

Haematuria 1: risk factors, clinical evaluation and laboratory investigations

Haematuria is a common complaint presenting to doctors in both community and acute centres. It can be a sign of underlying urinary tract malignancy. Appropriate investigation and management should follow evidence-based practice and recognized guidelines, and subsequently lead to a rapid diagnosis.

Haematuria can result in considerable patient anxiety and distress. The investigation and management of this common urological entity should be familiar to all doctors. The primary goal of investigation is to exclude urinary tract malignancy. The first of two articles examines the causes, clinical evaluation and laboratory investigations for haematuria. The second article focuses on imaging investigations and the immediate management of haematuria. Follow up of patients with negative investigations is also considered.

Definition

Haematuria is defined as the presence of blood in the urine determined on visual inspection or quantified on urine analysis. Blood in the urine may be difficult to visualize unless there is frank copious bleeding. Haematuria is broadly categorized into microscopic and macroscopic (gross/frank) haematuria.

Microscopic haematuria

Microscopic haematuria is the presence of non-visible amounts of blood in the urine. It is subdivided according to symptomatology and method of detection. Idiopathic haematuria is the term given to microscopic haematuria that has been investigated with no cause found.

Asymptomatic microscopic haematuria

Asymptomatic microscopic haematuria is usually an incidental finding at a health screen. Population-based studies have found a prevalence in the adult population between 0.19 and 16.1% (Woolhandler et al, 1989). Variables that affect the incidence of asymptomatic microscopic haematuria include age, urinalysis method (microscopy *vs* dipstick) and the cut-off level of red blood cells (RBCs) chosen for microscopy.

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Dipstick haematuria

In the vast majority of patients, microscopic haematuria is detected by dipstick testing. In health screening programmes, asymptomatic dipstick haematuria has been found to be present in 2–4% of men and 8–11% of women (Alwall and Lohi, 1973; Carel et al, 1987; Thompson, 1987). Dipstick haematuria should be confirmed routinely with urine microscopy.

Transient microscopic haematuria

Haematuria may be intermittent and can be caused by exercise, sexual intercourse, mild trauma or menstrual contamination. Because of this variation it has been suggested that two of three urine specimens should be positive for microscopic haematuria before further investigation (Grossfeld et al, 2001).

Gross haematuria

Gross haematuria is the presence of blood in the urine in sufficient quantity to be visible to the naked eye (Peacock et al, 2001). Urinalysis is required whenever there is doubt. Gross haematuria has a community prevalence of 2.5% and accounts for 4–20% of all urological consults (Khadra et al, 2000).

Exercise haematuria

Haematuria occurring after non-contact strenuous exercise such as running or swimming is known as exercise haematuria. It usually resolves within a few days (Baum, 2003) and is a result of mucosal microcontusions caused by blunt trauma from repeated impact of the posterior bladder wall against the trigone in a partially filled bladder. In its milder form, exercise haematuria may be myoglobinuria mimicking dipstick-positive haematuria.

Pseudohaematuria

Pseudohaematuria is red/brown urine that mimics the appearance of typical gross haematuria. It can occur following ingestion of certain foods and drugs (*Table 1*) or can be caused by free haemoglobin or myoglobin in the urine. Discoloured urine as a result of drugs or food does not cause dipstick-positive urine. However, in haemoglobinuria or myoglobinuria the dipstick will be positive for blood.

Factitious haematuria

Very rarely, haematuria may be self-induced by contaminating urine samples with blood by patients who have a pathological desire to seek ill health and undergo investigation (Munchausen syndrome) (Fries et al, 1977). Opiate addicts may try to seek drugs by mimicking renal colic and providing urine contaminated with venous blood.

Postcoital (post-ejaculatory) haematuria

This is extremely rare painless haematuria occurring in men immediately after sexual intercourse and may be associated with haemospermia. It is usually associated with a vascular anomaly such as a urethral haemangioma that bleeds during ejaculation.

Causes of haematuria

Urological

Tables 2 and 3 list the causes of haematuria in the urinary tract classified by anatomical site of origin. In a single centre evaluation of 1930 patients with gross or microscopic haematuria the rates of disease detection were: bladder cancer 12%; renal cancer 0.6%; prostate cancer 0.4%; upper tract urothelial cancer 0.1%; urinary tract infection 13%; nephrological disease 10%; and urinary calculi 3.6% (Khadra et al, 2000). The majority of patients had no diagnosis found after thorough evaluation. The most common cause of gross haematuria in men >60 years is benign prostatic hyperplasia (Fickenscher, 1999).

