Critical review

How should family physicians evaluate and manage haematuria?

M Jimbo*

Abstract

Introduction
In evaluating a patient with haematuria, the primary care physician must answer the following three questions: 1. Is it really haematuria? 2. Should this patient with haematuria be further evaluated, and if so, how? 3. Should this patient with haematuria be referred to a specialty, and if so, to which specialty? The aim of this critical review is to discuss whether family physicians should evaluate and manage haematuria.

Discussion
Haematuria must be confirmed by a microscopic examination. Complete urological work-up entails assessment of renal function, urine culture, upper urinary tract imaging usually with computer tomography urogram and a referral to urology for cystoscopy. If a renal disease is suspected, suitable laboratory studies followed by a referral to nephrology, is appropriate.

Conclusion
While most patients with haematuria will undergo urological work-up to some degree, it is important to efficiently recognise those patients, who are at a minimal risk of serious underlying urologic condition for whom detailed work-up is not necessary, those patients who are at a high risk for whom a complete work-up with cystoscopy is warranted, and those patients with likely renal causes for whom a nephrology referral is prudent.

Introduction
In evaluating a patient with haematuria, the primary care physician must answer the following three questions: 1. Is it really haematuria? 2. Should this patient with haematuria be further evaluated, and if so, how? 3. Should this patient with haematuria be referred to a specialty, and if so, to which specialty?

This critical review addresses these questions. Because few studies have good evidence, the recommendations are mostly based on expert consensus.

Discussion

Is it really haematuria?

Gross haematuria
Gross haematuria is defined as urine that is visibly discoloured by blood. It may occur with as little as 1 ml of blood in 1 l of urine. Because patients can recognise the abnormal colour of the urine, they typically present to their physician soon after the episode. Gross haematuria must be differentiated from other causes of discoloured urine. These are shown in Table 1.

Microscopic haematuria
For this critical review, the definition by the American Urological Association (AUA) is adopted as follows: the presence of three or more red blood cells (RBCs) per high-powered field (400× magnification), in one properly-collected urine sample. A urine dipstick positive for blood must be confirmed by microscopic examination before it is considered to be haematuria.

Prevalence of haematuria
The prevalence of microscopic haematuria in the adult primary care population ranges from 2.5%–4.3%. Transient microscopic haematuria occurs in 6%–39% of the population, but persistent microscopic haematuria in three or more consecutive urinalyses occurs less

Table 1 Causes of abnormal urine colour.

<table>
<thead>
<tr>
<th>Colour</th>
<th>Foods</th>
<th>Drugs</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red/Brown</td>
<td>Beets</td>
<td>Laxatives (e.g., Ex-Lax, phenolphthalein)</td>
<td>Porphyrin (e.g., lead, mercury poisoning)</td>
</tr>
<tr>
<td></td>
<td>Blackberries</td>
<td>Tranquilisers (e.g., chlorpromazine, thioridazine, propofol)</td>
<td>Globins (e.g., haemoglobin, myoglobin)</td>
</tr>
<tr>
<td></td>
<td>Rhubarb</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fava beans</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aloe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orange</td>
<td>Carotene-containing foods (e.g., carrots, winter squash)</td>
<td>Beta-carotene supplements</td>
<td>Urochrome (e.g., dehydration)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vitamin B supplements</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Warfarin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rifampin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pyridium</td>
<td></td>
</tr>
<tr>
<td>Green/Blue</td>
<td>Asparagus</td>
<td>Amitriptyline</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indomethacin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cimetidine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Promethazine</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td>Methyldopa</td>
<td></td>
</tr>
</tbody>
</table>

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often, in about 0.5% to 2% of the population\(^6,7\).

**Should this patient with haematuria be further evaluated, and if so, how?**

Sixteen studies examined the causes of asymptomatic haematuria\(^3,5,8–21\). Underlying causes were found in 32%–100%. Moderate significant disease (stones, inflammation and anatomical abnormalities) was observed in 3.4%–27%, and highly significant disease (malignancy) was observed in 0%–26%. Urinary tract malignancies are more common in men, with an incidence twice that of women\(^2,22\), even if we exclude prostate cancer. In particular, gross haematuria is associated with a urinary tract malignancy in up to 22%\(^2,23\).

