Statement

Consensus Statement on Evaluation of Hematuria

Indian Pediatric Nephrology Group, Indian Academy of Pediatrics

Pediatricians frequently encounter hematuria in children. The incidence of gross hematuria in children is estimated to be 0.13%. In more than half of the cases (56%) this is due to an easily identifiable cause(1). Asymptomatic microscopic hematuria is ten-fold 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%(2, 3). Coexistent hematuria and proteinuria signal the presence of significant renal disease.

Goals for the primary care physician in the management of a child with hematuria are:

1. To recognize and confirm the finding of hematuria
2. To identify common etiologies
3. To identify patients with significant urinary system disease that might require further expertise in either diagnosis or management.

An Expert Group Meeting of the Indian Pediatric Nephrology Group was held on 25 November 2005 in Bangalore to formulate recommendations for evaluation of patients with hematuria (Annexure 1). The consensus statement is designed to identify the patient with hematuria and then utilize the knowledge, skills, and laboratory studies available to proceed to an optimum management. The objective of the proposed algorithms is to provide a practical and systematic approach to hematuria in children. It is intended to discourage the random and often unnecessary use of laboratory investigations in every child with hematuria.

Correspondence to: Dr. Kishore D. Phadke, Children's Kidney Care Center, Department of Pediatrics, St John's Medical College Hospital, Sarjapur Road, Bangalore 560 034.
E-mail: kishorephadke@vsnl.com

Confirmation of hematuria and definitions

Children with hematuria may come to the attention of the practitioner with one of the following: (*i*) gross hematuria (*ii*) urinary or other symptoms with the incidental finding of microscopic hematuria; or (*iii*) inadvertent discovery of microscopic hematuria during a routine urinalysis.

A list of causes of hematuria is given in *Tables I and II*. Children with gross hematuria seek attention with the primary complaint of passage of dark, "cola-colored" or "smoky" urine. A small quantity of blood (1 mL in 1000 mL urine) is enough to make urine appear red. A positive dipstick reaction on urinalysis should be followed by a urine microscopy to confirm the presence of RBCs and/or casts.

The reagent strip reaction utilizes the pseudoperoxidase activity of hemoglobin (or myoglobin) to catalyze a reaction between hydrogen peroxide and the chromogen tetramethylbenzidine to produce an oxidized chromogen, which has a green-blue color. It is important to briefly dip the strip in the urine, tap off excess urine, and read the strip at the recommended time (usually one minute)(4). Dipsticks have a sensitivity of 100 % and a specificity of 99 % in detecting one to five red

TABLE I–*Causes of Hematuria*

Glomerular diseases	Non-glomerular causes
Acute post infectious glomerulonephritis	Nephrolithiasis*†
IgA nephropathy*	Hypercalciuria*†
Benign familial hematuria *†	Viral hemorrhagic cystitis
Systemic infections(malaria, leptospirosis, infective endocarditis)	Urinary tract infection
Membranoproliferative glomerulonephritis	Vascular abnormalities: Renal vein or artery thrombosis, A-V malformations
Focal segmental glomerulosclerosis	Trauma, Tumors*†, Exercise
Systemic lupus erythematosus	Hematologic
Hemolytic uremic syndrome†	Hydronephrosis
Henoch-Schonlein purpura	Renal cystic disease†
Alport's syndrome*†	Medications: NSAIDs, anticoagulants, cyclophosphamide, ritonavir, indinavir
Goodpasture's disease	Tuberculosis*
	Munchaussen syndrome/ Munchaussen by proxy

* Causes of recurrent hematuria
† Hematuria with familial association

TABLE II–*Causes of Hematuria in the Newborn*

Renal vein thrombosis
Renal artery thrombosis
Autosomal recessive polycystic kidney disease
Obstructive uropathy
Urinary tract infection
Bleeding and clotting disorders
Trauma, bladder catheterization

blood cells (RBCs) per high power field (hpf)(5).

