9 Evaluation and Management of Hematuria

Stephen A. Boorjian, MD, Jay D. Raman, MD, and Daniel A. Barocas, MD, MPH, FACS

Hematuria has been recognized as a sign of medical illness since antiquity (Ellis, 1979; Shokeir and Hussein, 1999; Armstrong, 2006). Yet it is only in the modern era that we have developed the technology to detect microscopic blood, the means to identify the source of hematuria, and the understanding of anatomy, physiology, and disease processes underlying this important sign. Today, hematuria is one of the most common indications for urologic evaluation (Mariani et al, 1989) and is recognized as a sign of potentially important illness. Therefore knowledge of the differential diagnosis, principles of evaluation, and strategies for management of hematuria is critical.

CLASSIFICATION AND TIMING OF HEMATURIA

Hematuria may be classified according to its visibility and timing during the urinary stream. That is, gross hematuria (GH), sometimes referred to as *frank hematuria*, *macrohematuria*, or *visible hematuria*, is hematuria that can be seen with the naked eye. GH may be further characterized as initial, terminal, or total, depending on the phase of the urinary stream in which it is visible. This characterization may give some indication of the source of hematuria, with initial hematuria most commonly emanating from a urethral source; terminal hematuria from the bladder trigone, bladder neck, or prostate; and total hematuria from the bladder or above (Sokolosky, 2001).

GH must be distinguished from pigmenturia, which may be due to endogenous sources (e.g., bilirubin, myoglobin, porphyrins), foods ingested (e.g., beets and rhubarb), drugs (e.g., phenazopyridine), and simple dehydration. This distinction can be made easily by urinalysis with microscopy. Notably, myoglobinuria and other factors can cause false-positive chemical tests for hemoglobin, so urine microscopy is required to confirm the diagnosis of hematuria. **GH also must be distinguished from vaginal bleeding in women,** which usually can be achieved by obtaining a careful menstrual history, collecting the specimen when the patient is not having menstrual or gynecologic bleeding, or, if necessary, obtaining a catheterized specimen. GH may also be detected by the presence of blood spotting on the undergarments of incontinent patients. After ruling out vaginal bleeding and mimics of hematuria, a urologic source must be suspected.

MICROSCOPIC HEMATURIA

In contrast to GH, microscopic hematuria, or microhematuria (MH), is a sign rather than a symptom; a laboratory diagnosis defined as the presence of red blood cells (RBCs) on microscopic examination of the urine not evident on visual inspection of the urine. **The prevalence of MH among healthy participants in screening studies is 6.5% (95% confidence interval [CI] 3.4 to 12.2),** with higher rates in studies with a predominance of males, older patients, and smokers (Davis et al, 2012). MH may be categorized by the presence or absence of associated symptoms and may be quantified according to number of RBCs per high-power field (HPF). The proper collection of a urine specimen and the details of urine dipstick testing and urinalysis are covered in Chapter 1.

Criteria for the Diagnosis of Microhematuria

A small number of RBCs may pass into the urine even under normal conditions, and normal processes (e.g., sexual activity, exercise) can result in minor amounts of MH (Kohanpour et al, 2012). **The American Urologic Association (AUA) guideline panel defined MH as three or more RBCs/HPF,** concluding that higher thresholds would lead to missed opportunities to diagnose treatable urologic conditions (Davis et al, 2012). Additionally, it has been shown that **MH caused by significant medical conditions, such as urinary tract malignancy, can be intermittent** (Davis et al, 2012). In fact, a meta-analysis reported that the rate of malignancy detected among patients evaluated for a single positive urinalysis was 3.6% (Davis et al, 2012). Thus the most recent AUA guideline panel has determined that **a single positive urinalysis is sufficient to prompt evaluation** (Davis et al, 2012).

Requirement for Microscopic Evaluation

The results of urine dipstick tests must be confirmed on urinalysis with microscopy and alone are considered insufficient to prompt an evaluation. Indeed, chemical tests for hematuria detect the peroxidase activity of hemoglobin using benzidine, and therefore conditions such as myoglobinuria can falsely activate the test (Mariani et al, 1984). Thus a positive dipstick test merits microscopic examination of the urinary sediment, but does not warrant full evaluation unless microscopy confirms the presence of three or more RBCs/HPF. If the urinalysis with microscopy is not confirmatory, but the clinician remains suspicious, repeat microscopic testing is reasonable with the frequency individualized based on provider judgment.

Specimens collected immediately after prolonged recumbency (first void in morning) or after vigorous physical or sexual activity may be falsely positive for hematuria (Addis, 1926; Kincaid-Smith, 1982). Additionally, dilute urine (osmolality <308 mOsm) may result in false-negative microscopic examination as a result of RBC lysis (Vaughan and Wyker, 1971).

Evaluation of Patients with Microhematuria

In most studies, **one third to two thirds of patients evaluated for MH have been found to have a demonstrable cause** (Mohr et al, 1986; Murakami et al, 1990), including calculus (6.0%), benign prostatic enlargement (12.9%), urethral stricture (1.4%), and various other conditions (Table 9-1) (Davis et al, 2012). Notably, **the evaluation of patients with MH yields a diagnosis of malignancy in 1.8% to 4.3% of cases,** depending on the characteristics of the population evaluated, the threshold for evaluation, and the completeness of the evaluation (Davis et al, 2012). **The likelihood of identifying a malignancy is higher among patients with higher levels of microscopic hematuria (>25 RBCs/HPH), GH, or risk factors for malignancy** (Sultana et al, 1996; Shephard et al, 2012; Loo et al, 2013). Risk factors for malignancy among patients with hematuria include male gender, older age, and tobacco use (Box 9-1).

Selecting Patients for Evaluation of Microhematuria

Recognizing that one third to two thirds of patients with MH will have a negative hematuria evaluation, interest is growing in an evidence-based selection of patients for hematuria evaluation to

TABLE 9-1 Differential Diagnosis of Asymptomatic Microhematuria*

CATEGORY	EXAMPLES	COMMON CLINICAL PRESENTATION AND RISK FACTORS
Neoplasm	Any	See Box 9-1
	Bladder cancer	Older age, male predominance, tobacco, occupational exposures, irritative voiding symptoms
	Ureteral or renal pelvis cancer	Family history of early colon cancers or upper tract tumors, flank pain
	Renal cortical tumor	Family history of early kidney tumors, flank pain, flank mass
	Prostate cancer	Older age, family history, African-American
	Urethral cancer	Obstructive symptoms, pain, bloody discharge
Infection/inflammation	Any	History of infection
	Cystitis	Female predominance, dysuria
	Pyelonephritis	Fever, flank pain, diabetes, female predominance
	Urethritis	Exposure to sexually transmitted infections, urethral discharge, dysuria
	Tuberculosis	Travel to endemic areas
	Schistosomiasis	Travel to endemic areas
	Hemorrhagic cystitis	See Box 9-2
Calculus	Any	
	Nephroureterolithiasis	Flank pain, family history, prior stone
	Bladder stones	Bladder outlet obstruction
Benign prostatic enlargement		Male, older age, obstructive symptoms
Medical renal disease†	Any	Hypertension, azotemia, dysmorphic erythrocytes, cellular casts, proteinuria
	Nephritis	
	IgA nephropathy	
Congenital or acquired anatomic abnormality	Polycystic kidney disease	Family history of renal cystic disease
	Ureteropelvic junction obstruction	History of UTI, stone, flank pain
	Ureteral stricture	History of surgery or radiation, flank pain, hydronephrosis; stranguria, spraying urine
	Urethral diverticulum	Discharge, dribbling, dyspareunia, history of UTI, female predominance
	Fistula	Pneumaturia, fecaluria, abdominal pain, recurrent UTI, history of diverticulitis or colon cancer
Other	Exercise-induced hematuria‡	Recent vigorous exercise
	Endometriosis	Cyclic hematuria in a menstruating woman
	Hematologic or thrombotic disease	Family history of personal history of bleeding or thrombosis
	Papillary necrosis	African-American, sickle cell disease, diabetes, analgesic abuse
	Arteriovenous malformation	
	Renal vein thrombosis	
	Interstitial cystitis	Voiding symptoms
	Trauma	History
	Recent genitourinary surgery or instrumentation	History

*Differential diagnosis, having ruled out obvious benign causes, such as menstruation, recent instrumentation, uncomplicated cystitis, etc.
†Presence of hematologic illness, medical renal illness or use of anticoagulants or antiplatelet agents does not preclude the need for a hematuria evaluation.
‡Exercise-induced hematuria is a diagnosis of exclusion. Absence of hematuria after abstinence from exercise must be confirmed.
IgA, immunoglobulin A; UTI, urinary tract infection.

