Evaluation and Workup of Hematuria in Adults

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DEFINITION

Hematuria is defined as the presence of red blood cells (RBCs) in the urine. It is classified as follows:

- **Microscopic Hematuria**
  
  Microscopic hematuria is defined as ≥3 RBCs per high-power field (×400 magnification) in a single properly collected urine sample.\textsuperscript{1}

- **Gross Hematuria**

  Gross hematuria is defined as blood in the urine visible by the naked eye. Patients often present to the emergency department or at the physician’s office after

KEY POINTS

- Hematuria is the presence of blood in the urine and can be stratified into glomerular or nonglomerular causes as well as microscopic or gross hematuria.
- Nonglomerular hematuria can represent urologic disease ranging from infection to trauma to malignancy and requires further workup by a urologist.
- The use of laboratory and imaging testing is necessary to discern the cause of hematuria especially in those with high risk for malignancy.
- Triple-phase computed tomography urography is the gold standard in initially visualizing the urinary tract for stones or other lesions in the upper and lower urinary tract.
- For asymptomatic microscopic hematuria, cystoscopy should be performed on all patients older than 35 years or those with risk factors for urothelial malignancy (ie, chemical exposure, smoking history).

KEYWORDS

- Adults
- Microscopic hematuria
- Gross hematuria
- Guidelines
- Evaluation
- Best practice

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such an episode. Gross hematuria must be differentiated from other causes of discolored urine. Causes of abnormal urine color are shown in Table 1.

**EPIDEMIOLOGY**

The incidence and prevalence of hematuria varies widely depending on age, gender, and the population screened. Britton and colleagues reported the prevalence between 13% and 20% in men older than 60 years; however, according to Messing and colleagues, microscopic hematuria (detected by urinary dipstick) was found in 10% to 21% of high-risk and asymptomatic men older than 50. The prevalence of microhematuria in adults ranges from 2.5% to 21.1%. Thorough examination and evaluation of these patients is necessary, as 5% of patients with microscopic hematuria and 20% to 40% of patients with gross hematuria are likely to have an underlying malignant condition.

**ETIOLOGY**

Hematuria can represent underlying disease, the causes of which can be benign or malignant. Microscopic hematuria is further classified into glomerular (hematuria from the glomeruli suggesting intrinsic renal disease and is not discussed further being beyond the scope of this article) managed by nephrologists and nonglomerular (hematuria from nonglomerular sites, such as renal pelvis, ureter, and bladder, suggesting a urologic etiology) managed by urologists. Glomerular from nonglomerular causes can be distinguished by the color or urine, presence/absence of RBC casts, degree of proteinuria, and presence of clots (Table 2). The most commonly reported causes of hematuria may include urinary tract infections (UTIs), urinary tract stones, bladder and kidney tumors, urethritis, benign prostatic hyperplasia (BPH), and prostate cancer.

The following are some of the common causes of hematuria classified by symptom and location (Table 3):

- **Infection:** cystitis, tuberculosis, prostatitis, urethritis, schistosomiasis.
- **Malignancy:** renal carcinoma, Wilms tumor, carcinoma of the bladder, prostate cancer, urethral cancer, or endometrial cancer.

<table>
<thead>
<tr>
<th>Color</th>
<th>Foods</th>
<th>Drugs</th>
<th>Condition/Substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red/Brown</td>
<td>Beets, blackberries, rhubarb, fava beans, aloe</td>
<td>Laxatives (eg, Ex-Lax phenolphthalein), tranquilizers (eg, chlorpromazine, thioridazine, propofol)</td>
<td>Porphyrin (eg, lead, mercury poisoning), globins (eg, hemoglobin, myoglobin)</td>
</tr>
<tr>
<td>Orange</td>
<td>Carotene-containing foods (eg, carrots, winter squash)</td>
<td>Beta carotene supplements, vitamin B supplements, warfarin, rifampin, Pyridium</td>
<td>Urochrome (eg, dehydration)</td>
</tr>
<tr>
<td>Green/Blue</td>
<td>Asparagus</td>
<td>Amitriptyline, indomethacin, cimetidine, promethazine</td>
<td></td>
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<tr>
<td>Black</td>
<td>Methyldopa</td>
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</table>
Trauma: renal tract trauma due to accidents, catheter, or foreign body; prolonged severe exercise; rapid emptying of an overdistended bladder (eg, after catheterization for acute retention).

