
Hematuria: etiology and evaluation for the primary care physician

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Asymptomatic microscopic and gross hematuria are common problems for the primary care physician. The exact definition of microscopic hematuria is debated, but is defined by one group as > 3 red blood cells/high power microscopic field. While the causes of hematuria are extensive, the most common differential diagnosis for

both microscopic and gross hematuria in adults includes infection, malignancy, and urolithiasis. Clinical evaluation of these patients often involves urological consultation with urine cytology, urine culture, imaging studies, and cystoscopy. Patients who have no identifiable cause after an extensive workup should be monitored for early detection of malignancy or occult renal disease.

Key Words: asymptomatic microscopic hematuria, gross hematuria, primary care

Introduction

Blood in the urine can originate from any site along the urinary tract and can be a sign of a serious underlying disease process. The prevalence of hematuria in adults ranges from 2.5% to 21.1%¹ and appropriate evaluation of these patients is critical as 5% of patients with microscopic hematuria and 20% to 40% of patients with gross hematuria will be found to have a malignancy.² This is an important point for the primary care physician who is often the first to see these patients. Patients may present with

symptomatic (fever, nausea, vomiting, flank pain, dysuria, urgency, frequency, etc.) or asymptomatic hematuria. Patients who are symptomatic often have a readily identifiable cause such as urinary calculi stone or urinary tract infection. Appropriate evaluation is based on the presenting signs and symptoms. The focus of this article will be the etiology and evaluation of asymptomatic microscopic and gross hematuria in adults.

There are no formal guidelines from the American Urological Association, American Cancer Society, or the U.S. Preventive Services Task Force in screening asymptomatic patients for hematuria, although a routine urinalysis is often included as part of a routine physical examination.³ It is imperative that the decision to screen an asymptomatic patient be left to the primary care physician after a thorough history and

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TABLE 1. Risk factors for significant urological disease

Smoking history
Occupational exposure to chemicals or dyes (benzenes or aromatic amines)
History of gross hematuria
Age > 40 years
Previous urological history
History of irritative voiding symptoms
History of urinary tract infection
Analgesic abuse
History of pelvic irradiation
Cyclophosphamide

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physical along with careful attention to risk factors. Table 1 reviews risk factors for significant urological disease in patients with hematuria.

Definitions

Hematuria can be classified as gross (visible to the naked eye) or microscopic. Gross hematuria must be distinguished from other causes of red urine outlined in Table 2. There is controversy in the literature over the exact definition of microscopic hematuria but the latest American Urological Association (AUA) guidelines define it as > 3 red blood cells (RBC) per high powered field on two of three properly collected urine analysis specimens in both males and females. Because the degree of hematuria does not necessarily correlate with the severity of disease, patients at high risk for malignancy, as outlined in Table 1, should have an evaluation after a single microscopic exam revealing 3 RBC per high powered field.³

Although there is considerable overlap, hematuria in the clinical setting can be most broadly classified into medical and surgical causes to help facilitate initial management, Table 3. Young patients with medical causes, such as glomerulonephritis, may benefit from a renal biopsy to guide medical management whereas patients with surgical causes often require urological intervention to diagnose and treat the problem.

TABLE 2. Causes of discolored urine

With a positive dipstick for blood

Red urine

Hematuria
Hemoglobinuria
Myoglobinuria
Menstrual contamination

Orange urine

Dark yellow urine

With a negative dipstick for blood

Drugs

Aminosalicylic acid
Phenazopyridine
Laxatives (Phenophtalein, Senna)
Ibuprofen
Rifampin
Methyldopa
Phenytoin

Foods

Beets, berries, food coloring (rhodamine B)

Metabolic

Porphyryns
Serratia marcescens
Urate crystalluria

Phenazopyridine
Sulfasalazine
Carrots

Bilirubin
Vitamin A

TABLE 3. Medical and surgical causes of hematuria

Medical	Surgical
Urinary tract infection	Urinary calculi
Glomerulonephritis (IgA nephropathy most common)	Urinary tract malignancy
Interstitial nephritis (most often drug related; many described including penicillins and a wide variety of antibiotics)	Benign prostatic hypertrophy
Exercise induced hematuria	Iatrogenic from recent instrumentation or surgery
Anticoagulation	Trauma
Papillary necrosis (ischemic in diabetics or sickle cell disease or drug related including non-steroidal anti-inflammatory agents)	Urethral stricture
Hypercalciuria	Cystocele
Radiation cystitis/nephritis	Abdominal aortic aneurysm
Lymphoma	Renal artery stenosis
Urethrorrhagia	Ureteropelvic junction obstruction
Arteriovenous malformation	Vesicoureteral reflux
Benign familial hematuria	Posterior urethral valves
Alport syndrome	
Hematologic or coagulation abnormalities	
Endometriosis	

