Haematuria

AG Rockall, APG Newman-Sanders, MA Al-Kutoubi, JA Vale

The finding of haematuria may herald the presence of pathology within the urinary tract. Indeed, early detection and investigation may lead to a potential cure of an underlying malignant disease.1-3 Presentation may be with symptomatic macroscopic haematuria, although patients with asymptomatic microscopic haematuria are commonly identified during health screening programmes. There has been considerable debate concerning the optimal investigation pathway to provide a swift diagnosis in those patients most at risk of a life-threatening illness.4,5 With the advent of the ‘fast track’ haematuria clinic, the best use of diagnostic services will be required to prevent swamping with non-urgent cases.6 There are several areas which are under debate in the current literature in which there appear to be widely varying opinions. In this article, we discuss the epidemiology of the underlying causes of haematuria, screening methods which may help detect a high risk group, the imaging modalities available for the investigation of the urinary tract, the recommended investigation pathways and the follow-up when no diagnosis has been made.

Epidemiology

Haematuria is a relatively common finding which has many potential underlying causes, ranging from the physiological to the life-threatening. The prevalence of haematuria on dipstick testing has been studied in several different populations such as patients attending hospital as out-patients, in occupational health programmes and in a large medical insurance health screening programme, and has been found to range from 2 to 16%.6-11 The prevalence of haematuria when using urine microscopy lies between 1 and 5%.1,2,4,7,12 The range varies depending on the definition of significant haematuria.

COMMON CAUSES OF HAEMATURIA

Physiological excretion of red blood cells is known to occur at low levels in healthy people.8,13 Haematuria may result from trauma during sexual intercourse or urine may be contaminated during menstruation. Vigorous physical exercise is also known to cause haematuria, although this is a diagnosis of exclusion. Pathological causes of haematuria may arise anywhere within the renal tract, from the glomerulus down to the distal urethra.

The underlying causes of haematuria were studied by Mariani et al13 in 1000 consecutive adult patients using a definition of haematuria as three or more red blood cells per high power field (HPF). They found the commonest causes of haematuria to be urethritis/trigonitis (37.7%) and benign prostatic hypertrophy (17.5%). This was followed by cystitis and transitional cell carcinoma of the bladder (6.5%). The commonest causes and life-threatening diseases of the renal tract are given in box 1.

In the under 40s, the epidemiology is somewhat different. Jones et al14 investigated 100 men under the age of 40 with confirmed microscopic haematuria, performing excretion urography and cystoscopy on all patients. The patients were followed up three months later. Only 32 patients had a positive finding (box 2). No diagnosis was made in the remaining 68 patients, although renal biopsy was not performed. There have been reports of malignant diagnoses in patients under the age of 40,14-16 but the incidence rates in the population are very low. Fromm et al17 retrospectively studied 1000 asymptomatic air force personnel between the ages of 18–33 years. After an average of 12 yearly examinations, a cumulative incidence of two to four or more red blood cells per HPF on at least one examination was reported as 38.7%, with a point prevalence of 5.2%. Of 161 cases with recurrent asymptomatic haematuria, only selected cases were investigated. Of these, six had renal calculi, one had a bladder calculus and another had urethritis. A single case of a bladder neoplasm was detected over 15 years and in this case there had been an episode of macroscopic haematuria.

Keywords: haematuria, epidemiology, diagnostic imaging, investigation pathways
Common and life-threatening causes of microscopic haematuria in 1000 adults (from1')

- urethritis/trigonitis 377
- benign prostatic hypertrophy 175
- cystitis (including cystitis cystica) 73
- transitional cell carcinoma of the bladder 65
- renal and bladder calculi 42
- bladder neck varicosities 33
- glomerulonephritis 12
- adenocarcinoma of the prostate 10
- renal cell carcinoma 10
- transitional cell carcinoma of the renal pelvis 5
- transitional cell carcinoma of the ureter 2

