

Paediatric Nephrology

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GLOMERULUS

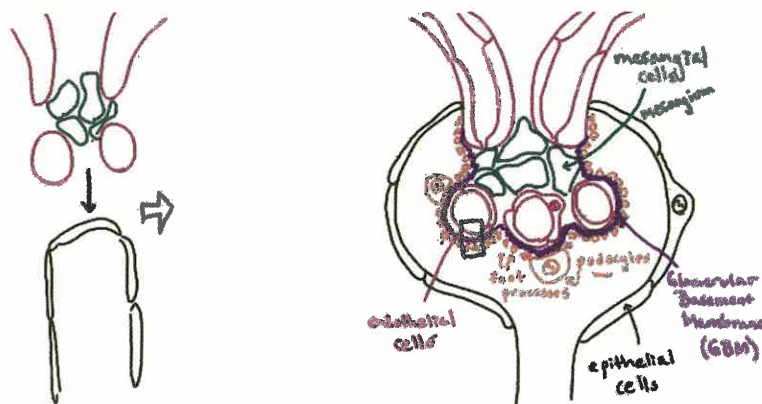
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Introduction

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Anatomy of glomerulus :

- Individual filtering unit of a nephron.
- Glomerulus consists of :
 - Bowman's capsule.
 - **Glomerular tuft** : Capillaries derived from afferent arteriole, their supporting cells, an envelope consisting of glomerular basement membrane (GBM) and visceral (**Podocyte**) layer of Bowman's capsule.
- At the vascular pole, the visceral epithelium becomes parietal epithelium, which then transforms into the proximal tubule epithelium at the urinary pole.
- Space between both layers : urinary space (**Bowman's space**).



Cut section view of glomerular apparatus

- Human glomerulus : Roughly ovoid, 150 to 240 micron in diameter.
- Afferent arteriole enters the renal corpuscle at the vascular pole, and ramify to form a network of anastomosing capillaries, called a **lobule**.
- The lobule has a supporting region called the mesangium and all lobules together establish the tuft.
- The converging mesangial regions are called the glomerular stalk, and it connects tuft to the extraglomerular mesangium (JGA).
- The capillaries coalesce toward centre of the capillary tuft to form efferent arteriole, which runs through the stalk and exits from the vascular pole.
- The efferent arteriole again breaks up to form a second capillary network, which surrounds the tubules and is called the peritubular capillary network.

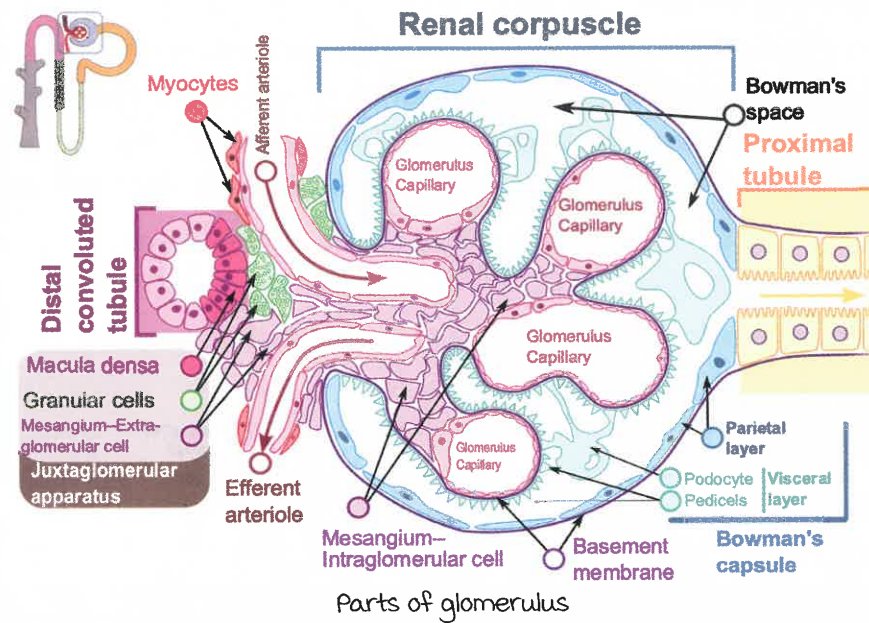
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Parts of glomerulus

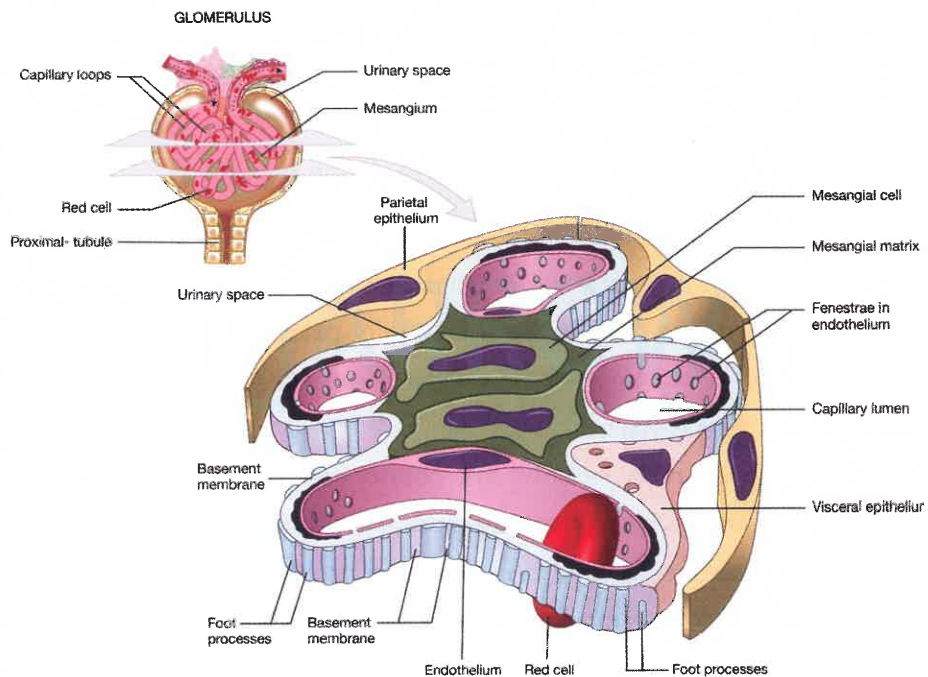
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Parts of a glomerulus include :

- Parietal epithelial cells.
- visceral epithelial cells (Podocytes).
- Glomerular basement membrane.
- Endothelial cells.
- mesangial cells.
- mesangial matrix.
- macula densa cells.



Parts of glomerulus



Structure of glomerulus in a cross section

Endothelium :

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- 1st barrier to filtration.
- Simple squamous layer of **fenestrated cells**.
- Fenestrae : 55% of surface area.
- Size of fenestrae : **50 to 100 nm**.
- Diaphragms present only in efferent arteriole.
- Polyanionic glycosaminoglycans : Glycocalyx.
- Receptors expressed : Class II HLA, VEGF receptor, endothelin, EDRF, PRGF.

