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Etiology and evaluation of hematuria in adults

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INTRODUCTION

Hematuria that is not explained by an obvious underlying condition (eg, cystitis, ureteral stone) is fairly common. In many such patients, particularly young adult patients, the hematuria is transient and of no consequence [1]. On the other hand, there is an appreciable risk of malignancy in older patients (eg, over age 35 years) with hematuria, even if transient [2-4]. However, even among older patients, a urologic cause for the hematuria can often not be identified (61 percent in a series of 1930 patients referred to a hematuria clinic) [2]. (See 'Transient or persistent hematuria' below.) (Related Pathway(s): Hematuria: Evaluation in adults.)

The etiology and evaluation of hematuria in adults will be reviewed here (figure 1 and algorithm 1). The approach in children is discussed separately. (See "Evaluation of microscopic hematuria in children" and "Evaluation of gross hematuria in children".)

DEFINITION OF HEMATURIA

Hematuria may be visible to the naked eye (called gross hematuria) or detectable only on examination of the urine sediment by microscopy (called microscopic hematuria).

Gross hematuria — Gross hematuria is suspected because of the presence of red or brown urine. The color change does not necessarily reflect the degree of blood loss, since as little as 1 mL of blood per liter of urine can induce a visible color change. In addition, the intermittent excretion of red to brown urine can be seen in a variety of clinical conditions other than bleeding into the urinary tract (see "Urinalysis in the diagnosis of kidney disease", section on 'Red to brown urine'). Gross hematuria with passage of clots usually indicates a lower urinary tract source but can be seen with some forms of intrarenal bleeding (eg, kidney cancer).

As contamination with blood is a possibility in menstruating and postpartum women, urine for analysis is best obtained when the other cause of bleeding has ceased. If this is not possible, a tampon can be inserted, and urinalysis can be obtained after the perineum is cleansed.

The initial step in the evaluation of patients with red urine is centrifugation of the specimen to see if the red or brown color is in the urine sediment or the supernatant (algorithm 2).

Hematuria is responsible if the red to brown color is seen only in the urine sediment, with the supernatant being clear. A rare exception is that lysis of red blood cells (RBCs) in patients with gross hematuria and very dilute urine can result in a red supernatant.

If, on the other hand, it is the supernatant that is red to brown, then the supernatant should be tested for heme (hemoglobin or myoglobin) with a urine dipstick:

- A red to brown supernatant that is negative for heme (hemoglobin or myoglobin) is a rare finding that can be seen in several conditions, including porphyria (table 1), the use of the bladder analgesic phenazopyridine, and the ingestion of beets in

susceptible subjects. (See "Urinalysis in the diagnosis of kidney disease" and "Porphyrias: An overview", section on 'Presenting findings'.)

- A red to brown supernatant that is positive for heme is due to myoglobinuria or hemoglobinuria. How these disorders can be distinguished is discussed elsewhere. (See "Urinalysis in the diagnosis of kidney disease", section on 'Hemoglobinuria and myoglobinuria'.)

Acute kidney injury — Gross (visible) hematuria occurring in patients with underlying glomerular disease has been associated with the development of transient acute kidney injury. Kidney biopsy shows distension of many renal tubules by intratubular RBCs and tubular cell injury consistent with acute tubular necrosis. This association has been best described in patients with IgA nephropathy but has also been noted in case reports of patients with thin basement membrane disease and lupus nephritis who were over-anticoagulated with warfarin (international normalized ratio [INR] >4.0) or other anticoagulants such as dabigatran [5-8]. (See "Treatment and prognosis of IgA nephropathy", section on 'Acute kidney injury with gross hematuria'.)

Microscopic hematuria — Microscopic hematuria refers to blood detectable only on examination of the urine sediment by microscopy.

Microscopic hematuria may be discovered incidentally when blood (either RBCs or hemoglobin) is found on a urinalysis or dipstick done for other purposes. Although abnormal hematuria is commonly defined as the presence of three or more RBCs per high-power field in a spun urine sediment, there is no "safe" lower limit below which significant disease can be excluded (picture 1) [9]. Lowering the cut-off value of RBCs chosen to define hematuria results in a greater number of false positive test results (ie, no underlying abnormality is found). On the other hand, if higher cut-off values are chosen, it is more likely that the test will miss the presence of significant abnormalities.

The role of the urinalysis in distinguishing glomerular from nonglomerular bleeding is discussed below. (See 'Glomerular versus nonglomerular bleeding' below.)

Urine dipstick — The urine sediment (or direct counting of RBC per mL of uncentrifuged urine) is the gold standard for the detection of microscopic hematuria (which is defined as 3 RBCs or more per high-power field). Dipsticks for heme detect 1 to 2 RBCs per high-power field and are therefore at least as, or more, sensitive as urine sediment examination, but they result in more false positive tests due to the following:

- Semen, which is present in the urine after ejaculation and may cause a positive heme reaction on the dipstick [10]
- An alkaline urine with a pH greater than 9 or contamination with oxidizing agents used to clean the perineum
- The presence of myoglobinuria or hemoglobinuria

Thus, a positive dipstick test must always be confirmed with microscopic examination of the urine. Rarely, a very dilute urine produces osmotic lysis of almost all of the urinary RBCs, resulting in an apparently false positive test (because the dipstick detects hemoglobin but no RBCs are visible). This does not constitute a false positive test.

False negative tests with the urine dipstick are unusual; as a result, a negative dipstick usually excludes abnormal hematuria [11]. False negative dipstick tests have been reported in patients ingesting large amounts of vitamin C; the clinical relevance of this observation is unknown [12].

ETIOLOGY

Hematuria may be a symptom of an underlying disease, some of which are life threatening and some of which are treatable (figure 1). The causes vary with age, with the most common being inflammation or infection of the prostate or bladder, stones, and, in older patients, a kidney or urinary tract malignancy or benign prostatic hyperplasia (BPH) (figure 2) [9,13-19].

Rarely, hematuria is factitious, with blood added to an unwitnessed urine specimen after voiding (eg, from a finger stick) [20]. Factitious hematuria can be documented by the absence of hematuria in a urine specimen obtained under direct observation.

INITIAL EVALUATION

As a general principle, hematuria itself is not imminently dangerous unless nonglomerular bleeding is so brisk that it causes clots that obstruct the ureter(s), clots that obstruct the bladder outlet causing urinary retention, or blood loss that results in anemia. Hematuria is common and frequently benign in young patients, and a cause is often not identified [1]. (See 'Transient or persistent hematuria' below and 'Unexplained hematuria' below.)

By contrast, even transient hematuria may be a symptom of an underlying serious condition, particularly in patients over age 35 years. (See 'Risk factors for malignancy' below.)

Overall approach to the evaluation — The first step in the evaluation of patients with a positive dipstick for heme or with red or brown urine is to confirm the presence of hematuria by microscopic analysis of a fresh, centrifuged specimen (algorithm 1). As noted above, hematuria is defined as 3 or more red blood cells (RBCs) per high-power field in a spun urine sediment. In patients with red or brown urine, the presence of hematuria can be confirmed if the sediment is red or brown after centrifugation of the specimen (algorithm 2). (See 'Definition of hematuria' above.) (Related Pathway(s): Hematuria: Evaluation in adults.)

Microscopic hematuria identified in a woman during her menses, or in a patient shortly after vigorous exercise or acute trauma, should be confirmed by repeating the urinalysis. In menstruating women, the urinalysis should be repeated later in the cycle once menstrual bleeding has ceased. If this is not possible, a tampon can be inserted, and urinalysis can be obtained after the perineum is cleansed. In patients who had hematuria identified in the setting of vigorous exercise, the urinalysis should be repeated approximately four to six weeks later during a period of no exercise. Patients with acute trauma and microscopic hematuria should have a confirmatory urinalysis after six weeks.

Patients who present with hematuria and unilateral flank pain suggestive of obstructive nephrolithiasis should undergo imaging (noncontrast computed tomography [CT] or ultrasound with or without an abdominal radiograph) as the first test in the evaluation (see "Diagnosis and acute management of suspected nephrolithiasis in adults", section on 'Diagnostic imaging'). Historical features and signs or symptoms that provide clues to specific causes of hematuria are presented below (see 'Historical clues' below). In other patients with hematuria, we take the following approach to the evaluation (algorithm 1):

- Patients who have findings suggestive of urinary tract infection (eg, fever, dysuria, presence of white blood cells [WBCs] in the urine, positive dipstick for nitrite) should undergo urine culture to evaluate for urinary tract infection. In patients with urinary tract infection, the infection should be treated and the urinalysis should be repeated approximately six weeks after completion of antibiotic therapy in order to determine if the hematuria is persistent. (See "Acute simple cystitis in women", section on 'Diagnostic approach' and "Acute simple cystitis in men", section on 'Diagnostic approach'.)

- In uninfected patients or those without findings suggestive of infection, the subsequent evaluation depends upon whether the hematuria is gross or microscopic:

  - If there is gross hematuria with visible blood clots in the urine (which may lead to urinary tract obstruction), then CT of the abdomen and pelvis without and with contrast for urography, also called CT urography (CTU), should be performed, and the patient should be referred for urgent urology evaluation for cystoscopy and further evaluation.

  - If there is gross hematuria without visible blood clots in the urine:

    - Patients with acute kidney injury or findings suggestive of glomerular bleeding should be referred to nephrology. (See 'Glomerular versus nonglomerular bleeding' below and "Definition and staging criteria of acute kidney injury in adults".)

    - Nonpregnant patients without acute kidney injury or findings suggestive of glomerular bleeding should have CTU and urology referral for cystoscopy. (See 'Imaging' below and 'Cystoscopy' below.)

    - Pregnant patients should have kidney and bladder ultrasound rather than CT, largely to rule out ureteral obstruction or urolithiasis. If ultrasound demonstrates hydronephrosis, magnetic resonance urography (MRU) without contrast is

used to localize the point of obstruction (see 'Imaging' below). Further evaluation should be avoided, if possible, until after delivery.

