Haematuria

Blood may originate from the kidney or the collecting system. Urine testing for haematuria should only be performed for identifiable clinical reasons; there is currently no evidence to support opportunistic screening of the general population.[1]

Definitions[1]

- Visible haematuria (VH): also called macroscopic haematuria or gross haematuria.
- Non-visible haematuria (NVH): also called microscopic haematuria or dipstick-positive haematuria:
  - Symptomatic non-visible haematuria (s-NVH) - associated symptoms include voiding lower urinary tract symptoms (LUTS): hesitancy, frequency, urgency, dysuria.
  - Asymptomatic non-visible haematuria (a-NVH) - incidental detection in the absence of LUTS or upper urinary tract symptoms.

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

Epidemiology

The prevalence of a-NVH varies from 0.19% to as high as 21%. [2]

There is evidence for an association between glomerular haematuria and adverse renal outcomes. [3]

Aetiology

Common causes include UTI, bladder tumours, urinary tract stones, urethritis, benign prostatic hypertrophy (BPH) and prostate cancer.

The most common causes of NVH are UTI, BPH and urinary calculi. However, up to 5% of patients with a-NVH are found to have a urinary tract malignancy.[4]

- Infection: cystitis, tuberculosis, prostatitis, urethritis, schistosomiasis, infective endocarditis.
- Tumour: renal carcinoma, Wilms' tumour, carcinoma of the bladder, prostate cancer, urethral cancer or endometrial cancer.
- Trauma: renal tract trauma due to accidents, catheter or foreign body, prolonged severe exercise, rapid emptying of an overdistended bladder (eg, after catheterisation for acute retention).
- Inflammation: glomerulonephritis, Henoch-Schönlein purpura, IgA nephropathy, Goodpasture's syndrome, polyarteritis, post-irradiation.
- Structural: calculi (renal, bladder, ureteric), simple cysts, polycystic renal disease, congenital vascular anomalies.
- Haematological: sickle cell disease, coagulation disorders, anticoagulation therapy.
- Surgery: invasive procedures to the prostate or bladder.
- Toxins: sulfonamides, cyclophosphamide, non-steroidal anti-inflammatory drugs.
- Others: genital bleeding, including child abuse; menstruation; Münchhausen's syndrome or fabricated or induced illness by carers.
Presentation

- Take a full urological history and include palpation of the abdomen, and blood pressure.
- Features suggesting a renal cause include hypertension, altered renal function tests, proteinuria, known previous renal problems, renal mass and glomerular red cells (red cells with irregular contours and shape) in the urine. [5]
- Haematuria without proteinuria does not necessarily indicate a non-glomerular origin, as glomerular bleeding is not necessarily accompanied by proteinuria. [6]

Differential diagnosis

Other causes of red or dark urine:

- **Haemoglobinuria**: dipstick-positive but no red cells on microscopy.
- **Myoglobinuria**.
- **Food** - eg, beetroot.
- **Drugs** - eg, rifampicin, nitrofurantoin, senna.
- **Porphyria**: urine darkens on standing.
- **Bilirubinuria**: obstructive biliary disease.

Investigations and management

Transient causes that need to be excluded before establishing the presence of significant haematuria are UTI, exercise-induced haematuria or, rarely, myoglobinuria, and menstruation. [1]

- All children with haematuria should be referred.
- All definite haematuria, whether VH or NVH, requires investigation to exclude serious underlying conditions, especially urinary tract neoplasm. [1]
- Patients on anticoagulants should also be investigated. Anticoagulants are more likely to provoke, rather than be the cause of, haematuria.

**Initial investigations for a patient with s-NVH and persistent a-NVH** [1]

- Exclude UTI and/or other transient cause.
- Plasma creatinine and estimated glomerular filtration rate (eGFR).
- Measure proteinuria: send urine for protein:creatinine ratio (PCR) or albumin:creatinine ratio (ACR) on a random sample (according to local practice). 24-hour urine collections for protein are rarely required. An approximation to the 24-hour urine protein or albumin excretion (in milligrams) is obtained by multiplying the ratio (in mg/mmol) x 10.
- Measurement of blood pressure.

