Crystals

Table 3 highlights the crystals commonly observed in the urine, along with morphology and associated conditions. Certain medications, including sulfadiazine, intravenous acyclovir, methotrexate, and indinavir, can result in crystals in the urine.

TABLE 3. Urine Crystals

Type	Morphology/ Shape	Associated Conditions
Calcium oxalate	Envelope; dumbbell; needle	Hypercalciuria; hyperoxaluria; calcium oxalate stones; ethylene glycol poisoning
Calcium phosphate	Prism; needle; star-like clumps	Distal renal tubular acidosis; urine pH >6.5; tumor lysis syndrome; acute phosphate nephropathy
Uric acid	Rhomboid; needle; rosette	Diabetes mellitus; obesity; gout; hyperuricemia; tumor lysis syndrome; urine pH <6.0
Magnesium ammonium phosphate (struvite)	Coffin-lid	Chronic urinary tract infection with urease-producing organisms
Cystine	Hexagonal	Cystinuria

KEY POINTS

- Isomorphic erythrocytes usually arise from a urologic process such as a tumor, stone, or infection.
- Erythrocyte casts are highly specific, but not particularly sensitive, for glomerulonephritis.

Measurement of Albumin and Protein Excretion

Proteinuria is most commonly comprised of albumin, but other proteins, including kidney-derived low-molecular-weight proteins, monoclonal immunoglobulins and light chains, myoglobin, and hemoglobin, may be present. Low-molecular-weight proteinuria is more common in tubulointerstitial disease or in generalized proximal tubular dysfunction (termed *Fanconi syndrome*), whereas a predominance of albuminuria favors a glomerular process.

Protein detected by urine dipstick should always be quantified. Quantification of proteinuria has traditionally been performed with a 24-hour urine collection, which measures all proteins present in the urine. Due to challenges in feasibility, accuracy, and patient adherence, measurement of proteinuria is now typically performed by determining the ratio of protein or albumin to creatinine on random urine samples. These ratios are easily obtained and correlate well with timed collections. See **Table 4** for the definitions of proteinuria and albuminuria.

The urine protein-creatinine ratio measures all proteins present in the urine, and a value of ≤150 mg/g is considered

TABLE 4. Definitions of Proteinuria and Albuminuria

Total Urine Protein			
Urine Collection Method	**Normal**	**Clinical Proteinuria**	
24-Hour Excretion	<150 mg/24 h	≥150 mg/24 h	
Spot Urine Protein-Creatinine Ratio[a]	≤150 mg/g ≈ ≤150 mg/24 h	>150 mg/g ≈ >150 mg/24 h	
Urine Albumin			
Urine Collection Method	**Normal**	**Moderately Increased Albuminuria (Microalbuminuria)**	**Severely Increased Albuminuria (Macroalbuminuria)**
24-Hour Excretion	<30 mg/24 h	30-300 mg/24 h	>300 mg/24 h
Conventional Spot Urine Dipstick[b]	Negative	Negative	Positive
Albumin-Specific Spot Urine Dipstick[c]	<3.0 mg/dL Negative	≥3.0 mg/dL Positive	Positive
Spot Urine Albumin-Creatinine Ratio[a]	<30 mg/g ≈ <30 mg/24 h	30-300 mg/g ≈ 30-300 mg/24 h	>300 mg/g ≈ >300 mg/24 h

[a]Because of the difficulty of obtaining a 24-hour urine collection, urine protein-creatinine ratio or urine albumin-creatinine ratio on random (spot) urine samples are used to estimate 24-hour excretion. Measurement of either urine protein or albumin concentration in a sample is divided by the creatinine concentration of the same sample to derive a unitless value. These ratios correlate well with the 24-hour excretion of protein or albumin. Although these calculations are technically dimensionless, they may be expressed by different laboratories with their units of calculation, such as mg/g (mg protein or albumin/g creatinine) or with units to reflect the proportional 24-hour excretion amount (mg or g protein or albumin/g creatinine).

[b]Conventional urine dipsticks are more sensitive for detection of albumin than non-albumin proteins; the detection limit is approximately 30 mg/dL, although they are not highly accurate for determining the degree of albuminuria if present.

[c]Urine dipsticks designed specifically to detect small amounts of albuminuria. Similar to conventional urine dipsticks, these dipsticks detect albumin above a concentration threshold but are sensitive to the presence of albumin at lower levels and can be used to indicate the presence of moderately increased albuminuria (microalbuminuria).

normal. Levels of proteinuria may be diagnostically helpful. Urine protein-creatinine ratios >150 mg/g but <200 mg/g may indicate either tubulointerstitial disease or glomerular disease, whereas nephrotic-range proteinuria, defined as a urine protein-creatinine ratio >3500 mg/g, usually indicates a glomerular process. In patients with evidence of proteinuria, at least two samples on different days should be collected to confirm the diagnosis. It is important to characterize the proteinuria (such as in suspected cast nephropathy) with urine electrophoresis with immunofixation of monoclonal immunoglobulins when indicated.

The urine albumin-creatinine ratio measures only albumin in the urine and is helpful in evaluating for diabetic kidney disease. Because albuminuria is one of the earliest indicators of diabetic kidney disease, the American Diabetes Association (ADA) recommends annual assessment of urine albumin excretion by measuring the urine albumin-creatinine ratio in patients with type 1 diabetes mellitus of 5 years' duration and in all patients with type 2 diabetes starting at the time of diagnosis. Normal albumin excretion by this method is considered <30 mg/g. Although screening for albuminuria is commonly performed in patients with diabetes, the American College of Physicians (ACP) found the current evidence insufficient to evaluate the benefits and harms of screening for CKD in asymptomatic adults with CKD risk factors, including diabetes, hypertension, and cardiovascular disease.

