Hematuria

Many substances can cause the urine to become red in color. Urine tests are used to find the cause for the red urine and to establish whether there is blood in the urine (hematuria). Microscopic hematuria occurs in about 1.5% of children.

I. **Pathophysiology of Hematuria**

A. Blood in the urine is usually first detected with a dipstick test, which reacts with hemoglobin. A reaction greater than 1+ is considered positive. The dipstick is not a test for red blood cells (RBCs); therefore, the dipstick screen must be followed by microscopic examination of the urine to confirm the presence of RBCs (hematuria).

B. Two significant causes of a positive dipstick and a negative microscopic examination are free hemoglobin from hemolysis and myoglobinuria from rhabdomyolysis. Certain drugs and toxins also can cause red urine, although the urine will be heme-negative.

C. The presence of greater than 2 RBCs per high-power field of urine sediment from a centrifuged urine sample is considered abnormal.

Causes of Factitious Hematuria
Heme-positive
Hemoglobinuria
Myoglobinuria
Heme-negative
Metabolites
Homogentisic acid
Porphyrin
Melanin
Drugs
Salicylates
Sulfa
Chloroquine
Nitrofurantoin
Methyldopa
Metronidazole
Levodopa

II. **Clinical Evaluation of Hematuria**

A. **History**

1. The history often will suggest a presumptive diagnosis and will usually narrow the differential diagnosis.
2. Persistent microscopic hematuria and recurrent episodes of gross hematuria, associated with viral illnesses, suggests IgA nephropathy.
3. Dysuria, back pain, or flank pain suggests urinary tract infection, hypercalciuria, or nephrolithiasis.
4. Hematuria from a glomerular lesion may cause the urine to appear to be brown, green, or tea-colored.

B. **Associated Symptoms**

1. **Upper respiratory tract infection** suggests IgA nephropathy.
2. **Sore throat or an impetiginous lesion,** preceding hematuria by 7-21 days, suggests poststreptococcal glomerulonephritis.
3. **Abdominal pain** may suggest an urinary tract infection or Henoch-Schoenlein purpura (HSP)
4. **Petechial or purpuric rashes** of the lower extremity may suggest HSP. A malar rash suggests systemic lupus erythematosus (SLE).
5. **Edema or hypertension** suggests glomerulonephritis and requires aggressive evaluation.

6. **Voiding difficulties or dysuria** are associated with urologic causes of hematuria.
7. **Transient hematuria** can be caused by significant trauma to the back, bladder or genitalia, or by vigorous exercise, especially running.
8. **Gross hematuria** associated with minimal trauma may indicate the presence of an abnormal kidney, usually stenosis of the ureteropelvic junction.
9. If the patient has heme-positive urine without RBCs, causes of hemolysis or rhabdomyolysis should be sought.

Clinical Evaluation of Hematuria: History
Associated Complaints
Concurrent illnesses
Edema
Rashes
Arthralgia
Back or flank pain
Trauma
Menstruation
Past Medical History
Congenital heart disease
Malignancy
Sickle cell disease
Cystic kidney disease
Systemic lupus
Social History
Abuse
Family History
Hematuria
Deafness
Renal failure
Cystic kidney disease
Systemic lupus
Nephrolithiasis
Sickle cell

C. **Conditions Associated with Hematuria**
1. **If sickle cell disease or trait, cystic kidney disease, and SLE** are suggested, appropriate laboratory testing should be completed.
2. **Congenital heart disease** may be associated with hematuria. Septal defects, valvular lesions, and cardiac surgery predispose to endocarditis, which may cause an immune complex glomerulonephritis (glomerulonephritis of chronic infection).
3. **Furosemide** can cause hypercalciuria, nephrolithiasis and nephrocalcinosis, which may lead to hematuria.
4. **Chemotherapy, radiation, or surgery** often is associated with nephrologic hematuria.
5. **An umbilical catheter** can cause thrombosis of the renal vein or artery and subsequent hematuria.
6. **Interstitial nephritis** may be associated with microscopic hematuria, pyuria, and proteinuria. Causes of interstitial nephritis include a number of antibiotics and over-the-counter nonsteroidal anti-inflammatory drugs.

D. **Genetic or Familial Disorders Associated with Hematuria**
1. **Alport syndrome**, thin basement membrane disease, polycystic kidney disease, and sickle cell disease/trait can cause hematuria.

2. **Nephrolithiasis** and **IgA nephropathy** are familial disorders associated with hematuria.

E. **Child abuse** should be considered if the physical examination is suspicious or if the cause of hematuria is thought to be trauma.

