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Review

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Hematuria in Children

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Abstract

Presence of red blood cells (RBCs) in urine is hematuria that even in microscopic amounts alarms the patient and parents of the patient, and often prompts physician for many laboratory investigations. Hematuria can be red, dark or cola colored or brown known as macroscopic hematuria, and when it is not visible to unaided eye, it is known as microscopic hematuria. RBCs in urine is one of the most important signs of genitourinary tract disease; however, it is almost never a cause of anemia, since few drops (1 mL) of blood can turn 1 L of urine into red colored urine. Overall the physician should be alert enough not to overlook serious conditions like neoplasms and underlying bleeding disorder, to avoid unnecessary and often expensive laboratory studies. This article provides an approach to the evaluation and management of hematuria in children, and the detection of preventable and treatable conditions at the earliest to limit the disease progression, and overall reduction in cost, energy and anxiety.

Keywords: Children; Kidneys; RBC cast; Red blood cells; Urine

Introduction

The definition of microscopic hematuria is based on urine microscopic examination findings of red blood cells (RBCs) of more than 5/μL in a fresh uncentrifuged midstream urine specimen or more than 3 RBCs/high-power field (HPF) in the centrifuged sediment from 10 mL of freshly voided midstream urine [1]. However, considerable controversy still exists about the number of RBCs required for diagnosis of microscopic hematuria. Some investigators have used a definition of greater than 2 RBCs/HPF in 12 mL of a midstream urine specimen spun at 1500 rpm for 5 min [2]. Regardless of the criterion used, important cofactors to consider when a child has hematuria include the presence of proteinuria, urinary casts, hypertension and a family history of renal disease.

Incidence and prevalence

Macroscopic hematuria has an estimated incidence of 1.3 per 1,000 [3]. The incidence of microscopic hematuria in school children was estimated at 0.41% when four urine samples per child were collected and 0.32% in girls and 0.14% in boys when five consecutive urine specimens were analyzed over 5 years [1]. Overall hematuria is present in about 5-6% of the general population [4] and 4% of school children. In the majority of children, follow-up urinalyses are normal [5]. In most people, the hematuria emanates from the lower urinary tract, especially in the conditions affecting the urethra, bladder and prostate. Less than 10% of hematuria is caused by glomerular bleeding [6].

Pathophysiology

RBCs in urine may originate from the renal tissue (glomeruli, renal tubules and interstitium), or urinary tract (collecting systems, ureters, bladder and urethra). The urine dipsticks that are commonly employed to detect microscopic hematuria are very sensitive. When used correctly, urine dipsticks have a sensitivity of 100 and a specificity of 99 to detect 1-5 RBCs/HPF, which translates to 5-10 RBCs/μL of urine [7]. False-positive results can be seen with hemoglobin, myoglobin, or hypochlorite in the urine and false-negative results can be seen when the urine specific gravity is high or there are reducing agents like ascorbic acid in the urine [8]. In children, the source of bleeding is more often from glomeruli than from the urinary tract [5]; however, distinction may be made by careful microscopy of the urine, with glomerular hematuria being characterized by deformed, misshapen

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RBCs. Red cell casts and proteinuria also point to a glomerular origin, but a urologic disorder, particularly tumor, hydronephrosis, or stone, must always be ruled out by careful ultrasound examination, even if there is obvious evidence of glomerular disease. The renal papillae are susceptible to necrotic injury from microthrombi and anoxia in patients with a hemoglobinopathy or in those exposed to toxins. Patients with renal parenchymal lesions may have episodes of transient microscopic or macroscopic hematuria during systemic infections or after moderate exercise.

Causes of Hematuria

The causes of hematuria [5] include the following types.

Glomerular diseases

1) Recurrent gross hematuria (IgA nephropathy, benign familial hematuria and Alport's syndrome); 2) acute poststreptococcal glomerulonephritis; 3) membranoproliferative glomerulonephritis; 4) systemic lupus erythematosus; 5) membranous nephropathy; 6) rapidly progressive glomerulonephritis, Henoch-Schonlein purpura (HSP) and Goodpasture's disease.

Interstitial and tubular

1) acute pyelonephritis; 2) acute interstitial nephritis; 3) tuberculosis.

