

DEFINITION

Hematuria implies blood in the urine. If the urine is reddish to naked eye, it is called macroscopic hematuria and if blood is detectable only by microscopy it is called microscopic hematuria. Even one ml of blood in a litre of urine is enough to result in reddish urine. Microscopic hematuria is defined as presence of three or more red blood cells (RBCs) per high-power field. For urine analysis urine should be freshly voided, should be midstream, clean catch and not the first morning specimen. Urine samples collected following strenuous exercise, trauma, sexual intercourse, during febrile illness and during menstruation can show transient hematuria and hence be better avoided.

URINE TESTING

Analysis of urine should be performed as early as possible following collection. Dip stick is very sensitive and can detect microscopic hematuria of 1-5 RBCs/hpf with a sensitivity of 100 % & specificity of 99 %. The dipstick actually detects haemoglobin/ myoglobin and can show false positive results in case of hemoglobinuria and myoglobinuria. Therefore a positive dipstick reading merits microscopic examination for confirmation. A negative dip stick test virtually excludes hematuria. One needs to keep in mind that in dilute urine (urine osmolality <308 mosm/l) RBCs lyse, thereby reducing the quantum of microscopic hematuria.

Significance of hematuria in patients following catheterization or on anticoagulant drugs

Studies performed by testing pre and post bladder catheterization urine samples for microscopic hematuria, revealed that a microscopic hematuria following catheter related urothelial trauma was indeed rare. Likewise control studies of patients on anticoagulants also show that anticoagulants don't increase the risk of hematuria. Hence it seems prudent not to outright neglect microhematuria in catheterised patients or those on anticoagulants. However exceptions can be there in patients with clotting or bleeding abnormality or difficult catheterizations.

Significance of Dysmorphic RBCs in differentiating upper or lower tract bleeding

Isomorphic RBC are normal dumbbell shaped and have smooth round outline. Their presence implies bleeding from lower tract. Dysmorphic RBCs (as name implies) are distorted, broken, less hemoglobinised. This change of shape occurs due to passage of RBCs through slit

membranes of glomerulus and different osmolality. Some of these RBCs can be ring shaped with vesicle shaped protrusions on their surface and are called acanthocytes (G1 cells). Dysmorphic RBCs are best seen by phase contrast microscopy/ scanning microscope. Presence of dysmorphic RBCs is s/o glomerular origin however level of cut off required for dRBCs is not clear. In a study by Crop et al, at a 40% cutoff point the sensitivity of urinary dRBC for excluding glomerular disease in patients with urological diseases was 100%, while still 78% of the patients with a glomerular cause of hematuria had less than 40% dRBC. None of the patients with proven urological disease showed dRBC above the cutoff of 40%. Another study suggests that presence of >80% dysmorphic RBC or presence of >5 % acanthocytes is highly suggestive of glomerular and >80% normal RBCs is suggestive of lower tract bleeding.

INCIDENCE AND ETIOLOGY

In five population based studies, the prevalence of asymptomatic hematuria varied from 0.19- 16.1%. This wide variation is due to difference in age, sex, amount of follow up and number of screening studies performed. In older population with risk of urologic diseases the prevalence was as high as 21%.

Etiology of hematuria varies with age, sex and race. Common causes of hematuria are: urinary tract infections, stones, BPH, trauma, tumours, cyst rupture etc. Glomerular diseases form an important cause of both macroscopic and microscopic hematuria.

In a study of 105 young men referred to a hospital with asymptomatic hematuria (mean age 24.8 years [range 18-53], 10% of the participants were > 40 yrs), 46.7% (49 patients) had abnormal findings; 24.8% had nephrological causes and in another 21.9% hematuria was of urologic origin.

In a study by Messing et al involving healthy males >50 yrs of age, 1340 men were screened at home for hematuria with dipstick. 21.1% had at least 1 episode of hematuria. Of the 192 hematuria positive men who received a complete urological evaluation, 16 (8.3%) had urological cancers and 47 (24.5%) had other hematuria-causing diseases that required immediate treatment.

In children between 8 to 15 years, Bergstein et al observed microscopic hematuria in 4.1% of the participants and among adults the frequency of hematuria was reported between 2.4% to 31.1%; with higher rates in males over 60 yrs.

