MARROW

2024 NEET-SS

UPDATED PEDIATRICS NOTES

NEPHROLOGY

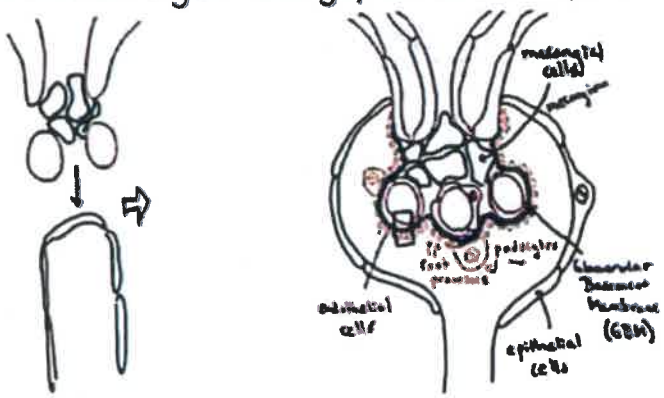
GLOMERULUS

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,

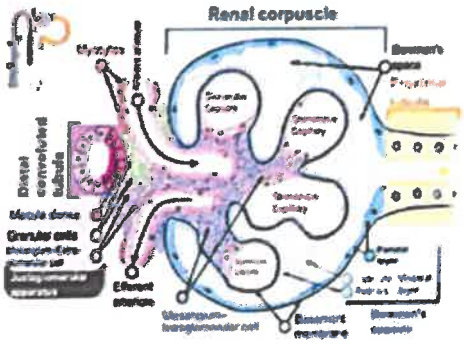
Feedback

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

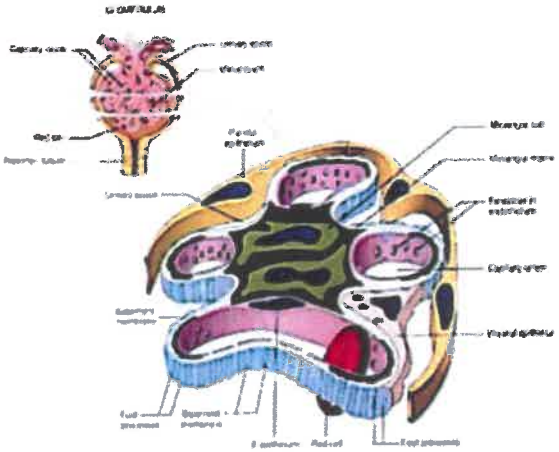
Parts of glomerulus 00:04:50

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.
- Polyanionic glycosaminoglycans : Glycocalyx.
- Receptors expressed : Class II HLA, VEGF receptor, endothelin, EDRF, PREF.

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.

Feedback

- 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.

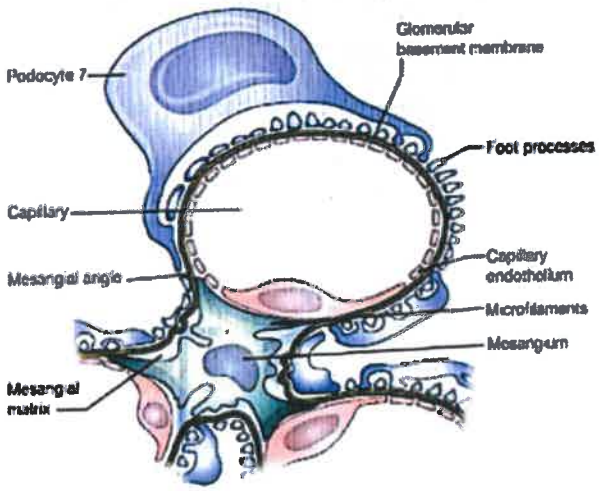
Mesangium :

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.