For renal causes, the most common cause of isolated glomerular haematuria (without significant proteinuria) is immunoglobulin A (IgA) nephropathy, followed by thin basement membrane disease, hereditary nephritis (Alport’s syndrome) and mild focal glomerulonephritis of other causes. Other common renal causes include renal stones, pyelonephritis, polycystic kidney disease and renal-cell carcinoma\(^24\). The common causes of haematuria, classified by location and mechanism, are listed in Table 2.

### Clinical evaluation

#### History

Microscopic haematuria has a benign cause in many patients, particularly younger women. The causes of transient haematuria may include vigorous exercise, sexual intercourse, mild trauma and menstrual contamination. Thus, particular attention should be paid to any history that suggests a benign cause, such as menstruation, recent exercise, sexual activity, viral infection or trauma. If any of these conditions are found and the patient has no other risk factors, urinalysis may be repeated 48 hours after stopping these activities. Further work-up can be stopped if the result is negative\(^2\).

Certain factors raise the risk of the significant disease. These include age greater than 35 years; tobacco use; occupational exposure to chemicals or dyes (benzenes or aromatic amines); history of gross haematuria, urolologic disorder or disease, irritative voiding symptoms, urinary tract infection or pelvic irradiation; and analgesic abuse\(^2\). In these cases, full urologic work-up is indicated. The exception may be a young woman, with symptoms and urinary findings, suggestive of urinary tract infection. In this case, if urine culture is positive, she may be treated with an appropriate antibiotic, and urinalysis may be repeated, performed 6 weeks after the treatment. If the subsequent result is negative, no further work-up is necessary\(^2\).

### Table 2: More common causes of microscopic haematuria\(^34,31\).

<table>
<thead>
<tr>
<th>Site</th>
<th>Malignancy</th>
<th>Inflammation</th>
<th>Stones</th>
<th>Anatomical abnormality</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>Renal-cell carcinoma</td>
<td>IgA nephropathy*</td>
<td>Renal stones</td>
<td>Thin basement membrane disease*</td>
<td>Hypercalciuria</td>
</tr>
<tr>
<td></td>
<td>Renal transitional-cell carcinoma</td>
<td>Hereditary nephritis*</td>
<td></td>
<td>Polycystic kidney disease*</td>
<td>Hyperuricosuria</td>
</tr>
<tr>
<td></td>
<td>Renal lymphoma</td>
<td>Other glomerulopathies*</td>
<td></td>
<td>Medullary sponge kidney disease*</td>
<td>Renal trauma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pyelonephritis</td>
<td></td>
<td>Hydronephrosis</td>
<td>Papillary necrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal tuberculosis</td>
<td></td>
<td>Hypercalciuria</td>
<td>Sickle-cell disease/trait</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hyperuricosuria</td>
<td>Renal infarction</td>
</tr>
<tr>
<td>Ureter</td>
<td>Ureteral transitional-cell carcinoma</td>
<td></td>
<td>Ureteral stones</td>
<td>Ureteral stricture</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>Bladder cancer</td>
<td>Bacterial cystitis</td>
<td>Bladder stones</td>
<td>Vesicoureteral reflux</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tuberculous cystitis</td>
<td></td>
<td>Cystocele</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radiation cystitis</td>
<td></td>
<td>Bladder papilloma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Schistosoma haematobium</td>
<td></td>
<td>Trabeculated bladder</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>Prostate cancer</td>
<td>Prostatitis</td>
<td>Prostate stones</td>
<td>Benign prostate hypertrophy</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Urethral cancer</td>
<td></td>
<td></td>
<td>Urethral stricture</td>
<td>Abdominal aortic aneurysm</td>
</tr>
<tr>
<td></td>
<td>Penile cancer</td>
<td></td>
<td></td>
<td></td>
<td>Over-anticoagulation</td>
</tr>
<tr>
<td></td>
<td>Metastatic cancer</td>
<td>Urethritis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Denotes glomerular disease.
To avoid overlooking a glomerular cause, attention to past medical history, medication use, family history and review of systems would be important. The patient should also be asked about any symptoms of chronic kidney disease, such as hypertension, abnormal kidney function results, oedema and other signs of volume overload.

