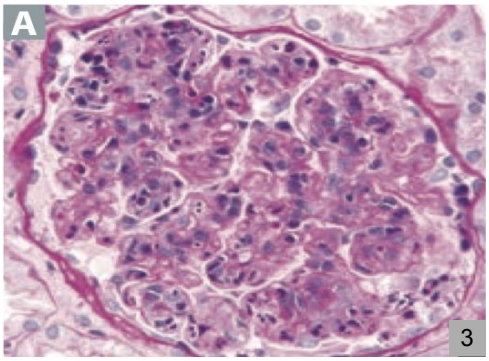
Examples:

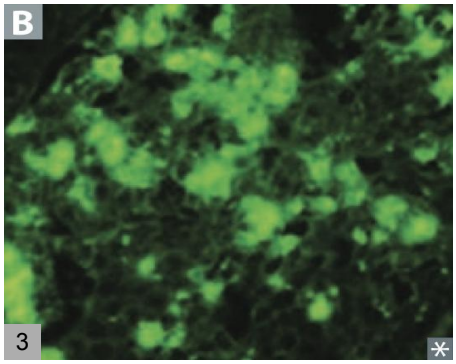
1. Acute poststreptococcal glomerulonephritis
2. Goodpasture syndrome
3. IgA nephropathy (Berger disease)
4. Alport syndrome
5. Membranoproliferative glomerulonephritis

Nephritic Syndrome

1 Acute poststreptococcal glomerulonephritis

Epidemiology	Most frequently seen in children.	
Etiology	~ 2–4 weeks after group A streptococcal infection of pharynx or skin. Also called postinfectious glomerulonephritis when caused by non-streptococcal pathogens.	
Pathogenesis	Type III hypersensitivity reaction. Characterized by glomerular deposition of immune complexes resulting in proliferation and damage to glomerular cells and infiltration of leukocytes, especially neutrophils.	
Morphology	**LM**	Diffuse glomerular enlargement and hypercellularity caused by proliferation and swelling of endothelial and mesangial cells and by infiltrating neutrophils and monocytes.
	IF	("Starry sky") granular appearance ("lumpy-bumpy") due to IgG, IgM, and C3 deposition along GBM and mesangium. A
	EM	Subepithelial IC humps. B
Clinical features	Presents with peripheral and periorbital edema, tea or cola-colored urine, HTN. ↓complement levels (C3) due to consumption.	
Prognosis	Resolves spontaneously in most children; may progress to renal insufficiency in adults.	





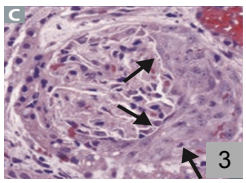
Nephritic Syndrome

2 IgA nephropathy (Berger disease)

Epidemiology	- Children and young adult. - Renal pathology of IgA vasculitis (Henoch-Schonlein purpura HSP). - ↑incidence in celiac disease.	
Pathogenesis	- **Abnormally glycosylated IgA1 (galactose-deficient IgA1)** plays a central role, it elicits an autoimmune response forming large immune complexes. -The presence of C3 in the mesangium and the absence of C1 and C4 points to activation of the **alternative complement pathway.**	
Clinical manifestation	- Episodic hematuria that usually occurs concurrently or 1-2 days after **respiratory** or GI tract infections.	
Morphology	**LM**	The glomeruli may be normal or may show: **- Focal proliferative GN:** mesangial widening and segmental inflammation confined to some glomeruli. **- Mesangioproliferative GN:** diffuse mesangial proliferation. **-Overt crescentic GN:** rare.
	IF	IgA-based IC deposits in mesangium (hallmark).
	EM	mesangial IC deposition.
Prognosis	-End-stage renal disease occurs in 25-50% of cases in 20 years. -Poorer prognosis in: Mesangioproliferative GN, endocapillary proliferation, segmental sclerosis, or tubulointerstitial fibrosis.	

Nephritic Syndrome

3 Rapidly progressive (crescentic) glomerulonephritis

	Anti-GBM antibody-mediated crescentic GN (Goodpasture's)	Immune complex-mediated crescentic GN	Pauci-immune crescentic GN
Pathogenesis	If pulmonary alveolar capillary BM affected>Goodpasture syndrome (pulmonary hemorrhage). - Autoantibodies directed against GBM.	Complicates any of the immune complex nephritides (e.g SLE, IgA nephropathy)	Anti-neutrophil cytoplasmic ab (ANCA) + in the serum. May be a component of systemic vasculitis (microscopic polyangiitis or granulomatosis with polyangiitis).
Morphology	**LM**: - Glomeruli show proliferation outside the capillary loops, These are called crescents as they fill Bowman's space. - Crescents are formed by epithelial cells, monocytes, macrophages, fibrin and plasma proteins. - Cellular proliferation within the capillary loops and/or in the mesangial areas in **immune complex-mediated GN only.** 		
	IF: Anti GBM: Strong linear staining with **IgG** + C3 along the GBM. Immune complex: Granular pattern of glomerular staining. Pauci-immune: Negative.		
	EM: Immune complex: Electron-dense immune complex deposits within the glomeruli.		
Clinical features	-Clinical syndrome of rapid loss of renal function, laboratory findings typical of the nephritic syndrome, and oliguria. -Azotemia and proteinuria that reaches nephrotic range.		
Prognosis	- Poor prognosis, rapidly deteriorating renal function (days to weeks). -Predicted by the fraction of involved glomeruli. If <80% → favorable prognosis.		
plasmapheresis	Yes	No	Some cases

Nephritic Syndrome

4 Membranoproliferative glomerulonephritis Type I

Overview	- MPGN is a nephritic syndrome that often co-presents with nephrotic syndrome. - Hematuria or proteinuria in the non-nephrotic range.	
Etiology	Usually secondary to SLE, hepatitis B or C, bacterial infection. May also be idiopathic.	
Morphology	**LM**	Proliferation of mesangial and endothelial cells. GBM is thickened, and the glomerular capillary wall often shows a double contour, or "tram track" appearance.
	EM	Subendothelial IC deposits.
	IF	granular C3 deposit.
Prognosis	Poor prognosis.	

5 C3 Glomerulopathy

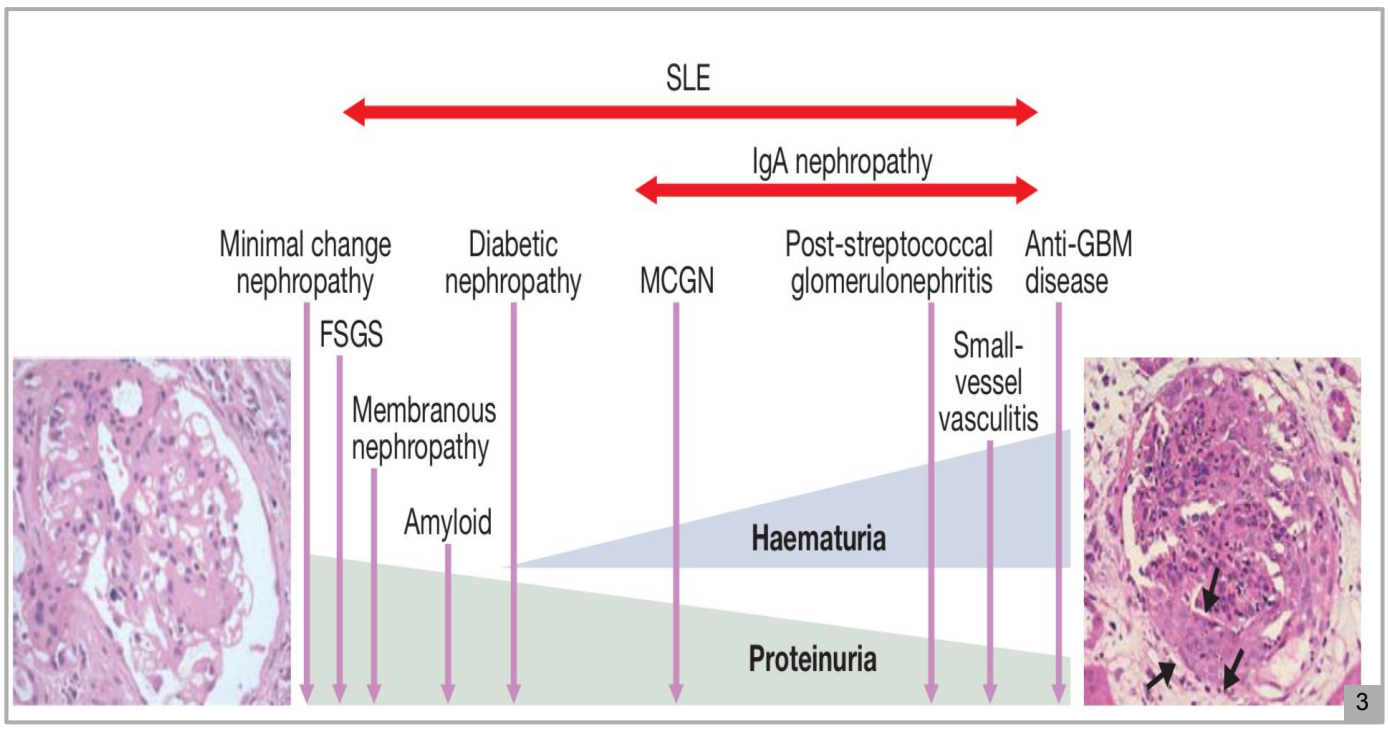
	Dense deposit disease (MPGN type II)		C3 GN
Overview	-Present with nephrotic or nephritic syndrome. - Dense deposit disease are usually younger and more likely to have low serum C3.		
Prognosis	- Underlying cause: Complement dysregulation due to acquired or hereditary abnormalities of the alternative pathway of complement activation. Autoantibodies against C3 nephritic factor (C3NeF) or mutations in complement regulatory proteins.		
Morphology	IF	bright mesangial and glomerular capillary wall staining for C3.	
	EM	Subendothelial space of GBM are transformed into an irregular, ribbonlike, electron-dense structure, resulting from the deposition of C3-containing material.	Mesangial and subendothelial electron-dense "waxy" deposits.
Prognosis	Poor prognosis.		

Nephritic Syndrome

6 Hereditary Nephritis (Alport Syndrome)

Etiology	- Mutation in α5 chain type IV collagen - Most commonly X-linked dominant.	
Clinical Features	- 5-20 year male with hematuria that progresses to renal failure. - Rare in female, non progressive course. - Eye problems (eg, retinopathy, anterior lenticonus), glomerulonephritis, sensorineural deafness. "can't see, can't pee, can't hear a bee."	
Morphology	**LM**	Late stage> glomerular and vascular sclerosis, tubular atrophy, and interstitial fibrosis,
	EM	Early>GBM is thin and attenuated. Late> "basket-weave" appearance due to irregular thickening of GBM.

Nephritic and Nephrotic syndrome:



Nephritic Syndrome

7 Lupus Nephritis

Minimal mesangial (class I)	**- Characterized by**: immune complex deposition in the mesangium.
Mesangial proliferative (class II)	
Focal (class III)	- < 50% of all glomeruli - Swelling and proliferation of endothelial and mesangial cells + leukocyte accumulation, capillary necrosis, and hyaline thrombi. **-Clinical manifestation**: From mild hematuria and proteinuria to acute renal insufficiency.
Diffuse (class IV) (Also called Diffuse proliferative GN)	- >50% of all glomeruli. - Most common and severe form. - Same as focal but with cellular crescents. Immune complex deposits> thickening of capillary "wire-loop". **-Clinical manifestation**: hematuria, proteinuria, hypertension and renal insufficiency.
Membranous (class V)	**- Characterized by**: diffuse thickening of the capillary walls due to deposition of subepithelial immune complexes + increased basement membrane-like material, resulting in "holes" and "spikes". **- Clinical manifestation**: severe proteinuria/ nephrotic.
Advanced sclerosing (class VI)	**Characterized by**: Sclerosis >90% of the glomeruli.

Major Primary Glomerular Diseases

	Clinical Presentation	Pathogenesis	Light Microscopy	Fluorescence Microscopy	Electron Microscopy
Minimal-change disease	Nephrotic.	Unknown; podocyte injury.	-	-	Effacement of foot processes; no deposits.
Focal segmental glomerulosclerosis	Nephrotic w/ ↓ proteinuria.	Unknown: reaction to loss of renal mass.	Focal & segmental, sclerosis & hyalinosis.	Usually negative; ± IgM & C3 in areas of scarring.	Effacement of foot processes; epithelial denudation.
Membranous nephropathy	Nephrotic.	Immune complex; PLA2R antigen> primary disease.	Diffuse capillary wall thickening & subepithelial spike formation.	Granular IgG & C3 along GBM.	Subepithelial deposits.
Membranoproliferative GN type I	Nephrotic/ nephritic.	Immune complex.	Membrano-proliferative pattern; GBM splitting.	Granular IgG, C3, C1q & C4 along GBM & mesangium.	Subendothelial deposits.

Major Primary Glomerular Diseases

	Clinical Presentation	Pathogenesis	Light Microscopy	Fluorescence Microscopy	Electron Microscopy
C3 glomerulopathy (dense deposit & C3 GN)	Nephrotic/ nephritic.	Activation of alternative complement pathway; antibody or hereditary defect.	Mesangial proliferative or membrano-proliferative patterns.	C3	Mesangial, intramembranous & subendothelial electron-dense or waxy deposits.
Acute post-infectious GN	Nephritic.	Immune complex; circulating or planted antigen.	Diffuse endocapillary proliferation; leukocytic infiltration	Granular IgG, C3, in GBM & mesangium.	Primarily subepithelial humps.
IgA nephropathy	hematuria or proteinuria.	Immune complexes containing IgA.	Mesangial or focal endocapillary proliferative GN.	IgA ± IgG, IgM, & C3 in mesangium.	Mesangia & paramesangial dense deposits.
Anti-GBM disease	Rapidly progressive GN.	Antibodies against collagen T-IV α3 chain.	Extracapillary proliferation w/ crescents; necrosis.	Linear IgG & C3; Fibrin in crescents.	No deposits; GBM disruption; fibrin.
Pauci-immune GN	Rapidly progressive GN.	Anti-neutrophil cytoplasmic antibody.	Extracapillary proliferation w/ crescents; necrosis.	Fibrin in crescents.	No deposits; GBM disruption; fibrin.

Immune-complex Nephritis

Immune Complex–Mediated Diseases (Type III Hypersensitivity):

Deposition of antigen-antibody complexes → complement activation → recruitment of leukocytes by complement products and Fc receptors → release of enzymes and other toxic molecules

- Antigen–antibody (immune) complexes that are formed in the circulation may deposit in blood vessels, leading to complement activation and acute inflammation.
- Less frequently, the complexes may be formed at sites where antigen has been "planted" previously (called in situ immune complexes).

The antigens that form immune complexes may be exogenous, such as a foreign protein that is injected or produced by an infectious microbe, or endogenous, if the individual produces antibody against self antigens (autoimmunity).
Immune complex–mediated diseases tend to be systemic, but often preferentially involve the kidney (glomerulonephritis), joints (arthritis), and small blood vessels (vasculitis), all of which are common sites of immune complex deposition.

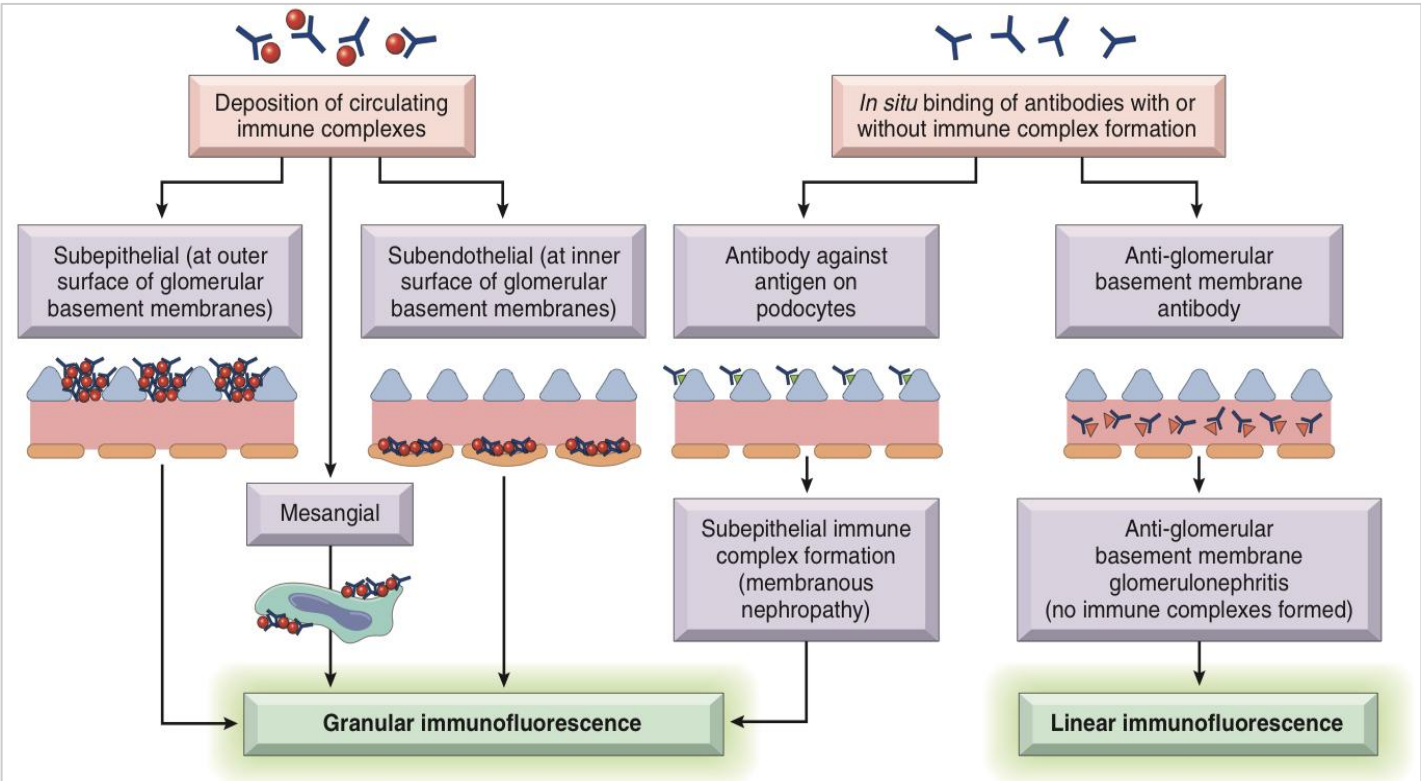


Fig. 14.3 Antibody-mediated glomerular injury. Injury can result either from the deposition of circulating immune complexes or from antibody-binding to glomerular components followed by formation of complexes in situ. Deposition of circulating immune complexes gives a granular immunofluorescence pattern. Anti-glomerular basement membrane (anti-GBM) antibody glomerulonephritis is characterized by a linear immunofluorescence pattern; there is no immune deposit formation in this disease.

10

Immune-complex Nephritis

Inflammation and Tissue Injury:

Once deposited in tissues, immune complexes initiate an acute inflammatory reaction via complement activation.Typically, the antibodies are IgG or IgM. Deposition of complement proteins can be detected at the site of injury.

Consumption of complement during the active phase of the disease decreases serum levels of C3, which can be used as a marker for disease activity. During this phase,there are clinical features such as fever, urticaria,arthralgia, lymph node enlargement, and proteinuria appear.

Site of Deposition:

The localization of antigen, antibody, or immune complexes determines the glomerular injury response. Electron microscopy reveals electron-dense immune deposits in one or more of three locations:

- **subendothelial deposits** — between the endothelial cells and the GBM.
- **subepithelial deposits** — between the outer surface of the GBM and the podocytes.
- **mesangium**

- **Studies in experimental models have shown that:**

endothelium or subendothelium	**subepithelial**
Complexes deposited in the endothelium or subendothelium elicit an inflammatory reaction in the glomerulus with infiltration of leukocytes and exuberant proliferation of glomerular resident cells.	Antibodies directed to the subepithelial region of glomerular capillaries are often noninflammatory, as seen in primary membranous nephropathy.

Types of Immune-Mediated Renal Disease

Disease		Site
Post-infectious Glomerulonephritis		deposited immune complexes arrayed as subendothelial, intramembranous, or, most often, subepithelial "humps" nestled against the GBM. Mesangial deposits also are occasionally present.
Membranous Glomerulonephritis		Subepithelial.
Membranoproliferative Glomerulonephritis	Type I	Subendothelial deposits.
	Type II	Intramembranous deposits, also called dense deposit disease.
IgA Nephropathy		Mesangial deposits.
Rapidly progressive Glomerulonephritis	Type I	GMB.
	Type II	GMB.
	Type III	GMB.

Clinical Integration

Glomerular Disease

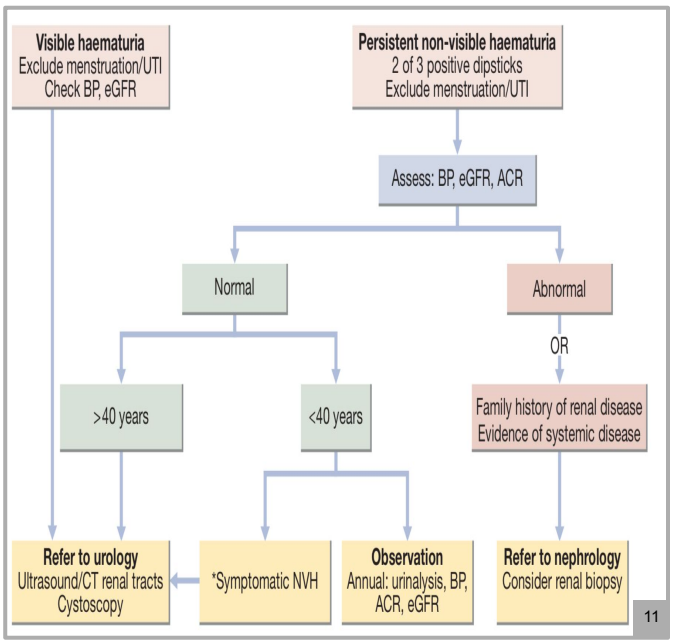
- Chronic.
- Not caused by toxins/drugs.
- Biopsy is the most accurate test to establish a diagnosis (though not always needed).
- They are often treated with steroids (several resolve spontaneously).

Poor prognostic indicators in glomerular disease:

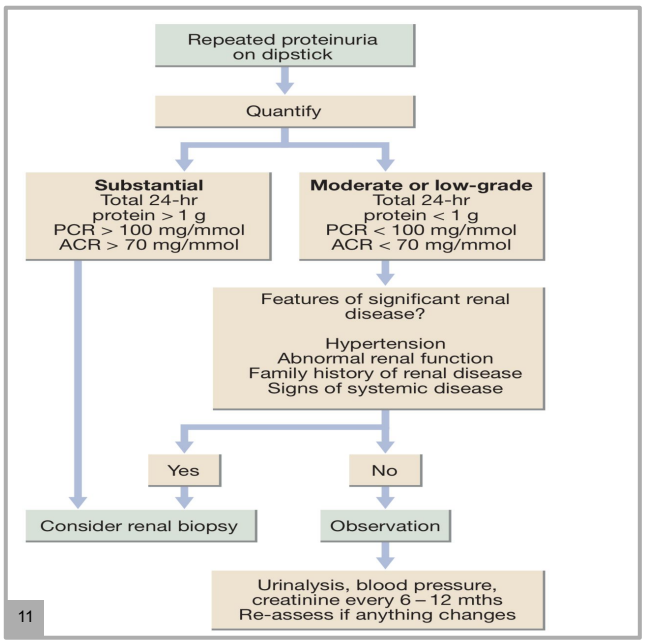
- Male sex.
- Hypertension.
- Persistent and severe proteinuria.
- Elevated creatinine at time of presentation.
- Rapid rate of decline in renal function.
- Tubulointerstitial fibrosis observed on renal biopsy.

The degree or amount of proteinuria is the main difference between glomerulonephritis and nephrotic syndrome.

Approach to Hematuria:



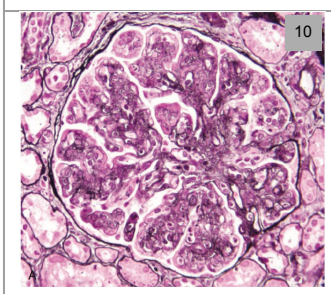
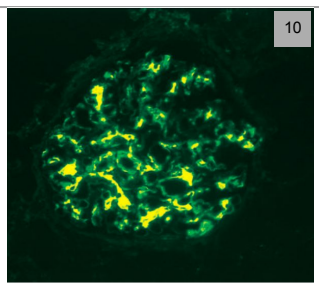
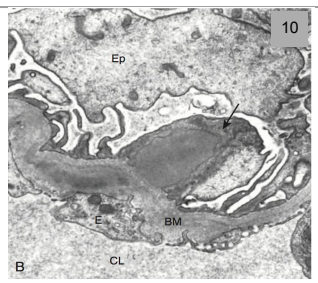
Approach to Proteinuria:



Kidney Diseases

Renal Biopsy

The tissue obtained is used to make slides for:

Light microscopy (LM)	Immuno-Fluorescence (IF)	Electron microscopy (EM) (ultrastructural)
Studies the histology in renal cortex & medulla.	Used detect The presence of: • Immunoglobulins (IgA, IgG, IgM). • Complements (C3 & C1q). in the glomerular mesangium or in the wall of the glomerular capillary loops.	Used to detect: • The presence of effacement of the epithelial cell (podocytes) foot processes. • The presence of electron-dense immune complex deposits and its location in the glomeruli (mesangial, subepithelial, subendothelial).
		

