Haematuria: visible and non-visible: what to do?

Abstract
Haematuria is a common symptom and in some patients it is the first symptom of urological cancer. It is therefore important to investigate it promptly in such cases. There are, of course, many other causes of haematuria, some urological, some nephrological. This article aims to give clear guidance on how to manage these patients.

Keywords
Visible haematuria, Non-visible haematuria, Urothelial cell cancer, Bladder cancer, Chronic Kidney Disease (CKD).

Introduction
Haematuria is a common symptom. Between 2.5% and 20% of the general population have non-visible haematuria (also known as microscopic or dipstick haematuria).1,2 Haematuria is often the first and only symptom of both bladder and renal cancers and therefore needs to be investigated urgently. However, only 5% of patients with persistent non-visible haematuria will have urological cancers, rising to around 20% of patients with visible haematuria (also known as macroscopic or frank haematuria).3 Many clinicians are unsure about when haematuria is significant, particularly non-visible haematuria, and also whether specialist opinion should be sought from urology, nephrology or both.

The aims of this article are to:
• Define haematuria
• Discuss possible pathological causes of haematuria
• Explain who should be referred to a urologist
• Discuss what patients can expect in a haematuria clinic
• Discuss the management of patients in the community following negative urological investigations
• Explain who should be referred to nephrology
• Discuss when patients should be re-referred to urology


Definitions
Haematuria is divided into 3 categories
• Visible haematuria
• Symptomatic visible haematuria
• Asymptomatic non-visible haematuria

These terms were suggested in 2008 by BAUS and the Renal Association and have started to become used more widely.

Visible haematuria
This refers to urine which is visibly coloured pink or red by blood. It is also known as macroscopic, frank or gross haematuria. It may be painless or painful and may appear at the beginning, end or throughout the urinary stream. Regardless of this additional information, which starts to point towards certain
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differential diagnoses, all of these patients have significant haematuria and should be referred urgently to a urologist under the two-week suspected cancer referral pathway. This is because malignancy is common and found in about 20% of patients with visible haematuria referred to a haematuria clinic. Urological malignancy is often associated with painless haematuria but if there is bleeding in a renal cancer the subsequent blood clot can temporarily occlude the ureter and cause “clot colic”. This loin pain and haematuria might be confused with a ureteric calculus and therefore delay diagnosis.

Some drugs can discolor urine, such as rifampicin and doxorubicin, as can beetroot. Myoglobinuria can also be confused with haematuria.

Non-visible haematuria

Non-visible haematuria is detected by dipstick urinalysis or microscopy. Microscopically the definition varies. Some use a cut off of more than 2 red cells per high power field, whereas others use more than 5 red cells per high power field. However, in primary care there is no need to confirm a dipstick result with microscopy because false negatives occur. This is because red cells are lysed during transit to the laboratory, with a drop in red cell counts of up to 10% five hours after the sample was voided. A urine sample should be sent to the laboratory though to investigate for infection if the dipstick is positive for leucocytes or nitrites or there is strong clinical suspicion of a urinary tract infection. The finding of blood on dipstick analysis or haemolysed and non-haemolysed samples are of equal importance and should be managed the same way. The finding of a trace amount of blood on dipstick analysis of haemolysed and non-haemolysed samples is equal importance and should be managed the same way. The finding of a trace amount of blood on dipstick analysis probably represents less than 3 to 5 red blood cells per high power microscopic field and therefore is considered a negative finding in the consensus report by BAUS and the Renal Association.

Non-visible haematuria is divided into:

• Symptomatic non-visible haematuria
• Non-visible haematuria associated with symptoms such as loin or suprapubic pain, or lower urinary tract symptoms (LUTS) including urgency, frequency, nocturia, hesitancy and/or dysuria.
• Asymptomatic non-visible haematuria
• Non-visible haematuria detected incidentally. The patient has no other urinary symptoms.

Causes of haematuria

There are many reasons why people develop haematuria (Tables 1 and 2). Many of the causes are benign but 20% of visible haematuria and 5% of persistent non-visible haematuria, especially symptomatic, can be attributed to malignancy. Sometimes no cause is found. Symptoms may give clues to the differential diagnosis. Loin pain and haematuria may be due to a renal or ureteric calculus, or pyelonephritis if there is associated fever. However, it may also be “clot colic” related to a renal or ureteric cancer. Painless visible haematuria is worrying and may be due to bladder cancer. However, benign prostatic hyperplasia may be the cause. Lower urinary tract symptoms and haematuria may be due to many benign causes, such as a urinary tract infection, benign prostatic hyperplasia, bladder calculi or radiation cystitis but may also be due to bladder cancer.

Haematuria may also be related to exercise and may be wrongly diagnosed due to menstrual contamination, myoglobinuria following rhabdomyolysis, or foods or drugs discolouring the urine such as beetroot, doxorubicin and rifampicin.