Inflammation: postirradiation.

Structural: calculi (renal, bladder, ureteric), simple cysts, polycystic renal disease, BPH, congenital vascular anomalies.

Hematological: sickle cell disease, coagulation disorders, anticoagulation therapy.

Surgery: invasive procedures to the prostate or bladder.

Drugs: analgesics, anticoagulants, sulfonamides, cyclophosphamide, nonsteroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, penicillin (extended spectrum), quinine, vincristine.

Others: genital bleeding, menstruation, excessive exercise, Münchausen syndrome, or fabricated or induced illness by caregivers.

PATIENT HISTORY

Given the wide differential diagnosis of microscopic and gross hematuria, a thorough history, review of systems, and physical examination are essential in the evaluation of a patient with hematuria. History should be directed at using a system-based approach in conjunction with a localization-based approach to determine the cause of the hematuria. Ruling out major mimics of hematuria (beeturia, menses, drugs, vigorous exercise, trauma, or recent urinary instrumentation) should be considered, as it can prevent further unnecessary laboratory and imaging evaluation.

Important questions to include when taking a history:

- Have you experienced fever or chills?
  ○ Fever and chills could indicate an underlying UTI resulting in hematuria
- Do you have urinary frequency or urgency?
  ○ Irritative voiding symptoms (frequency or urgency) can be a sign of UTI or bladder malignancy
- Is the hematuria associated with pain?
  ○ Painless hematuria is more concerning for malignancy, whereas painful hematuria is more suggestive of an infectious or inflammatory cause
- Do you have flank pain? Radiation to the groin?
  ○ Flank pain and radiation to the groin can be indicative of ureteral obstruction or urinary tract stones
- When during urination does the blood appear?
  ○ Initial hematuria, blood or clots at the beginning of the urine stream, is a symptom of urethral cause
  ○ Terminal hematuria suggest prostatic or bladder neck source

<table>
<thead>
<tr>
<th>Table 2</th>
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<tbody>
<tr>
<td>Characteristics of glomerular and extraglomerular hematuria</td>
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<tr>
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<tr>
<td>Indication</td>
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<table>
<thead>
<tr>
<th>Location</th>
<th>Organ Site</th>
<th>Tumor/Malignancy</th>
<th>Inflammation</th>
<th>Stones</th>
<th>Anatomic Abnormality</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper urinary tract</td>
<td>Kidney</td>
<td>Renal cell carcinoma, renal pelvis urothelial cell carcinoma, renal lymphoma, angiomyolipoma, oncocytoma</td>
<td>Nephropathy, pyelonephritis, renal abscess, renal tuberculosis</td>
<td>Renal stones</td>
<td>Polycystic kidney disease, medullary sponge kidney, hydronephrosis, arteriovenous malformation</td>
<td>Hypercalciuria, hyperuricosuria, renal trauma, papillary necrosis, sickle cell disease, renal infarction</td>
</tr>
<tr>
<td></td>
<td>Ureter</td>
<td>Ureteral urothelial cell carcinoma</td>
<td></td>
<td>Ureteral stones</td>
<td>Ureteral stricture, fibroepithelial polyp</td>
<td>Ureteral polyp, ureter vascular/ileal fistula</td>
</tr>
<tr>
<td>Lower urinary tract</td>
<td>Bladder</td>
<td>Bladder urothelial carcinoma, bladder squamous cell carcinoma</td>
<td>Bacterial cystitis, tuberculous cystitis, radiation cystitis, <em>Schistosoma haematobium</em></td>
<td>Bladder stones</td>
<td>Vesico-ureteral reflux, cystocele, bladder papilloma, trabeculated bladder</td>
<td>Bladder diverticulum, interstitial fistula, endometriosis</td>
</tr>
<tr>
<td></td>
<td>Prostate</td>
<td>Prostate cancer</td>
<td>Prostatitis</td>
<td>Prostate stone</td>
<td>Benign prostatic hyperplasia</td>
<td>Prostatic trauma/ procedures</td>
</tr>
<tr>
<td></td>
<td>Urethra/Penis</td>
<td>Urethral cancer, penile cancer</td>
<td>Urethritis</td>
<td></td>
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</tbody>
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Table 3
Anatomic classification of causes of hematuria

