

NEPHROLITHIASIS

Li Song, M.D. Assistant Professor of Medicine, Department of Internal Medicine and Charles and Jane Pak Center for Mineral Metabolism and Clinical Research, University of Texas Southwestern Medical Center. Li.Song@UTSouthwestern.edu

Naim M. Maalouf, M.D. Associate Professor of Medicine, Department of Internal Medicine and Charles and Jane Pak Center for Mineral Metabolism and Clinical Research, University of Texas Southwestern Medical Center. Naim.Maalouf@UTSouthwestern.edu

Received March 8, 2020

ABSTRACT

Kidney stones are concretions of different mineral salts mixed with an organic matrix that form in the upper urinary tract. As a stone moves from the kidney to the ureter, it can present with renal colic symptoms, and may cause urinary tract obstruction and/or infection. In fact, acute passage of a kidney stone is one of the leading reasons for visits to an emergency room. Over the past four decades, the lifetime prevalence of nephrolithiasis has more than doubled in the United States (and several developed countries), afflicting around 11% of men and 7% of women. Unless the underlying etiology of stone formation is adequately addressed, kidney stones can recur at a rate of around 50% ten years after initial presentation. The evaluation of a kidney stone former requires an extensive medical history (to identify environmental, metabolic, and/or genetic factors contributing to stone formation), imaging studies to evaluate and track stone burden, and laboratory studies (serum and urinary chemistries, stone composition analysis) to guide lifestyle and pharmacological therapy. The majority of kidney stones are composed of calcium (calcium oxalate and/or calcium phosphate), either pure or in combination with uric acid. Calcium oxalate stones can be caused by hypercalciuria, hyperoxaluria, hyperuricosuria. hypocitraturia, and/or low urine volume. Calcium phosphate stones occur in patients with hypercalciuria, hypocitraturia, an elevated urine pH, and/or low urine volume. In addition to lifestyle changes (increasing fluid intake, reduction in salt intake, moderation of calcium and animal protein intake), pharmacological therapy directed at the underlying metabolic abnormality (thiazides for hypercalciuria,

inhibitors for hyperuricosuria) can significantly reduce calcium stone recurrence rate. Pure uric acid stones account for 8-10% of all stones, although their prevalence is significantly greater in stone formers with type 2 diabetes and/or the metabolic syndrome. Uric acid stones are primarily caused by an excessively acidic urine, and urinary alkalinization with medications such as potassium citrate can dissolve uric acid stones and prevent recurrent uric acid nephrolithiasis. Cystine stones result from inactivating mutations in genes that encode renal tubular transporters that reabsorb the amino acid cysteine, typically present in childhood, are highly recurrent, and require aggressive control of cystinuria with specific pharmacological therapy. Infection (struvite) stones often present as staghorn, and require careful surgical removal of all of the stone material.

potassium citrate for hypocitraturia, xanthine oxidase

OVERVIEW

Urinary stone disease is a common clinical condition that afflicts 1 in 11 individuals in the United States, and is increasing in incidence. It typically presents with renal colic symptoms following the passage of a calculus from the kidney to the ureter. The pathophysiology of kidney stone formation is diverse, and includes a combination of genetic and environmental factors. In fact, kidney stone formation should not be viewed as a diagnosis but rather a symptom of an underlying abnormality. Evaluation of a kidney stone former with a detailed history, and appropriate laboratory and imaging studies helps to identify risk factors for stone formation and provides an opportunity to institute therapy that reduces the risk of stone recurrence. This chapter reviews the epidemiology of kidney stone disease, discusses the pathophysiology underlying the most commonly encountered stone types, and details the evaluation and management of patients with nephrolithiasis.

EPIDEMIOLOGY AND NATURAL HISTORY

Epidemiology

Nephrolithiasis is a common clinical condition encountered in both developed and developing countries. Its prevalence in the United States has more than doubled over the past 4 decades from 3.8% in 1976-1980 to 5.2% in 1988-1994 to 8.8% in 2007-2010 (1, 2). Similar increases in the prevalence of nephrolithiasis have been reported in other developed countries (3). Factors underlying this rising prevalence include changes in diet and fluid intake, greater use of medications and procedures that predispose to stone formation, the association of stone disease with the rampant epidemics of obesity and type 2 diabetes, climate change, and increased use of abdominal imaging (2). In the United States, stone disease afflicts Caucasians at a greater frequency than Hispanics (Odds Ratio: 0.60 vs. Caucasians) and African Americans (Odds Ratio: 0.37 vs. Caucasians) (2). It is also more prevalent in men than women, although recent reports suggest a narrowing in this gender gap, with the greatest increase in stone incidence in recent years occurring in younger women (4). A marked geographic variability in the prevalence of nephrolithiasis is also reported, with 20-50% higher prevalence of stone disease in the U.S. Southeast ("stone belt") than the Northwest, primarily due to differences in exposure to temperature, humidity, and sunlight (5). Recent predictions suggest a likely northward expansion of the present-day U.S. "stone belt" as an unanticipated result of global warming (6). In 2000, the total cumulative costs for caring for patients with urolithiasis were estimated at US \$2.1 billion (7). The rising prevalence of obesity and diabetes, together with population growth, is projected to contribute to dramatic increases in the cost of urolithiasis by an additional \$1.24 billion/year estimated by 2030(8).

Natural History

RECURRENCE

The natural history of stone disease was studied in detail in all validated cases presenting with incident kidney stones in Olmsted County, Minnesota between 1984 to 2003 and followed for stone recurrence through 2012 (9). For the first episode, 48% of patients passed their stone spontaneously with confirmation, 33% required surgery for stone removal, 8% presumably spontaneously passed their stone (without confirmation), and 12% had no documentation of passage (9). This cohort was followed for a median of 11.2 years with recurrence occurring in 11%, 20%, 31%, and 39% at 2, 5, 10, and 15 years, respectively. The stone recurrence rates per 100 person-years were 3.4 after the first stone episode, 7.1 after the second episode, 12.1 after the third episode, and 17.6 after the fourth or higher episode (10). Independent risk factors for incident stone recurrence include younger age; male sex; higher body mass index; family history of stones; pregnancy; history of a brushite, struvite, or uric acid stone; number of kidney stones on imaging; and diameter of the largest kidney stone on imaging (10). These studies have led to the development and refinement of the Recurrence Of Kidney Stone (ROKS) tool to predict the risk of symptomatic recurrence by using readily available clinical characteristics of patients with kidney stones (9, 10).

