Haematuria: testing to improve patient outcome

Haematuria can be a symptom of acute kidney injury or chronic kidney disease, but diagnosis is often hampered by lack of clarity with regard to description, analysis and referral criteria. Here, Shahid Muhammad provides a general overview in the context of renal disease.

The source of, and reason for, haematuria is often confused due to lack of clarity over description, analysis and patient referral criteria. A thorough haematuria review has been carried out[1] and as a result the Renal Association (RA) and British Association of Urological Surgeons (BAUS) formed a joint working party to agree on guidelines to update training of staff providing care for patients presenting with haematuria.[2]

Urinary screening for haematuria should only be performed for recognisable medical reasons as there is presently no evidence to support opportunistic point-of-care testing (POCT) for the general population. The nephrological aspects of analysis and control have been covered by the National Institute for Health and Care Excellence (NICE) Chronic Kidney Disease (CKD) guidelines,[3] which replaced the existing UK (Royal College of Physicians) CKD Framework.[4]

The article provides a general overview of haematuria, offering background information and definitions in the context of CKD. From a primary care perspective, it is perhaps also important that biomedical scientists appreciate the GP curriculum on haematuria and men's health (Table 1).[5]

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Haematuria is defined as the presence of red blood cells (RBCs) in urine, either visible (macroscopic haematuria) or detected by direct microscopy (microscopic haematuria).[6] Substantiated numbers of RBCs have provided ranges used for the classification of microscopic or occult haematuria, with established definitions using values of >3 RBCs per high-power field[7,8] >5 RBCs per high-power field.[9]

Haematuria can be broadly classified as nephrological or urological in origin. Any glomerular disease may result in microscopic haematuria. Active glomerular nephritis and acute interstitial nephritis are associated with large numbers of usually dysmorphic RBCs and RBC casts. Other reasons for haematuria include i) non-visible haematuria (s-NVH),[10] which is connected to the lower urinary tract; these can include reluctance to void, voiding frequency, voiding desperation or painful voiding dysuria; and ii) asymptomatic non-visible haematuria (a-NVH),[11] which is an incidental finding in the absence of lower or upper urinary tract symptoms.[8] Microscopic haematuria may also be detected in the absence of any underlying pathology, such as after vigorous exercise.[9]

Table 1. Men's health and the requirements placed on GPs.[5]

- Manage primary contact with patients who have a male genitourinary problem.
- Know that men may be both more reticent and less articulate about their health than women, and describe strategies to compensate for this during the consultation.
- Describe the particular difficulties that adolescent and young adult males have when accessing primary care services.
- Demonstrate a non-judgmental, caring and professional consulting style to minimise embarrassment.
- Use consultations with infrequent attendees opportunistically for health education.
- Know how to evaluate the effectiveness of the primary care service provided from the male patient's point of view.

CAUSES OF HAEMATURIA

Asymptomatic haematuria is often caused by inherited thinning of the glomerular membrane. It can sometimes be dismissed as being due to contamination with menstrual blood or to a urinary tract infection[12] Many studies of the causes of haematuria have examined patients referred to nephrology or urology clinics and have not used phase contrast microscopy to differentiate between glomerular and nonglomerular sources. Haematuria in otherwise well adults is more often due to bleeding from the glomerulus than from elsewhere in the urinary tract.[12]

In unselected individuals with glomerular haematuria, a renal biopsy most often illustrates basement membrane disease.[13] This condition is characterised by thinning of the glomerular basement membrane on ultrastructural examination and a very mild proliferative glomerulonephritis (GN). Thin basement membrane disease is also known as benign familial haematuria,[14] and other family members may have haematuria. Affected individuals typically have lifelong glomerular haematuria, minimal proteinuria, and normal renal function, as well as often having a family history.[15]

SIGNIFICANT HAEMATURIA

Haematuria is most usefully divided into i) visible (macroscopic) haematuria (VH) and ii) non-visible (microscopic) haematuria (NVH).[15] These can be subdivided as a) symptomatic (s-NVH), associated with lower urinary tract symptoms, frequency, pain on voiding, loin pain, or suprapubic pain, and b) asymptomatic (a-NVH). Persistent a-NVH

