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Practical CE Newsletter for Clinicians

Hematuria: Updates in Management and Considerations for the Obstetrician/Gynecologist

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Learning Objectives: *After participating in this continuing professional development activity, the provider should be better able to:*

1. Outline the diagnosis of gross and microscopic hematuria based on standard criteria.
2. Identify patients who are at increased risk for urinary tract malignancy.
3. Explain assessment of patients with hematuria based on risk stratification.

Key Words: Gross hematuria, Hematuria, Microscopic hematuria

Hematuria is defined as the presence of red blood cells (RBCs) in the urine. Clinically, it is classified as either macroscopic (gross) or microscopic. With gross hematuria, urine is visibly discolored by blood. Microscopic hematuria is often identified incidentally when urine is being evaluated for another indication. Multiple definitions of microscopic hematuria have existed over the years. The standard definition of microscopic hematuria, established by the American Urological Association (AUA), is 3 or more RBCs per high-powered field (HPF) on microscopic evaluation of a single, properly collected urine specimen in patients without another apparent benign cause of the blood.[1]

Although benign causes are numerous and common, hematuria can be a clinical indicator of urinary tract malignancy. Only a small proportion of women with microscopic hematuria are likely to have an underlying urinary tract malignancy.[2] To minimize the risks of overevaluation, a patient-specific approach to identify women at high risk for urinary tract malignancy is recommended.[1,3] Still many patients, especially women, do not undergo evaluation, potentially delaying diagnosis.[4-6] Obstetrician/gynecologists (OB/GYNs) have the opportunity to identify high-risk women with hematuria and ensure appropriate evaluation, which may improve patient outcomes.

The goal of this article is to review diagnostic criteria for hematuria, describe risk factors for urinary tract malignancy, and review relevant changes to the recommended evaluation for microscopic hematuria based on patient-specific risk stratification.

Prevalence

Hematuria is a common condition. The prevalence of microscopic hematuria ranges from 2.4% to 31.1%.[7] This wide variation is likely due to factors such as sex, age, and nature of the heterogeneous group characteristics of the multiple studies. A study of a large database of only women evaluated more than 3 million urinalyses (UAs) and demonstrated 20% had evidence of microscopic hematuria (with or without known benign cause).[8] Given how common

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microscopic hematuria is, OB/GYNs are likely to encounter this clinical situation frequently.

Potential Causes of Hematuria

The differential diagnosis of hematuria is quite extensive. Although a comprehensive list is beyond the scope of this article, it is important to remember that hematuria can originate from anywhere along the genitourinary system including kidneys, ureters, bladder, and urethra. The most common etiologies include urinary tract infections (UTIs), urolithiasis, urothelial cancer, and renal disease. Potential renal sources include both glomerular (eg, glomerulonephritis) and nonglomerular (eg, polycystic kidney disease) conditions. Other notable causes include hematologic sources, such as sickle cell disease or bleeding dyscrasias (eg, hemophilia), vascular sources, such as hemangioma, and trauma (eg, exercise-induced).

Gynecologic causes should be considered and evaluated if suspected. Menstrual or intermenstrual bleeding should be ruled out, as vaginal bleeding can often contaminate urine samples. Urethral prolapse or diverticulum, genitourinary syndrome of menopause, pelvic organ prolapse, and sequelae from prior pelvic surgeries such as prior incontinence or prolapse surgeries with mesh should also be considered.

Guidelines for Screening and Evaluation of Hematuria

Routine screening for urinary tract malignancy is generally not recommended in low-risk women. The US Preventive Services Task Force in 2011 concluded there was insufficient evidence to assess the balance of benefits and harms in screening for bladder cancer in asymptomatic adults.[9] If screening is offered, clinicians should understand the uncertainty about the balance of benefits and harms and counsel patients regarding this. The American College of Physicians does not recommend that clinicians use screening UA for cancer detection in asymptomatic adults.[10] Although it is not recommended to screen for malignancy, many patients may undergo routine urine testing in primary care and OB/GYN offices with an incidental finding of microscopic hematuria.

