Pathology & Evaluation: Urolithiasis

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1. Introduction

One in 9 adults in the United States (U.S.) will be diagnosed with a kidney stone in their lifetime.[1] As the prevalence of nephrolithiasis increases, the associated morbidity and attendant costs to individuals and the healthcare system mount. Prevention of stone disease is the key to breaking the cycle of recurrence, patient suffering, and growing costs. Knowledge of the physiochemistry and the pathophysiologic theories of kidney stone formation provides the foundation for understanding the rationale behind prevention and treatment strategies. Nephrolithiasis is recognized as a chronic, systemic medical condition affected by genetics, diet, lifestyle factors, as well as systemic comorbidities. While basic screening evaluation should be done in all newly diagnosed stone patients, further metabolic testing should be done in recurrent stone formers, high risk patients or interested first-time stone formers to help tailor dietary and possibly medical therapies to the individual. [2] This section will review the epidemiology, pathophysiology, and metabolic evaluation of nephrolithiasis.

2. Epidemiology

2.1 Prevalence

Kidney stone disease is relatively common in the U.S, affecting 1 in 9 persons during their lifetime.[1] Over the past several decades, the prevalence increased **significantly and more than doubled from 5% in 1994 to 11% in 2018.**[1]

2.2 Demographics

The incidence of stone disease peaks in the fourth to sixth decade of life. Historically, **adult men were two to three times more likely to be affected by a kidney stone than adult women;**[3] **however**, **recent evidence suggests that the gender gap is narrowing.**[3,4,5] The most recent NHANES data showed the prevalence of stones was 10.6% in men compared to 7.1% in women

(ratio 1.49).[6] Although men are still more likely to form a stone, there is a disproportionately higher rate of incident stone formation in women likely due, in part, to a higher rate of obesity.[7,8,9] Race and ethnicity also impact stone risk. In the U.S., white men and women have the highest and black men and Asian women have the lowest prevalence of stone disease. [3,10] Kidney stones are relatively rare before age 20 except in cases of genetic disorders such as cystinuria and primary hyperoxaluria. Nonetheless, the prevalence of stones among children and specifically adolescents has dramatically risen over the last 25 years. While the etiology of this increase is unclear, it may be due to a parallel increase in childhood obesity. [11]

2.3 Environmental Factors

Geographic areas with environmental risk factors for stone formation such as hot, dry climates have a higher prevalence of stone disease. In the U.S. **the risk of stones increases in a gradient from north to south and west to east**. The southeastern U.S. is often referred to as the "Kidney Stone Belt" since it has the highest age-adjusted prevalence of stones. Interestingly, predictions of climate modeling indicate this may expand northward as an unanticipated result of global warming. [12] In fact, the portion of the U.S. population living in high-risk zones for nephrolithiasis is anticipated to increase from 40% in 2000 to 56% by 2050. Consequently, there may be a climate-related rise of up to 2.2 million lifetime cases over this time, or a 30% increase in some climate divisions. **Similarly, occupations associated with exposure to excessive heat and conditions that promote dehydration are associated with an increased stone risk**.[11,13] Nephrolithiasis is an occupational hazard in professional drivers and health care professionals due to infrequent voiders syndrome, or the intentional restriction of fluid intake in order to reduce the need to urinate.[14,15] Additionally, occupations such as airline pilots have strict professional guidelines concerning whether pilots can fly when urinary stones are present.

2.4 Systemic Factors

The concurrent rise in obesity and urolithiasis has led to investigation of the association of metabolic syndrome (MetS) and kidney stone formation. The cluster of conditions that occur together in MetS (hyperglycemia, obesity, hypertension, and dyslipidemia) increase the risk of cardiovascular disease and diabetes mellitus type 2 (DM2). [16,17] Multiple studies have demonstrated a definitive association between MetS and kidney stone disease. Increased odds of nephrolithiasis was found among patients with increased number of MetS traits, with those with three or more traits having the highest stone prevalence.[18]

Obesity, particularly central obesity, has been shown to be associated with the occurrence of nephrolithiasis.[19,20] Various measures of obesity including BMI, waist circumference, and visceral adipose tissue have been shown to increase the risk of stones.[21,22,23] Those with higher BMI have been found more likely to have hyperuricosuria, hyperoxaluria, hypercalciuria, low urinary pH[24] and incidence of symptomatic uric acid stones.[25]

The association between DM2 and kidney stone disease has also been well described.[9,26,27]

Furthermore, the pathophysiologic mechanism for this association has been elucidated. Hyperglycemia leads to the accumulation of advanced glycation end products inducing a proinflammatory state, vascular endothelial dysfunction, and urinary acidification due to decreased production and transport ammonium [26] (see **Core Curriculum Renal Physiology**).[28] Similarly, hypertension, cardiovascular disease, and dyslipidemia are also associated with increased stone risk due to lower urinary pH.[29,30,31,32,33,34,35] **Insulin resistance is now recognized as the common link between MetS and urolithiasis**[36] **through the above described pathway**.[37] Acidic urine leads to precipitation of uric acid crystals and may also facilitate calcium oxalate (CaOx) stone formation by way of heterogeneous nucleation. [38] Indeed, studies confirm that stones in obese patients are generally of CaOx and uric acid composition.[39]