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Blood equally dispersed throughout stream that does not clot signifies renal origin

- Is the hematuria cyclic in nature?
  - This can be a symptom of endometriosis or other gynecologic sources

- Have you lost weight?
  - Unintentional weight loss could signify underlying malignancy

- Are you training for a marathon, decathlon, or so forth?
  - New or vigorous exercise can be a cause

- Have you recently been in any accidents?
  - Blunt or penetrating trauma must be ruled out

- Have you traveled recently to regions in which schistosomiasis is endemic?
  - Schistosomiasis is associated with squamous cell carcinoma of the bladder

- Do you experience dribbling, weak stream, intermittent stream during urination?
  - These obstructive symptoms are associated with benign prostatic enlargement, but can often indicate urinary obstruction from bladder, prostate cancer, or urethral cancer

**Medications**

- Are you taking medications that may cause hematuria?
  - Analgesics, anticoagulants, sulfonamides, cyclophosphamide, or NSAIDs can commonly cause hematuria

**Past Medical History**

- Bleeding disorder or anticoagulation
  - Coagulopathies and arteriovenous malformations, history of nose bleeds, or hemoptysis are causes of hematuria

- Rule out infection (UTI):
  - Chronic cystitis/pyelonephritis, perinephric abscess can lead to bleeding

- Prior chemotherapy or radiation
  - Pelvic radiation and cyclophosphamide are associated with malignancy

- Urinary retention
  - Chronic indwelling catheter is a risk factor for malignancy

**Past Surgical History**

- Recent instrumentation/surgery
  - Catheter insertion/removal and so forth cause trauma and bleeding
  - Urinary tract surgery can be complicated by fistula formation
  - Chronic catheterization can increase the risk for squamous cell carcinoma of the bladder

**Social History**

- Are you a current or former smoker? Are you exposed to passive smoking at work or at home?
  - Smoking is strongly linked to bladder cancer

- Work in a field with exposure to chemicals or dye?
  - Chemical/dye exposure is a risk for genitourinary (GU) malignancy

**Physical Examination**

- Focused abdominal examination
  - Flank pain: suggestive of stone or malignant obstruction of kidneys
  - Flank mass: suggestive of renal malignancy
Suprapubic pain: suggestive of UTI
Suprapubic mass: suggestive of bladder malignancy
Evaluation for trauma (broken ribs, pelvic fracture, perineal/scrotal bruising)

- GU examination
  - Perineal pain: suggestive of prostatitis
  - Vaginal bleeding: possible cause of urine contamination

HEMATURIA WORKUP

After completing a thorough history and physical examination, patients without obvious mimics of hematuria require further evaluation. This must be performed in all patients with gross hematuria in the absence of infection, as well as in patients with microhematuria who are older than 35, or those with risk factors such as smoking, irritative voiding symptoms, exposure to schistosomiasis, or chemical exposure. Confirmation of microscopic hematuria should be performed using a properly collected urine specimen with a formal microscopic analysis with reporting of the number of RBCs per high-power field. All patients with irritative voiding symptoms (urinary urgency or frequency), dysuria, suprapubic pain/tenderness, or fevers, should undergo a urine culture to rule out UTI. Cytologic examination of cells in the urine should be done to evaluate for urothelial malignancy in all patients with gross hematuria, patients with microscopic hematuria and suspicion of bladder urinary malignancy, or microscopic hematuria with negative initial hematuria workup. An estimate of renal function should be obtained as part of the initial evaluation and may include blood urea nitrogen, creatinine, and calculated estimated glomerular filtration rate, because intrinsic renal disease can have consequences for renal-related risk during the radiographic evaluation.\(^1\) Once laboratory tests have been performed, radiographic studies are required to further work up causes of hematuria. These consist of intravenous urography, computed tomography (CT) urography, magnetic resonance (MR) urography, noncontrast CT + retrograde pyelogram + renal ultrasound. Direct visualization of the bladder and urethra (lower urinary tract) is also achieved by imaging with cystoscopy, which is oftentimes performed in the clinic using a flexible fiberoptic cystoscope.