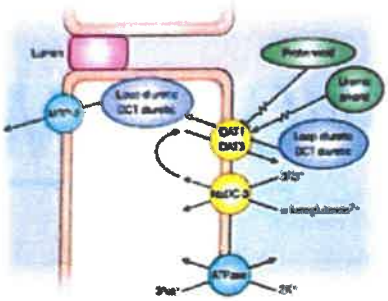
This shows a capillary, the axial position of the mesangium, and the visceral epithelium (podocytes). At the capillary mesangial interface, the capillary endothelium directly abuts the mesangium.

Feedback

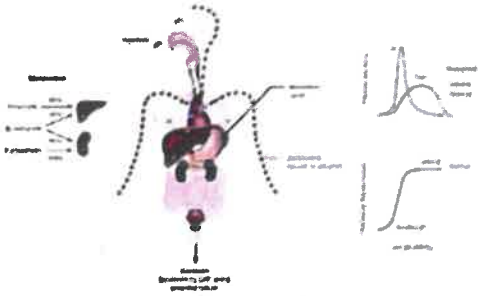
Pharmacokinetics and pharmacodynamics 00:03:02

Pharmacokinetics :

4 processes : Absorption, distribution, metabolism and excretion.



Mechanism of diuretics secretion by proximal tubule cells.



Absorption and distribution.

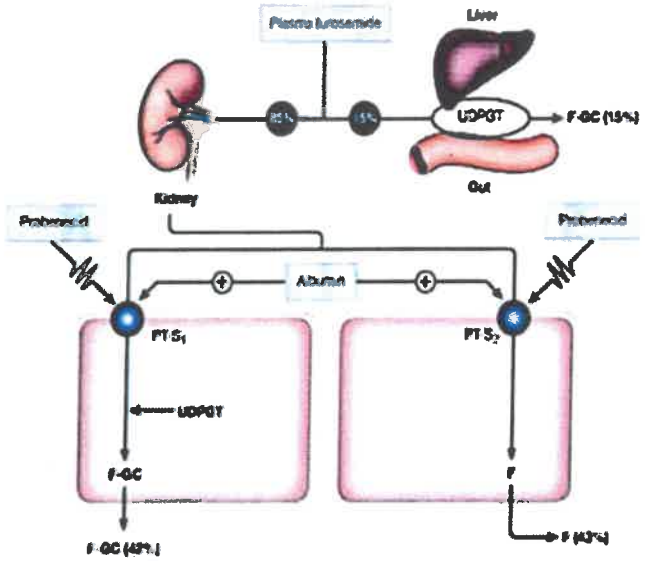
Absorption & distribution :

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.

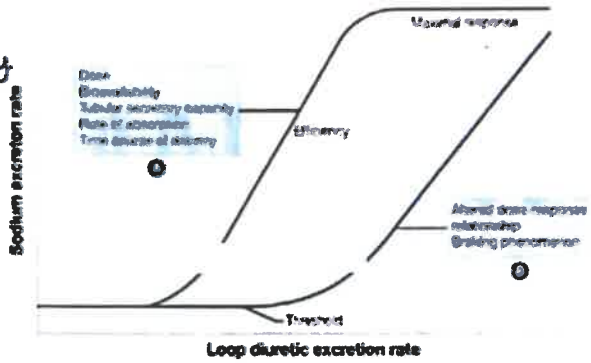


Metabolism and excretion.

Feedback

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.

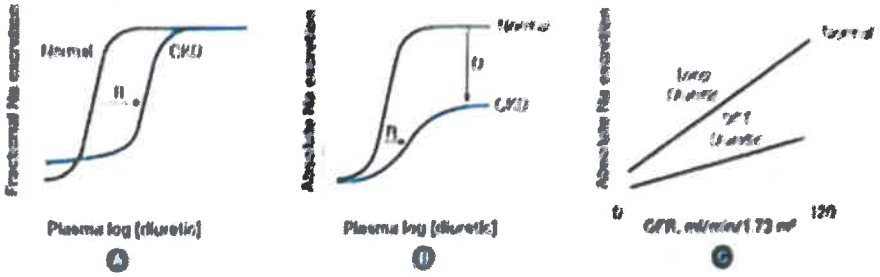
Highest doses that can be given in various conditions :