Confirmation of hematuria by microscopic examination of the urine requires the identification of more than 5 RBCs/ hpf(3, 6). It is done by centrifuging 10 mL of a fresh urine sample at 2000 rpm for 5 min, decanting the supernatant and re-suspending the sediment in the remaining 0.5 mL(4). The sediment is examined by microscopy at high power, counting RBCs in twenty fields and the average is reported. In the absence of gross hematuria, the persistent finding of hematuria in at least two of three urinalyses, performed over 2-3 weeks, warrants further evaluation(3,7,8). A positive dipstick reaction and an absence of RBCs and RBC casts in the urine suggest hemoglobinuria or myoglobinuria. A simple test is to centrifuge a fresh urine sample and evaluate the colour of the supernatant. In hemoglobinuria the supernatant fluid will be clear pink with minimal or no deposits(9). In hematuria the supernatant will be cloudy red or dark brown with RBC deposit. The absence of hemoglobin, red cells, or myoglobin should prompt a search for other causes of red urine since several substances may discolor the urine (*Table III*)(10).

Categorizing the patient with hematuria

Confirmed hematuria could be of either glomerular or non-glomerular origin. A detailed history, comprehensive physical

examination and relevant laboratory tests are indispensable to the evaluation of hematuria. In patients with true hematuria the next step in evaluation is localization of the bleeding. A history of early morning periorbital puffiness, oliguria, dark urine and the presence of edema and/or hypertension on examination, suggest a glomerular cause. Hematuria due to glomerular causes is painless. The presence of red cell casts and preponderance of dysmorphic cells are also consistent with glomerular bleeding(9,11,12). Characteristics that help in distinguishing between glomerular and nonglomerular hematuria are given in *Table IV*. Identification of dysmorphic RBCs requires light microscopy following staining with Wright's stain (*Figs.* 1 and 2) or phase contrast microscopy. RBC morphology should be examined in 100 RBCs and the presence of greater then 20% dysmorphic RBCs is suggestive of glomerular hematuria with a sensitivity of 96%, and specificity of 93%(9,13,14). RBC casts are best seen at the edge of the cover slip, in an undiluted (specific gravity greater than 1010), uncentrifuged sample of fresh urine or urine

TABLE III–Agents that may Color Urine

Red or pink urine
Red cells, free hemoglobin, myoglobin,
Urates
Drugs: chloroquine, phenazopyridine
Beets, red dyes in food
Porphyrins
Dark yellow or orange
Normal concentrated urine
Rifampicin, pyridium
Dark brown or black
Bile pigments
Methemoglobinemia
Homogentesic acid

TABLE IV– *Distinguishing Features of Glomerular and Non-Glomerular Hematuria*

Features	Glomerular diseases	Non-glomerular causes
History		
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 and 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
Urinalysis		
Color	Brown, tea, cola	bright red, clots may be present
Proteinuria	2+ or more	Less than 2+
Dysmorphic RBCs	More than 20%	Not common, less than 15%
RBC casts	Common	Absent
Crystals	Absent	Positive in few

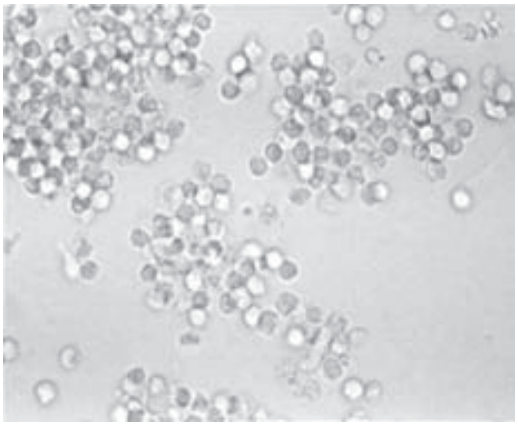

Fig. 1 Microscopy of urinary sediment. Typical appearance in non-glomerular hematuria: RBCs are uniform in size and shape, along with numerous polymorphs.