POTENTIAL COMPLICATIONS

Urinary Tract Infection

There is a bi-directional relationship between urinary tract infections (UTI) and nephrolithiasis, as chronic UTIs lead to the formation of struvite stones, and stone disease increases the risk of UTI. Struvite stones typically occur in patients infected with urea-splitting organisms, and their pathogenesis and management are described in more detail in a later section. Gram-negative bacilli are the most common pathogen in UTI in patients with urolithiasis. Independent risk factors for UTI among patients with kidney stones include female gender, older age, presence of obstruction, and higher number of kidney stones (11). Low fluid intake is a reversible risk factor for both UTI and nephrolithiasis (12). Infectious (13) as well as non-infectious stones (14) can harbor bacteria inside, making the bacteria resistant to antimicrobial therapy. In patients with recurrent UTIs, removal of non-struvite non-obstructing stones is associated with elimination of further UTI recurrence in nearly 90% of cases (15).

Chronic Kidney Disease and End-Stage Renal Disease

Loss of renal function in patients with kidney stones may occur as a complication of obstruction by a stone lodged in the ureter, a complication of the urological procedure to remove a stone, or from the disordered pathophysiology underlying some stones. Staghorn stones caused by uric acid nephrolithiasis, cystinuria, renal tubular acidosis (RTA), or chronic infection are well-recognized causes of decreased renal function. Additional risk factors for the development of chronic kidney disease in stone formers include a solitary kidney, ileal conduit, neurogenic bladder, and development of hydronephrosis (16). In the Olmsted County cohort, end-stage renal disease incidence in patients with recurrent symptomatic kidney stones was twice that of the general non-stone forming population even after adjusting for baseline hypertension, diabetes mellitus, dyslipidemia, gout, obesity, and chronic kidney disease (17). Still, the absolute risk of ESRD from kidney stone disease was low.

Stone Disease in Pregnancy

Pregnancy-related mechanical and physiological changes alter risk factors for kidney stone formation, and management of acute nephrolithiasis in pregnancy is significantly more complicated than in non-pregnant women, at least in part due to imaging limitations and treatment restrictions (18). In an observational study, stones in pregnancy were associated with recurrent abortions, mild preeclampsia, chronic hypertension, gestational diabetes mellitus, and cesarean deliveries (19). Urinary tract infections and pyelonephritis and signs of ureteral obstruction including hydroureter and hydronephrosis were common, while premature rupture of membranes and preterm delivery were not more frequent. The newborns also were affected by perinatal complications including low birth weight, lower Apgar scores, and perinatal mortality. The majority of stones during pregnancy are calcium phosphate with a lesser number of calcium oxalate, in

contrast to non-pregnant women in whom calcium oxalate stones are most common (20).

ASSOCIATION WITH OTHER CONDITIONS

Traditionally, nephrolithiasis was thought of as a condition caused by poor diet and abnormal renal handling of electrolytes, with complications limited to the kidneys and the urinary tract. However, recent investigations suggest that kidney stones may in fact be a systemic disorder associated with serious disorders including osteoporosis and greater fracture risk (21), metabolic syndrome features including diabetes, hypertension, and dyslipidemia (22), and greater incidence of cardiovascular disease (23).

CLINICAL MANIFESTATIONS

Symptoms and Signs

A classical episode of renal colic has a sudden onset, with fluctuation and intensification over 15 to 45 minutes. The pain then becomes steady and unbearable and often is accompanied by nausea and emesis. As the stone passes down the ureter toward the bladder, flank pain changes in a downward direction toward the groin. As the stone lodges at the ureterovesical junction, urinary frequency and dysuria appear. The pain may clear as the stone moves into the bladder or from the calyceal system into the ureter. Hematuria, generally microscopic but occasionally frank, frequently accompanies stone passage. The presence of bleeding alone does not predict a more severe outcome. Episodes of rapid onset of pain, bleeding, and then rapid clearing, often called 'passing gravel', is the result of passing a large amount of crystals of calcium oxalate, uric acid, or cystine. "Non-classical" presentations of kidney stones include dull low back pain, gastrointestinal symptoms such as diarrhea, isolated microscopic hematuria, asymptomatic urinary obstruction with renal insufficiency, recurrent urinary tract obstruction, or incidental discovery on abdominal imaging.

Likelihood of Passage

The size, number, and metabolic composition of new stones strongly influence the natural history and complication rates. Smaller stone size and more distal location in the ureter at presentation predict greater likelihood of spontaneous stone passage. Furthermore, the clinical presentation can be in part classified by metabolic type (Table 1). Spontaneous stone passage may occur with calcium oxalate, calcium phosphate, uric acid, and cystine stones. Rarely does a struvite stone or a staghorn stone of other composition (cystine, uric acid) pass spontaneously.

Table 1. Clinical Manifestations of Stones by Composition				
Clinical feature	Calcium	Uric acid	Struvite	Cystine
Crystalluria	+	+	-	+
Stone passage	+	+	-	+
Small discrete stones	+	+	-	+
Sludge and obstruction	-	+	-	+
Radiodense	+	-	+	+
Staghorn	-	+	+	+
Nephrocalcinosis	+	-	-	-

EVALUATION

History

Evaluation of kidney stones starts with a detailed history focusing on medical conditions associated with higher risk of kidney stones (*e.g.* primary hyperparathyroidism, gastrointestinal disorders or surgeries, frequent urinary tract infections, gout, metabolic syndrome, *etc.*), family history

suggestive of genetic causes of kidney stones (*e.g.* cystinuria, idiopathic hypercalciuria, young age at onset, *etc.*), dietary history (*e.g.* intake of fluid, salt, protein, dairy products, oxalate-rich foods (Table 2) (24), *etc.*), medications associated with increased risk of kidney stones (*e.g.* topiramate, zonisamide, excessive vitamin C, *etc.*) (25, 26), and medications that directly precipitate and form stones (*e.g.* indinavir, triamterene, *etc.*) (Table 3). This history can provide guidance on the biochemical evaluation and management of kidney stones.

