

## Haematuria: from identification to treatment

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## **Abstract**

Haematuria has a prevalence of 0.1% - 2.6%. Potential diagnoses may include infection, kidney stones, trauma, exercise or spurious causes, such as foods, drugs or menstruation, and a tumour. Approximately 40% of patients with haematuria are found to have a significant underlying pathology, with half of these having a urological malignancy.

Haematuria is subsequently known as the “classic presentation” of bladder cancer with 70 - 80% of patients experiencing painless, gross (visible) haematuria. However, in all cases of visible haematuria, a tumour should be suspected until proven otherwise.

A patient with visible haematuria requires urgent, stringent investigation warranting specialist assessment and subsequent selective referral through a series of patient centred investigations at a Haematuria clinic. One-stop clinics have shown to improve the patient experience in early diagnosis of potentially life threatening conditions although such clinics are less common in Urology settings, despite morbidity and mortality from bladder cancer increasing. This paper will discuss the tests and investigations that need to be undertaken in an individual with either visible or non-visible haematuria, and outline the care that is needed to support patients through the investigation process.

**Key words:** haematuria; diagnosis; investigations; management; haematuria clinics; nursing.

## **Introduction**

Blood in the urine, known as haematuria, is classified as microscopic or macroscopic, or more recently, (based upon joint guidelines from the Renal Association and the British Association of Urological Surgeons) visible haematuria (VT) and non-visible haematuria (NVH) (BAUS/RA, 2007; Lotan, et al, 2009) and can indicate significant underlying disease. In visible haematuria, which has also been referred to as gross haematuria, urine is coloured pink or red and is reported by the patient or seen by the healthcare practitioner during urinalysis. Non-visible haematuria has also been referred to as dipstick-positive haematuria, is subdivided into symptomatic NVH (where the symptoms include urinary hesitancy,

urgency or dysuria) and asymptomatic NVH (where detection is incidental and in the absence of symptoms).

Haematuria is a common urological condition, occurring in up to 10-20% of individuals, presenting in any age group, and accounting for up to 20% of Urology referrals (Miah and Catto, 2010). Causes of haematuria vary by age, gender, ethnic group, duration or a combination of these (Ng, et al.2012). Irrespective of the cause, haematuria requires investigation due to its potential to indicate malignancy. Although haematuria is not always a herald of malignancy (Watkins, 2007), between 85 - 90% of patients that present with *painless* haematuria have a tumour of the urinary tract.

Transient causes of haematuria, for example urinary tract infection (UTI), exercise induced haematuria and menstruation, need to be excluded before the extent of the severity of haematuria can be established (Henning, et al. 2013). Vigorous exercise, for example long-distance running and swimming, can cause transient haematuria that usually resolves within 24-48 hours (Rees, et al. 2008). Women are at greater risk than men of experiencing haematuria, as they are more likely to develop UTI, for example cystitis, which are the most common causes of haematuria (Fernandes, et al, 2012). This is because the female urethra is shorter and straighter, and closer to the anus (and gut flora) compared to males, hence the increased occurrence of urinary tract infection in women. This frequency of UTI/cystitis may result in failure to appropriately investigate females, resulting in delayed diagnosis (Watkins, 2007; Johnson, et al.2008). In view of this potential to under- or misdiagnose females, Kelly, et al. (2009) contends that urinalysis should only be performed after menstruation has finished.

Although haematuria is more common in the elderly (particularly males, over 60 years) than in the young, it is important to gather clues as to the underlying cause of the haematuria, for example, loin pain suggests renal origin; colicky pain indicates stones/calculi; and painless haematuria may indicate a tumour (Ng et al., 2012). Visible haematuria conveys a higher risk of urological malignancy (14.7%-21.8% of cases) compared with non-visible haematuria (2% - 11% of cases) (O'Regan et al, 2009), although the additional factors of positive smoking history, age >40 years, previous malignancies and occupational exposure to rubber, dyes and chemicals, significantly increase the risk of developing bladder cancer.

Although, when these risks are eliminated or reduced, for example, following the removal of aromatic amines from dyes, bladder cancer incidence decreases (Christiani, 2011).

The aim of this paper is to outline the tests and investigations that are undertaken once a patient is referred to a haematuria clinic, and to discuss the role of the nurse in supporting the patient and improving patient satisfaction.