Conversely, there is data to suggest that kidney stones could increase one's risk of comorbid conditions including hypertension, cardiovascular disease, DM2, as well as chronic kidney disease.[7,8,9,11,40,41] While MetS and its components appear to be associated with CaOx and uric acid urolithiasis due to changes in urinary parameters, both dietary indiscretion, systemic inflammation, and oxidative stress prevalent in this population may also be contributory.[42]

3. Pathogenesis of Stone Formation

3.1 Physiochemistry of Calculus Formation

3.1.1 Supersaturation

Urinary supersaturation (SS) is the driving force for a phase change from a dissolved salt to a solid and **is a requisite condition for urinary stone formation.**[43,44] There are three primary states of saturation in the urine: undersaturated, metastable, and unstable. At a SS <1, urine is **undersaturated** with respect to a stone-forming salt, favoring crystal dissolution. As the SS exceeds 1, urine is considered **metastable** and salts are generated that allow for the formation of crystals on an existing nidus. **Heterogeneous nucleation** occurs in the metastable zone when the primary component of a stone and the nidus are composed of different substrates. Once SS reaches an upper limit of metastability (ULM), the urine is considered **unstable**, allowing for de novo crystal formation or **homogenous nucleation**. Factors that increase SS or decrease the ULM increase the likelihood of stone formation, and the closer SS is to the ULM the more likely a small perturbation in the urine will provoke stone formation. **SS values measured in 24-hour urine collections have been shown to correlate with stone composition** supporting the role of SS in stone formation.[45]

3.1.2 Nucleation and Crystal Growth

The first step required to produce a crystal is **nucleation**, which occurs in a homogenous fashion when the **SS > ULM** or in a heterogeneous fashion when the urine is metastable. **Epitaxy** is the process of one crystal type growing on a different crystal type with a similar lattice structure. Examples of epitaxy include CaOx stones that develop on a nidus of uric acid crystals or organic proteins. [43]

3.1.3 Crystal Aggregation

Crystal aggregation describes the process by which multiple crystals collect into a single unit. The combined processes of crystal growth and aggregation have been hypothesized to promulgate stone formation by leading to the genesis of particles that are too large to be excreted from the collecting system. [43,44]

3.1.4 Crystal Retention and Calculus Generation

Persistence of crystals in the collecting system is the final event necessary for calculus formation and occurs via either **interaction with the renal epithelium** or as a result of **stasis** in the urinary tract. Whereas the **fixed particle hypothesis** supports a primary role for adhesion in crystal retention, the **free particle hypothesis** advocates that size is the crucial factor leading to retention.[44]

3.1.5 Inhibitors and Promoters of Crystallization

Various stone promoters and inhibitors have been identified **(Table 1)**.[43,44] **Citrate is a potent inhibitor of calcium phosphate** that directly reduces crystallization in four ways (1) complexing with ionized calcium to reduce its availability, (2) directly inhibiting the spontaneous precipitation of calcium oxalate, (3) preventing the agglomeration of CaOx crystals, and (4) preventing heterogeneous nucleation of CaOx with monosodium urate. **Pyrophosphate**, **phosphate**, and **magnesium** have also been shown to inhibit CaOx crystallization.

Table 1. Promoters and Inhibitors of Stone Formation

Promoters	Inhibitors
Calcium Stones	***Inorganic***: • Citrate • Magnesium • Pyrophosphate • Phosphate
Sodium	
Oxalate	
Urate	***Organic***: • Glycoproteins • Glycosaminoglycans • Nephrocalcin • Osteopontin (Uropontin) • Tamm-Horsfall protein • Urinary Prothrombin fragment 1
Cystine	
Tamm-Horsfall protein (Uromodulin)	

Organic macromolecules such as glycoproteins and glycosaminoglycans comprise another category of particles that interact with crystals under various physiologic conditions and typically inhibit stone formation.[43] **Glycosaminoglycans** (**heparin sulfate**, **chondroitin sulfate A**, **chondroitin sulfate C**, **dermatan sulfate**, **hyaluronan**, and **keratin sulfate**) occur naturally in the urine and inhibit CaOx crystal aggregation.[43] **Nephrocalcin** is an acidic glycoprotein that exists in four isoforms, two of which are potent inhibitors of CaOx monohydrate crystal aggregation. **Osteopontin (Uropontin)**, another acidic glycoprotein found in bone matrix and renal epithelial cells, has been shown to interfere with CaOx crystal nucleation, growth, aggregation, and binding to renal epithelial cells. **Tamm-Horsfall protein** (**Uromodulin**), also expressed in renal epithelial cells, is the most abundant protein in human urine. Uniquely, this serves as either a strong inhibitor or promoter depending on urinary pH. While in alkaline urine it is a strong inhibitor of CaOx monohydrate crystal aggregation, it polymerizes into a configuration that promotes crystal aggregation in acidic urine.

3.1.6 Stone Matrix

Organic matter, primarily comprised of proteins in the urine and renal parenchyma, only constitutes approximately 3% of the structure of most stones. However, stones that develop as a result of urinary tract infection can contain nearly 65% matrix. Matrix is hypothesized to act as a nidus for stones and promotes adsorption of organic compounds on growing crystals.[43,44]

3.2. Pathogenesis of Calculus Formation

Several theories and factors have been proposed to explain lithogenesis and likely all play a role to some degree.