Detection of microscopic hematuria

Urine should be collected from a freshly voided, clean catch, midstream urine specimen. A urine sample for analysis should not be left at room temperature for more than 2 hours and if necessary, it should be refrigerated.² The urinary dipstick is the most common test used to evaluate urine. Hemoglobin catalyzes an oxidation reaction resulting in a color change proportional to the concentration of hemoglobin, thus providing a semi quantitative analysis of the number of RBCs. A positive dipstick (whether trace or 3+) should immediately be followed by a confirmatory microscopic examination as a false positive test can result from hemoglobinuria, myoglobinuria, or contaminants such as hypochlorite and povidone-iodine.¹⁻³ Dip sticks may also yield additional information concerning the etiology of hematuria such as the presence of proteinuria suggesting intrinsic renal disease or the presence of leukocytes suggesting infection or inflammation. In a patient with a urinary diversion such as a urostomy, microscopic hematuria

is frequent benign finding and the need for further evaluation based on the clinical setting.

A formal microscopic exam of the urine involves centrifuging 10 cc of urine at 2000 rpm for 5 minutes. The supernatant is discarded and the sediment is resuspended in 1 cc and examined under high power (40X). Significant hematuria is defined as more than 3 RBCs per high power field.^{1,3} Numerous squamous or epithelial cells suggest contamination and, if necessary, a catheterized specimen should be obtained.

Etiology

The most common causes of hematuria in adults include urinary tract infections (UTI), neoplasms, and urolithiasis. In children, glomerulonephritis accounts for half the cases of hematuria followed by UTI as the second most common cause. The most common causes of hematuria by age are outlined in Table 4.² Hematuria can be further categorized into the following areas: inflammatory, neoplastic, metabolic, traumatic, and miscellaneous causes.

TABLE 4. Most common causes of hematuria by age

Age	Cause
0 to 20 y/o	Acute glomerulonephritis
	Urinary tract infection
	Congenital anomalies
	Hypercalciuria
20 to 60	UTI
	Bladder cancer
	Urolithiasis
60 and older	UTI
	Bladder cancer
	BPH

Modified from Gillenwater JY, Grayhack JT, Howards SS, et al (ed): Adult and Pediatric Urology, 3rd ed. Chicago, Mosby-Year Book, 1996.

Inflammatory

Urinary tract infections (pyelonephritis, cystitis, prostatitis, urethritis) can lead to hematuria and are often found in association with pyuria or bacteruria.

Glomerulonephritis is a common cause of hematuria in the pediatric population and is less commonly seen in adults. Primary IgA nephropathy (Berger disease) is the most common type of glomerulonephritis throughout the world. History and physical findings suggestive of glomerulonephritis can include flank pain and hematuria which usually starts within 24 hours a day of an upper respiratory tract infection. IgA nephropathy can also be seen in poststreptococcal glomerulonephritis (PSGN), Henoch Schonlein purpura (HSP), systemic lupus erythematosus (SLE), and hemolytic uremic syndrome (HUS). Rarely, HIV, liver failure, celiac disease, and autoimmune diseases (rheumatoid arthritis, ankylosing spondylitis, etc) and be causative of IgA nephropathy. Other less common types of glomerulonephritis include membranoproliferative glomerulonephritis, focal glomerular sclerosis and rapidly progressing glomerulonephritis.

Glomerulonephritis is responsible for 30% of all cases of pediatric hematuria. It has the potential to cause progressive renal failure in up to 40% of patients. PSGN often follows a streptococcal pharyngitis and presents as a nephritic syndrome (hypertension, proteinuria, hematuria, and peripheral edema). HSP is a systemic vasculitis caused by deposition of antibodies in the skin and kidney. The etiology of HSP is unclear but may result from streptococcal or viral (Coxsackie, Parvovirus B19, adenovirus) infection.⁴ It is characterized by palpable purpura on the buttocks and legs, abdominal pain, and vomiting. SLE has

many systemic manifestations including arthralgia, joint swelling, and a malar rash on the cheeks and nose. Hemolytic uremic syndrome (microangiopathic hemolytic anemia, renal failure, and thrombocytopenia) often follows an E. coli O157:H7 diarrhea.