BOX 9-1 Common Risk Factors for Urinary Tract Malignancy in Patients with Microscopic Hematuria

- Male gender
- Age older than 35 years
- Past or current smoking history
- 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 irritative voiding symptoms
- History of pelvic irradiation
- History of chronic urinary tract infection
- Exposure to known carcinogenic agents or chemotherapy such as alkylating agents
- History of chronic indwelling foreign body

Modified from American Urological Association guidelines.

minimize the financial burden and risks in evaluating all patients (Mohr et al, 1986; van der Molen and Hovius, 2012; Loo et al, 2013). For example, the Kaiser Permanente group demonstrated that, among patients undergoing a complete evaluation for hematuria, those at high risk for malignancy (age >50 years, history of GH, tobacco use, male gender, or >25 RBCs/HPF) had higher rates of malignancy (10.7% to 11.6%) than patients at intermediate (1.1% to 2.5%) or low (0 to 0.3%) risk (Loo et al, 2013). However, although the Kaiser study shows that we may be able to decide which patients referred to urologists can safely avoid complete evaluation, the reality is that **fewer than 25% of patients found to have hematuria are referred for evaluation and fewer than 10% undergo a complete evaluation with cystoscopy and imaging,** even among patients at high risk for malignancy (Elias et al, 2010; Buteau et al, 2012). Taken together, these studies suggest that ample room exists for improvement in developing evidence-based algorithms to guide the use of hematuria evaluation and in reducing nonclinical sources of variability in adherence to evidence-based practices.

The AUA guidelines recommend evaluating patients with MH "in the absence of an obvious benign cause" such as infection and menstruation. Therefore **it is imperative that patients who are found to have MH in the setting of a suspected benign cause have that benign cause substantiated by clinical evidence and be further evaluated once the suspected benign cause is resolved.** Unfortunately, uniform agreement does not exist on how to identify benign causes of hematuria. Perhaps, as a result, substantial delays in diagnosis and inferior bladder cancer outcomes have occurred related to repeated empirical treatment of urinary tract infection (UTI) and voiding symptoms, particularly among women (Henning et al, 2013; Lyratzopoulos et al, 2013; Tracey et al, 2014). Our recommendation is that the **presence of infection should be confirmed with a urine culture and the urinalysis should be repeated after treatment of the UTI to document resolution of the hematuria.** If hematuria persists, further evaluation is warranted.

In addition, recent vigorous exercise may be associated with MH, but this entity should be considered a diagnosis of exclusion (Kincaid-Smith, 1982; McInnis et al, 1998; Kohanpour et al, 2012). Thus it is necessary to confirm the absence of MH after a period of abstinence from exercise. In addition, **patients who develop hematuria (microscopic or gross) who are taking anticoagulation or antiplatelet medications (e.g., warfarin, enoxaparin, heparin, aspirin, clopidogrel, nonsteroidal anti-inflammatory agents) should undergo a complete evaluation in the same manner as patients not taking such medications,** because the prevalence of hematuria, as well as the likelihood of finding genitourinary cancers, among patients with hematuria on anticoagulation has been reported to be no different from patients not taking such medications (Culclasure et al, 1994; Khadra et al, 2000; Davis et al, 2012; Jeong et al, 2013). In fact, it has been noted that these medications may unmask genitourinary lesions at an earlier stage (Antolak and Mellinger, 1969; Kraus et al, 1984; Schuster and Lewis, 1987; Mariani, 1989). In one series, 82% of anticoagulated male patients evaluated for GH were found to have significant urologic lesions (Antolak and Mellinger, 1969), and 13.9% of such lesions in another series were found to be malignant (Schuster and Lewis, 1987). Meanwhile, MH in the setting of trauma is detailed elsewhere (see Chapters 50 and 101) and will not be covered here.

The Question of Screening for Hematuria and Bladder Cancer

Bladder cancer is the sixth most commonly diagnosed cancer in the United States, and although no large-scale screening trials have been performed, **most believe that the harms and costs of mass screening for bladder cancer would prove to outweigh the potential benefits** (http://seer.cancer.gov/statfacts/html/urinb.html; Chou and Dana, 2010). Nonetheless, many primary care providers perform urinalysis as part of routine health examinations, creating numerous opportunistic screening events (Prochazka et al, 2005).

KEY POINTS: MICROSCOPIC HEMATURIA

- MH is defined as three or more RBCs/HPF, identified on one or more occasions on urine microscopy. Urine dipstick testing is insufficient for the diagnosis of MH.
- MH is quite common, with a prevalence of approximately 6.5% of adults, varying according to the characteristics of the population.
- Malignancy has been detected in approximately 4% of patients evaluated for asymptomatic MH. The proportion of malignancies detected is higher in patients with higher degrees of hematuria and/or risk factors for malignancy.

EVALUATION OF PATIENTS WITH MICROHEMATURIA

See Figure 9-1 for the evaluation algorithm of MH from the most recent AUA guidelines (Davis et al, 2012). Importantly, it is recommended that **patients meeting criteria for evaluation undergo a complete evaluation, even if one phase of the evaluation shows a suspected cause for the MH.** For example, a patient found to have a kidney tumor or stone disease during initial workup of MH should still undergo cystoscopy for clearance of bladder and urethral pathologic processes.

The evaluation of an appropriately selected patient with MH begins with a thorough history and physical examination. Specifically, one should aim to identify causes that would warrant variation from the standard evaluation, such as infection, menstruation, recent vigorous exercise, known medical renal disease, acute viral illness, trauma, and the presence of foreign bodies in the urinary tract or recent urologic instrumentation. The history also should include an assessment of associated symptoms, such as GH, voiding symptoms, or flank pain. Patients' risk factors for known causes of hematuria also should be queried. It is important to know the patient's urologic history, particularly any surgeries or febrile UTIs. It is also critical to ask about the patient's general medical history, to identify potentially contributory diagnoses, such as hypertension, renal insufficiency, bleeding disorders, or sickle cell disease. Current medication use, including anticoagulants and antiplatelet therapies, should be elicited, along with recent coagulation values and any concomitant medications that would potentiate the effects of blood thinners. Family history of nephritis, polycystic kidneys, and rare familial tumor syndromes of the kidney (e.g., von Hippel-Lindau) or urothelium (e.g., Lynch syndrome) also may

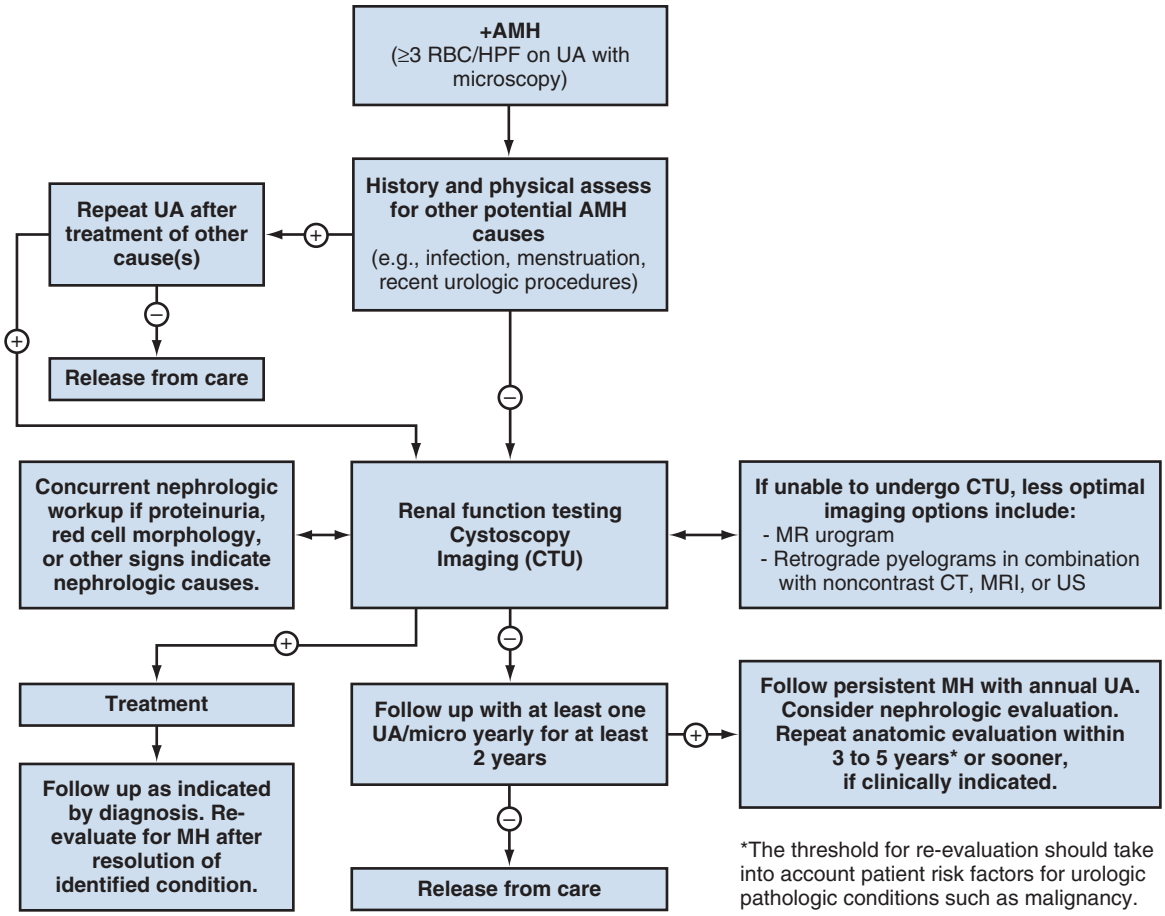

Figure 9-1. American Urological Association guideline algorithm for evaluation of adult patients with asymptomatic microhematuria. AMH, asymptomatic microhematuria; CT, computed tomography; CTU, computed tomography urogram; HPF, high-power field; MH, microhematuria; MR, magnetic resonance; MRI, magnetic resonance imaging; RBC, red blood cell; UA, urinalysis; US, ultrasound. (From the American Urological Association.)

be informative. In addition, the possibility of finding a tobacco-related illness, such as bladder cancer, makes this a potential "teachable moment" for tobacco users (Bassett et al, 2012; Fiore and Baker, 2013). Thus smoking cessation counseling should be a standard component of the hematuria evaluation discussion.

