

# Haematuria

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## Abstract

Visible or non-visible haematuria could represent a range of urological or nephrological diseases, or bear no significance at all. The challenge for clinicians is to get the correct patients assessed rigorously so that life-altering or life-limiting disease is not missed. Up-to-date definitions and epidemiological data is discussed. This article provides a clear framework to help decide which patients have significant haematuria and which patients are suitable for urological referral; a decision algorithm is also included. We discuss how to investigate such patients further, including points not to forget when taking a history or conducting physical examination. Explanations are provided as to why current management strategies exist and what the potential flaws are of each method, including the ubiquitous urine dipstick test, urine cytology, cystoscopy and the modern radiological techniques used in everyday clinical practice. We provide guidance on which patients should be referred for nephrological assessment and how to manage patients with negative investigations but ongoing significant haematuria.

**Keywords** Cancer; cystoscopy; dipstick; haematuria; nephrology; non-visible; visible

## Definition of haematuria

Haematuria is either visible or non-visible.<sup>1</sup> Visible haematuria (VH) requires consideration of other causes of discoloured urine, such as myoglobinuria, haemoglobinuria, beeturia and medications such as rifampicin or doxorubicin.<sup>1</sup> Non-visible haematuria is either symptomatic (s-NVH), with voiding lower urinary tract symptoms (LUTS), such as hesitancy, frequency, urgency and dysuria, or asymptomatic (a-NVH) and detected incidentally.<sup>1</sup>

## How common is haematuria?

‘A little blood goes a long way’ and just 1 ml of blood can cause a litre of urine to become red. Under normal circumstances a healthy individual excretes up to a million red blood cells in their urine a day. Therefore, one to three red corpuscles per high power field of spun urine is considered unremarkable in the absence of any other significant abnormality.

Population screening estimates that haematuria (NV and NVH) is prevalent in 2.5–20%, depending on subgroup<sup>2,3</sup> and accounts for up to 20% of all urological referrals.<sup>3</sup>

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Demographic factors do not appear to have a major influence on the prevalence of NVH, with conflicting evidence on whether haematuria is more prevalent in women, or with increasing age.<sup>4</sup>

## History and physical examination of patients presenting with haematuria

The medical history can often give a strong indication as to the cause of haematuria. **Box 1** is a comprehensive list of points to consider when taking a focused history.<sup>4</sup> A detailed drug history is an important part of this, including over the counter and herbal medications.<sup>4</sup> The long list of drugs that can induce haematuria is a testament to this.<sup>4</sup>

The physical examination should include inspection for irregular heart rhythm, petechiae, angiomas, hearing loss (Alport’s syndrome), peripheral oedema and inspection of the external urethral opening.<sup>4</sup> Auscultation for cardiac murmurs and palpation for abdominal masses, lesions of the prostate and testicles should be conducted.<sup>4</sup>

### Points to remember in haematuria history

- Exclude pseudohaematuria – drugs, vegetable dyes, pigments
- Factitious – Munchausen’s syndrome, narcoticseeking behaviour
- Bleeding diathesis
- Clots – indicate non-glomerular bleeding, large thick clots (bladder): small, stringy clots (upper tract)
- Gross haematuria e relation to exercise, infection
- Relation of gross haematuria to urinary stream – initial (urethra distal to urogenital diaphragm), total (bladder proper or upper urinary tract), terminal (bladder neck of prostatic urethra)
- Painful haematuria – urinary tract infection or calculus, papillary necrosis, passage of clots, obstruction, loin-pain haematuria syndrome, glomerulonephritis
- Genitourinary history – flank trauma or pain, frequency, nocturia, dysuria; prior stones, tissue passage, or infections: vaginal or penile discharge, sexual activity: presence of urinary catheter
- Relation to menstruation – endometriosis
- Sickle cell disease or trait
- Medications
- Systemic symptoms – fever, rash, joint pain, weight loss
- Infectious aetiology – night sweats, sore throat, impetigo, tooth extraction or other invasive procedures, diarrhoea, travel to areas endemic for *Schistosoma haematobium*
- Risk factors for urologic cancer – age >40 year, tobacco use, analgesic abuse, pelvic irradiation, cyclophosphamide. *S haematobium*, occupational exposure to dyestuffs and rubber compounds
- Family history – haematuria, renal disease, sickle cell disease, deafness, bleeding diathesis
- Prior testing – blood pressure, urinalysis, serum chemistries, intravenous pyelogram
- Pregnancies – proteinuria, hypertension (and month of onset)