Renal failure classification

Duration	**Acute**: sudden, rapid reduction in urine output, reversible (AKI)
	Chronic: gradually progressive and irreversible (CKD)
Etiology	Pre-renal(55-60%)
	Renal (35-40%)
	Post-renal (5-10%)
Urine output	**Oliguric:** < 400cc/24hr.
	Non-oliguric: > 400cc/24hr.
	Anuric: <100cc/24hr.

Types of AKI

Causes

Prerenal	Intrinsic	Postrenal
The renal tubular and glomerular function are normal. The GFR is decreased due to reduced renal perfusion.	Is due to diseases of the kidney itself (associated with release of renal afferent vasoconstrictors).	
Hypovolaemia: • Haemorrhage. • Burns. • Diuretic use.	Glomerular disease: • Glomerulonephritis. • Vasculitis. • Immune complex disease, e.g. systemic lupus erythematosus.	Obstruction of the ureter: • Stones. • Tumour.
Oedematous conditions: • Heart failure. • Nephrotic syndrome.	Vascular lesions: • Bilateral renal artery stenosis. • Microangiopathy. • Malignant hypertension.	Obstruction of the bladder neck: • Stones. • Tumour. • Benign prostatic hypertrophy. • Prostate cancer.
Hypoperfusion: • Hepatorenal syndrome. • NSAID use. • Angiotensin converting enzyme (ACE) inhibitor use.	Tubulointerstitial disease: • Acute tubular necrosis. • Acute tubulointerstitial nephritis. • Multiple myeloma. • Nephrotoxic drugs.	Obstruction of the urethra: • Tumour. • Stricture.
Shock: • Sepsis. • Cardiogenic.	-	-

Acute Kidney Injury

Definition

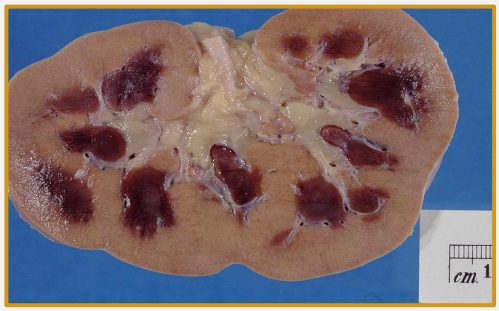
is when a kidney fails over a short time period (days to weeks) and is characterised by a rapid fall in glomerular filtration rate (GFR) and an increase in creatinine and urea levels. It may be reversible.

Clinical manifestations of AKI

1. **Oliguria**/anuria.
2. **Pulmonary oedema.**
3. Hyperkalaemia.
4. Metabolic acidosis.
5. Hyperphosphatemia.
6. Confusion.
7. Hypertension.
8. Nausea and vomiting.
9. Abdominal/flank pain.
10. Signs of fluid overload.

Gross morphology of AKI

Kidney showing marked pallor of the cortex, contrasting to the darker areas of surviving medullary tissue.



https://slidetodoc.com/renal-block-pathology-practical-i-ii-prepared-by/

Treatment of AKI

01 Treat underlying cause.

02 Monitor electrolytes.

03 Maintain renal blood flow and fluid balance.

04 Stop all nephrotoxic drugs.

Acute tubular injury/ necrosis

Definition

Acute tubular necrosis (ATN) is acute renal failure associated with potentially reversible injury to the tubular epithelium.

Clinical features

ATN is the most common cause of acute renal failure. It is characterized by oliguria with elevation of blood urea nitrogen (BUN) and creatinine; metabolic acidosis and hyperkalemia; and dirty brown granular casts and epithelial casts on urinalysis.

Etiology

ATN can be due to ischemia or nephrotoxins.

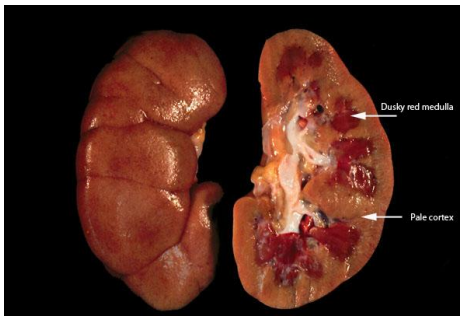
Ischemic ATN	Nephrotoxic ATN
Ischemic ATN is the most common cause of ATI. The condition is due to decreased blood flow caused by severe hemorrhage, severe renal vasoconstriction, hypotension, dehydration, or shock.	Nephrotoxic ATN has a large number of causes, including: • Radiographic contrast agents. • Heavy metals (e.g., mercury, lead, gold). • Drugs (e.g., poly-myxin, methicillin, gentamicin, sulfonamides). • Organic solvents (e.g., carbon tetra-chloride, chloroform, methyl alcohol).

Acute tubular injury/ necrosis

Morphology

Gross morphology is characterized by

- Bilaterally enlarged and swollen kidneys (due to edema).
- Cut surface shows a pale cortex and a dark and congested medulla.



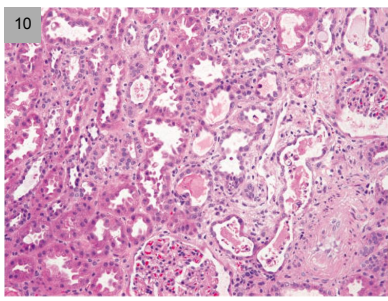
https://www.slideshare.net/msjacklynkong/5094-excretion-2014

Histologically

Ischemic ATI:

- Characterized by lesions in the straight proximal tubules and the ascending thick limbs.
- **Tubules**:
  - Attenuation, blebbing, and sloughing brush borders, vacuolization of cells, and detachment of tubular cells from basement membranes with sloughing of into the urine.
  - Presence of proteinaceous casts (Tamm-Horsfall protein), hemoglobin and other plasma proteins in the distal tubules and collecting ducts.
- **Interstitium**:generalized edema + inflammatory infiltrate (neutrophils, lymphocytes, and plasma cells).

Nephrotoxic ATI: similar to ischemic ATN.
Overt necrosis is usually more prominent in the proximal tubule than in ischemic ATI, and the tubular basement membranes generally are spared.



later stage> epithelial regeneration in the form of a low cuboidal epithelial covering and mitotic activity in the surviving tubular epithelial cells.

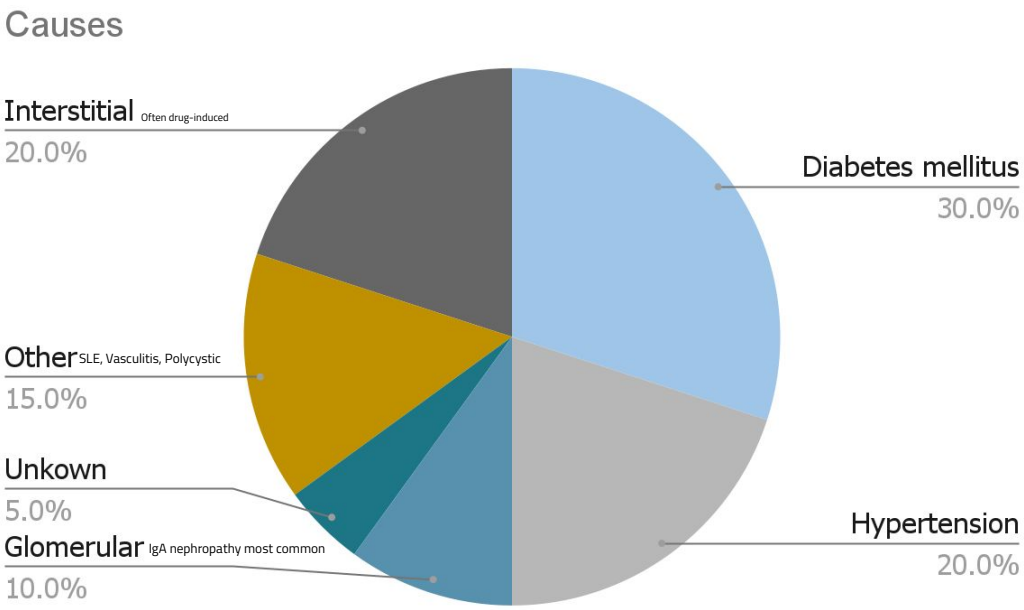
Chronic kidney disease

Definition

CKD is an irreversible deterioration in renal function that usually develops over a period of years, it implies longstanding (>3 months), potentially progressive impairment in renal function.

Pathophysiology

In many cases, the underlying diagnosis is unclear. Common causes of CKD are shown below.



Staging

GFR and ACR categories and risk of adverse outcomes			Description	ACR (mg/mmol) / description		
				<3	3–30	>30
				A1	A2	A3
GFR (mL/min/1.73 m²)	≥90	G1	Normal or increased GFR with other evidence of kidney damage	No CKD markers of kidney damage		
	60–89	G2	Slight decrease in GFR with other evidence of kidney damage			
	45–59	G3a	Moderate decrease in GFR with or without other evidence of kidney damage			
	30–44	G3b	Moderate to severe increase in GFR			
	15–29	G4	Severe decrease in GFR with or without other evidence of kidney damage			
	<15	G5	End-stage renal disease			

Increasing risk

Increasing risk

12

* GFR: glomerular filtration rate, ACR: albumin- creatinine ratio

Chronic kidney disease

Complications of CKD:

01 Mineral and bone disorders

Renal phosphate retention and impaired production of 1,25-dihydroxyvitamin D lead to fall in serum calcium Which lead to excessive PTH.

02 Anaemia

It is due to reduced erythropoietin produced by the kidney, Increase blood loss from the gut and during hemodialysis, shortened RBC survival.

03 Neurological complications

Neurological complications occur in almost all patients with severe CKD and improved by dialysis.

04 Metabolic abnormalities

CKD increase the risk of gout, increase the risk of insulin and abnormalities in lipid metabolism.

05 Cardiovascular disease

The highest mortality in CKD is from cardiovascular disease, particularly myocardial infarction, cardiac failure, sudden cardiac death and stroke.

06 Other complications

pericarditis, calciphylaxis, and increase risk of peptic ulcer, pancreatitis and hyperuricemia.

Chronic kidney disease

Morphology of CKD:

- Grossly the kidney **small** and contracted with **granular surface.** Markedly damaged kidneys are designated "**end-stage kidneys**".

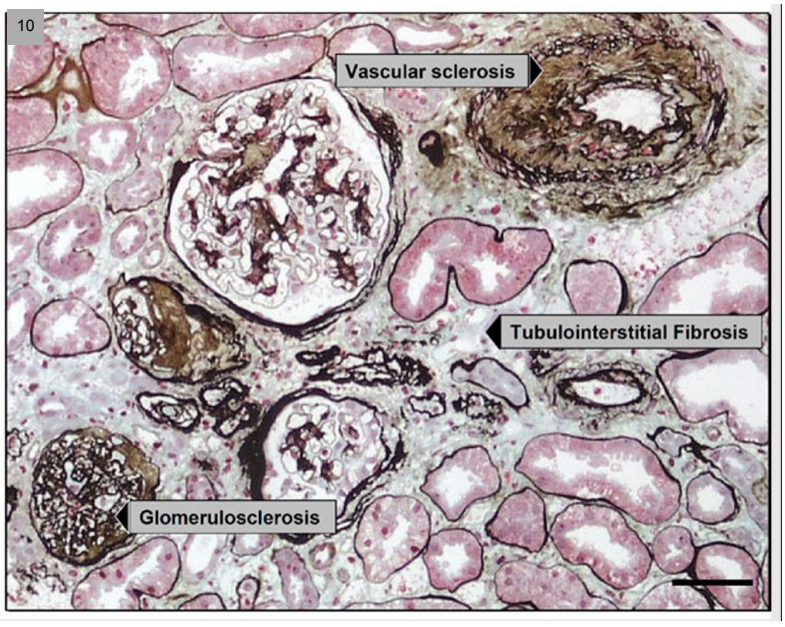
- **light microscopy:**

Glomeruli: most of the glomerular are sclerosed (fibrosed/scarred) called glomerulosclerosis.

Tubules : show prominent atrophy with thyroidization of tubules (tubules are filled with eosinophilic hyaline casts resembling colloid of thyroid gland).

Interstitium: prominent interstitial fibrosis with lymphocytic infiltrate

Blood vessels: show thick walled arteries and arterioles with narrowed lumen.



Fibrosis in the kidney: Is a problem shared a problem halved?

Chronic kidney disease: Clinical integration

Natural history of chronic kidney disease

Early: usually asymptomatic in its early stages.
Late: symptoms and signs usually related to:

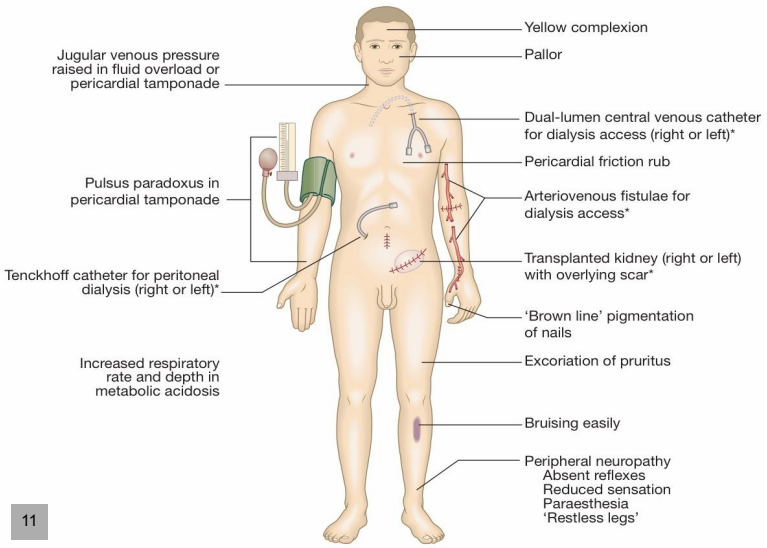
- Sodium and water retention > **hypertension**, edema.
- Metabolic and hormonal complication > **anemia**, vitamin D deficiency, increase parathyroid hormone.
- Increased incidence of cardiovascular diseases, infection, and impaired physical function.

Evaluation of patient with chronic kidney disease

- The history should document the presence of uremic symptoms and possible etiology from: Diabetes Mellitus, Hypertension, Congestive heart failure, MM, NSAID.
- Family history can suggest polycystic kidney disease or hereditary nephritis.
- Volume depletion and obstructive nephropathy should be identified and treated promptly.
- Ultrasound: small, shrunken kidneys.
- Normal kidney size with CKD: DM, amyloid, MM.

Clinical features

- Most patients with slowly progressive disease are asymptomatic until GFR falls below 30 mL/min/1.73 m². The typical presentation is for a raised urea and creatinine to be found incidentally during routine blood tests.



- When GFR falls below 15–20 mL/min/1.73 m², symptoms and signs are common and can affect almost all body systems like : tiredness, breathlessness, pruritus, anorexia, weight loss, nausea, vomiting and hiccups.

Chronic kidney disease: Clinical integration

Test	Indication
Serum creatinine	Most important.
CBC	Normocytic, normochromic anemia.
Urinalysis	Proteinuria and hematuria .
Urea & electrolytes	Uremia, hyperkalemia, hypocalcemia, hypermagnesemia, and hyperphosphatemia.
PTH	Secondary hyperparathyroidism.
Vit-D	Hypovitaminosis D.
Cr clearances	To estimate GFR.
Renal ultrasound	To evaluate size of kidneys/ rule out obstruction.
Urine pro/cr ratio.	
Liver function tests.	

Managements of CKD

1. Conservative management:
    a. Salt and water restriction.
    b. Hyperkalemia management (IV calcium gluconate and 50% dextrose solution with insulin).
    c. Hyperphosphatemia and secondary hyperparathyroidism management.
    d. Anemia management (iron treatment).
2. If progress to ESRD
    a. Peritoneal Dialysis.
    b. Kidney Transplantation.
    c. Hemodialysis: Vascular access > AVF, AVG, Permcath.

Acute Kidney Injury: Clinical integration

Definition

AKI can be defined based on RIFLE criteria:

RIFLE	GFR	Serum creatinine	Urine output
Risk	Low by 25%	Higher by 1.5 folds	Lower than 0.5 mL/kg/hr for 6h
Injury	Lower by 50%	2 fold increase	Less than 0.5 mL/kg/hr for 12h
Failure	Lower by 75%	3 fold increase	Less than 0.5 mL/kg/hr for 24h or anuria for 12h
Loss	Complete loss of kidney functions for more than 4 weeks.		
ESRD	Complete loss of kidney functions for more than 3 months..		

Azotemia

A characteristic feature of AKI known as abnormal elevation in BUN and Cr.

- Abnormally high BUN maybe seen in high protein intake, GI bleeding, or drugs use such as steroids.
- Abnormally high Cr is seen in muscle damage.

Prognosis

- It depends on comorbid conditions.
- However 80% of patients achieve full recovery.
- The most common cause of death in AKI patients is infections followed by cardiopulmonary failure.

Acute Kidney Injury: Clinical integration

Diagnosis

For any patient with AKI order the following:

01

Blood tests

Show elevated BUN and Cr, Abnormal electrolytes (potassium, calcium and phosphate).

02

Urinalysis

A positive urine dipstick for protein (3+,4+) suggest an intrarenal damage.

03

Microscopic urine sidemen the examination

Hyaline casts (in prerenal), RBC casts (in glomerular diseases), WBC casts (in kidney parenchymal inflammation), Fatty casts (in nephrosis).

04

Urine chemistry

- Classic BUN:Cr ratio is 20:1.

Labs	Bun:Cr ratio	Urine osmolality	Urine Na	FENa	Urinalysis
Prerenal	>20:1	>500 mOsm	<20	<1%	Hyaline casts.
Intrarenal	<20:1	250-300 mOsm	>40	>2%-3%	Abnormal casts.

05

Suspect infection?

Perform urine culture and sensitivity.

06

Others

Renal radiography (US or Non-contrast CT), renal biopsy and renal arteriography.

Acute Kidney Injury: Clinical integration

Complications

- **Pulmonary edema.**
- Hyperkalemia.
- Metabolic acidosis.
- Hypocalcemia.
- Hyperphosphatemia.
- Hyperuricemia.
- Uraemia.
- Infections such as pneumonia, UTI and sepsis.
- Hyponatremia (when water intake is higher than body losses, or the patient receives excessive hypotonic solutions).

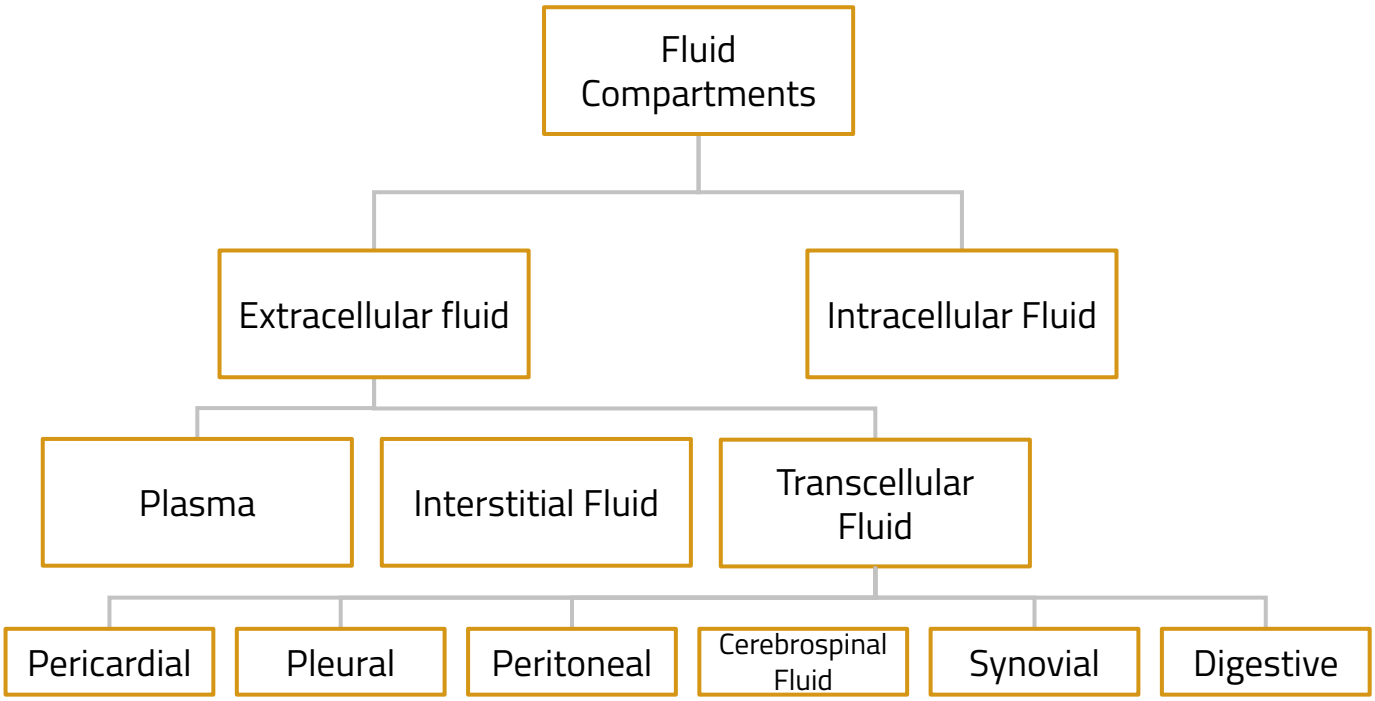
Treatment

1. Treat symptoms (HTN, edema, and metabolic disorders).
2. Prerenal (treat underlying cause, Give NS to maintain euvolemia and normalise blood pressure but do not give to patients with edema or ascites, and eliminate offending agents such ACEis or NSAIDs.
3. Intrarenal (ATN? Supportive, oliguric? Furosemide may help).
4. Postrenal (urinary tract decompression with bladder catheter, and consult Urology).

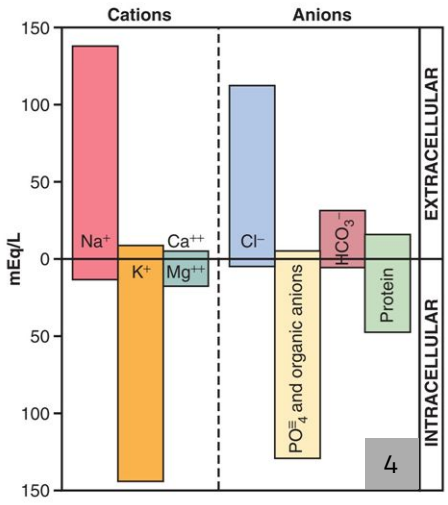
Renal Regulation of Body Fluids

Renal Regulation of Body Fluids

Body Fluids Compartments



- Maintaining normal ECF volume and osmolarity is crucial.
- Normal ECF volume is important in maintaining ABP and tissue perfusion.
- Normal ECF volume is controlled by adjusting Na content.
- Normal ECF osmolarity is controlled by adjusting water content.



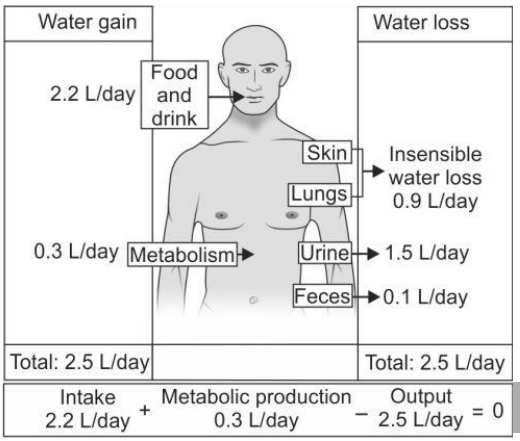
➔ Extracellular Fluid:
- The chief cation is Na^+.
- The chief Anion is Cl^- then HCO_3^-.

➔ Intracellular Fluid:
- The chief Cation is K^+.
- The chief Anion is PO_4^-.

Renal Regulation of Body Fluids

Water Regulation

- To remain hydrated water intake = water output.



- Increases in plasma osmolality (concentration) trigger the hypothalamic thirst center in the brain and release of antidiuretic hormone (ADH).

- Thirst is quenched as we drink water by 2 negative feedbacks:

1. Moistening of mouth mucosa
2. Stretch of stomach and intestines

Osmolality Vs Osmolarity

- The concentration of a solution expressed as osmoles per kilogram of water is called osmolality.
- The concentration of a solution expressed as osmoles per Liter of water is called osmolarity.
- In dilute solutions such as the body fluids, these two terms can be mostly used interchangeably.