The terminology for describing abnormal albumin excretion has changed. A urine albumin-creatinine ratio of 30 to 300 mg/g, previously termed *microalbuminuria*, is now referred to as *moderately increased albuminuria*, and levels >300 mg/g, previously known as *macroalbuminuria* or *overt proteinuria*, are now termed *severely increased albuminuria*. The diagnosis of moderately increased albuminuria in patients with diabetes is made when two or three random samples obtained over 6 months show a urine albumin-creatinine ratio of 30 to 300 mg/g; the use of ACE inhibitors or angiotensin receptor blockers in these patients has been shown to delay progression of CKD, underscoring the importance of early detection. Once a diagnosis of moderately increased albuminuria has been established and treatment initiated, the ACP recommends against further screening for albuminuria because it will not significantly influence management decisions.

In other patients at increased risk for kidney disease, the urine protein-creatinine ratio is appropriate to evaluate for suspected proteinuria. Transient proteinuria is common and is associated with febrile illnesses or rigorous exercise; it requires no further evaluation. Orthostatic proteinuria occurs when proteinuria increases when the patient is in an upright position and decreases when the patient is recumbent; this benign condition, more common in adolescents, can be assessed with a split urine collection. This test should be obtained in patients younger than 30 years of age who appear to have persistent proteinuria.

KEY POINT

- Measurement of proteinuria is typically performed by determining the ratio of protein or albumin to creatinine on randomly obtained urine samples; these ratios correlate with daily excretion determined by timed collections.

Clinical Evaluation of Hematuria

Hematuria is defined as >3 erythrocytes/hpf and may be either macroscopic (grossly visible) or microscopic (detectable only on urine testing). Hematuria has many potential causes and a wide range of clinical significance. False hematuria or hematuria mimics may be caused by contamination from menstrual bleeding or from substances that produce red-colored urine not due to erythrocytes or hemoglobinuria, including medications (rifampin, phenytoin), food (rhubarb, beets), acute porphyrias, and myoglobinuria. Hemoglobinuria results from the release of free hemoglobin intravascularly in conditions such as hemolysis from perivalvular leak and delayed transfusion reaction. Benign causes of hematuria include infections such as UTIs, nephrolithiasis, trauma, and exercise. Potentially life-threatening and often clinically urgent causes of hematuria include rapidly progressive glomerulonephritis and urinary tract malignancy. Glomerular causes of hematuria also include more benign or indolent diseases such as thin glomerular basement membrane disease, IgA nephropathy, and other forms of chronic glomerulonephritis.

Glomerular hematuria typically features brown- or tea-colored urine with dysmorphic erythrocytes (or acanthocytes) and/or erythrocyte casts on urine sediment examination. Urologic hematuria may include passage of blood clots or pure blood and nondysmorphic erythrocytes. Examination of the urine is not definitive in determining glomerular versus urologic sources of hematuria, especially in patients at risk for genitourinary tract malignancies. Patients with a bleeding diathesis or on anticoagulation merit a complete evaluation; hematuria should not be attributed to the coagulopathy or anticoagulation until other causes have been excluded.

Evaluation of the patient with hematuria begins with a careful history, especially for more benign causes (**Figure 4**). False hematuria should be excluded. Historical and/or laboratory clues may point to a glomerular etiology and the need for nephrology consultation. In patients with suspected glomerular hematuria, extrarenal manifestations of a systemic disease such as vasculitis should be sought.

The American Urological Association (AUA) guidelines for the evaluation of asymptomatic microhematuria recommend CT urography as the imaging modality of choice (**Table 5**, on page 9). The AUA guidelines also recommend cystoscopy for all patients over 35 years of age or those with risk factors for urologic malignancy. The AUA guidelines do not recommend urine cytology for routine evaluation of asymptomatic microhematuria. The U.S. Preventive Services Task Force recommends against using