Physical examination
When a urological condition is suspected, a detailed genitourinary examination is essential, including pelvic examination in women and rectal examination, particularly in men. When a renal condition (such as glomerular haematuria) is suspected, checking the blood pressure and performing a detailed cardiovascular examination for evidence of volume overload are important.

Laboratory evaluation
Urinalysis
The sensitivity and specificity of urine dipstick test for blood vary from 91%–100% and from 65%–99%, respectively. Due to its high sensitivity, urine dipstick test is generally sufficient to rule out haematuria. However, to confirm the presence of RBCs in those who test positive for blood, it is crucial to look at the urine microscopically. An exception, in which the urine dipstick is more accurate than urine microscopy, is when the urine is very dilute, with specific gravity of less than 1.007 (308 mOsm). In this environment, RBCs may break down and may not be visible, causing the urine microscopic examination to be falsely negative for haematuria.

When performing urine microscopy, proper care should be given to prepare the sample. A fresh sample of 10–15 ml urine should be centrifuged at 3000 rpm for 5 minutes. The supernatant is then decanted and the sediment agitated in the remaining supernatant of approximately 0.3 ml. A single drop is applied to a clean glass slide, and a cover slip is applied.

The urine microscopic evaluation can not only confirm haematuria, but also help differentiate glomerular from non-glomerular sources of bleeding. In glomerular haematuria, the RBCs are exposed to large changes in pH and osmotic pressure as they go through the renal tubules, making them dysmorphic. In non-glomerular haematuria, the RBCs tend to be homogeneous and normal in shape. The presence of proteinuria of 2+ or greater by dipstick also suggests glomerular haematuria, because haematuria alone does not result in such a large protein excretion. Blood clots do not occur in glomerular haematuria, because of the presence of urokinase and tissue-type plasminogen activators in the glomerular filtrate. RBC casts are virtually pathognomonic for glomerular haematuria, because the protein matrix of the cast is secreted by the distal tubule. The presence of other casts also suggests a renal cause.

Urine cytology
Checking voided urine for abnormal cells is not very sensitive (66%–79%), but is highly specific (95%–100%) for bladder cancer. In their most recent guidelines, the AUA has dropped the recommendation of obtaining cytology for all patients with microscopic haematuria and suggest it for only those with suspicion for urological malignancy despite negative imaging studies and cystoscopy.

Urinary tumour markers
Urinary tumour marker tests detect antigens and other substances unique to cancer cells, mostly of the bladder. These tests include the bladder tumour antigen (BTA) test, nuclear matrix protein 22 (NMP22), carcinoembryonic antigen (CEA), cytokeratin tissue polypeptide-specific antigen (TPS), fluorescence in situ hybridisation (FISH) assay, Lewis X antigen, telomerase activity and urinary bladder cancer tumour marker (UBCTM) tests. Although these tests potentially hold promise in complementing or supplanting urine cytology, none is widely used at this time, and the AUA does not recommend its use.

Urine culture
It is prudent to obtain a urine culture in patients with haematuria, particularly for younger women with irritative voiding symptoms or a history of urinary tract infection.

Serum creatinine and calculation of glomerular filtration rate
Renal function should be measured in all cases of haematuria, not only to exclude a renal cause but also to ensure that the imaging studies to evaluate haematuria are safe to use. Glomerular filtration rate (GFR) is the most reliable estimate of the renal function and is the foundation of the chronic kidney disease staging system used by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI). GFR cannot be measured directly, so it is estimated by calculating the urinary clearance of creatinine. Currently, the most often used equation is the modification of diet in renal disease (MDRD) equation. Its advantage is that only patient’s age, gender and serum creatinine are necessary for calculation; thus, many laboratories will now automatically calculate the GFR. The equation is illustrated in Box 1. The NKF has a link in their website, where the GFR can be quickly calculated using the equation. As noted in their website, other equations [e.g., Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation may supersede MDRD as the GFR calculating formula of choice.