Renal Regulation of Body Fluids

Regulation of Osmolality

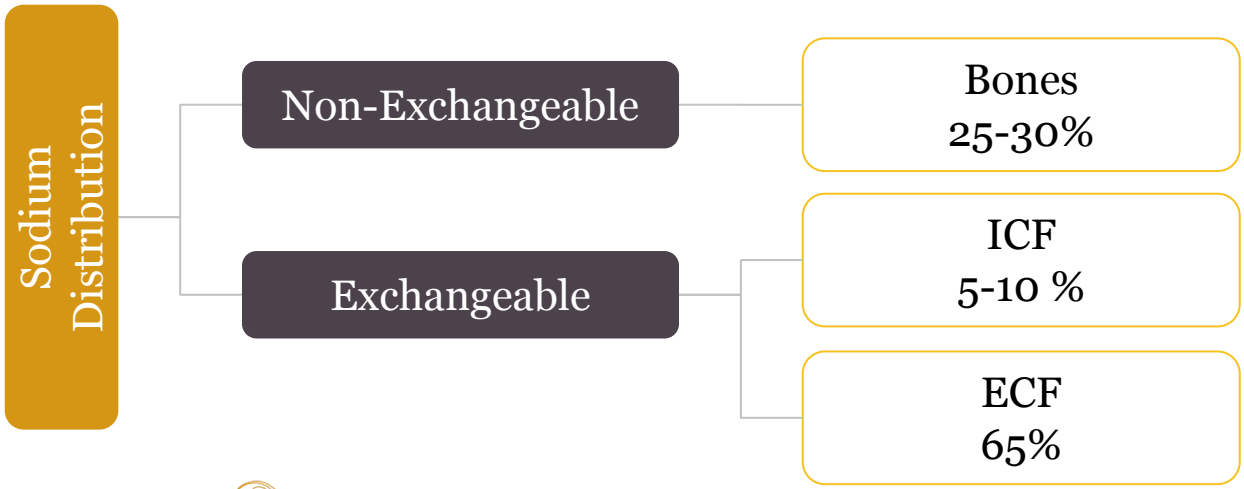
- If decreased water intake → hypoosmotic urine.
  - Diluted 50 mOsm.
  - Large volume up to 18 L/day.
- If increased water intake → hyperosmotic urine.
  - Concentrated 1200 mOsm.
  - Small volume as low as 0.5 L/day.
- Renal water excretion mechanism is independent of solutes.
- It can allow water to be excreted without damaging solutes homeostasis.

Sodium Balance and Regulation

- ECF volume is closely linked to Na^+ balance.
- The body regulates ECF volume by monitoring and adjusting total body content of Na^+, through absorption & excretion.
- The signal that triggers sodium excretion is the ECF volume specifically the effective circulating volume (ECV).
- **Effective circulating volume** is a blood volume that reflects the extent of tissue perfusion is specific region.

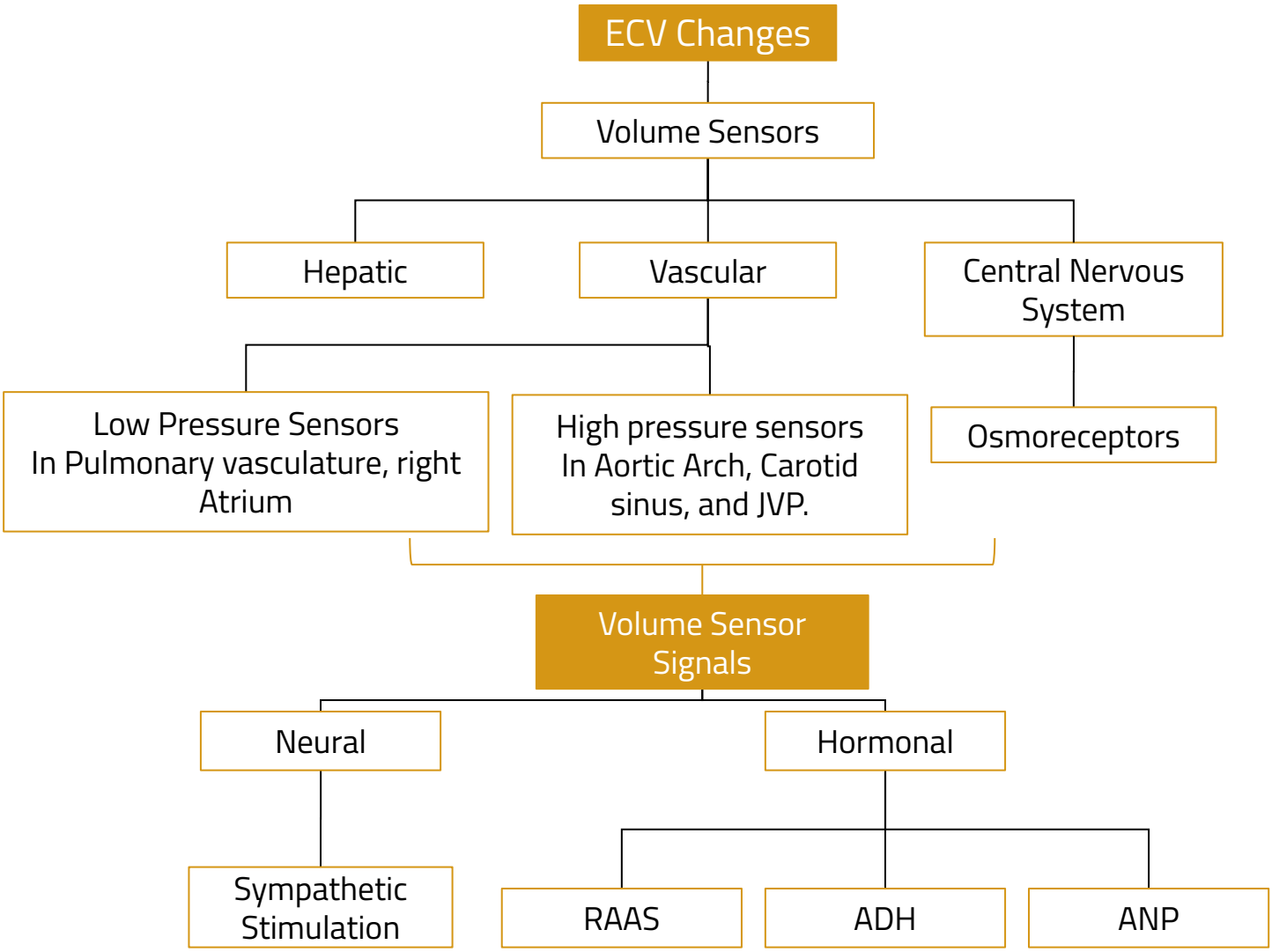
Increased ECV → trigger Na^+ excretion → decrease ECF
Decreased ECV → trigger Na^+ retention → increase ECF

- Sodium intake is usually 1.5-2.3 g/day.
- Sodium is mainly excreted by the kidney.
- GI and sweat are minor sodium excretory pathways.



Renal Regulation of Body Fluids

ECV Regulation Overview



A.Neural: Sympathetic Nervous System

If the pressure decreased, Renal sympathetic will be stimulated and acts:

1. Directly, Afferent & Efferent arterioles constrict:
    i. ↓GFR → ↓ Na^+ filtration.
    ii. More Na^+ tubular reabsorption by Proximal convoluted tubule.
2. Indirectly, Renin released:
    i. increase Aldosterone secretion → Na^+ reabsorption.
    ii. increase angiotensin II formation → vasoconstriction.

Renal Regulation of Body Fluids

B.Hormonal

1- Renin-angiotensin-aldosterone system (decreased pressure):

Renin secreted by:

- Sympathetic stimulation.
- decrease perfusion pressure.
- decrease Na^+ reaching macula densa.

Angiotensin II

- Angiotensin II is the body's most powerful sodium-retaining hormone.
- Increasing sodium and water reabsorption from the renal tubules through three main effects:

First action

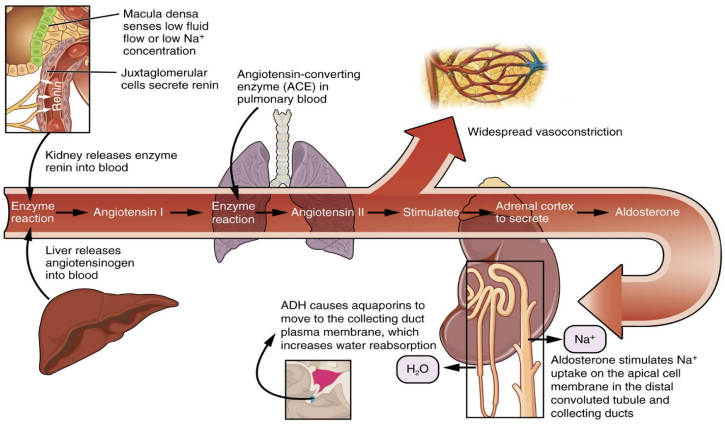
- Angiotensin II **stimulate Aldosterone secretion** from the zona glomerulosa cells of the adrenal cortex. Aldosterone acts on the distal tubule and collecting duct to cause sodium retention.

Second action

- Angiotensin II is one of the most potent vasoconstrictors.
- Constriction of vascular smooth muscle> prompt rise in blood pressure.
- **Efferent arteriolar constriction**, by reducing renal blood flow, decreases GFR, this increases the reabsorptive force and raises tubular reabsorption of sodium and water.

Third action

- Angiotensin II **directly stimulates sodium reabsorption in the proximal tubules, the loops of Henle, the distal tubules, and collecting tubules.**



Openstax, Rice University

Renal Regulation of Body Fluids

Aldosterone

- Aldosterone Increases Sodium Reabsorption and Potassium excretion.
- Aldosterone, secreted by the zona glomerulosa cells of the adrenal cortex.
- The most important stimulus for aldosterone, which typically occur in conditions associated with sodium and volume depletion or low blood pressure, are:

1. increased extracellular K^+ concentration
2. increased angiotensin II levels

- A major renal tubular site of aldosterone action is on the principal cells of the cortical collecting tubule

2- ANP: (Atrial natriuretic peptide)

Released from atrial myocytes by stretch of atrium, increase NaCl & water excretion.

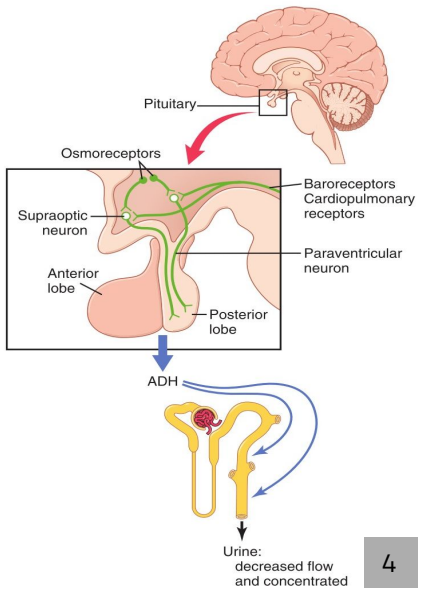
↑ECV ⟶ ↑ANP release ⟶ ↑Na^+ & water excretion.
↓ECV ⟶ ↓ANP release ⟶ ↓Na^+ & water excretion.

Actions:

- Small increase in GFR.
- Directly inhibits Na^+ and water reabsorption in collecting duct.
- Inhibits Renin and angiotensin II secretion. (thus↓ tubular reabsorption).
- Increases urinary excretion (to compensate for the excess blood volume).

3- ADH:

- ADH or vasopressin is a small protein hormone that has a fast-acting short half-life action.
- ADH is synthesized in the neuroendocrine cells located within the supraoptic and paraventricular nuclei of the hypothalamus.
- The hormone is packaged in vesicles and stored in the neurohypophysis or the posterior pituitary gland.



Renal Regulation of Body Fluids

3- ADH (continued):

ADH has two main functions:

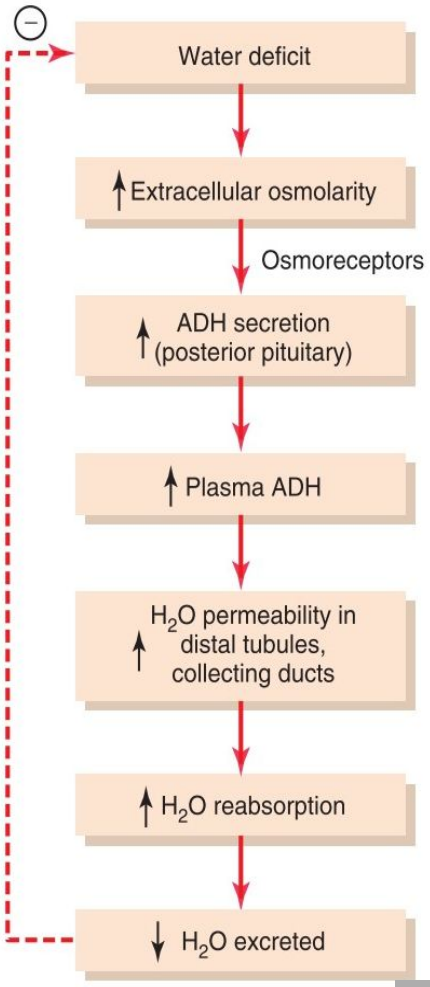
1. Water & urea reabsorption
2. Stimulate thirst centers, also thirst will stimulate secretion of ADH.

ADH release and thirst centers are influenced by the following:

1. ↑Plasma osmolality
2. Hemodynamic factors: 5-10% decrease in BP/BV

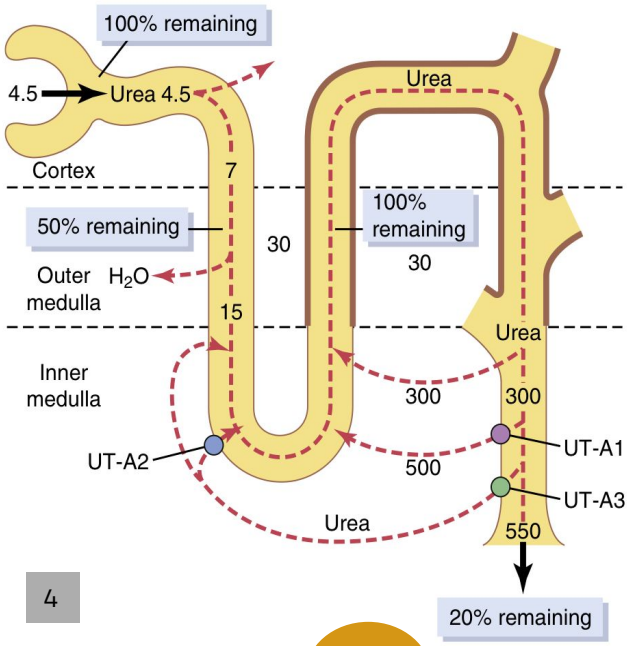
Osmoreceptor-ADH Feedback System

1. An increase in extracellular fluid osmolarity causes osmoreceptor cells, located in the anterior hypothalamus near the supraoptic nuclei, to shrink.
2. Shrinkage of the osmoreceptor cells causes them to fire and send nerve signals to additional nerve cells in the supraoptic nuclei, which then relay these signals down the stalk of the pituitary gland to the posterior pituitary.
3. This stimulates the release of ADH, which is stored in secretory granules (or vesicles) in the nerve endings.
4. ADH enters the bloodstream and is transported to the kidneys, where it increases the water permeability of the late distal tubules, cortical collecting tubules, and medullary collecting ducts.
5. The increased water permeability in the distal nephron segments causes increased water reabsorption and excretion of a small volume of concentrated urine.
6. Thus, the rate of ADH secretion determines whether the kidney excretes dilute or concentrated urine.



Renal Regulation of Body Fluids

Urea and ADH



1 **Proximal tubule:** 40-50% of filtered urea is reabsorbed. However, urea concentration increases because water is more permeable.

2 **Thin loop of Henle**: urea continues to rise because of A) water reabsorption and B) passive diffusion of urea inside from the medullary interstitium by urea transporter UT-A2.

3 **Thick loop of Henle, distal tubule, and cortical collecting tubule:** are all less permeable to urea. If ADH is high> reabsorption of water further raises urea concentration.

4 **Medullary collecting duct**: the A) high urea and B) UT-A1 and UT-A3 cause urea to diffuse into the medullary interstitium, part of it diffuses back into loop of henle (Step 2).

- This is called **Recirculation of urea**, it helps trap urea in the renal medulla and contributes to the hyperosmolarity of the renal medulla.

- When the kidney is forming concentrated urine, with high levels of ADH, reabsorption of water from the distal tubule and cortical collecting tubule further raises the tubular fluid concentration of urea.

- Rate of urea excretion is determined by:
1. Concentration of plasma urea.
2. GFR.
3. Renal tubular urea reabsorption.

Chemical Examination of the Urine

Proteinuria

- In healthy individuals, less than 150-200 mg of protein is excreted in the urine each day, as low molecular proteins get completely reabsorbed by receptors on tubular cells.
- The presence of large amounts of protein is usually indicative of significant renal disease.
- Proteinuria is usually asymptomatic and is often picked up by urinalysis, although large amounts of protein may make the urine frothy.

1) Prerenal proteinuria:

- Increase plasma protein levels that exceeds normal reabsorptive capacity of renal tubules.
- Example: Multiple Myeloma.

2) Renal proteinuria:

A. Glomerular Proteinuria

Causes filtration of high molecular weight proteins (e.g. glomerulonephritis).

B. Tubular Proteinuria

- Low tubular reabsorption with normal glomerular permeability.
- Causes excretion of low molecular proteins (e.g. chronic nephritis).

C. Orthostatic (Postural) Proteinuria

- Persistent benign proteinuria
- In these patients, typically less than 1 g/24 hrs of protein is excreted only in association with an upright posture.

3) Post-renal proteinuria:

- Proteins are added to the urine after kidney filtration while passing through the lower urinary tract.
- Due to: Lower urinary tract infection, trauma, tumors, stones.

Moderately elevated albuminuria (microalbuminuria)

The presence of of small amounts of albumin in the urine 20–200 mg/L.

Causes: Long term hyperglycemia (Patients with diabetes) and Hypertension.

Chemical Examination of the Urine

Choluria

the presence of bile pigments in the urine

1) Bilirubin and bile salt

Normally bilirubin is not detected in urine, bilirubin is detected in:

- Hepatocellular damage
- Obstruction of bile duct:
    - Extrahepatic (stone).
    - Intrahepatic (hepatic tumors).

2) Urobilinogen

Normally trace Urobilinogen is present in urine (5%)

High urobilinogen is found in:

- Hemolytic anemia.
- Hepatocellular damage.

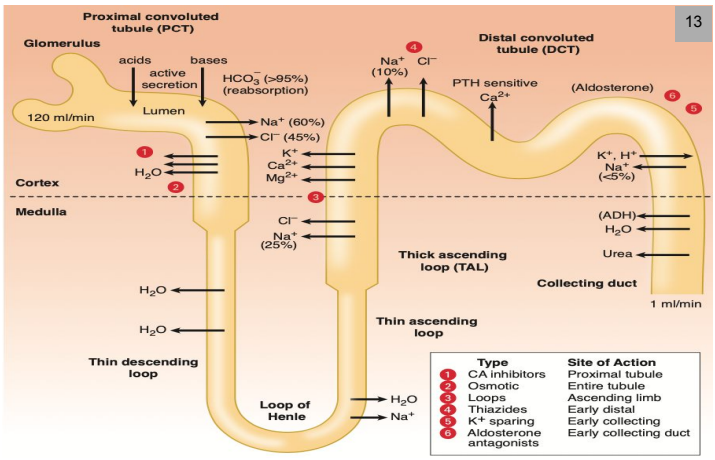
Pharmacology of Diuretics

Diuretics

Diuretics act on the kidney with the primary purpose of reducing blood volume by increasing the rate of urine excretion.
Reduction of blood volume leads to a decrease in BP.
Natriuresis: is the process of sodium excretion in water. All diuretics have natriuretic effect.
Uses: Edema, CHF, HTN, elimination of toxins.

Types of Diuretics

01 Osmotic Diuretics
02 Carbonic Anhydrase Inhibitors
03 Loop Diuretics
04 Thiazides
05 K -Sparing Agents



1.Osmotic Diuretics e.g. Mannitol	
Mechanism of action	**Increase kidney tubular fluid osmolarity**. The drug is filtered through the glomerulus into the kidney tubule, where it pulls water from the interstitial space into the tubules via osmosis. This process results in more water excreted into the urine and less water reabsorbed into the circulation. ↑water excretion with relatively less effect on Na^+ [aquaretic].
Site of action	In the kidney at the proximal tubule (site of major water reabsorption).
Clinical use	Rarely used for hypertension. More commonly used for Drug overdose, to decrease intracranial/ intraocular pressure before ophthalmic or brain procedures.
Adverse Effect	- Pulmonary edema, dehydration, hypo- or hypernatremia. - Contraindicated in anuria, HF.

Pharmacology of Diuretics

	2.Carbonic Anhydrase Inhibitors e.g. Acetazolamide	**3.Loop Diuretics** e.g. Furosemide, Ethacrynic Acid, Bumetanide
MOA	Inhibits carbonic anhydrase, thereby preventing the conversion of bicarbonate (HCO_3^-) into CO_2. This results in excretion of HCO_3^- with water into the urine causing alkaline urine. ↓ reabsorption of bicarbonate in the proximal tubule.	**Inhibit Na^+-K^+-$2Cl^-$ channel** thereby preventing Na^+ and K^+ reabsorption into the renal medulla, they abolish the hypertonicity of the medulla. This results in marked diuresis. They also increase Ca^{2+} excretion because they reduce the lumen positive potential in the loop of Henle.
Pharmacokinetics	Administered orally or intravenously. It is approximately 90% protein bound and eliminated renally by both active tubular secretion and passive reabsorption.	Administered orally or parenterally. Their duration of action is relatively brief (2 to 4 hours).↑renal blood flow. They are secreted into urine.
Site of action	Brush border of the proximal convoluted tubule.	Thick ascending limb of loop of Henle.
Clinical use	Rarely used for hypertension. More commonly used for metabolic alkalosis, altitude sickness, glaucoma, or intracranial hypertension (eg, due to pseudotumor cerebri).	The most efficacious diuretics, used for edema (CHF, cirrhosis, nephrotic syndrome, and pulmonary edema), moderate to severe hypertension, hypercalcemia, and hyperkalemia. (acute situations)
Adverse Effect	- Metabolic acidosis due to increased excretion of HCO_3^-/ Paresthesias/ NH^3 toxicity/Sulfa allergy/ Hypokalemia/ Promotes calcium phosphate stone formation (insoluble at high pH).	**O**totoxicity/ **H**ypokalemia/ **H**ypomagnesemia/ **D**ehydration/ **A**llergy (sulfa)/ metabolic **A**lkalosis/ **N**ephritis (interstitial)/ **G**out. **"OHH DAANG"** Hypocalcemia.

Pharmacology of Diuretics

	4. Thiazides e.g. Hydrochlorothiazide, Metolazone	**5. K -Sparing Agents** e.g. Spironolactone, Triamterene, Amiloride, and Eplerenone
MOA	**Inhibit Na^+-Cl^- symporter,** thereby blocking Na^+ and Cl^- reabsorption in the distal convoluted tubule. NaCl is excreted along with water into the urine. They also increase Ca^{2+} reabsorption.	**Spironolactone and eplerenone**: Competitive antagonists at the aldosterone receptor (indirectly inhibit Na^+ reabsorption). **Triamterene and amiloride**: Directly block Na^+ channels.
Pharmaco kinetics	Effective orally. Take 1-3 weeks to produce a stable reduction in blood pressure. Exhibit a prolonged half-life. Secreted by the organic acid secretory system of the kidney.	Well absorbed from the GIT Converted into active metabolite, t½=16. Highly protein-bound Undergoes enterohepatic recycling Delayed onset of action, maximum diuretic action 4 days.
Site of action	Early distal convoluted tubule.	Collecting tubule and **collecting duct.**
Clinical use	**First line** for moderate/mild hypertension; **mild** CHF, nephrogenic diabetes insipidus, nephrolithiasis secondary to idiopathic hypercalciuria, osteoporosis. Renal failure.	HTN in combination with more efficacious diuretics to prevent associated K^+ wasting. Increase survival in patients with CHF. Used to treat ascites in patients with cirrhosis. Treatment of primary (Conn's syndrome) and secondary hyperaldosteronism. The antiandrogen effect (spironolactone) is useful for treating hirsutism in polycystic ovarian syndrome. Renal failure.
Adverse Effect	Hyperglycemia/ hyperlipidemia/ hyperuricemia/ hypercalcemia/ sulfa allergy (hydrochlorothiazide)/ hypokalemia/ Metabolic alkalosis.	Hyperkalemia/ gynecomastia (Spironolactone).

Clinical Integration

Investigations

Urine Investigations

Microscopy
-Dysmorphic Erythrocytes.
-RBC casts.
-WBCcasts.
-Crystals.