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

Feedback

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

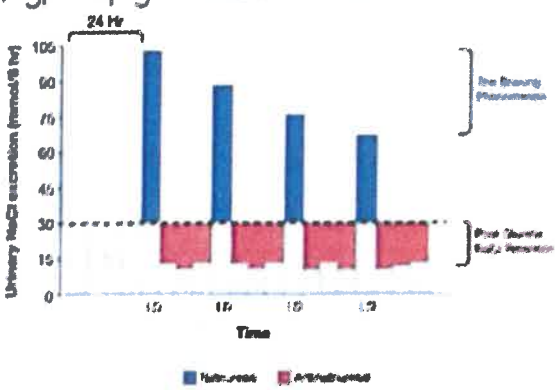
1. Decreased delivery/decreased secretion (Threshold dose is higher).
2. Increased renal metabolism.
3. Decreased blockade by the diuretic.
4. Increased Na, Cl reabsorption by other nephron segments.

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.

Feedback

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.

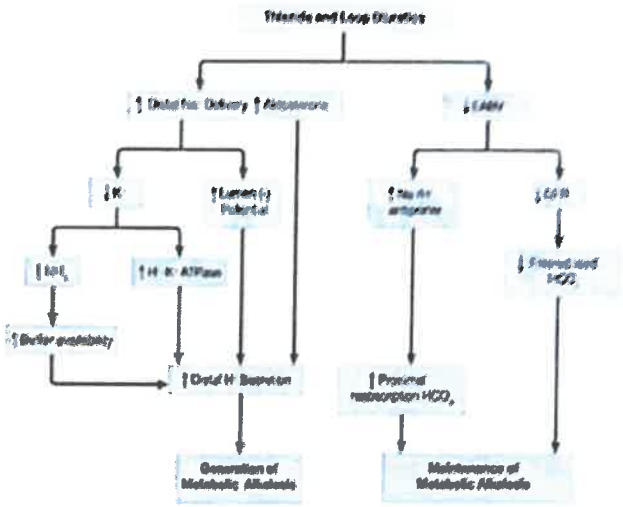
Causes :

- 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.

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

APPROACH TO HEMATURIA

Definition :

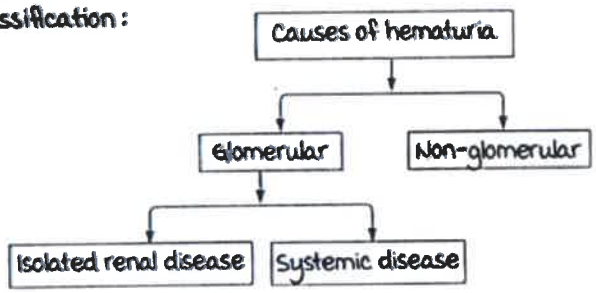
- Presence of at least 5 red blood cells (RBCs) per μL of urine.
- >3 RBC per high power field (HPF) of 10 ml of centrifuged urine.
- >5 RBC per mm³ of freshly voided, unspun urine.
- Significant hematuria : >50 RBCs/μL.
- Incidence of gross hematuria in children is estimated to be 0.13%.
- In 56% cases, 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
• 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 hypercalcuria. • Drugs : NSAIDs, cyclophosphamide. • Hematological : Sickle cell anemia, Disseminated intravascular coagulation • Wilm's tumor. • Bladder hemangioma. • Renal vein/artery thrombosis.

Feedback

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.

Feedback

- Abdominal mass : wilms tumour, hydronephrosis
- Fever, dysuria, urgency, lumbar or suprapubic pain, foul smell in urine : Urinary tract infection.
- Bleeding disorder : Thrombocytopenia, coagulation disorder.
- Sickle cell anemia.
- Colicy 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.