### **Referral**

To balance the need for unnecessary investigations, Loo, et al. (2009) recommend urgent referral for specialist opinion or investigations for all male and female patients with visible haematuria on a single urinalysis, irrespective of age (and irrespective of whether anti-coagulants or anti-platelet therapy is present). For those experiencing non-visible haematuria, both asymptomatic and symptomatic patients should be referred if they provide at least two of three positive urinalysis tests, again, irrespective of age. This is in line with the referral criteria by NICE (2005) for suspected cancer and follows the 'two week wait' directive within Primary Care (Department of Health, 1997).

Despite previous research showing evidence for unequal referral patterns for the urological evaluation of haematuria (Johnson et al, 2008) the NICE guidelines do not discriminate between genders. Patients with haematuria need to be monitored and reviewed from a medical and economic perspective (Mostafid et al, 2010), with investigations being specific and accurate to prevent over-investigating, avoid under or misdiagnosing cancer, whilst simultaneously maximising patient satisfaction and reducing patient anxiety.

### **Investigations**

Once the patient has been referred to the haematuria clinic, patients will undergo a series of investigations (refer to Figure 1 and Table 1).

*Insert Figure 1*

*Insert Table 1*

Within both referral and initial investigations, the patient will be asked to provide their background history (see Table 2), to identify possible causes of haematuria.

*Insert table 2*

At the clinical visit, the potential causes, along with any associated risk factors, will be established. Patients will be informed of the range of causes of haematuria, for example, some foods (e.g. beetroot) can indicate the presence of blood, but this is 'normal' discolouration of the urine. These samples would create 'false positive' results where a test incorrectly indicates a positive result, but the disease is not present. Normally, the cause of these cases is not serious or does not require further investigation.

For most patients however further tests will be needed. Local policies and corresponding investigation protocols may dictate the tests which patients receive (Loo et al, 2009). It is important that the rationale for each test is given to the patient, as well as explaining what the test may (or may not) indicate, and which further investigations may be required. Patients should also be advised that not all tests will show urological or renal pathology and a negative result does not always mean absence of disease.

*Blood tests*

Blood profile (full blood count) is needed to detect the presence of anaemia, and serum urea, creatinine and electrolytes are needed to identify any renal impairment (Miah and Catto, 2010). If there is evidence of a declining glomerular filtration rate (GFR) (by 10ml/min at any stage within the previous 5 years or by >5ml/min with the last year) and if urea/electrolyte/creatinine indicate stage 4 or 5 kidney disease, a referral to a nephrologist will be needed (BAUS/AR, 2007).

*Urine tests*

Urinalysis: As the primary test for detecting blood in the urine, urinalysis involves the patient voiding a fresh sample into a sterile urine pot. Using a chemical reagent strip, an array of tests can be performed to measure the presence of cells and substances, such as haemoglobin, protein (which can indicate renal disease), nitrites (which can indicate the presence of infection) and pH levels are assessed. The strip is fully immersed into the urine and placed on a dry surface, allowing the test results to develop and appear as colour changes on the strip (Steggall, 2007). Urinalysis is a test frequently performed in G.P practices, as well as both Outpatient and Inpatient clinical services as a screening test, and Nurses must be competent in conducting urinalysis, as well as interpreting, reporting and explaining findings of this test.

-Urine Cytology: The urine will also be used in cytological (cell) analysis, by sending the sample for microscopy, culture and sensitivity (Nash, 2010). Cells passed out of the bladder in the voided sample can be used to exclude UTI and detect inflammation or urothelial cancers. The sample is processed in a laboratory and examined under the microscope to look for abnormal cells. The use of cytology testing is diminishing however, following several reviews stating its sensitivity is too low (Blick, et al, 2011). A new test, the NMP22®Bladderchek® test, has been found to be a quicker and cheaper alternative, and its use is becoming more prevalent. Potentially, this test can detect more urological tumours at an earlier stage by identifying elevated levels of nuclear matrix protein 22, which exist in high levels in cancer cells (Turner, 2008).