GBM (Glomerular basement membrane) :

- It covers capillary loops and reflex to mesangium in the axial regions.
- Three parts : Lamina rara interna, externa and lamina densa.
- Thickness : 320 to 340 μm .
- Podocytes are involved in synthesis & degradation.
- Constituents : **Type IV collagen**, laminin, entactin, nidogen and sulfated proteoglycans.
- Collagen : 400 micron triple helix (Alpha 1-6).
- Proteoglycans : Heparan sulphate, agrin and perlecan.

Mesangium :

Two parts : mesangial cells and matrix.

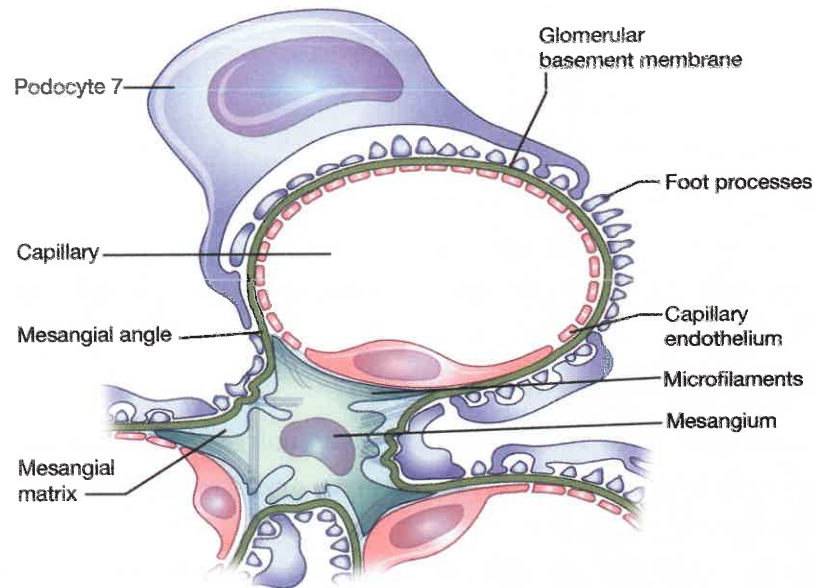
Found in **juxtacapillary region** and axial region.

Mesangial cell :

- Large, irregular cell with elongated cytoplasmic processes.
- Intermediate filaments are present in the processes.
- It bridges the gap between GBM and capillaries and protects capillaries from hydraulic pressure.
- **Phagocytic**, smooth muscle like properties.
- Involved in generation and degradation of mesangial matrix.
- Matrix : **Type IV and V collagen**, fibronectin, fibrillin, entactin.
- Mesangial cells produce vasoactive substances.
- Cross talk between endothelial cell and podocytes to maintain glomerular function.

Peripheral portion of a glomerular lobule

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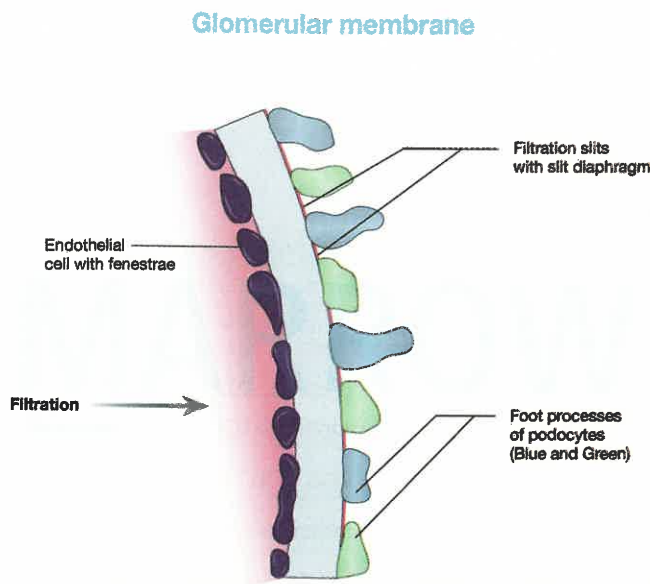
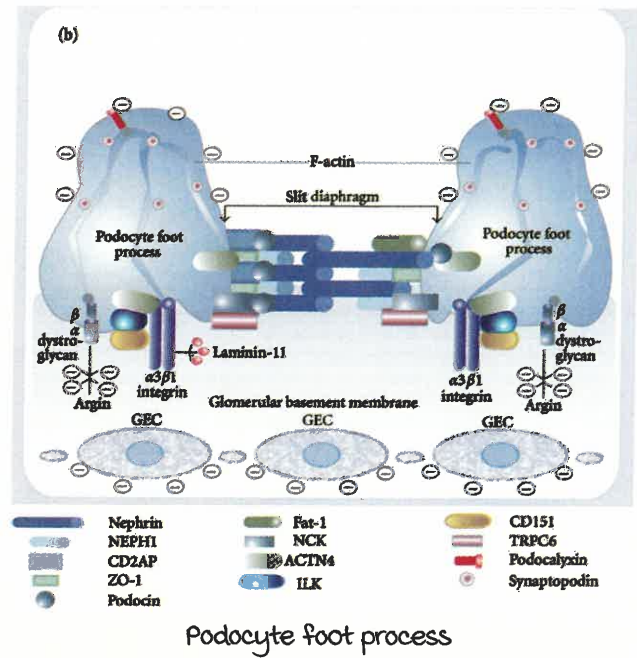
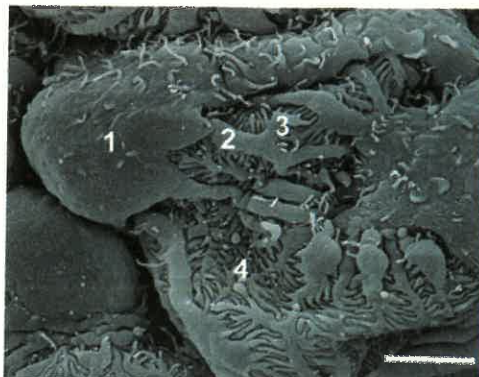
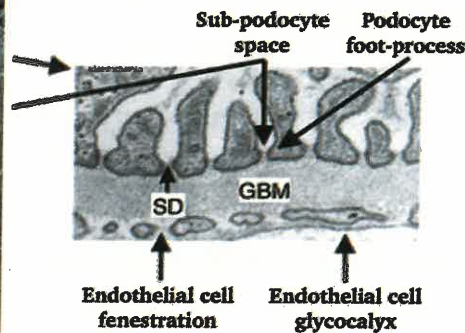
This shows a capillary, the axial position of the mesangium, and the visceral epithelium (podocytes). At the capillary-mesangial interface, the capillary endothelium directly abuts the mesangium.

Podocytes (visceral epithelial cells) :

- Octopus shaped cells, **largest cells**.
- Attach to the GBM by **foot processes**.
- Terminally differentiated cells.
- Contains golgi, lysosomes and are capable of endocytosis.
- microtubules, microfilaments and intermediate filaments are present in cytoplasm & actin filaments in foot processes.

Filtration slit-gap between the foot processes :

- Gap between two adjacent foot processes (25 to 60 nm).
- 11 nm wide central filament is connected to nearby foot process by regular cross bridges, 7 nm in diameter and 14 nm in length.
- Slit diaphragms are adherens junction and ZO-1 junction.



