Abstract

The causes of haematuria are vast and a systematic strategy is required in its investigation and management. Haematuria is visible or non-visible and may be symptomatic of asymptomatic. Associated symptoms are often distinct which lead to targeted investigations being employed, but the presence of non-specific symptoms or a lack of symptoms often suggests a more insidious cause which requires the careful use of imaging and biopsies. The battery of tests often distinguish the cause but when no cause is found, a decision is made whether to continue investigating based on the presence of further symptoms.

Investigation and management of haematuria

Definition of Haematuria

Haematuria can be classified into both macroscopic/visible haematuria(VH) and microscopic/non-visible haematuria(NVH), of which microscopic haematuria can be symptomatic (s-NVH) or asymptomatic (a-NVH). Macroscopic haematuria refers to a pink, red or brown discolouration of urine. The detection of microscopic haematuria is through dipstick testing or microscopy. Any dipsick reading of 1+ or more can be considered to be abnormal haematuria, which translates to a concentration of more than 3 red blood cells per high power field of spun urine sediment. A positive test need not be confirmed by microscopy but it is useful to be wary of possible mimics of a positive test.

Aetiology of Haematuria

The aetiologies of haematuria can be broadly classified into acute and chronic causes.

Mimics	Acute	Chronic
Drugs (Fpnotebook, 2008)	UTI	Glomerulonephritis
Beeturia	Urolithiasis	Cancer
Factitious (Abrol, 1990)	Trauma	BPH
Semen (Mazouz, 2003)	Infection	Haematological
Exercise (Bellinghieri, 2008)		Genetic
Menstruation/endometriosis		Rare causes: AVM, nutcracker syndrome, hypercalciuria, hyperuricosuria
Myoglobinuria		
Haemobloginuria		

Table 1

In general, acute causes should be excluded before investigating the chronic ones and s-NVH and VH indicate a urological cause whilst a-NVH indicates a glomerular cause except in malignancy where it presents in all 3 ways.

