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Dr Eimear McKenna
MB BCh
Specialty Trainee in Renal Medicine

Dr Aisling E Courtney
FRCP
Consultant Nephrologist
Regional Nephrology Unit, Belfast City Hospital, Belfast, UK

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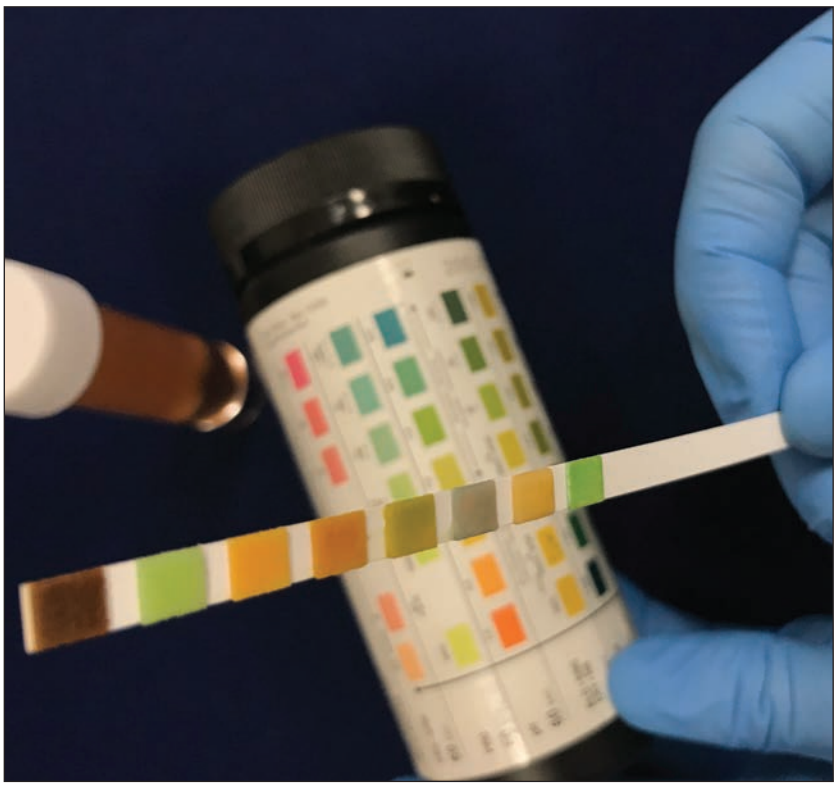
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Visible and non-visible haematuria may herald serious disease

AUTHORS
Dr Eimear McKenna
MB BCh
Specialty Trainee in Renal Medicine

Dr Aisling E Courtney
FRCP
Consultant Nephrologist

Regional Nephrology Unit, Belfast City Hospital, Belfast, UK



What are the potential causes of haematuria?

How should patients be assessed?

Which patients should be referred and to whom?

HAEMATURIA HAS BEEN DEFINED AS >2 RED BLOOD CELLS/HIGH POWER FIELD (RBC/HPF) ON TWO separate urinalyses in the absence of exercise, menses, sexual activity or instrumentation.[1]

In practice urine microscopy and the counting of red cells is impractical and unnecessary. Haematuria is detected either because it is visible to the naked eye, visible or macroscopic haematuria, or identified on a standard urine dipstick test when it is termed non-visible or microscopic haematuria. Dipstick tests depend on the oxidation of organic peroxide by haemoglobin in a fresh voided urine sample containing no preservative with a reported sensitivity of 95% and specificity of 75%.

Haematuria is important as both visible and non-visible haematuria may herald serious pathology (e.g. malignancy or vasculitis), and also because it is common. It is estimated that for every thousand patients registered in primary care five will consult with visible haematuria per annum,[2] with the prevalence of asymptomatic non-visible haematuria in the UK being approximately 2.5%.[3] In such a cohort (asymptomatic non-visible haematuria) the overall incidence of serious conditions such as urological malignancy is < 1.5%.[4]

It is estimated that a typical NHS GP will see a bladder or kidney cancer case once every 29 months.[5] A key skill therefore for all GPs is determining whether or not their patient's often incidental finding of haematuria should be pursued further. Who should be referred for investigation? And to whom - urology or nephrology? And how urgently?