### Box 1

### Dipstick testing for haematuria

The urine dipstick analysis for blood is confirmed via the chromogen indicator on the dipstick, orthotolidine, which is a peroxidize substrate. When haemoglobin, which contains peroxidase, comes in contact with orthotolidine, an oxidation reaction commences that results in the colour change to blue of the indicator.<sup>5</sup> It is important to be aware of the false positive results that can occur with a dipstick analysis with regards to NVH in order to prevent the ordering of unnecessary investigations. False-positive results can occur due to the presence of oxidizing agents in the urine from exercise, dehydration, menstrual blood, povidone iodine and hypochlorite solutions such as bleach.<sup>5</sup> False negatives can occur due to the presence of reducing agents such as vitamin C, gentisic acid and poorly mixed urine.<sup>5</sup>

In order to minimize the risk of inaccurate interpretation of urine dipsticks, electronic strip readers are used. Despite this, there is no substitution for urine microscopy performed in a regulated component laboratory.<sup>5</sup>

In the UK there are guidelines to determine the degree of positivity. With regards to dipstick versus microscopy diagnosis, the urine dipstick of a fresh voided urine sample containing no preservative is considered a sensitive means of detecting the presence of haematuria.<sup>5</sup> When patients are seen in outpatient clinics it is common for patient to carry urine into the clinic in a clean jar from home. This may result in an increase in a significant false negative urine microscopy rate. Urine microscopy is more labour intensive and adds little to establishing the diagnosis of haematuria. Routine microscopy for confirmation of dipstick haematuria is not necessary.<sup>5</sup>

When a urine result from a dipstick is reported as a 'trace' it is important to know the difference between a 'trace' versus '1+'. While the sensitivity of urine dipsticks may vary from one manufacturer to another, significant haematuria is considered to be 1+ or greater. Trace haematuria should be considered negative.<sup>5</sup>

In certain situations, haemolysed versus non-haemolysed urine dipstick results are reported. It has been found that there is no distinction in significance between non-haemolysed and haemolysed dipstick-positive haematuria. 1+ positive for either should be considered of equal significance.<sup>5</sup>

### Further investigations for haematuria

The next question is who should be investigated for haematuria and which patients should be discharged? The joint consensus statement on the initial assessment of haematuria from the Renal Association and the British Association of Urological Surgeons (BAUS),<sup>1</sup> helps define patients with 'significant haematuria'. These are patients who have had a single episode of VH, any single episode of s-NVH in the absence of a urinary tract infection or a possible transient cause or in a patient with persistent a-NVH. This is defined as the presence of two out of three dipsticks positive for NVH.<sup>5</sup> For this reason, it is not generally recommended that asymptomatic individuals be screened for microscopic haematuria.

Prior to proceeding to investigations for haematuria it is important to evaluate and exclude both transient causes and false positive cause of NVH. The most common transient cause is a urinary tract infection, exercise or menstruation.<sup>5</sup> Anti-coagulant

and anti-platelet therapy should not inhibit evaluation of patients with VH or NVH.<sup>1</sup>

As it is concentrated, the first urine voided on waking is the best sample for evaluation of microscopic haematuria. However, for patient convenience, a random sample of urine is considered acceptable for general evaluation since red cells and casts tend to deteriorate with time, especially if the specific gravity of urine is low or the pH of urine is high.