- If there is microscopic hematuria:
  - Patients with acute kidney injury or findings suggestive of glomerular bleeding should be referred to nephrology. (See 'Glomerular versus nonglomerular bleeding' below and "Definition and staging criteria of acute kidney injury in adults".)
  - Pregnant patients should have kidney and bladder ultrasound; further evaluation should be avoided, if possible, until after delivery.
  - Nonpregnant patients who have risk factors for malignancy of the kidney or bladder, or have a prior history of a urologic disorder (eg, benign prostatic hypertrophy, nephrolithiasis), should undergo CTU and urology referral for cystoscopy. (See 'Risk factors for malignancy' below and 'Imaging' below and 'Cystoscopy' below.)
  - Nonpregnant patients who have no findings suggestive of glomerular bleeding, no risk factors for malignancy, and no history of urologic disease do not require imaging studies or cystoscopy. However, nephrology evaluation and imaging may be appropriate in such patients who have persistent, unexplained microscopic hematuria for several years.

Historical clues — There are often clues from the history that point toward a specific diagnosis. These include:

- Concurrent pyuria and dysuria, which are usually indicative of a urinary tract infection but may also occur with bladder malignancy.
- A recent upper respiratory infection or symptoms of upper respiratory disease raise the possibility of postinfectious or infection-related glomerulonephritis, immunoglobulin A (IgA) nephropathy, vasculitis, anti-glomerular basement membrane (GBM) disease, or sometimes hereditary nephritis. (See "Glomerular disease: Evaluation and differential diagnosis in adults".)
- A positive family history of kidney disease, as in hereditary nephritis, polycystic kidney disease, or sickle cell disease.
- Unilateral flank pain, which may radiate to the groin, usually suggests ureteral obstruction due to a calculus or blood clot but can occasionally be seen with malignancy or IgA nephropathy.
- Symptoms of prostatic obstruction in older men such as hesitancy and dribbling. The cellular proliferation in benign prostatic hyperplasia (BPH) is associated with increased vascularity, and the new vessels can be fragile. There is some controversy about whether hematuria is more common in these patients than in age-matched controls [15,21]. However, there is general agreement that the presence of BPH should not dissuade the clinician from pursuing further evaluation of hematuria, particularly since older men are more likely to have more serious disorders such as cancer of the prostate or bladder. Among those with gross hematuria in whom no other cause can be identified, finasteride usually suppresses the hematuria [22,23]. (See "Medical treatment of benign prostatic hyperplasia".)
- Recent vigorous exercise or trauma in the absence of another possible cause. (See "Exercise-induced hematuria".)
- History of a bleeding disorder or bleeding from multiple sites due to excessive anticoagulant therapy. However, it should not be assumed that hematuria alone can be explained by chronic anticoagulation. In one report of 243 patients prospectively followed for two years, the incidence of hematuria was similar to that in a control group not receiving warfarin [24]. Furthermore, evaluation of patients who developed hematuria revealed a urinary cause in 81 percent of cases. Infection was most common, but papillary necrosis, renal cysts, and several malignancies of the bladder were also found.

  These observations indicate that hematuria in an anticoagulated patient should be evaluated in the same fashion as in other patients.
- Cyclic hematuria in women that is most prominent during and shortly after menstruation, suggesting endometriosis of the urinary tract [25]. Contamination with menstrual blood is always a possibility and should be ruled out by repeating the

urinalysis when menstruation has ceased. (See "Endometriosis: Pathogenesis, clinical features, and diagnosis".)

- Medications that might cause nephritis (usually with other findings, typically with kidney function impairment). (See "Clinical manifestations and diagnosis of acute interstitial nephritis", section on 'Drugs'.)
- Black patients should be screened for sickle cell trait or disease, which can lead to papillary necrosis and hematuria. (See "Renal manifestations of sickle cell disease".)
- Travel or residence in areas endemic for *Schistosoma haematobium* or tuberculosis.
- Sterile pyuria with hematuria, which may occur with renal tuberculosis, analgesic nephropathy, toxic nephropathy, and other interstitial diseases.

Glomerular versus nonglomerular bleeding — The identification of the glomeruli as the source of bleeding can optimize the subsequent evaluation. In particular, patients with clear evidence of glomerular hematuria may **not** need to be evaluated for potentially serious urologic disease unless there is some other reason to do so [26]. Although the identification of dysmorphic RBCs, proteinuria, cellular casts, and/or kidney function impairment warrants a nephrologic evaluation, they do not necessarily preclude the need for a urologic workup [27]. (See "The kidney biopsy", section on 'Indications'.)

Glomerular hematuria may result from immune-mediated injury to the glomerular capillary wall or, in noninflammatory glomerulopathies such as thin basement membrane nephropathy, from localized gaps in the glomerular capillary wall [28]. (See "Thin basement membrane nephropathy (benign familial hematuria)".)

Signs of glomerular bleeding (best identified by a nephrologist or other experienced examiner) include RBC casts, a dysmorphic appearance of some RBCs, and, in patients with gross hematuria, a brown, cola-colored urine (table 2 and picture 2A-C). Glomerular bleeding is indicated by proteinuria exceeding 500 mg/day that is temporally related to the onset of hematuria; however, new-onset hematuria in the setting of prior chronic proteinuria should elicit consideration of a nonglomerular or urologic source. (See 'Proteinuria' below.)

Red cell casts — The presence of RBC casts is virtually diagnostic of glomerulonephritis or vasculitis, although such casts are infrequently seen in acute interstitial nephritis (picture 2A) [29]. The absence of these casts, however, does not exclude glomerular hematuria.

RBC casts may accumulate at the edges of the coverslip. Thus, one has to examine all of the microscopic fields, initially at low power. Prolonged centrifugation may disrupt cellular casts, diminishing the likelihood of identifying such casts.

Red cell morphology — Evaluation of RBC morphology may be helpful in identifying the cause of hematuria. The RBCs are typically uniform and round (as in a peripheral blood smear) with extrarenal bleeding, but they usually have a dysmorphic appearance with renal lesions [30-32], particularly but not only in glomerular diseases [32]. This change in morphology is manifested by blebs, budding, and segmental loss of membrane, resulting in marked variability in RBC shape and a reduction in mean RBC size (picture 2B-C) [33]. RBC injury in this setting may be due both to mechanical trauma as the cells pass through rents in the glomerular basement membrane and to osmotic trauma as the cells flow through the nephron [34].

The potential importance of RBC morphology was illustrated in a report in which isomorphic (or normomorphic) RBCs were seen in all 30 patients with nonglomerular bleeding but only 1 of 87 patients with proven glomerulonephritis [31]. A predominance of normal-shaped (and -sized) RBCs can occasionally be seen in patients with glomerulonephritis who undergo a forced diuresis or have advanced kidney function impairment or gross hematuria [35].

It has been suggested that the magnitude of dysmorphic hematuria is best expressed in absolute terms rather than as a percentage of urinary RBCs. If, for example, only 25 percent of urinary RBCs are dysmorphic, but the patient is excreting 100,000 RBCs/mL (normal is less than 8000/mL in centrifuged urine and less than 13,000/mL in uncentrifuged urine) [30,31], then there are 25,000 dysmorphic RBCs/mL, indicating the presence of glomerular disease. However, such quantitative testing is rarely performed in routine practice.

Acanthocytes — The type of dysmorphic RBC may be of diagnostic importance. In particular, dysmorphic RBCs alone may be predictive of only renal bleeding, while acanthocytes (ring-shaped RBCs with vesicle-shaped protrusions that are best seen on phase-contrast microscopy) appear to be most predictive of glomerular disease (picture 2B-C) [35,36]. In one study, for example, the presence of acanthocytes comprising ≥5 percent of excreted RBCs had a sensitivity and specificity for glomerular disease of 52 and 98 percent, respectively [36]. Regardless of the absolute number or percentage, the presence of acanthocytes in the urine should lead the clinician to consider nephrology consultation rather than a lengthy urological evaluation.

Limitations — The major question regarding the utility of RBC morphology in determining the cause of hematuria is whether the findings in clinical studies can be replicated in clinical practice. Optimal assessment of RBC morphology requires phase-contrast microscopy [36], which is not generally available in a clinician's office and which requires experience in its use to gain proficiency.

The subjective nature of identifying "dysmorphism" is another potential limitation. Acanthocytes (also called G1 cells) may be easier to identify with certainty, even without phase-contrast microscopy. However, most clinicians do not have expertise in identifying dysmorphic RBCs or distinguishing RBC casts from RBCs overlying granular casts. In addition, the absence of these findings does not exclude glomerular disease. Proteinuria (and, more specifically, albuminuria) suggests the presence of glomerular disease and glomerular hematuria [37]. (See "Assessment of urinary protein excretion and evaluation of isolated non-nephrotic proteinuria in adults".)

Proteinuria tends to be higher in patients with glomerular hematuria than in patients with nonglomerular hematuria, but considerable overlap exists, such that mild to moderate proteinuria can be seen with both glomerular and nonglomerular hematuria. However, a higher percentage of urine protein in the form of albumin is consistent with glomerular hematuria. One study, for example, found that a urine albumin-to-protein ratio of ≥0.59 had a sensitivity of 97.1 percent for glomerular hematuria [38]. Thus, a high urine albumin-to-protein ratio can help to distinguish glomerular from nonglomerular hematuria.

The diagnostic importance of proteinuria varies with the **time of onset**. If, for example, the patient has previously identified proteinuria well before the onset of hematuria, then a separate disease may be responsible for the hematuria. As an example, if a patient with chronic kidney disease and proteinuria but no hematuria (eg, as in nephrosclerosis) develops new hematuria, it should not be assumed that the bleeding is due to the initial glomerular disease. Such patients should undergo a full evaluation for hematuria. (See "Clinical features, diagnosis, and treatment of hypertensive nephrosclerosis" and "Diabetic kidney disease: Manifestations, evaluation, and diagnosis".)

Red to brown urine — A change in the urine color with gross hematuria is an additional finding that may be helpful. The urine is typically red to pink with nonglomerular bleeding. Although red urine also may be seen with glomerular bleeding (particularly in alkaline urine), the combination of prolonged transit time through the nephron and an acid urine pH may result in the formation of methemoglobin, which has a smoky brown or cola color. (See "Urinalysis in the diagnosis of kidney disease", section on 'Red to brown urine'.)

Blood clots — Blood clots, if present, are almost always due to **nonglomerular** bleeding [39]. They are indicative of heavy focal bleeding in which whole blood is shed into the urine in amounts sufficient to support clot formation.

The characteristic absence of blood clots with gross hematuria due to glomerular bleeding may be due to one or more of the following factors:

- The presence of urokinase and tissue-type plasminogen activators in the glomeruli and tubules [40].
- Glomerular bleeding is typically a diffuse capillary process in which minute amounts of blood are added to relatively large volumes of glomerular filtrate [39]. Thus, clot formation is unlikely.