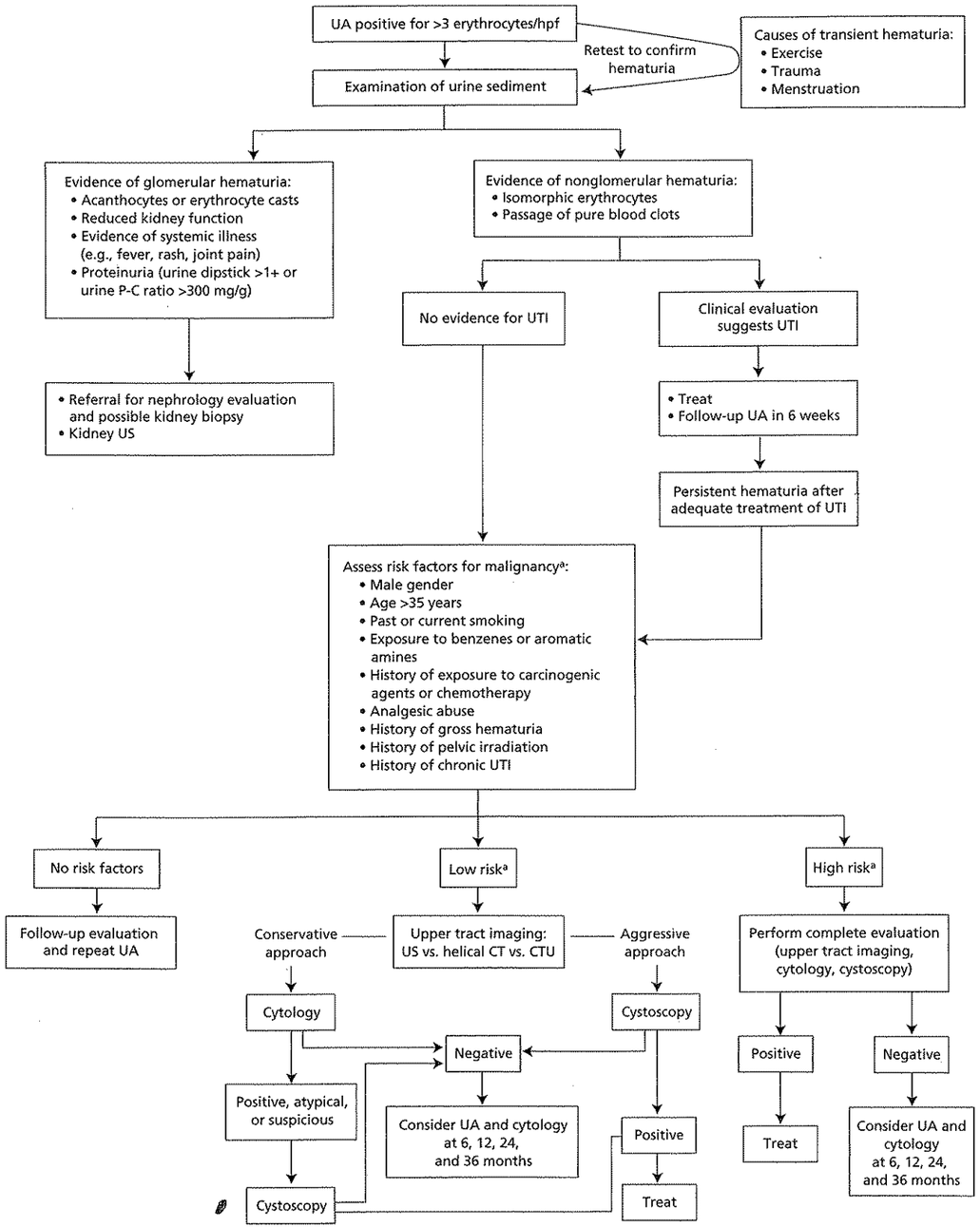

FIGURE 4. The clinical evaluation of hematuria. CTU = computed tomography urography; P-C = protein-creatinine; UA = urinalysis; US = ultrasonography; UTI = urinary tract infection.

[a]Modified from Urology. Grossfeld GD, Litwin MS, Wolf JS, et al. Evaluation of asymptomatic microscopic hematuria in adults: the American Urological Association best practice policy--part II: patient evaluation, cytology, voided markers, imaging, cystoscopy, nephrology evaluation, and follow-up. 2001 Apr;57(4):604-10. [PMID: 11306357] Copyright 2001, modified with permission from Elsevier.

TABLE 5. Imaging Used in the Evaluation of Hematuria

Study	Advantages	Disadvantages
CT urography (CTU)	High sensitivity (100%) and specificity (97%); image modality of choice	High radiation dose; Risk of CIN; contraindicated in pregnancy
MR urography	Useful in eGFR range of 30-60 mL/min/1.73 m^2 or when CTU is contraindicated	Contraindicated when eGFR <30 mL/min/1.73 m^2 (risk of gadolinium-induced nephrogenic systemic fibrosis); less sensitive than CTU for smaller cancers and stones
Ultrasonography	No contrast or radiation exposure; useful in pregnancy; lower cost	Limited sensitivity, especially for lesions <2 cm and ureteral lesions

CIN = contrast-induced nephropathy; eGFR = estimated glomerular filtration rate.

urinalysis for bladder cancer screening in asymptomatic patients, even those with risk factors.

KEY POINTS

- Potentially life-threatening and often clinically urgent causes of hematuria include rapidly progressive glomerulonephritis and urinary tract malignancy.
- Evaluation of asymptomatic microhematuria should include CT urography except in patients with chronic kidney disease, pregnant patients, or patients allergic to contrast; cystoscopy should be performed in patients over 35 years of age or those with risk factors for urologic malignancy.
- HVC Urinalysis should not be used to screen for bladder cancer in asymptomatic patients.

Imaging Studies

The four main modalities of kidney imaging (ultrasonography, CT, MRI, and radionuclide studies) provide information about structure and function of the urinary tract. Ultrasonography (US) is safe, noninvasive, relatively inexpensive, and easy to obtain. Often the first imaging test in the evaluation of kidney disease, US can assess kidney size and cortical thickness, detect renal cysts and tumors, and diagnose obstruction and hydronephrosis. US is useful for assessment of the bladder, postvoid residual, and the prostate in bladder outlet obstruction but is less helpful in evaluating diseases affecting the mid and distal ureter. Increased echogenicity of the kidney is nonspecific but implies parenchymal disease. Experienced centers have used Doppler US for detection of clinically relevant renal artery stenosis.

US is being increasingly used as an initial diagnostic study for uncomplicated nephrolithiasis. Although less sensitive than CT, particularly for detecting small stones and ureteral stones, it does not expose patients to radiation, is often more readily available, and is usually more cost-effective when compared with CT; it is also the indicated modality during pregnancy. A positive ultrasound may be adequate for initial diagnosis, with CT imaging for those with a nondiagnostic ultrasound or a more complicated clinical presentation.

Noncontrast abdominal helical CT has traditionally been the most commonly used imaging technique for suspected nephrolithiasis because it detects most stones, provides anatomic information, and visualizes the entire urinary tract; it may also suggest stone composition and potentially provide alternative diagnoses if nephrolithiasis is not detected. Contrast abdominal CT characterizes renal tumors and cysts, whereas CT urography is the preferred test for patients with unexplained urologic/nonglomerular hematuria. Intravascular iodinated contrast for CT and angiography may be complicated by contrast-induced nephropathy, especially in patients with CKD. The decision to use contrast depends on the clinical scenario, the patient's risk factors for contrast-induced nephropathy, and the availability and utility of alternative imaging modalities.

