Paediatrics Nephrology Part 1

Marrow ss
Paediatrics 2024

Paediatrics Nephrology

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Part -1

BASICS OF NEPHROLOGY

1. Glomerulus — 4.1 — 21 Min video
2. Loop Diuretics — 3.7 — 18 Min video
3. Approach to Hematuria — 4.3 — 29 Min video

HEREDITARY AND CYSTIC RENAL DISORDERS

4. ADPKD — 4.2 — 38 Min video
5. ARPKD & Other Cilia Related Renal Cystic Disorders — 4.4 — 38 Min video
6. ADTKD — 4.2 — 33 Min video
7. Antenally Detected Hydronephrosis — 4.3 — 19 Min video
8. Posterior Urethral Valve: Course & Complications — 4.1 — 24 Min video
9. Congenital Anomalies of Kidney & Urinary Tract (CAKUT) — 4.2 — 40 Min video

RENAL CALCULI

10. Nephrolithiasis in Children — 4.3 — 49 Min video
11. Nephrolithiasis (MCQ Discussion) — 4.2 — 6 Min video
12. Hyperoxaluria — 4.1 — 35 Min video

GLOMERULAR DISORDERS

13. Pathogenesis of Nephrotic Syndrome — 4.0 — 32 Min video
14. Nephrotic Syndrome - Diagnosis and Management — 4.3 — 26 Min video
15. Steroid Resistant Nephrotic Syndrome - An Update — 4.1 — 33 Min video
16. Ig A Nephropathy in Children — 4.3 — 47 Min video
17. Nephrotic Syndrome (MCQ Discussion) — 4.3 — 9 Min video
18. Membranous Nephropathy in Children — 4.4 — 34 Min video

TUBULOINTERSTITIAL DISEASES

19. Acute Tubulo - Interstitial Nephritis — 4.3 — 22 Min video
20. Ig A Vasculitis Nephritis — 4.3 — 16 Min video

VASCULAR DISORDERS OF THE KIDNEY

21. Thrombotic Microangiopathy — 4.1 — 40 Min video
22. Renal Vasculitis — 4.0 — 36 Min video
23. HUS (MCQ Discussion) — 4.2 — 4 Min video

ACUTE KIDNEY INJURY (AKI)

24. Evolution of Definition and Staging of AKI — 4.2 — 16 Min video
25. Pathophysiology of Ischemic AKI — 4.0 — 29 Min video
26. Drug Induced AKI — 4.0 — 28 Min video
27. Biomarkers in AKI — 4.0 — 31 Min video

INFECTIONS AND THE KIDNEY

28. Infection Related Glomerulonephritis — 4.3 — 43 Min video

Part -2

29. UTI ,BBD and VUR — 4.1 — 38 Min video

TUBULAR DISORDERS AND ELECTROLYTES

30. Renal Acidification and RTA in Children — 4.2 — 41 Min video
31. Pathogenesis, Management of Dents Disease & Lowe's Syndrome — 4.2 — 19 Min video
32. Bartter and Gitelman Syndrome — 4.1 — 46 Min video
33. Disorders of Magnesium Metabolism — 4.0 — 36 Min video

CHRONIC KIDNEY DISEASE (CKD)

34. CKD in Children: Classification, Progression & Growth failure — 4.0 — 35 Min video
35. Pathophysiology of Uremia & Uremic Toxins — 3.5 — 23 Min video
36. Hypertension in CKD — 3.9 — 32 Min video
37. Anaemia in CKD — 3.8 — 26 Min video
38. CAPD in Children — 3.6 — 33 Min video
39. CKD-MBD — 3.9 — 44 Min video

HEMODIALYSIS

40. Hemodialysis — 3.7 — 67 Min video

RENAL TRANSPLANTATION

41. Renal Transplantation in Children — 3.7 — 69 Min video
42. Complications of Post Renal Transplant — 3.6 — 71 Min video
43. MCQ - Renal Transplantation — 4.2 — 40 Min video