Scanning electron microscopical view of podocytes

Slit diaphragm :

- P-Catheidin, **nephrin**, nephl and FAT are involved in the inter foot process connection.
- ZO1, podocin, CD2AP and catenins connect actin cytoskeleton to the slit diaphragm proper.
- Nephlin : Ig superfamily.
- Nephl : Ligand for nephrin.
- Podocin : Raft associated stomatin family.
- Fat is the major component.

Podocyte attachment to GBM :

- Alpha3 beta1 integrins bind to collagen type 4, fibronectin and laminin II.
- Dystroglycan complex connects the intracellular molecule utrophin to laminin II, agrin and perlecan in the GBM.

----- Active space -----

- Both integrins and dystroglycans are coupled via adapter molecules (Paxillin, vinculin, actinin) to the podocyte cytoskeleton, allowing signalling as well as transmission of mechanical force.
- Actin connected to podocalyxin by negative charge.

monogenic nephrotic syndrome :

Mutation	Syndromes
NPHS1	Congenital nephrotic syndrome (CNS)
Nphs2 (Podocin)	Steroid resistant nephrotic syndrome
WT1	Denys-drash syndrome (DDS)
Laminin beta 2	Pierson syndrome (DMS)
PLCE1	Diffuse mesangial sclerosis (DMS)
CD2AP	AR focal segmental glomerulosclerosis (FSGS)
ACTN4	AD FSGS

Parietal epithelial cells :

- Squamous cells but transition to taller cuboidal cells at urinary pole.
- Continuous with visceral epithelium at vascular pole.
- Long cillium and microvilli but cell organelles are sparse.
- **Final filtration barrier.**
- Can transdifferentiate to podocytes.
- involved in **crescent** formation.

Glomerular filtration barrier :

- Size and charge selective.
- High permeability to water & small solutes.
- GBM is a unique barrier to anionic substances.
- molecules above radius of 4 micron are totally restricted.

Juxtaglomerular apparatus :

Portion of distal nephron comes into contact with the parent glomerulus.

Consists of :

- Tubular component : **macula densa.**
- Vascular component : Afferent arteriole.
- JG granular cells or myoepithelial cells.
- Agranular extra glomerular mesangial cells or lacis cells.

Granular cells contain renin and angiotensin II.

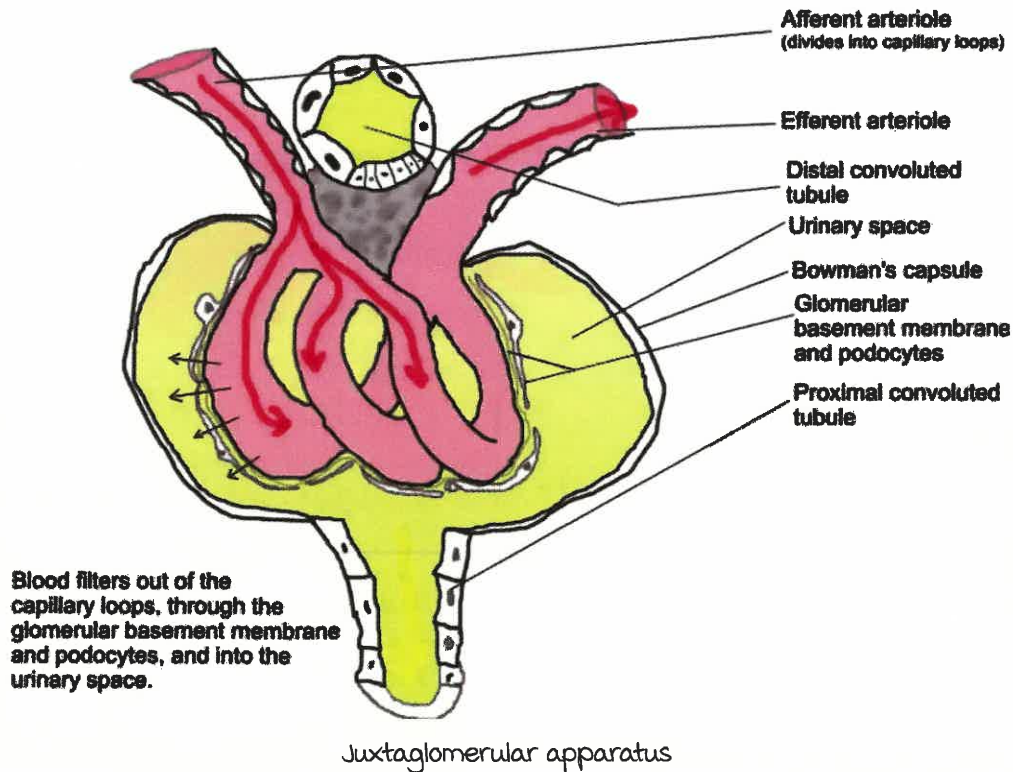
macula densa :

- Special area in the TAL DCT junction adjacent to hilum of parent glomerulus.
- Columnar cells with apical nuclei are present.

Extra glomerular mesangium interdigitate with extra glomerular mesangial cells.

Juxtaglomerular apparatus is rich in autonomic nerve endings and synapses.