Screening by Dipstick
-Blood.
-Protein.
-Glucose.
-Ketone.
-Nitrate.
-Leucocyte.
-Urine pH.
-Osmolality.

Glomerular Filtration Rate

Estimation of GFR
Requires knowledge of sex, age and serum creatinine level.

Direct Measurement
-Using labelled EDTA or insulin.
-Creatinine clearance (CrCl).

Biochemistry

1-Serum Cr
Maybe raised (causing reduced eGFR).

2-Serum Urea
↑: Kidney disease, protein intake, and GI bleeding.
↓: Chronic liver disease.

3-Urea:Cr
↑: Volume depletion and pre-renal failure.

4-Serum Bicarbonate
↓: Renal failure and renal tubular acidosis.

5-Serum Phosphate
↑: CKD.

6-Alkaline Phosphatase
↑: Renal osteodystrophy.

7-Serum Ca
↓: CKD

8-Albumin
↓: Liver disease.

Clinical Integration

Edema

Caused by: Excessive accumulation of fluid within the interstitial space.

Types

01

Pitting Edema

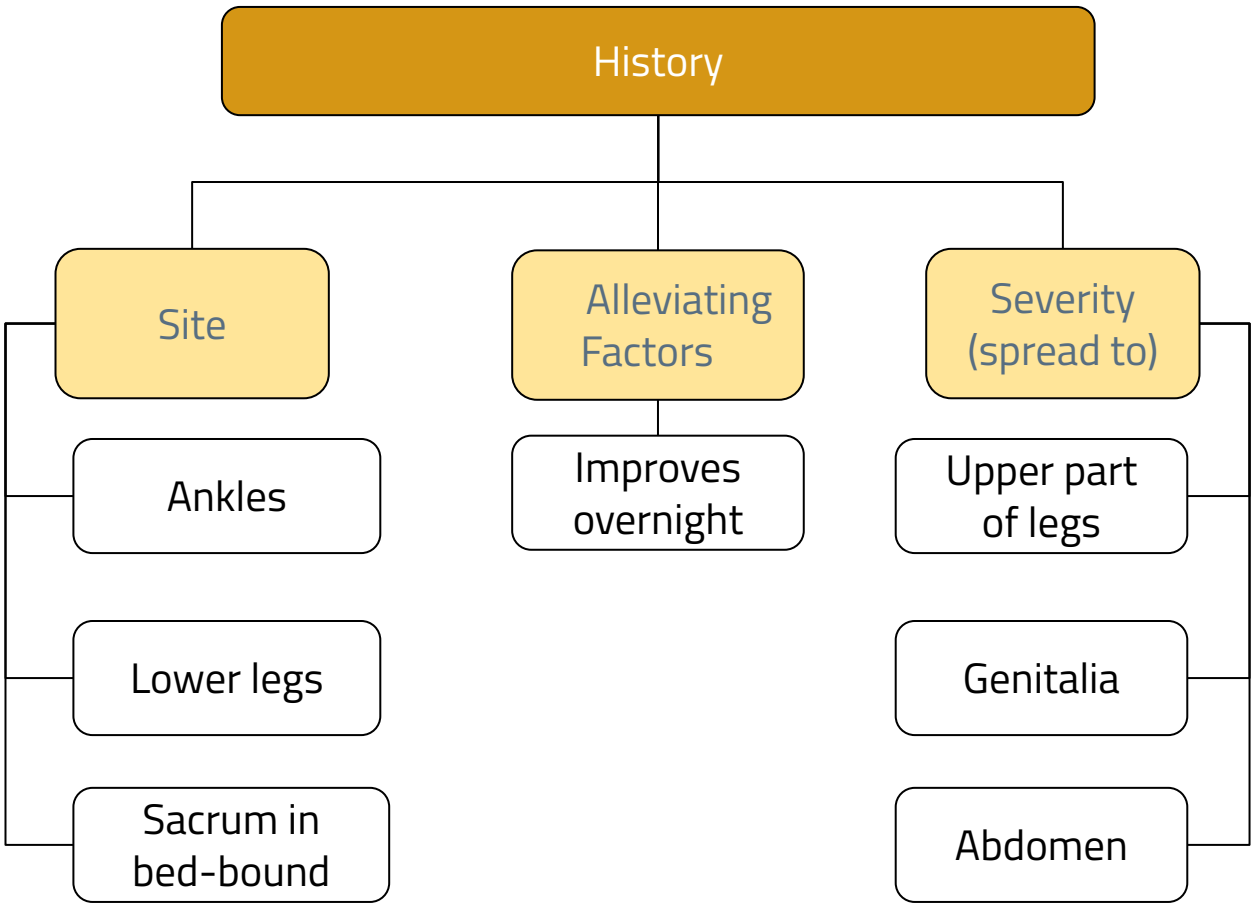
Applying pressure will leave a persistent indentation in tissue.

02

Non-pitting Edema

Lymphatic obstruction, hypothyroidism or systemic sclerosis.

History



Clinical Integration

Edema

- Features of intravascular depletion:
  Tachycardia and postural hypotension.

Due to decreased oncotic pressure or increased capillary permeability.

1.Lab tests

01 Urea and electrolytes.

02 Liver function test.

03 Serum albumin.

04 Protein in urine dipstick.

2.In case of ascites or pleural effusion:

01 **Aspirate for** Protein and glucose.

02 **Microscopy for** Cells to differentiate transudate from exudate.

3.Imaging of heart, kidney and liver

Management

01 Leg elevation, compression sockening, thiazide or low dose of loop diuretics. — Mild

Nephrotic, heart and renal failure — Large dose of diuretics, sodium and fluid restriction. 02

Clinical Integration

Hypertension

Definition

16.64 Definition of hypertension 11

Category	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Blood pressure		
Optimal	<120	<80
Normal	<130	85
High normal	130–139	85–89
Hypertension		
Grade 1 (mild)	140–159	90–99
Grade 2 (moderate)	160–179	100–109
Grade 3 (severe)	≥180	>110
Isolated systolic hypertension		
Grade 1	140–159	<90
Grade 2	≥160	<90

Cardiovascular risk associated with HTN, depends on

1. Age & gender.
2. Weight & physical activity.
3. Smoking.
4. Family history.
5. Cholesterol.
6. DM.
7. Pre-existing vascular disease.

Pathogenesis

- Renal dysfunction.
- Peripheral resistance.
- Vessel tone.
- Endothelial dysfunction.
- Autonomic tone.
- Insulin resistance.
- Neurohumoral factors.
- Environmental factors: smoking, high salt intake alcohol and obesity.

Clinical features

Asymptomatic until the diagnosis is made at a routine physical examination or when a complication arises.

Complications

1-Left ventricular failure.

2-Aortic aneurysm, PAD, or stroke.

3-'Cotton wool' exudates (associated with retinal ischaemia or infarction).

4-Central retinal vein thrombosis.

Clinical Integration

Blood Pressure Target

16.71 Optimal target blood pressures[1]

Age	Clinic BP (mmHg)	Ambulatory or home BP (mmHg)[2]
<80 years	<140/90	<135/85
≥80 years	<150/90	<140/85

[1]Both systolic and diastolic values should be attained. [2]Average BP during waking hours.

11

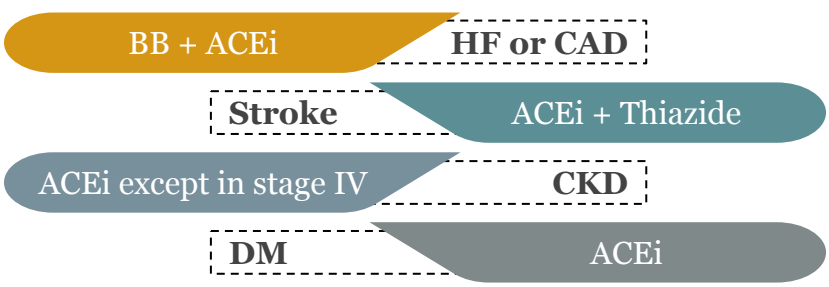
Lifestyle Modifications (LSM)

- Diet: <2.4g NaCl/day, DASH diet.
- Exercise: 30 min/day.
- Weight loss.
- Alcohol cessation.

Treatment

	Systolic BP	Diastolic BP	Tx
Normal	<120	<80	-Follow up/year.
Elevated BP	<130	<80	-LSM. -Follow up in 6m.
Stage I	<140	<90	-LSM -If risk CAD: start meds. -Follow up in 1m.
Stage II	>140	>90	-2 meds. -Follow up in 1m.
Urgency HTN Crisis	220	120	-IV meds -> oral.
Emergent HTN Crisis	220	120	-End organ damage (altered mental status, SOB, CP, ↑troponin). - ICU

Medications



If only HTN use any of the medications: thiazide, ACEi or CCB.

Diabetes Insipidus

Clinical Features

- Polyuria.
- Polydipsia.

Investigation

- Serum vasopressin is undetectable.
- Urine is not maximally concentrated (i.e. < 600 mmol/kg) in the presence of increased plasma osmolality (i.e. > 300 mOsmol/kg).
- Water deprivation test.
- Infuse hypertonic (5%) saline and measure vasopressin secretion in response to increasing plasma osmolality.

Management

- Central DI: des-amino-desaspartate-arginine vasopressin (desmopressin, DDAVP), an analogue of vasopressin.
- Nephrogenic DI: thiazide diuretics, amiloride and NSAIDs.

Polyuria

Investigation

- Urea.
- Cr.
- Electrolytes.
- Glucose
- Ca.
- Albumin.
- 24hr urine collection.

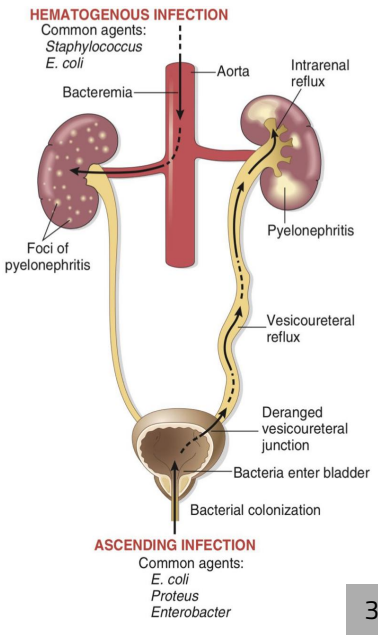
Infection of The Upper Urinary Tract

Acute Pyelonephritis

It's a common suppurative inflammation of the kidney and the renal pelvis, caused by bacterial infection.
It's an important Manifestation of urinary tract infection (UTI) which can involve the lower or upper urinary tract, the majority of cases of Pyelonephritis are associated with infections of the lower urinary tract .

Predisposing factors:

1- Urethral instrumentation (catheterization and cystoscopy).
2- Females are mostly affected because of the close proximity of the urethra to the rectum and the short urethra.
3- outflow obstructions or bladder dysfunction.
4- diabetes mellitus.
5- pregnancy.



Pathogenesis:

The principal causative organisms are gram negative bacilli, most commonly E.coli . Other important organisms are proteus, Klebsiella, Enterobacter and Pseudomonas.
Bacteria can reach the kidney from:
1- **Ascending infection** from the lower urinary tract (most frequent).
2- **Hematogenous infection** (through bloodstream).

Morphology:

One or both kidneys may be involved. Normal in size or enlarged. Yellowish abscesses on the renal surface.
Histologic features: liquefactive necrosis and abscess formation.

Clinical features:

- Chills, fever, nausea, and malaise.
- Dysuria, frequency, and urgency.
- Pyuria and hematuria.

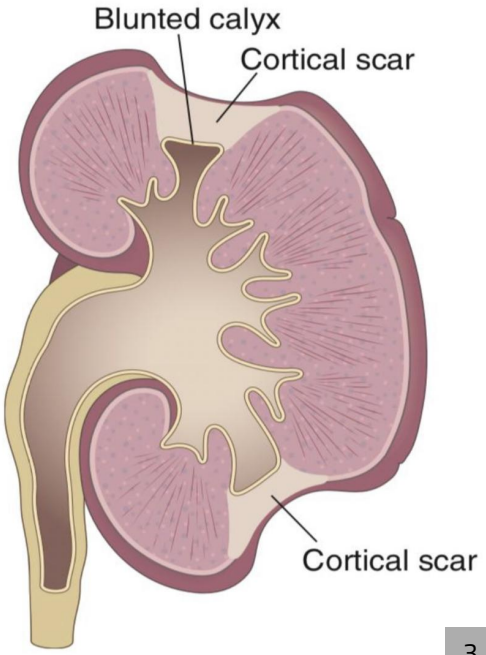
Chronic Pyelonephritis

It's when the interstitial inflammation and scarring of the renal parenchyma are associated with grossly visible scarring and deformity of the pelvicalyceal system as a result of recurrent or inadequately treated episodes of acute pyelonephritis.

It can be divided into two forms:
1- chronic obstructive pyelonephritis.
2- chronic reflux associated pyelonephritis (reflux nephropathy).

Morphology:

One or more kidney can be involved, uneven scarring, scarring involves the pelvis or calyces
Microscopic:
- Interstitial **fibrosis** and **inflammatory** infiltrate (**lymphocytes** & plasma cells)
- Tubules with atrophy of epithelial lining, colloid casts, Thyroidization (**thyroid**-like appearance).



Clinical features:

- Hypertension.
- Imaging shows: asymmetric **contracted** kidneys.

Drug induced tubulointerstitial nephritis

Its an **IgE and T cell mediated immune reaction** to a **drug**, it is characterised by interstitial inflammation, often with abundant eosinophils and edema.

Clinical features:

- Disease begins 15 days after exposure to the drug. (**penicillin or rifampicin**)
- Characterised by: fever, eosinophilia, rash, renal abnormalities.
- Hematuria, high serum creatinine, oliguria.

Management of UTI

- Each symptomatic episode of acute cystitis should be evaluated first with a **urinalysis and urine culture with sensitivity prior to treating with antibiotics**.
- The combination of clinical findings and urine evaluation is essential for diagnosis of UTI.
- Treatment is based upon **pathogen identification** and the **type** and **degree of clinical illness**, as well as the **presence or absence of predisposing host factors**.
- In general, the treatment consists of hydration, relief of urinary tract obstruction if present, removal of foreign body or catheter if feasible, and use of antibiotics.
- The type and duration of antibiotic treatment is dependent on: **site of infection** (pyelonephritis, cystitis, prostatitis, epididymitis, orchitis), **host factors**, and **severity of illness.**
- When considering treatment, first determine whether the UTI is complicated or uncomplicated in nature.

Uncomplicated	Complicated
• include acute cystitis in a non-pregnant, premenopausal female, and acute pyelonephritis in an otherwise healthy patient. • Young post–pubertal females are susceptible to uncomplicated UTIs because of sexual intercourse in combination with delayed post–coital bladder emptying.	• occur when certain predisposing factors are present, but in general should be considered in: ○ pregnant or post-menopausal females and men. • Patients with complicated UTIs are more likely to have medical comorbidities or conditions which require special consideration. • In addition, they may have a greater variety of pathogenic bacteria, more drug resistance, and require a longer duration of antibiotic therapy.

Management of UTI

Common Causative Pathogens in Adult UTIs:

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

Recurrent UTI:

Recurrent UTI is defined as 2 or more infection in a 6-month period or ≥ 3 culture proven infections in 12 months. Both re–infection and relapsing infection contribute to the development of recurrent UTIs.

Catheter associated UTI (CAUTI):

Patients with indwelling urethral catheter will universally develop bacteriuria over time; 10–25% of these will develops symptoms.
Risk factors included: female gender, elderly, DM, error in catheter care and bacterial colonization of the drainage bag.

Management of UTI

1 Co-trimoxazole (TMP-SMX) Trade names: Bactrim and septra

Drug	Sulfamethoxazole	Trimethoprim
Overview	• Inhibit gram-ve & gram+ve bacteria • Alone, each drug is **bacteriostatic** but together they are **bactericidal** (synergism).	
MOA	• Both drugs stop folic acid production in microorganisms. (folic acid is required for synthesis of coenzymes important for enzymes that catalyze purines and pyrimidines synthesis and cell cannot divide in their absence). • in microorganisms: PABA (para aminobenzoic acid) is turned into dihydrofolic acid by dihydropteroate synthetase **(SMX disturbs this step)**. • dihydrofolic acid is turned into tetrahydro folic acid by dihydrofolate reductase MOA **(TMP inhibits this enzyme).**	

ADRs	• **GIT**: Nausea and vomiting.
	• **Allergy**.
	• **Hematologic**:
	  ○ Acute hemolytic anemia, caused by:
	  ■ Hypersensitivity,
	  ■ G6PD deficiency.
	  ○ Megaloblastic anemia (in TMP).	

Drug interactions	• Displace bilirubin (from plasma proteins) ○ if severe; leads to kernicterus (Drug Interactions bilirubin encephalopathy). • Potentiate warfarin and sulfonylurea hypoglycemics.	
Contraindication	• Pregnancy and Breastfeeding. • Infants under 6 weeks. • Renal or hepatic failure. • Blood disorders.	

Management of UTI

2 Nitrofurantoins

Drug	Nitrofurantoins
Antibacterial spectrum	• Bactericidal for gram -ve & gram +ve bacteria. • Effective against **E.coli** & Staph. Saprophyticus. • Other common UT gram -ve bacteria may be resistant.
MOA	Sensitive bacteria reduce the drug to an active agent (by bacterial reductase) that inhibits various enzymes and damages DNA.
PK	• 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 turns to dark orange-brown (harmless).**
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.

ADRs	• GI disturbances: (Must be taken with food)
	  ○ Bleeding of the stomach
	  ○ Nausea
	  ○ Vomiting
	  ○ Diarrhea
	• Headache & Nystagmus.
	• **Hemolytic anemia (G6PD Deficiency).**

Contraindication	• Patients with G6PD deficiency → Anemia. • Neonates. • Pregnant women. (after 38 weeks of pregnancy)

Management of UTI

3 Tetracyclines

Drug	Doxycycline
MAO	• Bacteriostatic, **inhibits protein synthesis** by binding reversibly to 30s ribosomal subunit. • Against **gram +ve & gram -ve bacteria.**
Pharmacokinetics	• Long acting • Usually given orally. • Absorption is 90-100%. In the upper small intestine. • Food, divalent & trivalent cations (Ca, Mg, Fe, AL) impair absorption and reduce effectiveness. • Protein binding 40-80%. • Distributed well, including CSF. • Cross placenta and excreted in milk. • Largely metabolized in the liver.
Therapeutic uses	• Treatment of UTIs due to gram -ve & gram +ve bacteria including Mycoplasma & Chlamydia. • Prostatitis.
ADRs	• GIT: Nausea, vomiting, diarrhea, and epigastric pain (give with food). • Thrombophlebitis – I.V. • Hepatic toxicity (prolonged with high dose). • Brown discolouration of teeth (children). • Deformity or growth inhibition of bones (children). • Phototoxicity. (sensitivity to sunlight) • Vertigo. • Superinfections (broad spectrum alters flora)
Contraindication	• Pregnancy and Breast feeding. • Children (below 10 yrs) it binds to Calcium.

Management of UTI

4 Aminoglycoside

Drug	Gentamicin
MAO	• **Inhibit protein synthesis** by binding to 30S ribosomal subunits (irreversibly). • **Bactericidal,** only effective against **gram -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.
Therapeutic uses	• Severe infections caused by **gram -ve** organism (pseudomonas or enterobacter). Also combined with other antibiotics.
ADRs	• Ototoxicity (damage in vestibular nerve) • Nephrotoxicity. • Neuromuscular blocking effect.

5 Fluoroquinolones

Drug	ciprofloxacin
MAO	• Inhibits DNA gyrase enzyme and cell division resulting in bacterial cell death. • Active against **gram -ve** aerobic organisms.
Therapeutic uses	• UTIs by multidrug-resistance organisms (pseudomonas). • Prostatitis (acute/chronic).
ADRs	• GIT: Nausea, vomiting, and diarrhea • CNS: Confusion, insomnia, headache and anxiety. • Damage of growing cartilage (reversible arthropathy). • Phototoxicity (avoid excessive sunlight).

Management of UTI

6 Cephalosporins

Drug	Ceftriaxone & Ceftazidime
MAO	• Acts by inhibition of **cell wall synthesis.** • **Bactericidal**. • Mainly effective against **gram -ve bacteria.**
PK	They are given parenterally.
Therapeutic uses	• Given in severe / complicated UTIs . • Given in acute prostatitis.
ADRs	• Hypersensitivity reactions. • Thrombophlebitis • Superinfections. • Diarrhea.

Clinical integration

Examination:

Murphy's kidney punch: Bony tenderness is elicited by striking the patient's gently in the renal angle (costovertebral angle) (shown in the picture), this is a sign of renal infection.

*Talley

Investigation:

	men	women	both
Pyelonephritis	Rectal examination	Pelvic examination	Renal tract US and CT scan

Acid & Base

Objectives:

Basics of Acid base:

- Define: acid and base.
- Explain what is meant by strong and weak acids and bases
- List and identify the names/formulas for the common strong acids and strong bases.
- To explain the role of Henderson-Hasselbalch equation in acid-base regulation

Buffer system:

- define buffer system and discuss the role of blood buffers and to explain their relevant roles in
  the body
- describe the role of kidneys in the regulation of acid-base balance
- describe the role of lungs in the regulation of acid-base balance
  Introduction/Background:

Acid base disorders :

- explain the principles of blood gas and acid-base analysis
- interpret blood gas analysis and diagnose various acid base disorders
- describe causes of acid base disorders
- understand use of acid base nomograms

Basics of Acid-Base

Acid:
A molecule that **releases** H^+ in a solution

- Carbonic Acid (H_2CO_3)
- Hydrochloric Acid (HCL)

Base:
a molecule that **accepts** H^+ in a solution.

- Bicarbonate (HCO_3^-)
- Hydrogen phosphate (HPO_4^{-2})

Strong Acids dissociate all their H^+ when dissolved in H_2O.

Strong bases dissociate easily in H_2O and quickly bind to H^+

Weak Acids & Bases

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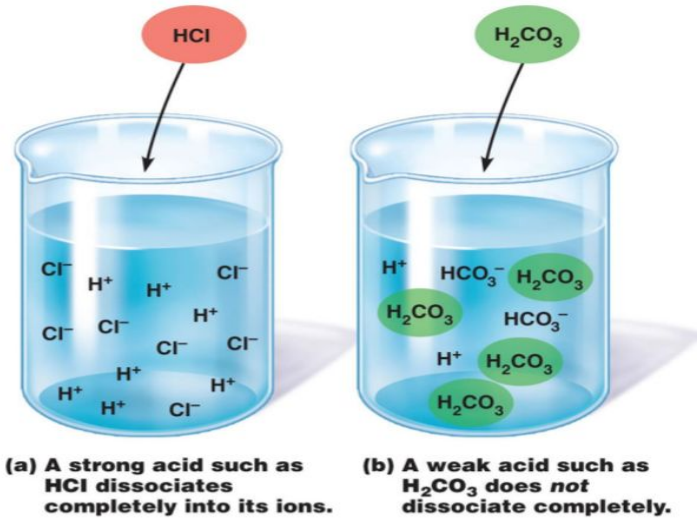


(a) A strong acid such as HCl dissociates completely into its ions.

(b) A weak acid such as H_2CO_3 does *not* dissociate completely.

- Dissociation constant (K): The extent to which a given acid dissociates in solution is constant.

$$K = \frac{[H^+][A^-]}{[AH]}$$

- H^+ ion concentrations are expressed as pH.
- pH = -log $[H^+]$
  - ↑ In $[H^+]$ → ↓ in pH (more acidic).
  - ↓ In $[H^+]$ → ↑ in pH (more alkaline).
- Normal pH=7.35-7.45

Buffering systems

Definitions

- **Buffer**: a solution that resists the change in pH when acids or bases are added to it, in order to keep the pH constant.
- There are 3 main types.
  - Chemical buffers: Bicarbonate, Phosphate, and proteins (1st line of defense).
  - Lungs (act within minutes).
  - Kidneys (within days, most powerful).

The Henderson-Hasselbalch Equation

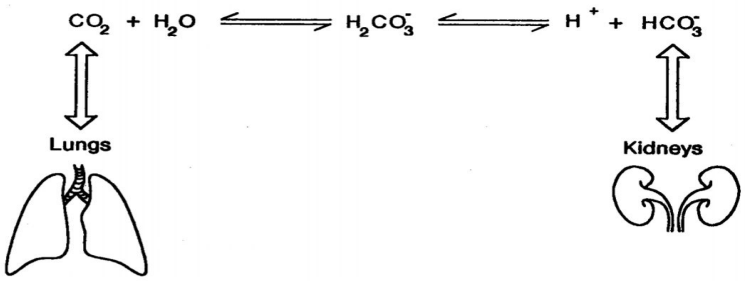
- It is an equation that enables the calculation of pH of a solution, where pH is directly correlated to HCO_3^-, and inversely correlated to CO_2. Also called Dissociation constant (K).
- The extent to which a given acid dissociates in solution is constant.

$$K = \frac{[H^+][A^-]}{[AH]}$$

Carbonic acid "weak acid"

$$H_2CO_3 \leftrightharpoons HCO_3^- + H^+ \longrightarrow K = \frac{[H^+][HCO_3^-]}{[H_2CO_3]}$$

Bicarbonate buffer system



Lung buffer system

- Works by modulating CO_2 excretion
- ↑ In $[H^+]$ → ↑ in respiratory rate → ↓ PCO_2.
- ↓ In $[H^+]$ → ↓ in RR → ↑ PCO_2.