The workup of hematuria includes the following:

- Urine studies:
  - Urine culture (if symptomatic for UTI)
  - Urine cytology to evaluate for urothelial cell carcinoma
  - All patients with gross hematuria, patients with microscopic hematuria and suspicion of bladder urinary malignancy, or microscopic hematuria with negative initial hematuria workup
- Cross-sectional imaging of the abdomen and pelvis with delayed contrast imaging
  - CT urogram of the abdomen/pelvis preferred imaging modality
  - Allows for evaluation of the kidney and ureter (upper urinary tract)
- Cystoscopy
  - Allows for direct visual evaluation of the urethra and bladder (lower urinary tract)

Indicated cases of hematuria require prompt urologic referral for timely care and appropriate evaluation, as urologists are best able to interpret appropriate radiographic imaging and perform cystoscopy.
LABORATORY TESTING

- Sample collection: Appropriate and contamination-free sample collection steps
  - (lid of the sample collection vial to be covered as soon as collected to avoid oxidation).

- Urinalysis
  - Dipstick analysis: Dipstick analysis is the initial first-line test to diagnose hematuria. The sensitivity of a urine dipstick test for blood varies from 91% to 100%, and the specificity varies from 65% to 99%. The test detects the peroxidase activity of RBCs; hence, hemoglobin and myoglobin can cause a false-positive result. Other causes of false-positive results may include dehydration, exercise, povidone iodine, and oxidizing agents, as well as semen in the urine causing a heme reaction. Causes of false-negative results include vitamin C (a reducing agent) and air exposure. Due to these false positives and negatives, as per the American Urologic Association (AUA) guidelines, microscopic examination should confirm the findings.
  - Microscopic analysis: Microscopic analysis is the gold standard tool to diagnose microscopic hematuria, not urine dipstick. Most providers will send out their microscopic evaluations to a laboratory; however, some providers will prepare and interpret their microscopic analyses in the clinic with a microscope. When performing urine microscopy, proper care should be taken in preparing the sample. A fresh sample of 10 to 15 mL should be centrifuged according to laboratory standards. The urine microscopic evaluation not only confirms hematuria but also helps differentiate glomerular from nonglomerular sources of bleeding. In nonglomerular hematuria, the RBCs tend to be homogeneous and normal in shape. Blood clots do not occur in glomerular hematuria because of the presence of urokinase and tissue-type plasminogen activators in the glomerular filtrate. RBC casts are virtually pathognomonic for glomerular hematuria, because the matrix of the cast is Tamms-Horsfall protein, which is secreted by the distal tubule. There is also a possibility that urine dipstick may be more accurate than urine microscopy when the urine is very dilute and has a specific gravity of less than 1.007. In case of diluted urine, RBCs may lyse and not be visible, causing the urine microscopic examination to be falsely negative for hematuria.

- Urine culture: It is prudent to obtain a urine culture in patients with hematuria, particularly from those with irritative voiding symptoms or a history of urinary tract infection.

- Urine cytology: Cytology helps in determining the presence of cancer cells in the urine. The sensitivity for checking voided urine for abnormal cells ranges from 66% to 79% and the specificity ranges from 95% to 100% in case of bladder cancer. Due to lack of reliability in patients with microscopic hematuria, it is recommended to perform urine cytology in patients with suspicion of bladder urinary malignancy or with an initial negative hematuria workup. All patients with gross hematuria should undergo urine cytology evaluation.

IMAGING

There are various imaging modalities used in evaluation of hematuria that can be used to image the urinary tract. Generally, these imaging modalities allow for
diagnosis of upper urinary tract (kidney and ureter) pathology, whereas lower urinary tract (bladder and urethra) pathology is diagnosed via direct visualization with cystoscopy.

Given its relatively high sensitivity and specificity, CT urography (CTU) is the preferred technique for evaluation of hematuria. CTU of the abdomen and pelvis consists of a noncontrasted CT (evaluation for renal/ureteral/bladder stones), a contrasted CT (evaluation for enhancing renal masses), and a delayed phase (evaluation for renal pelvis and ureteral masses). Many patients have an iodinated contrast allergy or renal insufficiency and cannot undergo contrasted imaging and thus MR urography or non-contrasted CT scan + retrograde pyelogram + renal ultrasound should be considered.