Proteinuria — As noted above, proteinuria that is temporally related to the hematuria is suggestive of glomerular disease. Microhematuria alone does **not** typically lead to a significant increase in protein excretion. A dipstick test for protein that is greater than 1+ is rarely observed with nonglomerular bleeding, even with gross hematuria, unless the amount of gross blood is very large. As an example, as little as 1 mL of blood in one liter of urine can produce a visible color change. This quantity of blood contains approximately 0.6 mL of plasma, which will contain only 36 mg of protein at a plasma protein concentration of 6 g/dL (60

g/L). A protein concentration of 36 mg/L is below the sensitivity of the urine dipstick for protein and therefore will not be detected on routine urine examination. (See "Assessment of urinary protein excretion and evaluation of isolated non-nephrotic proteinuria in adults".)

However, a large amount of gross bleeding can cause abnormal proteinuria. Extremely bloody urine, especially with clots, should trigger an evaluation for a nonglomerular source even if abnormal proteinuria is present. (See 'Imaging' below and 'Cystoscopy' below.)

Role of kidney biopsy

Indications — The main indication for performing a kidney biopsy in patients with glomerular hematuria (defined by the presence of dysmorphic RBCs and/or RBC casts) is the presence of risk factors for progressive disease such as proteinuria and/or an elevation in the serum creatinine concentration [41-43]. We typically biopsy patients with glomerular hematuria and a urine albumin excretion above 30 mg/day, except for those who have a clinical presentation consistent with diabetic nephropathy (see "Diabetic kidney disease: Manifestations, evaluation, and diagnosis"). New-onset hypertension or a significant elevation in blood pressure above a previous stable baseline that does not exceed 140/90 mmHg (eg, from 100/60 to 130/80 mmHg) is also associated with a greater likelihood of progressive disease but is primarily seen in patients who also have one or both of the other adverse predictors. (See "The kidney biopsy".)

Kidney biopsy is **not** usually performed for isolated glomerular hematuria (ie, no abnormal proteinuria [or albuminuria and a negative or trace dipstick result], no elevation in serum creatinine, no elevation in blood pressure about a previous stable baseline, and no systemic manifestations or family history of kidney disease), since there is no specific therapy for these conditions and since the renal prognosis is excellent as long as there is **no evidence** of progressive disease [41,43]. In addition, management of these patients is not usually affected by the biopsy results [43,44]. In one study, for example, the result of the biopsy altered management in only 1 of 36 patients with isolated hematuria compared with 9 of 28 patients with hematuria and proteinuria (3 versus 32 percent) [44].

When kidney biopsy is performed in such patients, the most common findings are a normal biopsy or one of four disorders: IgA nephropathy, thin basement membrane disease (benign familial hematuria), mild nonspecific glomerular abnormalities, and hereditary nephritis (Alport syndrome) [43]. Among the glomerular diseases, IgA nephropathy is the most common cause worldwide, particularly throughout Asia [45]. (See 'Glomerular disease' below.)

Kidney biopsy is also **not indicated** in patients with persistent, isolated **nonglomerular hematuria** (ie, no dysmorphic RBCs or RBC casts, no proteinuria). Such patients, particularly patients with malignancy, need a thorough evaluation with imaging and/or cystoscopy. These issues are discussed below.

Monitoring if kidney biopsy is not performed — If kidney biopsy is not performed in a patient with isolated glomerular hematuria, periodic monitoring is warranted during follow-up to detect progressive disease. Serum creatinine, urinalysis, and urine protein excretion should be monitored yearly for at least five years. The frequency with which progressive disease occurs can be illustrated by the following observations:

- In a study in which mass screening for asymptomatic hematuria or proteinuria was performed in over 56,000 adults, 432 had asymptomatic hematuria without proteinuria [45]. At a mean follow-up of 5.8 years, hematuria disappeared in 44 percent, persisted without proteinuria in 44 percent, and persisted with the development of proteinuria in 11 percent. None of the patients developed kidney function impairment, which was defined as a creatinine clearance less than 60 mL/min and/or a serum creatinine greater than 1.5 mg/dL (133 micromol/L). The prognosis was worse in the 134 patients with asymptomatic hematuria and proteinuria: Hematuria disappeared in only 16 percent, and kidney function impairment developed in 15 percent.

- In a population-based, retrospective study of 1,203,626 adolescents and young adults (age 16 through 25 years), 3690 (0.3 percent) were diagnosed with persistent, asymptomatic, isolated microscopic hematuria [46]. Over 21.88 years of follow-up, 26 patients (0.70 percent) with and 539 patients (0.045 percent) without persistent, asymptomatic, isolated microscopic hematuria developed end-stage kidney disease (ESKD) requiring dialysis or kidney transplant (adjusted hazard ratio [aHR] 18.5, 95% CI 12.4-27.6). An increased risk for ESRD caused by primary glomerular disease was observed in those with

persistent, asymptomatic, isolated microscopic hematuria, compared with those without the condition (aHR 32.4, 95% CI 18.9-55.7).

- The clinical course of isolated glomerular hematuria was evaluated in a series of 85 patients who were followed for a mean of 43 months [43]. Three patients developed proteinuria (two with IgA nephropathy and one without a biopsy), one developed proteinuria and kidney function impairment (membranoproliferative glomerulonephritis), and 11 developed hypertension (three with thin basement membrane disease, two with IgA nephropathy, two with a normal biopsy, one with focal segmental glomerulosclerosis, and three without a kidney biopsy). (See 'Glomerular disease' below.)

- Progressive disease is more common in patients with hematuria due to IgA nephropathy. This was illustrated in a study of 72 consecutive patients with hematuria due to IgA nephropathy and no or minimal proteinuria (400 mg/day or less) who were followed for a median of seven years [42]. Progressive disease occurred in 32 patients (44 percent), many of whom had more than one sign of progression: 24 developed proteinuria of 1 g/day or more, 19 became hypertensive, and five developed an increase in serum creatinine.

Transient or persistent hematuria — There is no cause of low-level hematuria that, in the absence of other signs and symptoms, requires immediate diagnosis. As a result, it is reasonable to repeat an abnormal urinalysis in a few days to determine if hematuria is transient or persistent.

Transient microscopic hematuria is a common problem in adults [1,4,13,47]. The following observations illustrate the range of findings:

- In a prospective cohort study including 2,421,585 members (of all ages) of a managed care organization with at least one urinalysis, 967,297 (40 percent) had asymptomatic microscopic hematuria [47]. Of these, a second urinalysis was positive for microscopic hematuria in 643,304 (66 percent). Thus, approximately one-third of individuals with an initially positive urinalysis had transient hematuria.

- Another study evaluated 1000 young men who had yearly urinalyses between the ages of 18 and 33 years; hematuria was seen in 39 percent on at least one occasion and 16 percent on two or more occasions [1]. Hematuria has also been found in up to 13 percent of men and postmenopausal women [13].

No obvious etiology can be identified in most patients with transient hematuria. Fever, infection, trauma, and exercise are potential causes of transient hematuria. (See "Exercise-induced hematuria".)

Transient hematuria can also occur with urinary tract infection (eg, cystitis or prostatitis). In this setting, hematuria is typically accompanied by pyuria and bacteriuria, and patients often complain of dysuria. A potential source of error is that dysuria (but not pyuria and bacteriuria) can also be seen with macroscopic hematuria from bladder cancer.

An important exception to the typically benign nature of transient hematuria occurs in patients over age 40 years in whom even transient hematuria carries an increased risk of malignancy (assuming there is no evidence of glomerular bleeding as described above). (See 'Risk factors for malignancy' below.)

Urine culture — All patients who have findings suggestive of a urinary tract infection (eg, fever, dysuria, presence of WBCs in the urine, positive dipstick for nitrite) should have a urine culture to exclude infection prior to evaluation of hematuria. Patients who have a positive urine culture should be treated for infection with close follow-up. The urinalysis should be rechecked in six weeks to determine whether hematuria has resolved. Patients who have resolution of hematuria do not require further evaluation. (See "Sampling and evaluation of voided urine in the diagnosis of urinary tract infection in adults" and "Asymptomatic bacteriuria in adults" and "Acute simple cystitis in men".)

Urine cytology — Voided urine cytology had been used historically to evaluate patients with gross and microscopic hematuria but is no longer recommended due to variable sensitivity and specificity. In addition, other urinary biomarkers (such as NMP22 or BTA stat) are not useful because of similarly poor performance characteristics. There may be a role for urinary cytology in patients with suspected carcinoma in situ (ie, with risk factors for malignancy and irritative voiding symptoms) but not in simple asymptomatic microscopic hematuria [27].

RISK FACTORS FOR MALIGNANCY

The American Urological Association (AUA) best practice policy recommendations and guidelines on asymptomatic microscopic hematuria included the following risk factors for malignancy [27,48]:

- Male gender
- Age >35 years
- Past or current smoking history in which the risk correlates with the extent of exposure
- Occupational exposure to chemicals or dyes (benzenes or aromatic amines), such as printers, painters, and chemical plant workers
- History of gross hematuria
- History of irritative voiding symptoms
- History of chronic urinary tract infection
- History of pelvic irradiation
- History of exposure to cyclophosphamide
- History of a chronic indwelling foreign body
- History of exposure to aristolochic acid
- History of analgesic abuse, which is also associated with an increased incidence of carcinoma of the kidney (see "Urinary tract malignancy and atherosclerotic disease in patients with chronic analgesic abuse")

The risk factors for bladder and renal cell carcinomas are discussed in detail elsewhere. (See "Epidemiology and risk factors of urothelial (transitional cell) carcinoma of the bladder" and "Epidemiology, pathology, and pathogenesis of renal cell carcinoma", section on 'Established risk factors'.)

The importance of gross (macroscopic) hematuria and older age was illustrated in several studies:

- In a prospective cohort study of 4414 members of a managed care organization with unexplained, asymptomatic microscopic hematuria who were referred for urologic evaluation, 111 cancers were identified (2.5 percent); 100 were bladder cancers, and 11 were renal cancers [47]. However, the prevalence of malignancy was 11.2 percent among patients 50 years or older who also had a history of gross hematuria plus at least one additional risk factor (male sex, smoking, or more than 25 red blood cells [RBCs] per high-power field). By contrast, the prevalence of cancer was 0.2 percent among patients younger than 50 years who did not have a history of gross hematuria. This study suggests that individuals at low risk for malignancy (ie, with none of the risk factors listed above) who have asymptomatic microscopic hematuria may not require a urologic referral.

