Hematuria

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Objectives

After completing this article, readers should be able to:

1. Define hematuria.
2. List the common conditions associated with hematuria.
3. Identify the important elements of the history and physical examination that suggest serious renal disease.
4. Plan a practical and systematic approach to the evaluation of hematuria.
5. Appreciate when consultation with a pediatric nephrologist is necessary.

Case Study

An 8-year-old white girl is referred for evaluation of hematuria, proteinuria, and hypertension. She has had recurrent episodes of gross hematuria. The first was at 3 years of age and was attributed to a urinary tract infection, but a urine culture was negative. She was treated with 10 days of antibiotics, and the symptoms resolved. The second episode, at age 5 years, was attributed to acute poststreptococcal glomerulonephritis, although an antistreptolysin O (ASO) titer was normal, and complement studies were not ordered. Blood pressure at that time was 120/80 mm Hg (normal for age and height is 94/54 mm Hg). The girl was lost to follow-up and presents 3 years later with blood pressure at the 95th percentile, gross hematuria, and generalized edema. Urinalysis of tea-colored urine shows too-numerous-to-count dysmorphic red blood cells (RBCs), white blood cells, proteinuria, and RBC casts. The differential diagnosis includes immunoglobulin A nephropathy, membranoproliferative glomerulonephritis, and hereditary nephritis, although the latter condition is unusual in a female. She is admitted for additional evaluation.

Introduction

Hematuria is a common finding in children and often comes to the attention of the pediatrician as a result of a routine screening urinalysis, as an incidental finding when evaluating urinary tract symptoms, or when a child has gross hematuria. Although the differential diagnosis for hematuria is extensive, most cases are isolated and benign. Generally, hematuria is a medical rather than a urologic issue. Only the rare child or adolescent who has hematuria needs initial screening radiographic imaging or invasive urologic procedures such as cystoscopy.

Definition

Hematuria is defined as the presence of five or more RBCs per high-power (40×) field in three consecutive fresh, centrifuged specimens obtained over the span of several weeks. (1) Confirmation of hematuria is critical. A positive urine dipstick test may result from myoglobinuria or hemoglobinuria, in which the urine often is discolored, but no RBCs are noted on microscopic evaluation. In addition, certain drugs (sulfonamides, nitrofurantoin, salicylates, phenazopyridine, phenolphthalein), toxins (lead, benzene), and foods (food coloring, beets, blackberries, rhubarb, paprika) may falsely discolor urine, in which case the urine dipstick test is negative for heme. In newborns, a red or pink discoloration in the diaper can be seen when urate crystals precipitate in the urine.

Hallmarks of glomerular bleeding are discolored urine, RBC casts, and distorted RBC morphology (Figs. 1 and 2). Evaluation of RBC morphology is helpful in distinguishing glomerular from extraglomerular sources (Table 1). The appearance of variable RBC

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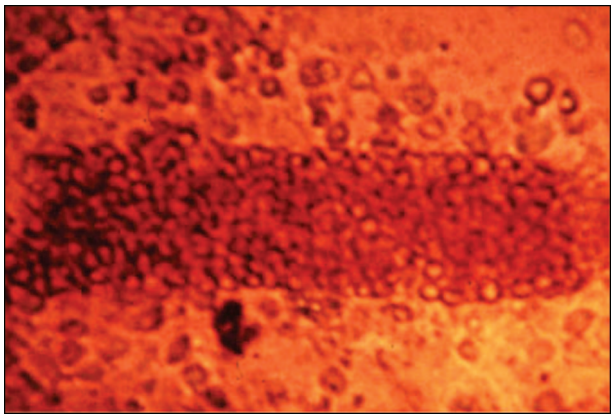

Figure 1. Urine sediment showing a red blood cell cast that is tightly packed with red blood cells. Red blood cell casts are virtually diagnostic of glomerulonephritis or vasculitis. Courtesy of Bruder Stapelton, MD.

shapes, such as budding or blebs, is more suggestive of glomerular sources. Phase-contrast microscopy is not readily available to most general practitioners, and if available, is limited by the experience of the observer. However, dysmorphic RBCs can be differentiated from eumorphic RBCs by using standard bright-field microscopy. The presence of blood clots is indicative of extraglomerular bleeding.