OTHER SPECIFIC CONDITIONS

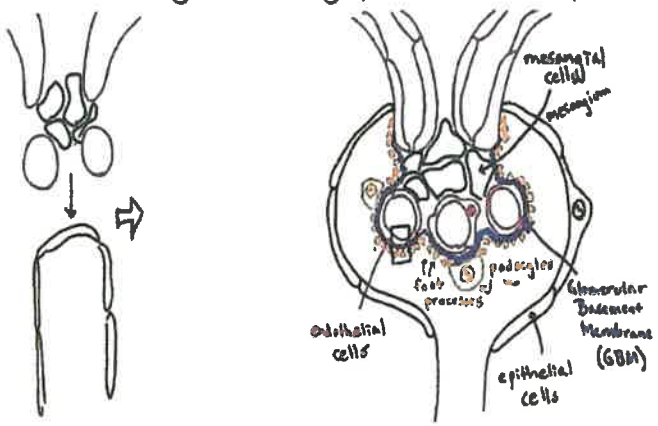
44. Management of Voiding Dysfunction — 3.9 — 36 Min video
45. Monogenic Hypertension — 3.8 — 46 Min video
46. Hypertension in Children — 3.9 — 24 Min video
47. Nephrogenic Diabetes Insipidus — 3.8 — 26 Min video
48. Cystinosis: Pathogenesis, Management and Outcomes — 3.7 — 34 Min video

GLOMERULUS

Introduction 00:00:40

Anatomy of glomerulus :

- Individual filtering unit of a nephron.
- Glomerulus consists of :
  1. Bowman's capsule.
  2. 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 the centre of the capillary tuft to form the 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,

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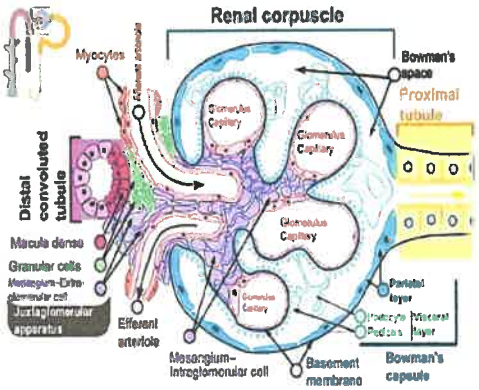
which surrounds the tubules and is called the peritubular capillary network.

Parts of glomerulus

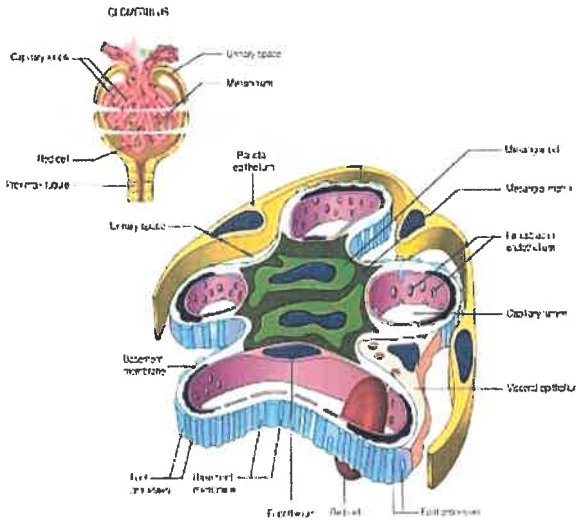
00:04:50

Parts of a glomerulus include :

- Parietal epithelial cells.
- Visceral epithelial cells (Podocytes).
- Glomerular basement membrane.
- Endothelial cells.
- Mesangial cells.
- Mesangial matrix.



Parts of glomerulus.



Structure of glomerulus in a cross section.

Endothelium :

- 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.
- Poluanionic 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.

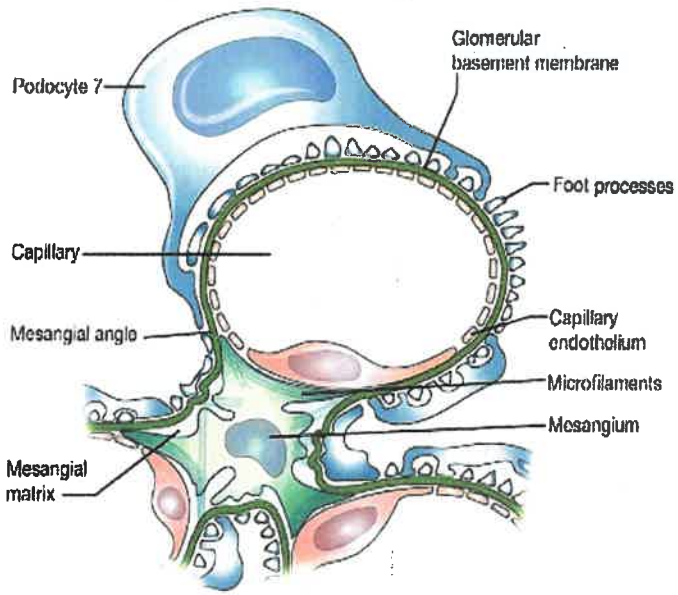
Mesangium :

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.