Kidney MRI can also identify renal masses, cysts, and renal vein thrombosis. MR angiography with gadolinium contrast can detect renal artery stenosis in the evaluation of possible renovascular hypertension, replacing standard angiography as the preferred modality. However, gadolinium can cause nephrogenic systemic fibrosis (NSF), a systemic fibrosing disorder that occurs predominantly in patients with CKD (typically stage 4 or 5), and gadolinium contrast must be avoided in patients with an estimated GFR <30 mL/min/1.73 m^2. See MKSAP 17 Dermatology for more information on NSF.

Often used for clinical research studies, radionuclide kidney imaging is the gold standard for measuring GFR and renal plasma flow and can be used in the evaluation of a kidney transplant donor candidate with borderline kidney function. In clinical practice, radionuclide scans are most useful for determining relative function of the kidneys, such as a hydronephrotic, atrophic, or cancerous kidney prior to nephrectomy.

KEY POINTS

- Ultrasonography is typically the first imaging test in the evaluation of the kidneys and upper urinary tract because of its safety, cost effectiveness, and general utility. HVC
- Contrast abdominal CT characterizes renal tumors and cysts, whereas CT urography is the preferred test for patients with unexplained urologic/nonglomerular hematuria.

CONT. neurohumoral activation, increased intra-abdominal pressure leading to venous congestion and increased renal venous pressure, reduced renal perfusion, and right ventricular dysfunction.

Management is challenging because treatment of one organ may cause worsening of the other. Treatment is mostly directed toward improving cardiac function with diuretics, ACE inhibitors or ARBs, vasodilators, and inotropes. Many of these medications may worsen kidney function. Ultrafiltration, or the removal of plasma water through an extracorporeal circuit, has been used in patients unresponsive to diuretics; however, current evidence does not support ultrafiltration over intensive diuretic management. Patients presenting with CKD or AKI at presentation of heart failure have an increased mortality.

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is a reversible form of AKI that occurs in patients with advanced liver cirrhosis or those with fulminant hepatic failure. HRS is characterized by marked reduction in GFR and renal perfusion in the absence of other causes of AKI. AKI in HRS is caused by intense renal vasoconstriction with peripheral arterial vasodilation. Tubular function is preserved with no tubular histologic changes, no proteinuria, normal urine sediment, FE_{Na} <1%, and urine sodium concentration <10 mEq/L (10 mmol/L).

Two subtypes of HRS have been identified based on the rapidity of AKI: type 1 HRS is rapidly progressive AKI defined by the doubling of initial serum creatinine to a level >2.5 mg/dL (221 μmol/L) in <2 weeks, usually with a precipitating event; and type 2 HRS is defined as a more gradual decline in kidney function associated with refractory ascites. Diuretic withdrawal and volume expansion are used to exclude a prerenal cause.

See Hepatorenal Syndrome in MKSAP 17 Gastroenterology and Hepatology for more information.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is characterized by the massive release of uric acid, potassium, and phosphate into the blood from rapid lysis of malignant cells. It is typically seen after initiation of cytotoxic therapy for hematologic malignancies with large tumor burden (such as high-grade lymphomas) or high cell counts (such as acute lymphoblastic leukemia), but TLS can also occur spontaneously. AKI results from intratubular precipitation of uric acid and calcium phosphate crystals. Clinical features include hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. General principles for the management of patients at high or intermediate risk for or presenting with TLS are aggressive volume expansion, management of hyperkalemia, and preventive therapy for hyperuricemia. Allopurinol decreases uric acid production, and rasburicase (a recombinant urate oxidase) catalyzes enzymatic oxidation of uric acid into water-soluble allantoin. Rasburicase is usually reserved for those at highest risk; it is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency because it can induce severe hemolysis and methemoglobinemia. Urine alkalinization in TLS is controversial and can promote calcium phosphate precipitation.

Abdominal Compartment Syndrome

Intra-abdominal hypertension (IAH) is defined as an intra-abdominal pressure (IAP) >12 mm Hg. Abdominal compartment syndrome (ACS) is defined as sustained IAP >20 mm Hg associated with new organ dysfunction. Both IAH and ACS are associated with AKI and increased mortality. ACS occurs in the setting of diminished abdominal wall compliance (abdominal surgery, trauma, prone positioning, respiratory failure, obesity), increased intraluminal contents (gastroparesis, ileus, bowel obstruction), increased intra-abdominal contents (hemoperitoneum, ascites), increased retroperitoneal contents (pancreatitis, retroperitoneal hemorrhage), and capillary leak (secondary to massive fluid resuscitation, coagulopathy, sepsis, burns). Increasing abdominal pressure compresses abdominal viscera and leads to intra-abdominal organ impairment and cardiac, respiratory, and neurologic impairment. Oliguric AKI develops from renal vein and artery compression.

The diagnosis is made by measuring IAP using bladder pressure. Management includes supportive care, management of ascites, correction of positive fluid balance, and abdominal compartment decompression. H

KEY POINTS

- Strategies to minimize the development of contrast-induced nephropathy include intravenous volume expansion with isotonic fluids, use of low- or iso-osmolal contrast media, minimization of contrast volume, and discontinuation of potentially nephrotoxic medications.
- Tumor lysis syndrome is characterized by the massive release of uric acid, potassium, and phosphate into the blood from rapid lysis of malignant cells; management of patients at high or intermediate risk includes aggressive volume expansion, management of hyperkalemia, and preventive therapy for hyperuricemia.
- Abdominal compartment syndrome is defined as sustained intra-abdominal hypertension >20 mm Hg associated with new organ dysfunction; oliguric acute kidney injury develops from renal vein and artery compression in this setting.