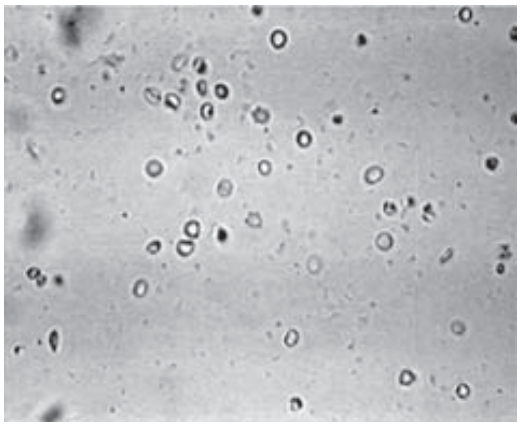

Fig. 2 Microscopy of urinary sediment. Typical appearance of RBCs in glomerular hematuria: RBCs are small and vary in size, shape, and hemoglobin content.

preserved in 1:1 dilution with 10% formalin (*Fig. 3*). RBC casts are a highly specific marker for glomerulo-nephritis(11-15).

Proteinuria may be present regardless of the cause of bleeding, but usually does not exceed 2+ (100 mg/dL) on dipstick evaluation, if the only source of protein is from blood in the urine. The combination of hematuria and proteinuria (>100 mg/dL) indicates a significant renal disease of glomerular origin. The amount of protein excreted is assessed by either determination of the ratio of protein to creatinine in a random sample of urine or by the quantitation in timed urine sample. The renal involvement, in most cases, correlates directly with the quantity of protein being excreted.

Glomerular hematuria

The most common glomerular cause of gross hematuria in children is postinfectious glomerulonephritis (PIGN). Indicators of associated complications should be sought by asking for history of headache, vomiting, blurring of vision, altered sensorium, seizures and breathlessness. A sore throat or skin infection within the past 2 to 4 weeks would indicate poststreptococcal glomerulonephritis (PSGN). A history of joint pains, skin rashes and prolonged fever in adolescents is suggestive of a collagen vascular disorder. Pallor (anemia) can never be accounted for by hematuria alone and other conditions like systemic lupus erythematosus and bleeding diathesis should be considered. Skin rashes and arthritis can occur in Henoch-Schonlein purpura and systemic lupus erythematosus.

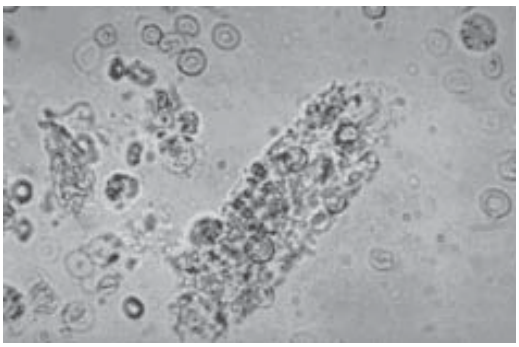

Fig. 3 Microscopy of urinary sediment. A cast containing numerous erythrocytes, indicating glomerulonephritis.

The following initial laboratory evaluations should be performed: urinalysis, urine culture, complete blood count, antistreptolysin O antibodies (ASLO), blood urea, creatinine, electrolytes and, whenever possible, complement (C3) levels. If these investigations are suggestive of a recent streptococcal infection, the diagnosis is PSGN. If these tests are negative and there is resolution of symptoms, a presumptive diagnosis of PIGN can be made. Several bacteria and viruses have been implicated in the etiology of PIGN. A patient with low C3 levels should be followed up, and re-tested after 12 weeks to ensure that these levels have returned to normal. If features of nephritis persist and/ or the diagnosis is not consistent with PIGN/ PSGN, the patient should be referred to a pediatric nephrologist. Though a biopsy is not needed in most children with acute PIGN, it may be required if the patient has severe or progressive renal failure, nephrotic-range proteinuria, gross hematuria or hypertension persisting beyond 4 weeks(16). Acute nephritic syndrome associated with systemic features, absence of hypo-complementemia or hypocomplementemia persisting beyond 12 weeks may also need biopsy(16). Many patients with PIGN may show persistent microscopic hematuria for up to two years.

Rapidly progressive glomerulonephritis (RPGN) presents with symptoms and signs similar to PIGN, but laboratory studies show progressive renal failure and renal biopsy shows crescents. A patient with RPGN requires the urgent attention of a pediatric nephrologist since prompt diagnosis by biopsy and aggressive immunosuppressive therapy may prevent progression to end stage renal disease.