Systemic disorders

There are a number of different systemic disorders which can lead to haematuria. These include systemic lupus erythematosus, Henoch–Schönlein purpura, malaria, sickle cell disease, coagulopathies, endometriosis and alcohol abuse (as a result of papillary necrosis).

Table 1. Causes of discoloured urine

Colour of urine	Cause
Dark yellow	Drugs (chloroquine, phenacetin, sulfonamides)
	Bilirubin
	Foods (carrots, riboflavin, vitamin A)
Orange	Drugs (phenazopyridine, rifampin, sulfasalazine, laxatives containing phenolphthalein)
Blue-green	Drugs (amitriptyline, promethazine, triamterene, non-steroidal anti-inflammatory agents)
	<i>Pseudomonas</i> infection
Red-brown	Drugs (senna, rifampin, phenytoin, nitrofurantoin, metronidazole, methyl dopa)
	Melanin
	Sorbitol
	Porphyria
	Food (colouring agent rhodamine B, rhubarb, aloe, fava beans)
	Red
	Foods (beets, blackberries)
	Haemoglobinuria/myoglobinuria
	Chronic lead and mercury poisoning

Table 2. Renal causes of haematuria

Congenital	Pelvi-ureteric junction obstruction	
	Arteriovenous malformations	
	Cystic renal disease	Adult polycystic kidney disease
		Medullary sponge kidney
	Solitary renal cysts	
Genetic	Renal tubular acidosis type I	
	Cystinuria	
	von Hippel-Lindau disease	
	Alport's disease	
	Thin basement membrane disease	
Trauma	Blunt and penetrating injury	
Neoplastic	Renal cell carcinoma	
	Oncocytoma	
	Transitional cell carcinoma	
	Metastatic tumours of the kidney	
	Angiomyolipoma	
Metabolic	Calculi	
Infection	Pyelonephritis	
	Genitourinary tuberculosis	
Inflammatory diseases	Interstitial nephritis	
	Poststreptococcal glomerulonephritis	
	IgA nephropathy	
	Goodpasture's syndrome	
Radiation	Nephritis	
Vascular	Renovascular arterial disease	
	Renal vein thrombosis	
	Left renal vein hypertension as a result of nutcracker syndrome (compression of left renal vein between superior mesenteric artery and aorta)	
	Haemangiomas	
	Renal papillary necrosis	
Foreign bodies	Stent	
	Nephrostomy tubes	
Iatrogenic	Renal biopsy	
	Partial nephrectomy	
	Percutaneous nephrolithotomy	
	Percutaneous nephrolithotripsy	

Drugs

Drugs can affect various parts of the urinary tract and lead to haematuria. Penicillin, non-steroidal anti-inflammatory agents, cephalosporins and furosemide may lead to drug-induced interstitial nephritis. Cyclophosphamide and methicillin may result in drug-induced haemorrhagic cystitis. Haematuria may also be a result of nephrotoxic drugs such as aminoglycosides and cyclosporine. Microscopic and gross haematuria may be present in 40% and 4–24% of patients on anticoagulation respectively (Golin and Howard, 1980). On investigation, cancer may be present in up to a quarter of these patients (Avidor et al, 2000).

Clinical evaluation

As patients with haematuria may have cancer, they should be urgently referred to a urological unit. In the UK, the Department of Health has ruled that there should be a wait of no longer than 2 weeks from referral by the primary care physician to the date of the first specialist consultation (Coxon et al, 2003). A history should seek to elucidate any of the risk factors for urological malignancy (Table 4). It should also aim to differentiate contamination (e.g. from per rectal or vaginal bleeding) or pseudo-haematuria from true haematuria.

The origin of the haematuria can be gauged by its timing in the urinary stream. Initial haematuria suggests a urethral source while terminal haematuria indicates a prostatic urethra or bladder neck source (e.g. secondary to a bladder calculus). Total haematuria occurring throughout the stream implies bladder or upper tract pathology.

Prostatic bleeding caused by benign prostatic hyperplasia or urethral stricture is usually associated with lower urinary tract symptoms. Dysuria, urgency and incontinence may be the result of prostatitis or urinary tract infection. Gross haematuria with clots demonstrates significant bleeding and increases the likelihood of malignancy. Haematuria associated with colicky abdominal flank pain and passage of stringy clots is indicative of upper tract bleeding. Constant severe lower abdominal pain may be caused by clot retention. Systemic symptoms such as loss of appetite, weight loss and night sweats could be the result of underlying carcinoma, or in association with a cough are suggestive of tuberculosis.

