Investigation and management of haematuria

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Introduction

Haematuria - bloody urine, is a fascinating clinical entity with the ability to provoke anxiety in patients, physicians and surgeons alike. Red blood cells (RBCs) may be passed in such numbers to evade visual inspection completely (non-visible haematuria, NVH), or be present in sufficient quantity to impart a grossly visible, red-brown discolouration to the patient's stream (visible haematuria, VH). Bleeding can occur at any point along the urinary tract, from the glomerulus to the urethra; however, knowledge of the common pathologies simplifies the workup of these patients (see Fig. 1).

Figure 1. Incidence of pathologies discovered at a haematuria clinic[1].

1. Bladder cancer: 19% (VH), 5% (NVH)
2. UTI: 13%
3. Nephrological causes: 10%
4. Urinary calculi: 8%
5. Renal cell carcinoma: 2%
6. Carcinoma in situ: <1%

Clinically significant haematuria

Clinically significant haematuria is a phrase used to distinguish a pathological quantity of haematuria from that which may occur 'physiologically'[2]. The challenge for organisations such as the American Urological Association (AUA) and the British Association of Urological Surgeons (BAUS), is to provide a threshold below which patients will not be investigated. AUA define this value (indirectly) as 3 RBCs/phf (per high powered field at microscopy)[3]; notably, around 10% of bladder malignancies will be missed using this cutoff[4]. BAUS choses a somewhat more pragmatic approach, based on dipstick results.

Haematuria in primary care

Investigations

Microscopy is an inefficient and insensitive way to detect haematuria. Red cell lysis is not only accelerated by the time lapse between collection and analysis, but also by the preparatory rituals and bright lights associated with microscopy; these factors may lead to false-negatives when urine is sent to the lab[5, 6]. For this reason, BAUS does not support routine microscopy in community based samples of urine[2], a stark contrast to AUA, which commands for microscopic confirmation of haematuria[3].

Modern urine dipsticks lack the specificity of microscopy for haematuria, given their need for an external agent to catalyse an internal oxidation reaction[7]. Within the context of haematuria, clinicians would hope this role would be performed by haemoglobin, acting as

an indirect marker of RBCs; much to their dismay, other oxidants such as myoglobin, haemoglobin and even semen may occasionally cause a false positive[7, 8]. Nevertheless, the impressive sensitivity of dipsticks makes them the ideal initial test for haematuria, producing a colour change in the presence of as little as 2 RBCs/phf[9]. Indeed, many regard dipsticks as *too sensitive*[10] and BAUS agrees, requiring for a reagent strip result of at least '1+' blood[2], which corresponds to approximately 10 RBCs/phf[6].

Visible haematuria

As a general rule, unexplained, painless, VH in adults should be regarded as a dangerous presentation, which almost always warrants urological referral[11]. Indeed, given that almost a third of such patients will be found to have a bladder malignancy, it is more a question of why *not* to refer these patients[12, 13].

Red-brown urine discolouration may be iatrogenic, as in patients taking rifampicin, or the result of an innocent diet, featuring the likes of beet, blackberries and rhubarb[14]. A dipstick is essential, serving as a means to rule *out* haematuria in these cases. In the presence of a positive result, the clinician should first rule out transient causes of haematuria (see Table 1). It is important to emphasise that these causes should be regarded as *transient* and where haematuria persists longer than would be expected, an urgent 2-week referral to a haematuria clinic is warranted. The absence of transient causes also warrants such a referral, unless the patient is under 40, where glomerulonephritis may be suspected. Blood tests (U&E and eGFR) should also be arranged alongside referral[2].

Table 1. Transient causes of haematuria, as outlined by BAUS[2, 15].

Cause	Comments
Menstrual blood	If suspected, re-evaluate at a different point in menstrual cycle.
Exercise-induced haematuria or myoglobinuria	• Haematuria may occur after prolonged exercise. For example, prolonged running ('march haematuria') can give a false positive result. It would be unusual for this to last more than 48h. • Myoglobinuria is much rarer after exercise as it requires for significant rhabdomyolysis. Rhabdomyolysis is classically said to occur after crush injuries, as in the elderly patient who sustains a fall and is subsequently immobile for a prolonged time period.
Urinary tract infection (UTI)	Urine should be sent for microscopy, culture and sensitivity. Patient should be followed up after treatment with another dipstick, to ensure that the haematuria and UTI have both resolved.

Non-visible haematuria

As with VH, it is important to firstly exclude transient causes of haematuria in these patients (see Table 1). Thereafter, urological causes must be excluded in certain patient groups. BAUS suggests urgent urological referral only in patients with associated lower urinary tract symptoms, or in older (>40) individuals with persistent NVH[2]. In contrast, AUA suggests all patients with NVH should be referred for a urological evaluation[3]. Patients with NVH have a small risk of malignancy of 1.2%[3], so it is easy to apply stereotype to the approach taken by AUA. It should be noted however, that routine

cystoscopy is not advocated by the latter unless the patient has risk factors for malignancy (see Fig. 2). This is a sensible approach and one that is supported by other guidance[16]; therefore, consideration should be given to referral where patients have risk factors for urological malignancy.

Figure 2. Risk factors for urinary tract malignancies in asymptomatic patients with NVH, as outlined by AUA[3].

