# Approach to hematuria in children

The definition varies according to the mode of detection, that is, greater than 5 RBC/microliter in a fresh uncentrifuged midstream urine specimen and greater than 3 RBC/high power field in a centrifuged sediment from 10 ml of freshly voided midstream urine.

Macroscopic

Microscopic

# Other Causes of Red Urine

| HEME POSITIVE |
| --- |
| Hemoglobin |
| Myoglobin |
| **HEME NEGATIVE** |
| ***Drugs*** |
| Adriamycin |
| Chloroquine |
| Deferoxamine |
| Hydroxycobalamin |
| Ibuprofen |
| Iron sorbitol |
| Levodopa |
| Metronidazole |
| Nitrofurantoin |
| Phenazopyridine (Pyridium) |
| Phenolphthalein |
| Phenothiazines |
| Phenytoin |
| Quinine |
| Rifampin |
| Salicylates |
| Sulfasalazine |
| ***Dyes (Vegetable/Fruit)*** |
| Beets |
| Blackberries |
| Blueberries |
| Food and candy coloring |
| Paprika |
| Rhubarb |
| ***Metabolites*** |
| Homogentisic acid |
| Melanin |
| Methemoglobin |
| Porphyrin |
| Tyrosinosis |
| Urates |

| Glomerular Hematuria |
| --- |
| Familial hematuria syndromes |
| Thin basement membrane nephropathy |
| Alport syndrome |
| Hereditary angiopathy, nephropathy, aneurysms, muscle cramps syndrome |
| MYH9 syndromes (associated thrombocytopathies) |
| C3 glomerulopathy |
| Glomerulonephritis |
| Postinfectious glomerulonephritis |
| Membranoproliferative glomerulonephritis |
| Membranous nephropathy |
| Crescentic glomerulonephritis |
| IgA nephropathy |
| IgA vasculitis nephritis (Henoch-Schonlein nephritis) |
| Lupus nephritis |
| Necrotizing vasculitis |
| Hemolytic uremic syndrome |

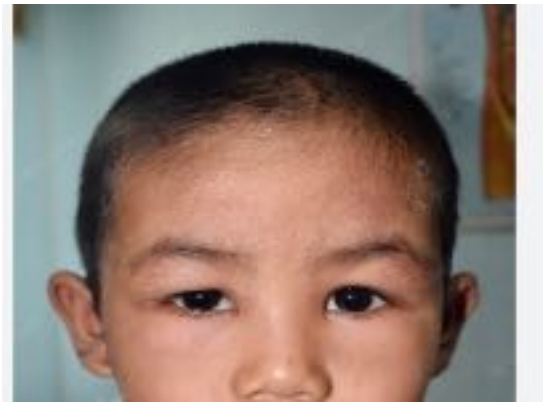
| Non-glomerular Hematuria |
| --- |
| Urinary tract infection (bacterial, viral and parasitic) |
| Hypercalciuria |
| Urolithiasis |
| Trauma |
| Exercise-induced |
| Chemical cystitis |
| Cystic kidney disease |
| Vascular malformations |
| Nutcracker syndrome |
| Papillary necrosis |
| Renal infarction |
| Malignancies |
| Nephroblastoma (Wilms tumor) |
| Renal cell carcinoma |
| Rhabdomyosarcoma of the bladder |
| Bleeding disorders |
| Renal vein thrombosis |
| Menarche |
| Factitious |