Laboratory urine studies will reveal dysmorphic erythrocytes, red cell casts, and proteinuria with glomerulonephritis. Renal biopsy is necessary to confirm the diagnosis.

Radiation cystitis can be seen following radiation therapy for pelvic malignancies such as prostate, cervical or rectal cancer. Its counterpart, radiation nephritis, typically occurs when the dose to the kidney exceeds 23 Gy. Radiation induced damage to the urinary tract is much less common today due to improved delivery techniques and shielding of the kidneys.

Other pathogens can cause inflammatory hematuria. Less frequent causes include genitourinary tuberculosis, malaria, and schistosomiasis. These are uncommon in the United States and are often found in endemic regions of the world.

Neoplastic

Any genitourinary cancer can cause hematuria including renal cell carcinoma, urothelial carcinoma, urethral cancer, and locally advanced prostate cancer. Benign tumors of the genitourinary tract, other than benign prostatic hypertrophy, are uncommon. Localized early stage prostate cancer rarely causes bleeding. Patients at high risk for neoplasia, Table 1, include age > 40 years, smoking history, chemical exposure, irritative voiding symptoms (urgency, frequency, dysuria, nocturia), gross hematuria, or history of any genitourinary cancer.³ Approximately 5% of patients with microscopic hematuria and up to 40% of patients with gross hematuria will ultimately be found to have a neoplasm, most commonly urothelial carcinoma of the bladder.² Painless gross hematuria should always be considered urothelial cancer until proven otherwise. The classic triad of hematuria, flank pain, and a palpable flank mass for renal cell cancer is now rarely seen as 48%-66% of renal masses are discovered incidentally on imaging studies for other reasons and thus treated before they progress to large tumors.⁵

Metabolic

Urinary calculi in the kidney, ureter, or bladder may account for one third of the cases of microscopic hematuria. The lifetime incidence of stone disease in men ranges from 4% to 9% and 1.7% to 4.1% in women. Caucasians are at highest risk and African American at lowest risk. History is particularly important as more than 50% of first time stone formers will have a second

stone in their lifetime.⁶ The most common urinary calculi are calcium oxalate, calcium phosphate and uric acid.

Hypercalciuria can lead to hematuria presumably through irritation of the urothelium by microcalculi. A spot urinary calcium to creatinine ratio > 0.2 is suggestive and can be confirmed with a 24 hour urine analysis for total calcium.⁶ Hypercalciuria can occur as a result of calcium supplementation, hyperparathyroidism, immobility, tubular leak of calcium, or increased GI absorption.

Traumatic

Exercise induced hematuria (also known as runner's hematuria or jogger's kidney) is thought to result from a combination of altered glomerular permeability and hypoxic damage to the nephron as a result of decreased renal blood flow during exercise and/or direct trauma to the bladder base. There is no gender predilection and hematuria is directly related to exercise intensity with hydration somewhat protective.⁷

Blunt and penetrating trauma to the genitourinary system often presents with a clearly defined history or as symptomatic hematuria. Hematuria is the best indicator of genitourinary system injury and such patients require imaging, preferably CT with intravenous contrast [8].

Miscellaneous

Urethral stricture should be considered in patients who complain of bladder outlet obstruction type symptoms (hesitancy, intermittency, weak stream, straining, or incomplete emptying of the bladder) and have a history of prior urinary tract infection, sexually transmitted infection, instrumentation or catheterization.

Anticoagulation or aspirin use should never be automatically attributed to be the cause of hematuria. A recent study examined patients hospitalized with gross hematuria on aspirin or warfarin and found malignancy in 24% and significant treatable findings in half. In the same study, 18% of patients supratherapeutic on coumadin were also found to have tumors, suggesting that any degree of gross hematuria should be evaluated in patients on anticoagulation.⁹

Medications can cause tubular necrosis and hematuria especially when given in excessive amounts. They include nephrotoxic agents (aminoglycosides, NSAIDs, antineoplastic drugs), analgesics (phenacetin), penicillins and sulfas (resulting in interstitial nephritis) and others.

Benign prostatic hypertrophy can lead to rupture of small periurethral veins and should only be a diagnosis

of exclusion after more serious diseases have been ruled out.