Nephrological causes can account for a large proportion of patients found to have non-visible haematuria with IgA nephropathy or thin basement membrane disease the common pathologies (Table 2). Renal biopsy abnormalities were found in nearly half of the patients referred with non-visible haematuria to one clinic in Leicester. Other nephrological causes include glomerulonephritis, vasculitis, systemic lupus and Henoch-Schönlein purpura. Acute glomerulonephritis can occur following an upper respiratory tract infection and the urine is often “cola” coloured.

Urological referral

Patients with haematuria can be referred along two-week rule suspected cancer pathways due to the risk of underlying malignancy with haematuria. Around 20%
of patients with visible haematuria will have urothelial (bladder, ureteric or renal pelvis) or renal cancer and around 5% of patients with persistent or symptomatic non-visible haematuria will have an underlying urological cancer.

Patients on anticoagulants, aspirin or clopidogrel should not be treated any differently. Studies have shown that visible haematuria in patients taking warfarin or aspirin has a pathological cause in about a quarter of cases. In addition, the incidence of non-visible haematuria is similar regardless of whether patients are on anticoagulants or not. Therefore, although these drugs undoubtedly contribute to haematuria they are not necessarily the cause of it and warrant further investigation.

All patients with haematuria should undergo some initial investigations in primary care. These should not delay referral to urology if appropriate (see below) but will help decide upon whether nephrological referral is necessary and also act as an important baseline in the ongoing surveillance that these patients require in the community after initial hospital investigations. The initial primary care investigations are:

- Serum creatinine and estimated glomerular filtration rate (eGFR)
- Blood pressure
- Urinary protein:creatinine ratio or urinary albumin:creatinine ratio (depending on local practice) measured on a single random sample of urine

Before patients are referred to a urologist as an urgent haematuria referral transient causes of haematuria such as a urinary tract infection or menstruation should be excluded. However, urinary tract infection may be the first presentation of significant urological pathology and therefore referral to a urologist should still be considered. This is strongly recommended for all men, where significant bladder outflow obstruction or prostatic disease is likely, and postmenopausal women and people with recurrent urinary tract infections who may be suffering with significant stone disease or bladder cancer, including urothelial and squamous cell cancers.

**Urgent referrals to a urologist for haematuria** (Table 3)

- All patients with visible haematuria and symptomatic non-visible haematuria, regardless of age, should be referred to a urologist urgently.
- Patients aged 40 years or over who have persistent asymptomatic non-visible haematuria should be referred to a urologist urgently. Persistent is defined as at least 2 out of 3 separate urine samples testing positive for blood on dipstick analysis over 2 to 3 weeks.

Patients with persistent asymptomatic non-visible haematuria who are under 40 years old are more likely to have a renal pathology than a urological one, such as IgA nephropathy or thin membrane disease. They therefore do not necessarily need referral to a urologist but may benefit from a nephrological opinion. A study from Leicester found renal biopsy abnormalities in 47% of patients with asymptomatic microscopic haematuria. A small number of patients with underlying renal pathologies may develop progressive kidney disease, which is often preceded by the development of proteinuria and hypertension. Although this risk is small, it is potentially preventable and therefore patients with asymptomatic non-visible haematuria may benefit from referral to a renal physician and require ongoing surveillance in the community. This will be covered in more detail later in this article.

**Haematuria clinic**

Haematuria clinics are run by urologists and tend to be “one-stop” in nature. As a result, patients can expect to have a clinical assessment including history and examination, an ultrasound scan to assess for renal abnormalities such as renal cancer and calculi, for hydronephrosis which may be due to a ureteric or lower urinary tract pathology and also to assess the bladder for any masses. A plain x-ray (KUB) is performed to assess for renal and ureteric calculi. A flexible cystoscopy is performed to visualise the lower urinary tract, including the bladder. This is an invasive procedure which carries a small risk (around 1-2%) of causing further haematuria or infection. It also causes some dysuria for 24 hours or so. It is important to remind patients that the majority will have either a benign cause or no obvious cause (possibly nephrological) for their haematuria. One study reported 88% had no worrying cause. If patients are found to have an aggressive looking bladder cancer, renal cancer or calculus then they will have a CT scan booked. They will also have a CT urogram if no cause has been identified for visible haematuria to look more closely for ureteric pathologies.

**Surveillance in the community**

Patients with no obvious urological cause for their haematuria possibly have IgA nephropathy or thin basement membrane disease, especially if they have non-visible haematuria. Although most of these patients will suffer no deleterious effects due to their conditions, a small number will develop progressive chronic kidney disease (CKD). This is normally preceded by the development of proteinuria and hypertension as well as deterioration in serum creatinine or eGFR. As a result, patients with a non-urological cause for their haematuria should be assessed annually in the community with a urinary protein:creatinine or urinary albumin:creatinine ratio.
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and also a measurement of serum creatinine and eGFR. Should their proteinuria be significant or should their eGFR be deteriorating then they will require a referral to the nephrologist (see below). Part of the community assessment should also involve trying to prevent renal deterioration and this is possible by managing hypertension and also encouraging exercise, a healthy balanced diet and reducing cardiovascular risk factors.