Table 2. Oxalate content of foods (24)			
Food category	High in oxalate	Low in oxalate	
Fruits	Figs, raspberries, dates	Apples, oranges, peaches, raisins, mango	
Vegetables	Spinach, okra, beans, beets	Lettuce, asparagus, carrots, avocado, corn	
Grains	Whole grain products	White rice, pasta, white bread	
Nuts	All nuts (peanuts, almonds)		
Other	Chocolate, cocoa, black tea	Coffee, milk products, meat products	

Table 3. Drugs associated with kidney stones (25, 26)			
Drugs associated with increased risk of stones	Drugs that precipitate and form stones		
Hypercalciuria (predispose to calcium stones):	Anti-viral:		
Excessive calcium and vitamin D supplement	Indinavir		
Loop diuretics	Atazanavir		
Glucocorticoids	Nelfinavir		
	Tenofovir disoproxil fumarate		
Hypocitraturia and high urine pH (predispose to calcium	Raltegravir		
phosphate stones):	Efavirenz		
Carbonic anhydrase inhibitors (acetazolamide,			
topiramate, zonisamide)	Antibiotics:		
	Sulfadiazine		
Hyperoxaluria (predispose to calcium oxalate stones):	Sulfamethoxazole		
Frequent use of antibacterial agents	Ciprofloxacin		
Excessive vitamin C supplement	Amoxicillin		
	Ampicillin		
Hyperuricosuria (predispose to uric acid stones and calcium	Ceftriaxone		
oxalate stones):			
Uricosuric drugs (probenecid, losartan)	Others:		
	Triamterene		
High urine ammonium (predispose to ammonium urate	Sulfasalazine		
stones):	Allopurinol		
Laxative abuse	Guaifenesin / Ephedrine		
	Magnesium trisilicate		

Laboratory Testing

The extent of biochemical evaluation depends on the risk of stone recurrence and patients' interest. For first-time stone formers, a basic evaluation including urinalysis, urine culture, and basic metabolic panel should be obtained. For high risk stone formers (Table 4) and interested first-time stone formers, a thorough evaluation (Table 5) is warranted which includes 24-hour urine stone risk profile (27-29).

BLOOD

The recommended blood testing of kidney stone formers includes assessment of renal function, serum electrolytes (including potassium, calcium, phosphorus, and magnesium), and serum uric acid. Assessment of serum PTH may be needed in patients with suspected primary hyperparathyroidism.

www.EndoText.org	

Recurrent kidney stones
Bilateral or multiple kidney stones
History suggestive of genetic causes of kidney stones:
Early onset of kidney stones (age < 18 years)
Family history of kidney stones
Stone types that are more commonly associated with metabolic abnormalities:
Pure calcium phosphate stones
Non-calcium stones (uric acid, cystine, struvite, and magnesium ammonium phosphate stones)
Any stone requiring percutaneous nephrolithotomy
History of medical conditions associated with increased recurrence risk:
Hyperparathyroidism
Sarcoidosis
Bowel disease (e.g. inflammatory bowel disease, chronic pancreatitis, chronic diarrhea)
Bowel resection (e.g. colon resection, ileostomy, small bowel resection, Roux-en-Y gastric bypass)
Cystic fibrosis
Metabolic syndrome (e.g. obesity, type 2 diabetes mellitus, dyslipidemia, hypertension)
Gout
Spinal cord injury
Neurogenic bladder
Recurrent urinary tract infection
Osteoporosis
Renal tubular acidosis
Polycystic kidney disease
Cystinuria
Primary hyperoxaluria
Anatomical abnormalities that result in impaired urine flow (e.g. medullary sponge kidney, ureteral stricture,
horseshoe kidney, <i>etc.</i>)
At high risk for complications of kidney stones:
Solitary kidney (functional or anatomical)
Chronic kidney disease
Complicated stone episodes that resulted in severe acute kidney injury, sepsis, or complicated hospitalization
At high risk occupations (e.g. pregnancy, pilots, police officer, military personnel, firemen, etc.)

Table 4. High Risk Stone Formers (27-29)

Recurrent stone formers:

Table 5. Biochemical Evaluation for High Risk Stone Formers and Interested First Time Stone Formers (27-29)

Serum: Basic metabolic panel, albumin, phosphate, magnesium, uric acid, PTH

Urinalysis and urine culture

24-hour urine: Volume, creatinine, pH, calcium, citrate, oxalate, uric acid, sodium, potassium, magnesium, chloride, sulfate, phosphate, ammonium and cystine (if cystine stone is confirmed or suspected)

Stone analysis

URINE

The initial 24-hour urine sample should be collected on the patient's typical random diet. It is controversial whether one or two 24-hour urine collections should be obtained (30-34). At least one collection is needed, but two collections are preferred (27-29). It is important to provide detailed instructions to patients to ensure an adequate collection and proper storage of urine sample. Patients start urine collection after their first morning void and end collection with the first morning void the next day. Storage of urine sample varies according to the instructions of the urine collection kits. Urine sample should be sent to a reliable lab for 24-hour urine stone risk profile analysis. 24-hour urine stone risk profile should be repeated at 8-16 weeks after dietary changes or if pharmacotherapy is initiated to monitor response to therapy and allow dose adjustment as needed (28). Once the therapeutic target is achieved, 24-hour urine stone risk profile is repeated annually (28).

24-hour urine stone risk profile typically provides information on 24-hour urine volume, creatinine, pH, calcium, citrate, oxalate, uric acid, sodium, potassium, magnesium, sulfate, phosphate, ammonium and cystine (if requested). In addition, relative supersaturations with respect to calcium oxalate, calcium phosphate and uric acid are reported. Relative supersaturations are calculated accounting for multiple factors including promotors and inhibitors associated with crystallization (35). Higher relative supersaturation is associated with higher likelihood of being stone formers and correlate with stone composition (36, 37).