Physical examination should focus on the genitourinary system (e.g., flank tenderness; masses in the flank, abdomen, suprapubic area, or urethra; and enlarged, nodular, tender, or fluctuant prostate.) Physical examination also may identify signs of coagulopathy (bruising), infection (fever), or renal disease (hypertension, edema). If urethral stricture or benign prostatic hyperplasia (BPH) is suspected, a urine flow rate and postvoid residual measurement may be helpful as well.

Laboratory testing includes urinalysis (if not performed previously) to confirm the presence of hematuria and check for dysmorphic red cells, cellular casts, or proteinuria; a urine culture if the urinalysis or clinical presentation suggests infection; renal function testing (serum creatinine) to determine whether concomitant nephrologic evaluation is indicated and to guide the selection of appropriate upper tract imaging; and prostate-specific antigen in the appropriate setting.

If a benign cause of hematuria is discovered during the initial history and physical (e.g., UTI), that cause should be verified and treated and then the urine should be retested to ensure that the hematuria has resolved in the absence of the presumed benign cause. Moreover, **if a medical renal cause of hematuria is suspected based on the presence of renal insufficiency, hypertension, or abnormalities on urinalysis, nephrology evaluation is recommended, but the patient should still undergo urologic evaluation.**

Cystoscopy in the Diagnostic Evaluation of Hematuria

Cystoscopy is a key component of the hematuria evaluation because it is the most reliable way to evaluate the bladder for the presence of bladder cancer and provides the opportunity to evaluate the urethra. **Cystoscopy should be performed in all adults who meet criteria for hematuria evaluation who are 35 years of age or older and/or have risk factors for malignancy.** The potential risks include discomfort, injury to the urethra, infection, and the need for additional procedures, such as biopsy. At the population level, bladder cancer is quite rare (<1 per 100,000) among persons 35 years old or younger (van der Molen and Hovius, 2012; http://seer.cancer.gov/statfacts/html/urinb.html). That is, among 3762 individuals with asymptomatic MH from 17 screening studies, 98 (2.6%) were diagnosed with a urinary tract malignancy, of whom 95 (97%) were older than 35 years of age. For these reasons, **cystoscopy may be omitted in persons younger than age 35 years without risk factors or clinical suspicion for bladder cancer** or urethral pathology (see Box 9-1).

Of note, blue-light cystoscopy using 5-aminolevulinic acid (ALA) or hexyl-aminolevulinate (HAL) instillation is approved by the U.S Food and Drug Administration (FDA) for evaluation of patients with suspicion of papillary bladder cancer, but the studies supporting its use have been conducted in patients with known bladder cancer, thereby limiting generalizability to MH patients

(Davis et al, 2012; Malmstrom et al, 2012). In light of the small incremental risk associated with ALA or HAL and blue-light cystoscopy (rare anaphylactoid shock, hypersensitivity, pain, cystitis, dysuria, hematuria) and the risk for unnecessary biopsies compared to conventional white light cystoscopy, the **AUA guideline recommends against using blue-light cystoscopy for evaluation of MH** (Davis et al, 2012).

Upper Tract Imaging in the Diagnostic Evaluation of Hematuria

Multiphasic computed tomography (CT) urogram (i.e., CT with precontrast, nephrographic, and excretory series) is the imaging study of choice for the evaluation of asymptomatic MH (Vikram et al, 2009), because CT urography offers complete imaging of the urinary tract and has the highest sensitivity and specificity for detecting lesions of the renal parenchyma and the upper tracts. Nonetheless, CT urography does carry risks and may not be appropriate for all patients (e.g., pregnancy, iodinated contrast allergy, renal insufficiency). Indeed, in the setting of a contraindication to CT urogram, magnetic resonance urogram may be used as the upper tract study. Moreover, for patients with a contraindication to magnetic resonance imaging (e.g., pacemaker), as well as in the setting of significant renal function compromise (i.e., estimated glomerular filtration rate <30) when the administration of gadolinium risks nephrogenic systemic fibrosis, renal parenchymal imaging with noncontrast CT or ultrasound, in conjunction with retrograde pyelography to evaluate the calyces, renal pelvis, and ureters, may be most appropriate.

Urine Cytology and Urinary Biomarkers in the Diagnostic Evaluation of Hematuria

Urine cytologic examination is highly sensitive and specific for the detection of high-grade urothelial carcinoma, but sensitivity decreases significantly for low-grade urothelial carcinoma, resulting in an overall sensitivity of 15.8% to 54.5%, and specificity of 95.0% to 100% for bladder cancer detection (Miyanaga et al, 1999; Zippe et al, 1999; Chahal et al, 2001; Grossman et al, 2005; Steiner et al, 2008). Indeed, in a large study of patients with hematuria, the sensitivity and specificity of positive/suspicious/atypical cytology were 45.4% and 89.5%, respectively (Mishriki et al, 2013).

Meanwhile, although several urine biomarkers have been approved or cleared by the FDA for detection and surveillance of bladder cancer, few studies have been conducted to evaluate these markers in patients with MH who do not have a history of bladder cancer. Available assays include nuclear matrix protein-22 (NMP-22), bladder tumor antigen, fluorescence in situ hybridization (FISH) for abnormalities of chromosomes 3, 7, 17, and 9p21 (UroVysion [Abbott Molecular, Abbott Park, IL]) and immunocytology for carcinoembryonic antigen and mucin glycoproteins (ImmunoCyt [Scimedx, Denville, NJ] and CertNDx [PCLS, Rock Hill, SC]).

NMP-22 offers a potential advantage in management of patients with MH in that it is available as a point-of-care test. However, only two studies to date have focused on the asymptomatic patient with MH, with one finding a high sensitivity (90.9%), and the other, in a screening population, demonstrating very low sensitivity (6.0%). Specificity was moderate or high in both studies (76.3% and 82.5%, respectively) (Miyanaga et al, 1999; Steiner et al, 2008). Meanwhile, one study assessed FISH testing in patients with asymptomatic MH with a negative cytology and found that sensitivity and specificity may be high for upper tract tumors in this setting (Huang et al, 2012). A separate FISH study in asymptomatic MH patients (albeit without prior negative cytologic findings) showed sensitivity and specificity of 61% and 93%, respectively, for bladder tumors (Steiner et al, 2008). Immunocytology has been tested in the asymptomatic MH setting in one study of 189 patients (Schmitz-Drager et al, 2007). Here, eight bladder tumors were identified, of which seven were identified by the ImmunoCyt test, for a sensitivity of 87%. However, studies in the urothelial carcinoma follow-up setting have found a far more modest sensitivity (68.1%) (Comploj et al, 2013). Finally, the multianalyte urine test CertNDx assesses several markers (mutant *FGFR3*, quantified matrix metalloproteinase-2 [MMP2], and hypermethylation of *TWIST1* and *NID2*). In a population of patients with hematuria (gross and microscopic) 50 years of age or older without diagnosis of bladder cancer, the sensitivity and specificity of this test were noted to be 87.9% and 56.3%, respectively (Karnes et al, 2012).

Together, because current evidence indicates that none of the available urinary biomarkers, including cytology, appear to be sufficiently sensitive or sufficiently validated to replace cystoscopy or imaging, **these studies are not recommended in the initial evaluation of patients with asymptomatic MH** (Davis et al, 2012). However, **cytologic examination may be considered in patients with a negative initial workup in whom urothelial carcinoma is still suspected, as well as in patients with symptomatic MH**.

Natural History of Microhematuria in Patients with a Negative Initial Evaluation

One of the most vexing questions in the management of MH is how to proceed in patients for whom the initial evaluation is negative. MH has been reported to resolve in approximately one third of these patients over a period of 3 months to several years (Yamagata et al, 1996; McGregor et al, 1998; Jaffe et al, 2001). Nevertheless, it is worth noting that these studies contained large proportions of younger patients, many of whom did not undergo a complete workup at any time, raising the possibility of persistent occult urologic disease. In a set of studies in which patients underwent further evaluation for MH after an initial negative evaluation, 41 malignancies were identified among 1475 patients (2.8%). However, the initial evaluations in these series were often incomplete, the follow-up evaluations were variable, and most of the malignancies were found in a study using CT urography in patients who were not evaluated by CT in the first evaluation (Davis et al, 2012).