Management H

General Considerations

Successful management of AKI requires early recognition, correction of the cause, and discontinuation of nephrotoxins. Other supportive measures include optimizing hemodynamics and renal perfusion, preventing further kidney injury, and medically treating complications of AKI. Potassium,

CONT. magnesium, and phosphate should be restricted. Supplemental bicarbonate can be used to correct metabolic acidosis. Diuretics should be used for volume overload. Nutrition should be managed carefully to ensure adequate caloric and protein intake.

Acute Dialysis

Dialysis is used to control complications of severe AKI. Several specific types of dialysis used in AKI are intermittent hemodialysis (IHD), peritoneal dialysis (PD), continuous renal replacement therapy (CRRT), and hybrid therapies such as prolonged intermittent renal replacement therapy (PIRRT). Absolute indications for dialysis include hyperkalemia, metabolic acidosis, and pulmonary edema refractory to medical therapy; uremic symptoms; uremic pericarditis; and certain drug intoxications.

IHD is delivered 3 to 6 times a week, 3 to 4 hours per session, through a temporary double-lumen hemodialysis catheter inserted into the internal jugular or femoral vein. Advantages of IHD include rapid correction of electrolyte disturbances (such as hyperkalemia) and rapid removal of drug intoxications. The main disadvantage is the risk of hypotension caused by rapid solute and fluid removal.

CRRT is a slow continuous type of dialysis that is delivered 24 hours a day in the ICU for unstable patients. CRRT removes solutes and fluid much more slowly than IHD. As a result, CRRT is used to treat hemodynamically unstable patients who cannot tolerate IHD due to hypotension or in patients in whom IHD cannot adequately control azotemia, acidosis, and volume overload. CRRT often requires anticoagulation.

PIRRT, also known as sustained low-efficiency dialysis (SLED), is slower than IHD and runs for 8 to 12 hours daily. PIRRT combines advantages of both CRRT and IHD: it allows for the improved hemodynamic stability that gradual solute and volume removal provide in CRRT while utilizing the less expensive technology of conventional IHD. PIRRT is an effective alternative to CRRT in hemodynamically unstable patients.

PD is not thought to be as effective as the other RRTs for management of AKI, although direct clinical comparisons are limited. PD may be useful when the other types of dialysis are unavailable or vascular access cannot be obtained. However, PD requires the insertion of a catheter into the peritoneal cavity, which is often complicated by catheter leakage and malfunction. In addition, PD is associated with increased protein losses and is contraindicated in patients with recent abdominal surgery.

Generally, IHD is used for stable patients with AKI, and CRRT or PIRRT for critically ill patients with unstable hemodynamics, multiorgan failure, or high catabolic states. Randomized clinical trials have not shown a benefit of CRRT over IHD or PIRRT for survival or renal recovery. However, CRRT is preferred in patients with acute liver failure and acute brain injury with increased intracranial pressure because rapid fluid and solute shifts in IHD may worsen cerebral edema. H

KEY POINT

- In patients with acute kidney injury, absolute indications for dialysis include hyperkalemia, metabolic acidosis, and pulmonary edema refractory to medical therapy; uremic symptoms; uremic pericarditis; and certain drug intoxications.

Kidney Stones

Epidemiology

Kidneys stones are common, with a lifetime incidence between 7% and 13% and a high recurrence rate in the United States. Without treatment, symptomatic nephrolithiasis will recur in 35% to 50% of patients within 5 years and 75% at 20 years. Asymptomatic stones are commonly seen on abdominal imaging and may progress to symptomatic disease in 11% to 32% within 4 years.

Clinical Manifestations

The classic presenting symptom in patients with kidney stones is paroxysmal waxing and waning pain, termed *renal colic*, which usually occurs in the affected flank or back. The pain radiates to the groin, labium, penis, or testicle as the stone travels down the ureter. Kidney stones can produce abdominal pain and symptoms such as nausea, mimicking an acute abdomen.

Diagnosis H

On physical examination, patients with kidney stones typically are restless. Although there may be tenderness in the general region of nephrolithiasis, the abdominal examination may be unremarkable.

A complete blood count, complete metabolic profile, and measurement of kidney function are indicated to rule out infection, electrolyte abnormalities, and acute kidney injury. Urinalysis typically reveals hematuria, although the absence of erythrocytes in the urine does not exclude the diagnosis. Urine crystals on microscopy may suggest the chemical composition of the stone, although this finding may not be definitive.

Radiologic imaging is indicated for diagnosis and to guide management based on stone size and location. Plain abdominal radiography has limited utility due to its inability to detect radiolucent uric acid stones and does not provide as much anatomic information as other modalities. However, it may be useful in assessing stone burden in patients with known radiopaque stones. Noncontrast helical CT has traditionally been the most commonly used imaging technique because it detects most stones, provides anatomic information, and visualizes the entire urinary tract; it may also suggest stone composition

CONT. and potentially provide alternative diagnoses if nephrolithiasis is not detected. However, CT is associated with significant radiation exposure and is contraindicated in pregnant women. Ultrasonography is increasingly being used as an initial diagnostic study. Although less sensitive than CT for nephrolithiasis, particularly for detecting small stones and ureteral stones, ultrasonography does not expose patients to radiation and is usually more readily available and has a lower cost compared with CT; it is also the preferred modality during pregnancy. A positive ultrasound may therefore be adequate for initial diagnosis in patients with a typical presentation for kidney stones, with more complex testing indicated for those with a high clinical suspicion but a nondiagnostic ultrasound or a more complicated clinical presentation.