#### *Investigation of the Upper Urinary Tract*

Imaging is used to detect upper tract pathology (Mostafid, et al. 2010), specifically a KUB (Kidneys, Ureter and Bladder) Radiographic test (X-ray and / or Renal Ultrasound scan) to obtain images of the abdomen. These diagnostic tests seek to identify gross abnormalities, such as kidney stones and gastrointestinal disorders. Although both tests require minimal patient preparation and aftercare, radiographic imaging involves minor exposure to radiation and so is not suitable for pregnant women.

Ultrasonography is however a relatively cheap, quick and harm-free investigation that involves only light, direct pressure to the skin and requires simple bladder filling for pelvic scanning (Malik, 2008). This procedure can identify cystic renal lesions, larger renal tumours

and is used for testing renal morphology and structure. However, ultrasound may fail to identify small lesions, and in these situations further investigation may be required with an X-ray of the Urinary system (Intravenous Urography or IVU). However IVU can also fail to diagnose small renal or bladder masses, or other causes of haematuria such as calculi. McDonald, et al. (2006) contends that the only reliable way of detecting bladder cancer is via the lower urinary tract, by flexible cystoscopy.

### *Investigation of the Lower Urinary Tract*

- Cystoscopy: A long, flexible tube (cystoscope) is inserted into the urethra and enables visualisation of the bladder. Cystoscopy is undertaken by an appropriately qualified practitioner and is performed under local anaesthesia (using a local anaesthetic and antibacterial gel), and can be done on an Outpatient basis or in a Urology clinic. Although pain and discomfort are commonly reported by the patient during this procedure (Soomro, et al. 2010), research has shown this can be minimised through pre-operative active patient involvement and counselling. Clements et al, (2004) outlined the patient benefits of encouraging visualisation of their flexible cystoscopy, which can lead to lower anxiety and pain, compared to patients who did not visualise their procedure.

Should any test/s identify an abnormality or the patient be considered high risk (including those aged > 50 years, have a history of smoking and / or occupational exposure), further investigations will be necessary to enable a more detailed assessment and minimise any false positives or negatives (Blick, et al. 2011). For example, Computerised Tomography (CT) may be used to image the entire urinary tract to detect upper tract pathology, due to their high sensitivity (Albani, et al. 2007).

### *Treatment and Follow-up*

In patients whose results are suspicious or a tumour is confirmed, local guidelines will dictate how patients should be followed-up. For superficial (non-muscle invasive) tumours, a patient will be typically referred for a repeat blue-light cystoscopy, using highly sensitive photodynamic detection (PDD) to improve identification and diagnosis. To remove superficial tumours, patients will undergo a surgical procedure known as a TURBT (Trans

Urethral Resection of the Bladder), whereby any unusual growth is removed from the bladder wall. To prevent progression, and in conjunction with surgery, additional therapies such as BCG (Bacillus Calmette-Guerin) intravesical therapy (a vaccination) or mitomycin C (chemotherapy) will be given.

For more aggressive tumours of the bladder (i.e. muscle invasive cancer) suitable patients will be given chemotherapy to shrink the cancer, followed by either radiotherapy or surgery. Current radiotherapy aims to maximise the delivery of radiation to tumour tissue, whilst minimising that to healthy tissues.

When the tumour is advanced and invasive, or if the patient has had repeated recurrence of non-muscle invasive cancer, a cystectomy may be required. This is the surgical removal of all or part of the bladder, with the formation of an ileostomy (if the entire bladder is removed).

Once treatment is complete, the patient will receive regular follow-up appointments to monitor their health status, due to the high risk of recurrence in bladder cancer. A typical follow-up plan includes repeated physical examination, blood tests, urine cytology and imaging tests, as well as regular cystoscopy (assuming the bladder has not been removed). Any recurrence of haematuria would warrant further/repeat investigation.

### **Support for Patients**

Irrespective of the investigations that the patient undergoes, recommendations for lifestyle changes may be appropriate along their journey to minimise, or if possible prevent, any current or future risks to the patient's health.

Treatment, combined with a diagnosis of any condition associated with haematuria, can involve symptoms and side effects, as well as being physically exhausting and emotionally stressful for the patient. The focus of healthcare is to provide compassionate and sensitive care based around six values, the 'Six C's' care, compassion, courage, communication, competence and commitment (Department of Health, 2012), and to deliver compassionate



care, patients will need the opportunity to talk and raise concerns that they might have. It is important that patients feel listened to, understood and actively involved with their care (Gourdji, et al.2003).