Hematologic causes

Sickle cell disease, coagulopathies, von Willebrand's disease, renal vein thrombosis and thrombocytopenia.

Urinary tract

1) bacterial or viral (adenovirus) infection-related; 2) nephrolithiasis; 3) hypercalciuria.

Structural anomalies

Congenital anomalies and polycystic kidney disease.

Trauma, tumors and exercise

Trauma, tumors and exercise related.

Medications

Aminoglycosides, amitryptiline, anticonvulsants, aspirin, chlorpromazine, coumadin, cyclophosphamide, diuretics, penicillin and thorazine.

Immediate Evaluation

The way of presentation and the color of urine may give the clue to probable diagnosis. Tea-colored, brown-colored or cola-colored urine includes differentials like post-infectious glomerulonephritis, membranoproliferative glomerulonephritis, rapidly progressive glomerulonephritis, IgA nephropathy, HSP and hemolytic-uremic syndrome. These conditions are usually associated with proteinuria and RBC casts along with life-threatening hypertension or oliguria/anuria. Bright red- or pink-colored urine is indicative of bleeding from the urinary tract, away from the glomerulus. The differential diagnosis includes calculus, tumor, trauma, hydronephrosis, cystitis, urinary tract infection, schistosomiasis, tuberculosis, sickle cell trait, vascular anomalies, polyps, coagulopathy, renal artery or renal vein thrombosis, terminal hematuria (urethrorrhagia), or polycystic kidney disease [9].

In systematically ill patients or in asymptomatic patients, it is imperative to repeat the urine dipstick test and microscopic urinalysis twice within 2 weeks following the initial result. If the hematuria resolves, no further tests are required. If microscopic hematuria persists on at least two of the three consecutive samples, then further evaluation is required [10]. Increased use of the urine dipstick test to screen for urinary tract infection in a febrile child or in children during routine school health examinations in many countries has resulted in the detection of asymptomatic microscopic hematuria. However, because microscopic hematuria and mild proteinuria may appear transiently during fever, illness, or extreme exertion, it is not practical or cost-effective to extensively investigate every child to find the cause of microscopic hematuria. Common illnesses in children with persistent microscopic hematuria without proteinuria are benign familial hematuria, idiopathic hypercalciuria, IgA nephropathy and Alport's syndrome. Benign familial hematuria, also known as thin basement membrane nephropathy (TBMN), is the most common cause of persistent microscopic hematuria in children [5].

Method of Urine Collection

The stepwise way to collect urine and subsequent handling can greatly influence the results. Written instructions should be given to the parents of the child/patient as to how to perform a urine collection [11]. First, strenuous physical exercise (for example, running and soccer match) must be avoided in at least 3 days preceding the collection to avoid exercise-induced proteinuria and hematuria. In women, urinalysis should also be avoided during menstruation because blood contamination can easily occur. The first or second morning urine specimen is recommended [11]. In neonates and young children, suprapubic aspiration and catheterized urine is collected, and in older children, clean catch midstream urine

Table 1. Causes of Discoloration of Urine

Dark yellow or orange urine	Normal concentrated urine, drugs such as rifampicin
Dark brown or black urine	Bile pigments methemoglobinemia alanine, cascara, resorcinol alkaptonuria, homogentisic acid, melanin, thymol, tyrosinosis
Red or pink urine	Red blood cells (hematuria), free hemoglobin (hemoglobinuria), myoglobin (myoglobinuria), porphyrins urates in high concentration (may produce pinkish tinge), foods (e.g. beetroot, blackberries, red dyes), drugs (namely, benzene, chloroquine, desferoxamine, phenazopyridine, phenolphthalein)

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collection is recommended. For all children, perianal area is cleansed and then dried, followed by midstream urine collection about 10-15 mL in 50-100 mL container. Generally, after washing the hands, females should spread the labia of the vagina and uncircumcised men withdraw the foreskin of the glans. The external genitalia are washed and wiped dry with a paper towel, and the "midstream" urine is collected after the first portion is discarded [11]. The urine specimen should be labeled for patient identification with time and date of urine collection. Several elements like leukocytes can lyse rapidly after collection, and refrigeration of specimens at +2 °C to +8 °C assists preservation but may allow precipitation of phosphates or uric acids, which can hamper examination of the sample. Formaldehyde, glutaraldehyde, CellFIX (a formaldehyde-based fixative) [4] and tubes containing a lyophilized borate-formate-sorbitol powder [5] are good preservatives for the formed elements of urine.