| Inheritance | Gene(s) | Protein | Estimated risk of ESKD* (Median age) |
|---|---|---|---|
| X-linked Alport syndrome | *COL4A5*<br>Hemizygous (male)<br>Homozygous (female) | α5(IV) | 100% (25 years)<br>Up to 25% (49 years) |
| Autosomal Alport syndrome | *COL4A3* or *COL4A4*<br>Recessive (homozygous or compound heterozygous)<br>Dominant | α3(IV) or α4(IV) | 100% (15 years)<br><1% if no risk factors (TBMN**);<br>≥20% if risk factors present (60 years) |
| Digenic Alport syndrome | *COL4A3* and *COL4A4*<br>Mutations in trans<br>Mutations in cis<br>Mutations in *COL4A5* and in *COL4A3* or *COL4A4* | α3(IV) and α4(IV) | Up to 100%<br>Up to 20%<br>Up to 100% (affected males) |
| Autosomal dominant macrothrombocytopathies | *MYH9*<br>Heterozygous | Nonmuscle myosin heavy chain IIA | 30% (15 years) |
| CFHR5 nephropathy | *CFHR5*<br>Heterozygous (males)<br>Heterozygous (females) | Complement factor H-related protein 5 | 80% (49 years)<br>20% (56 years) |
| Glomerulopathy associated with fibronectin deposition | *FN1* | Fibronectin 1 | >90% (2nd to 6th decade) |

*ESKD: End stage kidney disease

**TBMN: Thin basement membrane nephropathy

# Glomerular or non glomerular



Cola colored urine
Acute nephritis
Proteinuria
RBCs casts

# Clinical approach


## History

- Color of urine (cola colored in glomerular diseases, fresh blood with or without clots in hematuria of lower urinary tract origin).
- Timing of color change in relation to urinary stream (Hematuria occurring at the beginning of the urinary stream is seen in urethral causes such as urethritis, whereas terminal hematuria is indicative of a bladder cause such as bladder calculus or tumors and schistosomiasis)
- Lower urinary tract symptoms such as frequency, urgency, and dysuria
- Presence of flank pain or abdominal pain: suggest hydronephrosis, urolithiasis, nutcracker syndrome, or hemorrhage in polycystic kidney disease
- Recurrent episodes of gross hematuria: in Alport syndrome, IgA nephropathy, thin basement membrane disease, familial hypercalciuria
- Family history not only of hematuria but of ESRD, stones, polycystic kidney

# Physical examination

- Edema and hypertension, in addition to cola colored urine suggests acute glomerulonephritis
- Evaluation for extrarenal symptoms such as hearing loss and ocular abnormalities

- Systemic signs such as fever, pallor, bruising, rashes, joint swelling, mouth ulcers, hypertension, hepatosplenomegaly, and lymphadenopathy.
- Abdominal examination for ballotable kidneys and palpable bladder

# Investigations

- **Urine analysis:**
- Confirm hematuria
- Dysmorphic RBCs >30% is indicative of glomerular hematuria, whereas greater than 90% of isomorphic cells are seen in non glomerular hematuria
- Presence of RBCs cast suggests glomerular origin
- Presence of proteinuria (>0.2g/g creatinine) suggests glomerulopathy

# *Investigations (cont.)*

**In non glomerular hematuria:**

- **Urine culture:** specially if there is are lower urinary tract symptoms or fever
- **Spot urine calcium to creatinine ratio:** A value greater 0.2 mg/mg creatinine in children 2 years and older, and greater than 0.6 mg/mg creatinine in infants between the ages of 6 and 12 months is indicative of hypercalciuria
- **Plain abdominal radiograph:** If there is accompanying abdominal pain, in particular loin to groin pain suggestive of ureteric calculi
- **Ultrasound of the kidneys and bladder:** to exclude congenital malformations including cystic kidney disease, renal calculi, and tumors

# *Investigations (cont.)*

***In non glomerular hematuria:***

- **Doppler ultrasound of the left renal vein:** to exclude nutcracker syndrome in children who have recurrent left flank pain associated with hematuria
- **Coagulation screen** if there is a history suggestive of a bleeding disorder.
- **Cystoscopy** if a bladder or urethral pathology is suspected due to accompanying voiding symptoms, or when a mass is detected on bladder ultrasound, or to lateralize the source of bleeding.
- **Axial imaging by computed tomography or magnetic resonance imaging** in some cases of renal stones, renal tumors and nut cracker syndrome