- Radiographic testing
  - Intravenous urography (IVU) (oldest method): IVU (also known as intravenous pyelography or IVP) has been the traditional and oldest imaging technique for evaluating hematuria. However, IVU may miss smaller renal masses, with sensitivity of 21%, 52%, and 85% for masses smaller than 2 cm, 2 cm to 3 cm, and larger than 3 cm, respectively, when compared with contrast-enhanced CT. IVU also cannot distinguish solid from cystic masses, requiring another imaging technique, such as ultrasound or CT, to further characterize the lesion. Further, IVU has relatively low sensitivity of 52% to 59% for detecting urinary tract stones.
  
  - CT urography (replaced IVU): CT of the kidneys and urinary tract is better than ultrasound in detecting stones in patients with hematuria and it has the highest sensitivity of 94% to 98%. CTU is typically performed in noncontrast/contrast/delayed stages. Noncontrast helical CT is excellent for detection of urinary stones and hydronephrosis. Contrast CTU has increasingly superseded IVU when a urologic cause for hematuria is suspected, as a result of its higher accuracy in detecting lesions in the renal parenchyma and the rest of the urinary tract. It involves the injection of iodinated contrast media, with subsequent high resolution nephrogenic phase to evaluate renal parenchyma, pelvis and ureter for neoplastic lesions. This is followed by a delayed excretory phase to examine the lower tract including bladder and urethra for filling defects. Important limitations of CTU include radio-sensitive populations (eg, pregnant women), as well as patients with renal insufficiency or allergies to contrast media.

- MR urography: For patients with relative or absolute contraindications to CTU, such as renal insufficiency, contrast allergy or pregnancy, cross-sectional imaging alternatives exist in the way of MR urography with/without gadolinium contrast. Although it is poor at detecting stones, its sensitivity for detecting renal lesions is greater than 90% and is an acceptable substitute. Currently, the US Food and Drug Administration warns against the use of gadolinium-based contrast agents in patients with a glomerular filtration rate less than 30 mL per minute per 1.73 m² due to the risk of nephrogenic systemic fibrosis estimated to be 4%.
  
  - Noncontrasted CT + Retrograde Pyelogram + Renal ultrasound:
    Delayed excretory cross-sectional abdominal and pelvic imaging is necessary to evaluate the upper urinary tract and exclude upper tract malignancies. If contraindications to MR exist, such as metal in the body, a
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final alternative of noncontrasted CT with retrograde pyelogram and renal ultrasound can be used.

- **Endoscopic testing**
  - Cystoscopy
    
    The accepted reference standard for examining the bladder and urethra in patients with hematuria is direct visualization with flexible or rigid cystoscopy. Cystoscopy is recommended by the AUA guidelines in all patients at least 35 years of age with microhematuria and in all patients with gross hematuria. For patients younger than 35 with microhematuria, cystoscopy may be performed at the discretion of the clinician based on the presence of risk factors for malignancy.

    For all patients with microscopic hematuria, negative imaging, negative urine cytology, and low risk for malignancy, the AUA does recommend cystoscopy, due to its low morbidity and its unique ability to visualize the urinary tract.

With this evaluation strategy, a cause for hematuria is identified in roughly 57% of patients with microhematuria and 92% of patients with gross hematuria. Malignancy is identified in approximately 3% to 5% of patients presenting with microhematuria and 23% of patients presenting with gross hematuria.

**FOLLOW-UP**

Following an unrevealing workup for hematuria, a urinalysis with microscopic analysis should be checked annually for at least 2 years. Patients with persistent hematuria after a negative initial evaluation warrant repeat evaluation for 3 to 5 years, especially in those with risk factors for urologic malignancy.

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**Box 1**

Recommendations (American Urologic Association guidelines)

1. The assessment of the patient with asymptomatic microhematuria should include a careful history, physical examination, and laboratory examination to rule out benign causes, such as infection, menstruation, vigorous exercise, medical renal disease, viral illness, trauma, or recent urologic procedures.

2. Once benign causes have been ruled out, the presence of asymptomatic microhematuria should prompt a urologic evaluation.