Other blood tests
When suspecting renal disease, other tests to consider include complete blood count, blood urea nitrogen, coagulation studies and serological studies, such as complement levels, antinuclear antibody (ANA), hepatitis B and C titres, antiglomerular basement membrane antibody, antineutrophic cytoplasmic
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Box 1 MDRD formula for calculating GFR from creatinine.

\[
\text{GFR (ml/min/1.73 m}^2) = 186 \times \text{Creatinine}^{1.154} \times \text{Age}^{-0.203} \\
\times 0.742 \text{ (if female patient)} \\
\times 1.212 \text{ (if African–American patient)}
\]

GFR, glomerular filtration rate; MDRD, modification of diet in renal disease study group.

antibody (ANCA), antistreptolysin O titer (ASO) and cryoglobulin assay.25

Imaging studies
Numerous radiographic methods are available for both anatomic and functional assessment of the kidneys and urinary tract.36 Deciding on which modality to use initially depends on whether a urological or a renal cause for the haematuria is suspected. The three most currently used imaging modalities are ultrasonography (US), intravenous urography (IVU) and computed tomography (CT).

Ultrasonography
For evaluation of renal disease, US offers an accurate, non-invasive approach to rule out obstructive uropathy, determine renal size and cortical thickness and look for masses or cysts. Colour duplex to assess renal vascular flow and resistance provides additional information regarding renal parenchymal disease. The US is the first choice among the imaging studies to evaluate a patient with deterioration in renal function, because it does not involve the usage of nephrotoxic contrast media. US is also safe in pregnant patients. It is less accurate in detecting ureteral lesions such as non-obstructing stones (sensitivity 19%), and is not the first choice for evaluating a suspected urological cause of haematuria.39 For the radiologic evaluation of haematuria, the American College of Radiology (ACR) gives US an appropriateness rating of six, with eight being the highest and two being the lowest.36

Intravenous urography
IVU has been the traditional imaging modality of choice for evaluating haematuria. It is widely available and the most cost-efficient in most medical centres. Indeed, it scores the highest ACR appropriateness rating of eight.38 However, IVU may miss smaller renal masses, with sensitivities of 21%, 52% and 85%, for masses less than 2 cm, 2–3 cm and greater than 3 cm, respectively, when compared with contrast-enhanced CT.40 IVU also cannot distinguish between solid form cystic masses, requiring another imaging modality, such as US or CT for further lesion characterisation. Finally, IVU has relatively low sensitivity for detecting urinary tract stones, from 52%–59%.39 For these reasons, the AUA no longer recommends IVU as an imaging study to evaluate patients with haematuria.

Computed tomography
CT of the kidneys and urinary tract is better than ultrasound in detecting stones in patients with haematuria, and it has the highest sensitivity, from 94%–98%.39 Non-contrast helical CT is excellent for detection of urinary stones (Figure 1). CT urography involves the injection of iodinated contrast media, with subsequent high-resolution nephrographic phase and delayed phase imaging to evaluate the renal pelvis, ureter and bladder. CT urography also

Figure 1: Left renal stone with obstruction. (Courtesy of John Wei, MD, Department of Urology, University of Michigan, Ann Arbor, Michigan.)
scores eight in the ACR appropriateness rating.

**Should this patient with haematuria be referred to a specialty, and if so, to which specialty?**
The evaluation methods for haematuria discussed so far in this critical review are well within the scope of practice for family physicians. However, certain patients will require a referral to urology or nephrology for further evaluation.