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is defined as having greater than one positive result on a dipstick test.[16] Persistence is thus defined as having two out of three dipsticks positive for NVH. When there is a need to differentiate persistent invisible haematuria in the absence of proteinuria from transient haematuria, two out of three positive reagent strip tests is regarded as confirmation of persistent invisible haematuria. A trace of blood on a dipstick test is not regarded as significant. Urine microscopy is not reliable in detecting NVH so it is not necessary to confirm NVH in the laboratory.[16]

CHRONIC KIDNEY DISEASE

Haematuria can provide an index of glomerular basement thinning, but renal specialists tend to devote more attention to the presence of proteinuria. Recent reports, however, have propelled haematuria into the vanguard of clinical nephrology.[16,17] If severe or sufficiently progressive, haematuria can be indicative of acute kidney injury (AKI) and eventual CKD. Moderate to severe CKD is also associated with an increased risk of other significant adverse outcomes, and the risk of developing CKD increases with age.

As kidney dysfunction progresses, co-existing conditions become more common and increase in severity. Chronic kidney disease can progress to end-stage kidney failure in a small but significant percentage of people. Although usually asymptomatic, CKD is detectable, and tests are simple and freely available. There is evidence that treatment can prevent or delay the progression of CKD, reduce or prevent the development of complications, and reduce the risk of cardiovascular disease (CVD). However, CKD is often unrecognised because there are no specific symptoms, and it is often either undiagnosed or diagnosed at an advanced stage.

Over the past few years, collaborative efforts facilitated by a common definition of CKD have provided a description of the epidemiology and natural history of this disease, which has improved understanding of the pathophysiology involved. There is increased recognition that CKD is encountered in multiple settings and in all age groups, and that its course and outcomes are influenced by the severity and duration of the event. The effect of CKD on an individual patient and the resulting societal burden that ensues from the long-term effects of the disease is attracting increasing scrutiny. There is evidence of marked variation in the management of CKD due to a lack of awareness and an absence of standards for prevention, early recognition and intervention. These emerging data point to an urgent need for a global effort to highlight the fact that CKD is preventable, its course is modifiable and its treatment can improve outcomes.[16,17]

Analysis of patients with unidentified CKD suggests that their risk profile may be different to patients with identified CKD, and is an area that requires further research.[18] Table 2 gives definitions of the five stages of CKD in the adult population, based on glomerular filtration rate (GFR), which is a marker of renal function.