A recent history of an upper respiratory tract infection is associated with nephrological causes of haematuria such as poststreptococcal glomerulonephritis. A viral illness with haemoptysis is typical of Goodpasture's syndrome. Recent gastrointestinal infections may point to immunoglobulin A (IgA) nephropathy. Timing of the menstrual period must be noted along with any history

Table 3. Non-renal urological causes of haematuria

Ureteral	Metabolic	Calculi
	Neoplastic	Transitional cell carcinoma
	Trauma	Including iatrogenic
	Foreign bodies	Stent
Bladder	Neoplastic	Transitional cell carcinoma
		Squamous cell
		Adenocarcinoma
		Neuroendocrine tumours
	Anatomical	Diverticulae
		Vesicoureteric reflux
	Infection	Acute and chronic cystitis
		Schistosomiasis
	Inflammatory	Interstitial cystitis
		Non-specific cystitis
		Postchemotherapy cystitis (cyclophosphamide)
	Metabolic	Primary and secondary calculi
		Post-acute urinary retention (decompression bleeding)
Trauma		
Prostate	Benign prostatic enlargement	
	Adenocarcinoma of the prostate	
	Infection	Prostatitis
	Metabolic	Calculi
Urethra	Haemangioma	
	Tumour	
	Stone	
	Stricture	
	Trauma	
	Foreign bodies	Catheter
		Stents
		Inserted bodies
Iatrogenic	Instrumentation or catheterization	

Table 4. Risk factors for developing urological cancer

Age > 40 years
Chronic smoking
Occupational exposure to chemicals (benzenes, aromatic amines, aniline dyes)
Cyclophosphamide therapy
Analgesic abuse
Pelvic irradiation
Recurrent urinary tract infection
Previous urological disorder or disease
Gross haematuria
Schistosomiasis infestation

of endometriosis. Unprotected sexual intercourse increases the likelihood of acquiring sexually transmitted infections (such as gonococcal or chlamydial infections) which may rarely result in frank haematuria.

Prior instrumentation may lead to urethral stricture. Pelvic radiotherapy may lead to radiation cystitis. Chronic atrial fibrillation or recent myocardial infarct may result in renal emboli and haematuria. In endemic regions, a history of tuberculosis may indicate genitourinary tuberculosis. Urological cancer may be prevalent in first-degree relatives with von Hippel-Lindau disease. A family history of urolithiasis may point towards calculi as the cause of haematuria. Travel to areas where schistosomiasis or malaria is prevalent may suggest the diagnosis.

Clinical assessment of haemodynamic status is essential against a background of significant gross haematuria with immediate volume resuscitation if necessary. Other features such as fever, sepsis, lymphadenopathy and hypertension (caused by glomerulonephritis, renal parenchymal disease, renal failure, renal cystic disease or vascular disease) and pulse rhythm (atrial fibrillation) will give clues to the diagnosis. Generalized oedema may be the result of glomerular disease. The skin should be inspected for rashes (Henoch–Schönlein purpura, systemic lupus erythematosus) and deliberate self-harm marks suggestive of factitious haematuria. Abdominal examination is performed to exclude renal and bladder masses. Rectal examination assesses the prostate size, consistency, nodules, tenderness and presence of rectal bleeding. The genitalia should be examined for signs of infection, bleeding or discharge. In men, the penis should be examined for growths, meatal stenosis and phimosis.

Laboratory investigations

For optimal analysis, a clean catch mid-stream urine specimen should be obtained and examined within 1 hour or refrigerated at 4°C. False negative results arise when urine is stored at room temperature for longer than an hour because of changes in pH and disintegration of white or red cells.

Dipstick testing

The dipstick test is based upon the liberation of oxygen from peroxide in the reagent strip because of the peroxidase-like activity of haem from erythrocytes, free haemoglobin and myoglobin. The reaction causes the reagent strip to change colour and turn green. The degree of colour change is related to the amount of haem, haemoglobin and myoglobin in the urine. Intact red cells cause a punctate colour change on the strip whereas free haemoglobin leads to uniform staining. When >250 RBCs/ml are present in the urine, the number of punctate dots increases to become uniform. The overall sensitivity for the dipstick compared to phase contrast microscopy is over 90% with specificity of 65–90% (Fogazzi and Popticelli, 1996; Roy, 1996).

False-negative results occur in the presence of acidic urine (pH<5), high levels of ascorbic acid or certain drugs (captopril, rifampicin, phenolphthalein). As well as free myoglobin and haemoglobin, povidone and microbial peroxidase from bacterial infection can lead to false-positive readings. False-positive readings are much less common than false-negative results, and up to 40% of patients with dipstick haematuria may not have haematuria confirmed on bright field urine microscopy (Tomson and Porter, 2002). A positive dipstick result in the presence of negative urine microscopy or repeated dipstick test should not be discounted. The ideal standard for urine microscopy is phase contrast microscopy, which is not the standard investigation in most centres. One positive dipstick result, even if intermittent, should be considered worthy of full investigation, especially if risk factors for malignancy are present. If proteinuria is also present, this indicates a likely glomerular origin for the haematuria.