Table 1: Adult population (18-53 yrs) N= 105

Abnormalities	frequency
Glomerular Disease	26 (16.6%)
IgA nephropathy	16
PSGN	3
Thin basement membrane disease	2
MPGN	2
Interstitial nephritis	1
Urological Disease	23 (14.6%)
UTI	5
Trigonal Cystitis	5
Congenital Hydronephrosis	3
Urethral Stricture	3
Renal Scarring	3
Renal Calcifications	1
Cancer Of Renal Pelvis	1
Ureteric Stone	1
Bladder Cancer	1

Table 1 depicts the cause of asymptomatic microscopic hematuria as observed in an academic centre based study (involving referred patients).

Should all cases of asymptomatic microscopic hematuria be evaluated?

Hematuria without formed elements (blood cells casts) or proteinuria is called "isolated hematuria. In a study by Ritchie et al, among the 76 patients with microscopic hematuria who underwent some further investigations (all investigations excepting cystoscopy), abnormalities were found in 21 (28%); and among those who were fully investigated by examination of midstream urine, intravenous urography, and cystoscopy, abnormalities were found in 12 (50%). These included bladder neoplasms (two), epithelial dysplasia (one), staghorn calculi (one), and chronic reflux nephropathy (one). Hence All subjects with asymptomatic microscopic hematuria should be investigated.

Role of kidney biopsy in asymptomatic microscopic hematuria

A Japanese study by Hoshino et al. on patients with asymptomatic hematuria found 62% of the participants to have IgA nephropathy while 13% had Thin Basement Membrane Disease. However, in the study methodology there was no mention of any urologic evaluation prior to the renal biopsy. Majority of these did not warrant any specific therapy. Hence the role of renal biopsy in the management of these patients is contentious. In another study on the long term outcome of asymptomatic microscopic hematuria, only 28 of the total 90 patients underwent renal biopsy- the most common finding was a normal glomerulus while the second and 3rd most common finding were thin basement membrane disease (9/28) and IgA nephropathy (8/28) respectively. After a mean follow up of 5 years only one patient developed CKD (after

2.3 years). Interestingly 15 patients (17%) had complete resolution of hematuria. Hence, there is no consensus regarding the need and timing of renal biopsy in patients with asymptomatic microscopic hematuria. One can say that renal biopsy should not be the first investigation in these patients. We feel that all patients with isolated hematuria should be followed up. Those with persistent hematuria should have urological check. Renal biopsy should be resorted only if, hematuria is progressive or there is fresh appearance of proteinuria or renal functions are getting deranged.

Urologic evaluation principles¹

All patients with asymptomatic microscopic hematuria require evaluation. In older individuals even transient hematuria should raise the suspicion of malignancy. Hence, even a single episode of microscopic hematuria should prompt evaluation.

Radiologic evaluation is to be performed in all age groups. Following are the American Urology Association guidelines-

For Upper tract- (kidney +Pelvis & Ureter urothelium)-CT urography is recommended.

When CT is contraindicated in the patient, MR Urography can be done to delineate the upper urinary tract. When both CT and MRI are not possible, then USG and retrograde pyelogram may be performed for upper urinary tract evaluation.

For Lower tract (Bladder + Urethra) cystoscopy is the recommended modality.

Cystoscopy is also recommended in all patients >35 years of age or patients younger than 35 years but having risk factors for urothelial malignancy**.

Evaluation-includes evaluation of both upper and lower tract urothelium.

**Risk Factors for Urinary Tract Malignancy -

Male gender,

Age (> 35 years)

Past or current H/O smoking,

History of irritative voiding symptoms

History of pelvic irradiation

Occupational or other exposure to chemicals or dyes (benzenes or aromatic amines),

