Evaluation of a child with haematuria

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Introduction

Haematuria is a common presenting symptom indicating disease, injury or malformation of the renal and urinary tract, although population screening has revealed a 0.5-1.6% prevalence of asymptomatic microscopic haematuria in schoolchildren. Macroscopic haematuria is often a frightening symptom which calls for immediate attention while microscopic haematuria may go unnoticed for long periods of time. Haematuria may or may not indicate a serious underlying disease and it is therefore important to confirm the presence of haematuria and to document its severity and persistence. While the management of the child with haematuria and proteinuria or impaired renal function is not contentious, the management of the child with isolated haematuria is the subject of continuing debate.

These children present in various ways, with an episode of macroscopic haematuria, with a urinary tract or other symptom and the incidental finding of microscopic haematuria as an incidental finding during routine urinalysis or as a finding during family screening.

Clinical evaluation

When eliciting a history, attention should be focused on identifying the presence of non-specific symptoms such as fever, lethargy, loss of weight, abdominal pain, oedema or urinary tract-specific symptoms such as dysuria, recurrence of bedwetting or frequency of micturition which may suggest a urinary tract infection. Colicky loin pain preceding the onset of haematuria is suggestive of a renal or ureteric calculus and a history of a sore throat between 10-14 days or an infective skin lesion 3-4 weeks prior to the onset of haematuria is suggestive of a post-streptococcal nephritis. However, less commonly, other organisms may cause a similar illness mimicking post-streptococcal nephritis. It is also important to elicit any history of skin rashes, especially if features are suggestive of a facial butterfly rash or a photosensitive rash, as in systemic lupus erythematosus (SLE), or detect a purpuric rash, characteristically distributed in the extensor surfaces, as in Henoch-Schonlein purpura. Moreover, in the past medical history, specific enquiry should be made of symptoms suggestive of arthritis. Although haematuria is an unusual mode of presentation for a child with a clotting disorder, a history of easy bruising and delayed haemostasis may be relevant and will require investigation. A past history of trauma to back may be relevant, especially if the kidneys were known to have been involved. A detailed family history is essential in the assessment of any child with haematuria, especially if first-degree relatives are known to have haematuria or renal impairment. Deafness and renal failure in male relatives is especially relevant and points to a possible diagnosis of Alport syndrome. A family history of autosomal dominant polycystic kidney disease is similarly relevant.

Physical examination is rarely useful in identifying the cause of haematuria, although the abdominal examination should look for renal enlargement and the genitalia checked to exclude local trauma. Examination of the skin may identify a rash and examination of the joints may provide evidence of arthritis.

Examination of urine

Urinary abnormalities may be obvious or covert and may or may not be associated with renal or urinary tract disorders of a significant impact to the child. Routine screening of all children for urinary abnormalities has not been demonstrated to be cost effective but was found to be useful in Japan and in Korea. Moreover, it is increasingly common for urine to be tested routinely in general practice, outpatient and accident and emergency departments even if the presenting illness is not clearly related to the urinary tract. As a result, increasing numbers of
Visual examination

Visibly bloodstained urine (macroscopic haematuria) may contain only minute amounts of blood while apparently clear urine may contain significant numbers of red blood cells (microscopic haematuria). Bright-red blood staining, with or without clots, is indicative of heavy bleeding and is often associated with renal or urinary tract trauma although it can occasionally be caused by glomerular disease. Commonly there is a change to brown colour as haemoglobin is converted to acid haematin as a consequence of a chemical reaction with urinary acids. It is important to confirm whether the visual finding of red urine is as a result of haematuria and to distinguish haematuria from haemoglobinuria and myoglobinuria by demonstrating red cells on microscopy. Some drugs (e.g. rifampicin), foods (e.g. beetroot and some food colourings) and inborn errors of metabolism (e.g. porphyria and alkaptonuria) may also give a red or brown discolouration to the urine mimicking haematuria. Urate crystals in the urine of infants may cause a pink discoloration of nappies and cause anxiety in parents who mistake these appearances for haematuria. The possibility that the haematuria may be factitious should also be considered (Munchausen syndrome by proxy).

Blood may be noted at commencement of micturition, suggesting a urethral cause for the bleeding and requiring cystoscopy to make the diagnosis. Haematuria tends to be noted throughout voiding when there is a renal diagnosis while terminal haematuria suggests a bladder cause such as a bladder calculus or, rarely, schistosomiasis.

Dipstick testing of the urine

Urine testing sticks have entered widespread use because of convenience and increasing reliability, and it is now common practice to use dipsticks which can test many different urinary components. However, it is important to ensure they are stored in a dry environment in a moisture-proof container to maintain their efficacy. Blood is detected by the peroxidase-like action of haemoglobin and as little as 150 µg/l of free haemoglobin can cause this reaction; consequently, a negative result excludes significant haematuria. Because the degree of haemolysis is variable, it is not possible to correlate reagent pad colour changes with number of red cells in the urine. Reducing agents such as ascorbic acid reduce sensitivity of test and may give a false negative result, while oxidizing agents give a false positive result.