- In another study of 1930 patients (mean age of 58 years, 62 percent male) who were referred to a hematuria clinic because of gross or microscopic hematuria, 12 percent had bladder cancer, 0.7 percent had kidney and upper tract tumors, and 61 percent had no cause identified [2]. In addition:

  - At age 50 to 59 years, malignancy was identified in 20.4 versus 1.9 percent of men with macroscopic versus microscopic hematuria, respectively, and in 8.9 versus 1.9 percent of women with macroscopic versus microscopic hematuria, respectively.

  - At age 60 to 69 years, malignancy was found in 28.9 versus 7.9 percent of men with macroscopic versus microscopic hematuria, respectively, and 21.1 versus 4.5 percent of women with macroscopic versus microscopic hematuria, respectively.

- Another report evaluated 1034 patients with microscopic hematuria who had more than 5 RBCs per high-power field on at least one of three screening urinalyses [14]. All patients were evaluated by ultrasound, intravenous pyelography (IVP), urinary cytology, and cystoscopy. The incidence of malignancy (bladder, kidney, or prostate) was 2.4 percent. Among the remaining patients, 20 percent had kidney stones or glomerular or other intrinsic kidney disease, while 78 percent had either no identifiable cause or a minor lesion such as benign prostatic hypertrophy (BPH).

Neither cytology nor IVP reliably detected all of the tumors. Ultrasound was accurate for detecting renal tumors, while cystoscopy was required to reliably diagnose bladder or prostatic cancers. Tumors were more common in men, and all but one occurred in patients over the age of 50 years.

An important exception to the typically benign nature of transient hematuria occurs in patients at high risk for malignancy, in whom even transient hematuria carries an appreciable association with malignancy (assuming there is no evidence of glomerular bleeding as described above) [2,4,9,13,14,49,50]. As an example, screening studies limited to healthy men over the age of 50 to 60 years found that 8 to 9 percent of patients with intermittent asymptomatic hematuria, as detected by a dipstick for heme, had a urinary tract malignancy [49,50].

IMAGING

Once glomerular bleeding has been excluded in a patient with otherwise unexplained hematuria, the diagnostic evaluation is directed to the kidney, ureters, bladder, urethra, and prostate. The diagnostic yield in adults increases with age and may be higher for gross hematuria than for microscopic hematuria [51]. Imaging of the kidney, ureters, and bladder should be combined with cystoscopy, which is more sensitive for detection of bladder and urethral lesions. (See 'Cystoscopy' below.)

Selection of modality — Computed tomography (CT) of the abdomen and pelvis without and with intravenous contrast for urography, also called CT urography (CTU), is recommended in patients with otherwise unexplained hematuria [27]. Images of the kidneys, ureters, and bladder are acquired at least twice, initially without intravenous contrast to evaluate for nephrolithiasis and hydronephrosis and then after intravenous contrast administration to evaluate for renal and urothelial abnormalities. This includes imaging in the excretory phase, typically acquired 7 to 10 minutes after the administration of the bolus of intravenous contrast. These delayed set of images are necessary for evaluation of the renal collecting systems and ureters. Other available modalities include intravenous pyelography (IVP); retrograde pyelography; ultrasound of the kidneys and bladder; and magnetic resonance imaging (MRI) of the abdomen and pelvis without and with intravenous contrast for urography, also called MR urography (MRU) [52].

Although CTU is the preferred initial imaging modality in almost all patients, there are some exceptions to this general recommendation:

- In a young patient (eg, age <35 years) with no risk factors for urinary tract malignancy, post-contrast images should not be routinely acquired if noncontrast images of the CTU unambiguously demonstrate nephrolithiasis. This approach minimizes the radiation dose conferred and does not decrease the diagnostic sensitivity of the examination. In a study of 442 such patients, 64 had findings by CTU that could explain the hematuria; none were malignancy related, and all were identified on unenhanced imaging [53].

- Ultrasound of the kidneys and bladder, not CTU, is the initial examination in the evaluation of pregnant women as this avoids ionizing radiation. (See "Diagnostic imaging in pregnant and nursing patients".)

- In patients with markedly decreased kidney function (estimated glomerular filtration rate [eGFR] <30) where contrast excretion through the kidneys and renal collecting systems will be limited, CTU should be deferred. Instead, CT of the abdomen and pelvis without contrast is recommended. If this is negative for nephrolithiasis, MRU without contrast can be performed as this is more sensitive than noncontrast CT in detecting renal and urothelial tumors. Retrograde pyelography should be considered as an adjunct at cystoscopy to evaluate for ureteral abnormalities.

- In patients with history of a mild acute reaction to iodinated contrast, CTU should be performed following precautionary measures. In patients with a history of a moderate or severe acute reaction, contrast administration should be avoided. The preferred examination in this setting depends upon the suspected etiology. CTU with noncontrast images only can be performed to evaluate for nephrolithiasis, but this would be relatively insensitive for detection of malignancy. MRU can be performed to evaluate for renal or urothelial tumor, but this would be insensitive for detection of nonobstructing stones. (See "Patient evaluation prior to oral or iodinated intravenous contrast for computed tomography", section on 'Patients with past reactions to contrast'.)

Patients with a history of malignancy in the bladder or kidneys are at increased risk for malignancy at the other site and should always undergo further evaluation. (See "Clinical presentation, diagnosis, and staging of bladder cancer", section on 'Urinary tract imaging' and "Malignancies of the renal pelvis and ureter", section on 'Relationship to urothelial bladder cancer'.)

CT urography — Computed tomography (CT) of the abdomen pelvis without and with intravenous contrast for urography, also called CTU, is the preferred imaging modality in most patients with unexplained hematuria. This examination may be particularly indicated in those with an increased risk of urinary malignancy or disease [52,54,55]. The combination of CTU and cystoscopy, which together provide a complete evaluation of the urinary system, should be performed in almost all patients with unexplained hematuria. (See 'Cystoscopy' below.)

CTU combines the cross-sectional imaging of CT with an image acquisition protocol tailored to evaluate for nephrolithiasis and urothelial tumors. Although CTU protocols vary slightly with each site, in general, images of the kidney and the urinary collecting system are first obtained precontrast; after the administration of contrast, images are then obtained in the renal parenchymal phase and the excretory phase, either concurrently or successively. The noncontrast imaging evaluates for nephrolithiasis and hydronephrosis; the postcontrast imaging evaluates for renal and urothelial malignancy and, in the context of hydronephrosis, impaired function of the obstructed kidney. Thus, CTU provides anatomic and functional imaging of the kidneys, ureters, and bladder.

CTU is more accurate than IVP or ultrasound for the diagnosis of renal masses, urinary tract calculi, and pelvicalyceal and ureteric transitional cell carcinomas [52,54-63]. A meta-analysis of CTU yielded a pooled sensitivity of 96 percent (95% CI 88–100) and pooled specificity of 99 percent (95% CI 98–100) for detection of urothelial malignancy.

Because CTU involves imaging the abdomen and pelvis multiple times, the examination is tailored to minimize radiation dose. The median effective dose of CTU has been reduced from 13 mSv using conventional protocols to 6.1 mSv using dose-reduction techniques such as split contrast bolus and iterative image reconstruction [64]. With these innovations, low-dose CTU confers a radiation dose comparable with a conventional single-phase abdominopelvic CT.

Intravenous pyelography — IVP, also called intravenous urography (IVU), is radiographic imaging of the kidneys, ureters, and bladder before and after administration of intravenous iodinated contrast. In addition, postcontrast tomographic images of the kidneys are usually acquired. CTU has largely replaced IVP, which is less sensitive in detecting kidney stones and renal masses (particularly small masses) [54,55]. The magnitude of this effect was illustrated in a study of 115 patients with hematuria in which CTU imaging was more sensitive (100 versus 61 percent) and specific (97 versus 91 percent) than an IVP [55]. Despite these observations, some clinicians still perform IVP because of the belief that it is best able to characterize lesions in the urothelium [52,65]. However, increasing evidence suggests that this is not true given that IVP is associated with only 40 to 65 percent detection rates for urothelial neoplasms [52,66].

Effective radiation dose of IVP is 3 mSv.

Ultrasound — Ultrasound of the kidneys and bladder, when compared with CTU, demonstrates lower diagnostic yield and is less sensitive in detecting urothelium transitional cell carcinoma, small renal masses, and calculi [54,61,67]. However, when compared with IVP, ultrasound demonstrates higher sensitivity for the diagnosis of upper urinary tract causes of hematuria (25 versus 96 percent). The relative insensitivity of ultrasound in detecting small renal tumors was best shown in a study in which ultrasound detected only 26, 60, 82, and 85 percent of CT-confirmed lesions less than 1 cm, between 1 and 2 cm, between 2 and 3 cm, and 3 cm or more in size, respectively [54].

Ultrasound does not involve ionizing radiation. Hence, it is recommended as the initial imaging examination for hematuria in pregnancy.

For detection of cancer, ultrasound rather than CT is more cost effective when combined with cystoscopy [68]. Some groups outside of the United States prefer ultrasound over CTU as the initial imaging examination in all patients with hematuria [69,70].

Magnetic resonance urography — MRI of the abdomen and pelvis without and with intravenous contrast for urography, also called MR urography (MRU), is less widely available, and data on diagnostic performance are limited. When compared with CTU, diagnostic accuracy of MRU is comparable in detecting renal lesions but is likely less for urothelial tumors. Stones or calcifications

are nearly invisible on MRU. However, MRU, even without contrast, is more sensitive than noncontrast CT in detecting small renal masses and identifying tumors causing hydronephrosis (90 versus 42 percent) [71]. Thus, MRU is useful in patients where iodinated contrast is contraindicated and nephrolithiasis has been excluded or thought unlikely.

MRI does not involve ionizing radiation. Hence, it is useful in localizing the anatomic site of obstruction in pregnant women with hydronephrosis diagnosed on ultrasound.

Retrograde pyelography — Retrograde pyelography is a fluoroscopic examination where ureters are cannulated during cystoscopy and iodinated contrast is injected retrograde into the ureters. It is usually performed in an operative suite under sedation or general anesthesia and less commonly performed in an office setting.

The examination is comparable with CTU in diagnosis of upper tract urothelial tumors. A retrospective study of CTU and retrograde pyelography in diagnosing upper urinary tract urothelial tumors demonstrated sensitivities and specificities of 97 and 93 percent, respectively, for both modalities [62]. In patients with contraindications to intravenous iodinated contrast due to kidney function impairment, retrograde pyelography as an adjunct to cystoscopy is a reasonable option to evaluate the urothelium.