The color of normal urine ranges from pale to dark yellow and amber, depending on the concentration of the urochrome. The main pathologic conditions that can cause color changes of the urine are described in Table 1. Besides, conditions also include massive uric acid crystalluria (pink urine), urinary infection due to some types of *Escherichia coli* (velvet urine) and porphyrinuria and alkaptonuria (red urine turning black on standing). The main drugs responsible for abnormal urine color are rifampin (yellow-orange to red urine); phenytoin (red urine); chloroquine and nitrofurantoin (brown urine); triamterene, propofol and blue dyes of enteral feeds (green urine); methylene blue (blue urine); and metronidazole, methyldopa and imipenem-cilastatin (darkening on standing). Among foods are beetroot (red urine), senna and rhubarb (yellow to brown or red urine) and carotene (brown urine) [12].

Dipstick test is based on the principle of pseudoperoxidase activity of the heme moiety of hemoglobin, which catalyzes the reaction of a peroxide and a chromogen to produce a colored product. The presence of hemoglobin is shown as green spots, which are due to intact erythrocytes, or as a homogeneous diffuse green pattern, which is common with marked hematuria because of the high number of erythrocytes that cover the whole pad surface. It may also be observed if lysis of erythrocytes has occurred on standing or as a consequence of alkaline urine pH or a low specific gravity (especially < 1.010). The most important reasons for a positive test result in the absence of red cells are hemoglobinuria deriving from intravascular hemolysis, myoglobinuria deriving from rhabdomyolysis and a high concentration of bacteria with pseudoperoxidase activity (*Enterobacteriaceae*, *staphylococci* and *streptococci*). False-negative results are mainly due to ascorbic acid, a strong reducing agent, which can cause low-grade microscopic hematuria to be completely missed [8].

Erythrocytes in urine can be isomorphic, with regular shapes and contours, derived from the urinary excretory system, and dysmorphic, with irregular shapes and contours, which are of glomerular origin [13]. Hematuria has been defined as nonglomerular when isomorphic erythrocytes predominate (> 80% of total erythrocytes) and as glomerular [14] when dysmorphic erythrocytes prevail (> 80% of total erythrocytes). Some diagnose glomerular hematuria when the two types of cells are in the same proportion (so-called mixed hematuria) [15], or when at least 5% of erythrocytes examined are acanthocytes, a subtype of dysmorphic erythrocytes with a characteristic appearance that is due to the presence of one or more blebs protruding from a ring-shaped body. When 40% or more RBCs are dysmorphic or 5% or more acanthocytes are present [16] or one or more red cell casts in 50 low-power fields (× 160 magnification), glomerular hematuria is diagnosed. With this method in isolated microscopic hematuria, a good correlation between urinary and renal biopsy findings was found [17]. Erythrocyte dysmorphism is thought to result from deformation of the erythrocyte while it is passing through gaps of the glomerular basement membrane (GBM) followed by physicochemical insults occurring while the erythrocyte passes through the tubular system [18].

Brief Account on Common Illnesses Presenting as Hematuria

Poststreptococcal glomerulonephritis (PSGN) is an important cause of hematuria both microscopic and macroscopic, and is becoming less common in industrialized countries due to better health promoting resources and their implementation [19]. Nevertheless, PSGN remains common in developing countries, where it may affect 9.3 to 9.8 cases per 100,000 population [20], especially in communities with poor socioeconomic conditions. Most patients with hematuria of this condition give a history of a previous streptococcal infection, although it has often resolved at presentation. The incubation period is longer after skin infections (several weeks) than after throat infections (2 weeks). The classic presentation is acute nephritic syndrome, with hypertension in 80% and edema in 80-90%, while hematuria is universal and is macroscopic in 30% of cases [20]. Antistreptolysin O (ASO) titers are increased in more than two-thirds of patients with PSGN after throat infections, and anti-DNAse B titers are elevated in 73% of the post-impetigo cases. The streptozyme panel which measures antibodies to four antigens, anti-DNAse B, antihyaluronidase, ASO and antistreptokinase is more sensitive, and the result is positive in more than 80% of subjects. Serum C3 levels are depressed in more than 90% of patients in the first week of disease and return to normal in less than 2 months. C4, a measure of classical complement pathway activation, may be normal. Serum IgG and IgM are elevated in 80% of the cases, and in contrast with another poststreptococcal disease, rheumatic fever, IgA is normal. Cryoglobulins, elevated rheumatoid factor and anti-C1q antibodies are present in up to one-third of patients, and rare patients may have low titers of anti-DNA and ANCA. Urinalysis typically reveals RBC casts and proteinuria. Blood urea nitrogen and creatinine can be normal or elevated. In most patients, hematuria and proteinuria resolve within a few weeks. Microscopic hematuria may persist for as long as 2 years. The prognosis is excellent.