**Referral to a nephrologist**

Referral to a nephrologist can occur at several places in the haematuria pathway. Although IgA nephropathy and thin basement membrane disease account for many cases of non-visible haematuria, in the majority of patients there are no long term consequences. For the minority, progressive renal failure may be prevented with the management of blood pressure and other cardiovascular risk factors and nephrological input. Therefore if patients have other signs of renal disease, such as proteinuria, deteriorating eGFR and/or hypertension, in addition to their haematuria they should be referred to a nephrologist.

**Referral to a nephrologist**

This should be considered in the following circumstances:

- Non-visible haematuria, less than 40 years old with any of the following at presentation
- CKD stage 3 (eGFR <60ml/min)
- Hypertension (BP ≥140/90)
- Proteinuria (urinary protein:creatinine ratio > 50mg/mmol or urinary albumin:creatinine ratio >30mg/mmol)
- Any haematuria with any of the following
- CKD stage 4 or 5 (eGFR <30ml/min)
- Deteriorating eGFR (fallen by >5ml/min in the last 1 year or >10ml/min over the last 5 years)
- Proteinuria (urinary protein:creatinine ratio > 50mg/mmol or urinary albumin:creatinine ratio >30mg/mmol)

**When to re-refer to urology**

Although at first there may be no obvious urological cause for haematuria, particularly non-visible haematuria, general practitioners and patients become anxious about when they should be reassessed, particularly if the problem persists. A long-term study showed that significant urological conditions were sometimes found in patients whose asymptomatic non-visible haematuria became symptomatic or visible. Therefore, patients require annual assessment following discharge from the haematuria clinic not only to observe for renal disease but also to monitor the extent of haematuria. If at any point in their follow-up a patient experiences visible haematuria or symptomatic non-visible haematuria they should be re-referred to a urologist for further investigation.

A patient with ongoing visible haematuria and no abnormality on initial urological investigations, including a CT urogram, will require further urological investigation as the possibility of malignancy remains, including ureteric or renal pelvis urothelial cancer which are harder to detect. These patients will usually have urine cytology, and a rigid cystoscopy under general anaesthesia with biopsies and retrograde studies and possibly ureteroscopy.

**Summary**

Haematuria is common and may represent an occult urological malignancy. This is most likely with visible haematuria (around 20%) and symptomatic non-visible haematuria (around 5%). As a result urgent suspected cancer referral pathways are in place and should be used. Asymptomatic non-visible haematuria is usually caused by an underlying nephrological condition which is usually of little consequence. However, some may have urological conditions and should be referred if they are 40 years or older or if there are any clinical concerns. In addition, these patients require further nephrological input if they have signs or symptoms of worsening renal function, such as hypertension, proteinuria or deteriorating eGFR. As a result, they require annual surveillance in Primary Care. Deteriorating renal function can be averted in some patients by good blood pressure control and modification of cardiovascular risk factors. Patients should be re-referred to urology if they have recurrent visible or symptomatic non-visible haematuria.

**Key Points**

- Haematuria may be due to a urological malignancy
- Visible haematuria requires urgent 2 week rule referral to urology
- Symptomatic non-visible haematuria requires urgent 2 week rule referral to urology
- Persistent asymptomatic non-visible haematuria in people 40 years or over requires urgent 2 week rule referral to urology
- All haematuria patients should have their blood pressure, serum creatinine and eGFR and urinary protein (or albumin):creatinine ratios measured to assess for underlying nephrological disease
- Patients with haematuria and CKD stage 3, or deterioration to CKD stage 4 or 5 in eGFR of >5ml/min over 1 year or 10ml/min over 5 years require referral to a nephrologist
- Patients with haematuria and proteinuria (urinary protein:creatinine ratio > 50mg/mmol or urinary albumin:creatinine ratio >30mg/mmol) require referral to a nephrologist
- Patients under 40 years old with haematuria and hypertension (BP ≥140/90) require referral to a nephrologist
- Patients with haematuria require modification of cardiovascular risk factors, management of hypertension and annual measurement of serum creatinine and eGFR and urinary protein (or albumin):creatinine ratios
- Patients with recurrent visible or symptomatic non-visible haematuria require urgent re-referral to a urologist
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References


Further Reading

1. The British Association of Urological Surgeons (BAUS) and the Renal Association joint consensus statement on haematuria

Appendix A: An algorithm for managing haematuria.