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.

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Podocytes (Visceral epithelial cells) :

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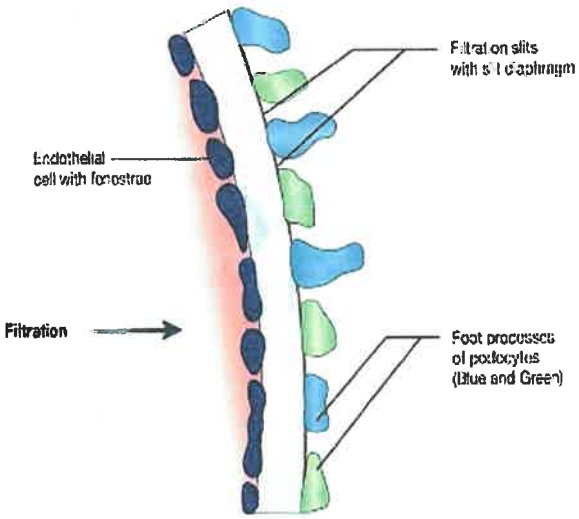
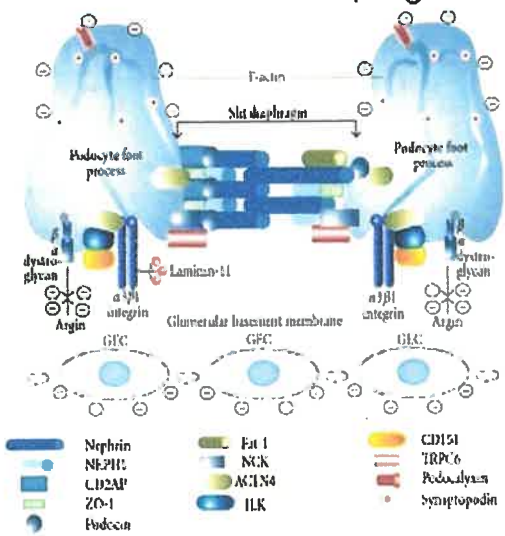
- Octopus shaped cells, largest cells.
- Attach to the GBM by foot processes.
- Terminally differentiated cells.
- Contains golgi, lysosomes and are capable of endocytosis.
- Microtubules, microfilaments and intermediate filaments are present in cytoplasm & actin filaments in foot processes.

Filtration slit-gap between the foot processes :

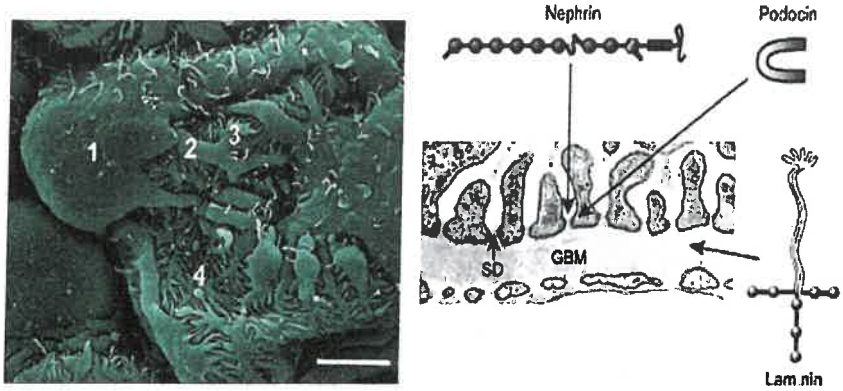
- Gap between two adjacent foot processes (25 to 60 nm).
- 11 nm wide central filament is connected to nearby foot process by regular cross bridges, 7 nm in diameter and 14 nm in length.
- Slit diaphragms are adherans junction and ZO-1 junction.



Filtration slits with slit diaphragm.



Podocyte foot processes.



Scanning electron microscopic view of podocytes.