3. The presence of dysmorphic red blood cells, proteinuria, cellular casts, and/or renal insufficiency, or any other clinical indicator suspicious for renal parenchymal disease warrants concurrent nephrologic workup but does not preclude the need for urologic evaluation.

4. Microhematuria that occurs in patients who are taking anticoagulants requires urologic evaluation and nephrologic evaluation regardless of the type or level of anticoagulation therapy.

5. A cystoscopy should be performed on all patients who present with risk factors for urinary tract malignancies (eg, irritative voiding symptoms, current or past tobacco use, chemical exposures), regardless of age.
6. The initial evaluation for asymptomatic microhematuria (AMH) should include a radiologic evaluation. Multiphasic computed tomography (CT) urography (without and with intravenous contrast), including sufficient phases to evaluate the renal parenchyma to rule out a renal mass and an excretory phase to evaluate the urothelium of the upper tracts, is the imaging procedure of choice because it has the highest sensitivity and specificity for imaging the upper tracts.

7. For the urologic evaluation of AMH, a cystoscopy should be performed on all patients aged 35 years and older.

8. The use of urine cytology and urine markers (NMP22, BTA-stat, and UroVysion fluorescence in situ hybridization) is NOT recommended as a part of the routine evaluation of the patient with AMH.

9. For persistent AMH after negative urologic workup, yearly urinalyses should be conducted.


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**Guidelines for Workup for Microscopic Hematuria**

Various associations, such as the AUA and the American Family Physician, have published peer-reviewed, evidence-based guidelines for hematuria. These guidelines overall generally share a similar evaluation strategy with minor differences. For a summary flow chart of the AUA microscopic hematuria guidelines, see Boxes 1 and 2, Fig. 1.

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**Box 2**

**Clinical pearls/handy tips**

- Even if a dipstick test for hematuria is positive, a key question is whether this truly represents blood in the urine versus free myoglobin or hemoglobin. Confirmation of positive dipstick test should be performed with a microscopic analysis of the urine.

- The combination of hematuria plus proteinuria suggests glomerular disease and prompts further evaluation by a nephrologist.

- Many food and drugs either cause hematuria or discolor the urine and should be considered in the evaluation of hematuria.

- Smoking, heavy analgesic use, age older than 35, chemical exposure, and chronic cystitis or indwelling foreign body increase urinary tract tumor risk.

- All patients with gross hematuria, microscopic hematuria in those older than 35, or with risk factors (smoking, irritative voiding symptoms, or chemical exposure) should undergo prompt hematuria workup by a urologist.

- Hematuria workup consists of the following:
  - Urine cytology
    - All patients with gross hematuria, patients with microscopic hematuria and suspicion of bladder urinary malignancy, or microscopic hematuria with negative initial hematuria workup.
  - CT urography (preferred)
  - Cystoscopy

- Before referral to a urologist, referring providers may obtain CT urography after an estimate of renal function and a urine culture to expedite evaluation.
SUMMARY

The etiologies for gross and microscopic hematuria are vast and include multiple systems in numerous anatomic locations along the urinary tract. Organization of these etiologies using a combination of systems and anatomic approach can help the provider make the appropriate diagnosis and treatment. During the initial evaluation of the patient it is important to consider the mimics of hematuria to avoid unnecessary laboratory and imaging evaluation: typical foods such as beets and blackberries; drugs and supplements like NSAIDs, warfarin, and vitamin B; processes including dehydration, exercise and menses. Malignancy is a common cause of hematuria and it is paramount to identify risk factors such as a history of current or past tobacco use, chemical or dye exposure, or irritative voiding symptoms. Once mimics have been excluded and a diagnosis of gross hematuria or microscopic hematuria is established, it is imperative that one appropriately receive prompt evaluation by a urologist to work up hematuria with appropriate cross-sectional imaging, cystoscopy, and possible urine cytology.

Fig. 1. Diagnosis, evaluation, and follow-up of AMH. a The threshold for reevaluation should take into account patient risk factors for urologic pathologic conditions such as malignancy. HPF, high-power field; MH, microhematuria; UA, urine analysis; US, ultrasound. (From Davis R, Jones JS, Barocas DA, et al. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. J Urol 2012;188:2473–81; and Courtesy of American Urological Association Education and Research, Inc, 2012.)
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