Microscopy

Urine microscopy provides a rapid answer but is less frequently performed because microscopes are not widely available in clinical settings and there is unfamiliarity with the technique. This is further compounded by the provision of a microscopy service by microbiology departments and a perception prevails in medical personnel that a laboratory opinion is necessary if results are to determine a therapeutic approach. Fresh, uncentrifuged urine should be examined in a counting chamber although a formal count is not necessary for most clinical situations. If the sample of urine is stale, the red cells may lyse due to osmosis and not be detected when eventually examined. White cells which are nucleated would resist lysis and be detected at microscopy and mistakenly inferred as evidence of infection.

Occasional red cells may be seen in the urine of healthy children but should not exceed 5 cells/l. The morphology of the red cells may help identify the origin of bleeding as dysmorphic cells indicate glomerular bleeding and may be identified by ordinary light microscopy although phase-contrast microscopy is the definitive technique.

Normal children have <10 white blood cells/l in a midstream specimen of urine although neonates can have up to 50 cells/l. Unstained white blood cells have a granular cytoplasm which easily distinguishes them from circular red blood cells which have a bland cytoplasm. Although neutrophils usually predominate, increased numbers of eosinophils may be found in cases of allergic interstitial nephritis. Epithelial cells may originate from tubules, collecting system, bladder or perineum.

The squamous epithelial cells reported by experienced laboratory technicians are large polygonal cells and their presence indicates that the sample may have been contaminated by contact with the perineum or foreskin. In such situations, urine culture often results in a mixed bacterial growth. Casts are easily broken by centrifugation and so are best seen in unspun urine. They have a cylindrical structure and consist of cellular debris bound by
Tamm-Horsfall protein and are classified by the predominant cellular constituent. Erythrocyte casts are pathognomonic of glomerular bleeding and either appear as clumps of red cells with abundant haemoglobin, easily seen on microscopy, or as components of granular casts with disintegrating red cells. White cell casts have a dense granular appearance and signify glomerular inflammation, and are best seen in unspun urine. Both these findings support the need for further nephrological investigations. Epithelial cell casts may be noted in the diuretic phase after acute tubular necrosis. Occasionally, hyaline casts may be noted in children with heavy proteinuria and these may appear waxy if lipid droplets are present.

**Microscopic haematuria**

Microscopic haematuria may be noted in a child with generalized symptoms (fever, lethargy, hypertension, oedema), symptoms not specific to the urinary tract (rash, purpura, arthritis, jaundice, respiratory, gastrointestinal) or symptoms related to the urinary tract (dysuria, urgency, frequency, enuresis). Fever, septicaemic illness, trauma and extreme exertion may all induce microscopic haematuria. When the haematuria is related to a non-renal disease/cause it can be expected to disappear when the primary illness resolves. However, having presented with haematuria, it is important to document its resolution and to investigate if further haematuria persists, especially if it is accompanied by proteinuria. The conditions with renal involvement which may be readily diagnosed include post-infectious glomerulonephritis, urinary tract infection, familial haematuria (both benign and Alport syndrome), Henoch-Schonlein purpura, systemic lupus erythematosus, renal tumours, hypercalciuria and urolithiasis. In most instances, microscopic haematuria associated with clinical symptoms will require referral to a paediatric nephrologist/specialist for further investigation and management.

The incidental finding of isolated microscopic haematuria is relatively common (0.5-4%), but varies because of different definitions used to diagnose haematuria. The incidence decreases in frequency as the stringency of the definition increases, indicating that the incidental finding of microscopic haematuria should prompt further testing on at least 3 or 4 occasions; many clinicians will issue parents with dipsticks and ask them to test their child's urine on a daily basis for 6-8 weeks to help ascertain whether the haematuria is persistent. Population studies have demonstrated that approximately 30% of children continue to demonstrate persistent microscopic haematuria after 6 months, confirming that investigations should be delayed until that time. Some clinicians are inclined to extend the period of observation for up to 2 years while stressing the importance of regular follow-up to document the absence of proteinuria and confirm that the nature of the haematuria is unchanged. The timing and value of renal biopsy remains contentious in this group of patients, although the views of families and children must be taken into account. A histological diagnosis should avoid unnecessary investigation such as cystoscopy and renal imaging later in life when haematuria is re-discovered during routine medical examinations. It is important to recognize that most children do not have a cause to worry in having presented with microscopic haematuria. However, the detection of significant symptoms, impaired renal function, heavy proteinuria or hypertension should prompt early referral to a paediatric nephrology/specialist centre.