Analgesic abuse,

History of gross hematuria,

History of urologic disorder or disease

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

In patients with persistent microhematuria following

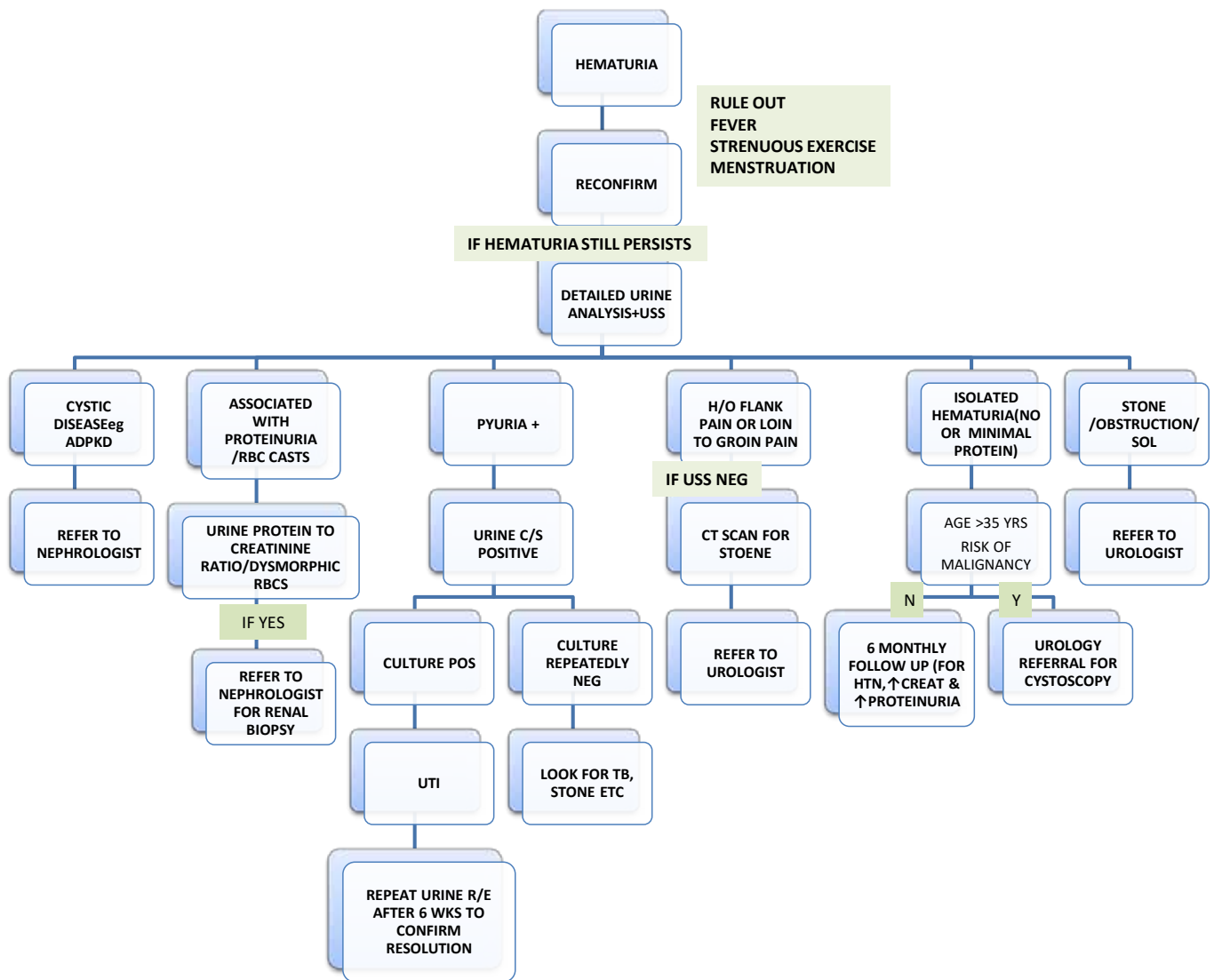


Fig. 1: An algorithm for hematuria

a negative work up or those with other risk factors for carcinoma in situ (e.g. irritative voiding symptoms, current or past tobacco use, chemical exposures) urine cytology may be useful.

Follow up of patients with a negative urologic workup

For persistent asymptomatic microhematuria after negative urologic work up, yearly urinalyses should be conducted. For persistent or recurrent asymptomatic microhematuria after initial negative urologic work-up, repeat evaluation within three to five years should be considered.

Approach to gross hematuria

The approach to gross hematuria remains practically the same as that to microscopic hematuria. The only difference is that here the emphasis shifts to urological causes from the glomerular causes. In a study in pediatric population 2/4 th of the participants were found to have urologic causes, 1/4th had glomerular causes and in 1/4 th the cause remained undiagnosed. Buntinx et al performed a meta-analysis to find out the diagnostic value of gross hematuria. Most of the studies included only adults. The pooled PPV

of gross hematuria for urological cancers was found to be 0.22 while the same in people older than 40 yrs was 0.44. According to AUA any adult with gross hematuria must receive a complete evaluation (CT Urography and Cystoscopy) for urological malignancy irrespective of age. There are only five glomerular conditions which can cause gross hematuria-IgA nephropathy, post infectious glomerulonephritis, pauciimmune glomerulonephritis, Alport's Syndrome and thin basement membrane disease.