Box 1

Commonest causes of microscopic haematuria in 100 men under the age of 40 (from14)

- urethritis/prostatitis 10%
- exercise haematuria 7%
- intramural papilloma 3%
- friable trigonal vessels 2%
- urethral stricture 2%
- bladder neck stenosis 1%
- urinary tract infection 1%
- glandular hypospasias 1%
- idiopathic hypercalciuria 1%
- baggy PC system 1%
- duplex system 1%
- ureteric calculus 1%
- trigonal cystitis cystica 1%
- no diagnosis made 68%

Box 2

Table Registrations of urinary tract malignancy in 1989 (percentage of total cancer registrations)17

<table>
<thead>
<tr>
<th>Site</th>
<th>Male (%)</th>
<th>Female (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostatic carcinoma</td>
<td>12.4</td>
<td>-</td>
</tr>
<tr>
<td>Bladder</td>
<td>7.9</td>
<td>3.2</td>
</tr>
<tr>
<td>Kidney</td>
<td>2.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Total</td>
<td>22.8</td>
<td>4.6</td>
</tr>
<tr>
<td>All malignancies</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

MALIGNANCY OF THE URINARY TRACT

The three commonest cancers of the urinary tract are prostatic (in men), bladder and kidney. In 1989, 23% of all cancers registered in men were in this group and 4.6% of all cancers registered in women (table). Prostatic adenocarcinoma is now the most common genitourinary cancer and the incidence rates are increasing rapidly, partly due to increased detection of the disease. Malignancy of the renal tract is rare in patients under the age of 40.

GLOMERULAR DISEASE

There is a considerable percentage of cases of unexplained haematuria following urological investigations. In studies which actively included renal biopsy in cases of unexplained haematuria, a high percentage have been found to have glomerular disease. In one study, Chen et al found that, in a group of Asian military recruits with asymptomatic haematuria aged 17–25 years, 54% had glomerular disease. Topham et al found glomerular disease in 47% of 165 patients with asymptomatic haematuria, with the highest frequency in the younger age groups. IgA nephropathy (Berger's disease), thin membrane nephropathy and global or segmental mesangial proliferative nephritis are the commonest glomerular causes of haematuria. Early diagnosis of IgA disease permits monitoring of renal function and control of hypertension which may improve clinical outcome.

Screening for haematuria

Screening for haematuria is now an integral part of the routine health checks carried out by general practitioners or at insurance medical examinations. Dipstick testing of urine is a simple, readily available and inexpensive method of detection of blood in the urine. This practice will hopefully lead to the early detection of pathology with an improvement in prognosis. However, dipstick testing is known to have a false positive rate of 9–15%, as they are very sensitive and indeed may detect physiological amounts of blood in the urine. Traditionally, a positive dipstick has been followed up by microscopic examination of the urinary sediment and culture. This has several benefits, including the detection of infection or red cell casts. However, haematuria is known to be an intermittent phenomenon and the level of haematuria has not been found to relate to the risk of serious underlying disease. Thus, it has been suggested that a single positive dipstick should be fully investigated. Opinion varies, however, and in the search for a distinguishing feature of a high-risk group, age has been recommended. Patients over the age of 40 have a greater risk of malignant disease and should have access to urgent and full investigation. In the under 40s, less invasive tests should be used to rule out simple diagnoses such as urethritis or a urinary tract infection prior to embarking on more invasive tests.