Slit diaphragm :

- P-Cathedim, nephrin, nephl and FAT are involved in the inter foot process connection.
- ZOl, podocin, CD2AP and catenins connect actin cytoskeleton to the slit diaphragm proper.
- Nephrin : 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 ll.
- Dystroglycan complex connects the intracellular molecule utrophin to laminin ll, agrin and perlecan in the GBM.
- 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
NPHSl	Congenital nephrotic syndrome (CNS).
Nphs2 (Podocin).	Steroid resistant nephrotic syndrome.
WTl	Denys-drash syndrome (DDS).
Laminin beta 2	Pierson syndrome (DMS).
PLCEl	Diffuse mesangial sclerosis (DMS).
CD2AP	AR focal segemntal glomerulosclerosis (FSGS).
ACTN4	AD FSGS.

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Parietal epithelial cells :

- Squamous cells but transition to taller cuboidal cells at urinary pole.
- Continuous with visceral epithelium at vascular pole.
- Long cilliumand 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 :

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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.

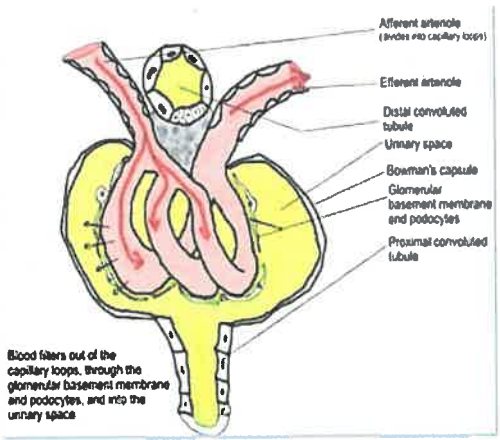
Granular cells contain renin and angiotensin II.

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.



Juxtaglomerular apparatus.

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LOOP DIURETICS

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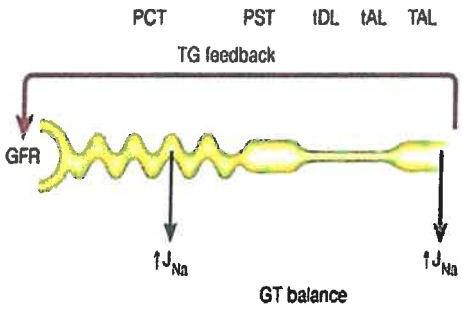
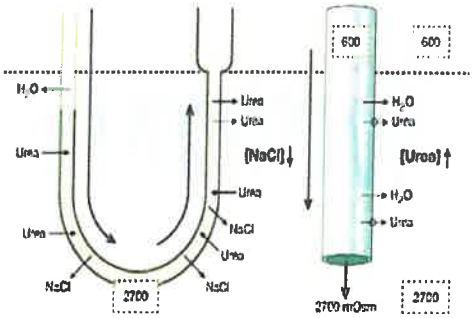
Mechanism of action 00:00:40

Role of NKCC2 in the Kidney :

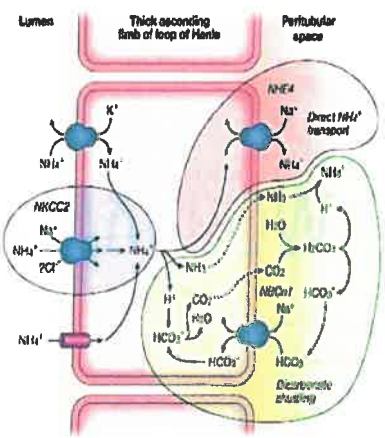
- Sodium/chloride reabsorption.
- Role in urinary concentration and free water excretion.
- Tubuloglomerular feedback.
- Indirect role in calcium/magnesium absorption.
- Effect on renal acidification.



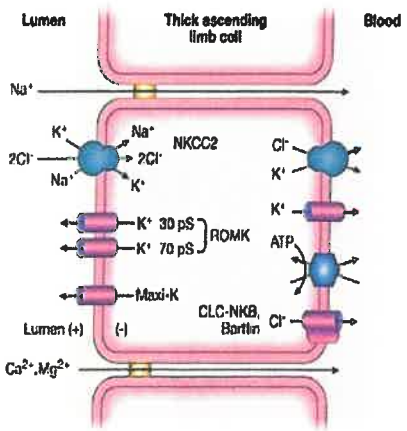
NKCC2 in urine concentration.