Many medical organizations including the American College of Obstetricians and Gynecologists (ACOG), the American Urogynecologic Society (AUGS), the AUA, and other international medical groups recommend evaluation of microscopic hematuria.[1,3,11] Given the multitude of organizations with recommendations, there are slight differences. The ACOG and AUGS committee opinion was published in 2017 in response to AUA guidelines from 2012 recommending evaluation (cystoscopy and CT urogram) for all patients older than 35 years with microscopic hematuria. The ACOG considers the decreased risk of urinary tract malignancy in women and the risk-benefit ratio of diagnostic testing, such as CT, and recommends that asymptomatic, low-risk, women aged 35 to 50 years with no history of smoking undergo evaluation only if they have more than 25 RBCs per HPF.

In 2020, the AUA updated its guideline for evaluation and management of microscopic hematuria.[1] The available evidence to inform these recommendations includes many studies that are observational, have small sample sizes or potential confounders, and most significantly are largely composed of male patients. Compared with the guideline from

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Table 1. Risk Factors for Urinary Tract Malignancy

Age >50
History of gross hematuria
Smoking history
Irritative lower urinary tract symptoms
Male sex
Degree of microscopic hematuria
Persistence of microscopic hematuria
Prior pelvic radiation therapy
Family history of urinary tract malignancy or Lynch syndrome
History of cyclophosphamide/ifosfamide chemotherapy
Occupational exposure to benzene chemicals or aromatic amines

2012, the 2020 AUA guideline recommends considering patient risk factors for urinary tract malignancy; therefore, it now includes female sex as recommended by the ACOG and the AUGS.[3,4] Based on presence or absence of risk factors, patients are stratified into low-, intermediate-, and high-risk groups. Individualized diagnostic testing strategies are based on risk. Use of this method balances the likelihood of malignancy with risks and costs associated with diagnostic testing. Further details regarding risk stratification and diagnostic evaluation are described later.

Risk Factors for Urinary Tract Malignancy

Urinary tract malignancy is the most concerning etiology for hematuria, and the reason for which evaluation is recommended. Bladder cancer is the more common urinary tract malignancy, followed by renal cancer. Table 1 lists several risk factors for malignancy of the renal pelvis, ureter, and bladder.

Smoking

The most significant risk factor is smoking. Current and past history of tobacco use both increase risk. Patients who smoke have a 2 to 4 times higher risk of developing urinary tract malignancy compared with nonsmoking patients.[12] The risk increases with the duration and quantity of smoking. Even those who have stopped smoking still have a higher risk than those who have never smoked before.[13]

Gross Hematuria

Gross hematuria is a risk factor for malignancy. The risk of bladder cancer is 13% in patients with gross hematuria compared with 3% in patients with microscopic hematuria.[14]

Sex

Women are at a decreased risk for urinary tract malignancies compared with men. Regardless of sex, bladder cancer is more common than renal cancer. When stratifying for sex, women have a decreased risk for urinary tract malignancies compared with men. When evaluating only women, there is a higher incidence of renal cancer than bladder cancer. SEER data reveal the incidence rate for renal cancer in women is 11.2 per 100,000 women compared with 8.5 per 100,000 women for bladder cancer.[15] Bladder cancer accounts for 2% of cancer cases in women, compared with 6% for men.[16] Likely due to delayed diagnosis, women with bladder cancer have more advanced disease at time of diagnosis and have less favorable outcomes compared with men.[15] Although not well studied, trans-woman patients may be at increased risk for malignancy, especially bladder cancer. Despite the lack of evidence, this should be considered if microscopic hematuria is diagnosed in this patient population.