APPROACH TO A CASE OF MICROSCOPIC HEMATURIA

Step 1

Confirm presence of hematuria. Fever, menstruation, exercise etc are common causes of transient hematuria. Urine should be retested after fever/ menstruation subsides.

Scenario 1

If patient has dysuria, fever, increased frequency and urine shows WBCs/WBC casts- urine culture should be done and patient be treated with suitable antibiotics on lines of UTI. A positive urine culture confirms the diagnosis of UTI. However, a negative urine culture does not rule

out the same because administration of antibiotics rapidly makes the urine culture sterile. However, if the suspicion of UTI is clinically low, then the patient should be evaluated for sterile pyuria which involves both urologic (for stone/tumor/genitourinary TB) and nephrology (acute interstitial nephritis) work up.

Scenario 2

If patient has flank pain or pain radiating from loin to groin, s/o nephrolithiasis, patients be subjected to USS/CT scan and referred to urologist. Recurrent stone formers should undergo metabolic evaluation. CT is much better modality for picking stone vis a vis USS.

Scenario 3

If patient is passing blood clots, it is most likely a urological problem e.g. bladder tumour, trauma, bladder stone etc. and patient needs referral to urologist.

Scenario 4

If urine shows dysmorphic RBCs, proteinuria, RBC casts etc. glomerular pathology is likely. A proteinuria of >2 gm is s/o glomerular pathology and such patients need renal biopsy and should be referred to Nephrologist.

Scenario 5

If patient has isolated hematuria or insignificant proteinuria (< 500 mg) and USS is normal. One should exclude urology cause. Many such patients have underlying IgA nephropathy or thin basement membrane disease or Alport's Syndrome and are unlikely to require any specific treatment even when diagnosed. Kidney biopsy in this setting is contentious and such patients need to be followed up periodically.

CONCLUSION

Microscopic hematuria is a common urinary abnormality across all age groups. Etiology varies with age and sex but Infections, stone disease and prostate related diseases are dominant causes. Patients with proteinuria, freshly diagnosed hypertension or deranged renal functions have generally an identifiable cause and need renal

biopsy. Every patient with persistent hematuria needs thorough evaluation. Despite thorough evaluation a large proportion still remain undiagnosed and need periodic follow up.

REFERENCES

1. Davis R, Jones JS, Barocas DA, Castle EP, Lang EK, Leveillee RJ, et al. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. *The Journal of Urology* 2012; 188(6 Suppl):2473-81.
2. Vehaskari VM, Rapola J, Koskimies O, Savilahti E, Vilska J, Hallman N. Microscopic hematuria in school children: epidemiology and clinicopathologic evaluation. *The Journal of Pediatrics* 1979; 95(5 Pt 1):676-84.
3. Messing EM, Young TB, Hunt VB, Roecker EB, Vaillancourt AM, Hisgen WJ, et al. Home screening for hematuria: results of a multiclinic study. *The Journal of Urology* 1992; 148(2 Pt 1):289-92.
4. Sparwasser C, Cimniak HU, Treiber U, Pust RA. Significance of the evaluation of asymptomatic microscopic haematuria in young men. *British Journal of Urology* 1994; 74:723-9.
5. Sklar DP, Diven B, Jones J. Incidence and magnitude of catheter-induced hematuria. *The American Journal of Emergency Medicine* 1986; 4:14-6.
6. Hockberger RS, Schwartz B, Connor J. Hematuria induced by urethral catheterization. *Annals of Emergency Medicine* 1987; 16:550-2.
7. Ritchie CD, Bevan EA, Collier SJ. Importance of occult haematuria found at screening. *British Medical Journal (Clinical Research Ed)* 1986; 292:681-3.
8. Crop MJ, de Rijke YB, Verhagen PC, Cransberg K, Zietse R. Diagnostic value of urinary dysmorphic erythrocytes in clinical practice. *Nephron Clinical Practice* 2010; 115:c203-12.
9. Hoshino Y, Kaga T, Abe Y, Endo M, Wakai S, Tsuchiya K, et al. Renal biopsy findings and clinical indicators of patients with hematuria without overt proteinuria. *Clinical and Experimental Nephrology* 2015; 19:918-24.
10. Chow KM, Kwan BC, Li PK, Szeto CC. Asymptomatic isolated microscopic haematuria: long-term follow-up. *QJM : monthly Journal of the Association of Physicians*. 2004; 97:739-45.