STONE ANALYSIS

Knowledge of stone composition may help direct the appropriate choice of urological procedures, evaluation of potential underlying metabolic abnormalities, and medical interventions to prevent stone recurrence (27-29, 38, 39). Current guidelines recommend obtaining stone analysis when feasible for all first-time stone formers (27-29). Stone composition may change in the same individual over time (40, 41) Discordant stone compositions may also coexist in the same individual with bilateral kidney stones (42, 43). Therefore, repeat stone analysis should be obtained in recurrence under pharmacological treatment, early recurrence after urological intervention and late recurrence after a prolonged stone-free period (28).

Multiple analytical techniques are available for stone The currently preferred methods are X-ray analysis. diffraction and Fourier transform infrared spectroscopy (44). X-ray diffraction uses monochromic X-rays to create a unique diffraction pattern of the crystalline structure of the stone (45). Fourier transform infrared spectroscopy uses infrared radiation to create a unique energy absorption band pattern of the molecular structure of the stone (45). These patterns can then be matched to a reference database to determine the stone composition. Both X-ray diffraction and Fourier transform infrared spectroscopy are very accurate in identifying pure stones; however, the majority of kidney stones in clinical practice are mixed stones (44, 45). Both methods have limitations in identification of certain mixed stone compositions. X-ray diffraction cannot identify noncrystalline structures thus is prone to high rates of error in the detection of apatite component in mixed stones which is mostly pseudo-amorphous (44). It is also time-consuming

and expensive which limit its broad use in clinical practice (45). Fourier transform infrared spectroscopy is quick and less expensive, but it cannot reliably detect small amounts of components in certain mixed stones (e.g. whewellite (hydrated calcium oxalate) in whewellite/uric acid stones and struvite in struvite/apatite stones) (44-47). The accuracy of stone analysis by Fourier transform infrared spectroscopy depends on the quality of the reference database and trained personnel (46, 47). While pure stones are reliably identified, there is variability in reporting the components of mixed stones in commercial laboratories which needs to be kept in mind when interpreting stone analysis results (47, 48).

Imaging

A number of imaging modalities are available to evaluate stone number, size, and location in patients with nephrolithiasis (Table 6). Abdominal computed tomography (CT) without contrast is the initial imaging test of choice for suspected stone disease due to its high sensitivity and specificity, along with its widespread availability and the rapidity of scan time. One downside to CT scan use is exposure to ionizing radiation, which may increase longterm cancer risk. Lower radiation doses are effective in the diagnosis of nephrolithiasis in most patients, leading to greater recent adoption of "low-dose" and "ultra-low dose" CT scan protocols for evaluation of stone disease (49, 50). Use of ultrasonography as the initial test in patients with suspected nephrolithiasis in the emergency department (ED) may reduce cumulative radiation exposure without significantly increasing subsequent serious adverse events, pain scores, return visits to the ED, or hospitalizations (51). Abdominal X-rays (KUB) may be used as an alternative to CT scan and ultrasonography for follow-up of stone burden, although this modality misses radiolucent stones such as uric acid stones. Magnetic resonance imaging is capable of identifying kidney stones, but cost and limited availability make it a less attractive imaging modality for nephrolithiasis.

Table 6. Comparison of Different Imaging Modalities in the Assessment of Nephrolithiasis					
	Availability	Cost	lonizing	Other Advantages	Other Drawbacks
			Radiation		
CT Scan	Wide	Moderate	Highest	-Detects extra-renal	-Major drawback is
				pathology	radiation
				-Useful in identifying uric	
				acid stone composition	
Ultrasound	Wide	Moderate	None	-Portable US available	-Does not visualize
				-Use in children,	ureteral stones
				pregnancy	-Large body habitus
					limits visualization
X-ray	Wide	Low	Low	-Useful in follow-up of	-Misses radiolucent
				known radiopaque stones	and/or small stones
				-Visualizes kidneys,	-Overlying bowel gas,
				ureters, and bladder	and extra-renal
					calcification impact
					stone visualization
MRI	Limited	High	None	-Use in children,	-Contrast risk in CKD
				pregnancy	patients
					-Cannot distinguish
					stone from blood clot
IVP	Limited	Moderate	High	-Occasional use in	-Contrast use
				preoperative planning	

SURGICAL MANAGEMENT

An obstructive stone in the setting of urinary infection is a urological emergency and requires urgent decompression with a ureteral stent or nephrostomy tube (28, 38). Patients should have urine and, if appropriate, blood cultures obtained and be started on broad spectrum intravenous antibiotics until culture results are available. These patients often require fluid resuscitation and monitoring in an intensive care setting. Definitive stone treatment is delayed until infection resolves.

Patients who present with a ureteral stone up to 10mm can be offered a trial of passage if they have no signs or symptoms of urinary tract infection, their renal function is at their baseline, and their pain is well controlled. The likelihood of ureteral stone passage is influenced by stone size and location with smaller, more distal stones having the highest chance of passage (52). Furthermore, smaller stones tend to pass guicker than larger stones (53). For those patients attempting spontaneous passage, a trial of medical expulsive therapy with pain control and α -blocker for 4-6 weeks can be offered in uncomplicated cases (i.e. in the absence of infection, uncontrolled pain, obstruction, renal insufficiency, or renal anatomy associated with low likelihood of spontaneous stone passage) (28, 38, 54-56). Nonsteroidal anti-inflammatory drugs (NSAIDs) including intravenous ketorolac are the treatment of choice for pain control. (57) Opioids are used as rescue therapy for pain refractory to NSAIDs. (58) In emergency room setting, IV lidocaine is a useful non-opioid option for pain control with close cardiac monitoring if there are no contraindications. (59, 60) Alpha-blockers inhibit basal tone and decrease

peristaltic frequency and amplitude in the lower ureters, decrease intraureteral pressure and increase fluid transport, thus they are proposed to be useful in stone expulsion. (61) However, the effectiveness of α -blockers as medical expulsive therapy remains controversial. A recent metaanalysis showed the use of α -blockers is associated with increased stone clearance and decreased time to stone passage with little major adverse events compared to standard therapy without α -blockers, but the guality of evidence is low. (62) The benefit of α -blockers was mainly demonstrated in individuals with ureteral stones with sizes 6-10mm. Little effect was found in stones measuring 5mm or smaller likely because these stones frequently pass spontaneously even without medical expulsive therapy. (62) Potential side effects of *a*-blockers include orthostatic hypotension. dizziness. tachycardia, palpitations, headache, and abnormal ejaculation in males. In large clinical trials, these were not found to be more frequent in individuals treated with α -blockers than placebo with the exception of ejaculatory dysfunction in males. (62, 63)