III. **Physical Examination**

Clinical Evaluation of Hematuria: Physical Examination
HEENT Periorbital edema Malformation of ears Retinal exam Erythema or exudate of the pharynx
Chest Rales Gallups Murmurs Rubs Strength and placement of precordial impulse
Abdomen Masses Ascites Bruits Trauma
Back Flank tenderness
Genitourinary system Meatal stenosis Discharge Trauma
Extremities Edema Arthritis
Skin Rashes Petechiae Purpura

IV. **Laboratory Evaluation**

A. **Evaluation of Symptomatic Hematuria**

1. **Patients who present symptomatically with hypertension, edema, proteinuria, or oliguria** are likely to have significant glomerular pathology and require a rapid evaluation. Evaluation should include a complete blood count (CBC), electrolytes, blood urea nitrogen (BUN), creatinine, measurement of C3, C4, fluorescent antinuclear antibody (FANA), hepatitis B serology, and a sickle cell prep or hemoglobin electrophoresis (in African Americans).
2. **Renal ultrasonography**, with a Doppler flow study of the renal vessels, will demonstrate structural renal or vascular abnormalities.

B. **Evaluation of the Asymptomatic Hematuria**

1. The asymptomatic patient with isolated hematuria on routine screening, should be evaluated in a step-wise manner.
2. **Urinalysis.** Urine should be screened for protein and should be examined microscopically for the presence of RBCs and RBC morphology.

a. **Red blood cell** size and contour may help determine the site of the blood loss. The presence of small and misshapen red blood cells with burrs and blebs (dysmorphic cells) indicates glomerular bleeding. Cells that originated somewhere other than the glomerulus are usually normal in shape and size (eumorphic) or small with a serrated edge (crenated).
   (1) The presence of dysmorphic RBCs in the urine suggests a glomerular lesion; however, they may sometimes be absent in glomerular disease.
   (2) The presence of protein of 1+ or greater in the absence of gross hematuria suggests a renal (glomerular) cause of the hematuria.
   (3) **Red blood cell** casts signify a glomerular lesion and require an evaluation for causes of glomerulonephritis.

b. **White blood cells**, in the absence of infection, suggest inflammation caused by nephritis; WBC's when associated with bacteria suggest infection. Urine culture is necessary if an infection is suggested by the presence of white blood cells and bacteria. If the culture is positive, a urinalysis should be repeated after the infection is treated to determine whether the microscopic hematuria is persistent.

c. **Evaluation of proteinuria** by dipstick consists of a timed (12 or 24-hour) urine collection for quantitation of urinary protein.
   (1) A protein <10 mg/M^2/hr is normal.
   (2) Values between 10-40 mg/M^2/hr are abnormal and require investigation.
   (3) Values >40 mg/M^2/hr represent proteinuria in the nephrotic range.

C. **Evaluation of Isolated Hematuria**

1. **A urinalysis should be performed** in as many family members as possible to identify familial causes of hematuria.
2. **A spot urine calcium/creatinine ratio** can exclude hypercalciuria (<0.21 is normal).
3. **Kidney and bladder ultrasonography** should rule out polycystic kidney disease, tumor, stones, and obstruction.

D. **Evaluation of Subacute Glomerular Disease**

1. A CBC, BUN, electrolytes and creatinine with a creatinine clearance will establish the degree of renal function impairment.
2. Children of African or Mediterranean descent should be screened for sickle cell disease or trait.
3. Additional laboratory evaluation for most patients includes a serum C3 level and an ASO titer or streptozyme. A depressed C3 level and positive streptococcal serology are consistent with poststreptococcal glomerulonephritis. The C3 concentration often will be depressed in SLE, membranoproliferative glomerulonephritis, and nephritis of chronic bacteremia.
4. If the diagnosis of SLE is a possibility, then a FANA and other serologic tests should be performed.
5. Hepatitis B antibody testing will detect glomerulonephritis secondary to hepatitis B infection.
6. If the patient has significant edema and/or nephrotic range proteinuria, serum albumin and cholesterol levels should be measured to document the presence of the nephrotic syndrome.
7. If hematuria and significant proteinuria are not associated with laboratory or clinical findings consistent with poststreptococcal glomerulonephritis, a referral should be made to a nephrologist.

E. **If the patient does not have dysmorphic RBCs and/or proteinuria**, then other causes than glomerulonephritis (eg, tumors, Alport's, thin basement membrane disease) should be considered.

1. Two or more urinalyses should be done over the next 2 months to confirm that the hematuria is persistent. In postmenarchal females, care should be taken to obtain all urine specimens either before or after the anticipated time of menses.
2. If the hematuria persists, the urinalysis should be repeated at regular intervals (every 2-4 months) for

a year.

3. If proteinuria or gross hematuria develops during this follow-up period, the patient should be referred to a nephrologist.
4. If isolated microscopic hematuria still is present after 1 year, even in the absence of other signs, a full evaluation should be performed. If no etiology can be found in the presence of persistent hematuria, a nephrology consult should be obtained.