Buffering systems

Renal Buffer system

- Works by either excreting acidic or alkaline urine.

To excrete acidic urine

1. Freely filter HCO_3^-
2. Reabsorb the majority of filtered HCO_3^-
3. Reabsorb some additional HCO_3^-
4. Secrete H^+ and NH_4^+
5. Excrete acidic urine containing NH_4^+

To excrete alkaline urine

1. Freely filter HCO_3^-
2. Reabsorb the majority of filtered HCO_3^-
3. Reabsorb some additional HCO_3^-
4. Secrete some HCO_3^-
5. Excrete alkaline urine containing HCO_3^-

Acid-Base Disorders

- Acid-base disorders are a group of conditions characterized by changes in the concentration of hydrogen ions (**H^+**) or bicarbonate (**HCO_3^-**), which lead to changes in the arterial blood pH.
- These conditions can be categorized as **acidosis** or **alkalosis** and have a **respiratory** or **metabolic** origin, depending on the cause of the imbalance.
- Normally, the body attempts to correct the disturbance by a compensatory response:
    - The lungs compensate for primary **metabolic** disorders.
    - The kidneys compensate for both primary **metabolic** and **respiratory** disorders.

01 Respiratory Acidosis:

- It occurs as a result of **decreased** ventilation and **increased** PCO_2.
- Causes include:
    - Inhibition of medullary respiratory center by drugs (e.g. opiates, sedatives, anesthetics), CNS tumors, trauma or CNS hypoxia.
    - Weakness/ paralysis of respiratory muscles by multiple sclerosis, myasthenia gravis, scoliosis or certain myopathies.
    - Decreased CO_2 exchange like in COPD.
    - Airway obstruction.

02 Respiratory Alkalosis:

- It occurs as a result of **increased** ventilation and **decreased** PCO_2.
- Causes can be:
    - Central (e.g .head trauma, stroke, or anxiety).
    - Pulmonary (e.g. pulmonary embolism, asthma, pneumonia, or high altitude).
    - Iatrogenic (e.g. increased respiratory rate on a ventilator).

Acid-Base Disorders

03 Metabolic Acidosis:

- It occurs as a result from **decreased** concentration of extracellular fluid HCO_3^-, either by loss of HCO_3^- or gain of H^+.
- General causes include:
  - Failure of the kidneys to excrete acids normally formed in the body.
  - Excess formation of acids in the body.
  - Ingestion or infusion of acids into the body.
  - Loss of base from the body fluids.
- Conditions that may lead to metabolic acidosis can be differentiated by the **anion gap**.

$$\text{Unmeasured serum anion} = [Na^+] - ([HCO_3^-] + [Cl^-])$$

Normal range is (10-12 mEq/L)

	Normal Anion Gap (Hyperchloremic Acidosis)	Greater than Normal Anion Gap
Meaning	Indicates that the concentration of Cl^- is increased to compensate for the loss of HCO_3^-	Indicates the presence of an unexpected unmeasured serum anion (e.g. lactate in lactic acidosis). In this situation the unmeasured serum anion is increased to compensate for the loss of HCO_3^-
Causes	**HARDUP:** • **H**yperalimentation • **A**cetazolamide • **R**enal tubular acidosis • **D**iarrhea • **U**reteroenteric shunt • **P**ancreatic fistula	**MUDPILES:** • **M**ethanol • **U**remia • **D**iabetic ketoacidosis • **P**henformin, **p**araldehyde • **I**soniazid, **i**nfection, **i**ron • **L**actic acidosis • **E**thylene glycol, **e**thanol • **S**alicylate

Acid-Base Disorders

04 Metabolic Alkalosis:

- It occurs as a result of **increased** concentration of extracellular fluid HCO_3^- ethir by excess retention of HCO_3^- or loss of H^+ from the body.
- Causes include:
  - Diuretics (except for carbonic anhydrase inhibitors).
  - Hyperaldosteronism.
  - Vomiting.
  - Ingestion of alkaline drugs (e.g. sodium bicarbonate for peptic ulcers).

Summary:

	PH	PCO_2	HCO_3^-
Normal Values	7.4	40	24
Respiratory Acidosis	↓	↑ (Primary Disturbance)	↑ (Compensation)
Respiratory Alkalosis	↑	↓ (Primary Disturbance)	↓ (Compensation)
Metabolic Acidosis	↓	↓ (Compensation)	↓ (Primary disturbance)
Metabolic Alkalosis	↑	↑ (Compensation)	↑ (Primary disturbance)

Interpretation of Acid-Base Disturbance

- Acid-base disorders can be diagnosed by analyzing 3 measurements of arterial blood gases: **PH**, **PCO_2** and **HCO_3^-**.
- To reach the right diagnosi:

1. Evaluate blood PH; to determine if the disorder is acidosis or alkalosis.
   - pH **<** 7.4 (acidemia).
   - pH **>** 7.4 (alkalemia).
2. Evaluate PCO_2; to determine the origin of the primary acid-base disorder.
   - PH and PCO_2 change in the **opposite** direction: respiratory disorder.
   - PCO_2 and pH change in the **same** direction: metabolic disorder.
3. Evaluate HCO_3^-
   - High: metabolic alkalosis or compensated respiratory acidosis.
   - Normal: uncompensated respiratory disorders.
   - Low: metabolic acidosis or compensated respiratory alkalosis.

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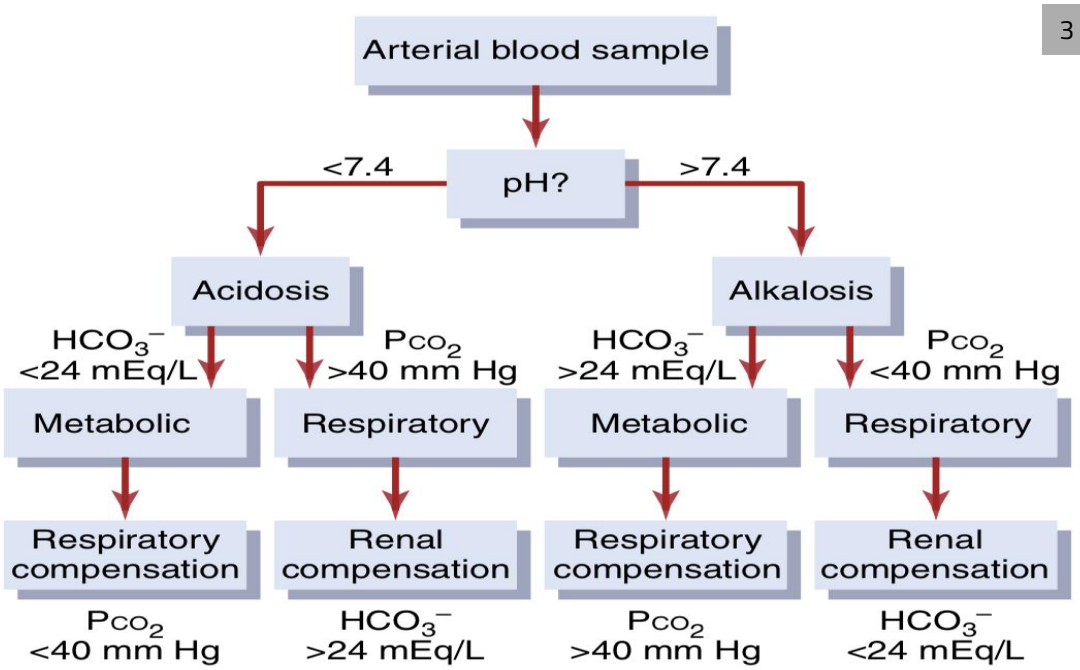
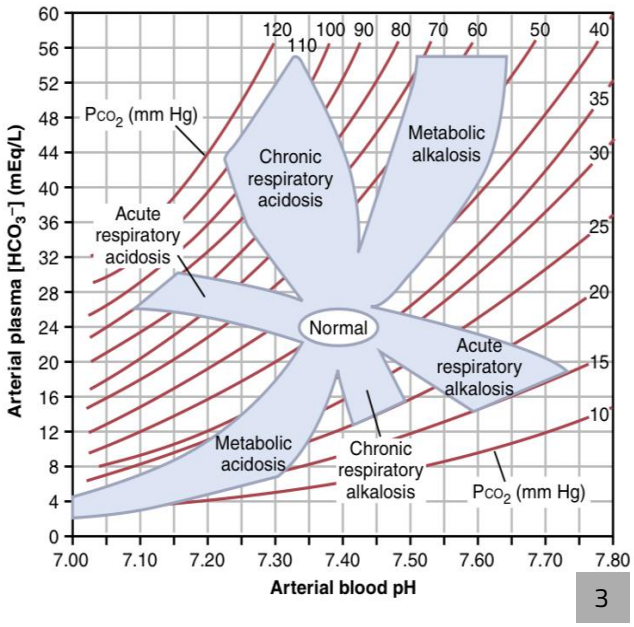


Mixed Acid-Base Disorders

- In some cases, when there is no appropriate compensatory response the abnormality will be referred to as **mixed** acid-base disorder. This means that we have **2 or more** underlying causes for the acid base disturbance.
- For example, a patient with a **low PH** and **low HCO_3^-** plasma concentration, after appropriate respiratory compensation, we should see a low PCO_2. However, if we see **elevated PCO_2**, one would suspect a respiratory component to the acidosis, as well as a metabolic component. Therefore, this disorder would be categorized as a mixed acidosis.
- A great way to diagnose such conditions is to use an acid-base **nomogram**.

Nomogram:



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- The central open circle shows normal values.
- If a value is within the shaded area, this suggests that there is a simple acid–base disturbance.
- if the values for PH, HCO_3^- or PCO_2 lie outside the shaded area, this suggests that the patient may have a mixed acid–base disorder.

- This diagram can be used to determine the **type** of acidosis or alkalosis, as well as its **severity**.
- When using this diagram, you must assume that sufficient time has passed for a full compensatory response, which is **6-12 hours** for lung compensation in primary **metabolic** disorders and **3-5 days** for the kidney compensation in primary **respiratory** disorders.
- It is important to understand that an acid–base value within the shaded area does **not always** mean that a simple acid–base disorder is present.

Clinical integration

Five steps of Acid-Base Analysis:

1 **Step 1:** Acidemia (pH <7.38) or alkalemia (pH >7.42)?

2 **Step 2:** Primary respiratory or metabolic disturbance? (Look at PCO_2 and pH)

> if pH and PCO_2 going in **same** direction? **Metabolic**
> if pH and PCO_2 going in **different** direction? **Respiratory**

3 **Step 3:** Is there appropriate compensation for the primary disorder?

Metabolic acidosis: $PCO_2 = [1.5 \times (\text{serum } HCO_3)] + 8 (\pm 2)$
Metabolic alkalosis: $\uparrow PCO_2 = 0.6 \times \uparrow HCO_3 (\pm 2)$
Respiratory acidosis: $\uparrow PCO_2$ 10, $\uparrow HCO_3$ by 1 (acute) or 4 (chronic)
Respiratory alkalosis: $\downarrow PCO_2$ 10, $\downarrow HCO_3$ by 2 (acute) or 5 (chronic)

After checking the primary disorder now I want to know is it compensated or is there another disorder? In this step the PCO_2 that I calculate is the expected, after that I compare it with the patient results, if it's the same or in the range (±2) that means it is compensated. If not then the patient has primary acid base disorder in respiratory.

4 **Step 4:** Is there an anion gap metabolic acidosis (AGMA)?
AG = Na - (HCO_3 + Cl). If > 12, an AGMA is present.

5 **Step 5: If metabolic acidosis**, is there another concomitant metabolic disturbance?

1-If AGMA, then calculate ΔGap = ΔAG – Δ HCO_3 = (AG -12) – (24 – HCO_3)
If the ΔGap is > 6, there is a combined AGMA and metabolic alkalosis.
If the ΔGap is < -6, there is a combined AGMA and NAGMA.
If between -6 and 6 there is no combined

2- If NAGMA, for every 1 mEq/L ↑Cl, there should be a 1 mEq/L ↓ HCO_3 (+5).
If HCO3 decrease is less than predicted, then NAGMA and metabolic alkalosis.

*AGMA = anion gap metabolic acidosis
NAGMA = normal anion gap metabolic acidosis

Clinical integration

❖ What are the body's defense mechanisms against changes in blood pH?

There are 3 main systems:

1. Body fluid buffers: Works within seconds by combining with an acid or a base to prevent excessive changes in H^+ concentration.
2. 2. Lungs: Works within minutes by regulating the removal of CO_2 (and, therefore, H_2CO_3) from the extracellular fluid.
3. 3. Kidneys: Works within hours-days by excreting acidic or alkaline urine, thereby readjusting the extracellular fluid H^+ concentration toward normal during acidosis or alkalosis. It is the most powerful of the 3.

Introduction to The Lower Urinary Tract

Objectives

Embryology:

- Identify the embryological origin of ureters.
- Describe the development of collecting & excretory parts of permanent kidney.
- Describe the cloaca and the formation of the urogenital sinus.
- Discuss the division of the urogenital sinus into various parts and name the adult organs that are derived from each part.
- Discuss the position of the urachus and its significance and fate.
- Describe the anomalies concerned with the urinary bladder and urethra.

Anatomy:

- course of ureter & identify the site of ureteric constrictions.
- identify certain areas in the base of urinary bladder.
- Differentiate between male & female urethra regarding length, structure, course & function.
- Describe the blood supply, nerve supply and lymphatic drainage of urinary bladder & urethra.

Histology:

- Describe the microscopic structures of the wall of ureter, urinary bladder and the male and female urethra.
- Define micturition.

Physiology:

- Identify and describe the functional anatomy of the urinary bladder.
- Describe the neural control of the urinary bladder and sphincters.
- Describe the mechanism of filling and emptying of the urinary bladder.
- Cystometrogram.
- Explain the neurogenic control of the micturition reflex and its disorders.

Embryology

Embryological origin of ureters:

At the 3rd week: the intermediate mesoderm originate from embryonic mesoderm (one of three germ layers) through process called **gastrulation**.
Embryonic mesoderm Differentiates into 3 parts (Paraxial mesoderm, intermediate mesoderm, lateral mesoderm).
The Intermediate mesoderm where the Kidneys and ureters arise.

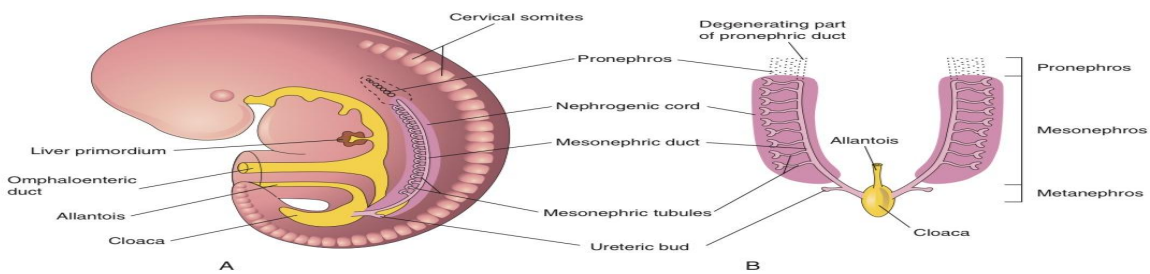
Formation of ureteric bud and its derivatives:

At the 5th week the Metanephric system appears and forms two parts.

Ureteric Bud originate from the end of **mesonephric duct** near its entrance into the cloaca. which gives Collecting part of kidney (ureter, pelvises, calyces, collecting ducts). It's fully canalized by week 10 of development.

during this it will interact with Metanephric mesenchyme (metanephric blastema) which is the second part and gives Excretory part of kidney (differentiation and formation of glomerulus).

As the ureteric bud elongates, it penetrates the metanephric blastema, and the stalk of the ureteric bud becomes the ureter.
The cranial part of the bud undergoes repetitive branching, which differentiate into the collecting tubules of the metanephros.



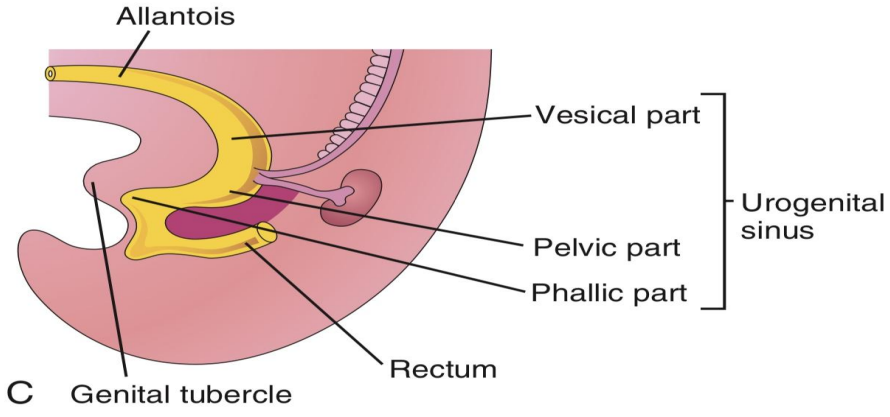
Reference:More KL (2002). The Developing Human. Philadelphia: Saunders WB.

Division of cloaca and the formation of the urogenital sinus:

- Cloaca is the expanded terminal part of the hindgut, it's an endoderm-lined chamber that is in contact with the surface ectoderm at the cloacal membrane. Cloaca receives the allantois and mesonephric ducts ventrally. The cloaca is divided into 2 parts dorsal and ventral by a urorectal septum forming these two parts the urogenital sinus (Ventral part) and anorectal canal (Dorsal part).

Division of the urogenital sinus into various parts and derivatives of each part:

Vesical part	the upper part that forms most of the urinary bladder and is continuous with the allantois.
Pelvic part	the middle part that becomes the urethra in the neck of the bladder, the prostatic part of the urethra in males, and the entire urethra in females.
Phallic part	The Lower part that grows toward the genital tubercle.



Reference:More KL (2002). The Developing Human. Philadelphia: Saunders WB.

Embryology

Urachus and its significance and fate:

At the beginning the allantois is connected with bladder then it's thickened forming thick fibrous cord called urachus .It extends from the apex of the bladder to the umbilicus.

After birth the urachus becomes the **median umbilical ligament.**

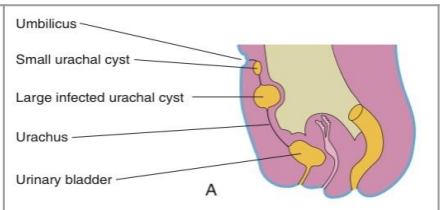
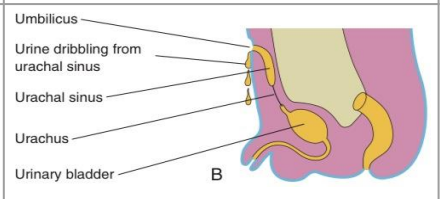
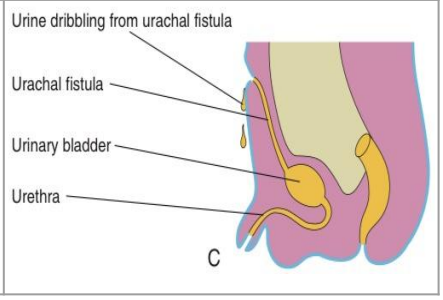
Exstrophy of the bladder:

Exstrophy (eversion) of the bladder usually occurs in males, it is a deficiency of the anterior abdominal wall, is caused by incomplete median closure of the inferior part of the wall.

This defect is characterised by the exposure and protrusion of the posterior wall of the bladder (The trigone and the ureteric orifices).

Urachal Anomalies:

In infants, a remnant of the urachal lumen may persist in the inferior part of the urachus. the lumen is continuous with the cavity of the bladder.

urachal cysts	Remnants of the epithelial lining of the urachus.	
urachal sinus	The patent inferior end of the urachus may dilate.	
urachal fistula	entire urachus remains patent and that allows urine to escape from its umbilical orifice.	

Reference:More KL (2002). The Developing Human. Philadelphia: Saunders WB.

Anatomy (ureters,bladder,urethra)

Ureters:

The ureters are muscular tubes considered as continuation of renal pelvis.
Ureters take urine that filtered in the kidney to bladder.
Course:

- Abdomen: descends retroperitoneally posterior to gonadal arteries, anterior to the end of common iliac artery (at bifurcation) to enter pelvis.
- Pelvic: Runs downward & backward to the level of ischial spine until it reaches posterolateral angle of the bladder. It courses obliquely through the detrusor muscle.

Constrictions of ureters:

There are 3 site of ureteral obstruction along their course to the bladder:

ureteropelvic junction	Between renal pelvis and ureters.
pelvic inlet	The ureters cross the end of common iliac vessels.
ureterovesical junction	Ureters enter the bladder at posterolateral angle.

Urinary bladder:

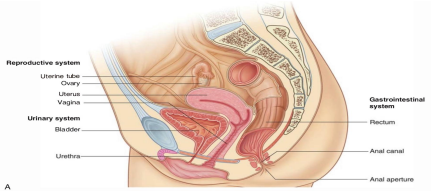
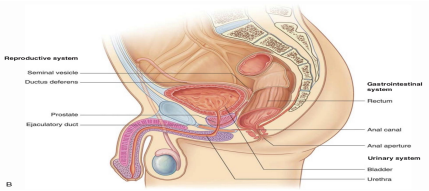
Site: It is pelvic organ. That has the shape of 3-sided pyramid placed on one of its angle (neck).

- Apex: Directed toward the upper border of the pubic symphysis. Connected to the umbilicus by median umbilical ligament,
- Base: Directed posteroinferiorly. Shaped like an inverted triangle.
- Superior surface and Infero-lateral surface.
- Neck: most inferior part of the bladder. Connects to urethra and pubic bone with pubovesical ligaments in females and puboprostatic ligament.

The smooth triangular area in base of bladder between the openings of the ureters and urethra on the inside of the bladder is known as the **trigone**.

Anatomy (ureters,bladder,urethra)

Differences between male and female urethra:

	Female	Male
Length	Short (4cm)	Long (20cm)
Structure	one part	three parts
Course	Curved	Nearly straight
Function	only urinary	urinary and reproductive
Reference:Drake RL, Vogl W and Mitchell AWM . Gray's Anatomy for Students. Philadelphia: Elsevier Churchill Livingstone.		

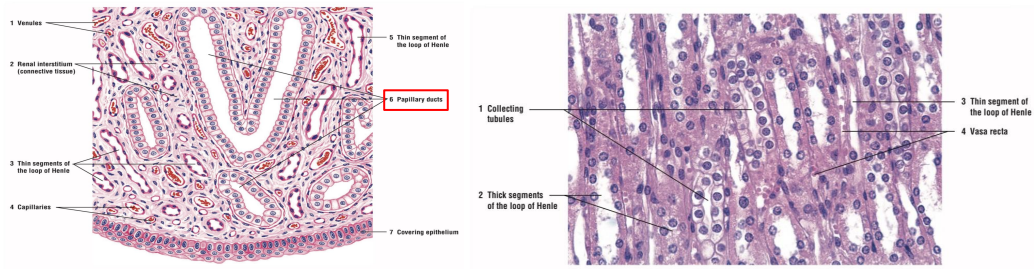
Blood supply		
Ureters	1.upper part—renal arteries. 2.middle part—abdominal aorta,testicular/ovarian arteries, common iliac arteries. 3.lower part —internal iliac arteries.	
Urinary bladder	internal iliac artery Into internal iliac vein.	
Urethra	Male	Female
	1. Prostatic urethra: inferior vesical artery 2. Membranous urethra: bulbourethral artery 3. Penile urethra: branches of the internal pudendal artery	Internal pudendal and vaginal arteries.

Anatomy (ureters,bladder,urethra)

	Ureters	Urinary bladder	Urethra	
			Male	Female
Lymphatic drainage	Upper: lateral aortic nodes. Middle: common iliac vessels lymph nodes. Lower: external and internal iliac vessels lymph nodes.	Drain into internal iliac lymph nodes.	Prostatic and membranous: drain into obturator and internal iliac nodes. Penile: drains into deep and superficial inguinal nodes.	Internal iliac nodes + superficial inguinal lymph nodes.
Nerve supply	Parasympathetic: S2 through S4. Sympathetic: input from T10 through L2.	Parasympathetic: through pelvic splanchnic nerves from S2,3 & 4. Sympathetic: from L1,2 through hypogastric nerves.	derived from the prostatic plexus.	Arises from vesical plexus and pudendal nerve.