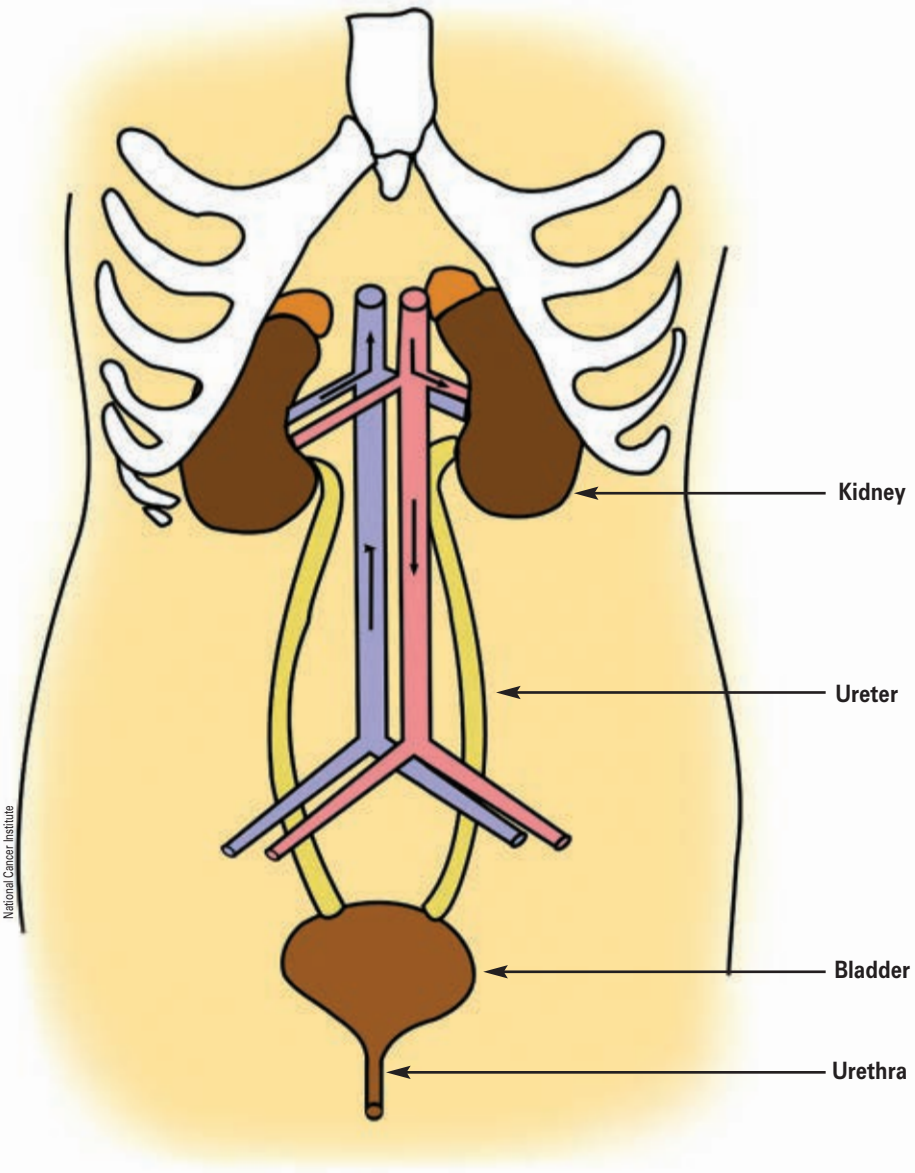

Fig 1. Components of the urinary system from which haematuria may arise.

PUBLIC HEALTH AND EPIDEMIOLOGY

Haematuria is a relatively common finding and has many potential underlying causes, ranging from the physiological to the life-threatening. The prevalence of haematuria on dipstick testing has been studied in several population groups, such as patients attending hospital as out-patients, in occupational health programmes, and in a large medical insurance health screening programme, and has been found to range from 2% to 16%.[19–23] Retrospective study of haematuria using urine microscopy shows a prevalence of 1–5%;[18,22,23] however, the range varies depending on the definition of significant haematuria.[24,25]

PRESENTATION

Haematuria may be idiopathic and/or benign, or it can be a sign of the presence of a kidney stone or a tumour in the urinary tract (Fig 1). If white blood cells are found in addition to RBCs then urinary tract infection (UTI) is the most likely diagnosis. Occasionally, the term haemoglobinuria is used to indicate a high RBC count in the urine, although this may not be directly indicative of haematuria.[7,13]

'Haematuria can sometimes be dismissed as being due to contamination with menstrual blood or to a urinary tract infection'

Table 2. Stages of CKD in the adult population.[18]

Severity	Classification	
Stage 1	Kidney damage with normal or raised GFR	(>90 mL/min/1.73 m²)
Stage 2	Kidney damage with normal or raised GFR	(60–89 mL/min/1.73 m²)
Stage 3	Moderately impaired GFR	(30–59 mL/min/1.73 m²)
Stage 4	Severely impaired GFR	(15–29 mL/min/1.73 m²)
Stage 5	End-stage renal failure with GFR	(<15 mL/min/1.73 m²)

It is important to take a full urological history and include palpation of the abdomen, and blood pressure (BP). Examination should include thorough investigation relating to features of potential renal involvement, including hypertension, altered renal function tests, proteinuria, known previous renal problems, renal mass and increased haematuria.[7,8] It is important to appreciate that haematuria without proteinuria does not necessarily specify a non-glomerular origin, as glomerular bleeding is not automatically associated with proteinuria.[7,8]

DIFFERENTIAL DIAGNOSIS

One study has summarised retrospective insights and epidemiology of the underlying investigations and differential diagnoses for haematuria, and suggested that urinalysis and imaging techniques together are needed to evaluate the extent of haematuria in suspect/high-risk patients.[25] Other work has provided a detailed insight into what diagnostic tests are required, and these range from basic urinalysis to more sophisticated nephrological/urological investigations;[1] however, the following can help in a differential diagnosis:[1,26]

- dipstick test (using validated reagent strips/kit)
- cell morphology via microscopy
- ascertaining cell culture results
- retrieving cytology context
- investigating voided biomarkers.

IMAGING

It is important to substantiate the differential diagnosis and conduct imaging investigations, especially if re-occurring/progressive haematuria is evident. The following exploratory modalities are used to validate a diagnosis in relation to severity:[1,26]

- plain radiography (X-ray)
- cystoscopy (CS)
- ultrasound (US)
- intravenous urography (IU)
- computerised tomography (CT)
- magnetic resonance imaging (MRI)
- renal biopsy (only warranted when there is a clear indication of renal function decline).