Radiation dose from retrograde pyelography is less than 1 mSv.

CYSTOSCOPY

Cystoscopy is associated with the following benefits:

- The entire bladder can be visualized for malignancy or other abnormalities. In the presence of concomitant prostatic hypertrophy, it may be difficult to visualize the entire bladder with video-assisted flexible cystoscopy under local anesthesia. If concerns persist, rigid cystoscopy under spinal or general anesthesia may be required. Analgesic abusers also have an increased incidence of carcinoma of the kidney. (See "Urinary tract malignancy and atherosclerotic disease in patients with chronic analgesic abuse".)
- Cystoscopy may identify the source of the bleeding among patients with gross hematuria. It may be possible to determine whether the bleeding is originating from the bladder or from one or both ureters. Unilateral bleeding may be due to an arteriovenous malformation (AVM), fistula, venous varices, or unilateral renal or upper urinary tract tumors or stones [72].
- Cystoscopy is the only modality that permits visualization of the prostate and urethra.

Gross hematuria — All patients who have gross (macroscopic) hematuria and no evidence of glomerular disease or infection should undergo cystoscopy since it permits direct visualization of the bladder and can detect malignant or other sources of bleeding [73,74]. (See 'Glomerular versus nonglomerular bleeding' above.)

Patients who have gross hematuria with blood clots should have cystoscopy even if they have evidence of a glomerular lesion since blood clots are virtually never associated with glomerular bleeding. Thus, the presence of blood clots in a patient with glomerular bleeding suggests the presence of disease in the upper or lower collecting system.

Microscopic hematuria — All patients with microscopic hematuria who have no evidence of glomerular disease, infection, or a known cause of hematuria such as exercise and who are at increased risk for malignancy should undergo cystoscopy [11,14,49-51,72,73]. (See 'Risk factors for malignancy' above.)

The diagnostic yield of cystoscopy is lower in patients who have microscopic hematuria, negative imaging, negative urine cytology, and who are at low risk for malignancy. For such patients, the American Urological Association (AUA) guidelines do recommend cystoscopy [27,73,74]; given its low morbidity, we discuss the risks and benefits of cystoscopy with all such patients.

UNEXPLAINED HEMATURIA

If no diagnosis is apparent from the history, urinalysis, imaging examinations, or cystoscopy, then the most likely causes of persistent isolated hematuria are a mild glomerulopathy and a predisposition to stone disease, particularly in young and middle-aged patients.

Glomerular disease — Although any glomerular disease may be associated with hematuria, most patients also have other signs such as proteinuria, red blood cell (RBC) casts, or kidney function impairment. When persistent glomerular hematuria is essentially the only manifestation of glomerular disease, one of four disorders is most likely [3,41,43,75-78] (see "Isolated and persistent glomerular hematuria in adults"):

- Immunoglobulin A (IgA) nephropathy, in which there is often gross hematuria and, sometimes, a positive family history but without any clear pattern of autosomal inheritance
- Thin basement membrane nephropathy (also called thin basement membrane disease or benign familial hematuria), in which gross hematuria is unusual and the family history may be positive (with an autosomal dominant pattern of inheritance) for microscopic hematuria but not for kidney failure [3]
- Mesangioproliferative glomerulonephritis without IgA deposits [3]
- Alport syndrome (hereditary nephritis), in which gross hematuria can occur in association with a positive family history of kidney failure and, sometimes, deafness or corneal abnormalities

In three series of 240 patients with isolated microscopic hematuria; no proteinuria; a normal serum creatinine concentration; and, in two studies, a negative radiologic and cystoscopic evaluation, IgA nephropathy was present in 20 to 30 percent, thin basement membrane disease was present in 4 to 43 percent, and, in one study, mesangioproliferative glomerulonephritis without IgA deposits was present in 10 percent [3,41,78]. In one of these reports, 86 percent of patients with hematuria persisting for four years had either IgA nephropathy or thin basement membrane disease [78].

Postinfectious glomerulonephritis and exercise are other causes of isolated glomerular bleeding. The hematuria in these settings is typically transient (not persistent, as in the above disorders). (See "Exercise-induced hematuria" and "Glomerular disease: Evaluation and differential diagnosis in adults".)

The distinction between glomerular and nonglomerular bleeding, and the indications for kidney biopsy in patients with glomerular hematuria, are discussed above. (See 'Glomerular versus nonglomerular bleeding' above and 'Role of kidney biopsy' above.)

Hypercalciuria and hyperuricosuria — As many as 30 to 35 percent of children with apparently idiopathic hematuria (no proteinuria or infection, negative radiologic evaluation) have hypercalciuria, while 5 to 20 percent of children with recurrent hematuria have hyperuricosuria [79-81]; both disorders are often associated with a positive family history (as high as 40 to 75 percent) of stone disease [79,81]. These children are at increased risk for the future development of kidney stones. Lowering calcium excretion with a thiazide diuretic typically leads to resolution of the hematuria among those with hypercalciuria [79]; a restricted purine diet or the administration of allopurinol commonly eliminates uricosuria and hematuria in those with hyperuricosuria. (See "Epidemiology of and risk factors for nephrolithiasis in children", section on 'Hypercalciuria'.)

Similar findings may be present in adults. Some patients have hypercalciuria or hyperuricosuria (as detected by a 24-hour urine collection) [82,83], while others have a history suggestive of stone disease without these biochemical abnormalities (although citrate excretion was not measured in this study) [78] (see "Kidney stones in adults: Epidemiology and risk factors"). Treatment with a thiazide diuretic for hypercalciuria or allopurinol for hyperuricosuria usually leads to disappearance of the hematuria [82].

Rare conditions — Rare causes of hematuria include hereditary hemorrhagic telangiectasis, radiation cystitis, schistosomiasis (which is not rare in endemic areas), arteriovenous malformations (AVMs) and fistulas, nutcracker syndrome, and the loin pain-hematuria syndrome. AVMs, nutcracker syndrome, and loin pain-hematuria syndrome will be briefly reviewed here; the other conditions are discussed separately. (See "Hemorrhagic cystitis in cancer patients" and "Schistosomiasis: Epidemiology and clinical manifestations".)

Arteriovenous malformations and fistulas — An AVM or fistula of the urologic tract may be either congenital or acquired. The latter is more common and usually secondary to trauma or intervention. The primary presenting sign is gross hematuria, but high-output heart failure and hypertension also may be seen [72,84]. The latter is presumably due to activation of the renin-angiotensin system resulting from ischemia distal to the AVM [85].

Ultrasound with Doppler is the examination used to evaluate for suspected renal AVM or fistula as it allows for detection of high-flow velocity. If positive, diagnosis is confirmed by conventional fluoroscopic angiography, which can be combined with selective embolization therapy in the same setting. Coils, gelatin sponges, or liquid glues such as N-butyl-2-cyanoacrylate (NBCA) are injected usually in combination for endovascular sclerotherapy [86,87]. Surgery or nephroscopy can be performed if embolization is ineffective or the hematuria recurs [85,88].

Nutcracker syndrome — The nutcracker syndrome refers to compression of the left renal vein between the aorta and proximal superior mesenteric artery. Nutcracker syndrome can cause both microscopic and gross hematuria, primarily in children (but also adults) in Asia [89-92]. The hematuria is usually asymptomatic but may be associated with left flank pain. Nutcracker syndrome has also been associated with orthostatic proteinuria. (See "Orthostatic (postural) proteinuria", section on 'Pathogenesis' and "Evaluation of microscopic hematuria in children", section on 'Etiology' and "Evaluation of gross hematuria in children", section on 'Asymptomatic hematuria'.)

Nutcracker syndrome is usually suspected when CT or MRI shows intrarenal and perirenal varices, and early enhancement of the left gonadal vein collateral. The diagnosis is confirmed on Doppler ultrasound demonstrating left renal vein compression with elevated velocities.

For patients who require treatment because of recurrent or persistent symptoms, a variety of therapies have been used, including stent placement in the left renal vein, transposition of the superior mesenteric artery or left renal vein, and autotransplantation of the left kidney [89,91,92]. In a 2007 review of 20 patients who required intervention, stenting (which has the advantage of minimal invasiveness) was performed in 15, and transposition of the superior mesenteric artery or left renal vein was performed in five [89,93,94].

Loin pain-hematuria syndrome — The loin pain-hematuria syndrome is a poorly defined disorder characterized by loin or flank pain that is often severe and unrelenting as well as hematuria with dysmorphic RBC features suggesting a glomerular origin. Affected patients usually have normal kidney function. This disorder is discussed elsewhere. (See "Loin pain-hematuria syndrome".)

FOLLOW-UP AFTER INITIAL NEGATIVE EVALUATION

A cause for hematuria is often not identified. Patients who have a negative evaluation for hematuria generally require follow-up with urinalysis, blood pressure monitoring, and, in some cases, repeat imaging and cystoscopy. The necessity for repeat imaging and cystoscopy largely depends upon whether hematuria was transient or persistent and upon the patient's risk for malignancy. (See 'Risk factors for malignancy' above.)

Follow-up of patients with transient hematuria — Patients who have even one episode of hematuria and are at high risk for malignancy require close follow-up after a negative evaluation. Such patients should be monitored with annual urinalyses. After two consecutive negative urinalyses, this follow-up may be concluded. If gross hematuria occurs at any time after the initial evaluation, the full evaluation should be repeated.

If hypertension, proteinuria, an increase in serum creatinine, or evidence of glomerular bleeding develops in a patient who has been evaluated for hematuria, the patient should be reevaluated for kidney disease. (See 'Glomerular versus nonglomerular bleeding' above.)

Follow-up of patients with persistent hematuria — Potentially, the most serious disorder in the patient with unexplained persistent hematuria is the presence of an undiagnosed carcinoma of the urinary tract. The combination of a negative computed tomography (CT) of the abdomen and pelvis without and with contrast for urography (CTU), negative cytology, and negative cystoscopy is usually sufficient to exclude malignancy in the urinary tract [14]. However, the cause will subsequently become

evident in some patients with careful follow-up. In a series of 421 patients with unexplained, asymptomatic microscopic hematuria who were followed at six-month intervals for more than one year, approximately 5 percent had an identifiable cause for hematuria within three years, and approximately 1 percent had a detectable urinary tract malignancy [14]. (See "Epidemiology and risk factors of urothelial (transitional cell) carcinoma of the bladder" and "Epidemiology, pathology, and pathogenesis of renal cell carcinoma".)