Tubulo glomerular feedback.



NKCC2 in renal acidification.



NKCC2 in sodium absorption.

Mechanism :

- 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.

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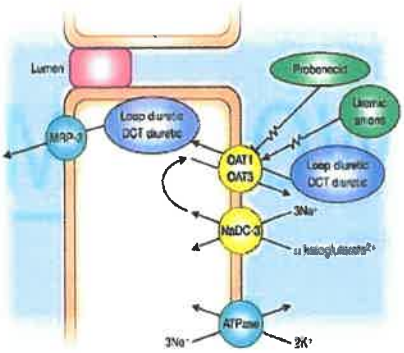
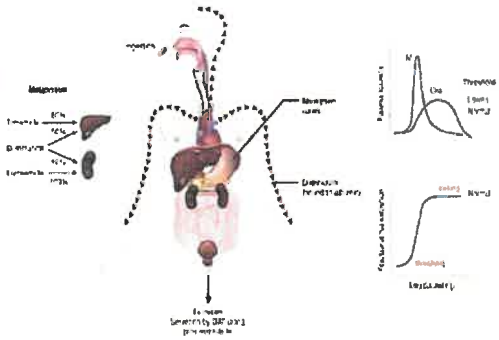
Pharmacokinetics and pharmacodynamics 00:03:02

Pharmacokinetics :

4 processes : Absorption, distribution, metabolism and excretion.



mechanism of diuretics secretion by proximal tubule cells.



Absorption and distribution.

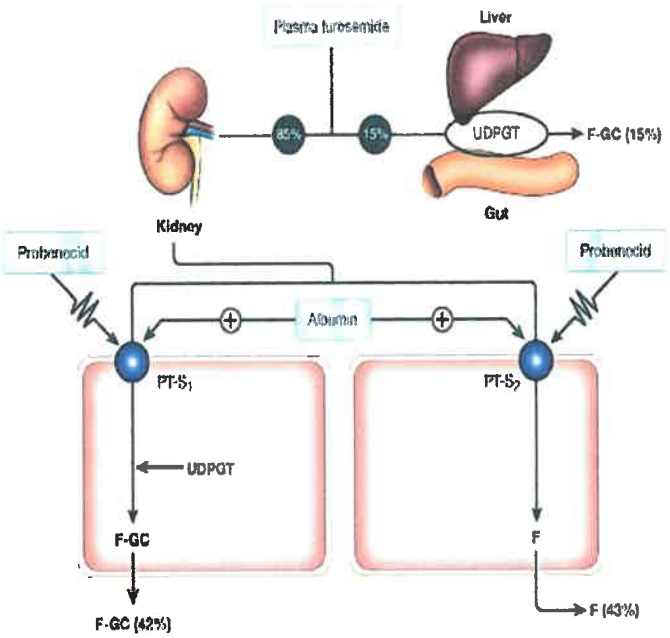
Absorption & distribution :

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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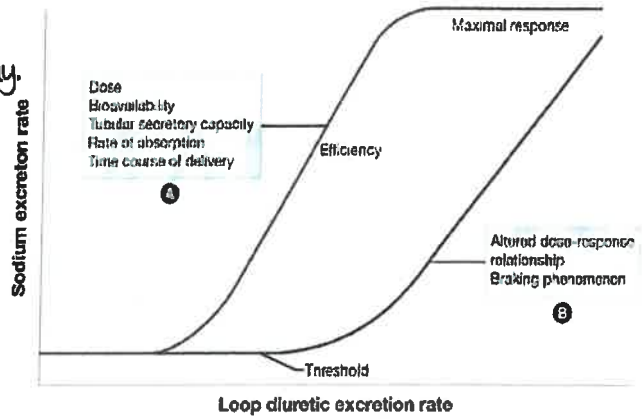
Pharmacodynamics :

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 (GFR20-50).	80-160	160	6	50
GFR (<20).	200	240	10	100
NS with normal GFR.	120	240	3	50