KEY POINTS

- Noncontrast helical CT is commonly used to evaluate for nephrolithiasis because it detects most stones, provides anatomic information, visualizes the entire urinary tract, may suggest stone composition, and potentially provides alternative diagnoses.

HVC

- Ultrasonography is increasingly being used as an initial diagnostic study for nephrolithiasis due to availability, lack of radiation exposure, and low cost; it is also the preferred modality during pregnancy.

Types of Kidney Stones

Calcium Stones

Approximately 80% of kidney stones contain calcium oxalate, calcium phosphate, or both. Calcium stones are radiopaque on plain radiograph. Hypercalciuria, hyperoxaluria, and hypocitraturia are risk factors for calcium stones.

Hypercalciuria

Hypercalciuria is the most common metabolic risk factor for calcium oxalate stones. In patients with hypercalcemia, increased filtered calcium results in hypercalciuria. However, hypercalciuria is often idiopathic and commonly familial, occurring without associated hypercalcemia.

Hypercalciuria due to hypercalcemia is treated by addressing the cause of increased serum calcium. In patients with other forms of hypercalciuria, thiazide diuretics reduce calcium excretion in the urine by inducing mild hypovolemia, triggering increased proximal sodium reabsorption and passive calcium reabsorption. A low sodium diet enhances the effect thiazides have in promoting calcium reabsorption from the renal tubule. However, restricting dietary calcium intake in patients with hypercalciuria may paradoxically increase the risk of kidney stone formation by causing decreased binding of calcium with oxalate in the gut with increased absorption and excretion of oxalate; therefore, dietary calcium should not be limited unless it is excessive (for example, >2000 mg/d).

Hyperoxaluria

Hyperoxaluria predisposes to calcium oxalate stones and can have several potential causes. Primary hyperoxaluria is a rare inborn error of glyoxylate metabolism resulting in overproduction of oxalate. Excessive dietary oxalate intake (chocolate, spinach, rhubarb, green and black tea) can cause hyperoxaluria. Excessive urinary oxalate may also occur due to significant restriction in dietary calcium intake, which decreases binding of calcium to dietary oxalate in the gut and increases oxalate absorption.

Enteric hyperoxaluria results from malabsorption when excessive free fatty acids in the gastrointestinal lumen bind calcium, increasing free oxalate absorption in the colon. Short bowel syndromes with an intact colon and malabsorptive bariatric procedures (such as Roux-en-Y gastric bypass) are the most common causes of enteric hyperoxaluria.

Avoiding excessive oral intake of oxalate is a primary therapeutic intervention for hyperoxaluria. Specific therapy for enteric hyperoxaluria is oral calcium carbonate or citrate supplementation (up to 4 g/d) to bind intestinal oxalate (the reduction in oxalate absorption counters the potential for increased calcium absorption). Cholestyramine may also be used to decrease oxalate absorption as it binds both oxalate and bile salts in the gut. Patients with primary hyperoxaluria are treated with high-dose pyridoxine.

Hypocitraturia

Urinary citrate inhibits stone formation by binding calcium in the tubular lumen, preventing it from precipitating with oxalate. Hypocitraturia is seen with high animal protein diets and metabolic acidosis from chronic diarrhea, renal tubular acidosis, ureteral diversion, and carbonic anhydrase inhibitors (including seizure medications such as topiramate).

Citrate excretion can be enhanced by alkalinizing the serum with potassium citrate or potassium bicarbonate, which decreases uptake of filtered citrate from the tubular lumen. Increased fruit and vegetable intake also increases citrate excretion, especially in patients who are hypocitraturic.

Struvite Stones

Struvite stones are composed of magnesium ammonium phosphate (struvite) and calcium carbonate-apatite and occur in the presence of urea-splitting bacteria such as *Proteus* or *Klebsiella* in the upper urinary tract. These organisms convert urea to ammonium, which alkalinizes the urine, decreases the solubility of phosphate, and leads to struvite precipitation. Although struvite stones affect less than 10% of patients with kidney stones, they occur more commonly in women and in patients predisposed to chronic or recurrent urinary tract infection, including those with urologic diversions or neurogenic bladder. Struvite stones can rapidly enlarge to fill the entire renal pelvis within weeks to months, taking on a characteristic "staghorn" shape.

Treatment of infections from urea-splitting organisms is the cornerstone of therapy for preventing struvite stone formation. Once struvite stones develop, antibiotic therapy is less effective, particularly for large stones, due to decreased penetration of antimicrobial agents into the stone, allowing for persistent infection and continued stone growth. Surgical stone removal provides definitive therapy.

Uric Acid Stones

Uric acid stones are uncommon (10% of stones), but the incidence increases in hotter, arid climates due to low urine volumes. The main risk factor is low urine pH, which decreases the solubility of uric acid. Hyperuricosuria is not a consistent finding. Comorbid risk factors for uric acid stones include gout, diabetes mellitus, the metabolic syndrome, and chronic diarrhea. Uric acid stones are radiolucent on plain radiograph but are visualized on CT scan or ultrasound.

Preventive measures include maintaining urine output >2 L/24 h and urine alkalinization to a pH of 6.1 to 7.0. Xanthine oxidase inhibitors (such as allopurinol) may be used in patients with hyperuricosuria (>1000 mg/24 h [59 mmol/d]) and patients without hyperuricosuria who have recurrent uric acid stones despite other treatments.

Cystine Stones

Cystine stones occur in cystinuria, a rare autosomal recessive disorder of proximal tubular transport of dibasic amino acids such as cystine. Patients typically present during adolescence, but earlier and later presentations occur. Cystine forms characteristic hexagonal crystals in the urine, and cystine stones can become large and form staghorn calculi. Treatment includes urine alkalinization to increase cystine solubility, dietary sodium and protein restriction to reduce cystine excretion, and thiol-containing agents (penicillamine, tiopronin, captopril) that increase the solubility of cystine.