Outpatient referral to urology is indicated for stones larger than 10mm, stones smaller than 10mm that fail to pass with medical expulsive therapy, and stones causing obstruction at the ureteropelvic junction, renal pelvis, or renal calyces especially in symptomatic patients and those at high risk for potential complications. Urological referral should also be considered for high risk stone formers (Table 4). Surgical intervention for stone treatment depends on symptoms, stone composition, size, and location (Table 7) (28, 38, 64).

Table 7. Surgical Management of Kidney Stones (28, 38, 64)			
Stone	Surgical procedure		
Urological emergency:			
Obstructive stone with infected urine	Obtain urinalysis, urine culture and start empiric antibiotics and IV fluid resuscitation		
	May need ICU care		
	Urgent decompression (ureteral stent or percutaneous nephrostomy tube)		
	Delay definitive stone treatment until infection resolves		
Ureteral stones:	•		
Uncomplicated ureteral stone \leq 10mm	Trial of medical expulsive therapy with pain control		
	(NSAIDS with narcotics if needed) and $\alpha\text{-blocker}$ for up to		
	4-6 weeks with reassessment of pain control, renal		
	function and stone passage		
Proximal ureteral stone < 10mm	SWL*		
	URS [#] if cystine stone or uric acid stone		
Proximal ureteral stone > 10mm	URS		
Mid ureteral stone of any size	URS		
Distal ureteral stone of any size	URS		
Renal stones:			
Asymptomatic renal stone < 15 mm	Conservative therapy with surveillance of symptoms and		
	imaging at 6 months and then annually for stone growth		
	and new stone formation		
Symptomatic non-lower pole renal stone \leq 20mm	SWL or URS		
Symptomatic non-lower pole renal stone > 20mm	PCNL [†]		
Symptomatic lower pole renal stone \leq 10mm	SWL or URS		
Symptomatic lower pole renal stone > 10mm	URS or PCNL		
Staghorn stones	PCNL		
Involved kidney with negligible function	Consider nephrectomy if recurrent infection or pain		

#URS: ureteroscopy;

†PCNL: percutaneous nephrolithotomy

*SWL: Shockwave lithotripsy. Calcium oxalate monohydrate, brushite and cystine stones are hard and resistant to fragmentation by SWL, thus alternative methods of stone removal are considered (28). SWL has a lower rate of complications and morbidity, but a lower stone free rate in a single procedure than URS.

MEDICAL MANAGEMENT

General Measures for All Patients with Kidney Stones

Some risk factors (e.g. low urine volume, hypocitraturia, high sodium intake, and high animal protein intake) are shared among different types of stones. General dietary measures (summarized in Table 8) targeting these risk

factors can be recommended for stone prevention. These can be especially useful when stone analysis and/or 24-hour urine stone risk profile are not available. Results from a 24-hour urine collection (Table 9) can further refine these recommendations.

Low urine volume is a risk factor for nephrolithiasis. High urine volume leads to urinary dilution of lithogenic constituents and reduced crystallization of calcium oxalate, calcium phosphate and uric acid (65, 66). Several prospective studies have demonstrated high urine volume achieved with high fluid intake is associated with reduction in incident stones and recurrent stones (67-69). Fluid intake of 2.5 to 3 liters per day or achieving a urine volume of at least 2-2.5 liters per day is recommended (27-29). Regarding the types of fluid other than water, orange juice, lemonade, coffee (caffeinated and decaffeinated), tea and alcohol have been associated with reduced risk of stone formation although with some controversial results (5, 68, 70-72). Cola and grapefruit juice have been associated with increased risk of stone formation (70).

A high dietary sodium intake is associated with increased risk of nephrolithiasis likely by causing increased urinary calcium and decreased urinary citrate (28, 66, 73, 74). For every 100 mmol/day increase in dietary sodium intake, urinary calcium increases by an average of 40 mg/day in non-stone forming adults and by up to 80 mg/day in hypercalciuric stone formers (66, 74-76). A low sodium diet reduced urinary calcium and recurrent stones in hypercalciuric stone formers (76, 77). Stone formers are therefore recommended to limit their dietary sodium intake to less than 2300 mg/day (or 100 mmol/day) which is equivalent to 5.9 grams of salt (sodium chloride) (27-29).

A high dietary animal protein intake (meat, fish and poultry) is a risk factor for nephrolithiasis in general (69, 78). It is associated with increased urinary calcium, uric acid, phosphate and reduced urinary citrate and pH (79). On average, urinary calcium increases by 1 mg/day for every 1 g/day increase in dietary animal protein intake (80, 81). In a randomized clinical trial of recurrent calcium oxalate stone formers, a diet with limited animal protein (52 g/day) and sodium (50 mmol/day) but normal calcium (1,200 mg/day) reduced stone recurrence by about 50% at 5 years when compared to a low-calcium diet (400mg mg/day) in

hypercalciuric stone formers (77). It is recommended to limit dietary animal protein intake to 0.8 to 1.0 g/kg weight per day (28, 82).