INDICATIONS FOR REFERRAL

Referral depends on a number of factors and these are summarised in Table 3. It is important to note, however, that all patients with visible haematuria should be referred to nephrology if GN or glomerular basement membrane (GBM) is suspected, which should be established via renal biopsy.[17] To ensure best practice, it is important to appreciate the context in which nephrology referral is required, and Table 4 highlights some of the indications for specific nephrology referral.

LONG-TERM MONITORING

It is important to establish the cause of haematuria as early as possible and Table 5 summarises some of the indications for long-term monitoring of patients. There are some pitfalls in monitoring consistent haematuria without formal point-of-care testing (POCT) programmes in the wider community (eg training and access to POCT). In addition, assessment of glomerular haematuria may be inhibited by the presence of non-glomerular haematuria. Microhaematuria is not monitored routinely, as is the case with albuminuria or proteinuria, and this presents a challenge to evaluation over the long-term. Patients with microhaematuria therefore require treatment earlier than those without haematuria.[18,28]

RESEARCH PERSPECTIVES

Haematuria is an important pathological finding and thus is included in the criteria for CKD.[29–32] However, its presence is not usually

Table 3. Haematuria: key indications for referral.

- Evidence of visible (macroscopic) haematuria which is a general concern. This usually requires a fast-track urology referral for imaging and cystoscopy, unless strong pointers to acute renal disease.[17] Referral to nephrology specialist if urological investigations prove negative.
- Invisible (microscopic) haematuria without proteinuria, with GFR >60 mL/min/1.73 m².[17]
- Patients older than 40 years and with consistent evidence of haematuria require referral to urology (recommended age and ethnicity may vary locally).
- Patients either less than 40 years or more than 40 years with negative urological investigations potentially require the same management as stage 1/2 CKD patients, but it is important to validate screening results with imaging. Patients with evidence of microscopic haematuria with significant proteinuria (ACR ≥30 mg/mmol, or polymerase chain reaction (PCR)-informing results ≥50 mg/mmol).

mentioned in large epidemiological studies when compared with proteinuria; most studies in the field of AKI do not focus on the role of haematuria. A few studies have described haematuria-associated AKI in certain clinical settings (eg IgA nephropathy or warfarin-induced nephropathy),[33,34] but it is difficult to apply these data directly to subjects with a high risk of AKI. A recent study demonstrated the associations of haematuria with both AKI and mortality in an intensive care unit (ICU) patient population, but concluded that further clinical and experimental studies are needed to delineate the role of haematuria in AKI.[29] Other nephrology and urology research suggests that there should be more pathways to POCT to identify haematuria and proteinuria because of their long-term complications.[13,28–31]

Evidence from the majority of studies suggests that dipstick testing may provide a moderately useful indicator of the presence of haematuria (ie a positive dipstick test is reasonably likely to represent the presence of haematuria), and this can be used in a GP environment. However, the context in which the dipstick test is used warrants particular consideration. Research indicates that the simple detection of microhaematuria cannot be considered a useful diagnostic test for the presence of significant underlying pathology or physiological predisposition.

The absence of haematuria on a single dipstick test cannot reasonably be used to rule out symptomatic patients from further examination; however, there are no data on the relationship between repeat positive tests for haematuria and the presence of disease,[1] so the usefulness of dipstick testing in this context remains problematic.

There are relatively few trial-based data regarding the effectiveness of screening for haematuria in the general population to identify life-threatening pathologies. Confirmation of haematuria using microscopy remains a valid option where further investigations are being considered. As stored samples are theoretically subject to degradation, the practice of sending a urine sample taken in the community for laboratory analysis of haematuria appears to be of questionable value, although such samples may still be useful to eliminate UTI as a cause of haematuria.

Campaigns in public and medical communities can help to delay, perhaps even prevent, the development CKD. One such example of raising CKD awareness through social media is work by the Renal Patient Support Group (RPSG).[36] Many cases of CKD are left unrecognised, but the condition can be treated even at late stages, so POCT is always advantageous.[15] ■

Table 5. Indications for long-term monitoring.

