Evaluating haematuria in primary care

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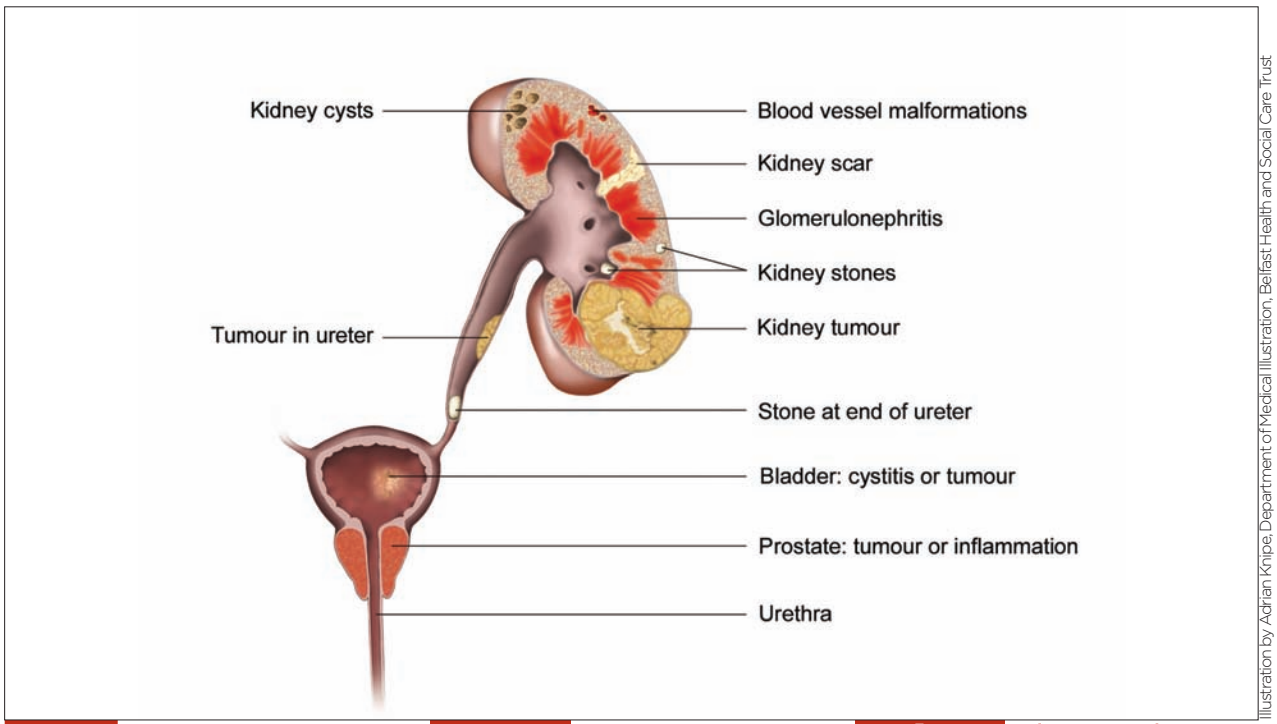


Illustration by Adrian Knipe, Department of Medical Illustration, Belfast Health and Social Care Trust

FIGURE 1
Causes of haematuria

How should haematuria be investigated?

HAEMATURIA IS A FAIRLY COMMON PROBLEM IN GENERAL PRACTICE WITH A HIGHER INCIDENCE IN patients over 40 years old.[1,2] In adults the reported prevalence of microscopic haematuria varies considerably, ranging from 1 to 20% and is highest in men over 60 years old.[3] In younger adults haematuria, particularly if it is transient, may have no obvious underlying cause. In contrast, persistent haematuria may herald the first presentation of serious urological or renal disease and there is an increased risk of malignancy in older patients. Nevertheless, in many patients no diagnosis for haematuria is established despite extensive investigation. Currently there is no evidence to justify widespread screening of the general population for asymptomatic haematuria.[4]

Although haematuria is a common clinical finding there has been controversy regarding its definition, appropriate investigation and need for referral. Recently the UK Renal Association and British Association of Urological Surgeons produced a useful consensus statement and algorithm to guide initial assessment of haematuria.[5] Definitions of haematuria are listed in table 1, p22.

DETECTION

Non-visible haematuria (NVH) is detected by oxidation of organic peroxide by haemoglobin on a urine dipstick of a fresh voided urine sample, containing no preservative. Routine microscopy for confirmation of dipstick haematuria is not necessary. Significant haematuria is considered to be 1+ or greater and trace haematuria should be considered negative.

There is no distinction in significance between non-haemolysed and haemolysed dipstick-positive haematuria and 1+ positive for either should be considered of equal significance.