Urinary calcium excretion increases with increased dietary calcium intake which can be more pronounced in individuals with hyperabsorptive idiopathic hypercalciuria (66, 83). However, a diet restrictive in calcium has not been demonstrated to prevent nephrolithiasis. On the contrary, several studies showed a lower dietary calcium intake is associated with a higher risk of both incident and recurrent stones than a higher dietary calcium intake in men and women (69, 73, 77, 84). A restricted calcium diet increases enteric absorption of oxalate and urinary oxalate which increases supersaturation of calcium oxalate (85, 86). In addition, a low calcium diet may lead to negative calcium balance and bone loss. Therefore, a normal calcium diet with 1,000-1,200 mg/day is recommended as a dietary measure for stone prevention (27-29). Dietary sources of calcium are preferred. However, if supplemental calcium is needed, it is best taken in divided doses with meals to reduce enteric absorption of oxalate (27-29).

A diet rich in fruits and vegetables is associated with a decreased risk of incident kidney stones (87) and current guidelines on medical management of nephrolithiasis also recommend a diet rich in fruits and vegetables for prevention of stone recurrence (27-29). In normal individuals, elimination of dietary fruits and vegetables decreased urinary potassium, magnesium, citrate and oxalate, and increased urinary calcium oxalate and calcium phosphate (88). In hypocitraturic stone formers, introduction of fruits and vegetables in the diet increased urinary potassium, magnesium, citrate, volume and pH, and decreased relative supersaturation of calcium oxalate and uric acid (88).

Table 8. General Dietary Measures for All Stone Formers (27-29)	
Dietary measures	Targeted risk factors
Fluid intake:	
Fluid intake of 2.5 to 3 liters per day	Low urine volume
Achieving urine output of 2-2.5 liters per day	
Salt intake:	
Sodium intake less than 100 mEq (2,300 mg) per day	Hypercalciuria
Animal protein intake:	
0.8-1.0 grams / kilogram body weight per day	Hypercalciuria
	Hyperuricosuria
	Hyperphosphaturia
	Hypocitraturia
	Low urine pH
Calcium intake:	
Calcium intake of 1,000-1,200 mg per day divided into 2 doses taken with meals (prefer	Hyperoxaluria
dietary source over supplemental calcium)	
Fibers, vegetables and fruits:	Hypocitraturia
	Low urine pH

Table 9. 24-hour Urine Stone Risk Profile Interpretation (89)				
Urine parameter	Reference range	Risk factor for stone types	Interpretation	
Volume	> 2-2.5 L/day	All	Reflect fluid intake and extra-renal fluid loss Goal is above 2-2.5 L/day	
Creatinine	Male: 20-25 mg/kg body weight/day Female: 15-20 mg/kg body weight/day		Assess adequacy of urine collection	
рН	5.7-6.3	High pH: calcium phosphate and struvite Low pH: uric acid and cystine	High pH: distal renal tubular acidosis (dRTA) or UTIs Low pH: excessive animal protein intake, chronic diarrhea, or idiopathic	
Calcium	Male: < 300 mg/day Female: < 250 mg/day Either sex: < 4 mg/kg body weight/day	Calcium oxalate Calcium phosphate	Hypercalciuria (see details in "Hypercalciuria")	

Oxalate	< 45 mg/day	Calcium oxalate	Enteric hyperoxaluria > 100 mg/day, consider primary hyperoxaluria
Citrate	> 320 mg/day	Calcium oxalate Calcium phosphate	Hypocitraturia (see details in "Hypocitraturia")
Uric acid	< 700 mg/day	Calcium oxalate Uric acid	High purine intake or production
Phosphorus	< 1,100 mg/day	Calcium phosphate	Excessive protein intake
Sodium	< 200 mmol/day	Calcium oxalate Calcium phosphate	Excessive salt intake
Chloride	< 200 mmol/day	Calcium oxalate Calcium phosphate	Varies with sodium and potassium intake
Sulfate	< 40 mmol/day	Calcium oxalate Calcium phosphate Uric acid	Excessive animal protein intake
Ammonium	< 40 mmol/day		Excessive animal protein intake Non-dietary acid load (<i>e.g.</i> diarrhea)
Potassium	> 40 mmol/day		Low urine potassium: Low alkaline intake Potassium loss (<i>e.g.</i> diarrhea)
Magnesium	> 80 mg/day		Low urine magnesium: Low magnesium intake Malabsorption
Cystine	< 40 mg/day	Cystine stone	Cystinuria

Calcium Stones

Approximately 80% of kidney stones are calcium stones (calcium oxalate and/or calcium phosphate) (44). The initiating events of stone formation are controversial (90-94), but there are three proposed pathways of stone formation: 1) Randall's plaque (interstitial calcium

phosphate deposit at the renal papilla) grows and erodes the urothelium and becomes a nidus for crystal growth in urine supersaturated with respect to calcium oxalate; 2) Randall's plug formed by fixed particle mechanism in which a crystal nidus is attached to the apical epithelium of the collecting duct and allows crystal growth in urine supersaturated with respect to the constituents of the stone; 3) Randall's plug formed by free particle mechanism in which a crystal nidus forms through homogenous nucleation in the lumen of the nephron in the supersaturated environment (92). Randall's plaque is a prominent feature in idiopathic calcium oxalate stone formers and patients with primary hyperparathyroidism; although plugging is also observed (93, 94). Randall's plug formed by fixed particle mechanism is seen in brushite stone formers and patients with dRTA and primary hyperparathyroidism. Randall's

plug formed by free particle mechanism is seen in cystinuric stone formers and intestinal bypass patients (92).

Calcium stones can be idiopathic or associated with systemic diseases (see Table 10) (89, 95). Idiopathic calcium stones formers may exhibit various urinary risk factors for calcium oxalate and calcium phosphate stones (Table 11) (89).