Ideally patients with potentially significant haematuria should be identified and referred to the most relevant specialty in a timely fashion without causing a significant service burden for the healthcare provider or subjecting those with insignificant haematuria to a battery of unnecessary investigations.

CAUSES

The pathophysiology of haematuria depends on whether the blood loss originates from the nephron (glomerular haematuria) or from any distal part of the urinary tract (extra-glomerular).

Glomerular bleeding indicates a defect in the structural integrity of the glomerular basement membrane (GBM) which is the barrier through which red blood cells pass to travel from the glomerular capillary to the urinary space.

Membrane disruption can result from a genetic aberration (e.g. defective collagen production in Alport's syndrome) or an acquired condition. There are several postulated injurious agents in the latter category, including leukocyte infiltration, immune complex deposition, cytokine release, endopeptidase activation etc.[6] Red blood cells which have passed through the GBM are usually dysmorphic due to a combination of physically squeezing through the membrane and »

exposure to the changes in osmotic environment encountered at various parts of the tubular system.

Non-glomerular haematuria is the result of anything which disrupts the urothelium or blood loss into the urinary space. The common causes of haematuria in the UK are detailed in table 1, below.

HISTORY

Question one:
Is it haematuria?
This may seem superfluous but is important. Red urine is not always caused by blood, or by blood originating from the urinary tract. Spurious causes include:

- Menstrual contamination/atrophic vaginitis/intrauterine coil/sexual intercourse
- Food colouring e.g. beetroot or rhubarb
- Myoglobin e.g. muscle injury (rhabdomyolysis)
- Medication e.g. rifampicin, methyldopa or phenothiazine
- Poisoning e.g. lead or mercury

Question two:
Is it transient?
Typically temporary haematuria is associated with trivial pathology e.g. urinary tract infection, physical exercise. A collaborative history and the resolution of the haematuria is required.

Question three:
Are there associated concerning features?
These three questions can be answered with a focused history. First, spurious or temporary causes can be quickly identified by a series of closed questions related to the list above. If these are excluded a second set of questions can frame the likelihood of malignancy (bladder/urothelial, prostate, renal, and endometrial) including for:
All: Age ($\geq$45 years – bladder and renal) and tobacco use
Prostatic neoplasia: Lower urinary tract symptoms (frequency, hesitancy, urgency, nocturia, retention), erectile dysfunction
Urothelial malignancy: Previous radiation or cyclophosphamide exposure, certain occupational exposures such as aromatic amines, dyes, and benzenes

Third, rarer but potentially devastating systemic conditions with renal involvement must be considered with questioning about constitutional symptoms including fever, rash, arthralgia, weight loss, and oedema.

Table 1

Common causes of haematuria

Glomerular	**Primary**	Genetic	● Alport's syndrome ● Fabry's disease ● Thin basement membrane disease
		Acquired	● Any glomerulonephritis (IgA nephropathy most common)
	Secondary	Associated with systemic disorder	● ANCA-associated vasculitis ● Anti-GBM disease ● Henoch Schönlein purpura ● Haemolytic uraemic syndrome ● Systemic lupus erythematosus
Non-glomerular	**Urothelial disruption**	Within wall	● Tumour (bladder/ureter/urethra) ● Inflammation/infection (cystitis)
		Within lumen	● Calculus ● Trauma (instrumentation)
	Blood loss into urinary space		● Prostatic (malignancy/infection) ● Renal parenchymal tumour ● Renal cyst ● Arteriovenous malformation

Dark brown, (or cola-coloured) urine suggests glomerular bleeding with alteration of blood as it passes through the urinary tract and may be associated temporally with upper respiratory tract infection symptoms.

A family history of renal disease, stones, or urological malignancy is pertinent. A drug history, particularly if the patient is taking anticoagulant or antiplatelet medication, is also useful. However, whether or not patients are taking anticoagulants is irrelevant when deciding upon referral as these agents generally exacerbate rather than cause haematuria.