Family history :

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

Urine examination 00:10:28

Gross examination :

Collection of appropriate mid catch urine.

Second urine sample in morning is used.

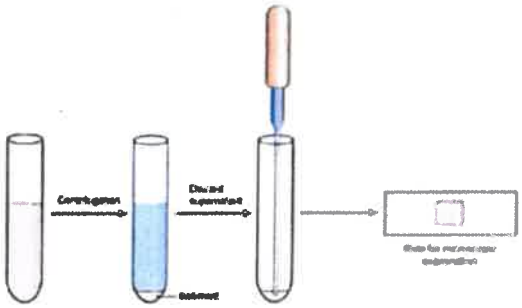
Uncentrifuged sample :

- 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 :

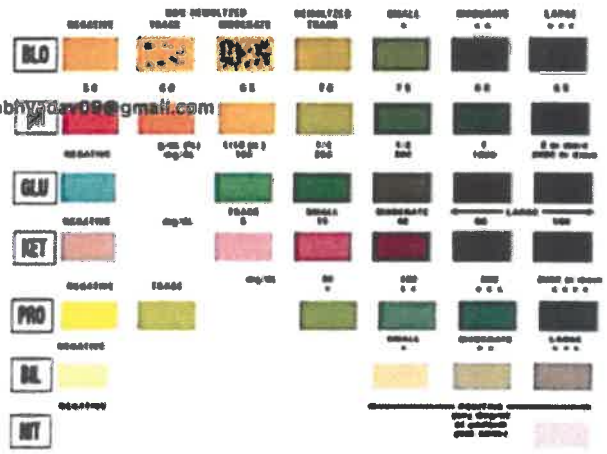
- Take 10 ml of urine centrifuge at 3000 rpm for 5 min.
- Discard supernatant.
- Re-suspend in 0.5 mL supernatant and prepare slide.
- View in microscope.
- In centrifuged sample if supernatant is clear : Hematuria.
- If supernatant is still red : Hemoglobinuria or myoglobinuria.

Preparation of urine sediment for microscopic examination

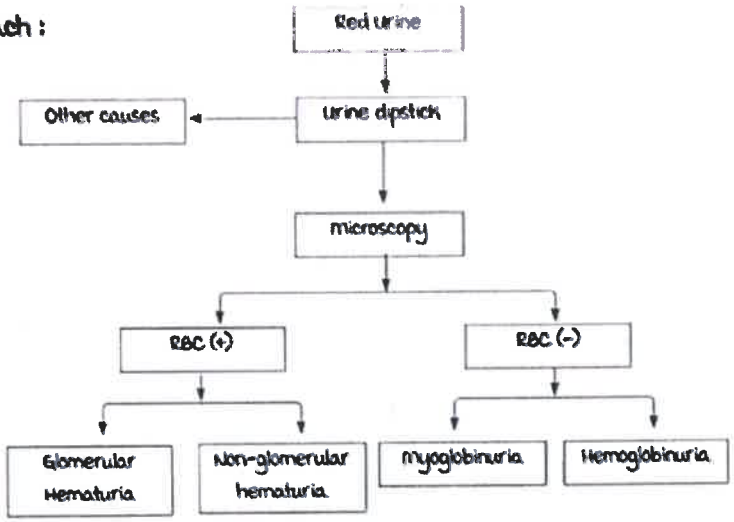


Dipstick method :

- 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 1–5 red blood cells per 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.



Approach :



Heme negative causes :

Drugs	Metabolites	Others
• Chloroquine • Deferoxamine • Ibuprofen • Iron sorbitol • metronidazole • Nitrofurantoin • Phenazopyridine (Pyridium) • Phenolphthalein • Phenothiazines • Rifampin • Salicylates • Sulfasalazine	• Homogentisic acid • Melanin • methemoglobin • Porphyrin • Tyrosinosis • Urates	• Dyes (vegetable/ fruit) • Beets • Blackberries • Food and candy coloring • Rhubarb

Urine microscopy :

RBCs seen in hematuria.