- Persistent unseen haematuria, with or without proteinuria, should stimulate investigation for a potential urinary tract malignancy in appropriate age groups.
- Consistent unseen haematuria in the absence of proteinuria should be followed up annually with repeat testing for haematuria, proteinuria or albuminuria, GFR/eGFR and BP monitoring while haematuria continues.[26]

Table 4. Indications for nephrology referral.

- Suspect/high-risk patients who have had a urological cause excluded or have not met the general referral criteria.
- For each potential referral to urology, a referral to nephrology should also be considered.[1,26]
- Patients who have evidence of declining GFR/eGFR >10 mL/min at any stage within the previous five years or >5 mL/min within the previous year.[1,26]
- Patients with haematuria who have Stage 4/5 CKD (where eGFR <30 mL/min).[1,26]
- Isolated haematuria with evidence of hypertension in those less than 40 years (this may be indicative of GBM disease or GN. Visible haematuria matching with subsequent infection (evidence of upper respiratory tract).[1,26]

REFERENCES

1 Rodgers M, Nixon J, Hempel S *et al.* Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation. *Health Technol Assess* 2006; **10** (18): iii-iv, xi-259.

2 Joint Consensus Statement on the Initial Assessment of Haematuria (www.ncchta.org/execsumm/summ1018.htm).

3 National Institute for Health and Care Excellence.Chronic Kidney Disease; NICE Clinical Guideline, 2008 (www.nice.org.uk/guidance/cg182).

4 Royal College of Physicians (2006). Identification, management and referral of adults with chronic kidney disease: Concise guideline, 2006 (www.rcplondon.ac.uk/resources/concise-guidelines-chronic-kidney-disease).

5 Royal College of General Practitioners. Statement 3.07 Men's Health. London: RCGP, 2010 (Revised: 7 May 2014).

6 Cameron JS. Common clinical presentations and symptoms in renal disease. In: Weatherall DJ, Ledingham JG, Warrell DA eds. *Oxford Textbook of Medicine*. Oxford: Oxford University Press, 1996: 3144–9.

7 Grossfeld GD, Carroll PR. Evaluation of asymptomatic microscopic hematuria. *Urol Clin North Am* 1998; **25** (4): 661–76.

8 Grossfeld GD, Litwin MS, Wolf JS *et al.* Evaluation of asymptomatic microscopic hematuria in adults: the American Urological Association best practice policy – part I: definition, detection, prevalence, and etiology. *Urology* 2001; **57** (4): 599–603.

9 Grossfeld GD, Wolf JS Jr, Litwan MS *et al.* Asymptomatic microscopic hematuria in adults: summary of the AUA best practice policy recommendations. *Am Fam Physician* 2001; **63** (6): 1145–54

10 Kore RN, Dow CS, Desai KM. A new automated system for urine analysis: a simple, cost-effective and reliable method for distinguishing between glomerular and nonglomerular sources of haematuria. *BJU Int* 1999; **84** (4): 454–60.

11 Jones GR, Newhouse IJ, Jakobi JM, LaVoie NL. Thayer R. The incidence of hematuria in middle distance track running. *Can J Appl Physiol* 2001; **26** (4): 336–49.

12 Savige J, Buzza M, Dagher H. Haematuria in asymptomatic individuals. *BMJ* 2001; **322** (7292): 942–3.

13 Kincaid-Smith P. Thin basement membrane disease. In: Massry SG, Glassock RJ eds. *Textbook of Nephrology*. Philadelphia: Lippincott, Williams and Wilkins, 1995: 760–4.

14 Blumenthal SS, Fritsche C, Lemann J Jr. Establishing the diagnosis of benign familial hematuria. The importance of examining the urine sediment of family members. *JAMA* 1988; **259** (15): 2263–6.

15 Iseki K. Nephrology for the people: Presidential Address at the 42nd Regional Meeting of the Japanese Society of Nephrology in Okinawa 2012. *Clin Exp Nephrol* 2013; **17** (4): 480–7.

16 Moreno JA, Martin-Cleary C, Gutierrez E *et al*. Haematuria: the forgotten CKD factor? *Nephrol Dial Transplant* 2012; **27** (1): 28–34.

17 Lewington AJ, Cerda J, Mehta RL. Raising awareness of acute kidney injury: a global perspective of a silent killer. *Kidney Int* 2013; **84** (3): 457–67.

18 Black C, Sharma P, Scotland G *et al*. Early referral strategies for management of people with markers of renal disease: a systematic review of the evidence of clinical effectiveness, cost-effectiveness and economic analysis. *Health Technol Assess* 2010; **14** (21): 1–184.