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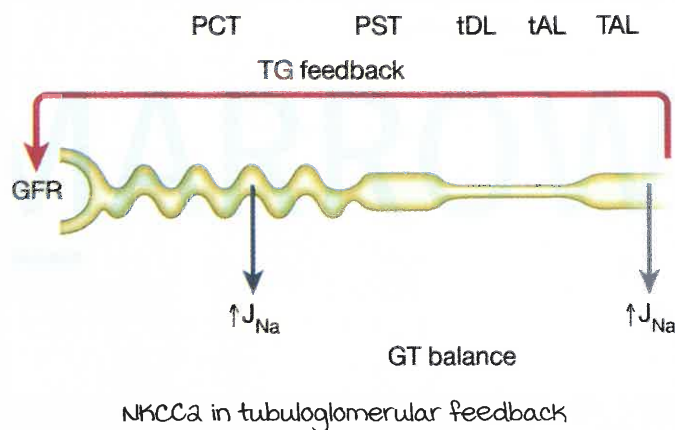
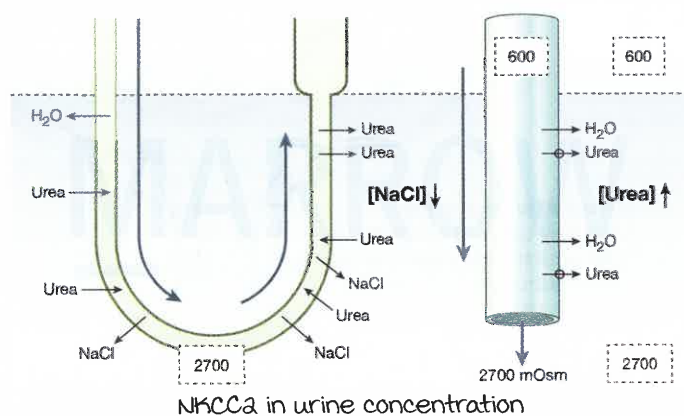
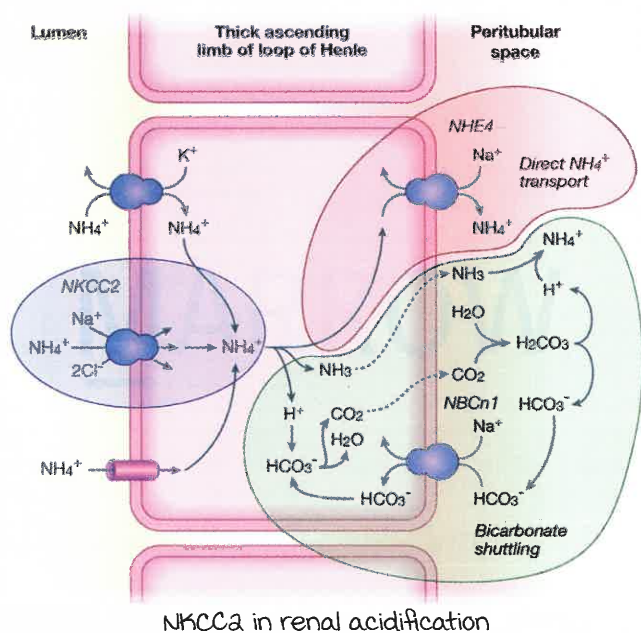
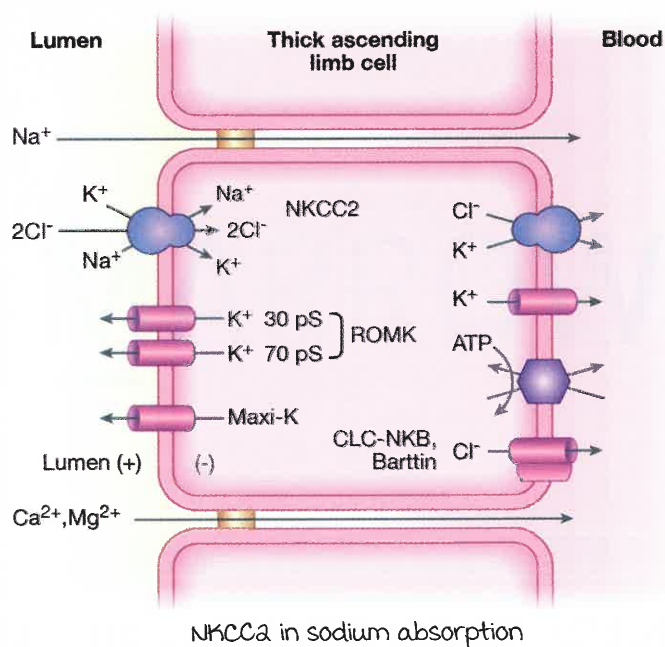
LOOP DIURETICS

Mechanism of action

00:00:40

Role of NKCC2 in the kidney :

- Sodium/chloride reabsorption.
- Role in urinary concentration and free water excretion.
- **Tubuloglomerular feedback.**
- Indirect role in calcium/magnesium absorption.
- Effect on renal acidification.



mechanism :

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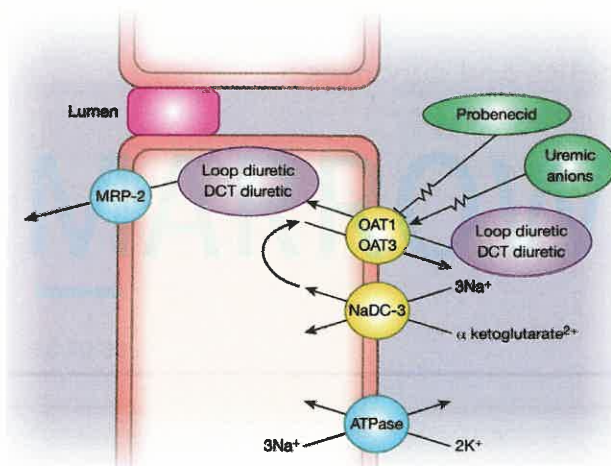
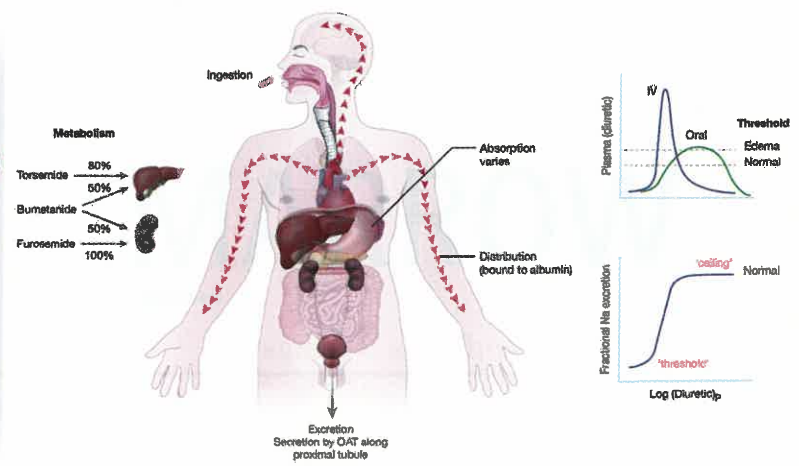
- Loop diuretics act on the NKCC2 channel by attaching on the Cl transporter.
- **Reversible inhibition.**
- Loop diuretics are organic anions and bind to NKCC2 from the luminal surface.

Pharmacokinetics and pharmacodynamics

00:03:02

Pharmacokinetics :

4 processes : Absorption, distribution, metabolism and excretion.

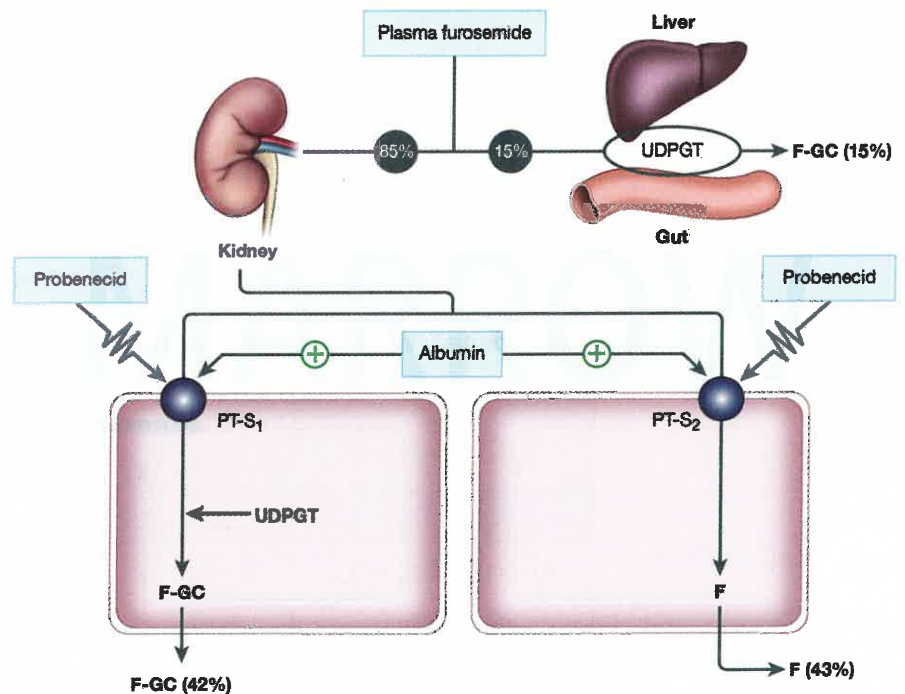
mechanism of diuretics secretion
by proximal tubule cells

Absorption and distribution

Absorption & distribution :

Ceiling dose : No increase in effect beyond a particular dose.