Urine microscopy

The two main methods of microscopic examination of urine are bright field and phase contrast microscopy.

Red blood cells

Bright field microscopy is the direct examination of centrifuged urinary sediment, which is reported as the number of RBCs per high power field (HPF). The upper limit of normal of RBC excretion in the urine is approximately two RBCs per HPF (Tomson and Porter, 2002). The American Urological Association defines microscopic haematuria as three or more RBCs per HPF in urinary sediment from two or three properly collected samples (Grossfeld et al, 2001). In the study by Khadra et al (2000), using a cut-off of ten, five and three RBCs per HPF, 20%, 15% and 10% of cancers of the urinary tract would have been missed respectively.

Phase contrast microscopy is regarded as the gold standard microscopic examination. It is able to show components in a cell or bacteria that would be difficult to see under an ordinary light microscope. Not only are RBCs detected better, their morphology can be better determined with the phase contrast microscopy. Circular isomorphic erythrocytes are characteristic of non-glomerular bleeding, while glomerular bleeding results in dysmorphic erythrocytes associated with proteinuria and RBC casts.

White blood cells

More than ten white blood cells per HPF are seen in significant inflammation. Pyuria with a negative culture may be indicative of urolithiasis, tuberculosis or tumour.

Casts

A cast is a protein coagulum that is formed in the renal tubule and traps any tubular luminal contents within the

matrix. Haematuria of glomerular origin is associated with casts. RBC casts are diagnostic of glomerular bleeding. White blood cell casts may also be found in acute glomerulonephritis, pyelonephritis and tubulointerstitial nephritis.

Culture

Urine specimens should be cultured within 24 hours of collection. Urinary tract infection is present when $>10^5$ colony-forming units (CFU) per millilitre are detected in a mid-stream specimen of urine.

Cytology

Cytological analysis of urine may detect transitional cell carcinoma but is highly operator dependent. Sensitivity is much higher for high-grade lesions and carcinoma in situ (Witjies, 2004). Voided urine analysis sensitivity may be improved using the first and second voided morning specimens over three consecutive days. Barbotage cytology at cystoscopy also increases sensitivity. Cytology does not add much in the diagnostic work up of transitional cell carcinomas, as most lesions are picked up on imaging or endoscopy. However, the real value of cytology lies in its ability to diagnose carcinoma in situ which can be easily missed during white light cystoscopy.

Urinary biomarkers

Various cancer-related proteins may be detected on urine analysis. Compared to cytology, it has a better sensitivity but low specificity. Extensively studied tests include nuclear matrix protein 22 (NMP-22) and bladder tumour antigen (BTA) stat test. NMP-22 can be increased 25-fold in patients with bladder cancer, and is detected in the urine by immunoassay with an NMP-22 detection kit (Grossfeld et al, 2001). The BTA stat test detects basement membrane protein antigen released into the urine of patients with bladder cancer. Currently, urine cytology remains the standard urine test for cancer detection.

Serum analyses

Screening laboratory tests typically consist of coagulation studies, a complete blood count, biochemistry and serological studies for glomerular causes of haematuria as

directed by the medical history. Serum glucose should be checked to exclude diabetes (papillary necrosis). Prostate-specific antigen levels should be checked in men to exclude prostate cancer.

Conclusions

A presentation of frank haematuria warrants immediate investigation to exclude urological malignancy. Similarly, microscopic haematuria in the absence of urine infection may indicate significant pathology. The causes of haematuria are vast and a thorough clinical evaluation may help point towards a surgical or medical diagnosis. Patients may be stratified according to risk factors to formulate an appropriate investigation plan. The minimum laboratory dataset should include urine microscopy, urine cytology, serum creatinine and prostate-specific antigen in older men. Further investigation and management strategies will be discussed in the second of these two articles. **BJHM**

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KEY POINTS

- Haematuria is urinary tract malignancy until proven otherwise.
- Risk factors can identify patients who may have malignancy.
- Benign prostatic hyperplasia is the commonest cause of haematuria in men >60 years old.
- Haematuria in the anticoagulated patient may unmask underlying pathology.
- Phase contrast microscopy is the gold standard evaluation for determining microscopic haematuria.
- Urine cytology may detect transitional cell carcinoma.
- Prostate-specific antigen levels should be checked in men >40 years of age.