EXAMINATION

With exemption of spurious causes, it is reasonable for all patients to have their weight and blood pressure recorded, along with an abdominal examination to exclude a mass or lymphadenopathy. Additional focused examinations will be indicated by the history and differential diagnosis e.g. digital rectal examination in men with lower urinary tract symptoms, external genitalia in women with vaginal symptoms, skin/joints if systemic symptoms, fundoscopy if severe hypertension.

INVESTIGATION

All patients with visible or symptomatic non-visible haematuria should have: urinalysis; urinary protein estimation (albumin:creatinine or protein:creatinine ratio depending on local availability); and a renal function test (creatinine/eGFR). These should also be requested if there is persistence of asymptomatic non-visible haematuria i.e. in two out of three samples tested over a 6-8 week period.[7]

Additional laboratory testing may be indicated in specific clinical situations e.g. PSA in men with obstructive lower urinary tract symptoms, full blood count in those with marked infective symptoms, or potentially substantial blood loss.[8]

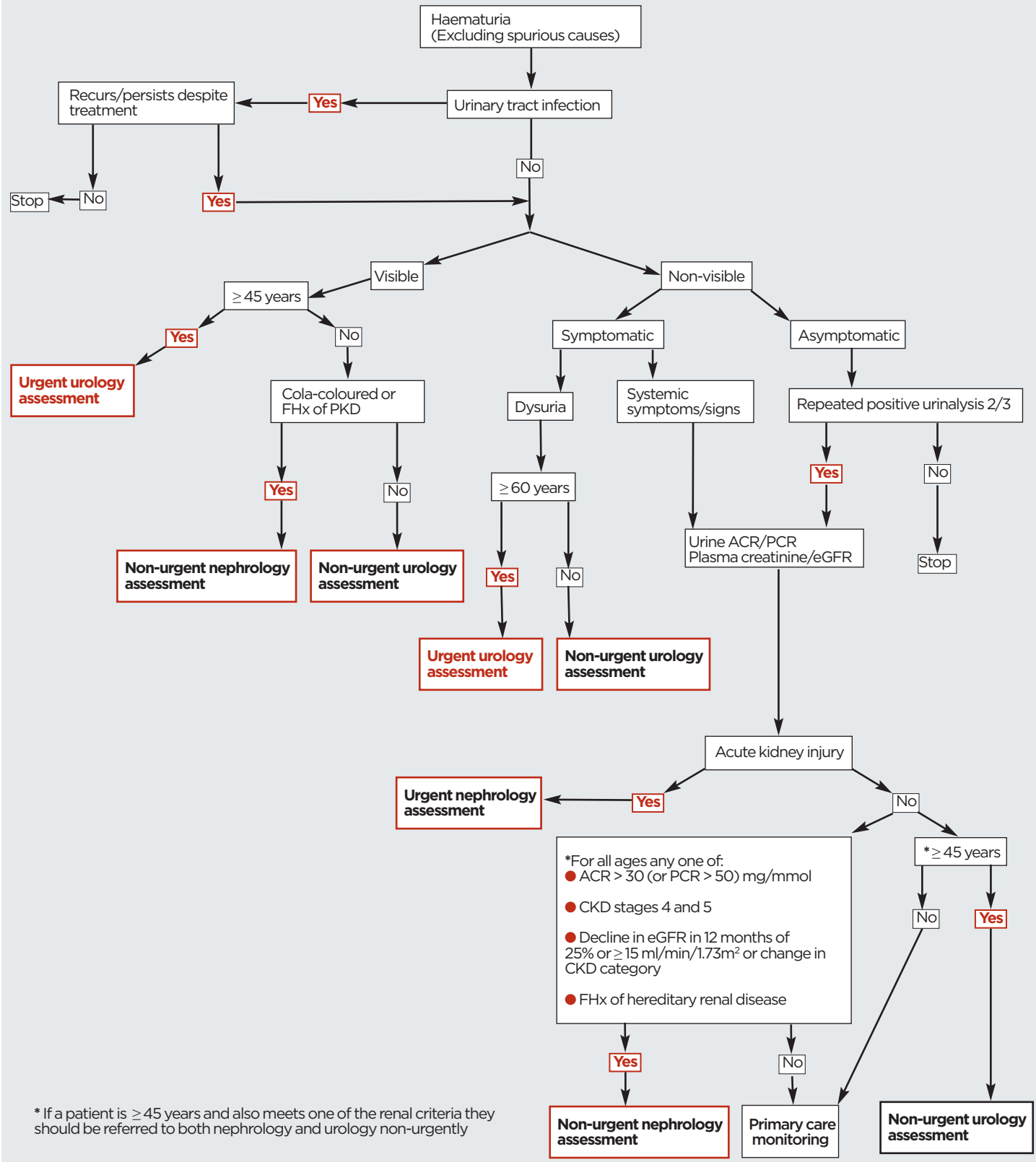
Routine radiological imaging is not required, but if there is a positive family history of polycystic kidney disease then an ultrasound scan should be requested. The NICE guidance relating to endometrial cancer recommends considering an ultrasound scan for women $\geq$55 years with visible haematuria and anaemia, or thrombocytosis, or raised blood glucose.[9]