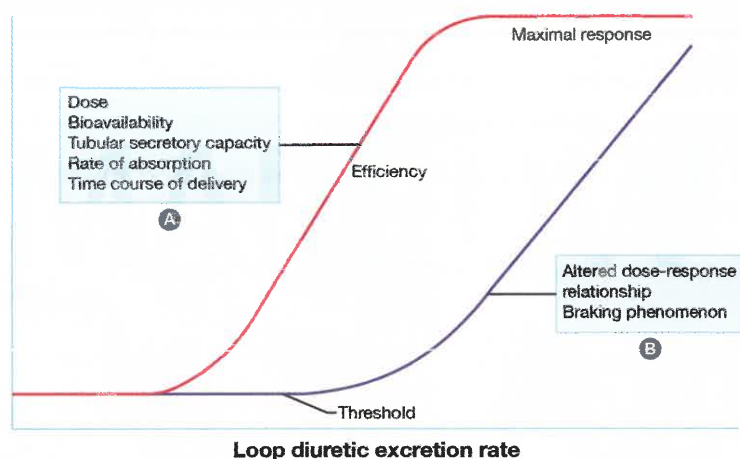
Dose of administration should be between threshold dose and ceiling dose.

metabolism & excretion :metabolised in **PCT** of kidney (Glucuronidation) and liver.

metabolism and excretion

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Pharmacodynamics :
Effect of drug on the body.



Clinical implications of pharmacokinetics and dynamics :

- Loop diuretics have steep dose-response curves.
- Threshold dose (Changes with disease conditions).
- Ceiling dose.
- Volume of distribution and **hypoalbuminemia**.

Individual drugs

00:07:31

	Furosemide	Bumetanide	Torsemide
Relative potency	4	160	16
Oral bioavailability	10-100%	80-100%	80-100%
Affected by food	Yes	Yes	No
metabolism	50% renal	50% hepatic	80% hepatic
Half-life	1.5-3 hrs	1-1.5 hrs	3-6 hrs
Onset	PO : 30-60 min IV : 5 min	PO : 30-60 min IV : 2-3 min	PO : 30-60 min
Elimination	88% renal 12% hepatic	81% renal 2% hepatic	24% renal

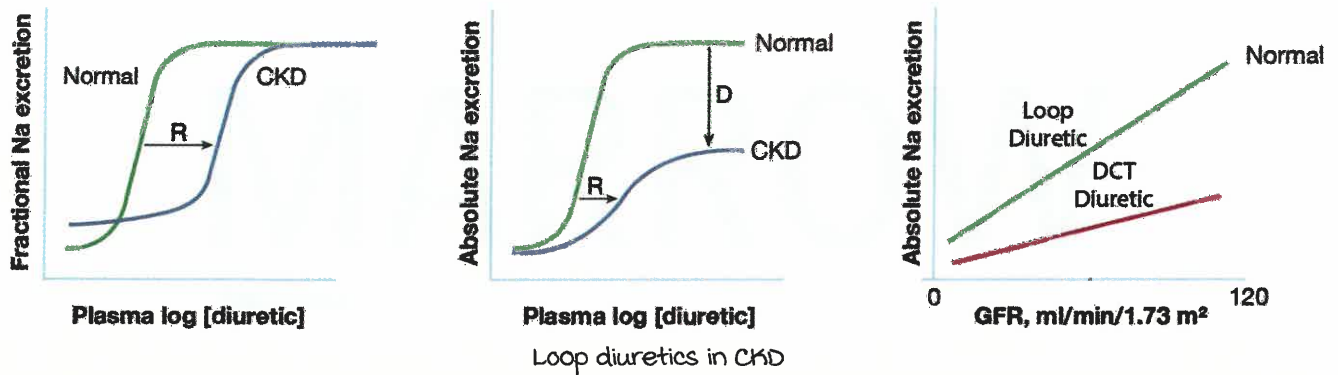
Highest doses that can be given in various conditions :

Condition	Furosemide (in mL)		Bumetanide (Oral/iv) (in mL)	Torsemide (Oral/iv) (in mL)
	IV	Oral		
CKD (GFR 20-50)	80-160	160	6	50
GFR (<20)	200	240	10	100
NS with normal GFR	120	240	3	50

Loop diuretics in CKD :

- Prolongation of $t_{1/2}$.
- Abnormal diuretic secretion due to metabolic acidosis/uremia.
- Flattening of dose response curve.
- Downward shift of ceiling natriuresis.

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Loop diuretics in nephrotic syndrome :

4 mechanisms of abnormal responsiveness to loop diuretics :

1. Decreased delivery/decreased secretion (Threshold dose is higher).
2. Increased renal metabolism.
3. Decreased blockade by the diuretic.
4. Increased Na, Cl reabsorption by other nephron segments.

Adaptation to diuretic therapy

00:09:58

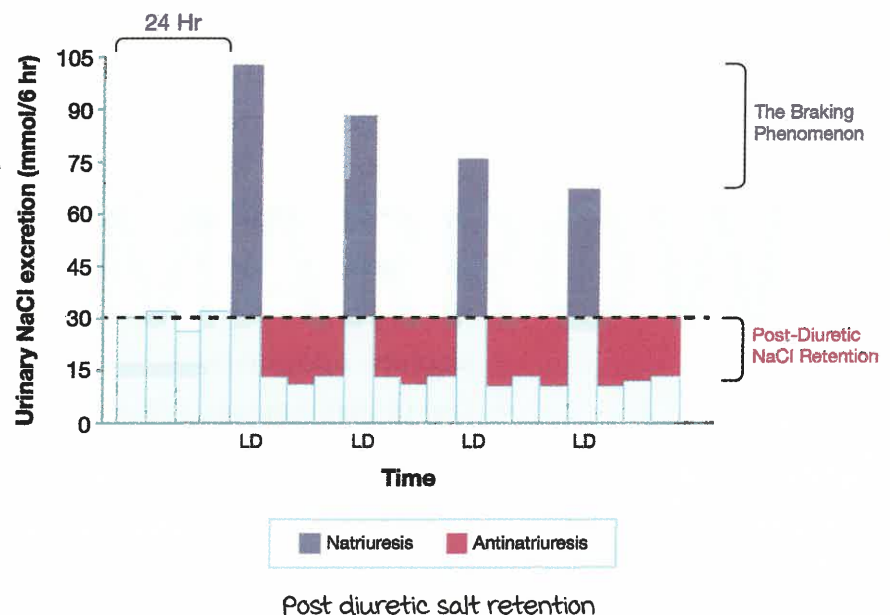
Adaptation :

Also known as **braking phenomenon**.