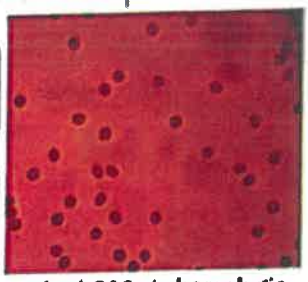
RBCs absent in myoglobinuria, hemoglobinuria.

History	Hemoglobinuria	myoglobinuria
CPK	Normal	Elevated
LDH	Elevated	Normal
Ammonium sulphate Salt precipitation	Precipitate : Present Supernatant : Clear	Precipitate : Absent Supernatant : Red brown

Feedback

Definitive diagnosis : Urine Spectroscopy, urine electrophoresis.

Urine electrophoresis



Intact RBCs in hematuria

Myoglobinuria

Comparison of features :

Features	Glomerular diseases	Non-glomerular causes
Dysuria.	Absent.	Present in urethritis and cystitis.
Systemic complaints.	Edema, fever, pharyngitis, rash, arthralgia.	Fever with UTI, pain with calculi.
Family history.	Deafness, hematuria in Alport's syndrome.	may be positive with calculi & hypercalcuria.
Physical examination		
Hypertension, edema.	Usually present.	Less common.
Abdominal mass.	Absent.	Present in Wilm's tumor, obstructive uropathy.
Rash, arthritis.	Lupus erythematosus, Henoch-Schonlein purpura.	Absent unless part of drug induced interstitial nephritis.

Feedback

Urinalysis		
Color.	Brown, tea, cola.	Bright red, clots may be present.
Proteinuria.	2+ or more.	Less than 2+.
Dysmorphic RBCs.	more than 20%.	Uncommon, less than 15%.
RBC casts.	Common.	Absent.
Crystals.	Absent.	Positive in few.

Further evaluation:

Cola/brown urine ?
Proteinuria (>30 mg/dL) ?
RBC casts ?
Acute nephritic syndrome ?

Yes → Glomerular hematuria

- CBC with differential
- Electrolytes, calcium.
- Blood urea nitrogen, creatinine.
- Serum protein/albumin.
- Cholesterol.
- C3/C4.
- ASO/anti-DNase B.
- Anti nuclear antibody.
- Antineutrophil antibody.
- Throat/skin culture (if indicated).
- 24 hr urine total protein creatinin clearance.

No → Extraglomerular hematuria.

Step 1 :

- Urine culture.

Step 2 :

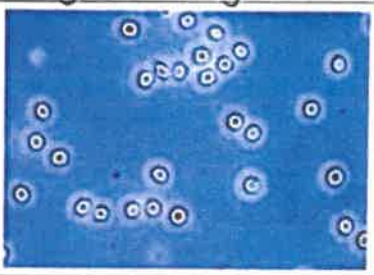
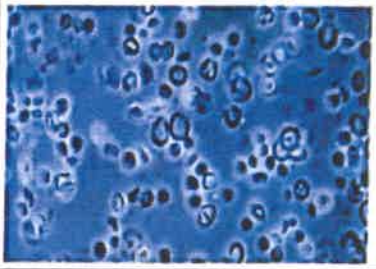
- Urine calcium creatinine.
- Sickle prep (African American).
- Renal/bladder ultrasound.

Step 3 :

- Urinalysis : Siblings, parents.
- Serum electrolytes, creatinine, calcium.
- If crystalluria, urolithiasis, or nephrocalcinosis : 24 hr urine for calcium, creatinine, uric acid, oxalate.
- If hydronephrosis/pyelocaliectasis : Cystogram + renal scan.