Familial benign essential hematuria (FBEH)

FBEH is a benign familial condition manifested as hematuria without proteinuria and without progression to renal failure or hearing defect. Diffuse attenuation of the GBM is usually considered the hallmark of the condition. From the evidence-based research, type IV collagen is involved in the pathogenesis of the disorder [21, 22]. Persistent but microscopic hematuria, with intermittent gross hematuria without any other finding, is often the usual presentation in childhood [23, 24].

Thin basement membrane nephropathy

Thin basement membrane nephropathy is usually considered as benign, but has potential to go in chronic renal disease. It is the most common cause of persistent glomerular bleeding in children and adults, and occurs in at least 1% of the population [25]. Most affected individuals have, in addition to the hematuria, minimal proteinuria, normal renal function, a uniformly thinned GBM and a family history of hematuria. Families with TBMN in whom hematuria does not segregate with the COL4A3/COL4A4 locus can be explained by *de novo* mutations, incomplete penetrance of hematuria, coincidental hematuria in family members without COL4A3 or COL4A4 mutations, and by a novel gene locus for TBMN. A renal biopsy is warranted in TBMN only if there are atypical features, or if IgA disease or X-linked Alport's syndrome cannot be excluded clinically. TMGN condition is found in patients with FBEH, but the lesion that seems to represent approximately 11% of non-transplant renal biopsies in some groups [26], is not specific and is not the guarantee of benign disease. Presence of substantial proteinuria and progression to end stage renal disease has been reported in adult patients with thin GBM [27].

IgA nephropathy

It is the disorder of kidneys where the kidneys become leaky for RBCs and in the early stages, IgA nephropathy has no symptoms. This disease can be silent for years, even decades. The first sign of IgA nephropathy may be blood in the urine. The blood may appear during a cold, sore throat, or other infection. If the amount of blood increases, urine may turn pink or the color of tea or cola. IgA nephropathy is probably the most common cause of hematuria in children [28]. The condition is diagnosed by histopathologic demonstration of mesangial deposition of IgA. IgA nephropathy usually is detected after periods of gross hematuria that follow minor infections [29]. Microscopic hematuria may be present between episodes of gross hematuria. There is also evidence suggesting that recurrent bouts of macroscopic hematuria predict a more guarded outcome in IgA nephropathy [30]. The prognosis of IgA nephropathy varies, and up to one-third of children have a guarded long-term renal prognosis [31]. As per some studies [32, 33], renal biopsy should be done in patients with microscopic hematuria and suspected IgA nephropathy to confirm the diagnosis and to increase awareness of the prognosis of patients with IgA nephropathy.

Alport's syndrome

Alport's syndrome is characterized by hematuric nephritis, hearing loss and ocular abnormalities and has familial occurrence of progressive hematuria, which is often missed initially because of isolated and microscopic presentation. Sensorineural hearing loss and ocular defects are commonly associated but present later than hematuria. Usually male

patients have severe renal disease leading to end stage renal disease before the fourth decade, whereas most female patients have a normal life span. Alport's syndrome has been reported in kindreds of all ethnic and geographic origins. Alport's syndrome is considered the cause of approximatively 0.6-2.3% of end stage renal disease in Europe and the United States [34, 35]. This proportion is probably underestimated because of diagnostic difficulties. The Alport's syndrome gene frequency is estimated to be 1 per 5,000 to 1 per 10,000.