Hemodynamic adaptation : Fall in effective circulatory volume (ECV) →

Sympathetic nervous system activation → Angiotensin and aldosterone axis activation.

Neurohormonal : Renin secretion independent of ECV → RAAS → JG hyperplasia → Hyperplasia & hypertrophy of distal tubular cells.



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Clinical implications of braking :

- Dietary salt restriction is very important for preventing post diuretic salt retention (<2 g/day, <90 mmol/day).
- Consider multiple daily dosing, diuretic with prolonged action or continuous administration.
- Sequential blockade with diuretics of other class.
- Diuretic therapy should not be abruptly stopped.
- Salt restriction should be continued after stoppage of diuretics as well.

Diuretic resistance

00:11:58

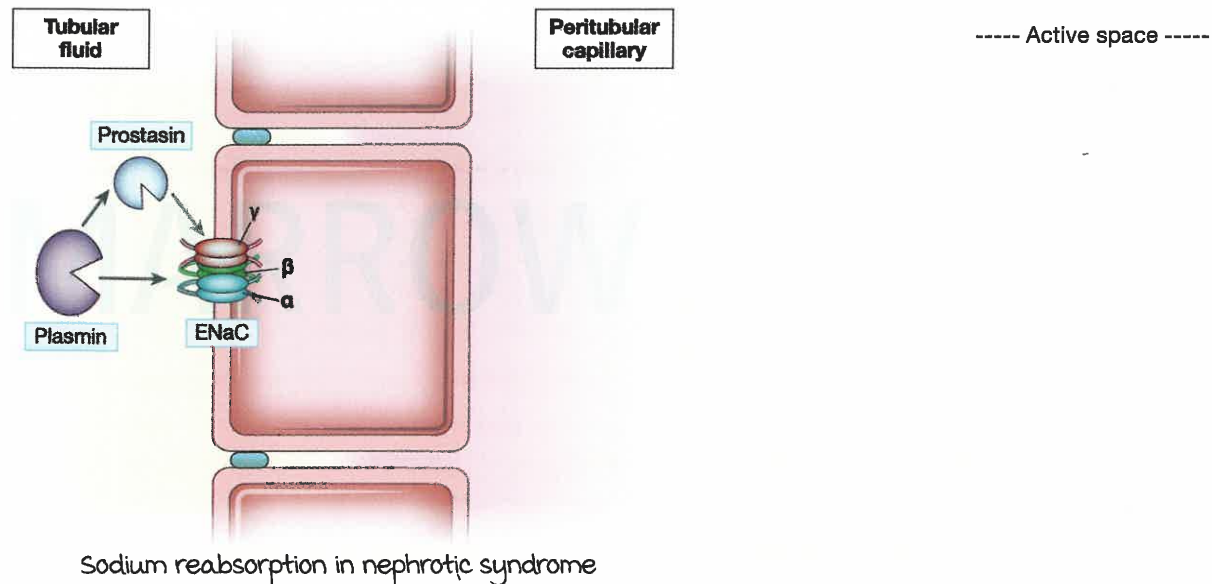
Diuretic resistance is defined as failure to achieve therapeutically desired reduction in edema despite a full dose of diuretic.

Causes :

- Incorrect diagnosis (E.g., : venous or lymphatic edema).
- Non-adherence to recommended sodium and/or fluid restriction.
- Drug not reaching the kidney :
 - Non-adherence.
 - Dose too low or too infrequent.
 - Poor absorption.
- Reduced diuretic secretion :
 - Tubular uptake of diuretic impaired by uremic toxins.
 - Decreased kidney blood flow.
 - Decreased functional kidney mass.
- Insufficient kidney response to drug :
 - Low glomerular filtration rate.
 - Decreased effective intravascular volume despite elevated total extracellular fluid volume.
 - Activation of the renin-angiotensin system.
 - Nephron adaptation (Braking phenomenon).
 - use of non steroidal anti-inflammatory drugs.

Diuretics in nephrotic syndrome :

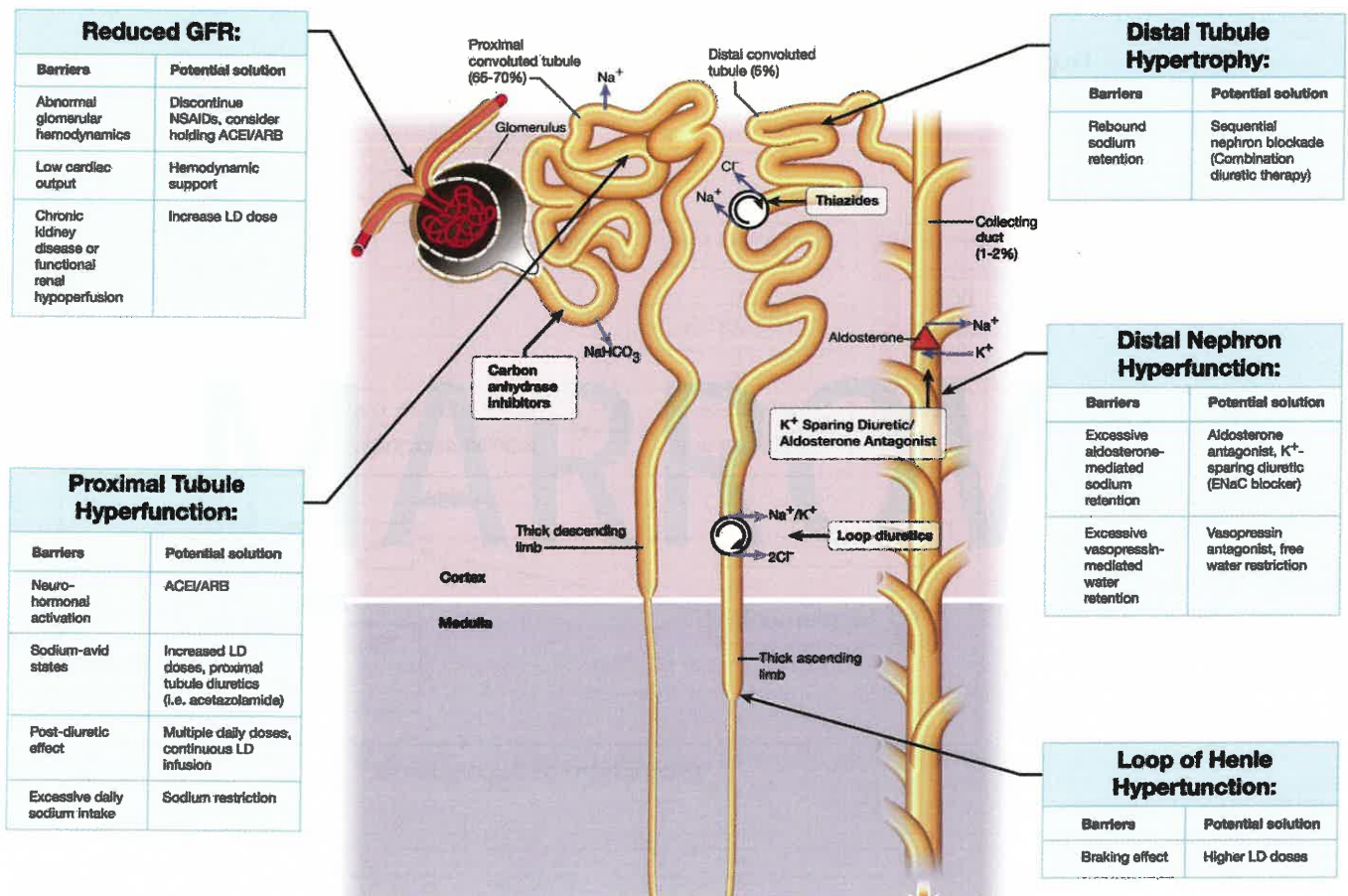
Plasminuria activates ENaC channels in collecting ducts and tubules → Sodium is reabsorbed.