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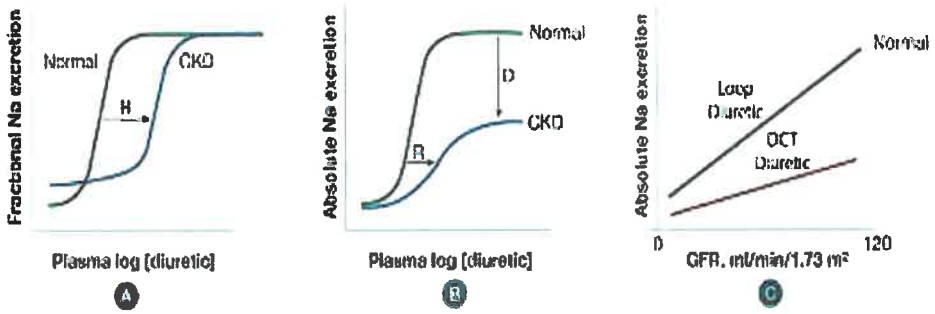
Loop diuretics in CKD :

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



Loop diuretics in CKD.

Loop diuretics in nephrotic syndrome :

4 mechanisms of abnormal responsiveness to loop diuretics

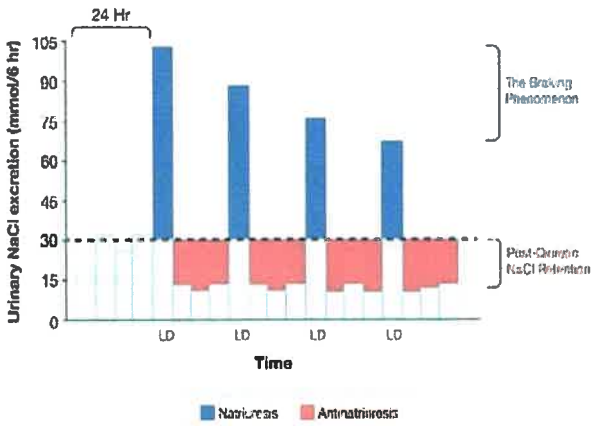
1. Decreased delivery/decreased secretion (Threshold dose is higher).
2. Increased renal metabolism.
3. Decreased blockade by the diuretic.
4. Increased Na, Cl reabsorption by other nephron segments.

Adaptation to diuretic therapy 00:09:58

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 independant of ECV → RAAS → JG hyperplasia → Hyperlasia & hypertrophy of distal tubular cells.



Post diuretic salt retention.

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Clinical implications of braking :

- Dietary salt restriction is very important for preventing post diuretic salt retention (<2g/day, <90mmol/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 (Eg : Venous or lymphatic edema).
- Non-adherence to recommended sodium and/or fluid restriction.
- Drug not reaching the kidney :
  a. Non-adherence.
  b. Dose too low or too infrequent.
  c. Poor absorption.
- Reduced diuretic secretion :
  a. Tubular uptake of diuretic impaired by uremic toxins.
  b. Decreased kidney blood flow.
  c. Decreased functional kidney mass.
- Insufficient kidney response to drug :
  a. Low glomerular filtration rate.
  b. Decreased effective intravascular volume despite elevated total extracellular fluid volume.
  c. Activation of the renin-angiotensin system.
  d. Nephron adaptation (Braking phenomenon).
  e. Use of non steroidal anti-inflammatory drugs.

Diuretics in nephrotic syndrome :