3.2.1 Oxalate-Induced Tubular Injury Theory

This theory proposes that hyperoxaluria triggers the generation of reactive oxygen species (ROS) that overwhelm anti-oxidant defense mechanisms, causing oxidative stress and renal damage.[43] Tissue culture studies have demonstrated that crystals preferentially adhere to injured renal epithelium over healthy inner medullary collecting duct cells. Additionally, oxalate increases the gene expression of macromolecules that promote crystal binding to renal epithelial cells. Crystal binding provides fixed nidi for CaOx deposition and stone formation.[43,46]

3.2.2 Randall Plaque Theory

Over 80 years ago, in 1937 Alexander Randall first described sub-epithelial plaques associated with areas of damage on renal papilla which he hypothesized represented the site of stone initiation. More recent work in idiopathic CaOx stone formers demonstrated that these plaques originate from **calcium apatite deposits in the basement membrane** of the thin loops of Henle. These deposits then propagate through the medullary interstitium to a sub-epithelial location where they erode through the papillary urothelium and provide an anchored surface on which CaOx grow as attached stones.[44,47] Other metabolically distinct populations of stone formers have been found to have plaque configurations that differ from the sub-epithelial plaques seen in idiopathic CaOx stone formers

(jejuno-ileal bypass patients and brushite stone formers). [43,44]

3.2.3 Vascular Hypothesis

This theory proposes that **turbulent blood flow in the vasa recta** at the renal papillary tip promotes endothelial injury that leads to stone formation by way of erosion into the ducts of Bellini, providing a fixed point for stone formation. [48,49]

3.2.4 Nanobacteria

Calcifying nanoparticles or nanobacteria are novel cytotoxic microorganisms isolated from bovine and human blood that have been implicated in the pathogenesis of stone disease by **promoting precipitation of calcium apatite on their exterior surface** and providing the initiating event for Randall plaque formation. Since the exact mechanism has not been elucidated, this theory remains controversial.[44]

3.2.5 Insufficient or Abnormal Inhibitors

Non-stone formers with crystalluria rarely demonstrate aggregation and stone formation, likely due in part to endogenous urinary inhibitors of crystallization. Consequently, insufficient or abnormal inhibitors have been postulated as a potential etiology for calculus formation.

3.2.6 Stasis

Anatomic renal abnormalities which promote urinary stasis such as **ureteropelvic junction obstruction**, **horseshoe kidney**, and **calyceal diverticulum** have been postulated to increase the risk of stone formation through retention of crystals and potential urinary infection caused by stasis. At the same time, stone formers with anatomic abnormalities have been shown to have metabolic abnormalities that are similar to stone formers without these anatomic anomalies.[43] As such, urinary stasis does not explain the entire picture in these patients and thus 24-hour urinary evaluation can still be helpful.

4. Pathophysiology of Stone Disease

The diagnostic classification of stone disease is broadly divided into calcium stones and non-calcium stones (**Table 2**). Low urine volume contributes to both calcium and non-calcium stone formation as low volume increases urinary supersaturation.

Table 2: Diagnostic Categories and Prevalence Of Nephrolithiasis	
Diagnostic Categories	**Prevalence**
Calcium Stones	
Hypercalciuria	28-56%
Hyperoxaluria	2-15%
Hyperuricosuria	10-40%
Hypocitraturia	10-50%
Low urine pH	15-30%
Low urine volume	10-50%
Infection Stones	1-5%
Cystinuria	<1%
Adapted from Levey and colleagues.[50]	

4.1 Calcium Stones

Uncomplicated calcium stone disease is associated with a number of metabolic abnormalities that can occur alone or along with other abnormalities.[51] Risk factors for **calcium stone formation** include low urine volume, **low or high urine pH, higher urinary excretion of calcium, oxalate, and uric acid, and lower urinary excretion of citrate.**[43,52] Low urine volume is seen as an isolated finding in approximately 10% of patients and in up to 50% of patients in combination with other metabolic abnormalities. Abnormal urinary parameters can be the result of environmental influences, genetic factors, and metabolic abnormalities.

CaOx is the main constituent in the majority of calcium-based stones. **CaOx** stones are further sub-divided into the **monohydrate (whewellite) or dihdyrate (weddellite) form,** which are respectively associated with hyperoxaluria and hypercalciuria.[53] In contrast, **calcium phosphate (CP)** is a minor constituent being present in amounts of approximately 1-10%.[54] When the majority (>50%) of the stone is comprised of CP, it is classified as CP and is present as either apatite or brushite (calcium monohydrate hydrogen phosphate). Importantly, brushite stones are known to grow rapidly, have high recurrence rates, and typically herald underlying hypercalciuria. [55]

4.1.1 Dietary Risk Factors

Diet impacts the risk of stone formation and will be addressed in detail in the section on **Medical Management**. Fluid consumption as well as dietary intake of calcium, oxalate, citrate, animal protein, and sodium have been shown in cohort studies, metabolic studies or **clinical trials** to influence stone formation with varying levels of evidence.[56]

4.1.2 Hypercalciuria

Hypercalciuria is the most common metabolic abnormality identified (up to 50%) in patients with calcium stones .[57] Higher urine calcium levels have been shown to correlate positively with increased risk of stone formation. **Hypercalciuria is defined as urinary calcium excretion >4 mg/kg/day or >200 mg/day on a calcium and sodium-restricted diet**. Higher urinary calcium may be a consequence of derangements in calcium handling in the gastrointestinal tract, kidney and/or bone. Patients with hypercalciuria are at increased risk of both stone disease and osteoporosis.