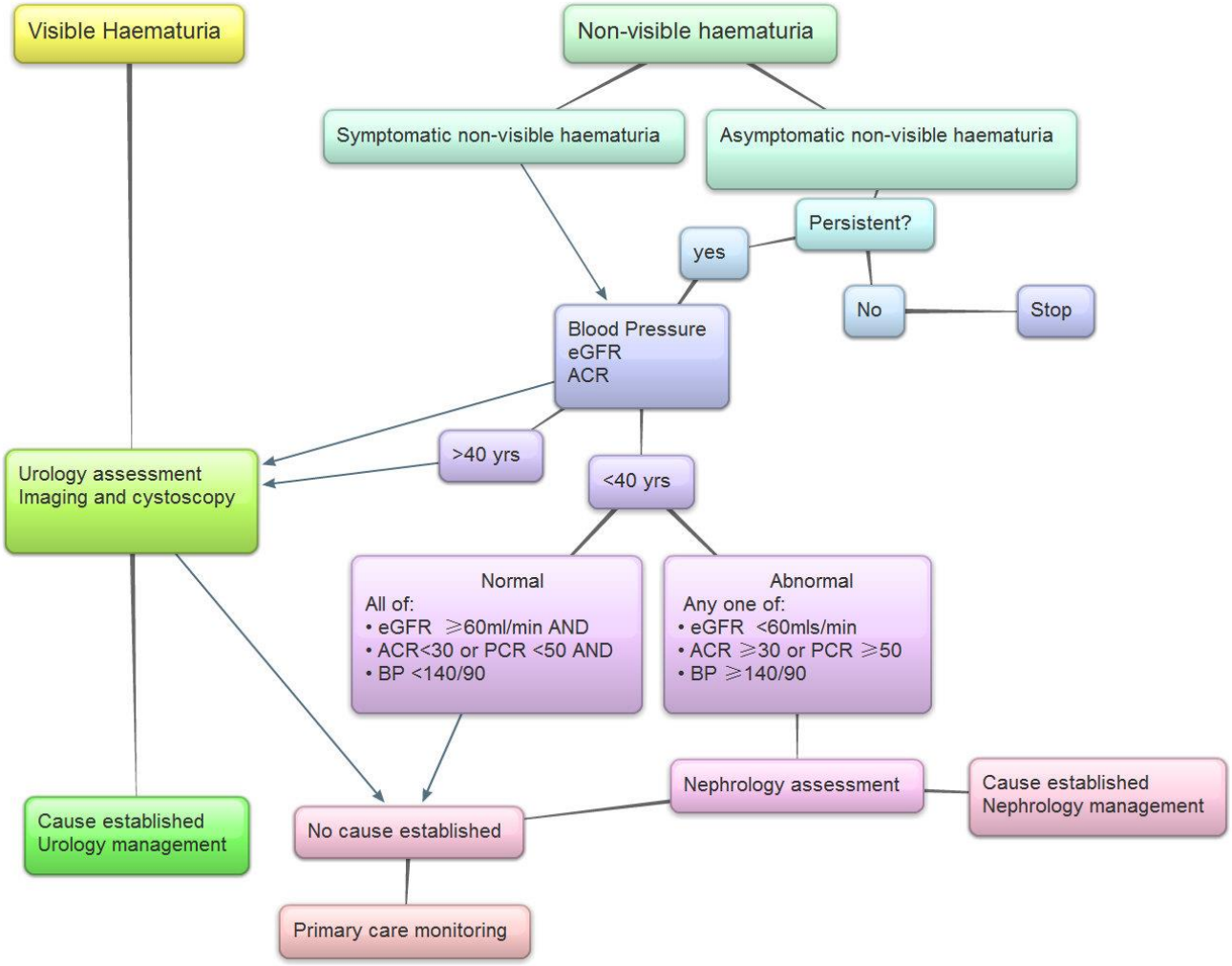

Fig. 1 Decision algorithm (Anderson J et al, 2008)

The most treatable cause of haematuria is a UTI and this should be diagnosed or ruled out from the results on the dipstick in women. In the event of a negative dipstick in women or the presence of symptoms in men, a urine sample should be sent for culture to confirm the diagnosis. UTI is then treated with antibiotics. An isolated UTI in women does not warrant further investigation but a UTI in males as well as recurrent UTIs (Kantor, 1984) in females is indicative of more serious pathology and further assessment is warranted. (SIGN, 2006)

The following table shows a list of clues from the history that may point to a specific diagnosis.

Signs and symptoms	Possible diagnosis
Unilateral loin to groin pain	Urolithiasis
Symptoms of prostatic obstruction	BPH but further investigation should still be carried out
Trauma	Traumatic injury and possible congenital malformation
Familial renal disease	Polycystic kidney disease, Alport's disease, sickle cell disease
Recent upper respiratory infection or coke coloured urine	Postinfectious glomerulonephritis, IgA nephropathy, Alport's disease
Bleeding disorder or anticoagulant therapy	Can predispose to haematuria but further investigation is warranted (Culclasure , 1994)
Overseas travel	Schistosomiasis and tuberculosis
Medication/sterile pyuria	Interstitial nephritis
Afro-carribean	Sickle cell disease
Cyclic haematuria	Endometriosis (NEJM case report, 1992)
Blood clots	Extraglomerular disease

Table 2

Without an obvious diagnosis, a urine culture should be performed to rule out a UTI following which, eGFR should be measured in all patients. In patients with s-NVH and persistent a-NVH, urinary albumin-creatinine ratio and blood pressure should be measured. (Anderson, 2008) An increased blood pressure particularly in young adults is strongly indicative of renal disease. (Buckalew, 1996) Persistent A-NVH should also

be confirmed with up to 3 separate testings. If 2 tests are negative out of 3, it should be treated as transient and no further investigation done given the relative frequency of transient haematuria in young adults (Froom, 1984) with no significant pathology. (Mohr, 1986) It is however recommended that patients with risk factors for malignancy in table 3 be investigated for transient haematuria. (Grossfeld, 2001)

Table3. Risk factors

- **Smoking history**
- **Occupational exposure**
- **History of gross haematuria**
- **Age>40 yrs**
- **History of chronic indwelling foreign body**
- **History of irritative voiding symptoms**
- **History of UTIs**
- **Analgesic abuse**
- **Previous pelvic irradiation**
- **Cyclophosphamide**

Urine Microscopy

The presence of red cell casts is diagnostic of glomerulonephritis and vasculitis. Examining red cell morphology also reveals additional clues.

Glomerular erythrocytes are smaller (Shichiri, 1988) and this can be measured with a Coulter counter. They also vary greatly in shape and size (Fairley, 1982) and are pale in colour due to loss of haemoglobin pigment. Non glomerular erythrocytes are uniform in size and shape and have variable pigmentation. Erythrophagocytes are renal tubular cells that have ingested erythrocytes are these are diagnostic of glomerular bleeding. (Kincaid-Smith, 2005) Acanthocytes are specific for glomerular damage. Microscopy can also reveal other information such as the presence of white cells or paraproteins indicating multiple myeloma. Urine microscopy however is logistically cumbersome. Red cells degrade with time in urine samples, centrifugation can lead to the breakdown of casts and casts do not form in dilute urine. Phase-contrast microscopy (Kohler, 1991) in experienced hands is required for accurate microscopy and this is not always rapidly available thus at present urine microscopy is not routinely indicated.