In the absence of high-quality evidence, the AUA has issued three guidelines statements, based on expert opinion, pertaining to the follow-up of patients with an initial negative workup (Davis et al, 2012). The first two can be summarized as recommending **following up annual urinalysis for 2 years after a complete negative hematuria workup and releasing the patient from care if the urinalyses confirm resolution of hematuria.** The third statement recommends **repeating the hematuria evaluation within 3 to 5 years in cases of persistent or recurrent asymptomatic MH or for development of symptoms or GH**. We would add that **patients with persistent or recurrent MH in the setting of an incomplete initial evaluation should have the evaluation completed or repeated.**

KEY POINTS: EVALUATION OF PATIENTS WITH MICROHEMATURIA

- Evaluation of adults with microscopic hematuria includes a history and physical examination, renal function testing, and upper tract imaging for all patients.
- White light cystoscopy is recommended in the evaluation of asymptomatic MH for patients 35 years of age or older and/or those with risk factors for malignancy.
- CT urogram is the preferred imaging modality for the evaluation of hematuria.
- Urine cytologic examination and biomarkers are not indicated in the initial evaluation of asymptomatic MH.
- Patients with a negative complete evaluation can be released from care if subsequent urinalyses confirm resolution of MH. Re-evaluation should be considered in patients with persistent/recurrent MH and those with an incomplete initial evaluation.

SYMPTOMATIC MICROSCOPIC HEMATURIA

The differential diagnosis for symptomatic MH is equivalent to that for patients with asymptomatic MH. However, the risk for malignancy may be significantly higher than in asymptomatic MH (10.5% vs. 5.0% or less) (Sultana et al, 1996; Shephard et al, 2012). To the extent that symptoms help identify an obvious benign cause of hematuria (e.g., infection), and the hematuria resolves after management of this (culture-documented) benign cause, a complete workup can be avoided. Nevertheless, in situations in which an obvious benign cause is not definitively identified, the hematuria does not resolve after treatment of the benign cause, or the symptoms or other risk factors could be consistent with malignancy, full evaluation is recommended. Moreover, because the presence of symptomatic hematuria has been linked to an increased risk for malignancy, current AUA guidelines include several slight modifications to the recommendations for evaluation. Specifically, **cystoscopy is recommended in such patients, regardless of age** (Davis et al, 2012). Moreover, although routine cytology is not recommended as part of the routine evaluation for the asymptomatic patient with microscopic hematuria, **cytologic examination is considered an option in the setting of irritative voiding symptoms,** although cystoscopy should not be omitted even if the cytologic findings are negative (Davis et al, 2012).

GROSS HEMATURIA

The differential diagnosis for GH remains the same as outlined earlier for MH. Of note, however, **as the degree of hematuria increases, so does the likelihood of finding clinically significant lesions during evaluation.** That is, the difference between the yield of life-threatening lesions in patients with gross versus microscopic hematuria has been found to be highly significant (Mariani, 1989). Specifically, among patients with GH, 50% have been found to have a demonstrable cause, with 20% to 25% found to have a urologic malignancy, most commonly bladder cancer and kidney cancer (Lee and Davis, 1953; Khadra et al, 2000; Alishahi et al, 2002; Edwards et al, 2006).

Given the increased frequency with which clinically significant findings are associated with GH, the recommended evaluation in this setting is relatively uniform. That is, **patients presenting with GH in the absence of antecedent trauma or culture-documented UTI should be evaluated with a urine cytologic examination, cystoscopy, and upper tract imaging, preferably CT urogram.** Meanwhile, patients with GH in the setting of a culture-documented UTI should have the infection treated and then a follow-up urinalysis obtained to ensure clearance of the hematuria. The initial assessment for patients presenting with GH should include the history, physical examination, and laboratory studies recommended for patients with MH. Further, patients with GH must be assessed for hemodynamic stability with careful attention to vital signs, anemia with a complete blood count, and, for patients on anticoagulation, coagulation parameters to ensure that levels are within the therapeutic range. After initial stabilization, diagnostic evaluation should then proceed, with cause-specific management as outlined below.

Although clear recommendations are lacking for the follow-up of patients with GH who are found to have a nondiagnostic initial evaluation, the follow-up schedule as outlined for patients with asymptomatic MH may be used as a reference, with consideration given for a full repeat evaluation if episodes of GH recur.

HEMORRHAGIC CYSTITIS

Intractable hematuria localizing to the bladder, or hemorrhagic cystitis, may range in severity from a transient condition that quickly resolves after conservative management to a life-threatening condition requiring urgent intervention. Unfortunately, patients in this situation are often elderly and infirm, with medical comorbidities that complicate plans for care.

Hemorrhagic cystitis is characterized by diffuse inflammation and bleeding from the bladder mucosa (Rastinehad et al, 2007). Numerous causes for this condition have been described (Box 9-2), a few of which merit particular mention here. Bacterial infections, for example, are a common cause of GH, with symptomatic resolution typically noted after appropriate treatment. Meanwhile, viral-induced hemorrhagic cystitis may affect children and immunosuppressed adults particularly, as following renal or bone marrow transplantation. **BK virus, a member of the polyomavirus family, is the most common virus associated with hemorrhagic cystitis** (Gorczynska et al, 2005), and adenovirus, particularly types 11 and 35, has been correlated with hemorrhagic cystitis in children and renal transplant patients (Lee et al, 1996; Hofland et al, 2004). Treatment for viral hemorrhagic cystitis is primarily supportive, with hydration, diuresis, and bladder irrigation, although case reports of antiviral therapy exist (Rastinehad et al, 2007).

Hemorrhagic cystitis also may result from exposure to the oxazaphosphorine class of chemotherapeutic agents, specifically cyclophosphamide and ifosfamide. Indeed, hemorrhagic cystitis has been reported to occur in 2% to 40% of patients treated with cyclophosphamide (Rastinehad et al, 2007) and is dose dependent.

BOX 9-2 Differential Diagnosis for Hemorrhagic Cystitis*

- Infectious
  - Bacterial
  - Viral (especially BK virus, adenovirus)
  - Fungal
  - Parasitic
- Trauma
  - External
  - Postsurgical (e.g., transurethral resection of the bladder)
- Malignancy
  - Bladder primary
  - Bladder invasion from local/distant primary
- Vascular malformation
- Chemical exposure
  - Cyclophosphamide
  - Ifosfamide
  - Busulfan
  - Thiotepa
  - Temozolomide
  - Aniline dye
  - Ether
  - Nonoxynol-9 (accidental urethral insertion of vaginal contraceptive)
- Radiation therapy history (e.g., prostate cancer, cervical cancer)
- Medication induced
  - Penicillin and derivatives (via immune reaction)
  - Bleomycin
  - Danazol
  - Tiaprofenic
  - Allopurinol
  - Phensuximide
  - Methenamine mandelate
  - Acetic acid
- Manifestation of systemic disease
  - Amyloidosis
  - Rheumatoid arthritis
  - Crohn disease

*Bleeding localized to bladder after diagnostic workup for gross hematuria with cystoscopy, urine cytology, and upper tract imaging is without clear cause of alternative bleeding source

Bladder toxicity results from renal excretion of the metabolite acrolein, which is produced by the liver and which stimulates bladder mucosal sloughing and subsequent tissue edema/fibrosis (O'Reilly et al, 2002). The onset of hematuria is typically within 48 hours of treatment (Cox, 1979; Stillwell and Benson, 1988). **2-Mercaptoethane sulfonate (mesna), which binds to acrolein and renders it inert, has been suggested for prophylaxis against cyclophosphamide-induced hemorrhagic cystitis** (O'Reilly et al, 2002). Nevertheless, 10% to 40% of patients will develop the condition despite preventive treatment (Shepherd et al, 1991), and debate continues as to whether mesna is more effective at preventing hemorrhagic cystitis than hyperhydration with forced diuresis and/or continuous bladder irrigation (Shepherd et al, 1991; Vose et al, 1993).

Meanwhile, **radiation therapy for pelvic malignancy represents another predisposing factor to hemorrhagic cystitis.** Indeed, moderate-to-severe hematuria has been reported in approximately 5% of patients after pelvic radiotherapy, with onset between 6 months and 10 years after treatment (Corman et al, 2003). Mechanistically, radiation damages the vascular endothelium, thereby inducing subsequent inflammation, fibrosis, and ischemia, with tissue necrosis and mucosal sloughing occurring through progressive obliterative endarteritis (Hader et al, 1993; Bevers et al, 1995; Chong et al, 2005). In the setting of such local vascular compromise, moreover, secondary infection frequently ensues, further compromising tissue healing (Del Pizzo et al, 1998).