Prevalence

Large population studies in Galveston, Texas, and Helsinki, Finland, evaluating the presence of asymptomatic microscopic hematuria in school-age children, have shown a prevalence of 3% to 6% when a single urine specimen is evaluated. (1)(2) However, with repeat urinary screenings, the prevalence declines to 0.5% to 1%. The prevalence of hematuria does not differ by ethnicity or socioeconomic level, but opinions differ as to whether the prevalence is slightly higher in females. In a study of 8,954 school-age children, persistent asymptomatic hematuria led to a kidney biopsy in 28 children, with only 5 having identifiable renal pathology. The lack of serious disease identified in this and other studies has led to the recommendation that a kidney biopsy is not warranted for asymptomatic microscopic hematuria alone.

Table 1. Glomerular Versus Extraglomerular Hematuria

Factor	Glomerular	Extraglomerular
Color	Smoky, tea- or cola-colored, red	Red or pink
RBC Morphology	Dysmorphic	Normal
Casts	RBC, WBC	None
Clots	Absent	Present (+/−)
Proteinuria	≥2+	<2+

RBC=red blood cell, WBC=white blood cell

Causes

Because annual screening urinalyses no longer are recommended by the American Academy of Pediatrics, hematuria comes to the attention of the practitioner either incidentally or when evaluating a child who has urinary tract symptoms or gross hematuria. Hematuria may be either microscopic or macroscopic (gross hematuria). Microscopic hematuria may be either persistent or transient. The diagnostic evaluation of hematuria depends on the category: gross hematuria, symptomatic microscopic hematuria, asymptomatic microscopic hematuria with proteinuria, or isolated asymptomatic microscopic hematuria (Fig. 3).

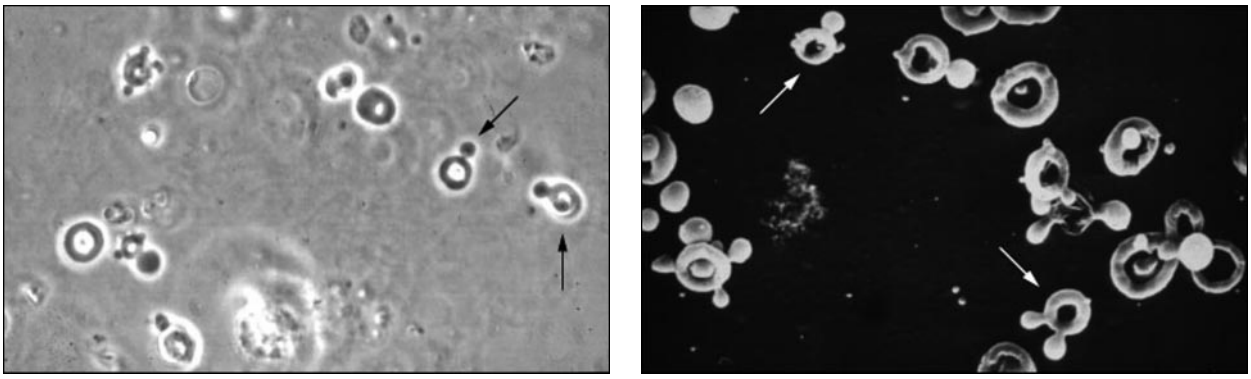

Figure 2. Phase-contrast microscopy showing dysmorphic red blood cells and red blood cell cast in a patient who has glomerular bleeding. Acanthocytes can be recognized as ring forms with vesicle-shaped protrusions. Courtesy of Bruder Stapelton, MD.