As a result, monitoring with annual urinalyses is recommended for patients with asymptomatic microhematuria; if persisting for three to five years, repeating the initial urologic workup is a reasonable consideration [73]. Some clinicians also recommend repeat ultrasound and cystoscopy at one year in high-risk patients [11,26]. (See 'Risk factors for malignancy' above.)

SCREENING FOR HEMATURIA

Population- or office-based screening for hematuria in patients who have no symptoms suggestive of urinary tract disease and who have no known risk factors for urothelial malignancies or hereditable glomerular disease is **not recommended**. The most plausible argument for screening would be for the early detection and treatment of cancers of the kidney, collecting system, or bladder in older adults. However, these and other diseases causing hematuria do not meet basic criteria for screening: The prevalence of undetected, asymptomatic, early disease is relatively low (<2 percent); there is little evidence that hematuria is a sensitive test for localized disease; and there is little evidence in patients with renal cancer that early treatment of local disease results in a better prognosis [95].

Thus, expert groups such as the US Preventive Services Task Force (USPSTF) on the periodic health examination do **not** recommend screening for hematuria. (See "Screening for bladder cancer", section on 'Recommendations of expert groups'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Glomerular disease in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Blood in the urine (hematuria) in adults (The Basics)")
- Beyond the Basics topics (see "Patient education: Blood in the urine (hematuria) in adults (Beyond the Basics)" and "Patient education: Glomerular disease (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Hematuria that is not explained by an obvious underlying condition (eg, cystitis, ureteral stone) is fairly common. In many such patients, particularly young adult patients under the age of 35 years, the hematuria is transient and of no consequence.

Fever, infection, trauma, and exercise are potential causes of transient hematuria. (See 'Introduction' above and "Exercise-induced hematuria".)

- Hematuria may be visible to the naked eye (called gross hematuria) or detectable only on examination of the urine sediment by microscopy (called microscopic hematuria) (see 'Definition of hematuria' above):
  - Gross hematuria is suspected because of the presence of red or brown urine. The initial step in the evaluation of patients with red urine is centrifugation of the specimen to see if the red or brown color is in the urine sediment or the supernatant (algorithm 2).
  - Microscopic hematuria may be discovered when blood (either red blood cells [RBCs] or hemoglobin) is found on a urinalysis or dipstick done for other purposes. Microscopic hematuria is defined as the presence of three or more RBCs per high-power field in a spun urine sediment (picture 1). The urine sediment (or direct counting of RBC per mL of uncentrifuged urine) is the gold standard for the detection of microscopic hematuria; a positive dipstick test should always be confirmed with microscopic examination of the urine.
- Hematuria may be a symptom of an underlying disease, some of which are life threatening and some of which are treatable (figure 1). The causes vary with age, with the most common being inflammation or infection of the prostate or bladder, stones, and, in older patients, a kidney or urinary tract malignancy or benign prostatic hyperplasia (BPH) (figure 2). (See 'Etiology' above.)
- Our approach to the evaluation of patients with a positive dipstick for heme or with red or brown urine is to confirm the presence of hematuria by microscopic analysis of a centrifuged specimen. After the presence of hematuria is confirmed, the general diagnostic approach is as follows (algorithm 1) (see 'Overall approach to the evaluation' above): (Related Pathway(s): Hematuria: Evaluation in adults.)
  - Microscopic hematuria identified in a woman during her menses, or in a patient shortly after vigorous exercise or acute trauma, should be confirmed by repeating the urinalysis. In menstruating women, the urinalysis should be repeated later in the cycle once menstrual bleeding has ceased. In patients with hematuria identified in the setting of vigorous exercise, the urinalysis should be repeated approximately four to six weeks later during a period of no exercise. Patients with acute trauma and microscopic hematuria should have a confirmatory urinalysis after four to six weeks.
  - Patients who present with unilateral flank pain suggestive of obstructive nephrolithiasis should undergo imaging (noncontrast computed tomography [CT] or ultrasound with or without an abdominal radiograph) as the first test in the evaluation. (See "Diagnosis and acute management of suspected nephrolithiasis in adults", section on 'Diagnostic imaging'.)
  - Patients who have findings suggestive of urinary tract infection (eg, fever, dysuria, presence of white blood cells [WBCs] in the urine, positive dipstick for nitrite) should undergo urine culture to evaluate for urinary tract infection. In patients with urinary tract infection, the infection should be treated and the urinalysis should be repeated approximately six weeks after completion of antibiotic therapy in order to determine if the hematuria is persistent.
  - If there is gross hematuria with visible blood clots in the urine, then imaging of the kidneys, ureters, and bladder should be performed, and the patient should be referred for urgent urology evaluation for cystoscopy and further evaluation. If there is gross hematuria without visible blood clots in the urine, patients with acute kidney injury or findings suggestive of glomerular bleeding should be referred to nephrology. Those without such findings should have imaging of the kidneys, ureters, and bladder and possible urology referral, depending upon whether or not they are pregnant. (See 'Glomerular versus nonglomerular bleeding' above and "Definition and staging criteria of acute kidney injury in adults".)
  - If there is microscopic hematuria, patients with acute kidney injury or findings suggestive of glomerular bleeding should be referred to nephrology. Those without such findings should have imaging of the kidneys, ureters, and bladder, and possible urology referral if they are pregnant or have risk factors for malignancy. (See 'Glomerular versus nonglomerular bleeding' above and "Definition and staging criteria of acute kidney injury in adults" and 'Risk factors for malignancy' above.)

- In unexplained hematuria that requires imaging of the kidneys, ureters, and bladder, CT of the abdomen pelvis without and with intravenous contrast for urography, also called CT urography (CTU), is recommended in most patients. Two main exceptions exist (see 'Imaging' above):
  - In a young patient (eg, age <35 years) with no risk factors for urinary tract malignancy, postcontrast images should not be routinely acquired if noncontrast images of the CTU unambiguously demonstrate nephrolithiasis. This approach minimizes the radiation dose conferred and does not decrease the diagnostic sensitivity of the examination.
  - Ultrasound of the kidneys and bladder, not CTU, is the initial examination in the evaluation of pregnant women as this avoids ionizing radiation.
- If no diagnosis is apparent from the history, urinalysis, imaging examinations, or cystoscopy, then the most likely causes of persistent isolated hematuria are a mild glomerulopathy and a predisposition to stone disease, particularly in young and middle-aged patients. (See 'Unexplained hematuria' above.)
- Screening for hematuria with routine urinalysis in patients who have no symptoms suggestive of urinary tract disease is **not recommended**. (See 'Screening for hematuria' above.)

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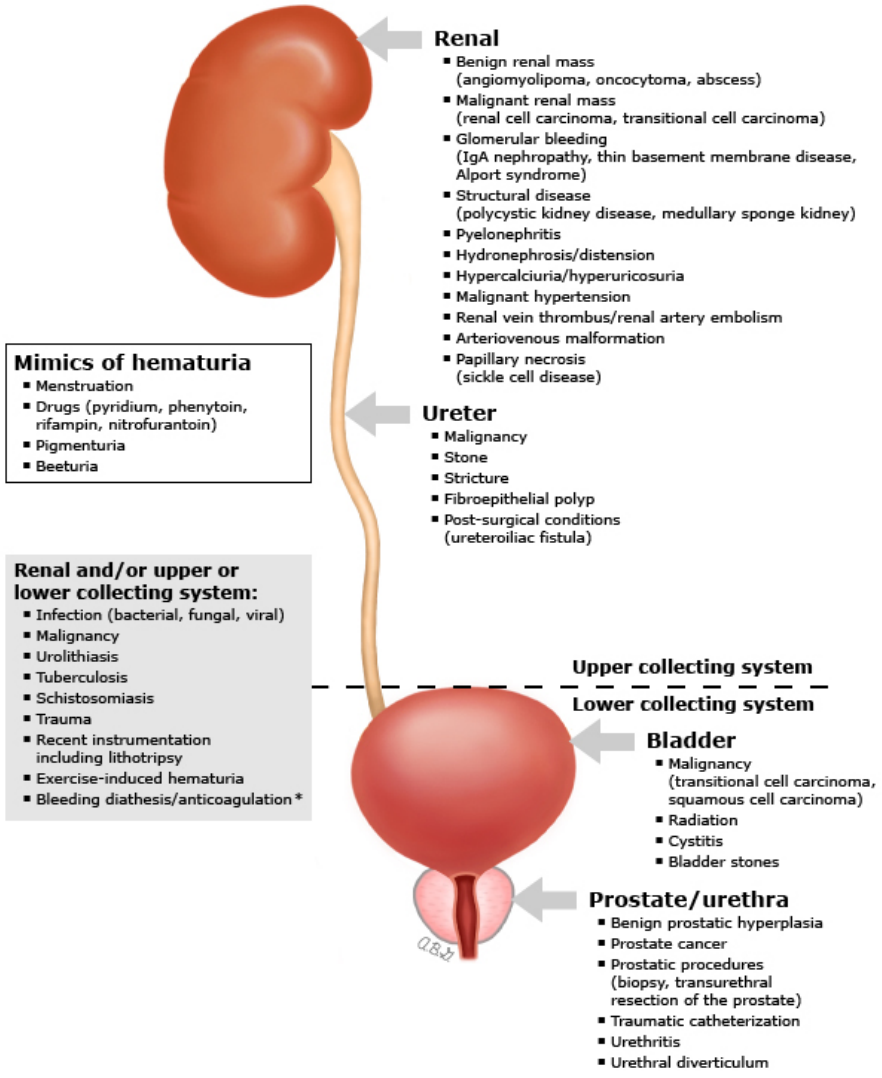
Topic 7208 Version 41.0