It is important to exclude transient causes of NVH. Potential causes of false positives, false negatives and transient causes of haematuria »

What are the common causes?

When should patients be referred?

Table 1

Definitions of haematuria

Visible haematuria (VH)
Usually reported by the patient and otherwise known as macroscopic or gross haematuria. Urine can be described as pink, red or brown ('cola' coloured)

Non-visible haematuria (NVH)
Also referred to as microscopic or dipstick-positive haematuria. NVH is further sub-divided as follows:
- Symptomatic non-visible haematuria (s-NVH) with voiding lower urinary tract symptoms (LUTS): such as hesitancy, frequency, urgency, and dysuria
- Asymptomatic non-visible haematuria (a-NVH) - incidental detection in the absence of LUTS or upper urinary tract symptoms

are listed in table 2, below.

In patients taking anticoagulant or antiplatelet drugs, the presence of haematuria (VH or NVH) should not be assumed to be caused by the drugs and these patients should also be evaluated.

Significant haematuria is deemed present in those with:
- Any single episode of VH
- Any single episode of s-NVH (in the absence of UTI or other transient causes)
- Persistent a-NVH (in the absence of UTI or other transient causes). Persistence is defined as 2 out of 3 dipsticks positive for NVH.

AETIOLOGY

The cause of haematuria varies depending on the clinical presentation and the patient's age. The most common aetiologies are kidney or urinary tract malignancy, renal stones, cystitis, prostatitis or benign prostatic hyperplasia (BPH).

Studies of patients attending haematuria clinics report that up to 15-20% of patients with VH may have an underlying genitourinary malignancy.[6]

Malignancy is more likely in:
- men
- older adults
- smokers
- chronic analgesic users
- those with a significant occupational history of benzene exposure.

In those individuals with NVH, the malignancy risk is lower but still remains significant at 2-10%. [1, 7]

Despite complete urological assessment of haematuria there will still be a large proportion of patients (up to 60%) with no diagnosis. [1]

Approximately 10% of patients with persistent haematuria will have a renal parenchymal cause where the haematuria arises as a result of leakage of red blood cells through the glomerular basement membrane. This is sometimes called glomerular haematuria and can be VH or NVH. When haematuria and proteinuria coexist, it is much more likely that there is an underlying glomerular disorder such as glomerulonephritis, particularly if hypertension and renal failure are also present.

INVESTIGATION IN GENERAL PRACTICE

If haematuria is detected the following steps should be followed:

1. Characterise the type of haematuria
Establish if it is transient or persistent and whether VH or NVH is present.

2. History and examination
Ask if there any clues from the history or physical examination that suggest a particular diagnosis?
- Presence of clots - VH with passage of clots almost always indicates a lower urinary tract source
- Lower urinary tract symptoms
- Symptoms of prostatic obstruction in older men such as hesitancy and dribbling. The cellular proliferation in BPH is associated with increased vascularity, and the new vessels can be fragile
- Unilateral flank pain, which may radiate to the groin, suggests ureteral obstruction caused by a calculus or blood clot, but can occasionally be seen with malignancy
- Colour of urine, pink or red suggests urological causes and brown or 'cola-like' suggests a glomerular origin
- Recent upper respiratory tract infection
- Positive family history of renal disease, as in polycystic kidney disease, hereditary nephritis, or sickle cell disease
- Cyclic haematuria in women that is most prominent during and shortly after menstruation, suggesting endometriosis of the urinary tract.

3. Initial assessment
- Measure blood pressure
- Check serum creatinine and estimated glomerular filtration rate (eGFR)
- Quantify proteinuria on a random urine sample for albumin:creatinine ratio (ACR) or protein: creatinine ratio (PCR).

4. Consider referral
Referral for urological evaluation including renal imaging and cystoscopy is appropriate for patients with:
- A single episode of VH (any age)
- s-NVH (any age)
- a-NVH aged ≥40 years

The only exception to this advice would be for an adult aged under 40 years presenting with a history characteristic of glomerular haematuria e.g. dark brown urine lasting several days coinciding with an upper respiratory tract infection. This history suggests that underlying glomerulonephritis is present and these younger adults will also typically have proteinuria and should be referred first for nephrological assessment.