Summary :

- Diuretic resistance is often accompanied by profound metabolic alkalosis.
- metabolic alkalosis is managed by administering KCL or K sparing diuretics.

Summary of diuretic resistance



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Adverse effects

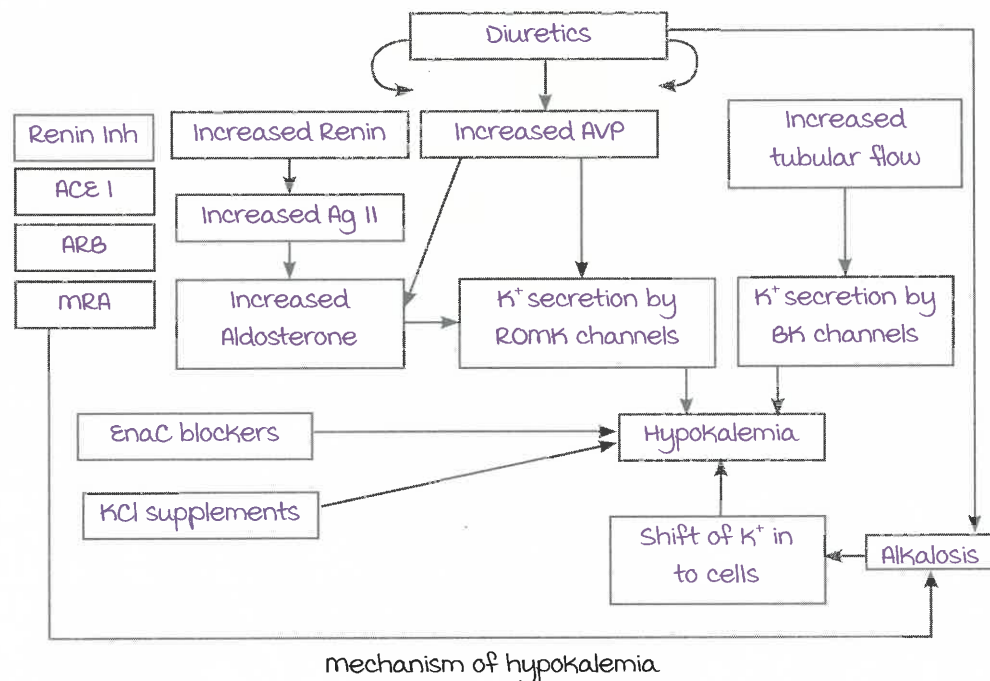
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Includes :

- Idiosyncratic effects including **acute interstitial nephritis (AIN)**.
- Hyponatremia (very rare).
- Hypokalemia.
- Hypomagnesemia.
- metabolic alkalosis.
- Ototoxicity.
- ECV depletion and AKI.

Hyponatremia :

- Seen **more with thiazides**.
- Loop diuretics inhibit Na^+ transport in the renal medulla : maximal osmotic gradient can not be achieved.
- Thus, loop diuretics impair the ability to produce concentrated urine.
- Thiazide type diuretics increase Na^+ excretion, prevent maximal dilution of the urine and maintain the innate concentrating capacity of the kidney.

Hypokalemia :

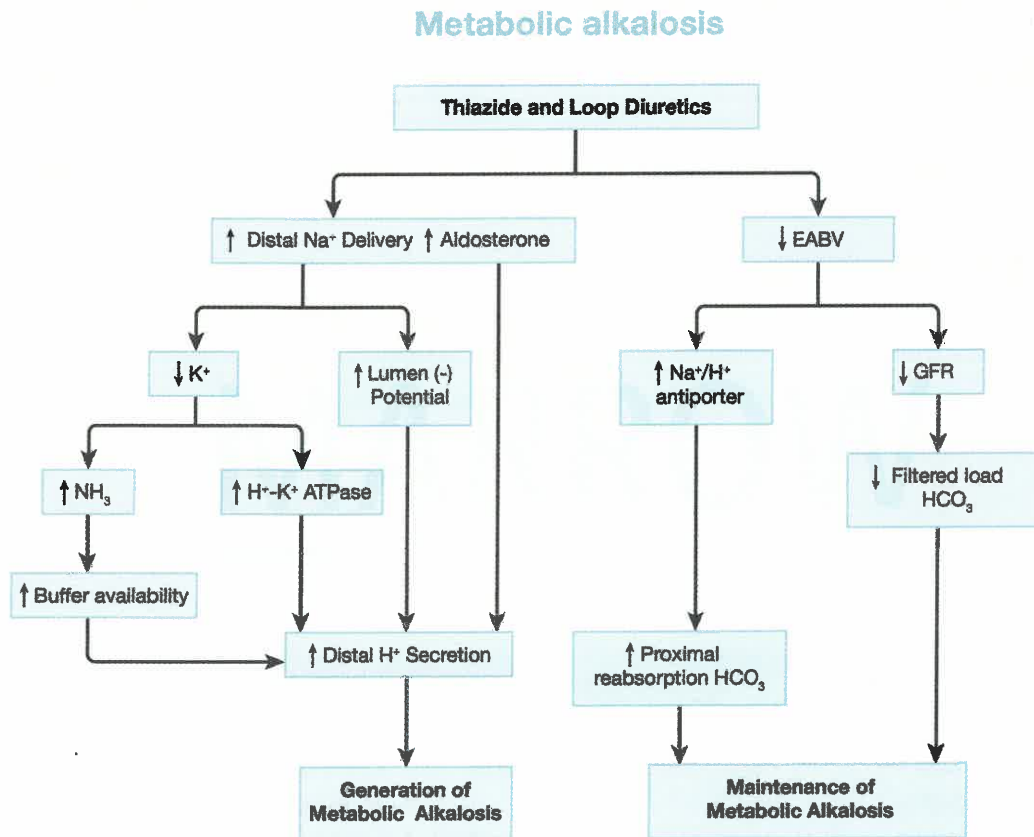
Hypomagnesaemia :

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- Loop diuretics inhibit paracellular mg reabsorption in the TAL.
- Though calcium absorption is also less, hypocalcemia is rare.
- Both calcium and mg have distal mechanisms of absorption (TRMP, TRPV5) which remains intact during loop diuretic therapy.

Ototoxicity :

- Inhibition of NKCC1 isoform in the striae vascularis of inner ear.
- Associated with high plasma levels.
- more in administering boluses/and in CKD patients.
- usually reversible toxicity.

metabolic alkalosis :**Drug interactions with NSAID/ACEI :**

Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs is associated with **risk of acute kidney injury** : Nested case-control study.