F. **Cystoscopy** is not usually indicated for the initial investigation of asymptomatic, isolated, microscopic hematuria. Isolated microscopic hematuria in children is a rare presentation for a tumor of the bladder and kidney.

V. **Diseases Associated with Hematuria**

A. **Poststreptococcal Acute Glomerulonephritis (PSAGN)**

1. This disorder typically begins 7-21 days after a group A beta-hemolytic streptococcal infection of either the throat or skin.
2. The nephritis develops despite antibiotic treatment for the infection, and children often present with tea-colored urine, edema, and hypertension. Patients may also present later with isolated hematuria.
3. Ninety percent of patients who have PSAGN have a low serum C3. It returns to normal within 6 weeks.
4. The ASO titer is increased initially in most cases. If the initiating infection was impetigo, the patient will have a normal ASO titer but a positive streptozyme.
5. Microscopic hematuria usually resolves 6-12 months after onset, but may be present for as long as 2 years. Most children who have PSAGN will have normal renal function after recovery. If the patient does not fit the typical pattern, a renal biopsy is warranted.
6. The treatment in the acute phase of PSAGN consists of salt restriction and diuretics. Antihypertensives are indicated for some patients. Dialysis is rarely required, and most patients can be expected to have a good long-term outcome.

B. **IgA Nephropathy (Berger's Disease)** is the most common type of chronic glomerulonephritis in children and adults of European or Asian descent.

1. Fifteen percent of children with isolated hematuria that persists for more than 1 year have IgA nephropathy. It presents with gross hematuria during a viral respiratory or gastrointestinal illness. Isolated microscopic hematuria or microscopic hematuria with proteinuria is typical.
2. A child diagnosed after presentation with microscopic hematuria often will have a subsequent episode of gross hematuria during an intercurrent illness. Children usually are normotensive and rarely are edematous.
3. Serum IgA concentration may be elevated, and circulating IgA-containing immune complexes may be present. Diagnosis is by renal biopsy. Up to 50% of patients identified during adulthood, and 25% of those identified during childhood will progress to chronic renal insufficiency.
4. Up to 20% of children who have biopsy-proven IgA nephropathy eventually will have an apparent remission in which the urinalysis becomes normal.
5. In the normotensive patient with mildly affected or normal glomeruli and low grades of proteinuria, no therapy is indicated. Significant proteinuria, hypertension or changes on biopsy are treated with alternate-day prednisone.

C. **Alport's Hereditary Nephritis**

1. Alport syndrome is present in 15% of patients who have isolated hematuria. A presumptive diagnosis often is made with a careful family history. It is inherited as an X-linked dominant trait.
2. Episodes of gross hematuria may occur in association with an intercurrent viral illnesses.
3. A family history often will reveal male relatives with nerve deafness and progression to end stage renal disease. Males are affected more severely than females.

4. If Alport syndrome is suspected, hearing testing and urinalyses should be performed on other family members. Renal biopsy confirms the diagnosis.

D. **Thin Basement Membrane Disease**

1. This disorder is a hereditary condition in which the lamina densa is decreased in width to <1000-2000 angstroms. It is associated with microscopic hematuria with dysmorphic RBCs, but without proteinuria. Other family members may have microscopic hematuria.
2. Renal biopsy confirms the diagnosis, but is not necessary if the child does not have significant proteinuria and other close relatives already have been biopsied.
3. This disease is non-progressive and benign, and no treatment is necessary, other than monitoring urinalyses and renal function at 1-2 year intervals.

E. **Hypercalciuria**

1. For healthy Caucasian children, hypercalciuria is the most frequent cause of isolated hematuria and occurs in 5%. About 30% of children with isolated hematuria will be hypercalciuric.
2. Hypercalciuria may cause episodic gross hematuria. Hypercalciuria is found with hyperparathyroidism, immobilization, vitamin D intoxication, and the use of furosemide.
3. Hypercalciuria places the child at risk for later development of renal stones. More than 2/3 of children who have urolithiasis will have associated hypercalciuria.
4. Screening for hypercalciuria consists of a spot urinary calcium/creatinine ratio. A ratio of 0.21 or greater is indicative of hypercalciuria. A 12- or 24-hour urine for calcium excretion confirms the diagnosis. An excretory rate of >4 mg/kg/day is abnormal.
5. Patients who have hypercalciuria and hematuria should have a renal ultrasound to rule out nephrolithiasis or nephrocalcinosis. All patients who have nephrolithiasis should have a complete metabolic evaluation.
6. **Treatment of Hypercalciuria** consists of dietary measures include increasing fluid intake and salt restriction and sometimes hydrochlorothiazide. Severe calcium restriction can worsen stone formation and should be avoided. §