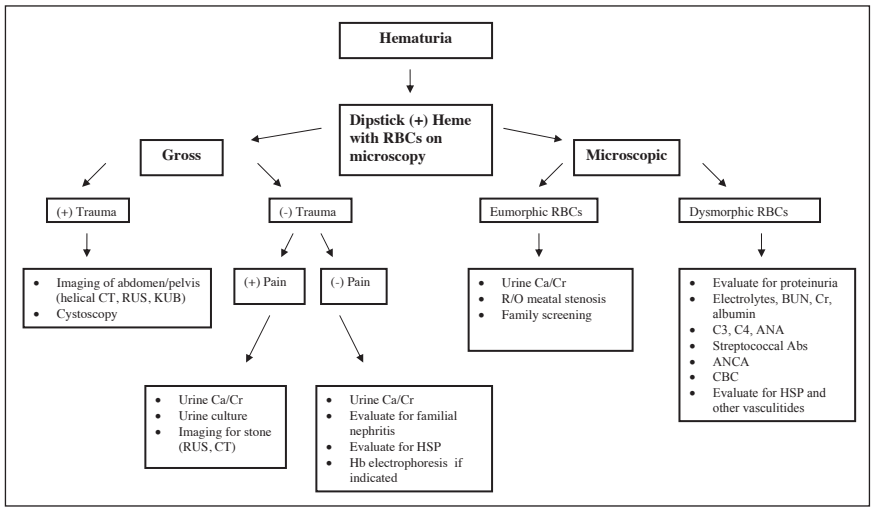

Figure 3. Algorithm for evaluation of hematuria. ANA=antinuclear antibody, ANCA=antineutrophil cytoplasmic antibody, Abs=antibodies, BUN=blood urea nitrogen, C=complement, Ca=calcium, CBC=complete blood count, Cr=creatinine, CT=computed tomography scan, HSP=Henoch-Schönlein purpura, Hb=hemoglobin, KUB=kidney-ureter-bladder radiograph, RBC=red blood cell, R/O=rule out, RUS=renal ultrasonography

Gross Hematuria

Gross hematuria is suspected when urine is discolored, usually red or tea-colored. In contrast to microscopic hematuria, underlying causes of gross hematuria are identified in 56% of cases (Table 2). (3)(4) In evaluating gross hematuria, it is important to confirm the presence of RBCs by microscopy. Following centrifugation of the urine, the finding of red urinary sediment with a positive dipstick test for hemoglobin is indicative of hematuria, whereas red supernatant with negative dipstick testing for hemoglobin is indicative of myoglobinuria, hemoglobinuria, or other causes of discolored urine. Aside from renal disease, common causes of gross hematuria include urinary tract infection, trauma, coagulopathy, crystalluria, and nephrolithiasis.

Suspicion of postinfectious acute glomerulonephritis (PIAGN) increases when gross hematuria is accompanied by a history of an antecedent illness, particularly streptococcal pharyngitis or impetigo. Other common features include edema (85%) and hypertension (85%). Confirmatory laboratory evidence includes a positive throat culture for group A *Streptococcus*, elevated streptococcal antibody titers, hypocomplementemia (depressed C3 value), and urinary RBC casts. PIAGN typically is a self-limited condition, and recurrence is rare. Complement values should normalize within 6 to 8 weeks. However, microscopic hematuria may persist for 6 to 12 months. Persistence of hematuria longer than 12 months or recurrent gross hematuria should lead to a reconsideration of the diagnosis of PIAGN.

Membranoproliferative glomerulonephritis commonly presents in older children and young adults, with a female predominance. Nephrotic syndrome is present in 50% of affected children; another 25% have a nephritic picture with edema, hypertension, and renal insufficiency. When it occurs in this condition, gross hematuria is more common in children than in adults and is infrequent after the first year of diagnosis. Hypocomplementemia is common in nearly all forms of this disease.

Gross hematuria in the presence of abdominal pain with or without bloody stools, arthralgias, and a purpuric rash suggests Henoch-Schönlein purpura nephritis. Pathologic proteinuria often is an accompanying finding if gross hematuria is present. The onset of renal findings may be delayed for 3 to 4 months after the initial presentation. Therefore, it is important to monitor urinalyses routinely in affected children.

Recurrent episodes of gross hematuria in children occur less commonly. When the hematuria coincides with acute illnesses or strenuous exercise, immunoglobulin A (IgA) nephropathy should be considered. In the adolescent population, IgA nephropathy is the most frequent cause of gross hematuria. (5) It is important to realize that although gross hematuria may resolve, patients may have persistent microscopic hematuria between episodes.

Evaluation of the family history for chronic kidney disease (end-stage renal disease, renal transplantation) may uncover conditions such as hereditary nephritis. Inherited mutations in type IV collagen of the glomerular basement membrane are responsible for X-linked, autosomal recessive, and autosomal dominant forms of Alport syndrome (AS) as well as for benign familial hematuria. (6)(7) The predominant form of AS is X-linked (85%), and as expected, males are affected more severely, with virtually all male patients developing kidney failure by the second or third decade of life, along with accompanying high-frequency sensorineural hearing loss and anterior lenticonus. Females who have X-linked AS may have only microhematuria. For the