- Male gender
- Age >35
- History of smoking
- Occupational or other exposure to chemicals or dyes (benzenes or aromatic amines)
- Analgesic abuse
- History of gross haematuria
- History of urologic disorder or disease
- History of irritative voiding symptoms
- History of pelvic irradiation
- History of chronic urinary tract infection
- History of exposure to known carcinogenic agents or chemotherapy such as alkylating agents
- History of chronic indwelling foreign body

Nephrology referral

In patients with persistent NVH not meeting the above referral criteria, glomerulonephritis should be considered[2]. IgA nephropathy is a particular subtype, which classically features recurrent episodes of VH, following an upper respiratory tract infection. Pathognomonic to these disorders are dysmorphic RBCs and RBC casts, necessitating the use of microscopy where they are suspected. However, these are by no means essential and therefore patients not meeting urological referral criteria may be treated as one group. Nephrologists do not generally undertake biopsies unless there are markers of significant renal disease, so it is these factors that should be screened for annually in this patient group (see Fig. 3)[17, 18]. Finally, urological referral criteria should not be forgotten.

Figure 3. Primary care monitoring and red flags[2]. 1-4 warrant a nephrology referral.

Patients being monitored in primary care should ideally have annual monitoring of blood pressure, eGFR and ACR/PCR. The red flags are:

1. Significant proteinuria: ACR >30, PCR >50
2. Hypertension: ≥140/90
3. Low eGFR: <60ml/min at first presentation, <30ml/min thereafter
4. Deteriorating eGFR: >5ml/min in 1 year, or >10ml/min in 5 years
5. VH or NVH with lower urinary tract symptoms

Haematuria in secondary care

Overview

The one-stop haematuria clinic aims to rule out urological causes of haematuria. Patients are usually asked to provide a sample of urine for microscopy and cytology, after which they undergo an ultrasound of their upper urinary tract and cystoscopy[19].

Investigations

Fluorescence cystoscopy has been in use for over a decade and is the investigation of choice for the detection of bladder cancer[20]. Flexible fluorescence cystoscopy (FFC) is the procedure of choice in most centres, though it is limited by its slightly inferior sensitivity when compared to rigid cystoscopy[20]. However, the convenience of using simple local anaesthesia tips the balance in favour of FFC as the test of choice in the first instance. Rigid cystoscopy may be used where there are technical difficulties such as heavy local bleeding, but it requires for either general or spinal anaesthesia[19]; it does however, have the added advantage of allowing for direct removal or biopsy of lesions[19].

Many consider ultrasonography too insensitive when used alone to exclude upper urinary tract malignancies[21]. Indeed, it will detect just one quarter of renal cell carcinomas sized <1cm, and only 60% of those sized 1-2cm[21]. CT urography (CTU) provides superior imaging of the urinary tract and though its relatively high radiation dose limits routine use, this risk is outweighed by its benefits in patients with risk factors for malignancy (see Fig. 2) and in those over 40[19]. Indeed, AUA regards this investigation as the procedure of choice for imaging of the upper urinary tract[3]. Of course, in pregnant women, this investigation is contraindicated.

Urinary cytology is a more controversial test, with the aim of detecting neoplastic cells which have exfoliated from carcinoma *in situ* (CIS), the achilles heal of cystoscopy[22]. Such cells clearly prefer to adhere to their parent mucosa, as shown by the poor sensitivity of cytology of around 66-79%[22, 23]. Indeed, AUA specifically advises against its use, or even that of urinary tumour markers, research around which is in its infancy[3]. In the UK at least, until a better test is found, which isn't hampered by existing infectious pathology or user dependence for example, use of cytology is likely to continue[24].

Follow-up

50% of patients with VH and 70% of those with NVH are found to have no demonstrable urological pathology, despite use of the aforementioned investigations and follow-up[4]. However, clinicians may worry about missing urological malignancy in such patients, even though it can usually be reliably excluded[25]. Some clinicians may repeat cystoscopy in patients with risk factors for bladder cancer, though no guidelines support this behaviour[19]. For patients without risk factors, the case is less clear.

Patients evaluated for VH, in whom initial investigations were normal, may be followed up for a variable time period, but discharge is probably safe, with subsequent monitoring in primary care (see Fig. 3)[26]. Indeed, one large prospective study showed that malignancy was unlikely to be missed unless VH reoccured[26]. Where VH reoccurs, complete urological reinvestigation is advisable, given that 11.6% of patients with persistent VH will be subsequently shown to have a urological malignancy[26].

The follow-up of patients with NVH is outlined in AUA guidance[3]; yearly dipsticks are recommended, primarily to detect recurrence[3]. Where NVH persists, AUA guidance suggests lifelong yearly dipsticks, a nephrology consult and repeat urological imaging in 3-5 years[3]. Such guidance is backed by studies which demonstrate pathology only in those individuals in whom NVH persists[4]; this is probably also why AUA suggests discharge where NVH fails to reoccur in the first 2 years of follow-up[3]. Again, patients can be subsequently monitored in primary care (see Fig. 3).

Conclusion

Even from the outset, the investigation and management of patients with haematuria is far from straightforward, with guidelines failing to cover this subject comprehensively. Differences between guidance issued by BAUS and AUA exist at every level, from confirmation of haematuria, to referral and workup of patients. There is still no optimal test for bladder CIS and no single imaging modality which can safely and reliably exclude urological malignancies. Further research is awaited.

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