Age

Age is an important risk factor for urinary tract malignancy. The rate of detection of urinary tract malignancy in women younger than 40 years with microscopic hematuria was 0.02%. The rate among women older than 40 years was 20 times higher, but still only 0.4%.[17] Age of 50 years or older has been found to be a strong predictor of cancer.[18]

Family History of Cancer

Some genetic syndromes predispose to an increased risk of urinary tract malignancy. Patients with Lynch syndrome have up to a 7% risk of bladder cancer.[19] There are also several known genetic renal tumor syndromes, which include Von Hippel Lindau, Birt-Hogg-Dubé, hereditary papillary renal cell cancer, and tuberous sclerosis.[1]

Other risks

Certain occupational exposures increase risk for urinary tract malignancy. Patients employed in manufacturing, oil/petroleum workers, and hairdressers may be at increased risk secondary to the exposure to certain chemicals such as benzenes and aromatic amines. Additional risks include exposure to chemotherapeutic agents such as cyclophosphamide and ifosfamide, prior pelvic irradiation, and chronic indwelling catheters.

Diagnosis and Evaluation

Clinical presentations of hematuria vary. Patients with gross hematuria usually seek immediate evaluation, as discoloration of urine may be alarming. Patients with gross hematuria may or may not present with other signs or symptoms. Common clinical scenarios in which patients present with gross hematuria include UTIs and urolithiasis. In the absence of these conditions, gross hematuria is concerning for urinary tract malignancy and should elicit timely evaluation and referral.

In contrast, microscopic hematuria is often identified incidentally on UA when urine is being evaluated or screened for another indication. Urine screening is often performed in physician offices. In particular, OB/GYNs, who are often the primary health care provider for women of reproductive age, frequently obtain UAs to assess many different types of genitourinary symptoms.

A detailed history and physical examination are initial steps to identify the etiology of hematuria. This also is necessary to accurately assess risk in patients with microscopic hematuria so that appropriate evaluation and referral can be obtained.