Microscopic structure of the renal pelvis:

Several collecting ducts merge in the papilla of the kidney medulla to form large, straight tubules called the papillary ducts.
The contents from the papillary ducts continue into the minor calyx that is adjacent to and surrounds the tip of each papilla.
Each minor calyx accepts urine from the renal papilla of a renal pyramid then, deliver the urine to a major calyx.
Minor calyx is covered by transitional epithelium, which acts as a barrier.
Deep to the lamina propria is a thin muscular coat composed entirely of smooth muscle, this muscular layer propels the urine into a major calyx. The major calyces are similar in structure to the minor calyces and finally open into the renal pelvis

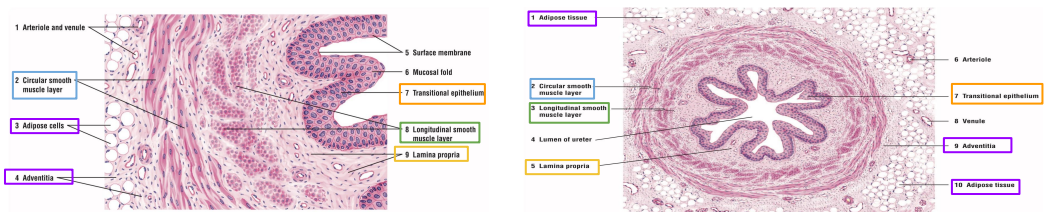


Reference:Young B, Lowe JS, Stevens A and Heath JW. Wheater's Functional Histology. 5th ed. London: Churchill Livingstone.

Microscopic structure of the ureter:

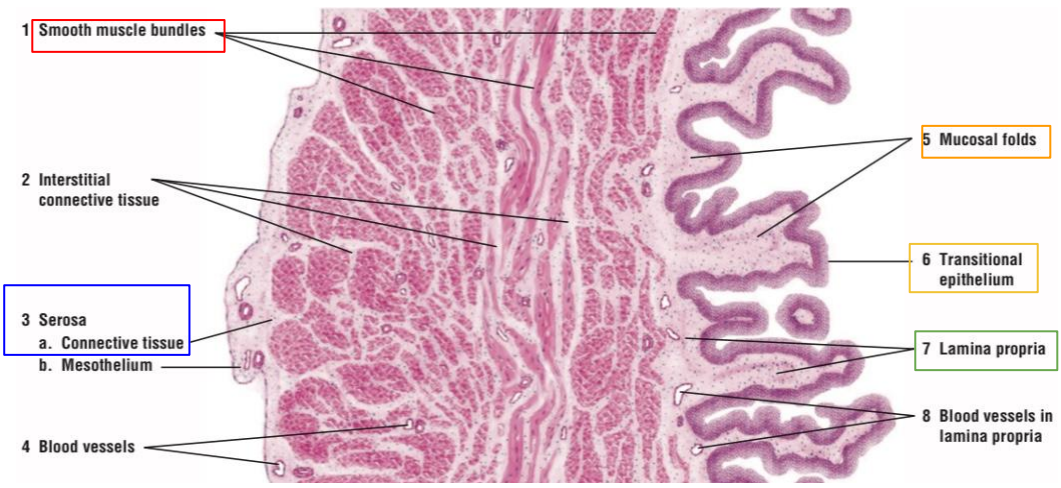
The wall of the ureter consists of 3 layers:

- Mucosa: which consists of **transitional** epithelium and a wide lamina propria.
- Muscularis: which consists of two muscle layers, an inner longitudinal smooth muscle and a middle circular smooth muscle layer. There is also an additional third outer longitudinal layer of smooth muscle which is found in the lower third of the ureter near the bladder.
- Adventitia: Which is fibroelastic connective tissue and adipose tissue.



Reference:Young B, Lowe JS, Stevens A and Heath JW. Wheater's Functional Histology. 5th ed. London: Churchill Livingstone.

Microscopic structure of the urinary bladder:

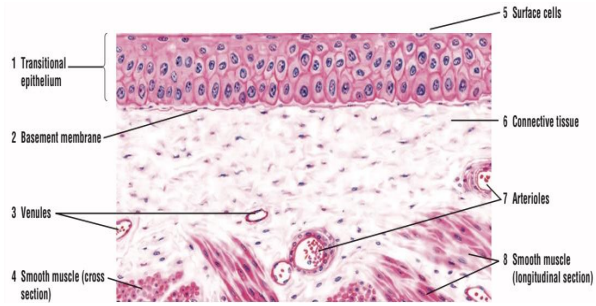
	Outer covering	Wall	Mucosa
Overview	Serosa or Adventitia	The bladder has a thick muscular wall. The wall is similar to that of the lower third of the ureter, except for its thickness. In the wall there are three layers of smooth muscle: -Inner longitudinal. -Middle circular (thick). -Outer longitudinal layer.	The mucosa from an empty and contracted urinary bladder wall exhibits numerous mucosal folds and composed of three layers (transitional epithelium, lamina propria, The deep loose connective tissue contains more elastic fibers and Numerous blood vessels)
Microscopic Picture	 Young B, Lowe JS, Stevens A and Heath JW. Wheater's Functional Histology. 5th ed.		

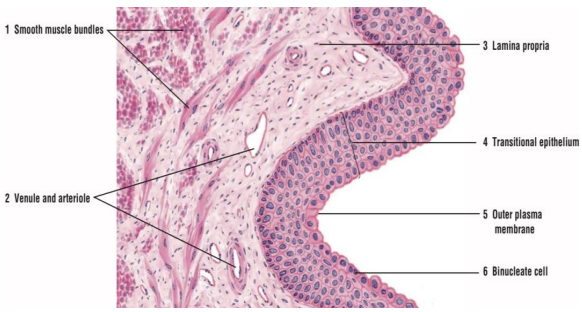
Microscopic structure of the urinary bladder:

Mucosa

Contracted:
In the mucosa from contracted urinary bladder the superficial cells of the transitional epithelium are low cuboidal, or columnar.
Also, some cells may be binucleate (contain two nuclei).

Stretched:
When fluid fills the bladder, the transitional epithelium changes its shape, reduces the number of cell layers, surface cells appear squamous, and the thickness of the transitional epithelium is reduced.





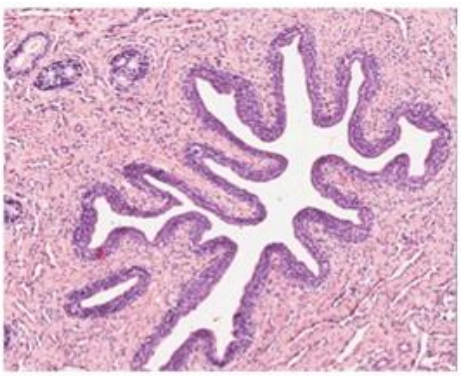
Reference: Young B, Lowe JS, Stevens A and Heath JW. Wheater's Functional Histology. 5th ed. London: Churchill Livingstone.

Urethra

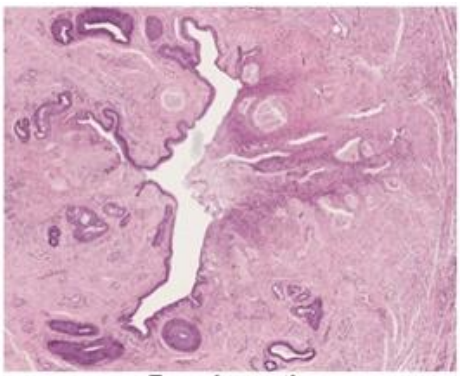
- The urinary bladder is drained by a single tubular structure, the urethra, which communicates with the outside, permitting elimination of urine from the body.
- As the urethra pierces the perineum, skeletal muscle fibers form the external sphincter muscle surrounding the urethra. This muscle permits voluntary control of micturition.
- The urethra of the male is longer than that of the female and has a dual function, acting as a route for semen as well as for urine.

Microscopic structure of the female urethra:

1. **Epithelium:** Which consists of three layer:
   a. Transitional epithelium near the bladder.
   b. Pseudostratified columnar epithelium.
   c. Stratified squamous nonkeratinized epithelium.
2. **Sub-epithelial fibroelastic CT:** Which contains glands of Littre (mucus-secreting glands).
3. **Smooth muscle:** Which consists of inner longitudinal and outer circular layers.



Male urethra



Female urethra

the Trustees of indiana university.

Microscopic structure of the male urethra:

1. **Prostatic urethra:** The urethra that leaves the bladder and passes through the prostate gland that's lined with transitional epithelium.
2. **Membranous urethra:** It is the intermediate part of male urethra and lined with pseudostratified,stratified columnar epithelium.
3. **Penile urethra:** Extends the entire length of the penis and and lined with pseudostratified,stratified columnar epithelium.
4. **In navicular fossa (enlarged terminal portion):** Stratified squamous non-keratinized epithelium. The lamina propria contains mucus-secreting glands of Littre.

Micturition

Functional anatomy of the urinary bladder

- The urinary bladder is a smooth muscle chamber composed of two main parts:
  - **Body**, which is the major part of the bladder.
  - **Neck**, which is a funnel-shaped extension of the body, passing inferiorly and anteriorly into the urogenital triangle and connecting with the urethra.

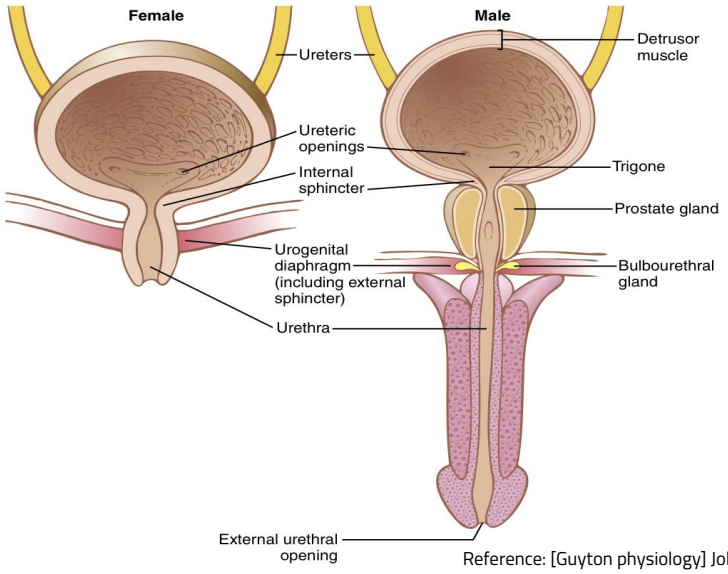
Trigone

- A triangular area in the internal urinary bladder bounded by 2 ureteric orifice and internal urethral orifice.

How many sphincters are there and how are they different?

1- Internal sphincter: which is made up of smooth muscle.

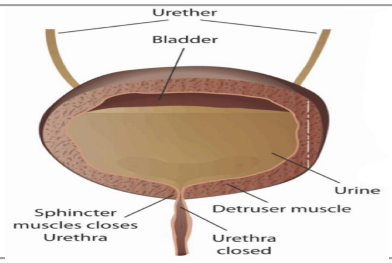
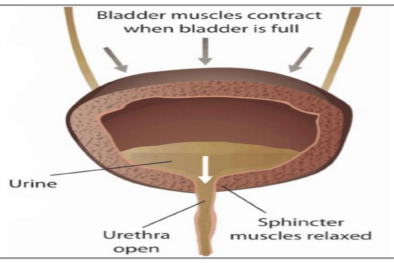
2- External sphincter: which is made up of skeletal muscle.



Reference: [Guyton physiology] John hall, Michael hall - Guyton and hall textbook of medical physiology (2020, Elsevier) - libgen.Lc.Pdf. (n.d.).

Micturition

Functions of the Lower UT

Urine storage	Urine voiding (micturition)
Bladder wall relaxed (to accommodate the amount of urine).	Bladder wall contracted.
Outlet / sphincter is closed (contracted).	Outlet / sphincter is open (relaxed).
Store without leakage.	**Empty when appropriate.**
	

Micturition

Is the process by which the urinary bladder empties when it becomes full.

- Filling of bladder.
- Stretches the wall.
- Stimulate stretch receptors.
- Signals are carried through pelvic nerve to sacral center.
- Excite parasympathetic efferent and inhibit pudendal discharge.

Micturition

Micturition reflex

is an autonomic reflex that can be facilitated or inhibited by higher centers, It occurs in two steps:

Progressive filling of the bladder until a threshold is reached.

At the threshold, a nervous reflex is initiated "micturition reflex" to empty the bladder.

Neural control of the urinary bladder and sphincters

1. Urine is transported through the ureters.
2. Urine is propelled through the ureter and into the bladder by the help of peristalsis.
3. Peristalsis is thought to be initiated by pacemaker cells in the renal pelvis.
4. -Sympathetic stimulation inhibits peristalsis.
   -Parasympathetic stimulation enhance peristalsis.

Micturition

Neural control of the urinary bladder and sphincters

	Nerve	Function
Autonomic	(Sympathetic) Hypogastric nerve.	• Relaxes the wall of the bladder bladder • Contracts internal sphincter **Afferent** (via lumbar dorsal nerve roots) (Sensory): • Pain receptor to upper lumbar segment. • Pain sensation from urethra and bladder. **Efferent** (Motor): • Inhibitory to the bladder wall (detrusor muscle). • Motor (contraction) to the internal urethral sphincter. • Motor to the seminal vesicle, ejaculatory duct.
	(Para sympathetic) Pelvic nerve.	• Contracts the wall of the bladder • Relaxes internal sphincter **Afferent** (via sacral dorsal nerve root) (Sensory): • Tension (stretch) and pain receptors present in the wall of urinary bladder. • Result in both reflex micturition and sensation of bladder fullness. **Efferent** (Motor): • Motor to the bladder wall (detrusor muscle). • Inhibitory to the internal urethral sphincter.
Somatic	Pudendal nerve (S2-S3).	• Contraction of the external sphincter. **Afferent** (Sensory): • sensation of urethra distention. • sensation of urine passage through urethra. **Efferent** (Motor): • motor to the external urethral sphincter.

Micturition

Emptying of the urinary bladder

- If the condition is **favourable**, the cortical centers facilitate micturition by discharging signals that leads to:

    1. Stimulation of sacral micturition center.
    2. Inhibition of pudendal nerves > relaxation of external urethral sphincter.
    3. Contraction of anterior abdominal muscle & diaphragm to increase intra-abdominal pressure > the intra-vesical pressure is increased. This intensifies the micturition reflex.

- If the conditions are **unfavourable**, the higher centers will inhibit the micturition reflex by:

    1. Inhibition of sacral micturition center.
    2. Stimulation of pudendal nerves contraction of external urethral sphincter.

Bladder sensations at different urine volumes

- 150ml - 300ml —> first urge to void.
- 300ml - 400ml —> sense of bladder fullness.
- 400ml - 600ml —> sense of discomfort.
- 600ml - 700ml —> sense of pain.
- 700ml —> micturition can not be suppressed (breakpoint).

Micturition

Cystometrogram

- **Bladder tone** (bladder function) = the relationship between bladder volume and pressure (intravesical pressure).
- The relationship between bladder volume and intravesical pressure can be studied.
- The volume-pressure record is called a **cystometrogram**.

1 Superimposed on the basal cystometrogram are periodic sharp increases in IVP that may last a few seconds to more than a minute.

2 These peaks are called "Micturition waves", and they are **caused by Micturition reflex**

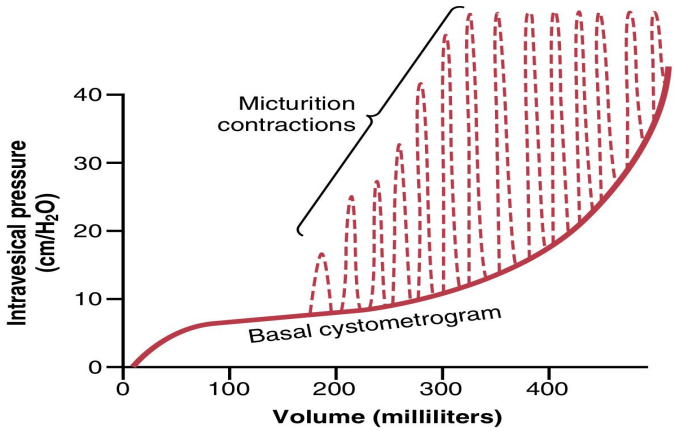


Figure 26-8. A normal cystometrogram, showing also acute pressure waves *(dashed spikes)* caused by micturition reflexes.

Reference: [Guyton physiology] John hall, Michael hall - Guyton and hall textbook of medical physiology (2020, Elsevier) - libgen.Lc.Pdf. (n.d.).

Micturition

Abnormalities In Micturition

1 Automatic Bladder Caused by Spinal Cord Damage Above the Sacral Region

- The **micturition reflex is intact**, but **lost higher center** control.
- **Acute phase:** Occurs due to the separation of the spinal centers from the brain > Loss of facilitatory impulses from CNS will lead to Micturition reflex is **inhibited**> Bladder fills but c**annot void (Retention with overflow incontinence)**. Bladder needs to be emptied periodically by catheterization.
- **Recovery from spinal shock:** Micturition reflex **recovers** > **Not** controlled by CNS > Bladder fills and voids automatically (**Automatic bladder)**.
- Voluntary reflex is controlled by higher CNS centers: brain stem (pons) & cerebral cortex.

2 Uninhibited neurogenic bladder Region

- Cause: Lesions to spinal cord or brain stem, that will affect inhibitory signals to spinal cord.
- It will cause:
  - Frequent relatively uncontrolled micturition (Frequent urination of small volume of urine).
  - Hyperactive detrusor muscle that will result in activation of micturition even at small urine volumes.

3 Atonic Bladder and Incontinence Caused by Destruction of Sensory Nerve Fibers

- **Cause**: Tabes dorsalis (Syphilis, Tabetic bladder)
- Micturition reflex contraction cannot occur if the sensory nerve fibers from the bladder to the spinal cord are destroyed, when this happens, a person loses bladder control, despite intact efferent fibers from the cord to the bladder and despite intact neurogenic connections within the brain.
- Instead of emptying periodically, the **bladder fills** to capacity and overflows a few drops at a time through the urethra. This occurrence is called overflow incontinence.

Infection of The Lower Urinary Tract

Cystitis

Cystitis is the term used to describe infection of the bladder. The primary feature of cystitis is frequent urination with burning sensation. Cystitis is usually self-limiting.

Symptoms

1. Dysuria (Painful urination)
2. Frequency
3. Urgency.

Etiology

Over 95% of UTIs are caused by a single bacterial species, and 90% of these are E. coli. Other Enterobacteriaceae, Pseudomonas, and Gram-positive bacteria become increasingly frequent with chronic, complicated, and hospitalized patients.

Staphylococcus saprophyticus, a coagulase- negative staphylococcus, is now recognized as the etiology in a significant minority of symptomatic infections in young, sexually active **women**.

Yeast (especially Candida) might be isolated, but they seldom produce symptomatic disease.

Manifestation

The clinical manifestations of UTI are variable. Approximately 50% of infections do not produce recognizable illness and are discovered incidentally during a general medical examination.

Cystitis

Epidemiology:

UTIs are more common in women, 40% of whom have an episode in their lifetime, usually when they are sexually active. The reservoir for these infections is the patient's own intestinal *E. coli* flora, which contaminate the perineal and urethral area. In individuals with urinary tract obstruction or instrumentation, environment sources assume some importance.

Pathogenesis:

Relatively minor trauma or the mechanical effect of sexual intercourse have been shown to allow bacteria access to the bladder. In most instances, these bacteria are purged by the flushing action of voiding. Factors that violate bladder integrity (urinary catheters) or that obstruct urine outflow (enlarged prostate) are also associated with infection.

Cystitis & urethritis

The findings above are similar to those of urethritis caused by sexually transmitted agents. The cystitis complex is, in fact, produced by irritation of the mucosal surface of the urethra as well as the bladder. It is clinically distinguished from pure urethritis by:

- more acute onset,
- more severe symptoms,
- presence of bacteriuria
- hematuria in 50% of cases
- pain and tenderness in the suprapubic area.

Fever and systemic manifestations of illness are usually absent unless the infection spreads to involve the kidney (pyelonephritis).

Diagnosis of cystitis

Specimen collection:

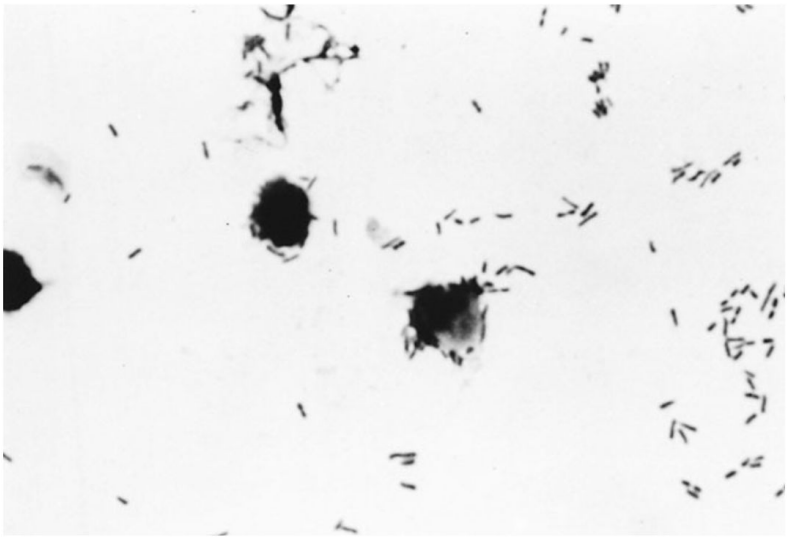
The diagnosis of UTI is based on examination of the normally sterile urine for evidence of bacteria or an accompanying inflammatory reaction. Critical to this examination is the use of appropriate techniques for specimen collection. collect the mid-stream urine. If the mid-stream urine wasn't accurate or inaccessible, catheterization & suprapubic aspiration from distended bladder may be necessary.

Approximately 90% of patients with acute symptomatic UTI have pyuria (that is, 10 white cells/mm3 of urine). Pyuria suggests UTI but is not specific

Chemical screening test:

A number of non-microscopic urinary screening tests have been commercially marketed within the past several years.

- The most successful detects leukocyte esterase from inflammatory cells and nitrite produced from urinary nitrates by bacterial metabolism.



From: Sherris medical microbiology 4th edition (P:870)

Diagnosis of cystitis

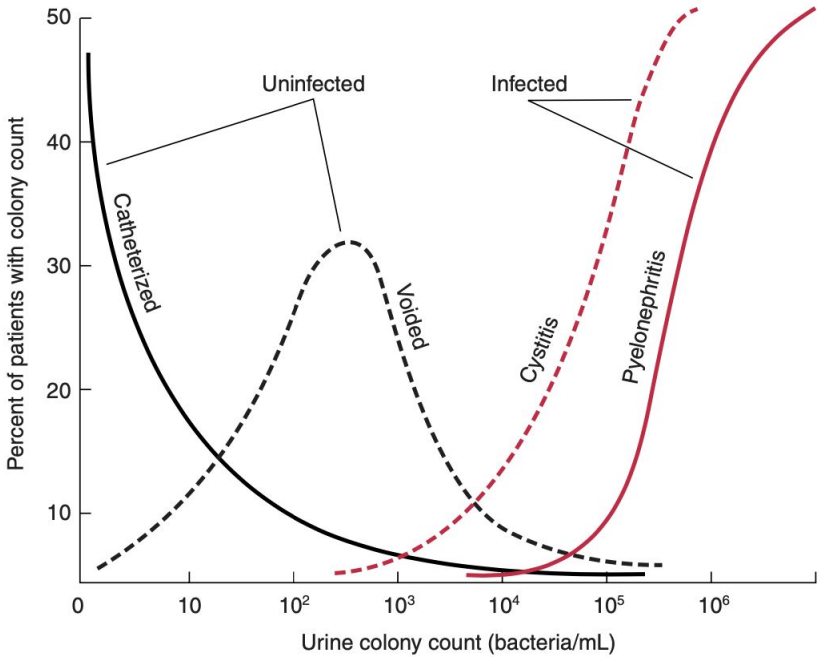
Urine culture:

the number of bacteria in infected urine is large, quantitative bacteriology has been the gold diagnostic standard for UTI.

Gold diagnostic standard for UTI

10^5 bacteria/mL of urine. Above it is UTI, below it is contamination.

Quantitative urine culture. Bacteria are routinely quantitated in the range of 10 to 10^5. Uninfected persons may show bacteria in the urine due to contamination from the perineal flora. The number are small if the specimen is collected by catheterization but voided (midstream method) specimens contain larger numbers. Patients with pyelonephritis have very high numbers of bacteria but those with only cystitis often have numbers less than 10^5.



From: Sherris medical microbiology 4th edition (P:870)

Management of UTI

- Each symptomatic episode of acute cystitis should be evaluated first with a urinalysis and urine culture with sensitivity prior to treating with antibiotics.
- The combination of clinical findings and urine evaluation is essential for diagnosis of UTI.
- Treatment is based upon pathogen identification and the type and degree of clinical illness, as well as the presence or absence of predisposing host factors. In general, the treatment consists of hydration, relief of urinary tract obstruction if present, removal of foreign body or catheter if feasible, and judicious use of antibiotics.
- The type and duration of antibiotic treatment is dependent on site of infection (pyelonephritis, cystitis, prostatitis, epididymitis, orchitis), host factors, and severity of illness.
- When considering treatment, first determine whether the UTI is complicated or uncomplicated in nature.