## **Conclusion**

There are two types of haematuria, visible (VH) and non-visible haematuria (NVH), with the latter category divided in to symptomatic (s-NVH) and asymptomatic haematuria a-NVH). All episodes of haematuria require investigation (to exclude non-uological causes, e.g. ingestion of foods that colour urine, as well as UTIs). For individuals with VH, s-NVH (in the absence of UTI or other transient causes) and persistent a-NVH, referral to a haematuria clinic is needed. At the clinic, causes of haematuria will be investigated using a variety of methods, including radiography and cystoscopy. Once the cause has been identified, further management can be provided by the Urology or Nephrology team. In the absence of clinical findings, patients will require long term monitoring by the primary care team. If VH or renal function develops, re-referral back to the haematuria clinic will be required.

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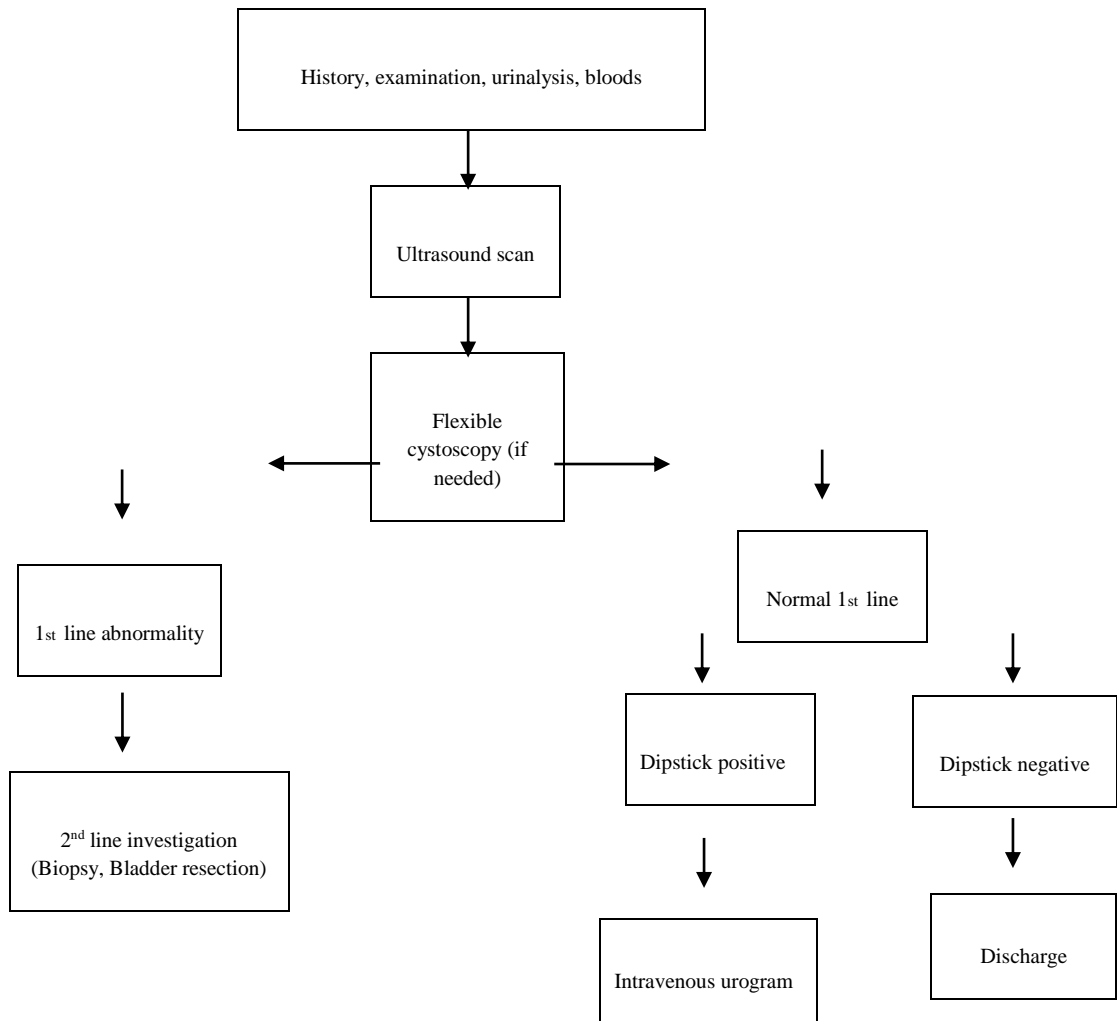
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Figure 1: An Investigatory Flowchart for patients referred to the Haematuria clinic