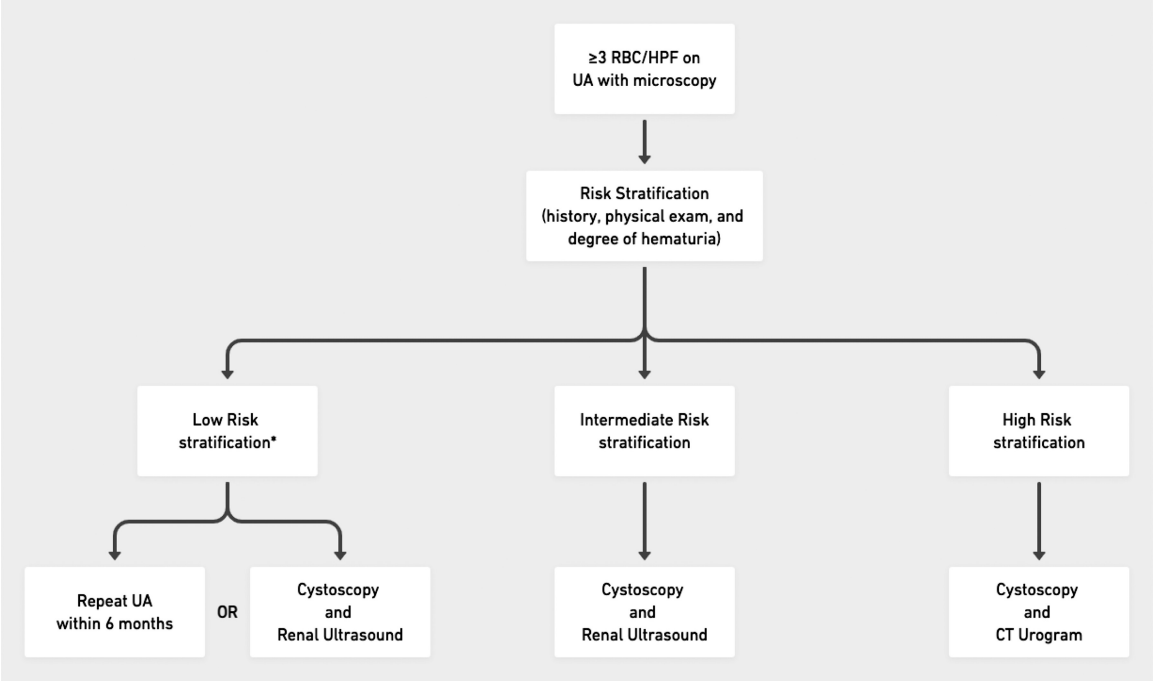

Figure 1. Simplified algorithm for evaluation of microscopic hematuria. *ACOG Committee Opinion: women younger than 50 year with no history of smoking and less than 25 RBCs/HPF are considered low risk and do not need evaluation. In this area of discrepancy between guidelines, shared decision-making should be utilized with patients. Adapted from Barocas DA, et al.[1]

Associated symptoms should be assessed, specifically pain or bladder symptoms, as they can reveal probable cause and the most appropriate path for evaluation. Symptoms such as incontinence, urinary urgency, and urinary frequency are common in women. New-onset symptoms of urinary urgency or urinary frequency should be considered irritative bladder symptoms. A review of a medical and surgical history is necessary to determine risks of renal disease, malignancy, or gynecologic and genitourinary causes. A menstrual history is essential to determine whether there is likely menstrual containment in the urine.

The physical examination should include assessment of blood pressure, cardiovascular examination, abdominal examination, and pelvic examination. The pelvic examination is key to identify alternate sources of hematuria, such as vulvovaginal atrophy or other vulvovaginitis, urethral prolapse, uterovaginal prolapse, or uterovaginal bleeding. If patients are not able to provide a clear history regarding the source of blood, uterine or rectal sources could be considered.

Evaluation of Urine

A voided midstream clean-catch urine sample is considered adequate for urine specimen collection. A midstream sample can be difficult for some patients to provide. Menstrual bleeding, vaginitis, significant pelvic organ prolapse, and body habitus can prevent adequate collection. Collection of a urine specimen by urethral catheterization could be considered in certain clinical scenarios, such as when the source of bleeding is unclear, with severe atrophic changes, significant pelvic organ prolapse, and with patients who have repeated difficulty collecting a midstream clean-catch specimen. If possible, providers should defer collection in menstruating patients.

Normal urine color varies depending on concentration. In patients who are well hydrated, dilute urine may appear nearly colorless, whereas with dehydration, concentrated urine may appear dark yellow or amber in color. As little as 1 mL of blood in 1 L of urine will be visible to the human eye, and can alter the color of urine.[20] Red, pink, or brown colored urine often suggests gross hematuria.

Several medications and foods are known to cause pigmented urine, which may be mistaken for hematuria. Foods, such as rhubarb and beets, and medications, including rifampin and phenazopyridine, can discolor the urine, which may be mistaken for hematuria. Other causes for discolored urine can include myoglobinuria and hemoglobinuria. Confirmation should be made by history and urine testing.

Urine Dipstick Analysis

The urine dipstick is commonly used to evaluate urine. It provides a quick assessment of urinary characteristics using colorimetric pads contained on a single test strip.[21] The dipstick test detects heme, which is the iron-containing portion of hemoglobin. The dipstick measures peroxidase activity. Heme is a pseudoperoxidase and will result in a color change on the dipstick. The urine dipstick is sensitive enough to detect 1 to 2 RBCs/microscopic HPF when examined within 2 hours of collection.[20] It is relatively inexpensive, easily available and performed frequently as a screening test. Other substances in addition to urinary RBCs may cause a positive result, including myoglobin, free hemoglobin, semen, alkaline urine, and oxidizing agents (eg, povidone iodine) contained in solutions used to cleanse the perineum. False-negative results are unusual. It is necessary to confirm any heme positive result of a

dipstick test with urine microscopy. Results of dipstick testing alone cannot be used to diagnose microscopic hematuria.