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

Findings in microscopy :

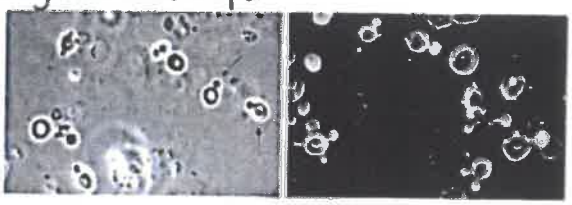
Non glomerular	Glomerular
Isomorphic RBCs.	Dysmorphic RBCs.
Cell outlines are smooth.	Irregular.
Hemoglobin uniformly distributed.	Margination of hemoglobin.
	

Note :

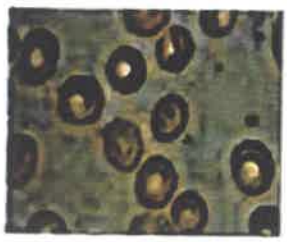
- Examine 100 RBCs.
- >20% Dysmorphic RBCs suggestive of glomerular etiology.
- Sensitivity : 96%.
- Specificity : 93%.
- Phase contrast microscope, Wright's stain required to visualize dysmorphic RBCs.

Acanthocytes :

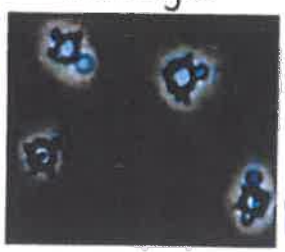
- >5% of examined RBCs.
- Subtype of dysmorphic RBCs.
- Ring shaped body with 1 or more protruding blebs of variable shape and size.
- GI cells, mickey mouse RBC shape.



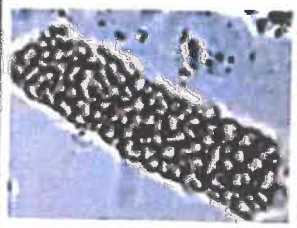
Acanthocytes



Isomorphic RBC



Dysmorphic RBC



RBC cast

Feedback

Focused investigations of glomerular hematuria :

- Serum creatinine.
- C3, C4, ASO titres, anti-DNase B titre.
- Quantification of proteinuria.
- Evaluation of underlying systemic disease : ANA, Anti-dsDNA, ANCA.
- Renal biopsy.

Indications for biopsy :

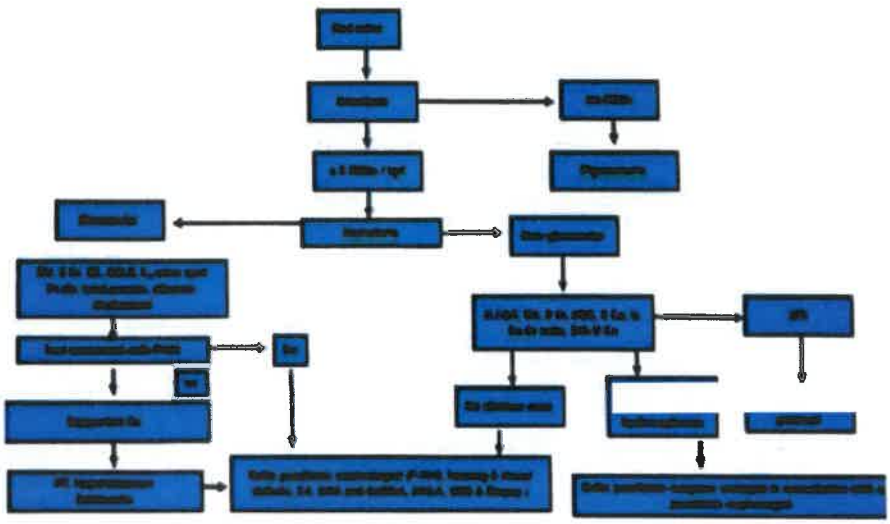
- Rapidly progressive renal failure.
- Nephrotic range proteinuria.
- Gross hematuria > 4 weeks.
- Sustained hypertension.
- Associated Systemic features.
- Normal C3.
- Low C3 >12 weeks.