History and examination

A wide range of pathologies can result in haematuria and thus a careful history and examination may help to direct the investigation pathway. A history of menstruation, recent urinary tract instrumentation or sexual trauma suggests that a repeat sample at a later date is most appropriate. Symptoms of frequency and painful micturition may suggest the presence of a urinary tract infection, the most common cause of haematuria in young women. Following confirmation of infection and subsequent treatment, follow up microscopy should be performed to rule out on-going haematuria. Pain may indicate the presence of stones, ureteric blood clot, or renal infarction. A recent streptococcal throat infection, a rash, or the finding of peripheral oedema may herald the presence of a nephritid condition. Certain sexually transmitted diseases may cause haematuria, such as non-specific urethritis, and this possibility must be considered. Foreign travel to Africa or the Middle East raises the possibility of schistosomiasis or malaria. The patient may suffer from an inherited condition such as sickle cell anaemia, haemophelia or some forms of glomerulonephritis. In the drug history, nonsteroidal anti-inflammatory drugs may cause papillary necrosis and certain chemotherapeutic agents such as cyclophosphamide may cause a haemorrhagic cystitis. Radiotherapy in the pelvis may cause a radiation cystitis.

Although in some cases the history may be helpful in elucidating the possible cause of haematuria, in many others the patient may have no other relevant history or symptoms. In these cases, the use of an established algorithm may help direct the investigation pathway (see later).
Haematuria

Figure 1 Incidence of prostatic carcinoma per 100 000\(^{17}\)

Figure 2 Incidence of bladder carcinoma per 100 000\(^{17}\)

Figure 3 Incidence of renal and renal pelvis carcinoma per 100 000\(^{17}\)

Imaging modalities

PLAIN RADIOGRAPHY

The main value of the plain radiography of the urinary tract is to exclude calcification. Renal tract calcification may be due to one of several causes, described below.

Calculi

Calculus disease affects about 5% of the population of the Western hemisphere. Characteristically, pain is the predominant symptom but occasionally calculi may be a cause of painless haematuria. Calcium oxalate and phosphate stones account for 70% of Western hemisphere stones, are more common in men and may have a dietary or metabolic cause. Magnesium ammonium phosphate stones are caused by infection with urease-producing organisms, form the basis of most staghorn calculi and are commoner in women. Cystine stones are caused by cystinuria and account for 1–2% of renal calculi. They have a characteristic ground-glass appearance and are often less dense than the adjacent bone. Uric acid stones, although very common in some parts of the Western world (accounting for 20% of stones in Germany), are radiolucent.

Infection

Tuberculosis may cause calcification anywhere in the urinary tract but most commonly in the kidney where it is characteristically unilateral or, if bilateral, asymmetrical (figure 4). They may be punctate parenchymal calcification or cloudy calcification of a tuberculosis pyonephrosis. The endstage 'autonephrectomy' may appear as a homogenous calcific mass. Schistosomiasis causes curvilinear calcification of the bladder wall and of the distal ureters which may become dilated (figure 5).

Nephrocalcinosis

The deposition of calcium salts in the renal parenchyma itself may result in haematuria. Some of the principal causes of nephrocalcinosis include idiopathic hypercalciuria, medullary sponge kidney, in which calculi may form within the ectatic tubules (figure 6), renal tubular acidosis, hyperparathyroidism, and hyperoxaluria which presents with recurrent oxalate stones.

Tumours

Faint patchy calcification may be seen in up to 10% of renal parenchymal and urothelial malignant tumours.

ULTRASOUND

Ultrasound is the imaging method of first choice for investigating the renal parenchyma and for excluding significant upper urinary tract obstruction. It is cheap, portable and safe, requiring neither ionising radiation or iodinated contrast. It is able to detect renal masses and determine whether they are cystic, solid or complex (figure 7).\(^{25,26}\) It is also able to detect calcification with a reasonably high degree of accuracy. Increasingly the nature of the vascularity of...
both normal and abnormal kidney can be characterised with Duplex sonography (combining colour Doppler with real-time imaging).

In the clinical context of haematuria, a normal ultrasound scan will exclude all but the smallest renal cells malignancies but is less reliable at detecting upper tract urothelial tumours. Conversely, the detection of a parenchymal abnormality will often require further investigation to try and determine the nature of the lesion. Finally, the detection of hydronephrosis will direct further investigation to the distal urinary tract to find the cause which will often be responsible for the haematuria, for example, a calculus (figure 8), a urothelial tumour or benign outflow obstruction.