### Significant haematuria

Significant haematuria is a single episode of VH, a single episode of s-NVH in absence of UTI or other transient causes or persistent a-NVH (two out of three dipsticks) in the absence of UTI or other transient causes.<sup>1</sup>

Transient causes that need to be excluded are urinary tract infection (with a negative dipstick or mid-stream urine), exercise induced haematuria or rarely, myoglobinuria (can be VH or NVH) and menstruation.<sup>1</sup> Anti-coagulant and anti-platelet therapy should not inhibit evaluation of patients with VH or NVH.<sup>1</sup>

### Urological referral

Direct referral to urology for further investigation is required in patients depending on their age, as specified by the National Institute for Clinical Excellence (NICE) guidelines. Men and women aged 45 and over and have unexplained VH without urinary tract infection (UTI) or recurrent VH after successful treatment of UTI. Those aged 60 and over should be referred if experiencing unexplained NVH and either dysuria or a raised white cell count on a blood test. These patients should be referred using a suspected cancer pathway referral for bladder cancer. Patients aged 60 and over with recurrent or persistent unexplained UTI should be considered for non-urgent urology referral.

Patients aged 40 or under with cola-coloured urine and an inter-current infection may have acute glomerulonephritis and a nephrology referral may be more appropriate.<sup>1</sup> The decision algorithm for the investigation and referral of haematuria is summarized in [Figure 1](#).<sup>1</sup> These guidelines may change with emerging evidence from large volume national and international contemporary prospective observational studies.

### Management of a patient with haematuria

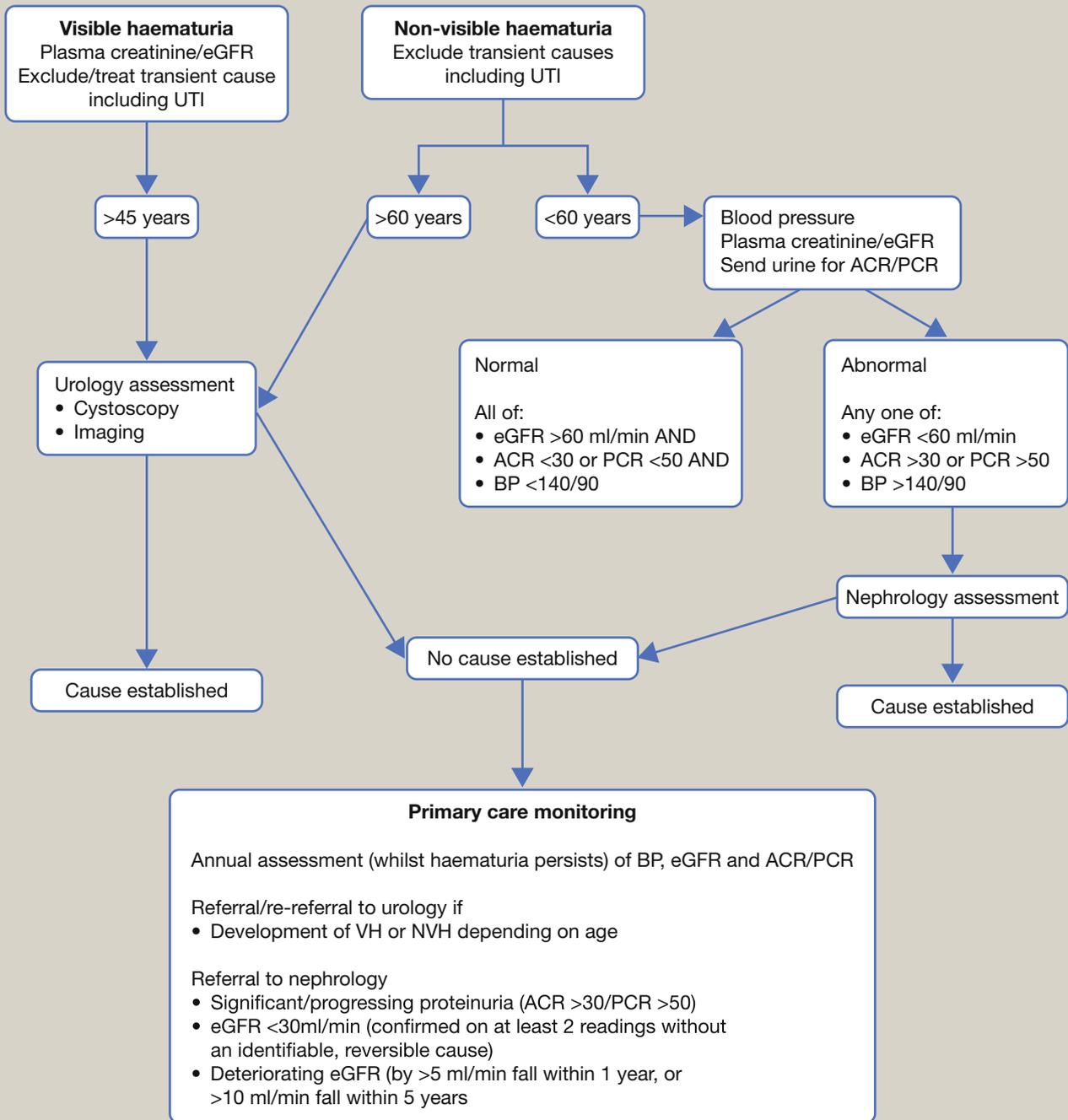
The initial investigations for a patient with s-NVH and persistent a-NVH are:

- exclude UTI and other transient causes
- measure blood pressure
- measure plasma creatinine/eGFR
- measure proteinuria and protein:creatinine (PCR) or albumin:creatinine ratio (ACR) on a random urine sample.<sup>1</sup>

As shown in [Box 1](#), patients who are eligible for urological referral will undergo cystoscopy and some form of imaging. A mid-stream urine and a urine cytology may also be sent if indicated.

### Urine cytology

Voided urinary cytology is recommended for patients with risk factors for urological malignancy, which are listed in [Box 2](#).<sup>4</sup>

**Decision algorithm for the investigation and referral of haematuria****Figure 1**

Urine cytology is also advised in patients with irritative lower urinary tract symptoms, as this may be a presentation of carcinoma in situ.<sup>4</sup>

Depending on the number of urine specimens examined, the stage and grade of the bladder tumour and the expertise of the cytopathologist, the sensitivity of voided urine cytology ranges

from 40% to 76%.<sup>4</sup> Cytology samples obtained from urothelial washings have a higher sensitivity than voided samples, but requires an invasive procedure to obtain. A positive urine cytology is almost diagnostic of a urothelial cancer.<sup>4</sup> However, a negative cytology is less useful due to the large number of false-negative results and therefore cannot fully exclude a bladder tumour.<sup>4</sup>

### Risk factors for urological malignancy

- Smoking history
- Occupational exposure to chemicals or dyes (benzenes or aromatic amines)
- History of gross haematuria
- Age >40
- Previous urologic history
- History of irritative voiding symptoms
- History of urinary tract infection
- Analgesic abuse (e.g. phenacetin)
- History of pelvic irradiation
- Cyclophosphamide

#### Box 2

### Voided markers

A number of voided urinary markers have been evaluated as markers of low-grade bladder cancer. A summary of their estimated sensitivities, specificities, positive predictive values and negative predictive values is provided in Table 1.<sup>4</sup> There is currently insufficient evidence to warrant the routine use of such tests.<sup>4</sup>

### Diagnostic cystoscopy

Cystoscopy enables complete direct visualization of the bladder mucosa, urethra and ureteric orifices, which is important as multiple areas may be involved.<sup>4</sup> Cystoscopy is usually carried out using a flexible cystoscope, as this is a day case procedure, usually requiring only local anaesthetic. Flexible cystoscopy is associated with fewer post-procedure symptoms when compared to rigid cystoscopy<sup>1</sup> and procedure time is less as the due to patient positioning and preparation. It may also be of superior diagnostic value in certain cases, for example lesions at the anterior bladder neck.<sup>1</sup>

### A summary of the values of voided markers of bladder cancer

Marker	Studies (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
BTA	9	28–70	73–96	33–80	52–94
NMP22	8	48–100	61–99	29–65	60–100
BTA stat	4	57–83	33–95	20–56	70–95
BTA Trak	2	62–72	73–98	62	73
Lewis X Antigen	3	80–97	73–86	72–81	83–98
Telomerase	3	62–80	80–99	84	89
FDP	2	52–81	75–91	79	78
Cytokeratin	20	1	91	85	95
CD44v	1	77	100	100	76

Key: PPV, positive predictive value; NPV, negative predictive value.