# *Investigations (cont.)*

**In glomerular hematuria:**

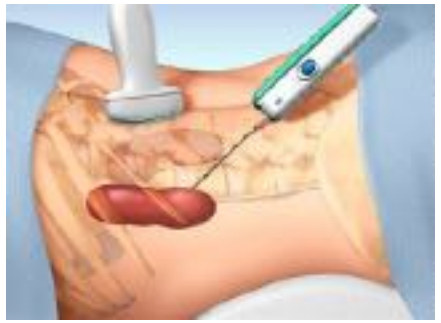
- **Kidney function tests, serum albumin** (in cases of significant proteinuria)
- **Urine screening of the family**
- **If suspected Alports syndrome: a**udiometry to detect high frequency sensorineural hearing loss and screening for ophthalmologic abnormality
- **If the rare MYH9 spectrum of disorders is suspected**: a peripheral blood smear will be useful to look for macrothrombocytopenia and basophilic cytoplasmic leukocyte inclusion bodies (Döhle-like bodies)

# *Investigations (cont.)*

***In glomerular hematuria:***

- **Genetic analysis:** in the presence of a positive family history or suggestive clinical, laboratory, or biopsy features.
- **If suspected glomerulopathies:** serum complements C3 and C4, anti-streptolysin O titers (ASOT) or anti-DNAse B antibody, anti-nuclear antibodies (ANA), anti-double-stranded DNA (dsDNA) antibody, anti-neutrophil cytoplasmic antibodies (ANCA), IgA levels, hepatitis B surface antigen, and viral titers**.**
- **Kidney ultrasound** to assess chronicity of the glomerulonephritis by determining kidney size and echogenicity.

# *Investigations (cont.)*



***In glomerular hematuria:***

- **Kidney biopsy is indicated in:**

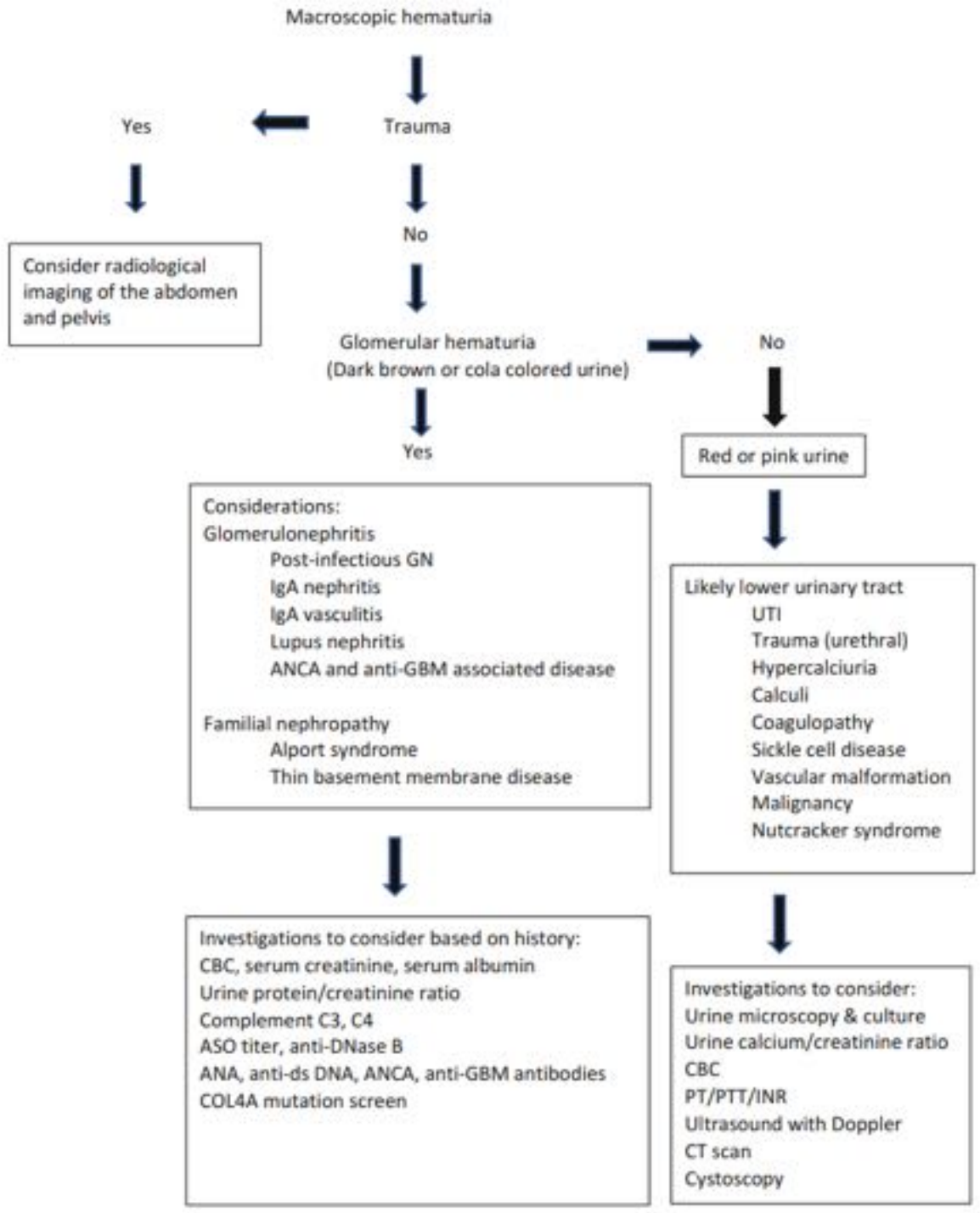
- Significant proteinuria (>1 g/1.73m2 /day) except in post-infectious glomerulonephritis