Traditionally, hypercalciuria was classified into three distinct types: Absorptive (intestinal), renal, and resorptive **(Table 3)**.[43,52] **Absorptive hypercalciuria is due to increased absorption of calcium from the intestine**, leading to a transient increase in serum calcium, suppression of parathyroid hormone (PTH), and increased filtered load of calcium. Depending on urinary calcium response to dietary calcium restriction, absorptive hypercalciuria is categorized as type 1 (no response) or 2 (normalization of urinary calcium). The primary defect in **renal hypercalciuria is impaired reabsorption of calcium from the proximal and distal renal tubules**, leading to calcium loss in the urine, increased PTH secretion, and stimulation 1,25-dihydroxyvitamin D synthesis. In turn, this causes increased intestinal calcium absorption and bone resorption. **Resorptive hypercalciuria is**

most commonly caused by primary hyperparathyroidism (HPT) due to a parathyroid adenoma. **High levels of PTH** lead to bone resorption and increased intestinal absorption of calcium via calcitriol, leading to increased urinary calcium excretion. Despite academic interest in the distinction between these types of hypercalciuria, detailed fasting and calcium load tests are of historical interest only and highly impractical. Rather, it is only clinically relevant to distinguish primary HPT, which prompts referral to endocrinology and endocrine surgery.

Table 3. Characteristic Serum and Urine Findings in Hypercalciuria

	Urine Calcium		Route	
Hypercalciuria	**Random Diet**	**Restricted Diet**	**Calcium**	**PTH**
Dietary	↑	NL	NL	NL
Absorptive, type I	↑	↑	NL	NL or ↓
Absorptive, type II	↑	NL	NL	NL or ↓
Renal	↑	↑	NL	↑
Resorptive: 1° Hyperparathyroidism	↑	↑	↑	↑

Hypercalcemia and hypercalciuria are also seen in association with **granulomatous diseases**, such as **sarcoidosis**. Granuloma macrophages express **1-alpha-hydroxylase** which stimulates synthesis of the active form vitamin D called calcitriol, normally made in the kidney. Calcitriol increases blood calcium mainly by increasing the intestinal uptake of calcium and, to a lesser extent, resorption of calcium from bone. [52] Due to feedback inhibition, **PTH is typically suppressed in granulomatous disease**. The diagnosis of sarcoidosis can be further pursued by obtaining a chest X-ray to look for hilar adenopathy and checking 1,25-dihydroxy vitamin D levels.[51,58]

4.1.3 Hyperuricosuria

Hyperuricosuria, defined as urinary uric acid >700 mg/day, promotes CaOx stone formation through several mechanisms. At urine pH >5.5, sodium urate precipitates and leads to calcium stones through heterogeneous nucleation.[43,52] At urine pH <5.5, undissociated uric acid predominates and can lead to both uric acid and calcium stone formation. Uric acid crystals can also bind to urinary inhibitors of stone formation such as glycosaminoglycans, thus preventing them from binding to calcium. Although numerous conditions are associated with hyperuricosuria **(Table 4)**, the most common etiology is excessive dietary purine intake from animal protein or non-animal sources (nuts, seeds).

Table 4. Causes of Hyperuricosuria
Excessive dietary purine intake
Gout
Myeloproliferative Disorders
Hemolytic disorders/anemia
Chemotherapy/Tumor lysis syndrome
Chronic Diarrhea
Uricosuric drugs (probenecid, losartan, salicylates)
Hereditary conditions that lead to overproduction of uric acid: • Hypoxanthine guanine phosphoribosyltransferase deficiency • Phosphoribosylpyrophosphate synthetase overactivity • Glycogen storage disease types I, III, V, and VII

4.1.4 Hyperoxaluria

Hyperoxaluria is categorized as **dietary**, **enteric or primary.**[43,52] Approximately half of urinary oxalate is derived from the diet and half from endogenous synthesis.[56] Mild hyperoxaluria is most commonly caused by dietary oxalate excess or severe calcium restriction. Excessive intake of oxalate-rich foods (spinach, nuts particularly almonds, chocolate, potatoes, beets, brewed dark tea) or vitamin C (ascorbic acid) can lead to hyperoxaluria. **Factors that modulate intestinal oxalate absorption include dietary calcium intake and colonization of the intestine with *Oxalobacter formigenes***, an oxalate-degrading bacterium which uses oxalate as a substrate. Calcium and oxalate bind together within the intestinal lumen and are then fecally excreted. Consequently, a low calcium diet leads to a relative excess of unbound oxalate which is absorbed within the intestines and renally excreted thereby causing hyperoxaluria.