Table 2. **Clues to Diagnosing Causes of Gross Hematuria**

History	Possible Diagnosis
Lower tract symptoms (dysuria, urgency, frequency, suprapubic pain)	UTI
Recent illness (pharyngitis, impetigo, viral illness)	Postinfectious glomerulonephritis
Abdominal pain	UTI, HSP, crystalluria/stone
Concurrent illness	IgAN
Extreme exertion, influenza	Rhabdomyolysis
Arthralgias	HSP, SLE
Diarrhea (± bloody)	HUS
Cough, hemoptysis	Vasculitis
Hearing loss	Alport disease
Nail or patellar abnormalities	Nail patella syndrome
Sickle cell disease	Glomerulonephritis, papillary necrosis
Drugs (diuretics, cyclophosphamide)	Stones, hemorrhagic cystitis
Birth asphyxia	Renal vein thrombosis
Physical Findings	**Possible Diagnosis**
Suprapubic pain	UTI
Flank pain	IgAN, stones, renal vein thrombosis, pyelonephritis
Rash (purpura, petechiae)	HSP, SLE, HUS, bleeding dyscrasia, abuse
Edema	Glomerulonephritis, nephrotic syndrome
Abdominal mass	Wilms tumor, hydronephrosis, cystic kidney disease
Conjunctivitis, pharyngitis	Adenovirus (hemorrhagic cystitis)
Meatal stenosis	Infection, trauma
Nail or patellar abnormalities	Nail patella syndrome
Family History	**Possible Diagnosis**
Hematuria	Benign familial hematuria, thin basement membrane disease
Hearing loss or prominent history of renal failure in males	Alport syndrome
Cystic kidney disease	Autosomal dominant polycystic kidney disease
Nail/patellar abnormalities	Nail patella syndrome
Sickle cell disease or trait	

HSP=Henoch-Schönlein purpura, HUS=hemolytic-uremic syndrome, IgAN= immunoglobulin A nephropathy, SLE=systemic lupus erythematosus, UTI=urinary tract infection

minority of females afflicted with the more progressive disease, the risk of developing kidney failure occurs in fewer than 10% to 15% and much later in life. Most patients who have the autosomal recessive form of AS develop significant proteinuria in late childhood or early adolescence and kidney failure before 30 years of age. Tissue diagnosis now is available for both kidney and skin biopsy specimens. Immunostaining shows abnormal staining for alpha-3, -4, and -5 chains of type IV collagen. In contrast to AS, benign familial hematuria is characterized by microscopic hematuria with occasional episodic gross hematuria (<10%), but proteinuria and hypertension are unusual features. Benign familial hematuria has an autosomal dominant pattern of transmission, although many family members are unaware that they have hematuria.

The most common hematologic disorders causing gross hematuria are sickle cell disease and sickle cell trait. Occlusion of the vasa recta capillaries can result in renal papillary infarcts. Hematuria occurs more commonly in males and frequently is unilateral, with the left kidney more likely to be affected. Recurrence occurs in 40% of cases. Contributing factors include hypoxia, acidosis, high osmolality, and stasis.

Painless gross hematuria following minor trauma can occur in conjunction with ureteropelvic junction obstruction, which can be diagnosed easily by renal ultrasonography or nuclear renography. Finding this condition should prompt referral to a pediatric urologist. Idiopathic urethrorrhagia may present with either asymptomatic terminal hematuria or spotting of blood on underpants. This disorder is benign and self-limited.

Symptomatic Microscopic Hematuria

Patients who have symptomatic microscopic hematuria often require the greatest attention and a methodical approach toward categorizing the disease process. When accompanied by elevated proteinuria on a "first" morning urine sample (protein-to-creatinine ratio >0.2), the likelihood of underlying renal disease is higher. Clinical

manifestations in patients who have symptomatic microscopic hematuria may be nonspecific (fever, malaise, weight change), extrarenal (malar rash, purpura, arthralgia/arthritis, headaches), or localized, with urinary tract symptoms (dysuria, suprapubic pain, flank pain, edema, oliguria). Clearly, the history and physical findings direct the extent of the evaluation. For example, a patient who has malar rash, arthritis, pericardial rub, edema, and hypertension likely has systemic lupus erythematosus. Fever, flank pain, nausea, and vomiting suggest upper urinary tract involvement. Dysuria, frequency, urgency, and incontinence suggest crystalluria or urinary tract infection. It is believed that microcrystallization is irritating to the uroepithelium and leads to the symptom complex and hematuria.