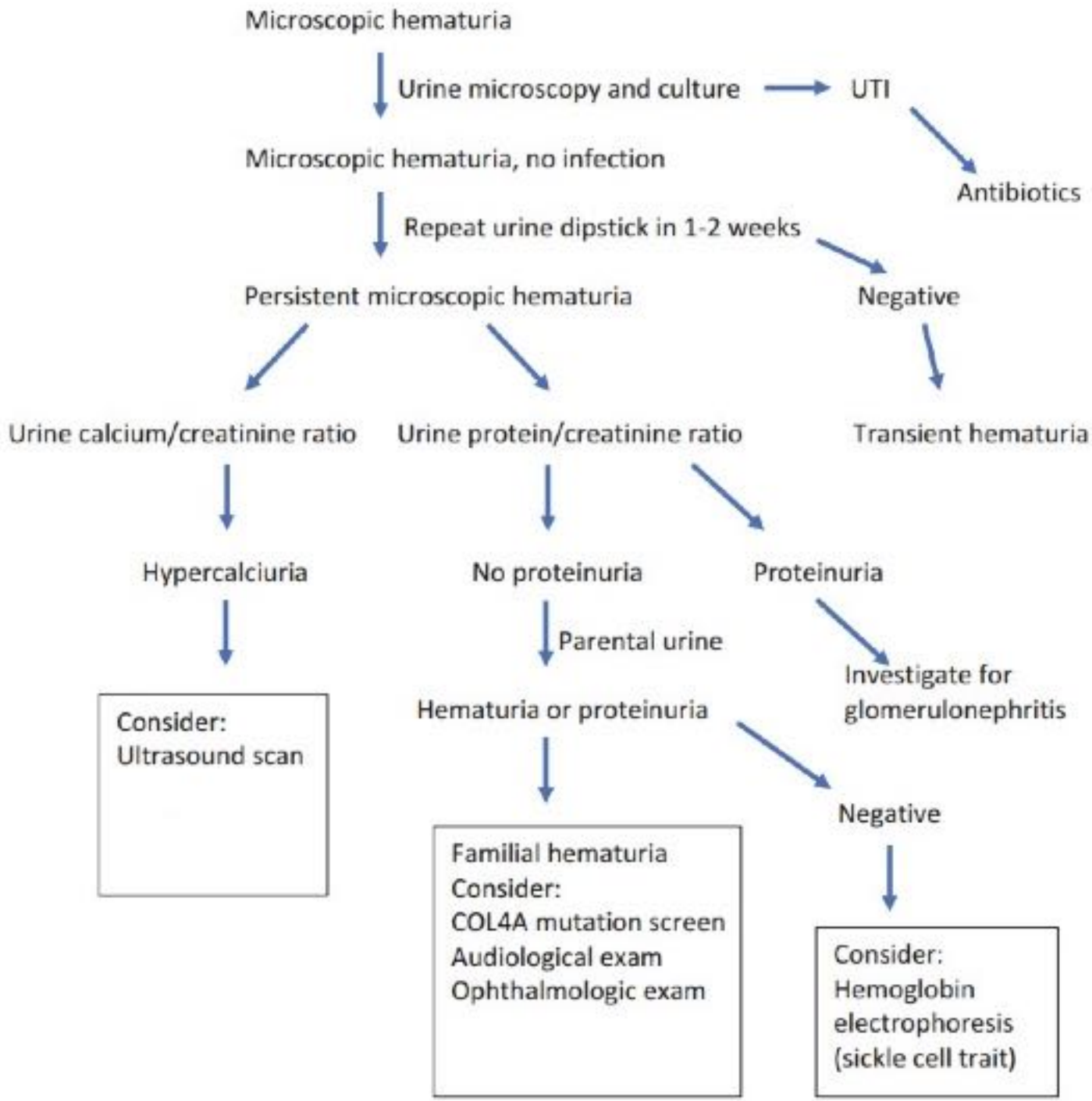
- Persistently low serum complement C3

- Unexplained kidney failure

- Family history of significant kidney disease suggestive of Alport syndrome where genetic analysis is not available

- Recurrent gross hematuria of unknown etiology.


Macroscopic hematuria
Trauma
Yes
Consider radiological imaging of the abdomen and pelvis
No
Glomerular hematuria
(Dark brown or cola colored urine)
Yes
Considerations:
Glomerulonephritis
Post-infectious GN
IgA nephritis
IgA vasculitis
Lupus nephritis
ANCA and anti-GBM associated disease
Familial nephropathy
Alport syndrome
Thin basement membrane disease
Investigations to consider based on history:
CBC, serum creatinine, serum albumin
Urine protein/creatinine ratio
Complement C3, C4
ASO titer, anti-DNase B
ANA, anti-ds DNA, ANCA, anti-GBM antibodies
COL4A mutation screen
No
Red or pink urine
Likely lower urinary tract
UTI
Trauma (urethral)
Hypercalciuria
Calculi
Coagulopathy
Sickle cell disease
Vascular malformation
Malignancy
Nutcracker syndrome
Investigations to consider:
Urine microscopy & culture
Urine calcium/creatinine ratio
CBC
PT/PTT/INR
Ultrasound with Doppler
CT scan
Cystoscopy


Microscopic hematuria
Urine microscopy and culture
UTI
Antibiotics