**INTRAVENOUS UROGRAPHY**

This investigation is usually carried out as follows. A plain film of the kidneys, ureters and bladder is performed as the pre-contrast control to detect calcification or an abnormal soft tissue mass. Following an intravenous injection of iodinated contrast medium, films of the renal outlines, pelvicalyceal systems, ureters and bladder are obtained. Intravenous urography is usually tailored to the particular clinical problem. A typical radiation dose is in the region of one year’s background radiation. Potential complications due to the contrast include renal failure, particularly in diabetics and patients with renal impairment, and possible severe allergic reaction, including anaphylaxis, although this is rare. Patients with asthma or a history of severe allergies have a higher incidence of contrast reactions. The principal positive finding relevant to the investigation of haematuria is a filling defect within the collecting system which may be due to urothelial malignancy (figure 9), a radiolucent stone (figure 10), vascular impressions, pyeloureteritis cystica due to chronic infection, papillary necrosis resulting in a sloughed papilla, blood clot, metastases, or cholesteatoma. A renal cell carcinoma may appear as a bulge or a discontinuity along the renal cortical outline and there may be displacement or distortion of the pelvicalyceal system.

Intravenous urography is also an important investigation in patients with haematuria associated with renal colic. In cases of obstruction, the nephrogram is dense and prolonged (figure 11). Delayed images demonstrate a dilated pelvicalyceal system and may identify the level of obstruction in the ureter (figure 12).

**COMPUTED TOMOGRAPHY (CT)**

CT with and without dynamic intravenous contrast enhancement has an important part to play in the further evaluation of renal tract masses detected by ultrasound or intravenous urography. In addition, it may pick up small renal masses that were not visible on ultrasound and may be used to evaluate the renal tract in cases where ultrasound was unsatisfactory. CT is able to assign attenuation values to different points or regions and can therefore be used to acquire certain information about the composition of a renal mass, particularly whether or not there is fat present. It also has a greater sensitivity to the presence of calcification than the plain film (figure 13). The presence or absence of fat and/or calcification is often very helpful in establishing whether a renal mass is likely to be malignant or benign. For example, a fat-containing
lesion containing no calcification would almost certainly be an angiomyolipoma. CT is also extremely useful in the staging of malignancies of the upper and lower urinary tract, particularly if fast or helical scanning is used with dynamic contrast enhancement.

MAGNETIC RESONANCE IMAGING (MRI)

MRI does not at present have a diagnostic role in the initial investigation of haematuria. It does, however, have a role in the staging of urinary tract carcinomas following diagnosis. The depth of invasion of bladder carcinoma, for instance, can be sensitively identified using gadolinium enhancement, thereby helping the clinician to follow the most appropriate clinical management.

ANGIOGRAPHY

Since the development of ultrasound and CT scanning, angiography no longer plays a diagnostic role in assessing a renal mass seen on intravenous urography. It is, however, used in certain cases in which embolisation of a tumour circulation is required, for example, pre-operatively, to reduce the operative risk of haemorrhage in a very vascular tumour.

NUCLEAR MEDICINE

This does not have a diagnostic role in assessing the cause for haematuria. However, it may play an important role in planning treatment. A renal DTPA scan may be used to assess the split renal function prior to a radical nephrectomy for renal cell carcinoma. A DTPA scan is also helpful in determining function in an obstructed kidney. A DMSA renal scan may be used to demonstrate whether a mass comprises functioning or non-functioning tissue.

CYSTOSCOPY

Cystoscopy remains a mandatory investigation for otherwise unexplained haematuria. It can be performed either using rigid instrumentation under general or regional anaesthesia, or it can be performed using the flexible cystoscope after topical application of lignocaine gel. The latter has the advantage that it is simple, quick, safe and avoids any risks of general anaesthesia. However, it does have the disadvantage that it is largely a diagnostic tool and if significant pathology is detected then the patient will usually require a further procedure under general or regional anaesthesia at a later date.