Urine Microscopy

Microscopic examination of the urine sediment provides additional data beyond dipstick results. After urine sediment is isolated by centrifuge, it is then prepared and can be visualized under the microscope.[22] Examination of urine sediment can be completed on an automated platform, but is often performed by a trained clinician. Urine microscopy is needed to confirm the presence of RBCs as suggested by urinary dipstick or a history of pink-tinged urine. This procedure can also identify other cellular elements including white blood cells and epithelial cells. The number of RBCs is quantified under HPF. This is necessary to make the diagnosis of microscopic hematuria.

Urine microscopy may reveal other cellular components, microorganisms, or crystals, which can provide additional information as to the source of hematuria. Dysmorphic appearing RBCs indicate a renal/glomerular source; this usually occurs with other abnormal urine and laboratory findings including cellular casts, proteinuria, and possibly impaired renal function. Pyuria and bacteria suggest an infectious source such as cystitis or pyelonephritis and necessitate further testing with urine culture. Crystals may be suggestive of urolithiasis, although they can be observed in normal patients.

Other Urine Tests

Urine cytology and urine-based tumor markers are not recommended for the routine evaluation of asymptomatic microscopic hematuria.[10,11] Urologists may consider use of these tests in certain high-risk patients. Cytology may be useful in patients with persistent microscopic hematuria after a negative workup and irritative voiding symptoms or other risk factors for carcinoma in situ.

Risk Stratification and Diagnostic Evaluation

After diagnosis has been confirmed, other conditions ruled out, and risk factors for urinary tract malignancy assessed, patients can be categorized as low (<1%), intermediate (1%–2%), or high (up to 10%) risk for malignancy.[1,14,18] The AUA recommendation for risk stratification is shown in Table 2.

Appropriate risk stratification guides next steps for recommended evaluation. The 2020 AUA guideline has a few important changes related to recommendations for evaluation. The 2020 AUA guideline has a few important changes to recommendations for evaluation, and a simplified algorithm is displayed in Figure 1. These include:

1. Low-risk patients can be offered *either* repeat UA in 6 months *or* evaluation with cystoscopy and renal ultrasound.
2. Intermediate-risk patients should be evaluated with cystoscopy and renal ultrasound.
3. High-risk patients should be evaluated with cystoscopy and CT urogram.

Table 2. AUA Risk Stratification for Urinary Tract Malignancy

Low risk (must have all of the following)
Female age <50; male age <40
Never smoker or <10 pack-yr
3–10 RBCs/HPF on 1 UA
No additional risk factors for urinary tract malignancy
No prior episodes of MH
Intermediate risk (if any of the following)
Female age 50–59; male age 40–59
10–30 pack-yr smoking
11–25 RBCs/HPF on 1 UA
≥1 additional risk factors for urinary tract malignancy
Previously low risk, no prior evaluation, and 3–25 RBCs/HPF on repeat UA
High risk (if any of the following)
Female and male age ≥60 yr
>30 pack-yr smoking
>25 RBCs/HPF on 1 UA
History of gross hematuria
Previously low-risk, no prior evaluation, and >25 RBCs/HPF on repeat UA

AUA, American Urological Association; HPF, high-powered field; MH, microhematuria; RBC, red blood cell; UA, urinalysis.

There is a notable discrepancy between the 2020 AUA guideline and the 2017 ACOG committee opinion for a small subset of women younger than 50 years who have no risk factors and have less than 25 RBCs per HPF. The risk of urinary tract malignancy in this group of woman patients is less than or equal to 0.5%.[17] The committee opinion recommends these patients do not require evaluation whereas the AUA would recommend either repeat UA or cystoscopy with renal ultrasound. This is an area where shared decision-making should be used with patients.

Information regarding each diagnostic evaluation tool is described next.

Cystoscopy

Cystoscopy is an office-based procedure to assess the urothelial lining of the bladder and urethra. It is the optimal test to detect bladder cancer. The majority of malignancy diagnosed during a workup for hematuria is bladder cancer; therefore, the importance of a cystoscopy cannot be overstated.[6] Suspicious lesions seen during cystoscopy can be resected endoscopically to provide diagnosis and treatment. Risks of cystoscopy are low, although many patients report postprocedure dysuria and there is a low risk of UTI.[23] Cystoscopy is part of the evaluation for low-, intermediate-, and high-risk groups, and for patients with gross hematuria.