There are numerous less common causes that are beyond the scope of this article. They include loin pain hematuria syndrome, nutcracker syndrome, endometriosis of the urinary tract, cystic renal disease, vascular malformations, ureteropelvic junction obstruction, Alports syndrome, benign familial hematuria, and uncommon bleeding diathesis.²

History and physical

A thorough history is critical to the evaluation of any patient and should include tobacco use, exposure to rubber or dyes, and prior urological history. Menstrual history and evidence of abnormal uterine bleeding should be sought and can be a cause for a false positive hematuria determination. Physical examination should focus on hypertension which can be seen with underlying renal pathology (nephritic syndrome or renal vascular disease), rashes with HSP, edema with nephrotic syndrome, pallor secondary to anemia with hemolytic anemia or renal failure, and a palpable mass with hydronephrosis or malignancy. A pelvic exam in females may reveal a urethral mass (caruncle or diverticulum) and a rectal exam may reveal a nodule or enlarged prostate in males.

Laboratory studies

Basic laboratory studies including serum electrolytes and creatinine, complete blood count, urine analysis with microscopic examination, and urine culture are necessary. Based on the clinical setting, evaluation for bleeding diathesis may be indicated and must be obtained prior to invasive procedures such as renal biopsy.

Many soluble tumor markers and tumor cells are released into urine, especially with storage of urine in the bladder. As a result, numerous tests have been designed for testing voided urine for the presence of cancer. Point of care assays that can be performed in the office setting include bladder tumor antigen (BTA stat), nuclear matrix protein (NMP) 22, and urinary bladder cancer (UBC).¹⁰ Urinary cytology is the most widely used test for urothelial cancer with a sensitivity of 52% to 80% and a specificity of 92% to 97%.¹¹ It requires a urine sample to be sent to a central lab and the individual cells examined by a pathologist. Given its low sensitivity urine cytology is not used as a screening test. Instead, because of its high specificity, an abnormal cytology means an identifying lesion must be found. Urinary cytology has no role in the detection of renal or prostate cancer. The clinical

utility of bladder tumor markers (BTA stat, NMP-22, and UBC) will likely be in the decision to perform or delay surveillance cystoscopy in patients with already diagnosed bladder cancer and possibly to screen high risk patients for the early detection of bladder cancer. However, given the extensive experience with urine cytology and its reliably high specificity in the hands of experienced pathologists, urinary cytology should continue to remain the test of choice.

Red blood cell dysmorphism studies can help to identify glomerular from non-glomerular bleeding.¹² This is based on the principle that glomerular bleeding produces smaller and more dysmorphic erythrocytes than bleeding from other sites in the urinary tract. In the future, these studies may save patients with a glomerular source of bleeding from a full urological evaluation. However, the low sensitivity of these tests along with lack of prospective clinical data justifying their safety, reliability, and cost effectiveness currently precludes their routine clinical use.

Urology and nephrology evaluation

All patients with gross hematuria and any high risk patient with microscopic hematuria should be referred for a complete urological evaluation. The core components of urological evaluation may include upper tract (kidney and ureter) imaging, lower tract (bladder and urethra) evaluation with cystoscopy, urine analysis, urine cytology, and a urine culture. Figure 1 provides an overview of the evaluation of hematuria in adults as recommended by the American Urological Association Best Practices Guidelines.

Patients with asymptomatic microscopic hematuria and proteinuria, dysmorphic RBCs, red cell casts, or elevated serum creatinine should have an evaluation for primary renal disease by a nephrologist. Hypertension in the setting of hematuria is worrisome for chronic renal disease.

Low risk patients with microscopic hematuria attributed to benign causes such as exercise, sexual activity, or menstruation should have a repeat urinalysis in 48 hours.¹³ Patients with documented urinary tract calculi and asymptomatic microscopic hematuria should have a repeat urinalysis after stone has been cleared.

Approximately 10% to 20% of patients will have no identifiable cause of microscopic hematuria after extensive urological workup.¹⁴ These patients should be closely monitored with yearly physical examination, urine analysis, and cytology to facilitate the early detection of malignancy or primary renal disease.

It is appropriate to refer patients with microscopic

or gross hematuria for evaluation by a urologist after obtaining initial laboratory studies.

Imaging

Upper tract imaging can be performed via excretory urography (EU), CT urogram (CTU), or a combination of renal ultrasound (RUS), a kidney-ureter-bladder film (KUB) and retrograde pyelography in the operating room.