Urine cytology and markers

Urine cytology is indicated in older patients with a high risk of urothelial malignancy. It has a sensitivity of up to 90% in CIS and high grade tumours but is of limited value in low grade and upper tract malignancy with high specificity but a low sensitivity of 30%. (Lotan, 2003) The current urine markers available are bladder tumour antigen, nuclear matrix protein 22, ImmunoCyt/uCyt+ and UroVysion. The urine markers have comparable sensitivity in high grade tumours (Shariat, 2008; Mitra, 2010) but suffer from the same problems of low sensitivities in low grade tumours (Mitra, 2010) and have variable specificities (Bassi, 2010), of which UroVysion has the highest. Their value lies in the detection of occult tumours not seen on cystoscopy and tumour surveillance but need to be combined with other tests and is not part of routine investigation. (Wadhwa, 2012)

Investigation of suspected glomerular bleeding (NVH)

The incidence of urothelial malignancy in NVH is lower and patients with the presence of symptoms of glomerular disease or deranged clinical tests (NICE, 2008) should be investigated by nephrologists.

Table 4. Criteria for further investigation

- **eGFR<15 (stage 4/5 CKD)**
- **>ACR 70mg/mmol not due to diabetes**
- **>ACR 30mg/mmol with haematuria**
- **Decrease of 5ml/min/1.73m^2 in a year**
- **Decrease of 10 ml/min/1.73m^2 in 5 years**
- **Hypertension resistant to 4 anti-hypertensives**
- **Suspicion of genetic causes**
- **Suspected renal artery stenosis**

Ultrasound imaging is used to detect renal abnormalities. A renal biopsy is not indicated in patients with isolated haematuria without evidence of progressive disease as the glomerulopathy is likely to be of a benign nature and is unlikely to influence management. (Hall, 2004; Richards, 1994; McGregor, 1998) In these patients, the most likely diagnoses are IgA nephropathy, thin basement membrane disease, mesangioproliferative glomerulonephritis and

Alport's syndrome. A renal biopsy is indicated in all other patients who fit the criteria with subsequent management by nephrologists.

Visualisation of the urinary tract

The presence of glomerular bleeding does not rule out lesions in the rest of the urinary tract and imaging should be considered for all patients with persistent haematuria. (Rodney, 2012)

CT urography (CTU) is emerging as the imaging modality of choice in patients due to its proven effectiveness in the imaging of both normal (Caoili, 2002) and abnormal lesions (Caoili, 2002;2005) as well as its ability to view extra-renal structures. It has shown to be effective in detecting malignancy when compared with retrograde pyelography (Cowan, 2007) and cystoscopy. (Sadow, 2008) There is a concern of a higher radiation dose compared with intravenous urography but further testing is required following a positive IVU as IVU is unable to distinguish between solid and cystic masses. There is also evidence that non-enhanced CTU is comparable with enhanced CTU in younger patients. (Lokken, 2012) Only imaging certain contrast phases can also reduce the radiation dose such as in urinary tract trauma where nephrographic and excretory phases are sufficient. (Goldstein, 1985) Unenhanced CTU is also sufficient for the imaging of stones. (Smith, 1995)

Ultrasonography (USS) is used to complement CTUs as USS on its own has a lower diagnostic yield and is less sensitive in detecting urothelial malignancy (Browne, 2005), small renal masses (Warshauer, 1988) as well as calculi. (Fowler, 2002) It can however detect uric acid stones which are radiolucent. There is also the advantage of no radiation dose and as such is the imaging modality of choice in pregnant women. It is also used in patients with poor renal function.

IVU was shown to be less sensitive than CTU in the assessment of a-NVH in study of 115 patients. (Gray Sears, 2002) It has also been shown to be less sensitive in detecting urothelial malignancy.

(O' Connor, 2008) Retrograde pyelography is also gradually being replaced by CTU for the imaging of the upper urinary tract.

MR urography is effective in the visualisation of the urinary tract (Roy, 1998) but there is no evidence on the effectiveness of MR urography compared with CTU (Silverman, 2009) and is insensitive to calcification. It is reserved for patients unable to tolerate iodine contrast as well as pregnant women and children.

The Health and Technology assessment report led by Rodgers in 2006 suggests the usage of ultrasound as the initial investigation followed by CT on the grounds of cost-effectiveness as it deemed the evidence for inter-modality comparison insufficient.

Cystoscopy remains the gold standard for the visualisation of the bladder as well as the prostate and urethra. VH is a predictive factor of malignancy (Khadra, 2000) and as such all patients with VH should have cystoscopy done for diagnosis and treatment. All other patients who have an increased risk of malignancy or blood clots should also undergo cystoscopy. There is a field cancerization effect of urothelial malignancy (Herr, 1996) and any patient with a diagnosis of malignancy on cystoscopy as an initial investigation should have imaging of the entire tract and vice versa.

Conclusion

The causes of haematuria are vast and a systematic strategy is required in its investigation and management. Systematic investigation based on evidence and expert opinion often reveal the underlying cause but in patients with no cause found, follow-up should be considered. In patients with no abnormalities found on assessment and resolution of haematuria, routine follow-up is not required. (Mishriki, 2008) Patients with persistent a-NVH should have annual assessment of BP, eGFR and ACR. Reassessment is indicated with the development of s-NVH, VH or any of the criteria in table 4.

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