**When to refer to urology evaluation?**
Urological referral for haematuria is indicated when the work-up has identified a urological disease or when cystoscopy should be considered. Patients with microscopic haematuria, except for low-risk patients with benign causes of transient haematuria or uncomplicated urinary tract infection, should first have upper tract imaging. Imaging should be with CT urography in most patients, renal US for patients suspected of glomerular haematuria or who are pregnant, and non-contrast-enhanced CT, if a urinary tract stone is strongly suspected. If an abnormality is observed, with the possible exception of urinary tract stones of 4 mm or less, for which spontaneous passage can be expected with medical management, the patient should see an urologist.

**Cystoscopy**
Cystoscopy is the best way to evaluate the lower urinary tract, including the bladder, urethra and urethral orifice. Initial diagnostic cystoscopy can be performed in the urologist’s office using a flexible cystoscope under local anaesthesia. This is a quick procedure that does not require sedation. Flexible cystoscopy has diagnostic accuracy equal or superior to rigid cystoscopy. It is superior in the evaluation of the anterior bladder neck. However, if a lesion is detected that requires a biopsy, a rigid cystoscopy will be required to be performed.

**When to refer to nephrology evaluation?**
If the urinalysis is strongly suggestive of glomerular haematuria, the patient needs further work-up for renal causes. In the absence of significant proteinuria and RBC casts, recognising glomerular haematuria, based solely on RBC dysmorphism may be difficult. Accurate assessment of RBC dysmorphism through careful urine microscopic examination may be beyond the scope of a busy primary care physician. Therefore, these patients will likely undergo urological work-up with urinary tract imaging, and may also have cystoscopy if indicated. However, the presence of elevated blood pressure and decreased GFR increases the suspicion that the patient may have a renal cause of haematuria.

Nephrology referral should be strongly considered in the following situations:
- Acute renal failure, defined as an increase in the serum creatinine level > 0.3 mg per dl, > 50% or greater increase in the serum creatinine level above baseline, urine output < 0.5 ml/kg/hour × 6–12 hours, or the requirement for acute dialysis.
- Significantly diminished renal function (GFR of less than 30 ml/min per body surface area [BSA] 1.73 m²) of chronic or unknown duration.
- Possible indication for renal biopsy, including persistent proteinuria of 2+ or greater by urine dipstick, haematuria with persistent proteinuria or persistent isolated glomerular haematuria for over 1 year with negative urological work-up.
- Underlying cause of haematuria unclear.
- For management of a nephrological cause (such as primary glomerulopathy).

**Follow-up of patients with a negative work-up**
Initial work-up may fail to reveal the underlying cause of haematuria in at least 8%–10% of cases. Because subsequent urological malignancies (1%-3%) are found within three years of the initial negative results,

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**Figure 2:** Bladder mass.
(Courtesy of John Wei, MD, Department of Urology, University of Michigan, Ann Arbor, Michigan.)
regular follow-up would be prudent. The AUA recommends annual urinalysis; for those with two consecutive negative results, no further testing is performed. For those with persistent microscopic haematuria, repeat evaluation with imaging and cystoscopy in 3–5 years is recommended. Patients with persistence of haematuria, development of proteinuria, evidence of glomerular haematuria, new onset of hypertension or decreased GFR, also warrant a referral to a nephrologist.

Conclusion
Haematuria is a relatively common complaint in the primary care patient population. It is generally benign in younger patients, with no risk factors, particularly in women. However, older individuals, particularly men, should be evaluated for potentially serious urologic conditions, such as malignancy. While most patients with haematuria will undergo urological work-up to some degree, it is important to efficiently recognise those at minimal risk of serious underlying urologic condition for whom detailed work-up is not necessary, those at high risk for whom a complete work-up with cystoscopy is warranted, and those with likely renal causes for whom a nephrological referral is prudent.

Abbreviations list
ACR, American College of Radiology; AUA, American Urological Association; CT, computed tomography; GFR, glomerular filtration rate; IVU, intravenous urography; NKF, National Kidney Foundation; RBC, red blood cell; US, ultrasonography.

References
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