The CTU has largely replaced EU as it provides superior sensitivity for stones, renal masses and when properly performed, comparable sensitivity to EU for urothelial lesions.^{15,16} The CTU is a three phase CT scan with a non contrast phase evaluating for stones, a contrast enhanced nephrographic phase for renal masses, and delayed images of the renal collecting system and ureters for filling defects. It does not require oral or rectal contrast and it can be done rapidly in an outpatient setting. The AUA guidelines suggest that low risk patients with microscopic hematuria who have a finding of urolithiasis on non contrast CT scan do not need further imaging with contrast.¹³ Disadvantages of CTU over EU include cost and recent concerns over radiation exposure.

RUS is a cost efficient and commonly used imaging modality in urology that does not expose the patient to radiation or potentially nephrotoxic contrast. It is good for differentiating solid from cystic masses, assessing for hydronephrosis, stones and evaluating the renal vasculature. Disadvantages of ultrasound include its low sensitivity for small renal masses and non-calcified urolithiasis along with the quality of the study being operator dependent.¹⁷ Currently there are no prospective trials comparing CTU with RUS but CT is thought to be far more sensitive for small renal masses and urolithiasis. Thus, in patients with risk factors for urological disease, as outlined in Table 1, who can tolerate contrast, a CTU is preferred. For low risk patients a KUB and RUS are appropriate initial imaging tests.¹³ A KUB can identify urinary tract stones that contain calcium, but may not identify uric acid calculi.

Magnetic resonance imaging (MRI) is not commonly used in the evaluation for hematuria because of cost, poor visualization of stones, and the time intensive nature of the study.¹⁷ MRI provides superior visualization of soft tissue structures, particularly the kidney and adrenal glands, when compared to CT. MRI is contraindicated in patients with pacemakers, aneurysmal clips, and retained foreign bodies as the magnetic field can cause object migration.¹⁸