An algorithm for investigation and referral of haematuria is shown in figure 1, opposite.

Important points to remember when

Figure 1

Algorithm for investigation and referral of haematuria



* If a patient is ≥ 45 years and also meets one of the renal criteria they should be referred to both nephrology and urology non-urgently

investigating haematuria in primary care are listed in box 1, below.

REFERRAL

The majority of patients with haematuria do not need to be referred, some do require secondary care, and a small but important minority need urgent specialist input.

The key diagnoses that should not be delayed are malignancy and systemic inflammatory conditions associated with acute and rapidly progressive renal injury e.g. vasculitis. The latter group are typically unwell with constitutional symptoms and hypertension.

The Renal Association and British Association of Urological Surgeons (BAUS) published a succinct joint consensus statement on the initial assessment of haematuria in 2008, and included a useful algorithm.[3] This advice has been withdrawn following updated clinical guidelines published by NICE in relation to the recognition and referral of suspected cancer in 2015[8] and chronic kidney disease (CKD) in adults.[7] BAUS has provided a helpful summary of the relevant uro-oncology section.[10] In the UK, only a minority of urological malignancies (30% of bladder, 19% of kidney) are diagnosed via the two-week referral pathway.[11]

It is important to note that there are patients that should have urological or renal assessment but do not need it urgently. There is less consistency in the literature regarding referral criteria in these groups, particularly the age threshold for those with persistent asymptomatic non-visible haematuria. The NICE CKD advice is appropriate for the latter cohort.[12]

Table 2, below left, summarises suggested criteria for urology and nephrology referral and the urgency required. However, crucially age per se does not exclude malignancy. Kidney cancer can and does present in people of younger age, albeit much less commonly. If the clinician has reason to be concerned, then they should use their clinical judgement to refer with appropriate urgency. A positive family history of renal carcinoma in a first-degree relative for example would increase clinical suspicion in a younger individual.

Box 1

Investigating haematuria in primary care

DO NOT:

1 Be concerned about 'trace' haematuria - it is irrelevant and is considered as negative

2 Assume it is due to infection unless the clinical picture is consistent with this – it could delay the diagnosis of serious pathology

3 Ignore haematuria because the patient is on antiplatelet therapy or anticoagulant treatment – it still needs to be assessed

4 Forget that the NICE guidelines regarding urology referral relate to urgent assessment for suspected cancer - other patients may still merit urological assessment

5 Leave the top off the dipstick container - or oxidation may occur resulting in false-positive results

Table 2a

Urology referral in unexplained haematuria

	Visible	Non-visible
Urgent	≥ 45 years plus either: ● No urinary tract infection (UTI) ● Recurs/persists despite treatment for a UTI	≥ 60 years plus either: ● Associated dysuria ● Elevated white cell count
Non-urgent	< 45 years	≥ 45 years ● Persistent