When a diagnostic cystoscopic examination is performed for haematuria, the main purpose of the procedure is to inspect the bladder, looking for evidence of papillary transitional cell carcinomas or any raised red plaques to suggest a diagnosis of carcinoma in situ (figure 14). However, clearly other pathology will also be detected, for example, an intravesical stone or chronic inflammation. Special attention should be paid to the ureteric orifices to ensure that no blood is emanating from the upper urinary tracts, and attention should be paid to the prostate to look for any evidence of friable prostatic vessels.

RENNAL BIOPSY

Percutaneous renal biopsy is a widely used and, in experienced hands, is a safe procedure. The main contraindications are small or significantly asymmetrical
Key points

- A single episode of microscopic haematuria may be the only indication of life-threatening disease, be it a bladder carcinoma in a man of 75 or IgA nephropathy in a woman of 25.
- Benign and/or easily treatable causes far outnumber sinister causes and many can be excluded by a basic assessment and simple laboratory tests.
- Sinister causes of haematuria can and do coexist with benign conditions.
- Ultrasound examination and plain abdominal radiography are cheap and widely available with negligible adverse effect.
- Flexible cystoscopy does not require a general anaesthetic.
- Renal biopsy and contrast-enhanced CT, although relatively safe, are more expensive and carry a certain risk of morbidity and even mortality.
- It is possible to direct investigation, in the first instance, to the glomerulus or the urothelium on the basis of clinical judgement and phase-contrast examination of the urinary sediment.

Box 3

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Figure 15  Algorithm for the investigation of asymptomatic microscopic haematuria (items in bold type form the basis of the fast-track clinic)

Kidneys and hydronephrosis. Before the procedure, a full blood count, serum creatinine and electrolytes, clotting screen, serum group and save, and renal ultrasound scan should be obtained, the latter to determine that there are two kidneys and to rule out a discrepancy in size. Informed consent is obtained and if renal function is significantly impaired, desmopressin acetate is administered intravenously to improve uraemic platelet dysfunction. Intravenous access may be obtained and in some cases sedation may be appropriate. Ultrasound is used to locate the lateral border of the lower pole and the depth and angle of approach may be determined. In most centres, the biopsy is then performed 'blind'. Alternative methods include biopsy under continuous ultrasound guidance and under CT guidance. Although probably safer, these alternatives are usually reserved for patients with difficult body habitus or small kidneys. The estimated risk of renal biopsy are as follows: the overall risk of death at 1:10 000, loss of kidney at 1:1000, the need for surgical intervention at 1:500–1000 and of blood loss requiring transfusion at 1:150–300. However, with more sophisticated spring-loaded needle systems and better visualisation of the kidneys as outlined above, it is likely that the morbidity and mortality can be improved still further.

The advantage of making a positive diagnosis of glomerular disease is that patients may be spared repeated urological investigation to explain the haematuria. However, despite this benefit, the role of renal biopsy in asymptomatic haematuria is uncertain. Many nephrologists feel that the small but definite risk of morbidity and mortality mitigates against its use unless there is associated proteinuria or impaired renal function.

Investigation pathways

The potential source of urinary tract bleeding is often not evident from the history or clinical examination, resulting in a wide differential diagnosis. In
these cases, it is helpful to use an algorithm which is based upon knowledge of the epidemiology and the best investigations to reach the diagnosis, with the least possible risk to the patient. There is no consensus of agreement on a universally applicable algorithm for the investigation of haematuria. In preparing a strategy for the investigation of haematuria the following points should be born in mind.

In a review of different investigation strategies for asymptomatic microscopic haematuria, Corwin and Silverstein compared the use of intravenous urography, cystoscopy and ultrasound scan as first-line investigations. Their conclusion was that strategies using ultrasound and cystoscopy as the initial test minimised cost and morbidity while maintaining diagnostic accuracy.