Haematuria may be found as a result of family screening. In those instances in which a histological diagnosis has been made in a first-degree relative, counselling will be required and the family advised on the need for follow-up. This most commonly occurs in Alport syndrome with the need for long-term follow-up and genetic counselling. When haematuria is familial, and a diagnosis of thin basement membrane nephropathy has been made in the index case, renal biopsy may still be indicated in other affected family members. The finding of thin basement membranes does not rule out a diagnosis of Alport syndrome and there are published cases of biopsy findings of thin basement membrane and Alport nephropathy in the same pedigree, suggesting that caution should be exercised when advising families on the merits of renal biopsy. The frequency of outpatient review for children with familial haematuria will vary with diagnosis. Boys with Alport syndrome require annual measurement of blood pressure, growth, quantification of urinary protein and a hearing test while girls with Alport syndrome and children with thin basement membrane nephropathy require less frequent visits to measure blood pressure, growth and to quantify urinary protein. An algorithm outlining the management of a child presenting with microscopic haematuria is shown in figure 1.
Macroscopic haematuria

Macroscopic haematuria is an uncommon presentation in children and has been reported to have an incidence of less than 0.2%\(^8\). In the majority a diagnosis can readily be made from the history, physical examination and microscopy of urine. Urine infections account for the majority of cases with perineal irritation and trauma accounts for many others.

Viral infections (e.g. adenovirus) can cause acute haemorrhagic cystitis. Exercise-induced haematuria may be caused by the repeated impact of the posterior bladder wall against the bladder base or, with sustained exercise, as a result of glomerular afferent and efferent arteriolar vasoconstriction and a consequent rise in filtration pressure. Exercise-induced haematuria is not associated with renal disease. Hypercalciuria and hyperuricosuria are also reported to be associated with macroscopic haematuria but the strength of this association has not been studied in a population-based study. Hypercalciuria may be noted in children with haematuria who also have a histological diagnosis suggesting that hypercalciuria should only be considered as the cause of haematuria when other diagnoses have been excluded\(^9\). Around 25% of renal tumours present with macroscopic haematuria but there are usually other associated signs, in particular, a palpable mass. Bladder tumours in children are much more likely to present with disorders of micturition rather than haematuria. Because of the likely potential causes, macroscopic haematuria should be investigated urgently. This can be done in primary care or in district hospital settings.

Early consultation should take place with a paediatric nephrologist /specialist if there is evidence of impaired renal function, proteinuria or hypertension at presentation. Where a clear diagnosis is made after the first stage of investigation (e.g. acute post-streptococcal glomerulonephritis), appropriate management may be instituted locally. Where complications or an atypical course ensues or where there is uncertainty about the diagnosis, referral to a paediatric nephrologist/specialist is necessary. Radiological investigations may reveal the presence...
of a renal structural abnormality or calculus. In such situations a referral to a paediatric urologist is recommended. An algorithm outlining the management of a child presenting with macroscopic haematuria is shown in figure 2.

Indications for renal biopsy

Not all children with haematuria require a renal biopsy. It is emphasized that a number of investigations should be undertaken prior to referral but children with persistent macroscopic haematuria of unknown aetiology require referral to a nephrologist/specialist for renal biopsy as do children with a diagnosis of SLE with renal involvement. The role of renal biopsy in the management of children found to have persistent microscopic haematuria is more contentious. However, children with persistent microscopic haematuria who have a systemic illness, significant proteinuria or microalbuminuria10, impaired renal function, hypertension or a family history of haematuria may have underlying renal disease and therefore warrant renal biopsy.

Macroscopic Haematuria

(Confirm presence of red blood cells on urine microscopy)

<table>
<thead>
<tr>
<th>History and physical examination</th>
<th>Treat</th>
<th>Positive</th>
<th>Investigate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MSU for culture</td>
<td>Negative</td>
<td>Plasma creatinine, electrolytes, acid-base status, ASOT, C3, C4, mycoplasma antibodies, antinuclear factor, anti-DNA antibodies, FBC, clotting studies, ESR, blood picture urine protein/creatinine ratio and calcium/creatinine ratio, ultrasound KUB, plain abdominal x-ray, urinalysis (casts, dysmorphic red cells), urinalysis of parents</td>
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Diagnosis

<table>
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<tr>
<th>No diagnosis, especially if proteinuria, diminished renal function or hypertension</th>
<th>Refer to nephrologist/specialist</th>
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<tr>
<td>Structural anomaly on ultrasound</td>
<td>Refer to nephrologist/specialist or urologist</td>
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Treat/observe

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<tr>
<th>If significant renal impairment, proteinuria or hypertension</th>
<th>Refer to nephrologist/specialist</th>
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<tbody>
<tr>
<td>Further complement studies, immunoglobulins, ANCA, Hepatitis B and C serology</td>
<td>Anti DNAse, HIV, Review radiology</td>
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<tr>
<td>Renal biopsy</td>
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Figure 2: Algorithm outlining the management of a child presenting with macroscopic haematuria

References