Table 1

However, if imaging demonstrates a cancer it is reasonable to proceed directly to an anaesthetic and rigid cystoscopy, biopsy, cystodiathermy and transurethral resection of bladder tumour, depending on the size of the lesion. Rigid cystoscopy should also be considered in the case of active bleeding, as adequate views are difficult to obtain with flexible cystoscopy.

### Diagnostic imaging

Imaging can reveal important causes of VH or NVH, including renal cell carcinoma, transitional cell carcinoma in the upper urinary tract, calculi in the renal tract and signs associated with renal infection.<sup>4</sup> There is a limited indication for identifying pathology in the bladder, where cystoscopy is the superior investigation.<sup>4</sup>

The advice regarding detection of urinary tract abnormalities by imaging is formulated on indirect evidence due to a lack of data on the direct impact of the various imaging modalities.<sup>4</sup> The key modalities used for imaging the upper tract are ultrasonography (US), computed tomographic urography (CTU), magnetic resonance urography (MRU), intravenous urography (IVU) and retrograde pyelography. Despite the many advantages of up to date technology and improved techniques, it is clear that not everyone with haematuria can be imaged with CT, and so a safe and reliable imaging strategy needs to be employed.

The imaging modality of choice is CTU as it provides anatomical detail and has the highest sensitivities and specificities for renal mass, stones and urothelial tumours. Because of this, CTU has superseded intravenous urography (IVU) in the detection of these pathologies.<sup>6</sup> The CTU is made up of four phases; non-contrast to demonstrate fat, haematoma and stones, arterial enhancement reveals inflammatory and neoplastic change, the corticomedullary phase shows sustained renal tissue changes and damage and a delayed excretory phase allows evaluation of the urothelium of the upper tracts and bladder.<sup>7</sup>

The major risks of CTU include contrast nephropathy, allergic reaction to intravenous contrast and a significant dose of ionizing radiation.<sup>9</sup> MRU is an alternative imaging modality to CTU for patients with relative or absolute contraindications. MRU provides less anatomical detail but avoids ionizing radiation and Gadolinium contrast can be used.<sup>8</sup> Retrograde pyelography also negates the need for intravenous contrast.

Ultrasonography is a non-invasive imaging modality, which is cost efficient but is without the risk of ionizing radiation.<sup>5</sup> It is reportedly more sensitive in detecting renal cell carcinoma than stones and transitional cell carcinoma, especially if these are low grade and there is no collecting system dilatation.<sup>5</sup> It has been suggested that ultrasonography can be used as the initial imaging modality in patients who are low risk, with an option to proceed to CTU if haematuria persists and cystoscopy has been normal.<sup>5</sup>

### Causes of haematuria

The causes of haematuria are described according to anatomical location in Table 2.<sup>1</sup> Malignancy, trauma, infection and stones can occur at any point along the urinary tract with varying frequency. Pathology of the prostate should not be omitted from the list of differentials when considering causes for haematuria in men.

A prospective analysis of 4020 patients presenting with haematuria (VH and NVH) found an overall prevalence of malignant

disease in 12.1%.<sup>2</sup> However, malignant disease was more prevalent in those presenting with VH (18.9%), rather than NVH (4.8%).<sup>2</sup> There seems to be no gender difference in the prevalence of malignant disease, however, this does increase with age, independent of gender or degree of haematuria.<sup>2</sup> Upper tract malignancy was identified in less than 3%, with the majority of these being renal cell carcinoma rather than upper tract transitional cell carcinoma.<sup>2</sup>

### The one-stop haematuria clinic

The one stop haematuria clinic model has been adopted after proving to be an efficient and effective model in the streamlined care of patients with haematuria. Delay in diagnosis of patients presenting with haematuria was suggested to be detrimental to the prognosis of those with invasive bladder cancer.<sup>9</sup> In an attempt to reduce the delay in hospital appointments and investigations, a pilot study was conducted at the Royal Marsden Hospital.<sup>9</sup>

This group firstly considered the referral process from the general practitioner to expedite the pathway of the patient from the community to the urology unit.<sup>9</sup> Secondly, they devised a streamlined pathway for the patient to have relevant investigations conducted before review by a senior urologist.<sup>9</sup> This

service was justified, as tumours found were mostly early stage, therefore theoretically improving the overall prognosis.<sup>9</sup>