(Kelly, Fawcett & Goldberg, 2009)

Procedure	Purpose	Advantages	Disadvantages
<b>Urinalysis</b>	Detection of haemoglobin from a urine sample, using chemical reagent strips	<ul style="list-style-type: none"> <li>- Effective: 65-95% specific</li> <li>- Inexpensive, convenient</li> <li>- Requires minimal training</li> <li>- Does not require presence of intact blood cells</li> </ul>	<ul style="list-style-type: none"> <li>- Limited in confirmation of true micro-haematuria</li> </ul>
<b>Cytology</b>	Examination of urinary cells from a urine sample, under the microscope	<ul style="list-style-type: none"> <li>- Non-invasive</li> <li>- Can detect Carcinoma in Situ (CIS) and high grade Transitional Cell Carcinoma (TCC)</li> </ul>	<ul style="list-style-type: none"> <li>- Expensive</li> <li>- Poor sensitivity</li> <li>- Poor positive predictive value of 8%</li> <li>- Delays the haematuria pathway</li> </ul>
<b>Cystoscopy</b>	Visual examination of the lower urinary tract - bladder via the urethra using a cystoscope	<ul style="list-style-type: none"> <li>- Fundamental Urological technique</li> <li>- "Gold standard of bladder cancer detection"</li> </ul>	<ul style="list-style-type: none"> <li>- Invasive</li> <li>- Expensive</li> <li>- Causes pain, discomfort and anxiety to patient</li> <li>- Does not provide 100% sensitivity; superficial bladder cancer is rarely found on physical examination</li> <li>- Enhances the risk of developing a urinary tract infection (UTI) by 10%</li> <li>- Complications of perforation and bleeding possible</li> </ul>
<b>Ultrasonography</b>	Diagnostic imaging of the upper urinary tract using an ultrasound	<ul style="list-style-type: none"> <li>- Cheap and Effective</li> <li>- Adequately sensitive for screening renal and bladder abnormalities</li> <li>- Avoids radiation exposure</li> <li>- Requires minimal preparation in terms of fasting and bowel preparation</li> <li>- Can be conducted on an Outpatient basis</li> </ul>	<ul style="list-style-type: none"> <li>- Additional investigatory route adds to haematuria diagnostic pathway</li> </ul>

Table 1: Diagnostic tests for Haematuria (Albani et al, 2007; Malik, 2008; Rao and Jones, 2008; O'Regan et al, 2009; Soomro, et al, 2010).

<b>Background Information</b>	<b>Rationale</b>
Age	Haematuria is more common in the older adult. Potential diagnoses include bladder cancer, prostate cancer, etc.
Sex	Females have an increased risk of haematuria due to Urinary Tract Infections (UTIs) and menstruation.
Occupation	Occupational exposure to dyes, rubbers, textiles and chemicals have found to be associated with bladder cancer.
Family history	An onset of persistent microscopic hematuria, typically during childhood is indicative of “familial haematuria;” a group of genetic kidney disorders for example.
Medical History	For example, a history of previous urological conditions may indicate recurrence.
Physical Activity	Vigorous exercise, mild trauma or sexual intercourse can all be a cause of transient haematuria.
Diet	Foods such as beetroot, blackberries and rhubarb can cause urine to look red or brown.
Medication	Haematuria may be drug-induced, by non-steroidal anti-inflammatory drugs, antibiotics or anticoagulants.
Smoking history	Smoking significantly increases the risk of bladder cancer and subsequent likelihood of haematuria.
Drug use	Ketamine dependence for example is associated with urinary tract effects.
Haematuria history	Number and type of episodes of haematuria, associated pain, urological symptoms, and point in the urinary stream when the haematuria is visible, will all enable the clinician to help identify potential causes

*Table 2: Information required for the Haematuria Patient’s History (Adapted from Turner, 2008; Nash, 2010).*