Asymptomatic (Isolated) Hematuria

Those who have asymptomatic hematuria rarely are found to have significant renal disease and, therefore, do not warrant an extensive evaluation. As many as 25% of patients have normalization of their urinalysis findings if followed for 5 years. Family history is particularly important to assess for benign familial hematuria, also known as thin basement membrane disorder, in which biopsy specimens are characterized ultrastructurally by diffuse thinning of the glomerular basement membrane. Often, multiple family members have a history of hematuria but are free of the long-term complications of progressive renal insufficiency, hearing, or ocular abnormalities seen in those who have AS. Rarely is gross hematuria seen in this group of patients (<10%). Patients should have regular monitoring for the development of hypertension and proteinuria.

Hypercalciuria frequently is associated with asymptomatic hematuria. Some affected patients are at risk for developing symptomatic urolithiasis. Hypercalciuria is defined as a urinary calcium-to-creatinine ratio of more than 0.2 (<6 months of age, >0.86; 7 to 18 months of age, >0.6) or 24-hour urinary calcium excretion exceeding 4 mg/kg per day. Hypercalciuria in most cases is idiopathic, but other considerations include immobilization, diuretics, vitamin D intoxication, hyperparathyroidism, and sarcoidosis.

Asymptomatic Hematuria and Proteinuria

The combination of hematuria and proteinuria is worrisome because it might be due to serious renal disease. However, finding both abnormalities is not uncommon; in most cases, serial urinalyses show resolution of one or both features. When evaluating this combination, it is important to determine initially if the proteinuria is orthostatic by evaluating a first morning urine protein (normal protein-to-creatinine ratio is <0.2). The persistence of pathologic proteinuria is more indicative of a glomerular process. This population deserves special attention and a thorough evaluation by a pediatric nephrologist.

Diagnostic Evaluation

Figure 3 provides an algorithm for evaluating a patient who has hematuria. The first step involves measurement of blood pressure. A dipstick urinalysis evaluates for pyuria, proteinuria, heme positivity, and urinary concentrating defects; microscopy evaluates for white blood cells and clumps, RBC morphology, crystals, and casts. Crystalluria can be caused by calcium oxalate, calcium phosphate, uric acid, or cystine crystals. Hypercalciuria is, by far, the most common cause of crystalluria. Urine culture should be reserved for those who have clinical symptoms or laboratory evidence (pyuria, hematuria, bacteriuria, positive nitrites) of a urinary tract infection. Radiographic studies should be delayed unless the symptom complex is highly suggestive of conditions such as nephrolithiasis.

The second stage of evaluation involves a more thorough search for underlying renal disease, particularly when edema, hypertension, alterations in urine output, or systemic symptoms are present. Serum chemistries (electrolytes, blood urea nitrogen, and creatinine) evaluate for renal insufficiency. Suspicion of acute PIAGN should prompt ordering of ASO and other streptococcal antibody titers and a C3 measurement. Secondary causes of renal disease, such as systemic lupus erythematosus, small vessel vasculitis, hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) disease, warrant checking an antinuclear antibody titer, complement levels (C3, C4), antineutrophil cytoplasmic antibodies, hepatitis serologies, or HIV serology, respectively. A complete blood count is helpful in the setting of petechiae, bruising, fatigue, abdominal masses, or suspicion of chronic disease. Evaluation for sickle cell disease or trait by hemoglobin electrophoresis is indicated if the family is unaware of the patient's status.

Renal ultrasonography can identify structural abnormalities, asymmetry, echogenicity, renal masses, and renal vein thrombosis. Abdominal radiographs may identify radiopaque stones comprised of calcium, struvite, and cystine. Radiolucent stones such as uric acid calculi are not detected. Spiral helical computed tomography scan is the most sensitive imaging modality for detecting nephrolithiasis but delivers a high radiation dose and is expensive. Radiocontrast should be used with caution in

the patient who has renal insufficiency and rarely when evaluating for stone disease.

Renal biopsy is reserved for the patients who have recurrent episodes of gross hematuria, coexisting nephrotic syndrome, coexisting hypertension with nephritic component, renal insufficiency, family history suggesting hereditary nephritis, and coexisting systemic symptoms (arthritis, purpura, malar rash, hemoptysis, anemia), as well as in those in whom nonglomerular causes have been excluded. At times, parental anxiety or the need for a definite diagnosis may prompt a renal biopsy.

Cystoscopy, an invasive and costly procedure, almost never is indicated for asymptomatic microscopic hematuria; it rarely discerns any underlying disease. Rhabdomyosarcoma typically causes gross hematuria and voiding dysfunction. Wilms tumor is identified best by radiographic imaging with ultrasonography.