### When to refer to nephrology

Nephrological referral should be considered for patients who have had a urological cause excluded or have not met the referral criteria for a urological assessment (as outlined above) and have the following concurrent features:

- evidence of declining GFR (by >10 ml/min in the last 5 years or by >5 ml/min in the last year)
- stage 4 or 5 CKD (eGFR <30 ml/min)
- significant proteinuria (ACR ≥30 mg/mmol or PCR ≥50 mg/mmol)
- isolated haematuria (without significant proteinuria) with hypertension in those <40
- visible haematuria with intercurrent infection (usually upper respiratory tract).<sup>1</sup>

If the above criteria are not met, haematuria itself does not require nephrology referral. However the patient should still be monitored in primary care.<sup>1</sup>

### The common nephrological causes of haematuria

The nephrological causes of haematuria can be remembered as either glomerular or non-glomerular, as listed in Table 3.<sup>1</sup> Such causes are often not at the top of our list of differentials in the context of a urology outpatients clinic, which makes them more likely to take longer to diagnosed or missed altogether.

### Long-term monitoring of patients with haematuria of undetermined aetiology

A prospective analysis of 1930 patients with haematuria found that in more than 60% of patients evaluated, no disease was found to account for their haematuria.<sup>2</sup> In those with NVH, no pathology is found in up to 90%.<sup>5</sup> It is suggested that patients who do not meet the criteria for referral to urology or nephrology, or who have been discharged with negative investigations still require long term monitoring due to the uncertainty of the underlying diagnosis.<sup>1</sup> This involves monitoring for the development of:

- voiding LUTs
- VH
- significant or increasing proteinuria
- progressive renal impairment (falling eGFR)

### Causes of haematuria

Anatomical location	Cause
Renal	<i>Renal malignancy:</i> TCC, adenocarcinoma, SCC, other <i>Trauma:</i> Penetrating, blunt <i>Nephrological:</i> IgA nephropathy (Berger's disease), diabetes, Alport's syndrome, thin basement membrane disease <i>Renal stones</i> <i>Infective:</i> TB, pyelonephritis
Ureteric	<i>Ureteric malignancy:</i> TCC, adenocarcinoma, SCC, other <i>Trauma:</i> Penetrating, blunt <i>Ureteric stone</i> <i>Infective:</i> TB
Bladder	SCC, other <i>Trauma:</i> Penetrating, blunt, pelvic fracture <i>Bladder stone</i> <i>Infective:</i> bacterial, TB, schistosomiasis
Prostate	<i>Prostate cancer</i> <i>Benign prostatic hypertrophy</i> <i>Infective:</i> Bacterial prostatitis, granulomatous prostatitis (e.g. TB)
Urethra	Urethral tumours: TCC, SCC <i>Penile tumours</i> <i>Infective:</i> Urethritis <i>Trauma:</i> Penetrating, blunt, catheterization <i>Stricture</i>
Other	<i>Epididymitis</i> <i>Menses</i>

Table 2

### Common nephrological causes of haematuria

Glomerular	Non-glomerular
IgA nephropathy	Cystic disease of the urothelium
Alport's syndrome	Interstitial nephritis
Thin basement membrane disease	Papillary necrosis
Henoch-Schonlein purpura	Renal artery stenosis
Vasculitis (e.g. lupus)	Inflammatory disorders
Goodpasture's syndrome	
Nephrotic syndrome	
Diabetic glomerulosclerosis	

Table 3

- hypertension (this may have no relation to haematuria in older people and therefore not increase the likelihood of underlying glomerular disease).<sup>1</sup>

There is some evidence to suggest that a significant proportion of these patients will have undiscovered neoplasia, whereas analyses of other series have shown that in this population repeat investigation reveals no urological malignancies, but may show IgA nephropathy or UTI.<sup>6</sup>

Patients with a-NVH that has resolved can be reassured and discharged after initial investigation. There has been prolonged follow-up (10–13 years) of this group, which found that in those with no haematuria on subsequent dipstick, no patient developed urological cancer<sup>6</sup> ◆

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