Renal Ultrasound

Renal ultrasound has adequate sensitivity to detect upper urinary tract malignancy, especially renal cell carcinoma, nearly reaching the sensitivity of a CT urogram.[24] It does have limitations to detect urothelial carcinoma of the ureter

and renal pelvis. Benefits of ultrasound include lack of ionizing radiation, and lower costs. Renal ultrasound should be used for upper tract imaging in low-risk and intermediate-risk patients with microscopic hematuria.

CT Urography

CT urography consists of 3 phases and requires administration of IV contrast. The first noncontrast phase detects urolithiasis. The second contrast-enhanced phase evaluates the renal parenchyma for abnormalities. The third phase captures delayed images to evaluate the renal pelvis and ureters. Given the multiphase images needed for complete evaluation of the upper urinary tract, care should be given to include the correct indication for CT scan. Risks of CT urography include contrast-associated nephropathy, adverse reactions related to contrast material, and potential increased risk of malignancy associated with radiation exposure.[25,26] CT urography is recommended to evaluate high-risk patients with microscopic hematuria and patients with gross hematuria.

Other Testing

Other alternative testing, such as magnetic resonance (MR) urography, could be considered in certain clinical situations, such as a high-risk patient with severe contrast dye allergy.

Referral

Referral to urology or urogynecology for cystoscopic evaluation is indicated in the setting of gross hematuria (without UTI), and confirmed microscopic hematuria (except for low-risk patients who may opt for repeat UA). Renal imaging studies, either renal ultrasound or CT urography, performed before or at time of referral may facilitate patient care.

Nephrology referral should also be considered if intrinsic renal disease is suspected. Consideration should be given with new findings of significant proteinuria, dysmorphic RBCs or RBC casts on urine microscopy, or laboratory findings of markedly impaired renal function. The potential for renal disease does not eliminate the need for evaluation of coexisting urologic malignancy if indicated.

Follow-up

Appropriate follow-up after evaluation of microscopic hematuria should be determined by the provider performing the workup. Many patients will have a negative evaluation, and repeat UA in 1 year is suggested. Patients with a history of microscopic hematuria and negative evaluation who develop new symptoms including gross hematuria, a significant increase in hematuria on microscopy, or new bladder symptoms, should have further evaluation.

Special Situations

The following clinical situations may be especially pertinent to OB/GYNs.

UTI

In patients found to have an underlying gynecologic or nonmalignant genitourinary source of microscopic hematuria, such as UTI, clinicians should repeat UA with microscopy after the resolution of the aforementioned cause. This is important for women who have an episode of gross hematuria related to UTI.

Anticoagulation and Hematuria

Routine anticoagulation or antiplatelet therapy usually does not cause microscopic hematuria, but may unmask underlying pathology. Patients with microscopic hematuria who are on antiplatelet or anticoagulation therapy should receive evaluation regardless of anticoagulation status.[10]

Conclusion

Hematuria is a common condition in women and OB/GYNs are likely to encounter it in patients of all ages. Providers should understand the criteria for diagnosis of gross and microscopic hematuria, which are based on history, physical examination findings, and microscopic UA. Providers should evaluate patients for benign causes and assess a patient's risk for urinary tract malignancy. When indicated, providers should initiate evaluation and referral for gross and microscopic hematuria.

Practice Pearls

- Hematuria can be a clinical indicator for urinary tract malignancy; however, the chance of urinary tract malignancy in most women is low.
- Although gross hematuria is strongly associated with malignancy, microscopic hematuria is more common and has a lower malignancy risk.
- Diagnosis of hematuria cannot be made on dipstick testing alone. Urine microscopy is necessary to make the diagnosis of microscopic hematuria.
- The definition of microscopic hematuria is 3 or more RBCs/HPF on UA with microscopy.
- The 2020 AUA guideline recommends risk stratification to determine evaluation of microscopic hematuria.
- Consider repeating UA in women with hematuria associated with UTI after treatment of UTI.