Uncomplicated	Complicated
include acute cystitis in a non-pregnant, premenopausal female, and acute pyelonephritis in an otherwise healthy patient. Young post–pubertal females are susceptible to uncomplicated UTIs because of sexual intercourse in combination with delayed post–coital bladder emptying. Use of diaphragm and spermicidal contraceptives alter the normal vaginal flora and may allow colonization by pathogenic E. coli.	occur when certain predisposing factors are present, but in general should be considered in pregnant or post-menopausal females and men. Patients with complicated UTIs are more likely to have medical co-morbidities or conditions with require special consideration. In addition, they may have a greater variety of pathogenic bacteria, more drug resistance, and require a longer duration of antibiotic therapy.

Management of UTI

Common Causative Pathogens in Adult UTIs:

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

Goal of Management of UTI:

- The principal goal of management of UTI is to eradicate the offending organisms from the urinary bladder and tissues.
- The main treatment of UTI is by antibiotics.

Recurrent UTI:

Recurrent UTI is defined as 2 or more infection in a 6-month period or ≥ 3 culture proven infections in 12 months. Both re–infection and relapsing infection contribute to the development of recurrent UTIs.

Catheter associated UTI (CAUTI):

Patients with indwelling urethral catheter will universally develop bacteriuria over time; 10–25% of these will develops symptoms. Risk factors included female gender, elderly, DM, error in catheter care and bacterial colonization of the drainage bag.

Clinical integration

Lower urinary tract infection Symptoms

01 Dysuria

02 Storage (irritative) symptoms: Frequency - Urgency - Nocturia - Incontinence.

03 Voiding (obstructive) symptoms: Hesitancy - Weak stream "interrupted stream" - Dribbling - Urine retention - Reduced flow - Sensation of incomplete emptying.

1- Urethritis

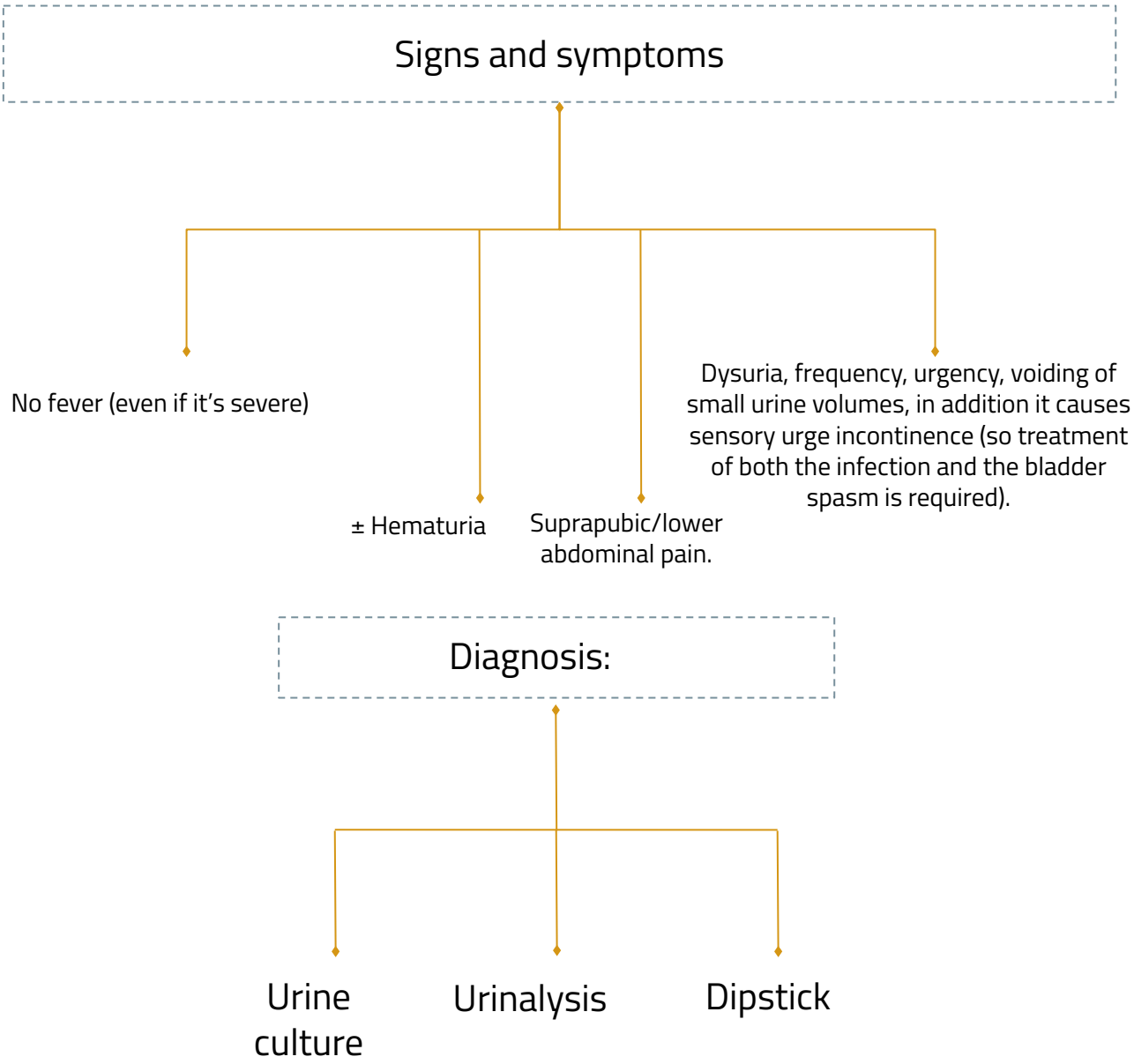
Signs and symptoms:

- Usually related to unprotected sexual intercourse.
- Urethral discharge.
- Dysuria and frequency.
- Burning on urination.
- Could be asymptomatic.

	Gonococcal	Nongonococcal
Organism	Neisseria gonorrhoeae.	Chlamydia trachomatis.
Organism type	Gram -ve diplococci.	Intracellular facultative organism.
Incubation period	3-10 days.	1-5 weeks.
Urethral discharge	Usually profuse, purulent (Whitish).	Usually scant.
Asymptomatic carriers	40% - 60%	
Diagnostic test	Ligand chain reaction and Gram stain culture.	Polymerase/ligand chain reaction (PCR) and culture immunoassay.
Treatment	Ceftriaxone +(Azithromycin or Doxycycline; for possible chlamydial coinfection)	Doxycycline or Azithromycin + (ceftriaxone; for possible gonorrheal coinfection)

Clinical integration of lower urinary tract infection

2- Cystitis



Treatment

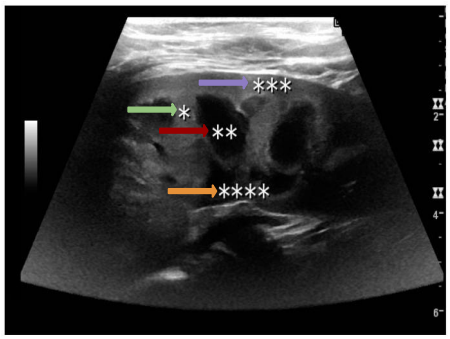
1-For a Healthy woman with a simple cystitis: 3 days of wide spectrum antibiotic (Ciprofloxacin,levofloxacin).
2-For a Men/ Older patients/ Diabetic/ Pregnancy/ Complicated cystitis: 7 days of antibiotic (TMP-SMX or Fluoroquinolones).

Miscellaneous

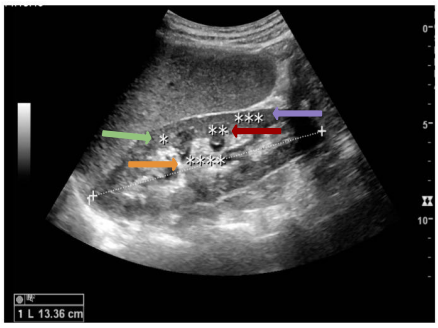
Radiology of Renal System

Normal anatomy of kidney:

Location: The kidneys are located on the posterior abdominal wall, with one on either side of the vertebral column, in the perirenal space.
Size :In adults, the normal kidney is 10-14 cm long in males and 9-13 cm long in females.



Normal pediatric kidney.
* Column of Bertin
** pyramid
*** cortex
**** sinus



* Column of Bertin
** pyramid
*** cortex
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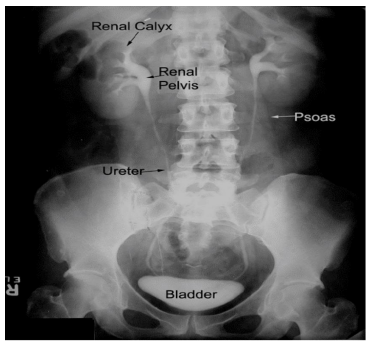
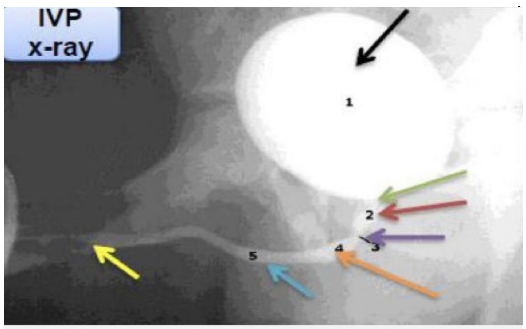
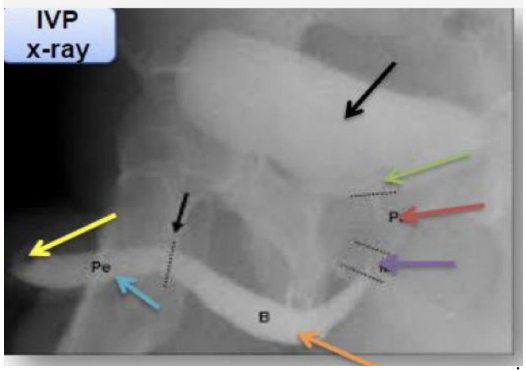


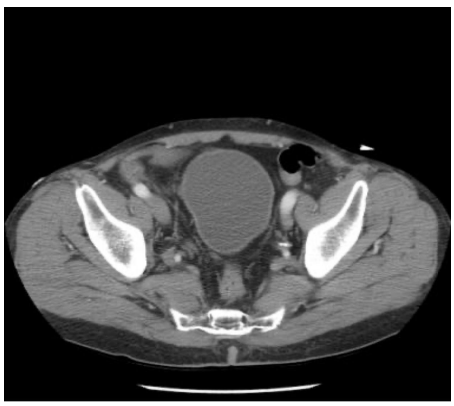
Ureters





1- Bladder
2- Bladder neck
3- Prostatic urethra
4- Membranous urethra
5- Bulbar urethra
6- Penile urethra
7- Urethra meatus

Urethra

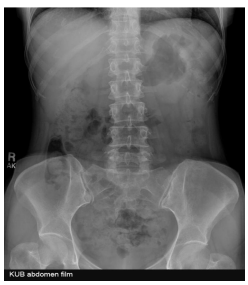


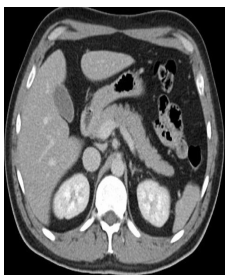
Urinary bladder

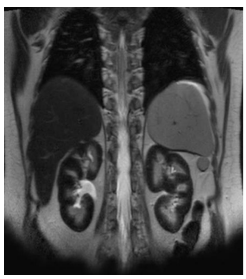
Radiology of Renal System

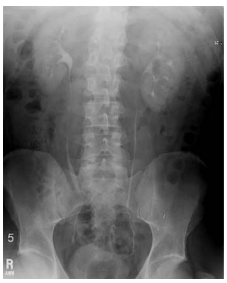
Modality used for assessment of the urinary system:

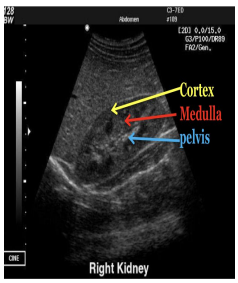
Modalities	X-ray	IVP	CT	US	MRI	Nuclear
Key	-White= bone and calcification. -Grey= soft tissue. -Black= air.	An intravenous pyelogram is an x-ray examination of kidneys, ureters and urinary bladder that use iodinated contrast material injected into veins. (so it's used to asses the excretion function)	-White= bones and calcification -Grey= soft tissue. -Black= air.	White= stones and calcification. Grey=soft tissue. Black=fluid Note: renal fat hyperechoic.	-White= high intensity. -Grey to black= low intensity.	Dark gray to black= nuclear fluid flow pathway.
Pros	Inexpensive and quick.		Quick and a lot of information	No ionizing radiation , inexpensive , and portable.	No ionizing radiation , and a lot of information	Assess the function.
Cons	Ionizing radiation and not definitive.		Ionizing radiation and expensive.	Operator dependent and time consuming.	Expensive and time consuming.	Time consuming and radioactive materials.





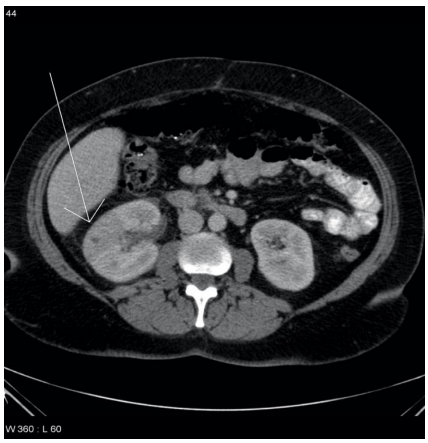


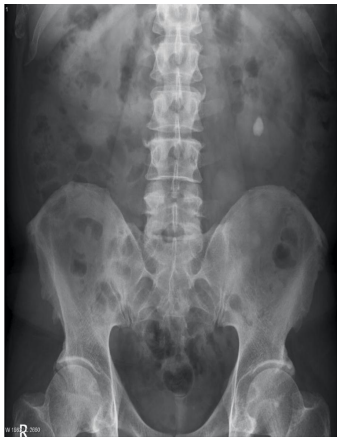




Radiology of Renal System

Common pathologies of urinary system:



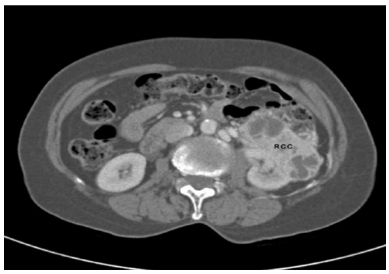


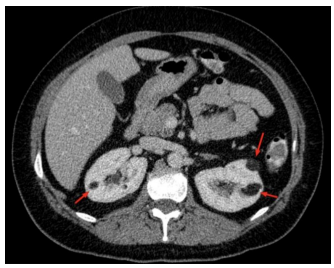
Pyelonephritis

- CT scan for a patient with pyelonephritis, we do it only if the patient doesn't respond to the treatment or it's recurrent pyelonephritis.

Stones

- Radio-opaque (calcium and struvite).
- Radio-opaque is visible on x-ray.
- Radio-lucent (uric acid and cysteine).

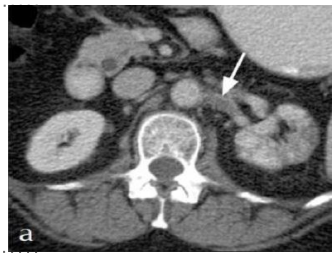




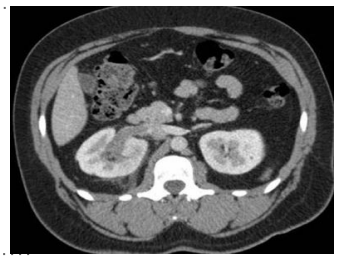
Tumors

- Most common benign is angiomyolipoma.
- Most common malignant is renal cell carcinoma.

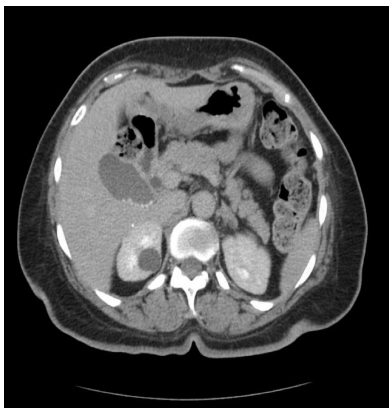
Artery



Vein

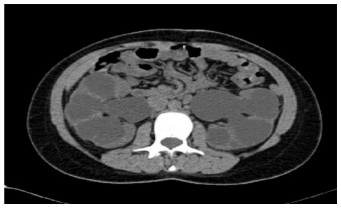


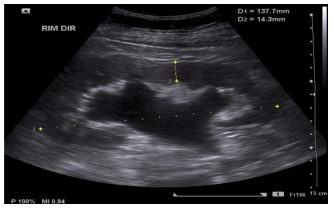
Renal thrombosis



Cysts

Benign and common





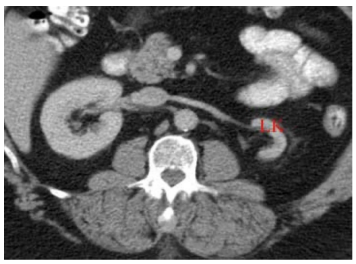
Hydronephrosis

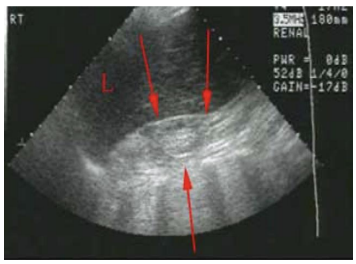
Hydronephrosis occurs when a kidney swells due to urine failing to properly drain from the kidney to the bladder, for diagnosis we use CT and US. Presence of dilation of collecting system, proximal tubules and renal pelvis.

Radiology of Renal System

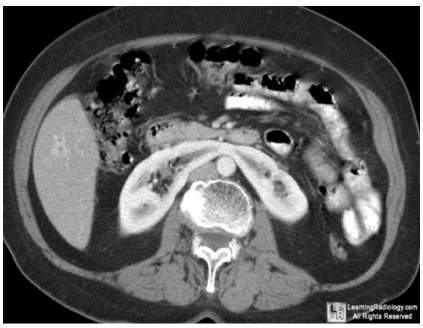
Common pathologies of urinary system:

End-stage kidney disease (ESKD)

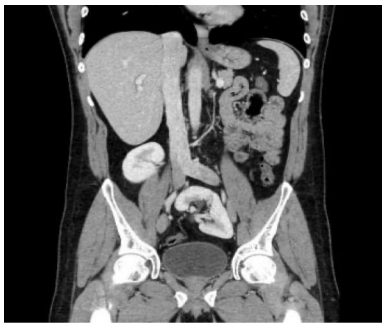




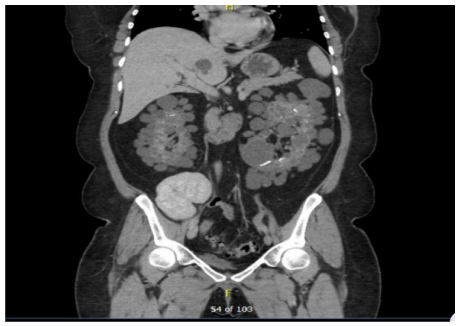
Congenital



Horseshoe Kidney

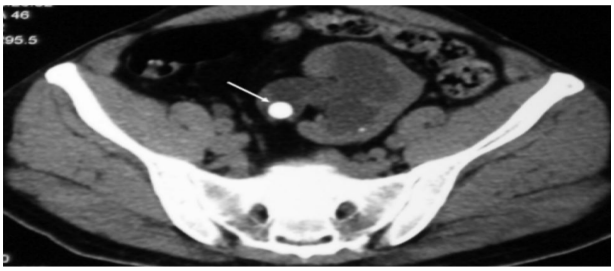


Ectopic Kidney

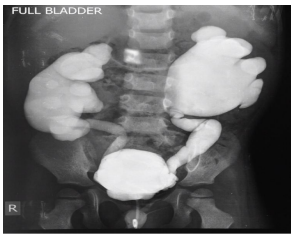


Polycystic Kidney Disease

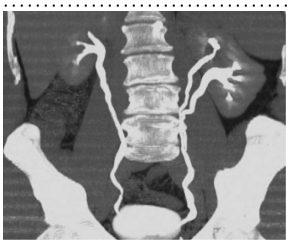
Common Ureter Pathologies:



Ureteric Stone:
stones in the ureter cause obstruction and block Urine from reaching the bladder.
(Risk of Hydronephrosis).
Dx with non- contrast CT.



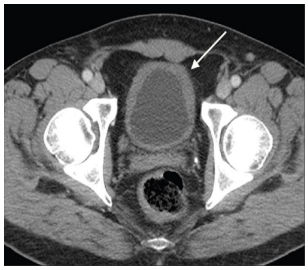
vesicoureteral reflux disease

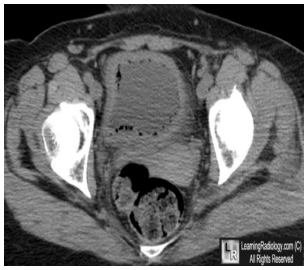


Duplicating Collecting System.

Common urinary bladder pathologies:

An inflamed urinary bladder (thick surrounding walls).



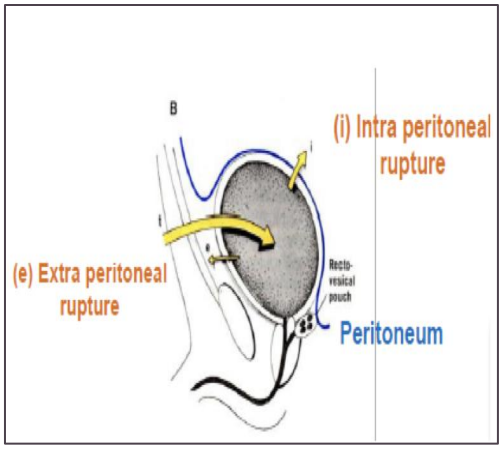


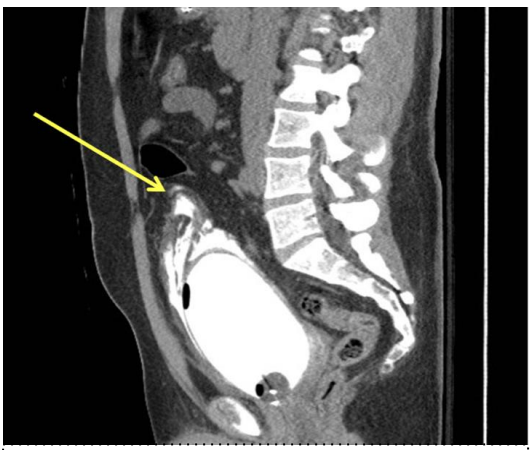
This bladder has gas bubbles that could be due to inflammation or infection from 'gas producing' bacteria.

Common urinary bladder pathologies:

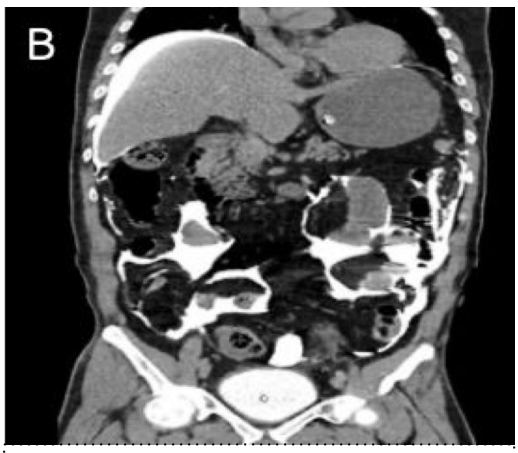
Bladder rupture:

- The abdomen is lined with the peritoneum from inside.
- The bladder is located below the membrane of the peritoneum.
- Dx with contrast CT.

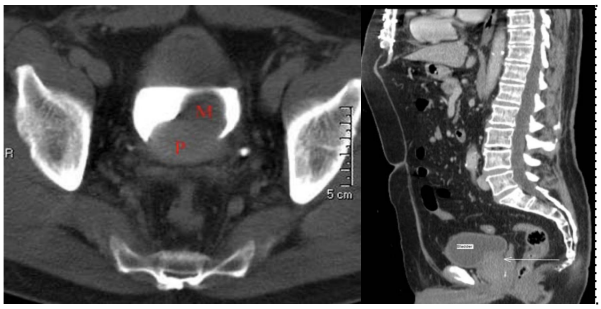




Extra peritoneum:
Any rupture or leakage to the content of the bladder does not enter the peritoneum. Patient does not need surgery.



Intra peritoneum:
There is rupture in both bladder and peritoneum. In this case, patient will need surgery.