Enteric hyperoxaluria is associated with intestinal malabsorption (Crohn's disease, ulcerative colitis, celiac disease, pancreatitis, cystic fibrosis), bowel resection or bariatric surgery. [43,52,59,60] Compared to restrictive gastric banding,[61] Roux-en-Y gastric bypass patients have a higher risk of hyperoxaluria causing nephrolithiasis due to dumping syndrome. A detailed patient history including bowel habits (chronic loose stools or diarrhea) may also unveil underlying enteric hyperoxaluria without an official gastrointestinal diagnosis and prompt referral. Malabsorption of fats in these conditions allows **saponification of fatty acids with calcium and magnesium, thereby reducing the binding of these cations to oxalate in the intestinal lumen**. Similar to the effect of a low calcium diet, the increased pool of luminal oxalate (unbound oxalate) is absorbed and ultimately excreted in the urine. Additionally, poorly absorbed bile salts increase colonic permeability to oxalate and also enhance oxalate absorption. Thus, the diagnosis of enteric hyperoxaluria is made on the basis of past medical or surgical history resulting in intestinal malabsorption along with characteristic urinary findings of **marked hyperoxaluria and concurrent low urine volume, low urine pH, hypocitraturia, hyponatriuria, and hypocalciuria**.[51,58] Although beyond the scope of this section, medical stone prevention for enteric hyperoxaluria includes taking calcium supplements with meals.

Calcium oxalate stone formers with markedly high urinary oxalate levels (>75 mg/day) **without evidence of intestinal malabsorption should undergo genetic testing for primary hyperoxaluria** (**PH**) to confirm the diagnosis and identify the specific mutation.[51,62,63] Although it accounts for the minority of hyperoxaluria cases, PH should be considered in cases of renal failure of unknown etiology, with approximately 50% presenting with end stage renal disease at the time of diagnosis. [64] Plasma oxalate level can also be obtained to aid in diagnosis (>100 µmol/L) yet will only be elevated in PH patients with at least moderate chronic kidney disease (CKD) >stage 3b (GFR 30-44 ml/minute/1.73 m^2).[64] If PH is detected, family members should be screened particularly siblings since early detection is important for treatment.

Primary hyperoxaluria (PH) is a group of rare autosomal recessive disorders that are characterized by the accumulation of oxalate in the kidney and other body systems. Affected individuals develop recurrent stones, renal damage, and other end organ damage.[62] There are **three**

main types of PH which are differentiated by the specific hepatic enzyme in **glyoxalate metabolism** that is defective. **PH Type I (PH1) is the most common (80% of cases)** and is the result of a defect in the enzyme alanine glyoxalate aminotransferase **(AGT)** which catalyzes the conversion of glyoxylate to glycine, leading to preferential conversion of glyoxylate to oxalate. **Patients usually present at a young age with recurrent stones and markedly elevated urinary oxalate levels (>100 mg/day. Most PHI patients inevitably progress to renal failure during by age 20-30 and nearly all by age 40-50**.[65,66] Renal injury occurs due to a combination of tubular toxicity from oxalate, nephrocalcinosis, and obstruction. Once GFR decreases to 30-44 ml/min (CKD stage 3b), renal excretion of oxalate is impaired, resulting in deposition of oxalate into tissues, so-called systemic oxalosis.[67] Although medical therapy can slow the progression of disease, **definitive treatment for PHI is combined liver/kidney transplant**. In 2020, the FDA approved the first pharmaceutical therapy to reduce urinary oxalate excretion, OXLUMO (lumasiran)®, for PH1 treatment in both adult and pediatric patients. Lumasiran is an RNA interference agent that targets glycolate oxidase (GO)[68] upstream from AGT. Less oxalate precursor is made and thereby oxalate production is reduced. Early detection of PH with treatment may prevent kidney failure and need for transplantation. [63]

PH Type II (PH2) accounts for **10% of diagnoses of PH** and is caused by a defect in the enzyme glyoxylate reductase/hydroxypyruvate reductase **(GRHPR)** which leads to the overproduction of oxalate and L-glyceric acid[69] and is generally less severe than PH I. Patients may, however suffer severe recurrent urolithiasis resulting in eventual loss of renal function.[70,71] In the event of progression to end stage renal disease **isolated kidney transplant is usually sufficient**.

PH Type III (PH3) also comprises **10% of PH cases.** However, PH3 is the **least severe** presentation of the three types with **progression to renal failure unlikely.** It is caused by a defect in mitochondrial 4-hydroxy-2-oxoglutarate aldolase **(HOGA).**

4.1.5 Hypocitraturia

Hypocitraturia (urinary citrate <320 mg/day) **alone and in combination** with other abnormalities is found in **up to 10% and 60%** of stone formers, respectively. Citrate is a stone inhibitor through various mechanisms **(Table 5)**. **The primary determinant of urinary citrate excretion is systemic acid-base status.**[43,52] Any condition associated with an acidotic state can lead to hypocitraturia. Acidosis increases citrate metabolism and reduces citrate excretion (see **Core Curriculum Renal Physiology**). **Type I (distal) renal tubular acidosis (dRTA) is due to impaired hydrogen ion secretion in the distal renal tubule**, leading to inability to excrete an acid load and subsequently, systemic acidosis.[72] dRTA is characterized by **hypokalemic, hyperchloremic metabolic acidosis and high urinary pH (>6.5)** and **severe hypocitraturia** with recurrent CaP stones. **Chronic diarrheal states** lead to systemic acidosis because of **bicarbonate loss in the stool. Thiazide diuretics** induce hypokalemia and intracellular acidosis, which also leads to hypocitraturia. Finally, **carbonic anhydrase inhibitors** such as acetazolamide, zonisamide, and topiramate prevent reabsorption of bicarbonate in the nephron leading to metabolic acidosis. Despite various possible causes, the **majority of hypocitraturia is idiopathic.**