Murakami et al. investigated 1034 patients with asymptomatic microscopic haematuria using cystoscopy, ultrasound scanning and, if the patient was not suspected of having a glomerulopathy, intravenous urography. In these cases, intravenous urography did not lead to a single diagnosis that had not been identified by one of the other modalities. Although intravenous urography has a role in identifying tumours of the renal pelvis and ureters, these lesions are extremely rare. The merit of subjecting all asymptomatic patients to intravenous urography as a first-line investigation must be questioned. The risk-to-benefit ratio must be considered, particularly when investigating patients under the age of 40 in whom upper tract tumours are extremely rare.

The algorithm in figure 15 is that now used at the authors’ institution. Once a potential source for haematuria is diagnosed, the patient no longer continues along the investigation pathway, but is followed up following treatment (eg, in the case of cystitis or prostatitis), or investigations are directed at evaluating the specific problem (eg, staging of a tumour).

A ‘fast track’ or ‘one-stop’ clinic has now been developed with the intention of reaching a diagnosis during a single out-patient visit. In patients over the age of 40 referred to the urologists, the clinic incorporates urine cytology, intravenous urography and flexible cystoscopy during one out-patient visit. This is efficient for the medical staff and very reassuring for patients. However, this setting possibly results in over-investigation and is inappropriate for young patients in whom sequential investigation may reach a diagnosis without exposure to ionising radiation.

FOLLOW-UP OF PATIENTS IN WHOM NO DIAGNOSIS IS MADE

There is further debate concerning the need to follow-up those patients in whom no cause is found for persistent microscopic haematuria. Schroder recommends repeating investigations at six months and a year or if symptoms develop. Howard and Golin devised a thorough follow-up schedule for patients in their institution. However, this was abandoned when a 10 to 20 year follow-up of 155 patients revealed not a single urinary tract cancer. Their final suggestion was that only patients who develop symptoms should be re-investigated. However, following negative urological investigations, a nephrological opinion should be sought prior to discharging the patient to longer term follow-up.

Conclusion

Haematuria is a finding which requires careful clinical management. Symptomatic patients with macroscopic haematuria need rapid access to comprehensive investigation. There is much debate, however, concerning the investigation of asymptomatic microscopic haematuria, particularly in patients under the age of 40. We suggest that formal liaison between urologist, nephrologist, pathologist and radiologist is essential to develop a cohesive strategy at a local level.

References

Queen Mary and Westfield College, University of London

PRESS RELEASE

British blood pressure study seeks brothers and sisters

High blood pressure arises from a combination of genes inherited from our parents and factors we are exposed to in everyday life such as adding table salt to our food, drinking too much alcohol and being overweight. At this time we know very little about the inherited factors which raise blood pressure. Since raised blood pressure increases a person’s risk of stroke or heart disease, understanding the genes which cause blood pressure to rise in some people may help us to prevent these complications.

In Britain, scientists and doctors from universities in Glasgow, Cambridge, Aberdeen, Leicester, Oxford and at St Bartholomew’s Hospital are working in partnership to discover the inherited factors which predispose people to high blood pressure. This partnership has been funded by the Medical Research Council to undertake The British Genetics of Hypertension Study which has now started recruiting families. Our aim is to identify 1500 families based on two or more brothers/sisters with high blood pressure over the next three years through the Medical Research Council GP Framework. From blood samples we will be able to search all 1500 families genes with the aim of identifying the genes contributing to raised blood pressure. Ultimately we hope this work will lead to new and improved treatments for high blood pressure and help to reduce stroke and heart disease.

Any families with two or more brothers or sisters with high blood pressure who would like more information should call our research nurses on 0171 415 3422.

For further information contact:
Dr Mark Caulfield – St Bartholomew’s and The Royal London School of Medicine, London, tel: 0171 415 3403, or
Professor John Connell – Western Infirmary, University of Glasgow, Glasgow, tel: 0141 211 2610.