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

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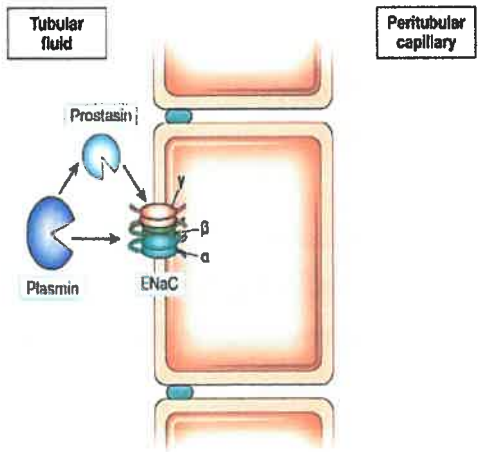
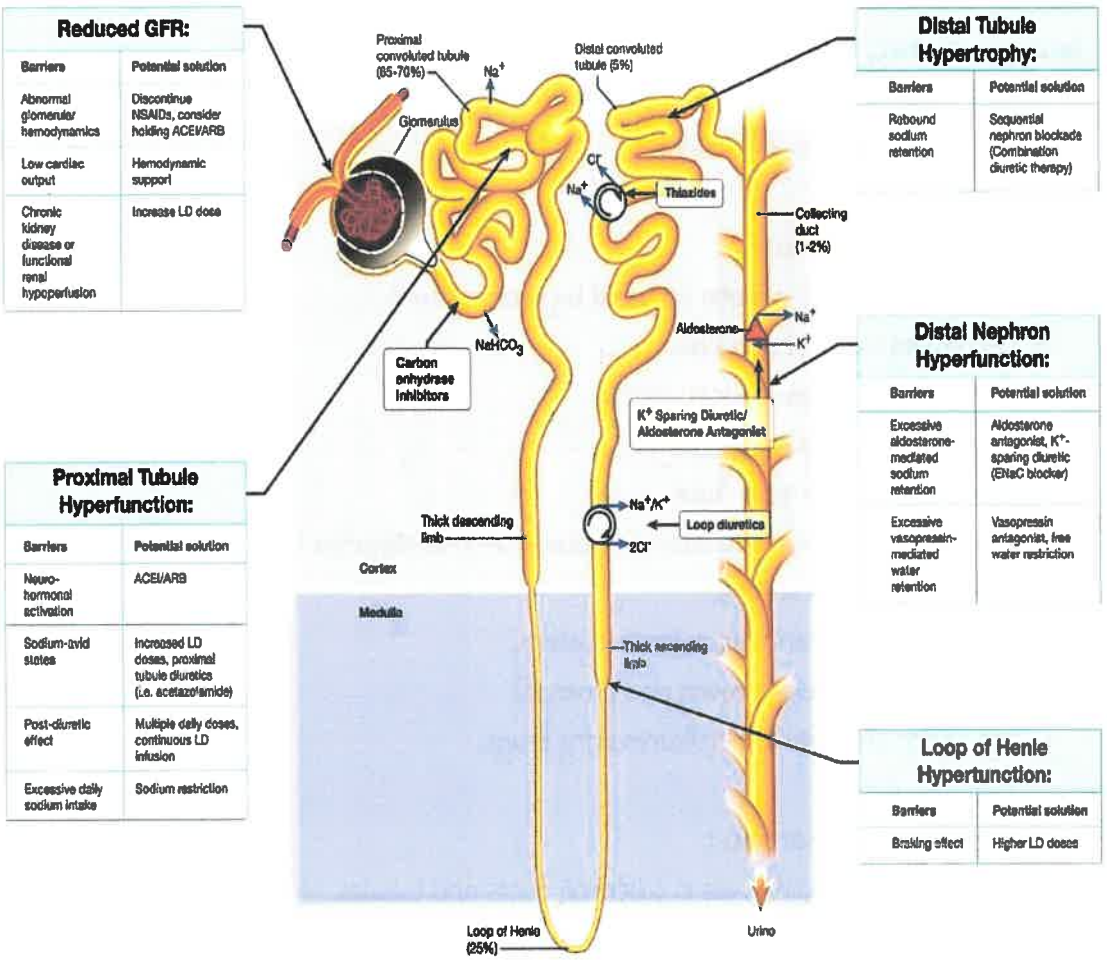


Sodium reabsorption in nephrotic syndrome.

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.

Adverse effects

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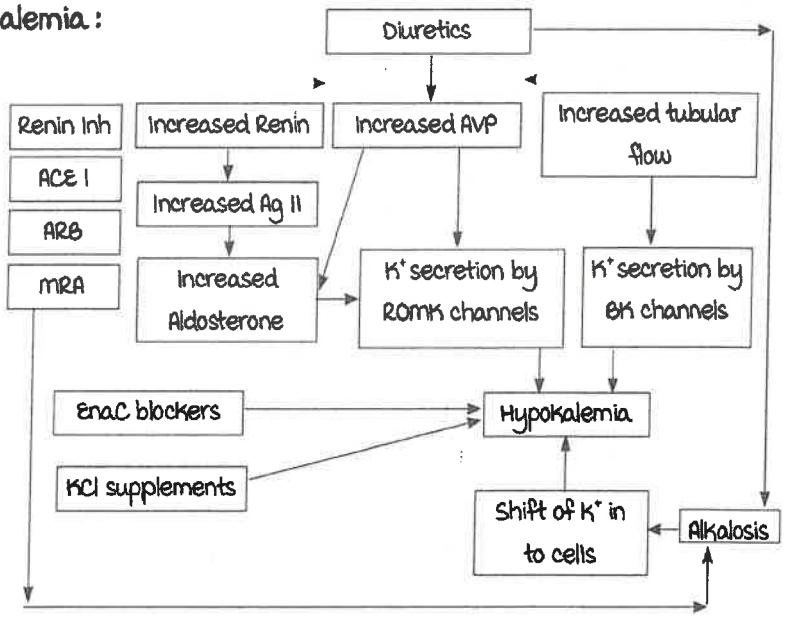
Include :

- 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 :



mechanism of hypokalemia.