Management of Hemorrhagic Cystitis

The management of hemorrhagic cystitis may occasionally be guided by the particular cause for the condition (e.g., treatment of infection), although in most cases no cause-directed therapy can be offered and instead a sequential approach, depending on the severity of the condition, should be undertaken (Fig. 9-2). Supportive management in the form of increasing urine output via hydration/diuresis, catheter placement with continuous bladder irrigation, and transfusion as needed represent the mainstay of first-line therapy and typically suffice for mild cases. If hematuria continues and/or clotting of the urine cannot be controlled with bladder irrigation, cystoscopy under anesthesia with clot evacuation and fulguration of discrete bleeding sites is then recommended.

For hematuria that persists despite such conservative measures, various agents have been investigated for bleeding control. Importantly, there is a lack of large, prospective trials reporting comparative treatment efficacy and safety. Nevertheless, an overview of these measures is warranted to facilitate a systematic approach to

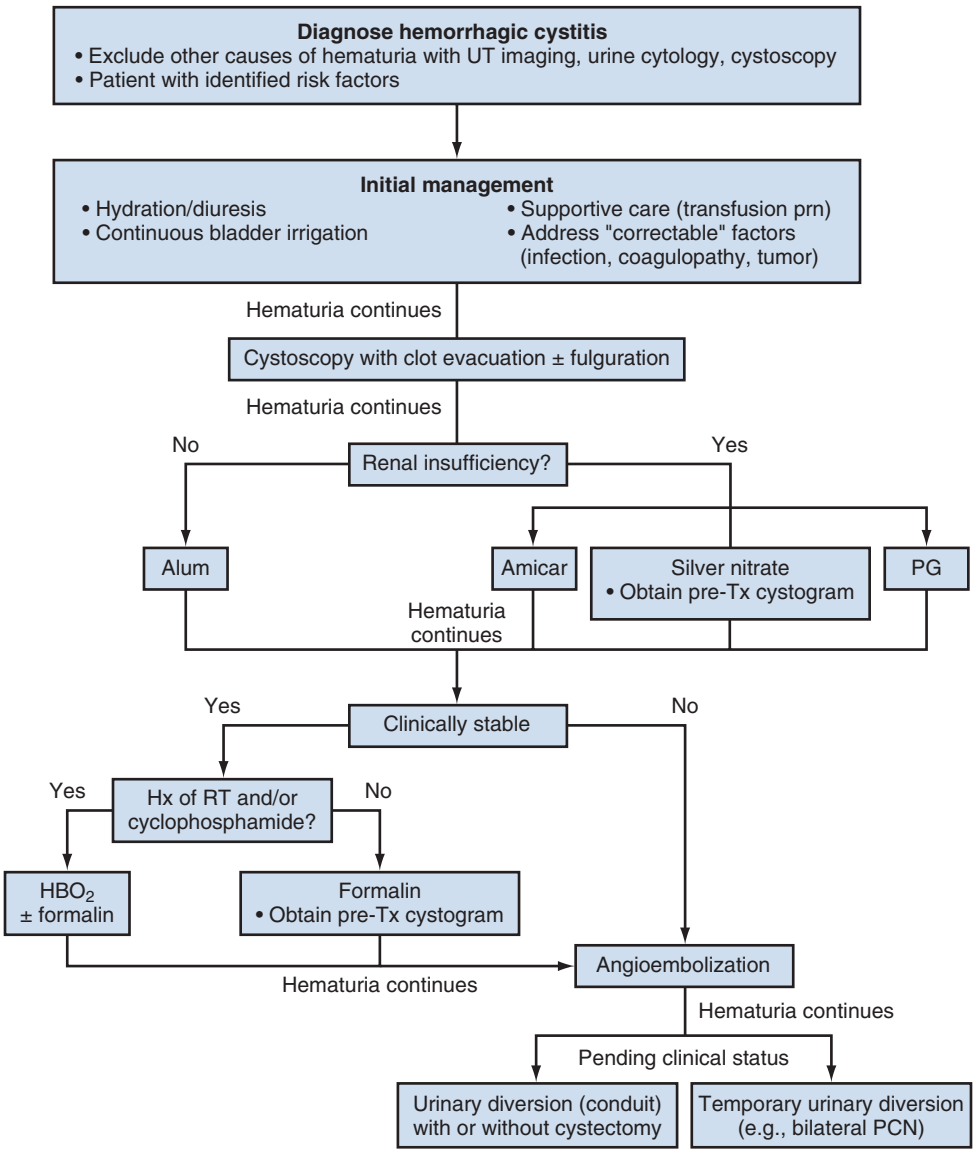

Figure 9-2. Management algorithm for patients with hemorrhagic cystitis. HBO_2, hyperbaric oxygen; Hx, history; PCN, percutaneous nephrostomy; PG, prostaglandin; Tx, treatment; UT, upper tract.

management. For one, alum (aluminum ammonium sulfate or aluminum potassium sulfate) may be dissolved in sterile water (50 g alum in a 5-L bag of sterile water [1% alum solution]) and then used to irrigate the bladder at a rate of 200 to 300 mL/hr. Through its action as an astringent at sites of bleeding, **alum may cause protein precipitation on the urothelial lining** (Ostroff and Chenault, 1982) **and thereby stimulate vasoconstriction and a decrease in capillary permeability** (Choong et al, 2000)**. In albeit small series to date, success rates of 66% to 100% have been reported after alum instillation** (Choong et al, 2000; Abt et al, 2013)**.** Although cell penetration and therefore overall toxicity of this agent are low (consisting mainly of suprapubic discomfort and bladder spasms), **systemic absorption may nevertheless occur and may result in aluminum toxicity, with consequent mental status changes, particularly among patients with renal insufficiency.** However, alum may be instilled without anesthesia and has an overall relatively favorable efficacy and safety profiles. Thus **this agent may be considered for first-line intravesical therapy among patients with hemorrhagic cystitis failing initial supportive measures, particularly among those who are without renal insufficiency.**

In addition, several alternative agents exist for intravesical instillation therapy. Prostaglandins (e.g., carboprost tromethamine [PGF2-α]) (Abt et al, 2013) have been used intravesically for hemorrhagic cystitis, and although the precise mechanism of activity remains unclear, these agents are thought to cause vasoconstriction, platelet aggregation, and cytoprotection via mucous barrier regulation (Choong et al, 2000; Abt et al, 2013). Response rates of 50% to 60% have been noted (Choong et al, 2000; Abt et al, 2013), and in fact in a small (19 patients) prospective randomized study, no significant difference in efficacy was noted between PGF2 and alum (Praveen et al, 1992). Notably, however, difficulties with PGF2 access, storage, and high costs have limited generalized utility (Abt et al, 2013). Alternatively, silver nitrate may be instilled into the bladder, resulting in chemical coagulation at bleeding sites. A 0.5% to 1% solution is instilled for 10 to 20 minutes (Rastinehad et al, 2007). The potential for precipitation and upper tract obstruction with this agent led to the recommendation for a cystogram to rule out reflux before administration (Rastinehad et al, 2007).

Aminocaproic acid represents another intravesical treatment alternative. A lysine analogue, aminocaproic acid is a competitive inhibitor of activators of plasminogen, including urokinase, and thus interrupts fibrinolysis and the cascade that perpetuates hemorrhage (Garber and Wein, 1989; Stefanini et al, 1990; Abt et al, 2013). **Continuous bladder irrigation with 200 mg aminocaproic acid/L of 0.9% normal saline has been described, with irrigation continued for 24 hours after hematuria resolves.** Symptom resolution has been reported in up to 92% of patients (Singh and Laungani, 1992). The risk for thromboembolic events may be increased with this treatment, and, importantly, aminocaproic acid must be given only after the bladder has been rendered clot-free, because the agent will otherwise lead to the formation of hard clots difficult to eradicate from the bladder (Rastinehad et al, 2007).

Management for patients in whom hematuria remains refractory to the aforementioned measures is particularly challenging and is often guided by the patients' clinical status. That is, for clinically stable patients, intravesical **formalin, a solution of formaldehyde that induces cellular protein precipitation and capillary occlusion** (Choong et al, 2000)**, may be used**. Control of bleeding has been reported in 80% to 90% of cases with formalin (Choong et al, 2000), which are relatively higher rates than what has been noted with other intravesical treatments. However, because formalin instillation may induce significant pain, administration under general or spinal anesthesia is recommended. Moreover, intravesical **formalin therapy is associated with significant complications, including bladder fibrosis with associated decreased bladder capacity and ureteral stricturing with proximal hydronephrosis/renal injury** (Choong et al, 2000; Abt et al, 2013). Thus **pretreatment cystogram is recommended to exclude the presence of vesicoureteral reflux and/or bladder perforation** (Donahue and Frank, 1989). If reflux is documented, placement of occlusive ureteral catheters is recommended to limit upper tract exposure to the medication. Regardless, moreover, low concentrations of formalin (1% to 2%) should be used initially, because complication rates (albeit efficacy rates as well) have been linked to dosage (Donahue and Frank, 1989). Irrigation (with volumes up to 300 mL or to bladder capacity) (Choong et al, 2000) should be done under gravity, with the catheter no more than 15 cm above the pubic symphysis. Irrigation should be limited to 10 to 15 minutes and should be performed with the catheter on light traction to prevent urethral exposure, with care taken to protect all external areas of skin from exposure. Given the potential toxicities of formalin, together with the requirement for administration under anesthesia, this agent should be reserved for second-line therapy.