Table 10. Systemic Conditions Associated with Calcium Stones (89, 95)	
Systemic diseases:	
Primary hyperparathyroidism	
Sarcoidosis	
Bone diseases (e.g. fractures, multiple myeloma)	
Immobilization	
Hyperthyroidism	
Distal renal tubular acidosis	
Polycystic kidney disease	
Bowel disease (e.g. inflammatory bowel disease, chronic pancreatitis, chronic diarrhea)	
Bowel resection (e.g. colon resection, ileostomy, small bowel resection, Roux-en-Y gastric	c bypass)
Cystic fibrosis	
Primary hyperoxaluria	
Gout	
Anatomical abnormalities that impair urine flow (e.g. medullary sponge kidney, ureteral s	stricture, horseshoe
kidney, <i>etc.</i>)	
Medications	
Carbonic anhydrase inhibitor (<i>e.g.</i> topiramate, acetazolamide, zonisamide)	
Calcium and vitamin D supplements	
Vitamin C supplement	
Loop diuretics	
Uricosuric agents (e.g. probenecid, benzbromarone)	

Table 11. Risk Factors for Calcium Stones (89)		
Risk factors for calcium oxalate stones	Risk factors for calcium phosphate stones	
Low urine volume	Low urine volume	
High urine calcium	High urine calcium	
Low urine citrate	Low urine citrate	
High urine oxalate		
	High urine pH	
High urine uric acid		



PATHOGENESIS AND RISK FACTORS

Hypercalciuria

Hypercalciuria is the most common risk factor of calcium stones and found in 30-60% of calcium stone formers (96). Hypercalciuria is classically defined as 24-hour urine calcium greater than 300 mg/day in men, greater than 250 mg/day in women, greater than 4 mg/kg body weight/day in either sex, or urine calcium > 140 mg calcium/gram creatinine/day (75). Although threshold values are provided to define hypercalciuria, there is no threshold value that predicts risk of stone incidence or recurrence. Rather, risk of stone incidence and recurrence increases progressively with higher urinary calcium excretion (97).

Environmental (diet, supplement, and medications) and metabolic disorders can contribute to hypercalciuria. One way to determine causes of hypercalciuria is to divide it into three broad categories: hypercalcemic hypercalciuria, normocalcemic hypercalciuria, and hypocalcemic hypercalciuria (Table 12).

Hypercalcemic hypercalciuria				
PTH-dependent causes				
Primary hyperparathyroidism				
Lithium-induced hyperparathyroidism				
PTH-independent causes				
Granulomatous diseases (e.g. sarcoidosis, tuberculosis, histoplasmosis, coccidoimycosis, lymphoma)				
Vitamin D toxicity				
Low level or activity of vitamin D 24-hydroxylase				
Hypercalcemia of malignancy (e.g. bone metastases, lymphoma, PTHrP, multiple myeloma)				
Immobilization				
Hyperthyroidism				
Paget's disease of bone				
Vitamin A toxicity				
Milk alkali syndrome				
Normocalcemic hypercalciuria				
Absorptive				
Excessive calcium intake (diet and/or supplement)				
Excessive animal protein intake				
Sarcoidosis				
Idiopathic hypercalciuria				
Resorptive				
Excessive animal protein intake				
Hyperthyroidism				
Immobilization				
Paget's disease of bone				
Osteoporosis				
Glucocorticoid excess				
Distal renal tubular acidosis				

Malignant tumors Idiopathic hypercalciuria Renal leak Excessive salt intake Loop diuretics Mineralocorticoid excess Glucocorticoid excess Distal renal tubular acidosis Idiopathic hypercalciuria

Hypocalcemic hypercalciuria

Autosomal dominant hypocalcemia (activating mutation in CaSR or GNA11)

Idiopathic Hypercalciuria

Idiopathic hypercalciuria is found in up to 50% of idiopathic calcium stone formers (98). It appears to be familial which suggests a genetic basis (99). It presents with a pattern of variable inheritance, and is likely polygenic in most stone formers, with described base changes in some candidate genes including *CaSR*, *VDR*, *TRPV5*, *TRPV6*, *CLCN5*, *ADCY10*, and *CLDN14* (75, 96). The pathophysiology of idiopathic hypercalciuria involves increased intestinal calcium absorption, renal leak of calcium, and increased bone resorption especially when challenged with a restricted calcium diet (75, 96).

Intestinal calcium hyperabsorption is the most common abnormality in idiopathic hypercalciuria (100). It can be 1,25(OH)₂D-dependent or independent. In patients with 1,25(OH)₂D-dependent absorptive hypercalciuria, there is generally an increased production of 1,25(OH)₂D when compared to normal individuals (101), although some patient with CYP24A1 mutations exhibit reduced 1,25(OH)₂D catabolism. The exact mechanism leading to increased 1,25(OH)₂D production remains unclear. There was a suggestion that renal tubular phosphate handling may play a role; however, others found that regulators of 1,25(OH)₂D production (PTH, serum phosphorus and renal tubular reabsorption of phosphate) in idiopathic hypercalciuric stone formers were comparable to non-stone (102-105). In patients with formers 1.25(OH)₂Dindependent absorptive hypercalciuria, intestinal absorption of calcium remains elevated despite a normal 1,25(OH)₂D level. Again, the mechanism is unclear. Animal studies demonstrated an increased abundance and half-life of vitamin D receptors (VDR) in the intestines of genetic hypercalciuric rats (106, 107). In male calcium oxalate stone formers with idiopathic hypercalciuria, an elevated level of VDR in monocytes was found when compared to non-stone formers (108). Both suggest increased tissue VDR may contribute to absorptive hypercalciuria in individuals with a normal 1,25(OH)₂D level.

Idiopathic hypercalciuric stone formers also display abnormal renal calcium handling with a lower postprandial renal calcium reabsorption than normal individuals without a difference in filtered load (109). There is evidence of defective renal calcium reabsorption in both proximal tubule and distal nephron (110-112). The reduced renal calcium reabsorption could not be explained by sodium excretion and PTH levels (109). The underlying mechanism of decreased renal calcium reabsorption remains to be elucidated.