**Other initial investigations**

These may include:

- **FBC** (anaemia) and clotting screen.
- Urine red cell morphology: dysmorphic erythrocytes suggest a renal origin.
- Cytological examination of urine. [7]

**Indications for urological referral** [1]

Direct referral to urology for further investigation is required for:

- All patients with visible haematuria; a nephrology referral may be considered more appropriate if glomerulonephritis is suspected.
- All patients with s-NVH (any age).
- All patients with a-NVH aged ≥40 years.
Indications for nephrological referral \[1\]

- For patients who have had a urological cause excluded or have not met the referral criteria for a urological assessment, a referral to nephrology should be considered.
- Evidence of declining GFR (by greater than 10 ml/minute at any stage within the previous five years or by greater than 5 ml/minute within the previous one year).
- Stage 4 or 5 chronic kidney disease (eGFR less than 30 ml/minute).
- Significant proteinuria (ACR 30 mg/mmol or higher, or PCR 50 mg/mmol or higher).
- Isolated haematuria (ie in the absence of significant proteinuria) with hypertension in those aged younger than 40 years.
- Visible haematuria coinciding with intercurrent (usually upper respiratory tract) infection.

Long-term monitoring of patients with haematuria \[1\]

Patients not meeting criteria for referral or who have had negative urological or nephrological investigations (including all of: eGFR 60 ml/minute or higher, and ACR less than 30 mg/mmol or PCR less than 50 mg/mmol, and blood pressure less than 140/90 mm Hg) need long-term monitoring due to the uncertainty of the underlying diagnosis. Patients should be monitored for the development of:

- Voiding LUTS.
- Visible haematuria.
- Significant or increasing proteinuria.
- Progressive renal impairment (falling eGFR).
- Hypertension (the development of hypertension in older people may have no relation to the haematuria).

Primary care monitoring should include an annual assessment (whilst haematuria persists) of blood pressure, eGFR and ACR/PCR.

- Referral or re-referral to urology is indicated if development of VH or s-NVH. \[1\]
- Referral to nephrology if:
  - Significant or increasing proteinuria (ACR higher than 30 mg/mmol or PCR higher than 50 mg/mmol).
  - eGFR less than 30 ml/minute (confirmed on at least two readings and without an identifiable reversible cause).
  - Deteriorating eGFR (by greater than 5 ml/minute fall within one year, or greater than 10 ml/minute fall within five years).

National Institute for Health and Care Excellence (NICE) referral guidance

NICE Cancer referral guidelines recommend: \[8\]

- Refer people using a suspected cancer pathway referral (for an appointment within two weeks) for:
  - Bladder or renal cancer: haematuria (visible and unexplained) either without UTI or that persists or recurs after successful treatment of UTI (patients aged 45 and over).
  - Bladder cancer: haematuria (non-visible and unexplained) with dysuria or raised white cell count on a blood test (patients aged 60 and over).

- Consider non-urgent referral for bladder cancer in people aged 60 and over with recurrent or persistent unexplained UTI.
- Endometrial cancer: haematuria (visible) with low haemoglobin levels or thrombocytosis or high blood glucose levels or unexplained vaginal discharge in women aged 55 years and over - consider a direct access ultrasound.
- Prostate cancer: haematuria (visible) in men. Consider a prostate-specific antigen (PSA) test and digital rectal examination.

Further investigations

- Ultrasound of the renal tract: if urinalysis does not explain the findings. Ultrasound is as sensitive as intravenous urography and more cost-effective. A plain film of the abdomen should also be obtained, mainly to rule out urinary calculi.
Cystoscopy: important in younger, as well as in older, patients. One study, looking at almost 2,000 patients with haematuria, found bladder cancer in 7 patients aged younger than 40 years.[8]

Intravenous urography is indicated if urinary tract stones are suspected or if ultrasound, abdominal X-ray and cystoscopy are negative.

Renal angiography, CT scanning or renal biopsy are indicated in specific circumstances.

Other imaging options include retrograde pyelography, multidetector CT urography and MR urography.[10]

If a definite diagnosis cannot be made, investigations should be repeated whenever gross haematuria occurs or after 4-6 months. Occult cancer will usually become evident within one year.

Further reading & references

- Rodgers M et al; Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation; Health Technology Assessment 2006; Vol 10: number 18
- Chronic kidney disease: early identification and management of chronic kidney disease in adults in primary and secondary care; NICE Clinical Guidelines (July 2014)

1. Joint Consensus Statement on the Initial Assessment of Haematuria; Renal Association and British Association of Urological Surgeons (July 2008)

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