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1. A 37-year-old, healthy woman presents for an intrauterine device insertion. The patient recently noticed a pink tinge to her urine without any other symptoms. A urine dipstick is obtained from a clean-catch urine specimen and is positive for blood. Which one of the following is the most appropriate next step?
- **A.** order UA with microscopy
- **B.** refer to urology for cystoscopy
- **C.** order renal ultrasound
- **D.** order CT urogram and refer for cystoscopy

2. Which one of the following patients would be stratified into the AUA high-risk category for urinary tract malignancy?
- **A.** 40-year-old woman with a 25-pack-year smoking history
- **B.** 40-year-old woman with 10 RBCs/HPF on 1 UA
- **C.** 40-year-old woman with 5 RBCs/HPF and known Lynch syndrome
- **D.** 40-year-old woman with a history of gross hematuria

3. A 62-year-old woman with hypertension, diabetes, and stage 3 chronic kidney disease presents for her well woman examination. Recent laboratory results ordered by her primary care physician include UA demonstrating 2 RBCs/HPF. This patient
- **A.** has gross hematuria.
- **B.** does not have microscopic hematuria.
- **C.** needs referral for a cystoscopy.
- **D.** needs a CT urogram.

4. Possible causes of abnormal urine color that could be misconstrued as hematuria include all of the following, *except*
- **A.** ciprofloxacin.
- **B.** rifampin.
- **C.** recent consumption of beets.
- **D.** myoglobinuria.

5. Which of the following patients would be stratified into the AUA intermediate-risk category for urinary tract malignancy?
- **A.** 71-year-old woman with 3 RBCs/HPF on 1 UA
- **B.** 61-year-old woman with 7 RBCs/HPF on 1 UA
- **C.** 31-year-old with a 15-pack-year smoking history
- **D.** 41-year-old woman with >25 RBCs/HPF on 1 UA

6. A 62-year-old woman reports intermittent episodes of bright red urine. Her history is notable for tobacco use since she was 20 years of age and no other associated symptoms. Her UA with microscopy demonstrates more than 25 RBCs/HPF. Which one of the following is the *most* appropriate evaluation?
- **A.** no workup needed given the patient's age
- **B.** renal ultrasound and CT urogram
- **C.** CT urogram
- **D.** CT urogram and cystoscopy

7. A 55-year-old woman has an incidental finding and diagnosis of microscopic hematuria on UA. Which one of the following is the appropriate next step in evaluation?
- **A.** repeat UA in 6 months
- **B.** renal ultrasound and cystoscopy
- **C.** cystoscopy
- **D.** CT urogram and cystoscopy

8. Which one of the following patients would be stratified into the AUA low-risk category for urinary tract malignancy?
- **A.** 49-year-old woman with 10 RBCs/HPF on 1 UA
- **B.** 32-year-old woman with 11 RBCs/HPF on 1 UA
- **C.** 62-year-old woman with 4 RBCs/HPF on 1 UA
- **D.** 59-year-old woman with 30 pack-years smoking

9. All of the following are risk factors for urinary tract malignancy, *except*
- **A.** female sex.
- **B.** gross hematuria.
- **C.** irritative lower urinary tract symptoms.
- **D.** a history of cyclophosphamide chemotherapy.

10. A 29-year-old woman presents to your office with dysuria and gross hematuria. UA demonstrates more than 25 RBCs/HPF and urine culture shows more than 100,000 colony-forming units of *Escherichia coli*. The patient is treated with antibiotics. After her UTI has been treated, follow-up
- **A.** is not needed.
- **B.** includes repeat urine culture.
- **C.** includes repeat UA with microscopy.
- **D.** includes cystoscopy.