GRAPHICS

Causes of hematuria

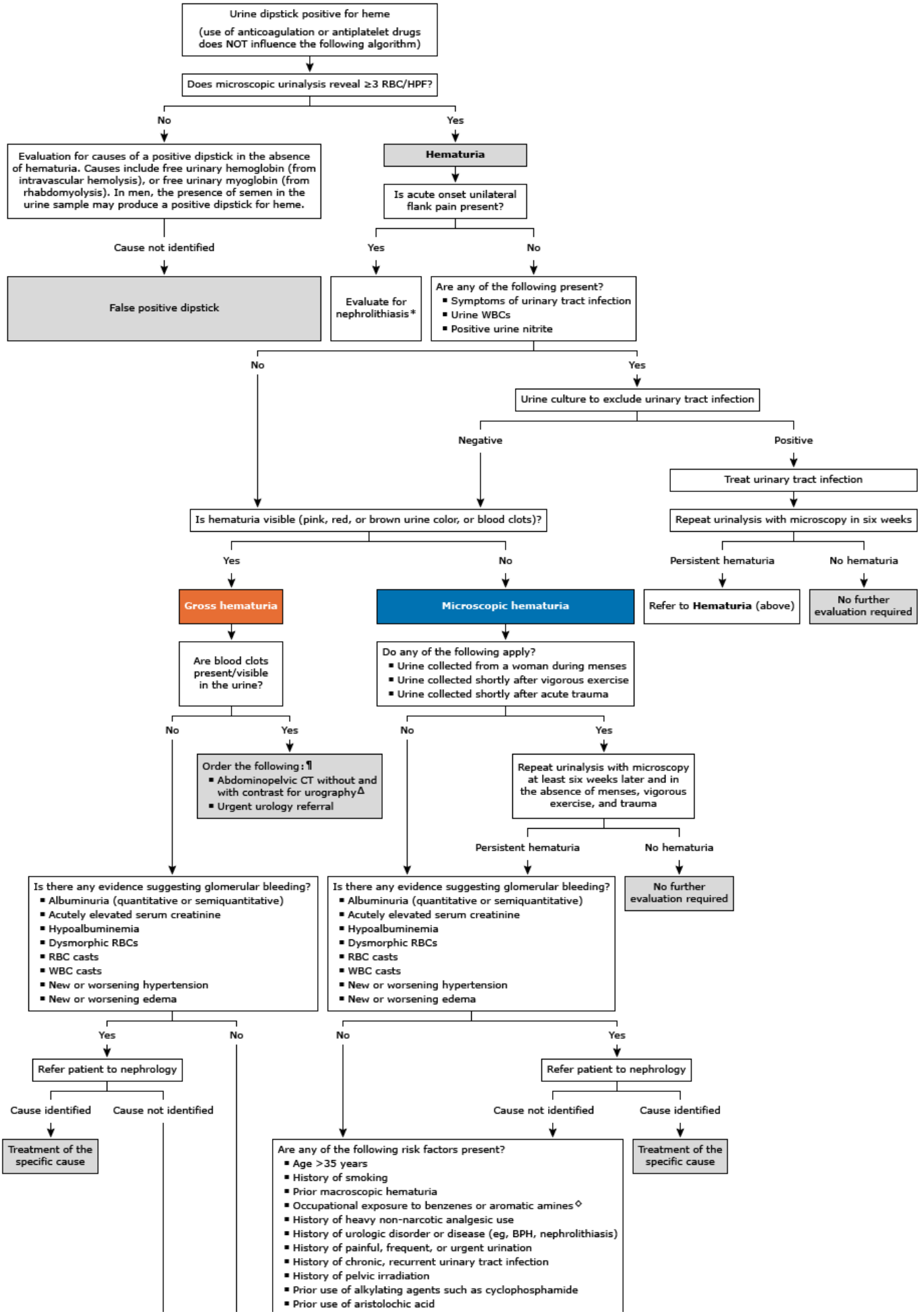


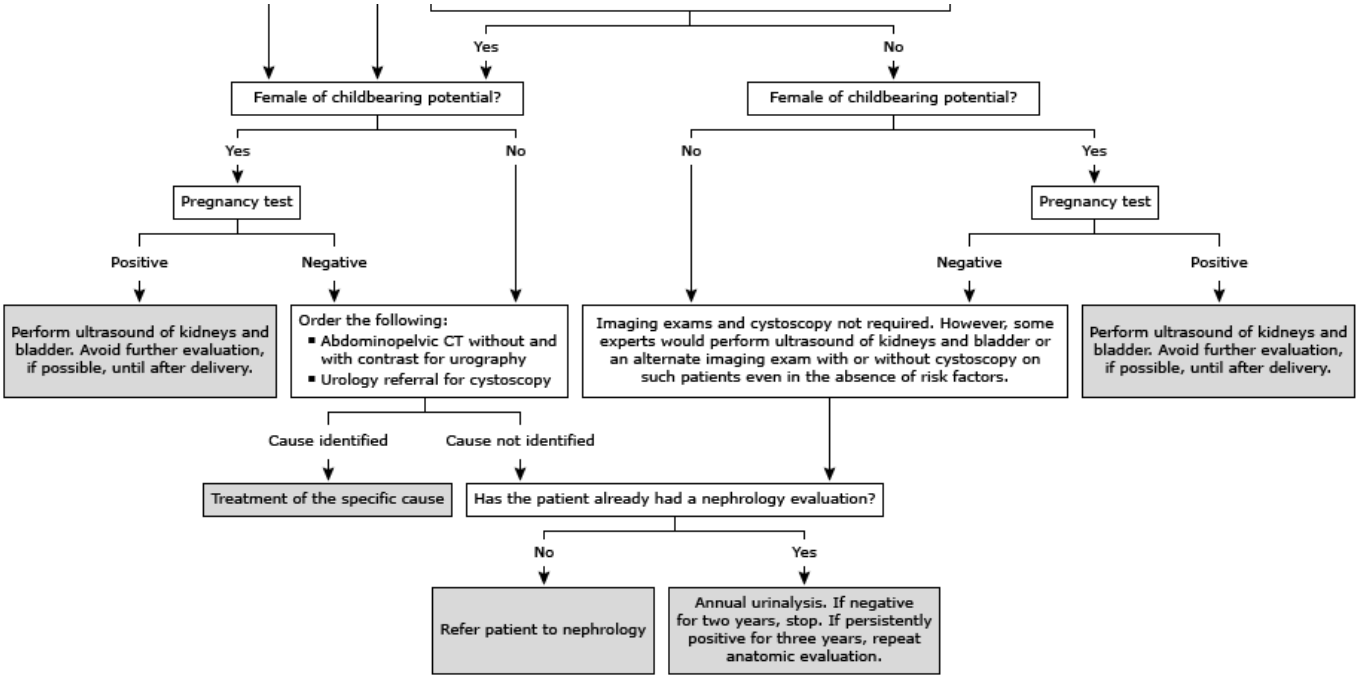
IgA: immunoglobulin A.
* Hematuria may not be attributed solely to alterations in coagulation or platelet function until competing causes have been ruled out.

Courtesy of Michael Kurtz, MD.

Graphic 63501 Version 8.0

Evaluation of the adult with asymptomatic hematuria


Urine dipstick positive for heme
(use of anticoagulation or antiplatelet drugs does NOT influence the following algorithm)
Does microscopic urinalysis reveal ≥3 RBC/HPF?
No
Yes
Evaluation for causes of a positive dipstick in the absence of hematuria. Causes include free urinary hemoglobin (from intravascular hemolysis), or free urinary myoglobin (from rhabdomyolysis). In men, the presence of semen in the urine sample may produce a positive dipstick for heme.
Hematuria
Cause not identified
Is acute onset unilateral flank pain present?
Yes
No
False positive dipstick
Evaluate for nephrolithiasis*
Are any of the following present?
▪ Symptoms of urinary tract infection
▪ Urine WBCs
▪ Positive urine nitrite
No
Yes
Urine culture to exclude urinary tract infection
Negative
Positive
Treat urinary tract infection
Repeat urinalysis with microscopy in six weeks
Persistent hematuria
No hematuria
Refer to Hematuria (above)
No further evaluation required
Is hematuria visible (pink, red, or brown urine color, or blood clots)?
Yes
No
Gross hematuria
Microscopic hematuria
Are blood clots present/visible in the urine?
Do any of the following apply?
▪ Urine collected from a woman during menses
▪ Urine collected shortly after vigorous exercise
▪ Urine collected shortly after acute trauma
No
Yes
Order the following:¶
▪ Abdominopelvic CT without and with contrast for urography△
▪ Urgent urology referral
Repeat urinalysis with microscopy at least six weeks later and in the absence of menses, vigorous exercise, and trauma
Persistent hematuria
No hematuria
No further evaluation required
Is there any evidence suggesting glomerular bleeding?
▪ Albuminuria (quantitative or semiquantitative)
▪ Acutely elevated serum creatinine
▪ Hypoalbuminemia
▪ Dysmorphic RBCs
▪ RBC casts
▪ WBC casts
▪ New or worsening hypertension
▪ New or worsening edema
Is there any evidence suggesting glomerular bleeding?
▪ Albuminuria (quantitative or semiquantitative)
▪ Acutely elevated serum creatinine
▪ Hypoalbuminemia
▪ Dysmorphic RBCs
▪ RBC casts
▪ WBC casts
▪ New or worsening hypertension
▪ New or worsening edema
Yes
No
No
Yes
Refer patient to nephrology
Refer patient to nephrology
Cause identified
Cause not identified
Cause not identified
Cause identified
Treatment of the specific cause
Treatment of the specific cause
Are any of the following risk factors present?
▪ Age >35 years
▪ History of smoking
▪ Prior macroscopic hematuria
▪ Occupational exposure to benzenes or aromatic amines◇
▪ History of heavy non-narcotic analgesic use
▪ History of urologic disorder or disease (eg, BPH, nephrolithiasis)
▪ History of painful, frequent, or urgent urination
▪ History of chronic, recurrent urinary tract infection
▪ History of pelvic irradiation
▪ Prior use of alkylating agents such as cyclophosphamide
▪ Prior use of aristolochic acid



RBC: red blood cell; HPF: high-power field; WBC: white blood cell; CT: computed tomography; BPH: benign prostatic hyperplasia.

* Abdominopelvic CT without contrast using a low radiation dose is recommended in most patients. For additional recommendations, refer to UpToDate topics on diagnosis of nephrolithiasis.

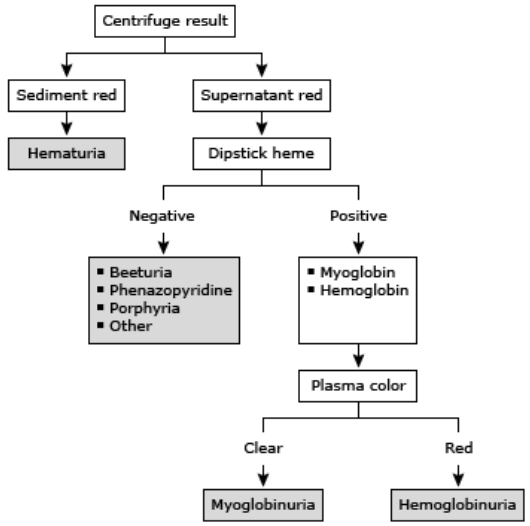
¶ Some patients with gross hematuria cannot empty their bladder due to severe clots and therefore develop urinary retention. Such patients should undergo prompt imaging and urology evaluation.