Table 2b

Nephrology referral in unexplained haematuria

	Visible	Non-visible
Urgent	No indication for urgent nephrology referral	● Acute kidney injury
Non-urgent	● Cola-coloured urine ● Polycystic kidney disease (if positive family history and haematuria request ultrasound scan)	Any one of: ● ACR > 30 (or PCR > 50) mg/mmol ● CKD stages 4 and 5 ● Decline in eGFR in 12 months of 25% or ≥ 15 ml/min/1.73m^2 or change in CKD category ● Family history of hereditary renal disease

MONITORING

There will be patients who meet none of the criteria for referral outlined above, or who have been assessed and subsequently care discharged back to primary care. In both cohorts, there remains a chance that in due course significant pathology will develop. Annual monitoring is recommended,[7] as long as haematuria persists, with:

- Blood pressure
- Urine dipstick and albumin (or protein) creatinine ratio
- Renal function

This should be conducted until there are two negative urinalyses. Patients with stable CKD should be monitored as per national guidelines according to the stage of CKD, and urological referral should be initiated according to recommendations detailed above.

CONCLUSION

Haematuria is common and occasionally the harbinger of serious illness. A focused history and directed examination are important skills for primary care in identifying those that require further investigation. It is crucial

key points

SELECTED BY

Dr Phillip Bland
Former GP, Dalton-in-Furness, UK

Haematuria has been defined as > 2 red blood cells/high power field on two separate urinalyses in the absence of exercise, menses, sexual activity or instrumentation. However, in practice urine microscopy and the counting of red cells is both impractical and unnecessary. Both visible (VH) and non-visible haematuria (NVH) may herald serious pathology e.g. malignancy or vasculitis. It is estimated that a typical NHS GP will see a bladder or kidney cancer case once every 29 months. Haematuria is common. It is estimated that for every thousand patients registered in primary care five will consult with VH per annum. The prevalence of asymptomatic NVH in the UK is approximately 2.5%.

Red urine is not always caused by blood or by blood originating from the urinary tract. These spurious causes should be excluded, as should temporary haematuria where this is associated with trivial pathology e.g. urinary tract infection or physical exercise. Further questioning can then assess the likelihood of malignancy. Patients should be asked about tobacco use (all cancers), lower urinary tract symptoms (prostate cancer), and previous exposure to radiation, cyclophosphamide or certain occupational chemicals (bladder cancer). Rarer but potentially devastating systemic conditions with renal involvement must be considered with questioning about constitutional symptoms including fever, rash, arthralgia, weight loss, and oedema. Dark brown (or cola-coloured) urine suggests glomerular bleeding and may be associated temporally with upper respiratory tract infection symptoms.

All patients with haematuria should have their weight and BP recorded, along with an abdominal examination to exclude a mass or lymphadenopathy. Additional focused examinations will be indicated by the history and differential diagnosis e.g. digital rectal examination in men with lower urinary tract symptoms. All patients with VH or symptomatic NVH should have urinalysis, urinary protein estimation (albumin:creatinine or protein:creatinine ratio depending on local availability), and a renal function test. These should also be requested if asymptomatic NVH persists, i.e. in two out of three samples over a 6-8 week period.

NICE has published updated guidance on urgent referral of patients with suspected cancer. It is important to note that there are patients who should have urological or renal assessment but do not meet the urgent referral criteria. However, there is less consistency in the literature regarding non-urgent referral criteria, particularly with regard to the age threshold for those with persistent asymptomatic NVH. Crucially age per se does not exclude malignancy. Kidney cancer can and does present in people of younger age, albeit much less commonly. If the clinician has reason to be concerned, then they should use their clinical judgement to refer with appropriate urgency. If a patient is taking anticoagulant or antiplatelet medication this should not influence the decision to refer that those with acute kidney injury or underlying malignancy are highlighted and referred urgently.

Competing interests: None

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See also Prompt investigation improves outcomes for kidney cancer, p17

Useful information

For healthcare professionals
Macmillan Cancer Support
www.macmillan.org.uk/documents/aboutus/health_professionals/primarycare/10toptips/primary-care-ten-tips-haematuria.pdf

For patients
NHS choices
www.nhs.uk/conditions/blood-in-urine

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