When to Refer to a Pediatric Nephrologist

Unless the cause of gross hematuria is clear (urinary tract infection, PIAGN), referral to pediatric nephrology for a detailed evaluation is indicated. Early referral often is necessary for those experiencing symptomatic microscopic hematuria because many of the associated conditions necessitate a targeted evaluation and management. The patient who has asymptomatic hematuria needs periodic evaluation every 1 to 2 years to re-evaluate for coexisting symptoms or proteinuria and to revisit the family history with respect to other family members having hematuria or hearing deficits. The child who has persistent asymptomatic hematuria and concomitant proteinuria needs additional evaluation, often including a renal biopsy, by a pediatric nephrologist.

Continuation of Case Study

Laboratory studies revealed moderate kidney failure, hypocomplementemia, negative ASO titer, and negative antinuclear antibody titer. Kidney biopsy was performed due to the chronicity and nephritic nature of the presentation and showed membranoproliferative glomerulonephritis. Following a prolonged clinical course of steroid therapy, the child's blood pressure, kidney function, and urinalysis normalized. This case emphasizes the acute and relapsing aspects of a chronic disease and the importance of systematically evaluating the child who has hematuria with appropriate laboratory studies and referrals.

Summary

Hematuria is a common finding in children and adolescents presenting to a pediatrician in a busy practice. More often than not, parents, and sometimes the child, are anxious and demand an immediate diagnosis, particularly when there is gross hematuria. Critical to the evaluation is distinguishing the difference between the child who has asymptomatic microscopic hematuria that often is benign and requires conservative management and the child who has hematuria and accompanying proteinuria, edema, hypertension, or other symptoms suggestive of underlying renal disease. A simple and practical approach to the child who has hematuria should result in fewer invasive studies, a less costly evaluation, and appropriate referral. A stepwise approach makes failure to identify the patient who has serious renal disease unlikely.

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PIR Quiz

Quiz also available online at www.pedsinreview.aappublications.org.

6. You are evaluating a 10-year-old boy of English ethnicity who is complaining of reddish urine for the past several days. He denies abdominal pain but reports having a fever intermittently for the past week. His mother thinks she remembers a similar episode, which resolved, when the boy was 5 years old. He appears well, and his blood pressure is 100/64 mm Hg. His physical examination findings are normal. Urinalysis reveals numerous red blood cells without casts, and his serum complement value is normal. Of the following, which is the *most* likely diagnosis?

   A. Henoch-Schönlein purpura.
   B. Immunoglobulin A nephropathy.
   C. Membranoproliferative glomerulonephritis.
   D. Postinfectious acute glomerulonephritis.
   E. Sickle cell trait.

7. A 15-year-old girl comes to your office complaining of dark urine for 1 day. She has no other complaints. A urine dipstick evaluation performed in the office reveals large blood concentration but no other abnormalities. Of the following, which is the *most* appropriate first step in the evaluation of this girl's findings?

   A. Complement measurement to evaluate for evidence of postinfectious acute glomerulonephritis.
   B. Complete blood count to evaluate for anemia.
   C. Microscopic urinalysis to look for the presence of red blood cells.
   D. Renal ultrasonography to evaluate for abnormal renal anatomy.
   E. Serum creatinine and blood urea nitrogen to assess renal function.

8. A 5-year-old girl is brought to the emergency department because of suprapubic pain and fever for the past day. Her physical examination findings are normal except for obvious abdominal discomfort on palpation. A clean-catch urinalysis reveals large blood concentration, moderate leukocyte esterase, 5 to 10 white blood cells per high-power field, and 50 to 100 red blood cells per high-power field. Which of the following tests is *most* likely to reveal the diagnosis?

   A. Abdominal radiograph.
   B. Complete blood count.
   C. Computed tomography scan of the abdomen.
   D. Serum complement measurement.
   E. Urine culture.

9. Your partner in the emergency department checks out to you a 4-year-old boy who has vomiting, diarrhea, and dehydration. A clean-catch urinalysis was negative for ketones, but 5 to 10 red blood cells per high-power field were seen. The remainder of the urinalysis was normal. Additional history reveals that the boy has been healthy until now, and there is no family history of renal disease or hematuria. Physical examination findings are normal except for evidence of mild dehydration believed to be due to gastroenteritis. Of the following, which is the *most* likely cause of his hematuria?

   A. Benign familial hematuria.
   B. Henoch-Schönlein purpura.
   C. Hypercalciuria.
   D. Ureteropelvic junction obstruction.
   E. Urinary tract infection.

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