Table 5. Mechanisms By Which Citrate Inhibits Calcium Stone Formation
Complexes with calcium, reducing ionized calcium and reducing urinary saturation of calcium salts
Prevents nucleation of calcium oxalate crystals
Binds calcium oxalate crystal surface, preventing crystal agglomeration
Enhances inhibitory effects of Tamm-Horsfall proteins

4.1.6 Low Urine pH

Idiopathic low urine pH, **or gouty diathesis**, **is defined as urinary pH <5.5**. At low urinary pH, calcium oxalate stones may form as a result of heterogeneous nucleation with uric acid crystals. Patients with low urine pH who preferentially form calcium oxalate stones have been shown to have higher urinary calcium and lower urinary citrate than those who form uric acid stones.[73]

4.1.7 Hypomagnesuria

Magnesium is an inhibitor of stone formation because it binds oxalate and reduces urinary saturation of calcium oxalate. Therefore, hypomagnesuria is a risk factor for calcium stone formation. **Importantly, hypomagnesuria is also associated with low urinary citrate**.[43]

4.2 Uric Acid Stones

4.2.1 Uric Acid Stones

Uric acid is the end product of purine metabolism in humans and highly insoluble compared to allantoin, which is the end product in most other mammals. **The primary pathophysiologic factor leading to uric acid stones is low urine pH, with or without associated hyperuricosuria.**[74,75] Uric acid has a pKa of 5.35; at this pH, half of uric acid is present as the more soluble urate salt and half as the poorly soluble uric acid. Other factors contributing to uric acid stone formation are low urine volume and hyperuricosuria. **Uric acid stones are over-represented among diabetic patients compared to the general population**. Low urine pH in patients with DM2 and insulin resistance is thought to be the result of both impaired renal ammonium excretion and increased net acid excretion, leading to reduced urinary buffering capacity and acidic urine. Uric acid stone formation has also been linked to MetS. For patients with known of suspected low urine pH (<5.5), it is important to note that when doing 24-hour urine testing uric acid can precipitate out in the collection jug and may not be properly measured. Rechecking uric acid levels after the urine has been adequately alkalinized may reveal a significant increase in uric acid levels due to resolubilization.

4.2.2 Cystine Stones

Cystinuria is an autosomal recessive disorder which leads to **defective renal proximal tubule and intestinal epithelium transport of the four dibasic amino acids:** cystine, ornithine, lysine and arginine **(COLA)**.[76,77] Cystinurics excrete abnormally high levels of all four, but only **cystine (cysteine-cysteine)** is poorly soluble and uniquely forms stones. Cystine is a **dimeric amino acid** formed by two oxidized **cysteine monomers linked by a disulfide bond.** Cystine **solubility is highly pH dependent** and increases exponentially with increasing urinary pH. Sodium enhances cystine excretion and methionine is a precursor in cystine synthesis. Therefore, dietary management for cystinurics includes high fluid consumption, sodium restriction, and low methionine diet, which most practically means decreased animal protein intake. Medical management is primarily urinary alkalinization with an oral agent such as potassium citrate or sodium bicarbonate. Thiol therapy is given to select patients and works by forming a cysteine-drug complex, which is 50 times more

soluble than cystine (cysteine-cysteine). Cystinuria is nearly always diagnosed on the basis of stone analysis. If cystine stone composition is detected, 24-hour urine testing should additionally include a cystine level. [58]

4.2.3 Infection Stones

Magnesium ammonium phosphate (MAP) and **carbonate apatite** stones comprise “infection” or struvite stones. **Urease**, an enzyme elaborated by some bacteria (***Proteus mirabilis***, ***Klebsiella pneumoniae***, ***Staphylococcus aureus and Staphylococcus epidermidis***), catalyzes the conversion of urea into ammonia and carbon dioxide.[78] The **alkaline urine** favors high levels of ammonium and phosphate formation, leading to struvite stone formation.

4.2.4 Drug-Induced Stones

Some medications are associated with stone formation, either because the drug or its metabolites are poorly soluble or because the drug changes the urinary environment and promotes typical calcium stone formation (**Table 6**). Conversely, medications are commonly given to prevent stone formation following a metabolic workup and will be discussed in a subsequent section. **Carbonic anhydrase inhibitors** such as acetazolamide, zonisamide, and topiramate (Topamax®) create a metabolic acidosis that causes high urine pH, hypocitraturia, and sometimes hypercalciuria. These medications essentially induce dRTA. **Thiazides** such as hydrochlorothiazide and chlorthalidone can induce hypokalemia which causes intracellular acidosis and promotes hypocitraturia. Medications that directly precipitate to form stones include some **protease inhibitors** (indinavir and ritonavir), **triamterene** as well as **metabolites of common cold medications (guaifenesin** and **ephedrine)**.[52]

5. Diagnostic Evaluation

According to the **AUA Guidelines on the Medical Management of Kidney Stones**, all stone formers should undergo a basic screening evaluation to identify risk factors that may increase their stone recurrence risk and thereby determine if they require more detailed evaluation. The screening evaluation consists of a careful history, blood work, urinalysis with microscopy/urine culture, stone analysis when available, and imaging. [2,79]