Focused investigations of non glomerular hematuria :

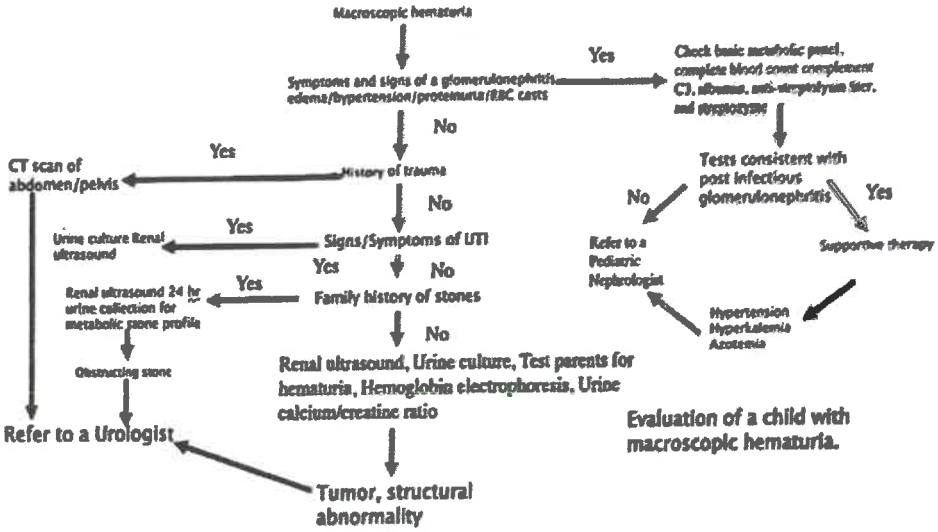
- Urine culture.
- Renal Ultrasound.
- Calcium creatinine ratio or 24-hour urine calcium.
- Non contrast CT.
- Cystoscopy.
- Evaluation for sickle cell anemia.

Summary

00:24:29



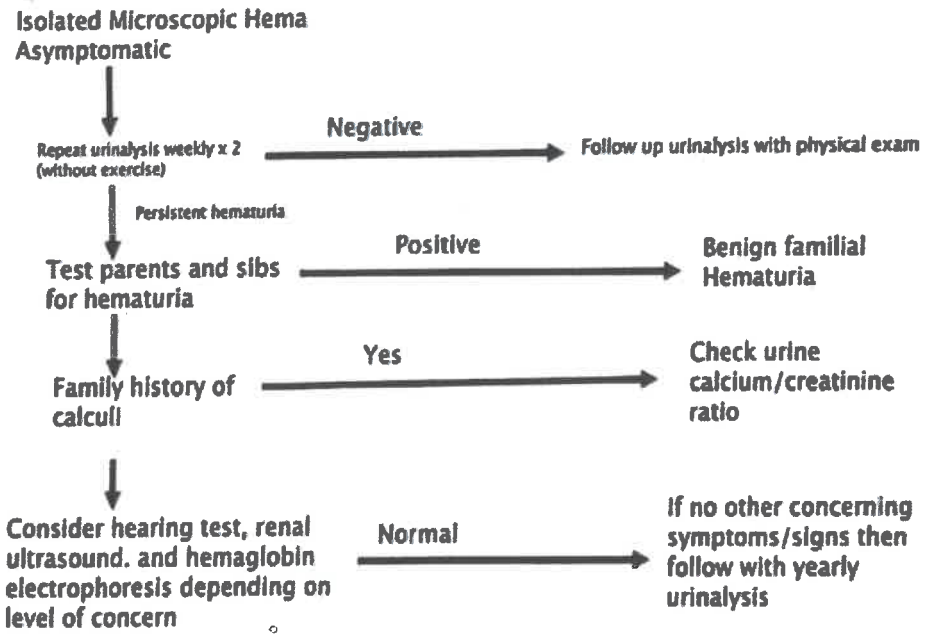
macroscopic hematuria :



Evaluation of a child with macroscopic hematuria.

microscopic hematuria :

Asymptomatic :



Feedback

Symptomatic :