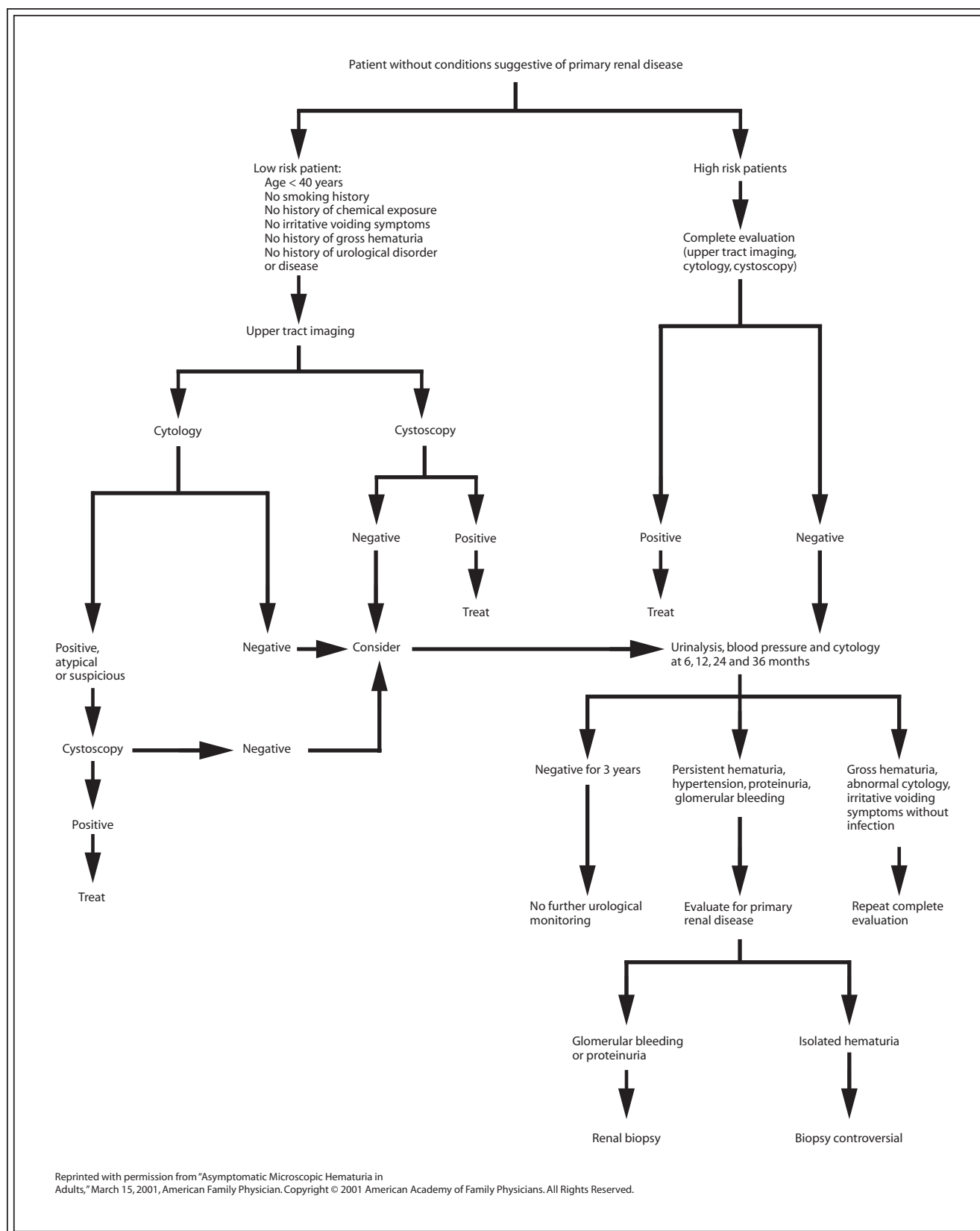


Figure 1. Workup of hematuria in adults based on AUA best practice policy recommendations

Patients with renal insufficiency and dehydration are at greatest risk for intravenous contrast nephrotoxicity and thus serum blood urea nitrogen and creatinine should be checked prior to contrast administration. Many centers consider a serum creatinine of 2.0 mg/dl or greater as a contraindication to the use of IV contrast. Diabetics should not take metformin for 48 hours before and after contrast administration to minimize the risk of fatal lactic acidosis. Adequate hydration is essential to minimize any nephrotoxicity. Patients with a prior adverse reaction to contrast, multiple drug allergies, and seafood allergy are at higher risk for adverse reactions to intravenous contrast.¹⁹ These patients should instead have retrograde pyelography performed in the operating room, to evaluate for urothelial lesions and stones, along with a renal ultrasound¹³ and KUB to evaluate for renal masses and stones.

Although the bladder can be seen on imaging, the lower tracts can only be evaluated via cystoscopy. There is no substitute for direct visualization of the urothelium to determine the presence of tumors on the lining of the bladder.

Conclusions

Asymptomatic hematuria is a common problem with numerous etiologies, most commonly infection, urolithiasis, and malignancy in adults, with medical renal diseases relatively uncommon in adults as a cause. The burden to initiate an investigation for hematuria often falls on the primary care physician and should be guided by history, physical examination, and assessment of risk factors. Additional evaluation is often required by the urologist or nephrologist. After confirmation of asymptomatic microscopic hematuria, patient evaluation often involves urine culture, urine cytology, upper tract imaging, and cystoscopy. These studies, while invasive, time consuming, and potentially costly to the health care system, represent the current standard for the workup of asymptomatic and gross hematuria. Future research will hopefully identify a time and cost efficient test that spares the majority of patients without malignancy an extensive initial workup.

Disclosure

Dr. Leonard Gomella is a consultant for GlaxoSmithKline and TAP Pharmaceuticals. He is a member of the Speakers' Bureau for Astra Zeneca. □

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DISCUSSION

Question (Dr. Laroche):

Do you routinely order a urinary sediment to exclude glomerulopathy?

Answer (Dr. Gomella):

A formal urinalysis that includes a microscopic evaluation of the urinary sediment is useful especially in patients who are suspected of having glomerulonephritis or other forms of intrinsic renal disease. In patients with urolithiasis it may allow detection of the specific type of stone. Today most initial screening is by urinary dipstick, with further testing, including microscopic evaluation of the sediment based on the clinical setting.

Question (Dr. Rosenberg):

How should a PCP evaluate a patient with risk factors for renal cancer (example: smoking) with long-standing, previously described and investigated hematuria?

Answer (Dr. Gomella):

This is an area that is not well defined and clinical judgement should be employed. The data suggests that only a small percentage of small renal masses presumed to be RCC grow significantly if managed conservatively and followed with serial imaging. In fact most renal masses exhibit slow or undetectable growth. This suggests that periodic imaging where there is an increased suspicion for renal cell carcinoma is likely to detect these lesions at an early stage. This is reassuring in a patient with hematuria where initial evaluation and imaging failed to demonstrate any renal masses.