If a urological cause is excluded a nephrology referral should be considered if the patient also has:
- Significant proteinuria (ACR ≥30mg/mmol or PCR ≥50mg/mmol or daily urinary protein excretion ≥0.5g/24hr)
- Evidence of declining eGFR (by

Table 2

Pitfalls in assessing haematuria by dipstick urinalysis

False negatives	False positives	Transient causes
Delayed examination of urine	Haemoglobinuria (intravascular haemolysis)	Menstruation Fever
Reducing agents e.g. ascorbic acid	Myoglobinuria (rhabdomyolysis)	Exercise or trauma induced
	Oxidising agents e.g. hypochlorite preservative	UTI*high concentration of bacteria with pseudoperoxidase activity: (enterobacter, staphylococci, streptococci)

*A UTI should be considered if nitrite and leukocyte are also positive on dipstick. Urinalysis should be repeated following treatment of a UTI to ensure haematuria is not persistent.

key points

SELECTED BY

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Non-visible haematuria (NVH) is detected by oxidation of organic peroxide by haemoglobin on a urine dipstick of a fresh voided urine sample, containing no preservative. Routine microscopy for confirmation of dipstick haematuria is not necessary. Significant haematuria is considered to be 1+ or greater and trace haematuria should be considered negative.

A UTI should be considered if nitrite and leukocyte are also positive on dipstick. Urinalysis should be repeated following treatment of a UTI to ensure haematuria is not persistent.

In patients taking anticoagulant or antiplatelet drugs, the presence of haematuria (VH or NVH) should not be assumed to be caused by the drugs and these patients should also be evaluated.

If haematuria is detected the following steps should be followed. Establish if it is transient or persistent and whether VH or NVH is present. Ask if there are any clues from the history or physical examination that suggest a particular diagnosis. Measure blood pressure. Check serum creatinine and estimated glomerular filtration rate (eGFR). Quantify proteinuria on a random urine sample for albumin:creatinine ratio (ACR) or protein: creatinine ratio (PCR).

Referral for urological evaluation including renal imaging and cystoscopy is appropriate for patients with: a single episode of VH (any age); s-NVH (any age); a-NVH aged ≥40 years. The only exception to this advice would be for an adult aged under 40 years presenting with a history characteristic of glomerular haematuria e.g. dark brown urine lasting several days coinciding with an upper respiratory tract infection. This history suggests that underlying glomerulonephritis is present and these younger adults will also typically have proteinuria and should be referred first for nephrological assessment.

In a large study more than 100,000 patients with microscopic haematuria were followed up for 10 years and the relative risk of developing end-stage renal disease was found to be 2.3.

Haematuria in the absence of proteinuria should be followed up annually with repeat testing for haematuria, proteinuria/albuminuria, eGFR and blood pressure monitoring as long as the haematuria persists. Those who develop abnormalities of these parameters should be referred to a nephrologist.

>10ml/min at any stage within the previous 5 years or by >5ml/min within the past year)
- Stage 4 (eGFR <30ml/min) or stage 5 chronic kidney disease (eGFR <15ml/min)
- Isolated haematuria (i.e. in the absence of significant proteinuria) with hypertension and/or renal failure in those aged <40 years
- VH coinciding with intercurrent (usually upper respiratory tract) infection.

In the event of the above criteria not being met, haematuria itself (visible or non-visible) does not require a nephrology referral. Such patients should however continue to be monitored in primary care.

LONG-TERM MANAGEMENT

Despite appropriate referral and further hospital-based investigations, many patients with haematuria will still not have a diagnosis established. This can be a difficult situation as patients (especially those with VH) will have ongoing concerns.

In one report, 421 patients with negative investigations for NVH were followed up for a mean of 3.8 years.[8] A small number later developed urological malignancy (3 patients were diagnosed with bladder tumours and 1 with prostatic cancer). In a large study more than 100,000 patients with microscopic haematuria were followed up for 10 years and the relative risk of developing end-stage renal disease was found to be 2.3 times that of the general population.[9]

It is advisable to rerefer patients with negative investigations for urological assessment if the clinical picture changes e.g. if new VH or s-NVH develops.

To help in the detection of potential chronic kidney disease in these patients with haematuria, the NICE guideline recommends that haematuria in the absence of proteinuria should be followed up annually with repeat testing for haematuria, proteinuria/albuminuria, eGFR and blood pressure monitoring as long as the haematuria persists. Those who develop abnormalities of these parameters should be referred to a nephrologist.[10]

The guideline also places particular emphasis on assessment and treatment of associated cardiovascular risk factors.[10]

CONCLUSION

Haematuria may be a symptom of an underlying disease, which may be life threatening or treatable. The most important step is to assess if this is significant haematuria and to arrange for urological assessment. Nephrological referral and/or long-term monitoring for chronic kidney disease may be required for some patients.

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Useful information

EdRenINFO
Information on kidney disorders for health professionals and patients. (Accessed from the Royal Infirmary of Edinburgh Renal Unit website)
www.edren.org

Lab Tests Online UK
For patients and health professionals
www.labtestsonline.org.uk

Patient UK
Patient information on haematuria and its evaluation
www.patient.co.uk