Urinary tract and abdominal trauma

In children, urinary tract infection is one of the common causes of hematuria. It is one of the most common bacterial diseases in children which is found in 7.8% of the girls and 1.6% of the boys by the age of 7 years [36]. Trauma to abdomen and/or chest injuries remains a potential cause for hematuria in children. The need for genitourinary tract evaluation in pediatric trauma patients is based as much on clinical judgment as on the presence of hematuria [37]. Children with microscopic hematuria of greater than 50 RBCs/HPF or macroscopic hematuria, even in the presence of a benign abdominal examination, should undergo imaging with an abdominal CT scan. Significant renal injuries are unlikely in pediatric patients with blunt renal trauma but no gross or less than 50 RBCs/HPF microscopic hematuria [38]. Most children with renal injury are managed conservatively [39]. When blood is present at the urethral meatus, cystourethrography is required to look for urethral or bladder injury [40].

Fabry disease

Anderson-Fabry disease is a rare X-linked recessive disorder of glycosphingolipid metabolism resulting from deficiency of the lysosomal hydrolase, α-galactosidase A [41]. Characteristic glycolipid accumulation within every glomerular, vascular and interstitial cell and within distal tubular cells has been observed in renal tissue from all hemizygous patients irrespective of their age at renal biopsy. In heterozygous females, a peculiar feature is the presence of two intermingled cell populations, one normal and one massively involved by the storage disease. Degenerative renal changes develop with age. They first affect vessels and are characterized by the presence of round fibrinoid deposits resulting from necrosis of smooth muscle cells. They are secondarily associated with nonspecific vascular, glomerular and tubulointerstitial lesions [42].

Henoch Schonlein Purpura

HSP is the inflammation of small blood vessels, in which these vessels become swollen and irritated. This inflammation occurs in the skin, intestines, joints and kidneys. Inflamed blood vessels in the skin can leak RBCs, causing a characteristic rash called purpura. Vessels in the intestines and kidneys also can swell and leak leading to abdominal pain, altered colored stools and hematuria. HSP occurs much more often in kids than in adults, usually between ages 2 and 11 years and boys get it about twice as often as girls. Its annual incidence is approximately 14 cases of 100,000 children [43]. HSP is frequent in the first decade of life; however, it rarely affects children younger than 2 years of age. The median age at onset is 4 to 5 years [44]. Renal involvement is more frequent between 6 and 10 years of age [45, 46]. Renal manifestations include hematuria, proteinuria, nephrotic syndrome, glomerulonephritis and acute renal failure. Hematuria and proteinuria are usually transient but may persist for several months. Relapses and remissions are seen during the course of the disease and may manifest with episodes of gross hematuria. The long-term prognosis of HSP directly depends on the severity of renal involvement. In an unselected population of children with HSP, an estimated 2% develop long-term renal impairment [47].

Rapidly progressive glomerulonephritis presents with symptoms and signs similar to PIGN, and although uncommon, requires the urgent attention. Rising blood urea, serum creatinine and potasium are the common lab findings, and renal biopsy demonstrates glomerular crescents. Untreated RPGN can result in end-stage renal disease (ESRD) in a few weeks [48].

Tumors

In pediatric population, Wilms' tumor is one of the commonest abdominal tumor related masses in preschool age group. Wilms' tumor does not always cause signs and symptoms, clinically children may appear healthy, or they may have abdominal swelling, abdominal mass, fever, abdominal pain and hematuria. Somatic deletion in the long arm of chromosome 16 (16q) is known to predict a less favorable outcome in Wilms' tumor, but the underlying molecular mechanisms are not known [49]. Bladder tumors usually manifest with voiding difficulties or occasionally with macroscopic hematuria.

Nephrocalcinosis

The term nephrocalcinosis is used when there is generalized increase in renal calcium content, as opposed to the localized increase observed in calcified renal infarct and caseating granulomas of renal tuberculosis [50]. It is often associated with hypercalciuria. The most frequent cause of nephrocalcinosis is prematurity with and without furosemide treatment [51]. Pain in abdomen, dysuria, incontinence and urinary tract infection are the common presentations. Microscopic hematuria usually occurs in the context of hypercalciuria or coexistant renal stone disease [52].