Another treatment option for patients with refractory hemorrhagic cystitis, particularly resulting from radiation therapy or cyclophosphamide-induced cystitis (Brastas et al, 2004)**, is hyperbaric oxygen (HBO_2) therapy.** Treatment is carried out in a specially designed chamber and involves administration of 100% oxygen at a pressure of 2 to 3 atmospheres for approximately 90 minutes in 30 to 40 sessions (Bevers et al, 1995; Del Pizzo et al, 1998; O'Reilly et al, 2002). With this, local tissue oxygen tension increases and thus oxygen extraction by tissues increases, thereby diminishing edema and promoting neovascularization, critical steps in the wound healing process (Hader et al, 1993). Response rates to HBO_2 of 80% to 90% have been reported (Bevers et al, 1995; O'Reilly et al, 2002; Corman et al, 2003; Chong et al, 2005) and have been maintained up to 2.5 years after treatment (Weiss et al, 1994). However, with longer follow-up, most patients become symptomatic again, such that the 5-year complete response rate has been noted to be only 27% (Del Pizzo et al, 1998). Reported complications include claustrophobia (20%), otalgia (17%), and, rarely, seizures (O'Reilly et al, 2002).

For clinically unstable patients, as well as for patients with continued intractable bleeding, **internal iliac artery angioembolization represents a potential next step** in management. As reported in 1974 (Hald and Mygind, 1974), angioembolization may be performed unilaterally or bilaterally, even in debilitated patients, with relatively limited risk (Ward et al, 2003). Selective embolization of the anterior branch of the internal iliac artery bilaterally is typically required to achieve hemostasis. Care should be taken to avoid embolization of the posterior branch of the internal iliac artery, which, because of subsequent occlusion of the superior gluteal artery, may result in significant gluteal pain.

In the setting of failed angioembolization and other conservative approaches, **cystectomy with urinary diversion may be necessary to control bleeding.** Of note, pending the patients' clinical/comorbidity profile, consideration may be been given to supravesical urinary diversion alone, including bilateral nephrostomy tube insertion with occlusion of the ureters (Gonzalez et al, 2001), or ileal conduit diversion without cystectomy. The intention of such efforts is to decrease exposure of the hemorrhagic bladder to urokinase and thereby theoretically facilitate hemostasis (Rastinehad et al, 2007) while minimizing procedure-related morbidity. However, complications have been reported in up to 80% of patients with a retained bladder, including rehospitalization in 43% (Eigner and Freiha, 1990), suggesting that cystectomy should be performed at the time of urinary diversion if feasible. Unfortunately, such patients are typically ill and therefore in poor condition for surgery. As a result, complication rates may be even higher than what has been reported after cystectomy for bladder cancer.

HEMATURIA FROM PROSTATIC ORIGIN

As with hemorrhagic cystitis, hematuria from prostatic origin is a diagnosis made after a complete GH evaluation (including cytology, upper tract imaging, and cystoscopy) to confirm that no other source of hematuria exists. Varied causes exist for prostate-related hematuria, and the severity of such bleeding likewise may range from transient self-limiting episodes to continuous bleeding

KEY POINTS: HEMORRHAGIC CYSTITIS

- Oxazaphosphorine chemotherapeutic agents have been linked to the development of hemorrhagic cystitis through exposure of the metabolite acrolein to the urothelium.
- Alum may be used as a first-line intravesical therapy for hemorrhagic cystitis in patients without renal dysfunction.
- Formalin is a highly effective form of intravesical therapy for hemorrhagic cystitis. A cystogram should be obtained before therapy to ensure no vesicoureteral reflux.
- HBO_2 has been associated with response rates of 80% to 100% for patients with hemorrhagic cystitis.

resulting in the obstruction of urinary flow and in transfusion dependence. Most commonly, prostate-related bleeding is due to BPH, prostate-related infection (prostatitis), or prostate cancer (Fig. 9-3).

BPH represents the most common cause of prostate-related bleeding and has been cited as the most common cause of GH in men older than 60 (Borth and Nickel, 2006). In fact, BPH has been reported to be the only pathologic condition identified in approximately 20% of cases from hematuria studies (Hasan et al, 1994; Lynch et al, 1994). **The cause for BPH-related hematuria has been thought to be increased prostatic vascularity resulting from higher microvessel density in hyperplastic prostate tissue** (Deering et al, 1995; Foley et al, 2000; Pareek et al, 2003; Borth and Nickel, 2006). This **noted increase in microvessel density has in turn been linked to higher levels of vascular endothelial growth factor (VEGF)** (Walsh et al, 2002; Pareek et al, 2003; Borth and Nickel, 2006).

Frequently, BPH-related hematuria episodes are mild and self-limiting, such that once the diagnosis has been established, expectant management with encouraged hydration can be undertaken. Interestingly, although GH has historically been considered an indication for surgery in the setting of BPH, increased understanding of the molecular pathway contributing to the pathophysiologic process (i.e., increased VEGF) has translated into the incorporation of what may be considered targeted medical therapy in the management of patients with BPH-related hematuria.

Specifically, because the pathophysiology of BPH-related bleeding has been postulated as increased cell proliferation stimulating increased vascularity, efforts to suppress prostate growth via androgen ablation have been explored (Marshall and Narayan, 1993; Foley et al, 2000). Both estrogens and antiandrogens have, in small case reports, been associated with decreased prostate bleeding, presumably through the repression of androgen-stimulated angiogenesis and the induction of programmed cell death within the prostate (Marshall and Narayan, 1993; Rittmaster et al, 1996). In particular, finasteride, a 5α-reductase inhibitor that blocks conversion of testosterone to dihydrotestosterone and is a treatment for

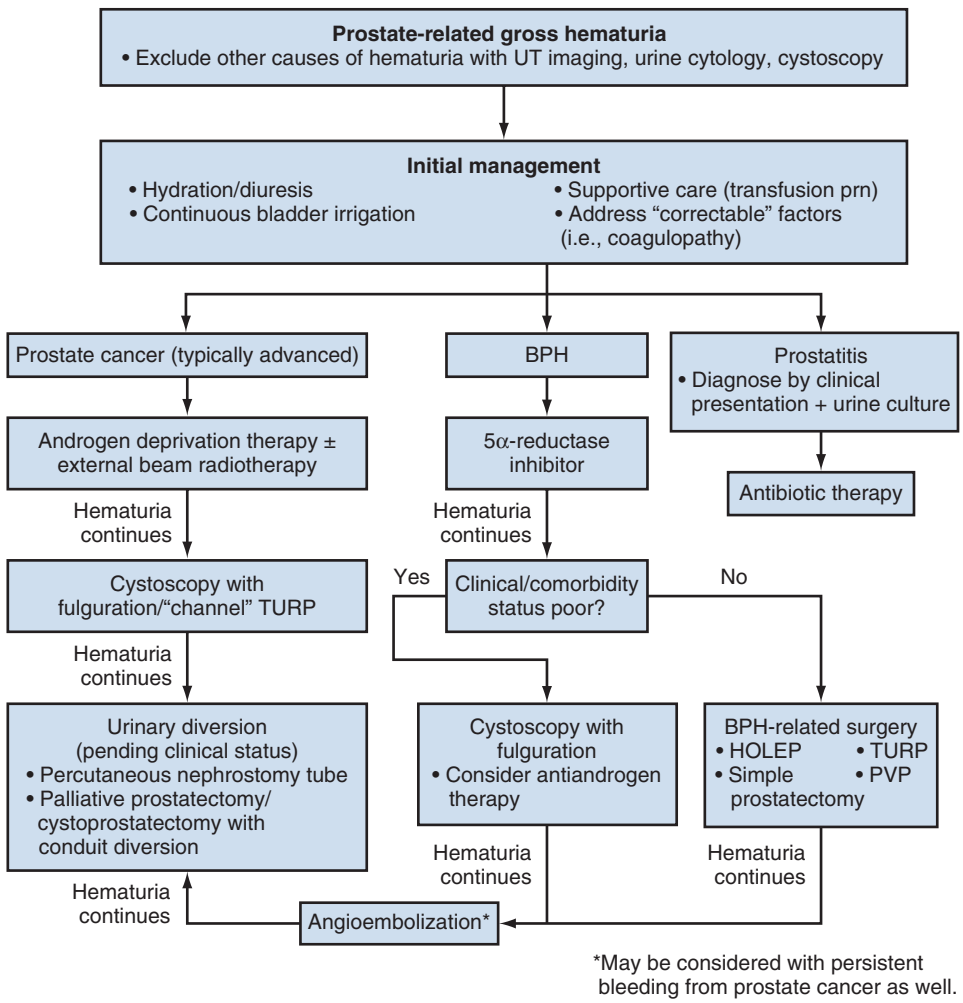

Figure 9-3. Management algorithm for patients with persistent hematuria of prostate origin. BPH, benign prostatic hyperplasia; HOLEP, holmium laser enucleation of the prostate; PVP, photovaporization of the prostate; TURP, transurethral resection of the prostate; UT, upper tract.

prostate-related outlet obstructive symptoms, has been investigated extensively for BPH-related bleeding. **Treatment with finasteride is associated with decreased VEGF expression** (Pareek et al, 2003)**, prostate microvessel density** (Pareek et al, 2003)**, and prostatic blood flow** (Frauscher et al, 2003).