Microscopic hematuria may be observed in 20% of children with minimal change nephrotic syndrome; gross hematuria usually indicates non-minimal change disease.

Hematuria may occasionally be recurrent; causes of recurrent gross hematuria are given in *Table I*. Two distinct patterns may be observed: with complete clearing of hematuria or persistent microscopic hematuria between the episodes of gross hematuria. The latter is of greater concern; a majority of these patients has IgA nephropathy or Alport's syndrome. Recurrent gross hematuria, especially when associated with infections (syninfectious) suggests IgA nephropathy, a diagnosis confirmed by renal histologic demonstration of mesangial deposits of IgA. Other conditions presenting with hematuria and requiring kidney biopsy for diagnosis are crescentic glomerulonephritis, lupus nephritis, benign familial hematuria, Alport's syndrome, inter-stitial nephritis, membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis and Goodpasture disease.

Familial or hereditary hematuria may be benign, non-progressive (thin basement membrane disease) or progressive (Alport's syndrome). Early in the course, in Alport's syndrome, hematuria may be found in the absence of proteinuria. Alport's syndrome is characterized by recurrent or persistent microscopic hematuria, progressive renal insufficiency and high-frequency, sensori-neural hearing loss with ophthalmologic defects (cataract, anterior lenticonus). The diagnosis is confirmed on kidney biopsy, including its electron microscopic examination. Family history should include questions about hematuria, renal failure, hearing loss or visual defects, nephrolithiasis and bleeding diathesis in first-degree relatives (*Table I*).

Non-Glomerular Hematuria

Common causes of non-glomerular hematuria are urinary tract infection (UTI) and nephrolithiasis. Cystitis causes hematuria more

often than upper urinary tract infection. Both UTI and nephrolithiasis may cause painful hematuria (flank pain or abdominal pain). Other symptoms that may be present are dysuria, frequency, urgency, and the patient may have fever and costovertebral angle tenderness. Hematuria occurring at initiation or termination of micturition represents hematuria of urethral or bladder origin. A urine culture should be obtained. Significant bacterial growth, indicative of UTI requires antibiotic treatment and further radiological evaluation of the genitourinary tract for obstruction, vesicoureteric reflux, cystic disease and other abnormalities.

A family history of renal calculi or renal colic with hematuria suggests urinary calculi. Investigations for calculi include plain *X*-ray and ultrasonography of kidneys, ureters and bladder area. When the clinical suspicion of calculi is high and the same are not visualized with the investigations mentioned above, non-contrast helical computed tomography is the imaging modality of choice. A urine sample should be sent for determination of the urine calcium-creatinine ratio. An abnormal result should prompt a 24 hour urine collection to confirm the diagnosis of hypercalciuria, except in very young children in whom timed collections are impractical. Hypercalciuria is considered to be present if the urine calcium/creatinine ratio of a random urine is greater than that expected for age (<7 months: 0.8; 7-18 months: 0.6; 19 months-6 years: 0.4; >6 years 0.2) and confirmed if the 24 hr urine collection for calcium is high (>4 mg/kg)(17). Hypercalciuria can cause recurrent macroscopic and occasional blood clots or microscopic hematuria probably as a result of irritation of the uroepithelium by microcalculi. Children with idiopathic hypercalciuria have increased urinary excretion of calcium despite normal serum calcium levels. They may have hematuria even in the absence of calculi on imaging studies. Some of these children eventually do develop urolithiasis. Hypercalciuria can also occur in hypercalcemic states such as hyperparathyroidism, prolonged immobilization and vitamin D intoxication. Evaluation of urinary uric acid may be done if no other cause for hematuria is found(17).

Bleeding disorders and coagulation defects may present as microscopic or gross hematuria. For most patients with classic hemophilia the diagnosis of hematuria has already been established, but in some children with von Willebrand disease, hematuria may be the first manifestation.

In a child with hematuria, an abdominal mass may suggest a tumor, hydronephrosis or polycystic kidney disease. The most common malignant renal tumor in childhood is Wilm's tumor.