Cystic renal disease

Cystic renal disease which can present with hematuria during abdominal trauma, is otherwise found incidentally after when abdominal ultrasound is performed for other indications [53] typically diagnosed in infancy or *in utero*, although less severe forms may be diagnosed later in childhood or adolescence. The estimated incidence is approximately 1 in 20,000 people [54]. Cysts may be solitary, associated with dysplasia, or associated with polycystic renal disease. Autosomal recessive means that the mutated gene must be present in both parents, who, because they carry one abnormal gene, are considered carriers.

Hypercalciuria

Excess than normal amount of calcium in urine is known as hypercalciuria. An association between hematuria and hypercalciuria in children with asymptomatic hematuria without signs of renal stones has been established [55]. Some were otherwise asymptomatic, but others eventually developed urolithiasis. Because of this, the measurement of urinary calcium excretion has become a standard part of the evaluation of hematuria in children. Idiopathic hypercalciuria may result from a tubular leak of calcium (renal hypercalciuria) or from increased gastrointestinal absorption of calcium due to high dose of calcitriol. The mechanism whereby hypercalciuria causes hematuria is unclear. It has been assumed either that hematuria is the result of irritation of the uroepithelium by microcalculi or that microscopic areas of nephrocalcinosis cause bleeding. Urine erythrocytes are shaped normally and RBC casts are absent. There is often a family history of renal stones, and some authors recommend evaluation of parents and siblings for hypercalciuria.

Idiopathic urethrorrhagia

It is presence of bloody spots in between the voiding periods and is usually presents in prepubertal boys. Symptoms included urethrorrhagia and dysuria. Cystourethroscopy reveals bulbar urethral inflammation. Routine radiographic, laboratory and endoscopic evaluation is unnecessary for evaluating urethrorrhagia. Spontaneous resolution occurs in over 90% of children. Watchful waiting is indicated. In children with prolonged urethrorrhagia, evaluation should be considered because urethral stricture may be identified [56].

Clinical Approach in Approaching a Child With Hematuria

A clinician should ensure that serious conditions are not missed while avoiding the unnecessary and expensive laboratory tests, and provide necessary advise for further evaluation whereever indicated. Obtaining a thoughtful history and thorough physical examination is the very important step in the evaluation of hematuria.

Parents, and children who can understand, should be asked about recent trauma, exercise, passage of urinary stones, recent respiratory or skin infections and intake of medications like NSAIDS and calcium or vitamin D, or traditional medicines. It is worth asking about family history of hematuria, hypertension, renal stones, renal failure, deafness, coagulopathy, jaundice and hemolytic anemias. In case of sexually active teenagers recent sexual activity and any known exposure to sexually transmitted diseases. Other conditions associated with hematuria like fever, sore throat, weight loss, failure to thrive, skin rashes, joint symptoms, face and leg swellings, dysuria, urinary frequency and urgency, back pain, should always be checked.

Physical examination

Vital parameters like blood pressure, temperature, heart rate and breathing pattern should be always noted first. Presence of high blood pressure, low urine output and edema prompt the clinician to think on lines of acute nephritic syndrome, while hematuria with skin rashes or arthritis may indicate systemic lupus erythematosus or Henoch-Schonlein nephritis or collagen vascular disease. However, ill-look, fever, vomiting, or loin pain may point to pyelonephritis. Palpable abdominal masses with hematuria should be looked for the presence of tumor, polycystic kidney, or hydronephrosis; however, IgA nephropathy, thin membrane disease, Alport's syndrome may present with recurrent hematuria only. Other uncommon causes of recurrent gross hematuria can be C1q nephropathy and nutcraker syndrome [57, 58].

Hematuria of glomerular origin is usually brown, tea-colored, or cola-colored, whereas macroscopic hematuria from the lower urinary tract is usually pink or red. Gross hematuria in the absence of significant proteinuria or RBC casts is an indication for a renal and bladder ultrasound to exclude malignancy, calculus, or cystic renal disease. Urologist's opinion should be sought when mass-lesion or a calculus is suspected.