Clinically, **multiple series have demonstrated efficacy of finasteride for BPH-related hematuria, including in patients being treated with anticoagulation. Symptom improvement or resolution has been consistently noted in approximately 90% of patients** (Puchner and Miller, 1995; Carlin et al, 1997; Miller and Puchner, 1998; Sieber et al, 1998; Kearney et al, 2002). A prospective randomized trial of finasteride versus expectant management in 57 patients with BPH-induced hematuria found that the rate of recurrent hematuria was significantly higher among patients in the control arm (63%) versus finasteride (14%) ($P < 0.05$), with 26% of patients in the control arm requiring surgery for bleeding versus none of the finasteride-treated patients (Foley et al, 2000). The onset of action for finasteride is variable, with improvement in bleeding noted from as short as 2 weeks to up to 9 months after initiating therapy. In addition, a randomized trial of finasteride versus cyproterone acetate versus watchful waiting demonstrated a significant decrease in recurrent hematuria in both the finasteride and in the cyproterone acetate cohorts, with no noted difference in efficacy between finasteride and cyproterone acetate in patients treated with this agent (Perimenis et al, 2002). Thus, although various forms of hormonal therapy remain options for BPH-related bleeding, the best data to date exist for 5α-reductase inhibition, which likely entails the least side-effect profile as well.

In cases of BPH-bleeding in which patients have difficulty with bladder emptying and/or presence of clot, large-bore catheter placement with irrigation to evacuate all clot material from the bladder should ensue, followed by continuous bladder irrigation until the urine has cleared. If such measures are not sufficient to control bleeding, patients should be taken for endoscopic management under anesthesia, with clot evacuation and electric or laser cauterization. Although the variety of nonspecific intravesical therapies as are used in hemorrhagic cystitis (e.g., aminocaproic acid) have been suggested for use in this setting as well (Borth and Nickel, 2006), limited evidence exists to support the efficacy of these agents for BPH-related bleeding. Thus **patients with persistent bleeding from BPH despite conservative therapies and/or endoscopic fulguration have traditionally been managed with transurethral resection of the prostate (TURP),** particularly when additional indications for BPH surgery coexist. Although alternative forms of such endoscopic prostate tissue removal/destruction are available (e.g., photoselective vaporization of the prostate, holmium laser enucleation of the prostate) and even suprapubic/retropubic prostatectomy may be undertaken, the principle with all such interventions is to remove the hyperplastic and friable transition-zone prostate tissue. In cases with persistent bleeding despite TURP, selective angioembolization (Michel et al, 2002) and even radical prostatectomy or cystoprostatectomy should be considered, although, as with hemorrhagic cystitis, often such patients are poor surgical candidates because of comorbidity status.

Prostatitis, traditionally secondary to bacterial infection, also may result in GH. Indeed, a prior study reported hematuria as the manifesting symptom in 2.5% of men with prostatitis (Rizzo et al, 2003). The mechanism of hematuria in prostatitis is unclear and may be related to inflammation (Borth and Nickel, 2006). Management in this setting should consist of antibiotics when culture-documented bacterial prostatitis is present. Significant recurrent hematuria in the setting of nonbacterial prostatitis is relatively uncommon, and it has been suggested that such cases should be treated with antibiotics in addition to standard supportive measures (Borth and Nickel, 2006).

Meanwhile, **hematuria from prostate cancer typically results in cases of significantly locally advanced tumors,** often with bladder base/trigonal invasion. Indeed, hematuria has been noted to be the most common local symptom among patients with advanced symptomatic prostate cancers (Din et al, 2009). Importantly, the hematuria in these patients, particularly in those who have previously received radiation therapy in the management of their prostate cancer, should be confirmed with endoscopic evaluation to be from a prostate source and not, for example, as a result of hemorrhagic cystitis or secondary bladder malignancy. Unfortunately, these tumors are typically invasive of the bladder and/or pelvic sidewall (T4) and the patients are often elderly and unwell. Thus treatment is primarily with palliative intent. Initial conservative measures, including catheter drainage with or without continuous bladder irrigation, suffice for most cases of mild prostatic bleeding. For patients in whom hematuria is not acutely life-threatening, palliative external beam radiotherapy with or without androgen deprivation therapy may be administered. Indeed, one series reported that hematuria from advanced prostate cancer responded to palliative radiation in 81% of patients at 6 weeks after treatment; however, durable symptom control was limited, such that the response rate 7 months after treatment in these patients was only 29% (Din et al, 2009). **Among patients who are not candidates for local therapy, as well as among patients in whom disease has recurred after previous local therapy, androgen deprivation therapy may resolve the hematuria** (Marshall and Narayan, 1993) **by decreasing prostate vascularity** (Kaya et al, 2005).

In the situation of persistent hematuria with prostate cancer, and in particular in the setting of bladder outlet obstruction, cystoscopy under anesthesia with fulguration and/or limited, or channel, transurethral resection of prostatic tissue should be undertaken. Moreover, selective internal iliac artery embolization, as has been reported for severe post-TURP bleeding (Barbieri et al, 2002; Michel et al, 2002), may be considered, although data on this approach in the setting of prostatic malignancy are scant. Ultimately, if bleeding persists or escalates, consideration should be given to urinary diversion, which initially may be attempted with percutaneous nephrostomy tube insertion. **With continued prostate hemorrhage, palliative extirpative surgery, which may be in the form of radical prostatectomy, but more typically requires cystoprostatectomy and conduit diversion, should be considered pending patients' clinical and comorbidity status.**

KEY POINTS: HEMATURIA FROM PROSTATIC ORIGIN

- BPH represents the most common cause of GH in men older than 60 years.
- 5α-Reductase inhibitors may be used for BPH-related GH.
- Androgen deprivation may be effective for patients with locally advanced prostate cancer with GH.
- Angioembolization and/or urinary diversion represent salvage options for management for patients with refractory hematuria, pending clinical status.

URETHRAL BLEEDING

Urethral bleeding (urethrorrhagia) is defined as bleeding emanating from the urethra at a point distal to the bladder neck, occurring separate from micturition (Gontero, 2013). A careful history and physical examination may help elucidate whether the source of bleeding is truly from the urethra as opposed to other sites within the lower urinary tract. For example, **blood at the urethral meatus in the absence of volitional micturition, initial hematuria, or blood at the start of urination frequently implies pathologic processes distal to the external urinary sphincter.** Of note, in women, differentiating urethral bleeding from that of gynecologic origin based on history alone may be challenging and pelvic examination is typically necessary to clarify the site of origin (Sandhu et al, 2009). Importantly, retrograde urethrogram and cystourethroscopy remain the mainstays for diagnosis in patients with suspected urethral bleeding, because direct visualization permits identification of pathologic processes in the urethra and biopsy and fulguration allow for histologic characterization and cessation of bleeding.

Causes of urethral bleeding are best classified by gender (Box 9-3). **In men, trauma to the urethral epithelium represents the most common cause of urethral bleeding.** For example, blunt trauma via straddle injury, kick to the perineum, or pelvic fracture often manifests with bleeding and concurrent urinary retention (Mundy and Andrich, 2011). Perineal or penile bruising, accompanied by a hematoma, often is a clear indication of injury related to trauma. **Retrograde urethrography is essential in instances of trauma when a urethral injury is suspected** (Avery and Scheinfeld, 2012). Meanwhile, a history of foreign body insertion in patients with hematuria may necessitate imaging to ensure no residual foreign elements remain that could perpetuate bleeding or result in subsequent calculus formation (Rahman et al, 2004). **Particular mention should be made to the evaluation of bloody urethral discharge and/or hematuria occurring in patients with a penile fracture. In this setting, prompt evaluation via retrograde urethrography or cystoscopy should be undertaken to evaluate for a urethral injury and to identify the nature and location of the injury before surgical exploration** (Avery and Scheinfeld, 2012).

Urethritis refers to infection or inflammation of the epithelial lining of the urethra and has been reported secondary to bacterial or viral infection, chemical irritants (i.e., spermicidal jelly), and, rarely, autoimmune systemic conditions (human leukocyte antigen B27 [HLA-B27] Reiter syndrome). Urethral discharge on palpation may be noted with urethritis in men. Urine microscopy and cultures, as well as urethral swabs for causative organisms, represent essential components of the evaluation.