Δ Patients age <35 with noncontrast CT positive for nephrolithiasis may not need postcontrast imaging. For patients with contraindications to iodinated contrast, refer to UpToDate content for imaging options.

◊ For a list of potential environmental/workplace exposures that increase risk for bladder cancer, see http://www.cancer.org/cancer/bladdercancer/detailedguide/bladder-cancer-risk-factors.

Graphic 107857 Version 4.0

Approach to the patient with red or brown urine



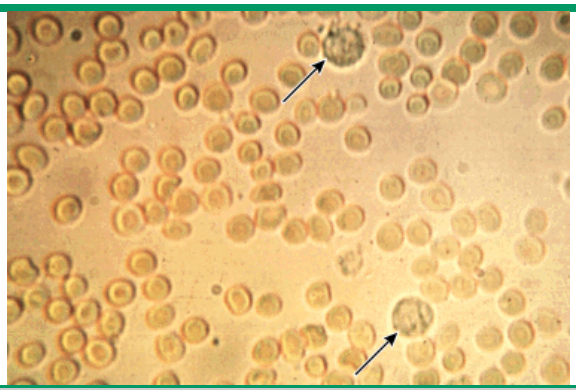
Graphic 55923 Version 5.0

Causes of heme-negative red urine

Medications
Doxorubicin
Chloroquine
Deferoxamine
Ibuprofen
Iron sorbitol
Nitrofurantoin
Phenazopyridine
Phenolphthalein
Rifampin
Food dyes
Beets (in selected patients)
Blackberries
Food coloring
Metabolites
Bile pigments
Homogentisic acid
Melanin
Methemoglobin
Porphyrin
Tyrosinosis
Urates

Graphic 56337 Version 3.0

Phase-contrast micrograph showing monomorphic red cells in urine sediment

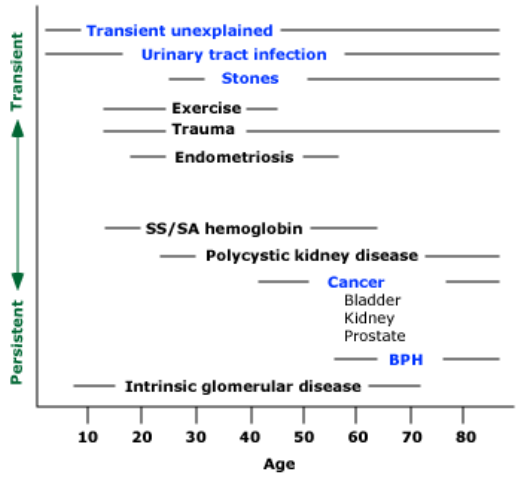


Urine sediment viewed by phase-contrast microscopy showing many red cells and an occasional larger white cell with a granular cytoplasm (arrows). The red cells have a uniform size and shape, suggesting that they are of nonglomerular origin.

Courtesy of Harvard Medical School.

Graphic 80282 Version 4.0

Major causes of hematuria by age and duration



Schematic representation of the major causes of hematuria in relation to the age at which they usually occur (horizontal axis), transience or persistence (vertical axis), and frequency (blue implies more frequent).

BPH: benign prostatic hyperplasia.

Graphic 61296 Version 1.0

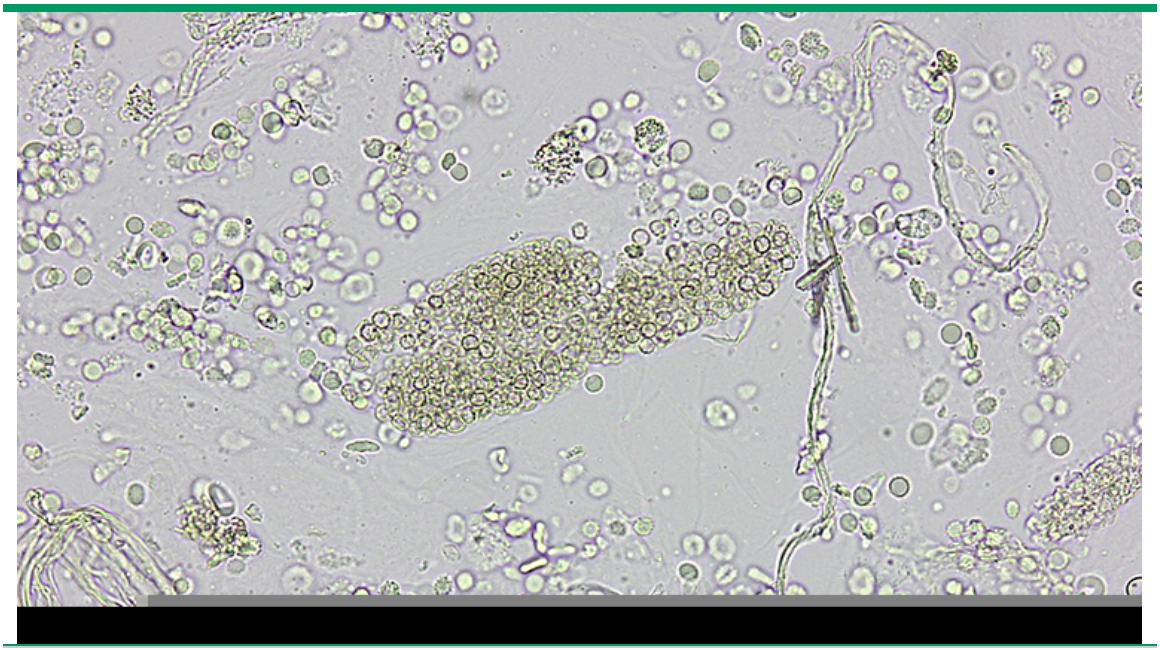
Distinguishing extraglomerular from glomerular hematuria

	Extraglomerular	Glomerular
Color (if macroscopic)	Red or pink	Red, smoky brown, or "Coca-Cola"
Clots	May be present	Absent
Proteinuria	<500 mg/day	May be >500 mg/day
RBC morphology	Normal	Some RBCs are dysmorphic
RBC casts	Absent	May be present

RBC: red blood cell.

Graphic 54067 Version 3.0

Photomicrograph of urine sediment with a red cell cast

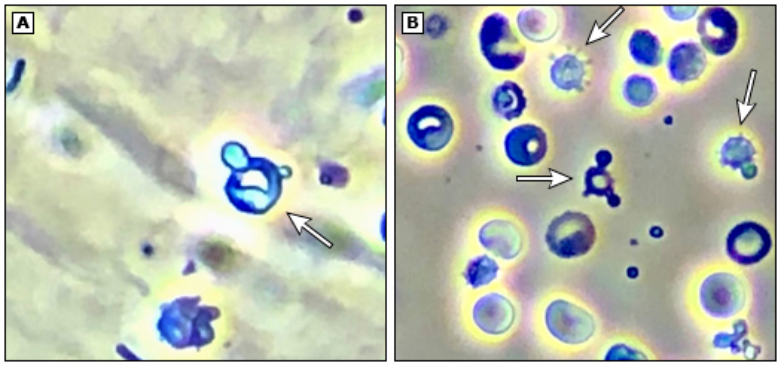


Urine sediment showing free red cells and a red cell cast that is tightly packed with red cells. It is more common for red cell casts to have fewer red cells trapped within a hyaline or granular cast. Red cell casts are virtually diagnostic of glomerulonephritis or vasculitis.

Courtesy of James F Simon, MD.

Graphic 55778 Version 4.0

Phase-contrast micrograph showing dysmorphic RBCs in urine sediment

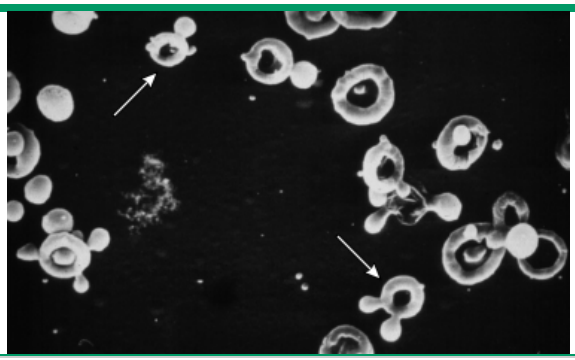


Phase-contrast microscopy showing dysmorphic red blood cells (RBCs) and acanthocytes in the urinary sediment of a patient with glomerular hematuria. Acanthocytes (arrows) can be recognized as ring forms with vesicle-shaped protrusions.

Courtesy of Juan Carlos Q Velez, MD.

Graphic 130438 Version 1.0

Scanning electron micrograph showing dysmorphic red cells in urine sediment



Scanning microscopy showing dysmorphic red cells in a patient with glomerular bleeding. Acanthocytes can be recognized as ring forms with vesicle-shaped protrusions (arrows).

Courtesy of Hans Köhler, MD.

Graphic 62064 Version 3.0

Contributor Disclosures

Mark A Perazella, MD, FACP Nothing to disclose **Richard J Glassock, MD, MACP** Employment: Karger Publishers [Associate Editor of Nephrology Viewpoints blog for American Journal of Nephrology]. Equity Ownership/Stock Options: Reata [Alport syndrome, pulmonary hypertension, diabetic nephropathy]. Consultant/Advisory Boards: Bristol-Myers Squibb [Lupus nephritis, focal segmental glomerulosclerosis]; ChemoCentryx [Vasculitis, C3 glomerulopathy, focal segmental glomerulosclerosis]; Retrophin [Focal segmental glomerulosclerosis, IgA nephropathy]; Omeros [IgA nephropathy]; Ionis [C3 glomerulopathy]; Apellis [Complement inhibition on glomerular disease]; Horizon [Glomerular disease]; BioCryst [Complement inhibition]; Aurinia [Voclosporin, lupus nephritis]; Calliditas [IgA nephropathy]; Renasight [Genetics]; Novartis [IgA nephropathy]. Speaker's Bureau: Genentech [Vasculitis]; Aurinia [Lupus nephritis]. **Michael P O'Leary, MD, MPH** Nothing to disclose **Albert Q Lam, MD** Nothing to disclose

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Conflict of interest policy