Indications for Instant Action

It is always mandatory for any pediatric nephrologist to address the potentially life-threatening causes of hematuria in any child who has hypertension, edema oliguria, significant proteinuria, or RBC casts, failure to thrive, or refractory anemia and rickets. These include systemic illnesses like SLE, HSP, hemolytic-uremic syndrome, or membranoproliferative glomerulonephritis, PIGN and focal segmental glomerulosclerosis [59]. Recurrent gross hematuria, especially soon after the onset of upper respiratory infection, is sugges-

tive of IgA nephropathy [60]. This initial evaluation should include a detailed history and thorough physical examination, followed by urine examination, complete blood count, throat culture, ASO titer and serum C3 and C4 levels, renal ultrasonography, serum creatinine and potassium concentrations. While awaiting the results of these tests, the child's vital parameters should be strictly monitored frequently. If the cause of the hematuria remains unclear after the results of the above tests have been obtained, a 24-h urine collection for protein, creatinine and calcium should be obtained. Children with microhematuria and protein excretion of less than 25 mg/dL (6 mg/h/m^2) usually do not have a glomerulopathy and can be considered to have isolated microscopic hematuria [5], who need a regular follow-up. However, common caveats to these conditions include the IgA nephropathy, early or mild Alport's syndrome, or thin basement membrane disease, where familial history of renal diseases, deafness and familial hematuria could be helpful for subsequent evaluation for these conditions. Cystoscopic examination in children rarely reveals a cause for hematuria but should be done when bladder pathology is a consideration.

Macroscopic hematuria is occasionally due to Schistosoma hematobium in endemic areas or emigrants which is diagnosed by finding ovae in the urine [61]. Painful gross hematuria usually is caused by infections, calculi, or urologic conditions while glomerular causes of hematuria are painless. Fever, dysuria and flank pain with or without voiding symptoms suggest a urinary tract infection, which is the most common cause of gross hematuria in children presenting to an emergency room. A CT scan of the abdomen and pelvis must be obtained promptly with a history of abdominal trauma [62] and the child must be referred to a urologist, although yield of abdominal CT in pediatric renal trauma is low in patients presenting with microhematuria [63].

A family history of renal calculi or severe renal colic with gross hematuria suggests urinary calculi. Hypercalciuria can cause recurrent macroscopic or microscopic hematuria in the absence of calculi on imaging studies [64]. If no obvious cause is found use of cystoscopy to lateralize the source of bleeding is performed best during active bleeding. In young girls with recurrent gross hematuria, it is important to inquire about a history of child abuse or insertion of foreign body in to genitourinary tract to obtain sexual gratification [65], where the genital area must be examined for signs of injury.

Management of Hematuria

After it is learnt from the history, physical examination and lab tests that condition does not need any immediate intervention, the parents and older children must be reassured and advised for the stepwise plan of action. However, clues like history of recent upper respiratory tract infection, trauma, recent exercise, menstruation, sore throat, skin infection, painful micturition, increased frequency, urgency, enuresis, urine color, abdominal and costovertebral angle pain, family history hematuria, deafness, hypertension, coagulopathy, calculi will be very helpful in appropriate management of hematuria.

Dipstick test and microscopic urinalysis should be repeated weekly within 2 weeks after the initial specimen. If the hematuria resolves, no further tests are needed [5]. If hematuria persists, with more than 5 RBCs/HPF and no evidence of hypertension, edema, oliguria, or proteinuria on at least two of three consecutive samples, determination of the serum creatinine levels and ultrasonography for the presence or absence of stones, tumors, hydronephrosis, structural anomalies, renal parenchymal dysplasia, medical renal disease, inflammation of the bladder, bladder polyps, and posterior urethral valves, should be performed. The cost effectiveness of renal ultrasonography for evaluation of an asymptomatic child with microscopic hematuria is equivocal though [66]. If there is no proteinuria, no RBC casts, no edema and oliguria, no hypertension, normal serum creatinine along with normal renal and bladder ultrasonography, reassurance to parents and patient with regular follow-up is advised. However, parents' and sibling urine should be tested with dipsticks [67], to rule in/out the familial causes of hematuria. Going for detailed investigations including invasive renal biopsy is still debatable in asymptomatic hematuria; however, for prognosis, insurance purposes and genetic counseling, renal biopsy has been recommended by some researchers [32, 33].

Conflict of Interests

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