Rarer causes

Transient hematuria may occur due to trauma, strenuous exercise, infections, drugs, toxins or menstruation. The hematuria is directly related to the primary disorder and will disappear once the primary disease resolves hence these patients do not need evaluation in detail.

Hematuria can occur in 3-7% patients with sickle cell disease, due to renal papillary necrosis. The diagnosis is suspected due to clinical features and confirmed by hemoglobin electrophoresis. In young girls with recurrent hematuria, it is important to inquire about a history of abuse or insertion of a vaginal foreign body; the genital area must be examined for signs of injury. A rare presentation of cyclical hematuria in adolescent children is seen at menarche in females with congenital adrenal hyperplasia and virilization, who have been raised as males.

Fig. 4 Algorithm for approach to a child with hematuria RBCs: red blood cells, F/H/O: family history of, Hb: hemoglobin, hpf: high power field, PIGN: post-infectious glomerulonephritis, C3: complement factor 3, ASLO: antistreptolysin O, CBC: complete blood count, BU: blood urea, S Cr.: serum creatinine, SE: serum electrolytes, Rx: treatment, C4: complement factor 4, ANA: antinuclear antibody, anti DsDNA: anti-doublestranded DNA antibody, ANCA: antineutrophil cytoplasmic antibody, U C&S: urine culture & sensitivity, U Ca: Cr: spot urinary calcium to creatinine ratio, 24h U Ca: 24h urinary calcium excretion, USG: ultrasonography of kidneys, ureter, bladder.

Loin pain hematuria syndrome refers to episodes of unilateral or bilateral lumbar pain accompanied by macroscopic or microscopic hematuria. The diagnosis is made by exclusion after patients are shown to have normal renal function, normal genitourinary system, no infection, malignancy, hypercalciuria, nephrolithiasis and no previous trauma. The pathogenesis of this condition is unresolved. The condition is rare in children.

Referral to a paediatric surgeon or urologist is required when a structural urogenital abnormality, an obstructing calculus or tumor are suspected. Cystoscopy is rarely needed in children as a routine investigation for a child with non-glomerular hematuria.

Isolated microscopic hematuria

Parents of children with isolated microscopic hematuria should be reassured that there is time to plan a stepwise evaluation. The dipstick and microscopic urinalysis should be repeated twice within 2 weeks(11). Though it has been mentioned in literature that a a urine culture may be done if a child has persistent hematuria, particularly in the younger child where symptoms of UTI may not be apparent, UTI presenting as isolated microscopic hematuria is very rare. Renal ultrasonography should be considered a screening test because it is noninvasive and provides important information. The yield of renal ultrasonography for evaluation of an asymptomatic child with microscopic hematuria is unproven, however, its value in terms of reassurance is significant(11).

In a small number of children with isolated microscopic hematuria, without proteinuria the cause of hematuria will not be found and they need to be kept under surveillance for the development of proteinuria or other features of an underlying disorder. Unless the patient falls into a category of illness that is easily identified, an early consultation should be obtained with a pediatric nephrologist, since most will require additional expertise in investigation and management(8).

Conclusions

The recommendations represent the consensus view of the Indian Pediatric Nephrology Group. They have been formulated on the basis of best current practice, which is supported by studies published in peer-reviewed journals and the experience of the Expert Group. They are intended to provide pediatricians with broad guidelines for managing children with hematuria.

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Annexure I

Participants of the Expert Group Meeting

Amitava Pahari, Arpana Iyengar, Anand Alladi, Arvind Bagga, B.R. Nammalwar, Indira Agarwal, Jayati Sengupta, Jyoti Sharma, Kamini Mehta, Kishore Phadke, Kumud Mehta, Sushmita Banerjee, M. Vijayakumar, Madhuri Kanitkar, Mehul Shah, Mukta Mantan, N. Prahlad, Premlatha, Uma Ali, V. Tamilarasi, Vinay Agarwal, V.K. Sairam

Compiled by: Dr. K.D. Phadke, Dr. M. Vijayakumar, Dr. Jyoti Sharma and Dr. Arpana Iyengar on behalf of the Indian Pediatric Nephrology Group