Hypomagnesemia :

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

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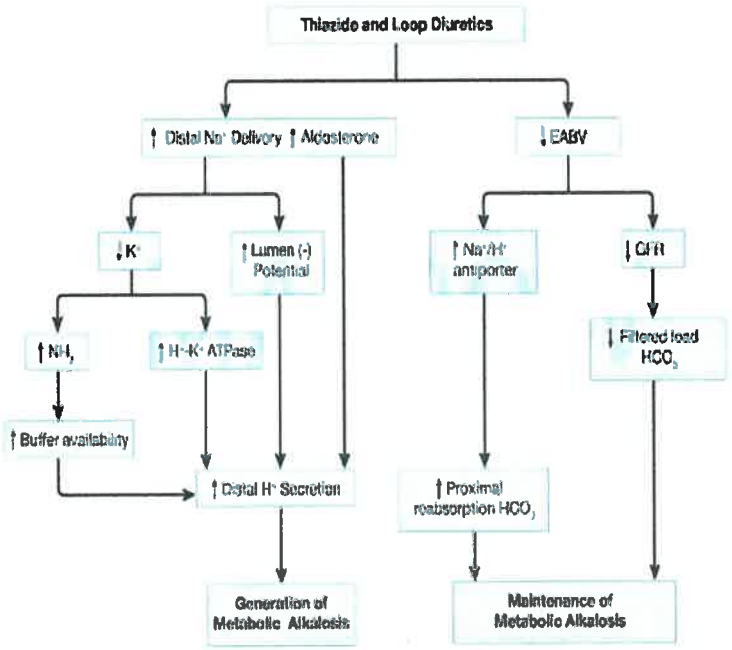
Ototoxicity :

- 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 (RBCs) 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

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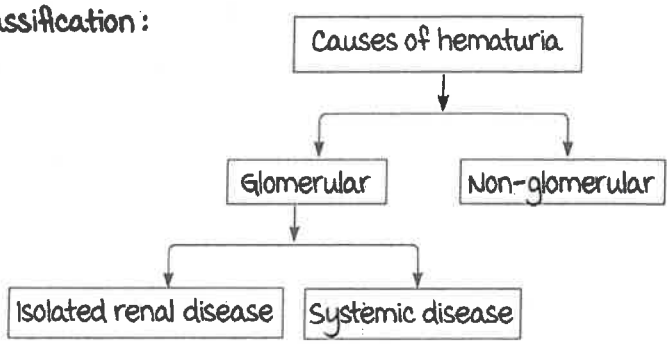
RBCs may originate from glomeruli, renal tubules, interstitium, or urinary tracts.

Etiological classification :



Isolated renal disease	Systemic disease	Non-Glomerular cause
• Post infectious glomerulonephritis. • IgA nephropathy. • Alport syndrome. • MPGN, FSGS. • Thin GBM disease.	• Systemic lupus erythematosus (SLE). • Henoch Schonlein purpura (HSP). • Hemolytic uremic syndrome (HUS). • Anti GBM disease. • Good pasture's disease. • Shunt nephritis. • Infective endocarditis.	• Trauma. • Urethral foreign body. • Infections. • Nephrolithiasis. • Idiopathic hypercalciuria. • Drugs : NSAIDs, cyclophosphamide. • Hematological : Sickle cell anemia, Disseminated intravascular coagulation. • Wilm's tumor. • Bladder hemangioma. • Renal vein/artery thrombosis.

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

Causes of hematuria in newborn :

- 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 :

a. Gross hematuria.
b. Urinary or other symptoms with incidental finding of microscopic hematuria.
c. 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 1-2 days : IgA nephropathy.
- Sore throat 1-2 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.

History d/t non-glomerular cause :

- Bright red colour urine or microscopic hematuria
- Trauma, fresh blood or clots in urine : Urethral injury.