Table 6. Stone Promoting Medications

Medication	Mechanism
Carbonic Anhydrase Inhibitors • Acetazolamide • Topiramate (Topamax®) • Zonisamide	Metabolic acidosis
Vitamin C (ascorbic acid)	Hyperoxaluria
Probenicid (uricosuric agent)	Hyperuricosuria
Ca / Vitamin D	Hypercalciuria
Phosphate-binding antacids	Hypercalciuria
Triamterene	Triamterene stones
Guaifenesin	Guaifenesin stones
Ephedrine	Ephedrine stones
Protease inhibitors	Indinavir stones, others
Chemotherapy agents	Hyperuricosuria

5.1 History

Evaluation of a urolithiasis patient should begin with a detailed history aimed at eliciting risk factors for stone disease (**Table 7**).[2,79] History of previous stone passage and surgical interventions for stones or other urinary tract pathology should be obtained, including age of onset as this may raise suspicion for hereditary causes of stone disease such as cystinuria or PH. Medical conditions associated with stone disease, such as DM2, gout, intestinal disease, bowel esection or bariatric surgery, hyperthyroidism, or granulomatous disease should be queried. Family history of stone disease should be noted. A careful dietary and medication history including use of supplements can identify risk factors for stone formation. Patients can be referred to the Urology Care Foundation website for a wide array of free educational resources on the causes, diagnosis, evaluation, and treatment of kidney stones (**www.urologyhealth.org**) in multiple languages and media platforms (printed, online, podcasts, videos).

Table 7. Risk Factors Associated With Stone Formation
Past stone history
Family history of stone disease
Bowel disease/Intestinal malabsorption
History of bowel surgery (resection, gastric bypass)
Gout
Hyperthyroidism
Type 2 Diabetes Mellitus
Obesity
Osteoporosis
Stone-Provoking Medications/Supplements (probenecid, protease inhibitors, vitamin C, carbonic anhydrase inhibitors, calcium supplements)

5.2 Laboratory Studies

5.2.1 Blood Tests

Serum studies are aimed at assessing overall renal function and identifying systemic conditions associated with stones, such as dRTA, primary HPT or hyperuricemia/gout. The panel should include **serum electrolytes**, **creatinine**, **calcium,** and **uric acid.**[2] Serum intact PTH is optional and should be obtained if primary HPT is suspected (high or high normal serum calcium). Most commonly HPT is due to vitamin D deficiency (secondary) and thus it is practical to also check a concurrent vitamin D level when checking PTH. Patients with suspected primary HPT should also **be referred to endocrine and endocrine surgery for further workup, including imaging for parathyroid adenoma**.

5.2.2 Urinalysis

Urinalysis with microscopy can provide clues as to the underlying pathophysiology for stone formation. The presence of crystals can be pathognomonic for stone composition and underlying pathophysiologic abnormalities.[2] **Hexagonal** crystals implicate **cystinuria** and **coffin lid-shaped** crystals suggest **struvite** stones (**Table 8**). Urine pH can also implicate the underlying etiology of stones; pH <5.5 is suggestive of uric acid stones and pH >7.0 is likely associated with infectious or calcium phosphate stones. Specific gravity provides a quick assessment of hydration status.

Table 8. Microscopic crystal shape of common stone types

Stone Type	Crystal Shape
Cystine	Hexagonal
Magnesium ammonium phosphate (struvite)	“Coffin-lid”, rectangular
Calcium oxalate monohydrate	Hourglass
Calcium oxalate dihydrate	Envelope, tetrahedral
Brushite	Needle shaped
Uric acid	Shards, plates
Calcium phosphate apatite	Amorphous

5.2.3 Urine Culture

Urine culture should be obtained in patients with recurrent urinary tract infections or in those with a urinalysis suspicious for infection. Infection with a urease-splitting organism should raise concern for MAP (struvite) stones **(Table 9)**.[2]

Table 9. Common Urease-Producing Bacteria	
Gram Negative Bacteria	**Gram Positive Bacteria**
Proteus mirabilis	*Corynebacterium sp*
Klebsiella Pneumoniae	*Staphylococcus aureus*
Pseudomonas sp	*Staphylococcus epidermidis*

5.2.4 Stone Analysis

Stone analysis should be obtained when possible. While most stones are calcium based, **stone composition can implicate the underlying pathophysiologic cause** and thereby direct therapy.[2,80] For example, cystinuria is nearly always diagnosed by the finding of cystine on stone analysis. Calcium phosphate stone composition raises suspicion of medical conditions associated with stones such as dRTA or primary HPT. Furthermore, studies have found that some stone subtypes are associated with certain abnormal urinary parameters. Calcium oxalate monohydrate and dihydrate are typically associated with hyperoxaluria and hypercalciuria, respectively. Clinically, this is useful in stone patients who decline or are unable to perform detailed 24-hour urine testing. Repeating stone analyses for subsequent stones after medical treatment is also useful to identify changes in the metabolic profile **(Table 10).**

Table 10. Metabolic Processes Commonly Associated with Certain Stone Compositions

Composition	Metabolic Process
Cystine	Cystinuria
Uric acid	• Low urine pH • Obesity, diabetes mellitus type 2, metabolic syndrome
• Struvite • Calcium apatite • Magnesium, ammonium, phosphate (MAP)	Infection
Predominance of hydroxyapatite	• Renal tubular acidosis • 1° hyperparathyroidism • Medullary sponge kidney • Carbonic anhydrase inhibitors

5.2.5 Imaging Studies

Baseline imaging studies should be reviewed or obtained in order to quantify stone burden and estimate metabolic activity. Multiple or bilateral stones at presentation suggest more aggressive stone disease, and **nephrocalcinosis implicates an underlying metabolic disorder**.