Urethral tumors are rare, although blood per meatus may be a manifesting sign in patients with urothelial carcinoma, specifically in men who have undergone a radical cystectomy with urethra still in situ (White and Malkowicz, 2010). At the same time, urethral caruncles are benign urethral lesions typically originating from the posterior lip of the urethra, most commonly found in postmenopausal women (Conces et al, 2012). These lesions are thought to arise from prolapse of distal urethra as a consequence of estrogen deficiency. In addition to the classic presentation of dysuria, dyspareunia, and dribbling, women with a urethral diverticulum also may report intermittent episodes of bleeding, and urethral discharge may be noted on examination.

BOX 9-3 Differential Diagnosis for Urethral Bleeding

MALE

- Trauma
  - Blunt (straddle injury, kick to perineum)
  - Penetrating (foreign body insertion, failed urethral catheterization)
  - Intercourse related (penile fracture, masturbation)
- Urethritis
  - Bacterial (gonococcal, nongonococcal)
  - Viral
  - Chemical
  - Autoimmune (Reiter syndrome)
- Malignancy
  - Urothelial carcinoma
  - Squamous cell carcinoma (meatus/glans)
- Condyloma
- Calculus disease

FEMALE

- Trauma
  - Blunt (pelvic fracture)
  - Penetrating (foreign body)
- Urethral diverticulum
- Urethral caruncle
- Urethritis
- Malignancy
- Calculus disease

HEMATURIA ORIGINATING FROM THE UPPER URINARY TRACT

Hematuria emanating from the upper urinary tract is frequently asymptomatic, although macroscopic bleeding with clots can result in subsequent ureteral obstruction, with patients experiencing "clot colic," as well as anemia, and even rarely hemodynamic instability (Lano et al, 1979). Most often, hematuria from the upper tract manifests as total hematuria, or bleeding throughout the duration of the urinary stream (Mazhari and Kimmel, 2002), and may be characterized by wormlike clots passed per urethra. A variety of causes can result in bleeding from the upper tract (Box 9-4), with

BOX 9-4 Differential Diagnosis for Upper Urinary Tract Bleeding

- Renal glomerular diseases
  - IgA nephropathy (Berger disease)
  - Thin basement membrane disease
  - Acute glomerulonephritis (e.g., poststreptococcal)
  - Lupus nephritis
  - Hereditary nephritis (e.g., Alport syndrome)
- Renal tubulointerstitial diseases
  - Papillary necrosis
    - Sickle cell nephropathy
    - Analgesic nephropathy
  - Polycystic kidney disease
  - Medullary sponge kidney
- Vasculitis
  - Henoch-Schönlein purpura
  - Wegener granulomatosis
- Infection
  - Pyelonephritis
  - Xanthogranulomatous pyelonephritis
  - Renal tuberculosis
  - Fungal infection
- Obstruction
  - Ureteropelvic junction obstruction
  - Ureteral stricture
- Nephrolithiasis
- Malignancy
  - Renal cortical tumors (renal cell carcinoma, benign tumors)
  - Upper tract urothelial carcinoma
- Fibroepithelial polyp
- Vascular diseases
  - Renal arteriovenous malformations (congenital, acquired)
  - Iliac arterio-ureteral fistula
  - Renal artery aneurysm (especially ruptured)
  - Renal artery pseudoaneurysm
  - Renal artery and/or vein thrombosis
  - Hemangioma
  - Atheroembolic disease
  - Nutcracker syndrome
  - Loin-pain hematuria syndrome
- Trauma
  - Blunt
  - Penetrating
- Lateralizing essential hematuria

the most common causes of hematuria from the upper urinary tract including stones, trauma, and malignancy. The evaluation and management of these entities is described elsewhere. Herein, we highlight several particularly salient, albeit less frequent, causes of upper tract hematuria.

Medical Renal Disease

Glomerular diseases are a constellation of acquired or inherited conditions in which the glomeruli are damaged. Consequences include loss of RBCs and protein in the urine, with the clinical sequelae of hematuria, hypoproteinemia with associated edema, and reduced glomerular filtration rate. **Urinary findings suggestive of a glomerular cause include the presence of RBC casts in the urinary sediment, dysmorphic RBCs, and proteinuria** (Yun et al, 2004). Common acquired causes of glomerular diseases are covered in Chapter 46.

Meanwhile, tubulointerstitial diseases broadly refer to kidney diseases affecting structures in the kidney outside the glomerulus. For example, **sickle cell nephropathy is associated with sickle cell disease, whereby sickled erythrocytes decrease medullary blood flow, causing local ischemia, microinfarction, and papillary necrosis** (Pham et al, 2000). Analgesic nephropathy can likewise cause renal papillary necrosis and subsequently chronic interstitial nephritis. Percutaneous renal biopsy may be a valuable diagnostic modality when a suspicion exists for glomerular or tubulointerstitial causes of hematuria.

Vascular Conditions Affecting the Urinary Tract

A variety of vascular conditions can cause hematuria. For example, ureteroiliac artery fistula is an uncommon but potentially life-threatening cause of hematuria. **Predisposing factors include pelvic or vascular surgery, pelvic irradiation, extensive ureteral mobilization, and chronic ureteral stenting** (Muraoka et al, 2008). With regard to management, high mortality rates have been reported with surgical repair of ureteroiliac fistulas, and as such **angiographic localization with vascular stenting has become the current preferred management approach** (Keller et al, 1990). Renal arteriovenous malformations (AVMs), meanwhile, are abnormal communications between intrarenal arterial and venous systems, with congenital and acquired (iatrogenic) causes. **Acquired AVMs account for 75% of such cases and have been associated with renal biopsy, renal surgery (partial nephrectomy, nephrolithotomy), and trauma** (Muraoka et al, 2008). **Arteriography with selective angioembolization is considered the primary diagnostic and therapeutic option for suspected renal AVMs,** affording symptom resolution with maximal preservation of functional renal parenchyma. Thus **expeditious angiography should be considered for patients with a recent history of a renal procedure presenting with GH.** The goal of AVM embolization is eradication of the site where abnormal arterial and venous communication exists. Renal artery aneurysms, moreover, may be related to connective tissue disorders and are generally asymptomatic. Hypertension may be present in up to 90% of affected persons, and dissecting aneurysms may cause flank pain with GH. Renal artery aneurysms and pseudoaneurysms are generally managed via endovascular approaches in the hemodynamically stable patient, whereas surgical intervention is typically necessary in the unstable patient (Mohan and Stephens, 2013).

Additionally, **"nutcracker syndrome" (i.e., renal vein entrapment syndrome) is defined as the compression of the left renal vein between the abdominal aorta posteriorly and the superior mesenteric artery anteriorly.** Hematuria has been postulated to occur as a result of increase in left renal vein pressure causing small-volume rupture of thin-walled capillaries into the collecting system (Wolfish et al, 1986). Left renal vein transposition, superior mesenteric artery transposition, and nephrectomy have been described as surgical approaches for management of this condition (Hohenfellner et al, 2002). More recently, endovascular stenting to maintain a patent renal vein has been reported as well.

Lateralizing Essential Hematuria and the Evaluation of Upper Urinary Tract Bleeding

Lateralizing essential hematuria, also termed *benign essential hematuria* or *chronic unilateral essential hematuria*, is defined as macroscopic hematuria cystoscopically localized to one side of the urinary system (Nakada, 2003). Patients have typically had normal prior radiographic studies. Although rare, manifestations of lateralizing essential hematuria may range from minimally symptomatic GH to clot retention and anemia (Nakada, 2003). The differential diagnosis for this entity is as noted earlier for upper tract bleeding (see Box 9-4), although in many such cases no identifiable cause can be determined.

Cystoscopy at the time of bleeding may allow lateralization of the source of hematuria. Subsequently, in the absence of a clear cause for bleeding localized to the upper tract in a patient with lateralizing essential hematuria, direct endoscopic inspection with ureteropyeloscopy is recommended as a diagnostic and potentially therapeutic modality (Nakada, 2003). **Critical components of diagnostic ureteropyeloscopy include the judicious use of guidewires (to avoid inadvertent urothelial injury), low-pressure irrigation, and systematic evaluation of all calices from a superior-to-inferior approach** (Ankem and Nakada, 2006). Biopsy samples can be obtained for lesions suspicious for malignancy, and fulguration of such tumors or other noted sources of bleeding (i.e., hemangioma) can be accomplished as well.

KEY POINTS: URETHRAL BLEEDING AND HEMATURIA ORIGINATING FROM THE UPPER URINARY TRACT

- Urethral bleeding should be suspected with blood at the meatus and/or initial hematuria.
- A concern for traumatic urethral injury should prompt retrograde urethrogram.
- Urinary findings suggestive of a glomerular cause include the presence of RBC casts in the urinary sediment, dysmorphic RBCs, and proteinuria.
- In patients with GH after a recent renal procedure, expeditious angiography should be considered to allow for the diagnosis and management of renal AVM.

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