Step by Step

4 Steps: Getting to the Bottom of Hematuria

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Step 1: *Confirmation of hematuria*

A positive heme urine dipstick can be a common finding in asymptomatic adult populations. The incidence may vary from 5% to 13%, depending on the population characteristics.[1]

The sensitivity of the dipstick tests for heme is very high, with as few as two or more cells per high-powered microscopic field returning a positive test. Microscopic hematuria is defined as two to three red cells per high-powered field on urine microscopy.

A positive dipstick may reflect hemoglobin or myoglobin. The result of a positive dipstick should, therefore, be confirmed with microscopic exam to establish a true hematuria diagnosis.

The most frequent causes of microscopic hematuria in the asymptomatic adult are transient hematuria, such as menses or vigorous exercise, and urinary tract infections (UTI).

A finding of hematuria should be followed by a repeat dipstick one to two weeks later to look for transient hematuria. During the period between tests, patients should be advised to avoid strenuous exercise. Protein and leukocytes (± nitrites) may be concomitantly detected by dipstick, in which case quantification of proteinuria or urine culture for bacteria are required.

The incidence of a serious, underlying disease in young adults with isolated microscopic hematuria is between 2% and 3%, making it dif-

Jane's case

Jane, 29, required a medical exam for disability insurance. Her physical exam, including vital signs, was normal, as were her complete blood count and serum creatinine. However, urine dipstick for blood showed 2+ hematuria.

She has no family history of renal disease, is sexually active, smokes approximately half a pack of cigarettes a day for the past 10 years, and participates in regular physical activity. Other than birth control, Jane is not currently taking any medications.

- **Is this finding significant?**
- **What steps should be taken, if any, to investigate her "microscopic hematuria"?**

ficult to justify extensive investigation of all cases.[2] The incidence of more serious conditions increases with age, making age an important consideration when determining the need for further investigation.

Step 2: *Rule out glomerular disease*

The next step in the investigation of confirmed microscopic hematuria is to determine the site of the problem: glomerular versus non-glomerular bleeding.

The accompanying history is helpful, as are physical signs, such as:

- edema,
- hypertension,
- symptoms of a systemic inflammatory disease, and
- concomitant proteinuria on urine analysis.

Microscopic analysis reveals a glomerular etiology for microscopic hematuria through the presence of dysmorphic red cells ± red cell casts. Assessment of renal function by serum creatinine estimation should be undertaken in this setting. A decline in renal function warrants prompt referral to nephrology, as does significant proteinuria (> 500 mg/day).

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Table 1

Risk factors for developing renal carcinoma before age 50

- Family history
- Occupational exposure (*i.e.*, cadmium, asbestos, and petroleum)
- Smoking
- Chronic analgesic ingestion
- Acquired cystic kidney disease (in dialysis patients)
- Increased central adiposity (in females)

Step 3: *Rule out urologic malignancy*

Once glomerular causes of persistent microscopic hematuria have been ruled out, urologic malignancies are the next conditions to consider. Age is the most important risk factor for these malignancies.

Renal carcinoma

Ultrasonography should be performed in patients over 50 to screen for renal carcinoma.

In those under 50, abdominal radiograph or X-ray of the kidneys, ureter, and bladder (KUB) could reveal the most common cause of isolated non-glomerular hematuria in this age group: renal calculus.

There is debate regarding the use of ultrasound to screen for renal carcinoma in patients under 50 with isolated non-glomerular hematuria. Despite the lack of evidence to support screening in this population, many practitioners still advocate ultrasound screening, as renal carcinoma appears to be less clearly age-restricted than other urologic malignancies.

Table 2

Risk factors for developing uroepithelial malignancy before age 50

- Occupational exposure to dyes
- Smoking
- Chronic analgesic ingestion
- Previous treatment with cyclophosphamide

Table 1 lists risk factors for developing renal carcinoma at an earlier age.

Uroepithelial malignancies

More than 95% of uroepithelial malignancies occur over the age of 50.[3] Risk factors for developing uroepithelial malignancy at an earlier age are listed in Table 2.

If isolated non-glomerular hematuria is found in patients over 50, or in those under age 50 with risk factors, urology referral for cystoscopy is warranted. Patients with isomorphic macroscopic hematuria should also be referred for cystoscopy.

The role of urine cytology as a screening test is unclear. In patients at risk for uroepithelial malignancy, the sensitivity of urine cytology is too low to confidently exclude the diagnosis. In low-risk patients, urine cytology may be helpful in deciding if patients should be referred for cystoscopy.

The incidence of a serious, underlying disease in young adults with isolated microscopic hematuria is 2% to 3%.

Frequently Asked Questions

1. What are the most common causes of hematuria?

The most common causes are transient, such as menses and exercise hematuria, as well as UTIs.

2. When should I refer to a urologist?

Macroscopic hematuria, not due to a UTI, warrants referral. Those patients over 50 should also be referred because of the increase in incidence of urologic cancers. These are uncommon under age 50, however, the presence of risk factors in those under 50 warrants further investigation.

3. When should I investigate microscopic hematuria?

Once it is confirmed, red flags are raised in patients with microscopic hematuria when it occurs in association with proteinuria (> 500 mg/day), renal insufficiency, or hypertension, all of which are suggestive of glomerular disease and warrant referral to a nephrologist.

Prostate cancer

Prostate cancer is unusual under age 50. The merits of screening all males for prostate cancer are unresolved and will not be addressed here. If, however, a male over 50 (or over 45 with a family history of prostate cancer) is being investigated for isolated non-glomerular hematuria, screening for prostate cancer by prostate-specific antigen (PSA) and digital rectal exam (DRE) should be considered, particularly if there are associated flow-related symptoms.

Step 4: Followup

Patients with isolated glomerular microscopic hematuria should be followed at least annually to look for factors increasing their risk of developing renal failure (*e.g.*, the presence of hypertension, edema, proteinuria, elevated serum creatinine), which should prompt referral to a nephrologist.

Patients who develop isomorphic macroscopic hematuria should be referred for urologic assessment. D_x

Take-home message

What are the important steps in diagnosing hematuria?

- **Step 1:** Confirm the diagnosis via urine dipstick. A positive result warrants a repeat test one or two weeks later.
- **Step 2:** Rule out glomerular disease. A microscopic analysis reveals glomerular etiology through the presence of dysmorphic red cells ± red cell casts.
- **Step 3:** Rule out urologic malignancies, such as renal carcinoma, uroepithelial malignancy, and prostate cancer. Tests for these conditions include, ultrasonography, urine cytology, and PSA/DRE, respectively.
- **Step 4:** Followup. Patients with isolated glomerular microscopc hematuria should be followed annually. Patients who develop isomorphic macroscopic hematuria should be referred for urologic assessment.

References
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2. Mohr DN, Offord KP, Owen RA, et al: Asymptomatic microhematuria and urologic disease: A population-based study. JAMA1986; 256(2):224-9.
3. Connelly JE (eds. Black ER, Bordley DR, Tape TG, et al.): Microscopic Hematuria in Diagnostic Strategies for Common Medical Problems. Second Edition. ACP-ASIM, Philidelphia.