5.3 24-Hour Urine Testing

5.3.1 Indications

In addition to basic screening evaluation, further metabolic workup should be performed on recurrent stone formers, first-time stone formers who are high risk for recurrent stones or interested first-time stone formers (Table 11).[81] This includes 24-hour urine testing to identify risk factors and thereby guide prevention strategies.[2,79,82] The need for one versus two 24-hour urine collections on initial evaluation has been debated without clear consensus. The use of the fast and calcium load test to distinguish among the three types of hypercalciuria is highly impractical and thus largely abandoned in clinical practice because of limited influence on treatment. 24-hour urine testing is not required in patients with pure struvite stones; however, a recent study suggests there may be a role for metabolic evaluation and directed medical therapy to reduce stone recurrence in these patients.[50] If the stone is of mixed struvite and calcium composition, 24-hour urine testing is also encouraged.

Although predictive models for stone recurrence have been developed,[82,83] true recurrence is difficult to discern owing to asymptomatic stone passage and self-managed episodes that are not reported.[84] Notably, only 8% of a group determined to be high risk in one study performed a 24-hour urine collection.[81] A more recent study using an administrative claims database showed an even lower utilization rate at 6.9% with no association between 24-hour urine collection and recurrence rates in either high-risk subgroups or the overall population. Whether these findings are due to ambivalence of provider or patient motivation, this along with the lack of prospective studies that directed medical treatment is superior to empiric therapy has led to consideration of the latter as a reasonable approach. [85]

Table 11. Indications For 24-Hour Urine Evaluation
Recurrent calcium stone former
Family history of stone disease
Intestinal or malabsorptive disease
Pathologic skeletal fracture
Osteoporosis
Gout
Young age of onset of stone disease
Uric acid nephrolithiasis
Cystine stones
Patient-specific risk factors (Solitary kidney, chronic kidney disease, vocation, infirm health)

5.3.2 Urinary Analytes

The 24-hour urine specimen should be analyzed for **total volume**, **pH**, **calcium**, **oxalate**, **uric acid**, **citrate**, **sodium, magnesium, and potassium.**[2] Importantly, **creatinine** should also be checked since this determines the completeness of the collection. Sulfate and urea nitrogen are optional but may provide an indication of animal protein intake. A screening qualitative cystine test should be performed in at risk individuals, especially for pediatric stone formers. Urinary supersaturation indices for stone-forming salts are available as part of some commercially available laboratory panels such as Litholink™ and may be useful in monitoring the effectiveness of treatment.[86]

5.3.3 Interpretation

Normal ranges for urinary analytes vary according to the laboratory performing the test. **Table 12** provides one example of normal ranges for 24-hour urine parameters. Stone formers are encouraged to produce >2.5-3 liters of urine daily.[2] As aforementioned, urine creatinine assesses the accuracy of the urine collection. Patients must be counseled how to properly perform the 24-hour urine collection. **Weight-based normal values for 24-hour urine creatinine vary by gender (15-20 mg/kg for women, 20-25 mg/kg for men)**. Urine collections that fall far outside this range should be considered for possible under- or over-collection, and the results should be carefully interpreted. Because diet can greatly influence the results of a 24-hour urine collection, patients should be counseled to adhere to their “normal” dietary routines when performing the test.

Table 12. Normal Range For 24-Hour Urine Analyses	
Calcium	<200 mg/day
Citrate	>450 mg/day in males >550 mg/day in females
Oxalate	<40 mg/day
pH	5.8 – 6.2
Uric Acid	<800 mg/day for males <750 mg/day for females
Sodium	<150 mg/day
Potassium	>40 mEq/day
Magnesium	>70 mg/day

5.3.4 Urine Studies in Children

All pediatric stone formers should undergo metabolic evaluation. Although spot urine tests are easy to obtain in children, it is unclear how well spots tests correlate with 24-hour values.[87] **Normal ranges in children for 24-hour urine parameters vary by age**, **gender**, **body weight, and surface area**.[76,77] Calcium <4mg/kg/24 hours and oxalate <30 mg/m^2/24 hours are considered normal in children. Normal citrate values are gender-dependent (>128 mg/g creatinine for boys, >300mg/g creatinine for girls).[88]

6. Related Podcasts

AUA2021 John K. Lattimer Lecture- Kidney Stones: Is Prevention Possible? (Episode 131)

Urolithiasis: Metabolic Evaluation and Medical Management (Episode 111)

Summer School- Surgical and Medical Management of Stones Guidelines Update (Episode 56)

Summer School - Urolithiasis Metabolic Evaluation & Medical Treatment Mixdown

Kidney Stone Disease: Rare and Challenging Cases

Presentations

Medical Stone Disease Pathology and Evaluation Presentation 1

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