Microscopic hematuria, no infection
Repeat urine dipstick in 1-2 weeks
Persistent microscopic hematuria
Negative
Transient hematuria
Urine calcium/creatinine ratio
Urine protein/creatinine ratio
Hypercalciuria
No proteinuria
Proteinuria
Parental urine
Investigate for glomerulonephritis
Consider: Ultrasound scan
Hematuria or proteinuria
Negative
Familial hematuria
Consider:
COL4A mutation screen
Audiological exam
Ophthalmologic exam
Consider:
Hemoglobin electrophoresis (sickle cell trait)


THANK YOU

Which of the following supports the diagnosis of glomerular hematuria?

a. Isomorphic RBCs >90% in urine analysis

b. RBCs casts in urine analysis

c. Presence of loin pain

d. Protein/creatinine ratio 0.15g/g creatinine

Which of the following cases of hematuria is least likely to need genetic testing?

a. Patient with acute glomerulonephritis and consumption of C3

a. Patient with unexplained bilateral renal stones

b. Ten year old male with renal impairment and perceptive deafness

c. Three year old patient with recurrent Coomb's negative hemolytic anemia, thrombocytopenia and AKI

Which of the following is NOT a tool for diagnosis of non glomerular hematuria?

a. CT scan of the abdomen

b. Renal biopsy

c. Cystoscopy

d. Urinary calcium/creatinine ratio