KEY POINTS

- Hypercalciuria is the most common risk factor for calcium oxalate stones; management includes thiazide diuretics and a low sodium diet.
- Treatment of urea-splitting *Proteus* or *Klebsiella* infections is the cornerstone of therapy for struvite stones, and surgical stone removal provides definitive therapy.
- The main risk factor for uric acid stones is low urine pH; management may involve increased urine volume, urine alkalinization, and xanthine oxidase inhibitors.

Management

Successful management of nephrolithiasis includes risk factor modification, laboratory and radiologic evaluation, dietary changes, and pharmacologic therapy. Referral to nephrology and/or urology may be necessary to treat recurrent or complicated disease.

Acute Management

Acute management of kidney stones includes analgesia, maintenance of adequate hydration, and evaluation for coincident infection. Although most cases may be managed in the ambulatory setting, hospitalization is typically indicated with ureteral obstruction in the presence of urinary tract infection or in a high-risk kidney (solitary or transplanted) or if adequate analgesia cannot be achieved.

Stone collection for chemical analysis is frequently used to guide subsequent therapy. Although there is limited evidence of effectiveness of therapy guided by stone analysis, physiologic and biochemical information suggest that interventions based on stone composition may be helpful in preventing recurrent stone formation. Therefore, it is reasonable to attempt to obtain a stone or its fragments in the acute setting for biochemical analysis.

Stones up to 10 mm can be managed conservatively, although the likelihood of spontaneous passage decreases with increasing size (**Figure 18**). Medical expulsive therapy with α-blocker therapy (such as tamsulosin) or a calcium channel blocker (such as nifedipine) can aid the passage of small stones (≤10 mm in diameter).

Urologic Management

Urgent urologic consultation is indicated for patients with urosepsis, acute kidney injury, anuria, refractory pain, or large stones requiring surgical removal. Complicated cases, including pyelonephritis, bilateral obstruction, and obstruction of a solitary kidney, may require urgent decompression via percutaneous nephrostomy or ureteral stenting depending on the location of the stone and other clinical circumstances. Urologic referral is also indicated for ambulatory patients who do not pass stones with conservative management or who have stones >10 mm in diameter.

Extracorporeal shock wave lithotripsy (ESWL) can be used for stones in the renal pelvis and proximal ureter, but it is less effective for stones located in the mid/distal ureter or the lower pole calyx, larger stones (>15 mm), and hard stones (calcium oxalate monohydrate or cystine). Potential complications of ESWL include incomplete stone fragmentation, kidney injury, and possibly increased blood pressure or new-onset hypertension. Proximal and mid-ureteral stones can also be managed with a percutaneous antegrade approach or retroperitoneal laparoscopy, but these techniques are typically reserved for large, impacted stones.

Ureteroscopy, in which an endoscopic device is introduced in a retrograde fashion into the ureter through the bladder, is most commonly used in the management of mid-ureteral and distal ureteral stones, using a combination of catheter-based stone disintegration methods (such as laser lithotripsy), stone baskets, and ureteral stent placement.

If ESWL and/or ureteroscopy are unsuccessful or if the patient has large complex stones, percutaneous nephrolithotomy may be necessary. Surgical stone removal is the gold standard for staghorn calculi.

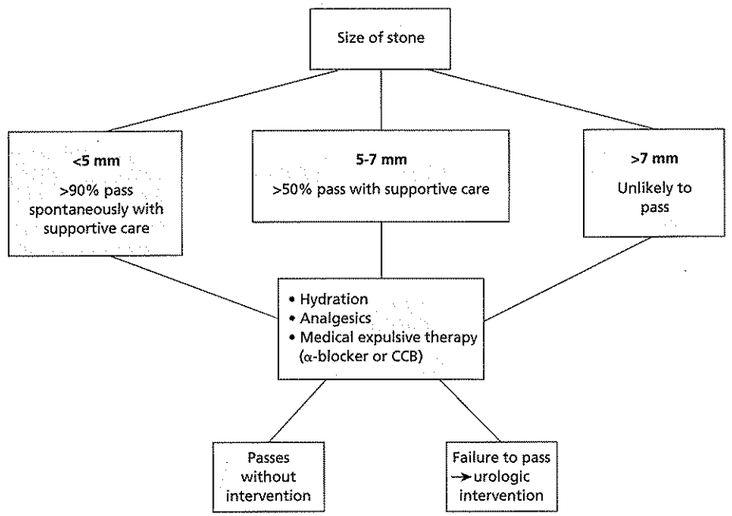

FIGURE 18. Acute management of symptomatic kidney stones. CCB = calcium channel blocker.

TABLE 38. Prevention Strategies for Nephrolithiasis

Stone Type	Treatment
General Stone Advice	
	Fluid intake ≥2 L/d regardless of stone composition; low sodium diet <100 mEq/d (100 mmol/d); age-appropriate calcium intake; consider recommending a low protein diet, 0.8-1 g/kg/d
Calcium[a]	
Idiopathic hypercalciuria	Thiazide diuretics: chlorthalidone, 12.5-25 mg/d, or hydrochlorothiazide, 25 mg twice daily
Hyperoxaluria	All patients: avoid high oxalate foods; reduce soft drink consumption
	Enteric hyperoxaluria: calcium carbonate or citrate, 1-2 g, with meals; cholestyramine, 4 g, with meals
	Primary hyperoxaluria: pyridoxine, 5-20 mg/kg/d
Hypocitraturia	Potassium citrate, 20-30 mEq twice daily; reduce dietary animal protein intake; increase fruit and vegetable intake
Uric Acid	
Urine pH <6.0	Potassium citrate or bicarbonate 40-80 mEq/d (40-80 mmol/d): titrate to urine pH 6.1 to 7.0
Hyperuricosuria	Allopurinol, 100-300 mg/d
Struvite	
Urinary tract infections with urea-splitting organisms	Aggressive treatment of infection; complete removal of stone material
Cystine	
Cystinuria	Potassium citrate or bicarbonate 3-4 mEq/kg/d (3-4 mmol/kg/d) to maintain urine pH >7.0; dietary sodium and protein restriction; chelating agents tiopronin, penicillamine (captopril if hypertension)