Benign Prostate Hypertrophy

Pathology and Immunology of Renal transplant

- Renal transplantation involves the anastomosis of an explanted human, either from a deceased or living (related/unrelated) donor, on to the iliac vessels of the recipient.
- The donor ureter is placed into the recipient's bladder.
- Unless donor is genetically identical, maintenance of immunosuppressive therapy is required to help prevent acute rejection and loss of the transplanted kidney.
- All transplant patients require life long follow-up to monitor renal function and complications of immunosuppression, which include the increased risks of infections and some cancers.

Renal replacement therapy is typically commenced when eGFR is 10 mL/min/1.73m^2.

- Preparation begins 12 months prior and that includes psychological, social, and physical preparations.

Physical preparations include: establishing timely access for haemodialysis or peritoneal dialysis, and hepatitis B vaccination.

Considerations in successful renal transplants

1. ABO (blood group) antigens compatibility between donor and recipient.
2. Major histocompatibility (MHC) especially at leukocyte antigen DR (HLA-DR), A (HLA-A), and B (HLA-B).
3. Preformed anti-HLA antibodies are crossmatched; a positive crossmatch means that the recipient has antibodies against HLA proteins expressed by the donor which will lead to hyperacute rejection.
   Most common technique used for crossmatching is the Luminex.
4. Timing of transplantation, prior to dialysis initiation (pre-emptive transplantation) offers benefits to both recipient and graft.

Pathology and Immunology of Renal transplant

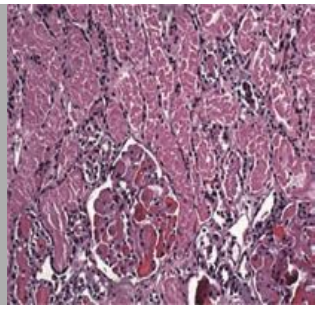
Pathologies of renal transplants

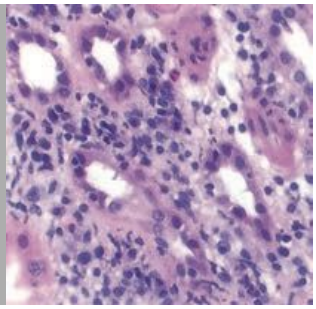
Harvest injury	-Tubular injury to the transplanted allograft kidney, due to cold ischemia time or the mode of donor death. -Can lead to non-functioning kidney immediately after engraftment in which the patient will have anuria. -Usually recovers. **-At time of transplant.**
Rejection	-Occurs when **transplanted tissue is rejected by the recipient's immune system** and the recipient's immune system destroys the transplanted tissue. -Rejection has been classified by a system called as the Banff Classification into: a) Hyper-acute b) Acute c) Chronic. **-Post transplant.**
Infections in the allograft	-Recipients are immunocompromised due to immunosuppressive drugs which predisposes to renal infections like adenovirus, cytomegalovirus and **polyomavirus** and (EBV). -They primarily infect the tubules and cause tubulointerstitial inflammation and acute tubular injury, cells also show viral nuclear changes. -can lead to graft loss.
Drug toxicity	-Calcineurin inhibitors (CNI) (Cyclosporine and Tacrolimus) are immunosuppressive drugs used to decrease the recipient's immune system response to the allograft but they can cause acute and chronic CNI toxicity. -Blood tests show: 1) Elevated of serum creatinine. 2) Elevated blood/ serum CNI levels.
Recurrence of primary disease	-The primary disease which lead to end stage kidney and eventual transplant can recur as early as 6 months post- transplant.
De-novo (glomerulo-nephritis)	-The development of another kidney disease in the renal allograft, different from the disease the patient originally suffered from. - It is rare.

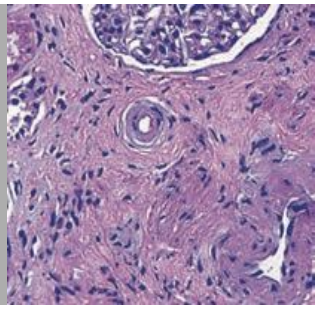
Pathology and Immunology of Renal transplant

Transplant rejection

types	On-set	pathogenesis	Characteristics
1-Hyperacute	Within minutes	Pre-existing recipient antibodies react to donor antigen (type II hypersensitivity reaction), activate complement.	-Widespread thrombosis of graft vessels (arrows within glomerulus) → ischemia and fibrinoid necrosis. -Graft must be removed.
2-Acute	Weeks to months	**Cellular**: CD8+ T cells and/or CD4+ T cells activated against donor MHCs (type IV hypersensitivity reaction) **Humoral**: similar to hyperacute, except antibodies develop after transplant (associated with CD4 deposition).	Cellular: The inflammation is primarily tubulointerstitial inflammation +- vasculitis . Humoral: Antibodies against endothelial cells in the allograft in blood vessels (esp. the glomeruli and peritubular capillaries)
3-Chronic	Months to years	CD4+ T cells respond to recipient APCs presenting donor peptides, including allogeneic MHC **Both cellular and humoral** components (type II and IV hypersensitivity reactions).	-Recipient T cells react and secrete cytokines→ proliferation of vascular smooth muscle, parenchymal atrophy, interstitial fibrosis. -Dominated by arteriosclerosis. -Organ-specific example: Chronic allograft nephropathy.

1- 

2- 

3- 

Biochemistry of Inborn Errors of Amino Acid Metabolism

Inborn errors of amino acid metabolism results from The loss or deficiency of a specific enzyme caused by gene loss or mutation

Enzyme
Substrate → Product
Cofactor

As a result

1. **Substrate** will **accumulate** in the body
2. **Deficiency** of the needed **product**

Normal pathway of phenylalanine

1

phenylalanine hydroxylase(PAH)
Phenylalanine → Tyrosine
Tetrahydrobiopterin(BH4) - - - - - - - - - > Dihydrobiopterin(BH2)

A deficiency in PAH or its cofactor BH4 will lead to Phenylketonuria (PKU).
BH4 is also used in synthesis of serotonin (from tryptophan) and DOPA (from tyrosine).

2

Tyrosine —(Tyrosinase)→ DOPA
1 → DOPAquinone → leucoDOPAchrome → DOPAchrome → Melanin
2 → Dopamine → norepinephrine → epinephrine

A deficiency in tyrosinase will lead to albinism.

3

Tyrosine → p-Hydroxyphenyl pyruvate →
Homogentisic acid(HA) —(Homogentisic acid oxidase)→ Maleylacetoacetic acid → Acetoacetate
Maleylacetoacetic acid → Fumarate

A deficiency in Homogentisic acid oxidase will lead to Alkaptonuria.

Biochemistry of Inborn Errors of Amino Acid Metabolism

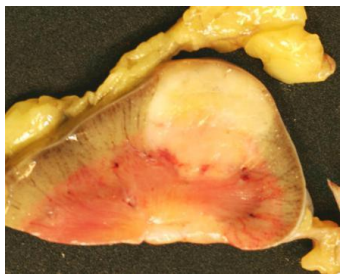
Diseases of inborn errors of amino acid metabolism

	Phenylketonuria		Alkaptonuria	Albinism	Maple Syrup Urine Disease (MSUD)	Homocystinuria
	typical	atypical				
Substrate	Phenylalanine (PHE)		Homogentisic acid (HA).	Tyrosine or DOPA.	Leucine, isoleucine, and valine.	Homocysteine
Deficiency	Phenylalanine hydroxylase (PAH)	Tetrahydrobiopterin (BH4)	Homogentisic acid oxidase.	Tyrosinase.	Branched chain α-ketoacid dehydrogenase.	Cystathionine β-synthase & cofactor Vit B6.
Characteristics	-PHE accumulation -Tyrosine deficiency		-HA accumulated in blood, tissue, cartilage.	-No Melanin pigment.	-Accumulation of leucine, isoleucine and valine in blood.	-High plasma and urine levels of homocysteine.
Symptoms	-Mousy urine odor. -Melanin deficiency and hypopigmentation. -CNS symptoms (eg. retardation)		-Early arthritis. -Black pigmentation of cartilage and tissue. -Dark pigmented urine.	-**White** hair, skin, and eyes. -Photophobia. -Vision defects.	-Metabolic acidosis. -Maple syrup odor in urine. -Mental retardation. -Physical disability.	-Vascular disease (atherosclerosis). -Displaced eye lens. -Spina bifida.
Treatment	-Lifelong phenylalanine restricted diet.		-Restricted intake of tyrosine and phenylalanine.		-Limited intake of leucine, isoleucine, & valine.	-Methionine restricted diet. -Oral administration of Vit B6, B12 and folate.

Neoplasms Of The Kidney

Angiomyolipoma

- Hamartoma composed of:
  1. Blood vessels
  2. Smooth muscles
  3. Adipose tissue



Radiopedia.org

- Increased frequency in tuberous sclerosis.

Renal Cell Carcinoma

- Malignant epithelial tumor arising from kidney tubules.
- Present with classical triad of:

01 **hematuria**

02 **Palpable mass**

03 **Flank pain**

04 **Paraneoplastic syndrome**

- People at higher risk are:

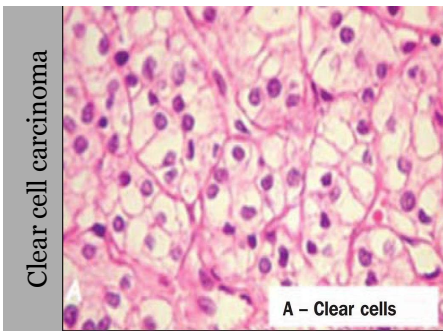
1. Smokers.
2. Hypertensive.
3. Obese.
4. Occupational exposure to cadmium.

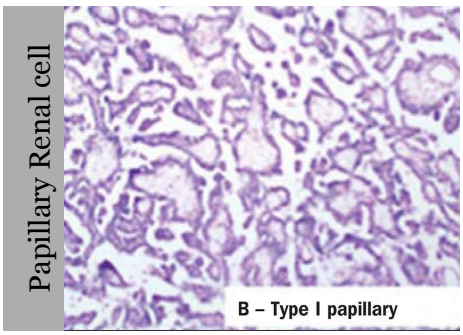
Renal cell carcinoma has three common forms

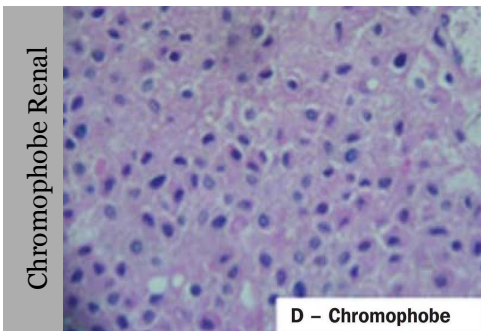
- Clear cell carcinoma
- Papillary renal cell carcinoma
- Chromophobe renal carcinoma

Neoplasms Of The Kidney

Forms of RCC	Characteristics
Clear cell carcinoma	-Most common type of renal cell carcinoma. -Most carcinomas are sporadic, also occur in familial forms or in associated with Von Hippel-Lindau (VHL) disease.
Papillary Renal cell carcinoma	-Occurs in familial and sporadic form. **-Not** associated with abnormalities of **chromosome 3.** - the culprit in most hereditary cases is the MET protooncogene located on **chromosome 7**q.
Chromophobe Renal carcinoma	-Least common type of renal cell carcinoma. -Arises from intercalated cells of collecting ducts. These neoplasms are unique in having multiple losses of entire chromosome leading to extreme hypoploidy.



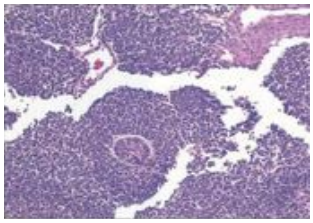


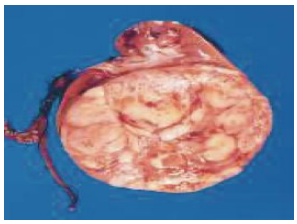


Neoplasms Of The Kidney

Wilms tumor

-The most common solid (non-hematologic) cancer in children younger than 10 years of age. Rare in adults.
-Associated with WT1 mutation, especially in syndromic cases.



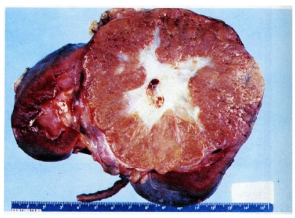


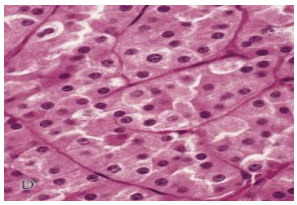
01 Wilms tumor, Aniridia, Gential abnormalities, mental and motor Retardation. — **WARG syndrome**

Beckwith-Wiedemann — Wilms tumor, neonatal hypoglycemia, muscular hemihypertrophy and organomegaly. **02**

Oncocytoma

-Is a benign neoplasm that arises from the intercalated cells of collecting ducts.
-These neoplasms are associated with genetic changes: loss of chromosomes 1 and Y.
-A central stellate scar provides a characteristic appearance on imaging studies.





Squamous Cell Carcinoma

-Malignant proliferation of squamous cell, usually involving the bladder.
-Arising on a background of squamous metaplasia.

Risk factors

1. Long standing nephrolithiasis.
2. Schistosoma haematobium infection.
3. Chronic cystitis.

Neoplasms Of The Kidney

Urothelial (Transitional cell) Carcinoma

-Malignant tumor arising from the urothelial lining of the renal pelvis, ureter, bladder or urethra.
-Major risk factor: .
-Generally seen in older adults, classically presents with painless hematuria.

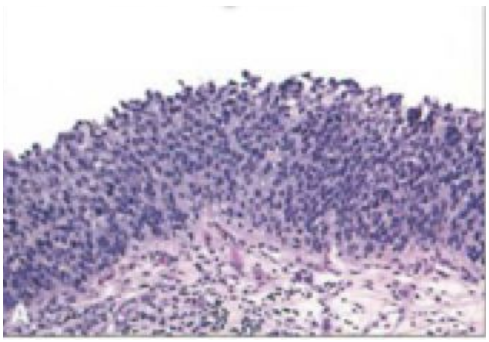
-Arises via 2 distinct pathways:

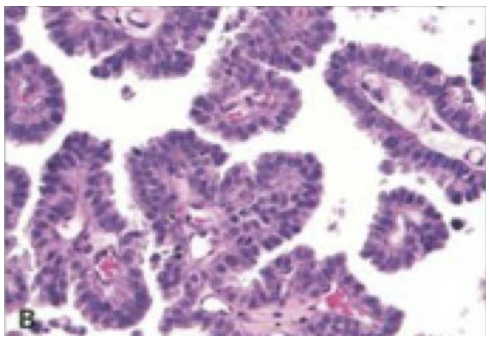
1 Flat

Develops as high grade flat tumor and then invades. Associated with early p53 mutations.

2 Papillary

develops as low-grade papillary tumor that progresses to a high-grade papillary tumor and then invades : not associated with early p53 mutations





Fundamental of pathology - pathoma

Kidney Stones

Kidney stones

(also called renal calculi, nephrolithiasis, or urolithiasis)

Refers to the presence of Calculi (stones) at any level in the urinary collecting system, but most often they arise in the kidney. High concentration of metabolic products present in glomerular filtrate (urea, creatinine, etc.) at levels near their maximum solubility contribute to stone formation. Kidney stones are formed due to many factors that have to be differentiated in order to achieve proper investigation and treatment. Kidney stones patients have a 50% chance in recurrence over the next five years.

Keep In Mind

cholestasis (gallstones) is a different condition than nephrolithiasis (kidney stones) with different etiologies and treatment, so DON'T mix them up!

Kidney Stones

Contributing Factors

Pathological factors

-Primary hyperparathyroidism.
-Hypercalciuria.
-Chronic Gout.
-crohn's disease.
-Alkaline or Acidic urine.

Decrease in stone forming inhibitors

such as
-Citrate.
-Pyrophosphate.
-Glycoproteins.

Urinary Stagnation
urinary outflow obstruction.

Change in urine pH
Mainly Due to Bacterial Infection.

High concentration of metabolic products inglomerular filtration.

There are many reasons for the initiation and formation of stones, the most important is increased urinary concentration of the stone's constituents, such that it exceeds their solubility (supersaturation), which is caused by:

1. low urinary volume (dehydration)
2. excessive fluid loss
3. High excretion of metabolic products

Kidney Stones

Investigations

- CT-scan is the most accurate test to detect kidney stones
- serum (Ca2+,Na+,uric acid,PTH, Mg2+, PO_4^{3-}) levels measurement.
- Stone analysis.
- 24-hour urine for volume test.

Table 14.5 Prevalence of Various Types of Renal Stones

Stone	Distribution (%)
Calcium oxalate and/or calcium phosphate Idiopathic hypercalciuria (50%) Hypercalcemia and hypercalciuria (10%) Hyperoxaluria (5%) Enteric (4.5%) Primary (0.5%) Hyperuricosuria (20%) No known metabolic abnormality (15% to 20%)	80
Struvite (Mg, NH_3, PO_4) Renal infection	10
Uric acid Associated with hyperuricemia Associated with hyperuricosuria Idiopathic (50% of uric acid stones)	6–7
Cystine	1–2
Others or unknown	±1–2

Robbins Basic Pathology 10th Edition

COMPOSITION	FREQUENCY	CAUSES	TREATMENT
Calcium oxalate and/ or calcium phosphate	Most common type; usually seen in adults	Most common cause is idiopathic hypercalciuria; hypercalcemia and its related causes must be excluded. Also seen with Crohn disease	Treatment is hydrochlorothiazide (calcium-sparing diuretic).
Ammonium magnesium phosphate	Second most common type	Most common cause is infection with urease-positive organisms (e.g., *Proteus vulgaris* or *Klebsiella*); alkaline urine leads to formation of stone.	Classically, results in staghorn calculi in renal calyces (Fig. 12.18), which act as a nidus for urinary tract infections. Treatment involves surgical removal of stone (due to size) and eradication of pathogen (to prevent recurrence).
Uric acid	Third most common stone (5%); radiolucent (as opposed to other types of stones which are radiopaque)	Risk factors include hot, arid climates, low urine volume, and acidic pH. Most common stone seen in patients with gout; hyperuricemia (e.g., in leukemia or myeloproliferative disorders) increases risk.	Treatment involves hydration and alkalinization of urine (potassium bicarbonate); allopurinol is also administered in patients with gout.
Cystine	Rare cause of nephrolithiasis; most commonly seen in children	Associated with cystinuria (a genetic defect of tubules that results in decreased reabsorption of cysteine)	May form staghorn calculi; treatment involves hydration and alkalinization of urine.

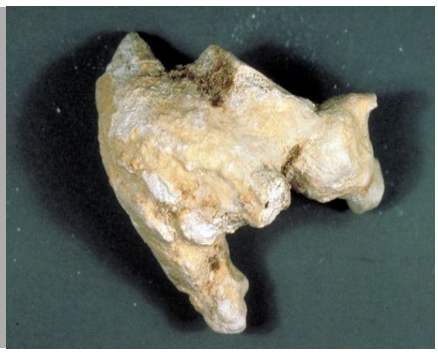
Fundamentals of Pathology

Kidney Stones

	Calcium Salts	Struvite
About	Consist of calcium oxalate and\or calcium phosphate. Calcium Oxalate stones are the most common type of kidney stones (80%). These form in patients with alkaline urine frequently. Developing of these stones depend on the Increased urinary Ca^{2+} excretion in the urine (Hypercalciuria) and present of Oxalate.	Second most common type (10%) Consist of Mg ammonium PO4.
Characteristics	-White, hard, radio-opaque (visible in X-ray photograph). -Calcium oxalate: present in ureter. -Calcium PO^{4}: staghorn (large and branching stones that fill part or all of the renal pelvis).	These stones are often large radiopaque staghorn calculi filling the renal pelvic system.
Etiology	-Hypercalciuria (high concentration of Ca2+in urine) **most common cause.** -Hypercalcemia (with primary hyperparathyroidism leading to stone formation). -Hyperoxaluria (Increased oxalate excretion): Primary hyperoxaluria, a rare inborn error, should be considered if renal calculi occur in childhood.	Mainly by UTIs with urea-splitting bacteria (e.g. Proteus) that produce urease which convert urea to ammonia and bicarbonate. This raises the urine pH >7 (alkaline urine).
Treatment	The main principle is to reduce calcium concentration in the urine. -Managing the underlying cause (hypercalcemia, hypercalciuria). -if not present, by reducing dietary calcium and oxalate intake with maintaining high fluid intake (unless there is glomerular failure). -Urine acidification to prevent calcium stones forming in alkaline urine. -hydrochlorothiazide to reduce calcium excretion.	Treatment of UTI and Urine acidification to prevent stones forming in alkaline urine. It may require surgical removal due to stone size.

Calcium salts Stones

Struvite Stones

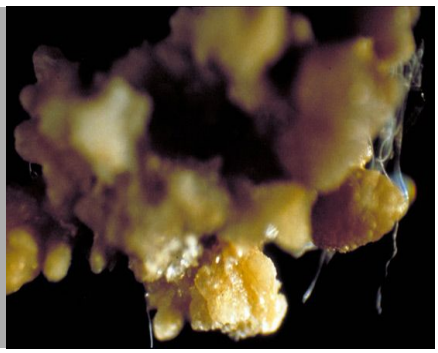


Kidney Stones

	Uric Acid	Cystine
About	High uric acid levels in the urine leads to low pH (>5.5) and the possibility of uric acid stones formation, these stones present in people with acidic urine. About 8% of kidney stones constitute of uric acid.	Rare type. Like uric acid stones, cystine stones are more likely to form in acidic urine. Excessive urinary excretion of cystine leads to the formation these stones. Generally seen in children.
Characteristics	-Small, friable, and yellowish brown stones. -If large enough they may form 'staghorn' calculi. -Radiolucent (can't be seen normally on x-ray) but may be seen by ultrasound or i.v. pyelogram.	-yellowish stone. -Present with faint radio-opaque (sometimes radiolucent) renal calculi. -Soluble in alkaline.
Etiology	In most cases, no predisposing cause can be found, tendency to excrete urine of pH <5.5 may predispose to uric acid stones. • They are associated with hyperuricemia, with or without gout • Patients with ileostomy (opening of the abdominal wall during surgery) are at risk of developing uric acid stones.	-Cystine stones are mainly due to genetic defect in the renal transport of cystine resulting in homozygous cystinuria (high urine cystine). -low pH (acidic) urine.
Treatment	-Treatment in case of hyperuricemia. -Urine alkalinisation. -increase fluid intake with purine restricted diet.	-Treatment is the same as for uric acid stones. -Penicillamine can also be used to treat the condition, to increase the solubility of cystine.

Uric Acid Stones

Cystine Stones



Clinical Integration

Cancer	Optimal Test for Diagnosis	Optimal Test for Staging	Treatment
Renal Cell Carcinoma	CT	CT	• Small: Partial nephrectomy • Invasion: Radical nephrectomy • Advanced: debulking surgery + adjuvant chemotherapy
Urothelial Tumors	CT urogram: if defect is seen, do retrograde ureteropyelogram, ureteroscopy and biopsy	CT of abdomen, pelvis and chest	• Low-grade: transurethral resection endoscopically • In-situ: BCG or more radical treatment • Invasive: radical cystectomy with urinary diversion

	Optimal first step management	Optimal Test for Diagnosis	Treatment
Kidney stones	Ketorolac for analgesia	CT scan without contrast	The best initial therapy: 1- analgesics and hydration 2- CT and sonography to detect obstruction 3- stones <5 mm pass spontaneously Stones 5-7 mm get nifedipine and tamsulosin to help them pass

Clinical integration

Clinical examination of patient with renal disease:

1 **General inspection**
Mental state, Hyperventilation (acidosis), Hiccups, Sallow complexion (uraemic tinge), Hydration, Subcutaneous nodules (calcium phosphate deposits).

2 **Hands**
Nails-leuconychia; white lines; distal brown arc, Arteriovenous fistulae, Asterixis, Neuropathy.

3 **Arms**
Bruising, Pigmentation, Scratch marks/ Excoriations, Myopathy.

4 **Face**
Eyes-anaemia, jaundice, band keratopathy.
Mouth-dryness, ulcers, fetor, gingival hypertrophy, Rash.

5 **Neck**
JVP, Carotid bruits, Scars from previous vascath insertion, Parathyroidectomy scars.

6 **Abdomen**
Tenckhoff catheter.
Scars-dialysis, operations.
Kidneys-transplant kidney.
Bladder, Liver, Lymph nodes, Ascites, Bruits. Rectal and pelvic examination- prostatomegaly, frozen pelvis, bleeding.

7 **Back**
Nephrectomy scar, tenderness, Oedema.

8 **Chest**
Heart-heaving apex, pericarditis, failure.
Lungs-infection, pulmonary edema.

9 **Legs**
Edema-nephrotic syndrome, cardiac Failure. Bruising, Pigmentation, Scratch marks/ excoriation, Neuropathy.

10 **Urine analysis**
Specific gravity, pH.
Glucose-diabetes mellitus.
Blood-'nephritis', infection, stone. Protein-'nephritis'.

11 **Other**
Blood pressure-lying and standing.
Fundoscopy-hypertensive and diabetic changes.
Rash, livedo reticularis.

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