19 Fraser CG, Smith BC, Peake MJ. Effectiveness of an outpatient urine screening program. *Clin Chem* 1977; **23** (12): 2216–8.

20 Froom P, Ribak J, Benbassat J. Significance of microhaematuria in young adults. *Br Med J (Clin Res Ed)* 1984; **288** (6410): 20–2.

21 Larcom RC Jr, Carter GH. Erythrocytes in urinary sediment; identification and normal limits, with a note on the nature of granular casts. *J Lab Clin Med* 1948; **33** (7) 875–80.

22 Mariani AJ, Luangphinith S, Loo S, Scottolini A, Hodges CV. Dipstick chemical urinalysis: an accurate cost-effective screening test. *J Urol* 1984; **132** (1): 64–6.

23 Mariani AJ, Mariani MC, Macchioni C, Stams UK, Hariharan A, Moriera A. The significance of adult hematuria: 1,000 hematuria evaluations including a risk-benefit and cost-effectiveness analysis. *J Urol* 1989; **141** (2): 350–5.

24 Messing EM, Young TB, Hunt VB,

IN SUMMARY

- Suspect/high-risk patients should be provided with education and understanding on biochemical parameters in lay terms in order to achieve best practice.
- Campaigning needs to include signposting and collaborative efforts between scientists and secondary care sector health professionals.
- More POCT collaborations are required in the community.[37]
- Biomedical scientists have knowledge of the haematological and microbiological elements related to haematuria and should be proactive in prompting more updates in this area.
- Absence of data on the impact of delayed detection on health outcomes and cost over the long-term should be factored into UK practice.

Emoto SE, Wehbie JM. The significance of asymptomatic microhematuria in men 50 or more years old: findings of a home screening study using urinary dipsticks. *J Urol* 1987; **137** (5): 919–22.
25 Ritchie CD, Bevan EA, Collier SJ. Importance of occult haematuria found at screening. *Br Med J (Clin Res Ed)* 1986; **292** (6521) 681–3.
26 Rockall AG, Newman-Sanders AP, al-Kutoubi MA, Vale JA. Haematuria. *Postgrad Med J* 1997; **73** (857): 129–36.
27 Jalalah SM, Alzahrani IH, Furness PN. Glomerular changes in microscopic haematuria, studied by quantitative immunoelectron microscopy and in situ zymography. *Nephrol Dial Transplant* 2002; **17** (9): 1586–93.
28 Palevsky PM, Liu KD, Brophy PD *et al*. KDIGO US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury (2012). *Am J Kidney Dis* 2013; **61** (5): 649–72.
29 Han SS, Ahn SY, Ryu J et al. Proteinuria and hematuria are associated with acute kidney injury and mortality in critically ill patients: a retrospective observational study. *BMC Nephrol* 2014; **15**: 93.
30 Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. *Kidney Int* 2003; **63** (4): 1468–74.
31 Khadra MH, Pickard RS, Charlton M, Powell PH, Neal DE. A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice. *J Urol* 2000; **163** (2): 524–7.
32 Spencer J, Lindsell D, Mastorakou I. Ultrasonography compared with intravenous urography in investigation of urinary tract infection in adults. *BMJ* 1990; **301** (6745): 221–4.
33 Gutierrez E, Gonzalez E, Hernandez E *et al*. Factors that determine an incomplete recovery of renal function in macrohematuria-induced acute renal failure of IgA nephropathy. *Clin J Am Soc Nephrol* 2007; **2** (1): 51–7.
34 Brodsky SV, Satoskar A, Chen J *et al*. Acute kidney injury during warfarin therapy associated with obstructive tubular red blood cell casts: a report of 9 cases. *Am J Kidney Dis* 2009; **54** (6): 1121–6.
35 Spencer J, Lindsell D, Mastorakou I. Ultrasonography compared with intravenous urography in the investigation of adults with haematuria. *BMJ* 1990; **301** (6760): 1074–6.
36 Muhammad S, Allan M, Ali F, Bonacina M, Adams M. The renal patient support group: supporting patients with chronic kidney disease through social media. *J Ren Care* 2014; **40** (3): 216–8.
37 Muhammad S. Renal point-of-care testing: collaboration between biomedical scientists and community pharmacists. *Br J Biomed Sci* 2015; **72** (1): 42–6.

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