[a]The 2014 American College of Physicians Clinical Practice Guideline on the Dietary and Pharmacologic Management to Prevent Recurrent Nephrolithiasis in Adults recommends monotherapy with either a thiazide diuretic, citrate, or allopurinol for patients with calcium composite kidney stones and active disease in which increased fluid intake fails to prevent the recurrence of kidney stones. This recommendation does not apply to patients with hyperparathyroidism or rare causes of nephrolithiasis.

Risk Factor Evaluation and Prevention Strategies

There is evidence that maintaining fluid intake spread throughout the day to achieve at least 2 L of urine per day is effective in reducing the risk of recurrent nephrolithiasis. Less evidence is available for the efficacy of a low protein diet or other dietary interventions to prevent recurrent kidney stones, although they are frequently recommended. There also is evidence that monotherapy with a thiazide diuretic, citrate, or allopurinol is effective in preventing recurrent nephrolithiasis with composite calcium stones if increased fluid intake fails to reduce the formation of stones.

Some clinicians perform a more extensive metabolic evaluation to help guide therapy in patients with recurrent kidney stones or those that occur in the context of an extensive family history of stone disease. If pursued, patients should be instructed to consume their typical diet and level of fluid intake, with at least two 24-hour urine collections to account for dietary variation. Urine collections should include urine volume, pH, creatinine (to assess adequacy of collection), sodium, calcium, phosphate, citrate, oxalate, and uric acid. In the absence of stone analysis, the 24-hour urine results may be suggestive of a particular stone composition but are not definitive.

Prevention strategies for nephrolithiasis are discussed in **Table 38** on page 70.

KEY POINTS

HVC
- For patients with kidney stones ≤10 mm in diameter, conservative management, including analgesia, hydration, and expulsive therapy, may be attempted.
- Larger stones in the renal pelvis and proximal ureter can be treated with extracorporeal shock wave lithotripsy, whereas mid- and distal ureteral stones can be managed with ureteroscopy.

The Kidney in Pregnancy

Normal Physiologic Changes in Pregnancy

Changes in Hemodynamics

During pregnancy, peripheral vasodilation and loss of response to vasoconstrictive hormones such as angiotensin II and antidiuretic hormone lower blood pressure in the first trimester, reaching maximal effect in the second trimester. Renal sodium and water retention increases plasma volume, which causes increased renal plasma flow and glomerular filtration rate (GFR). Kidney size may increase by up to 1.5 cm. Serum creatinine drops from a normal antepartum value of 0.8 mg/dL (70.7 µmol/L) to 0.5 mg/dL (44.2 µmol/L). Relatively normal serum creatinine levels (>1.0 mg/dL [88.4 µmol/L]) may indicate significant kidney dysfunction.

The increased GFR during pregnancy increases the upper normal limit for proteinuria from 150 mg/24 h to 250 mg/24 h. Patients with preexisting proteinuria may experience worsening proteinuria during pregnancy that can be difficult to differentiate from preeclampsia.

Changes in the Urinary Tract

The urinary system, including the renal pelvis, calices, and ureters, dilates during pregnancy due to the effects of progesterone or mechanical compression of the ureters at the pelvic brim. These normal physiologic changes may be mistaken for obstruction and take several weeks postpartum to resolve. The dilation increases the risk for ascending pyelonephritis; thus, women should have urine culture screening at the first prenatal visit and be treated for asymptomatic bacteriuria (>100,000 colony-forming units/mL).

Changes in Acid-Base Regulation

Progesterone stimulates the respiratory center during pregnancy, causing hyperventilation and respiratory alkalosis, with an average P_{CO_2} of 30 mm Hg (4.0 kPa) and a serum pH of 7.40 to 7.45. The renal response to hypocapnia is increased bicarbonate excretion, resulting in a serum bicarbonate of 18 to 20 mEq/L (18-20 mmol/L).

Changes in Water Homeostasis

While the plasma volume increases during pregnancy, water retention exceeds the concomitant sodium retention, resulting in mild hypo-osmolality and hyponatremia. The plasma osmolality decreases by 8 to 10 mOsm/kg H_2O, and the serum sodium decreases by 4.0 mEq/L (4.0 mmol/L). These hormonally mediated changes in plasma osmolality and serum sodium do not require therapy. Rarely, women develop gestational diabetes insipidus due to increased metabolism of antidiuretic hormone by the placenta, resulting in polyuria, polydipsia, and hypernatremia.

KEY POINTS

- Pregnancy is associated with increased glomerular filtration rate, decreased serum creatinine, decreased blood pressure, and increased proteinuria.
- Dilatation of the urinary system during pregnancy increases the risk for ascending pyelonephritis; therefore, urine culture screening and treatment for asymptomatic bacteriuria are appropriate at the first prenatal visit.
- While the plasma volume increases during pregnancy, water retention exceeds the concomitant sodium retention, resulting in mild hypo-osmolality and hyponatremia.

Hypertension in Pregnancy

Chronic Hypertension

Women with chronic hypertension may experience normal or lower blood pressures during pregnancy. Chronic