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APPROACH TO HEMATURIA

Definition :

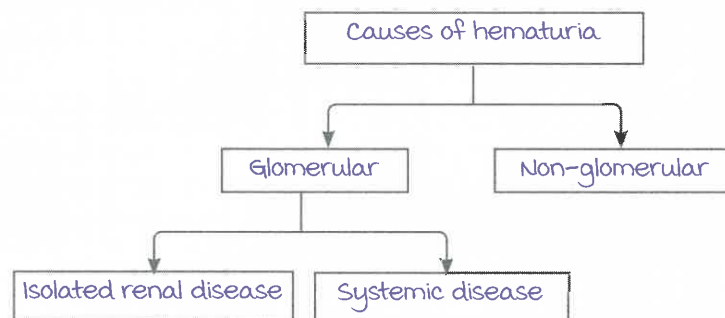
- Presence of at least 5 red blood cells (RBC's) per μL of urine.
- >3 RBC per high power field (HPF) of 10 ml of centrifuged urine.
- >5 RBC per mm^3 of freshly voided, unspun urine.
- Significant hematuria : >50 RBCs/ μL .
- Incidence of gross hematuria in children is estimated to be 0.13%.
- In 56% cases, this is due to an easily identifiable cause.
- Asymptomatic microscopic hematuria is 10x as prevalent as gross hematuria.
- most cases of microscopic hematuria in children are transient, and with repeated evaluations, the prevalence decreases to less than 0.5%.

Etiology

00:02:19

RBCs may originate from glomeruli, renal tubules, interstitium, or urinary tracts.

Etiological classification :



Isolated renal disease	Systemic disease	Non-Glomerular cause
<ul style="list-style-type: none"> • Post infectious glomerulonephritis • IgA nephropathy • Alport syndrome • MPGN, FSGS • Thin GBM disease 	<ul style="list-style-type: none"> • SLE • Henoch Schonlein purpura (HSP) • Hemolytic uremic syndrome • Anti GBM disease • Good pasture's disease • Shunt nephritis • Infective endocarditis 	<ul style="list-style-type: none"> • Trauma • urethral foreign body • Infections • Nephrolithiasis • Idiopathic hypercalciuria • Drugs : NSAIDs, cyclophosphamide • Hematological : Sick cell anemia, Disseminated intravascular coagulation • Wilms tumor • Bladder hemangioma • Renal vein/artery thrombosis

Causes of hematuria in newborn :

----- Active space -----

- Renal vein thrombosis.
- Renal artery thrombosis.
- Autosomal recessive polycystic kidney disease.
- Obstructive uropathy.
- Urinary tract infection.
- Bleeding and clotting disorders.
- Trauma, bladder catheterization.

Note :

Pink urine in newborn, negative for blood : uric acid crystals.

History

00:06:08

Presentation :

- Gross hematuria.
- Urinary or other symptoms with incidental finding of microscopic hematuria.
- Inadvertent discovery of microscopic hematuria during a routine urinalysis.

History d/t glomerular cause :

- Hematuria : Cola coloured urine.
- Edema : Periorbital edema, pedal edema.
- Hypertension features : Vomiting, head ache, seizure.
- Oliguria.
- Sore throat followed by hematuria within 1 to 2 days : IgA nephropathy.
- Sore throat 1 to 2 weeks prior or pyoderma 3 weeks prior : Post streptococcal glomerulonephritis.
- Purpuric rash, abdominal pain, joint pain : Henoch schonlein purpura.
- Loose stools, anemia, hematuria : HUS.
- Adolescence, female predominant, rash, joint swelling/pain : SLE nephritis.
- Sudden deterioration with AKI : Rapidly progressive glomerulonephritis (RPGN).
- Recurrent episode of gross hematuria : IgA nephropathy, Alport, thin basement membrane disease.
- Hearing impairment : Alport syndrome.

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History d/t non-glomerular cause :

- Bright red colour urine or microscopic hematuria.
- Trauma, fresh blood or clots in urine : **urethral injury**.
- Abdominal mass : **wilms tumour, hydronephrosis**.
- Fever, dysuria, urgency, lumbar or suprapubic pain, foul smell in urine : **Urinary tract infection**.
- Bleeding disorder : Thrombocytopenia, coagulation disorder.
- Sick cell anemia.
- Colicky abdominal pain, passage of stone in urine : **urolithiasis**.
- Unilateral loin pain preceding hemorrhage (**Nut cracker syndrome**).
- Relation with exercise or strenuous activity.

Note :

Painful hematuria is almost always non glomerular (**march hematuria**).

Family history :

- Hematuria, hearing impairment in family member especially maternal uncle : Alport syndrome.
- Sick cell disease.
- Chronic kidney disease.
- Visual defects.
- **Renal stones** : Hereditary hypercalciuria (Autosomal dominant).

Urine examination

00:10:28

Gross examination :

Collection of appropriate mid catch urine.

Second urine sample in morning is used.

Uncentrifuged sample :

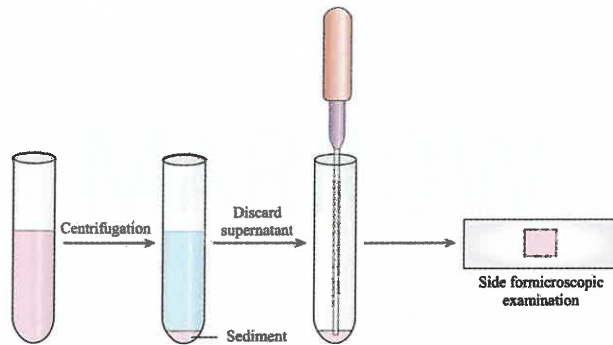
- Bright red color : **Lower urinary tract hematuria**.
- Cola coloured : **Glomerular hematuria**.
- Blood drops or clot initially while passing urine : **urethral injury**.
- Blood at end of passing urine : **Bladder cause**.

Centrifuged sample :

- Take 10 ml of urine centrifuge at 3000 rpm for 5 min.
- Discard supernatant.
- Re-suspend in 0.5 mL supernatant and prepare slide.
- View in microscope.
- In centrifuged sample if supernatant is clear : **Hematuria**.
- If supernatant is still red : **Hemoglobinuria or myoglobinuria**.

Preparation of urine sediment for microscopic examination

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Dipstick method :

- Reagent strip reaction utilizes **pseudoperoxidase activity** of hemoglobin (Or myoglobin).
- Catalyzes a reaction between hydrogen peroxide and chromogen tetramethylbenzidine to produce an **oxidized chromogen**, which has a **green-blue color**.
- Sensitivity of 100 % and a specificity of 99% in detecting **1 to 5 RBC's**/ high power field (HPF).
- False negative results :
 - **Formalin** (Used as a urine preservative).
 - High urinary concentrations of **ascorbic acid** (Patients with vitamin C intake >2000 mg/day).
- False-positive results :
 - **Alkaline urine** (pH >8).
 - Contamination with oxidizing agents such as **hydrogen peroxide** used to clean the perineum before obtaining a specimen.