Hypercalciuric stone formers were found to have lower bone mineral density (BMD) than non-stone formers even in those with absorptive hypercalciuria (21, 113). The decreased BMD is more pronounced in trabecular bone than cortical bone (21, 113). Nephrolithiasis was associated with an increased risk of vertebral fractures in both men and women in a population-based retrospective cohort study (114), and with an increased risk of prevalent vertebral and wrist fractures in men in a cross-sectional study in NHANES III (115). Prior bone histomorphometry studies demonstrated increased bone resorption in fasting hypercalciuria and decreased bone formation in absorptive hypercalciuria (113). The pathophysiology underlying bone loss in idiopathic hypercalciuria is not exactly clear; however, several risk factors have been associated with bone loss in this population. A restricted calcium diet sometimes used by patients or physicians to reduce urine calcium may generate negative calcium balance leading to increased bone resorption and bone loss without reducing risk of kidney stones (77, 116, 117). High dietary salt and protein intake increase urinary calcium excretion and create a subtle metabolic acidosis both of which may contribute to bone loss (21, 75, 113, 118). Inflammatory cytokines such as IL1, IL6, TNF-a and GM-CSF have been associated with hypercalciuria and bone loss by increased bone resorption (113). Idiopathic hypercalciuric stone formers were also found to have increased bone expression of RANKL and decreased expression of TGF- β which may be the mediators for increased bone resorption and decreased bone formation and mineralization, respectively (119). High 1,25(OH)₂D and/or increased expression of VDR found in idiopathic hypercalciuria may also increase bone resorption and decrease bone formation (21).

Hypocitraturia

Urinary citrate is an endogenous inhibitor of calcium stone formation. It forms a more soluble calcium citrate complex than calcium oxalate and calcium phosphate (89, 96). It reduces urinary supersaturation with respect to calcium oxalate and calcium phosphate (89, 96). Hypocitraturia is generally defined as urine citrate less than 320 mg/day and is a well-described reversible risk factor that is present in 20-60% of calcium stone formers (89, 96). Extracellular and intracellular pH affects renal citrate excretion. Systemic acidosis increases urinary citrate reabsorption and leads to hypocitraturia (120). Intracellular acidosis increases intracellular citrate metabolism in the cytosol and mitochondrial via the TCA cycle (120). Thus, hypocitraturia occurs mainly in conditions with extracellular or intracellular acidosis (89). Table 13 summarizes common causes of hypocitraturia (89, 96, 120).

Table 13. Causes of Hypocitraturia (89, 96, 120)

Systemic diseases:

- Complete dRTA (hypocitraturia, frank metabolic acidosis, hypokalemia, hypercalciuria, high urine pH)
- Incomplete dRTA (hypocitraturia without frank metabolic acidosis, high urine pH)
- Hypokalemia
- Chronic diarrhea
- Chronic kidney disease
- Primary hyperaldosteronism
- Idiopathic hypocitraturia

Dietary:

- High animal protein intake
- High sodium intake
- Low fruit / vegetable intake

Medications:

- Carbonic anhydrase inhibitor (e.g. topiramate, acetazolamide, zonisamide)
- Angiotensin converting enzyme inhibitors
- Angiotensin II receptor blockers
- Diuretic-induced hypokalemia



Hyperoxaluria

High urinary oxalate increases urinary supersaturation with respect to calcium oxalate (96). Hyperoxaluria is generally defined as urinary oxalate greater than 45 mg/day (0.5 mmol/day) (89). It is encountered in 8-50% of calcium stone formers (121). Etiologies of hyperoxaluria can be divided into three categories: 1) increased endogenous oxalate production due to inborn error of metabolism, 2) increased intake of foods rich in oxalate or its precursors (Table 2) or increased intestinal bioavailability of oxalate, and 3) increased intestinal oxalate absorption (89, 121). Table 14 summarizes causes of hyperoxaluria.

Primary hyperoxalurias (PH) are a group of rare autosomal recessive disorders involving overproduction of oxalate which results in markedly increased urinary oxalate excretion. There are three genetic forms: PH1 due to mutations in AGXT (encodes for a pyridoxal-5'-phosphateperoxisomal dependent hepatic alanine-glyoxylate aminotransferase, AGT), PH2 due to mutations in GRHPR (encodes for glyoxylate reductase and hydroxypyruvate reductase, GRHPR) and PH3 due to mutations in HOGA1 (encodes for hepatic mitochondrial 4-hydroxy-2oxoglutarate aldolase, HOGA) (122, 123). Deficiency in AGT in PH1 results in decreased conversion of glyoxylate to glycine. The accumulated glyoxylate is in turn converted to oxalate by lactate dehydrogenase (LDH) leading to increased production of oxalate (123). Deficiency in GRHPR in PH2 results in decreased conversion of glyoxylate and hydroxypyruvate to glycolate and Dglycerate, respectively. The accumulated glyoxylate and hydroxypyruvate are converted to oxalate and L-glycerate respectively by LDH (123). Mutations in HOGA1 in PH3 result in decreased enzymatic activity of HOGA which converts 4-hydroxy-2-oxoglutarate (HOG) to pyruvate and glyoxylate. This results in accumulation of HOG which inhibits mitochondrial GRHPR (which is the deficient enzyme in PH2) activity, thus increasing oxalate production (122, 124). Primary hyperoxalurias should be suspected if urinary oxalate is greater than 90 mg/day (1 mmol/day) (125). Measurement of other urinary metabolites including glyoxylate and L-glycerate can be helpful, but genetic

testing is required for definitive diagnosis of primary hyperoxaluria (123).

Dietary oxalate is estimated to range between 50 and 1,000 mg/day (121). Oxalate is absorbed mainly in the small intestine and to a lesser extent in the colon (121). Intestinal absorption of oxalate varies between 10% and 72% (121). On a normal calcium diet (1,000 mg/day calcium), urinary oxalate increases by 2.7 mg/day with every 100 mg/day increase in dietary oxalate between 50mg to 750mg/day (126). Table 2 provides a list of foods rich in oxalate and some alternative options with low oxalate content (24). Although there is considerable variation in the reported oxalate content in foods among the available online sources, the simplest strategy is to avoid the foods with high oxalate content (127). Attention should be paid to portion size even with foods with low to moderate oxalate contents. Excessive intake of vitamin C more than 1,000 mg/day is associated with increased urine oxalate because vitamin C is metabolized into oxalate in the body (128, 129).

A restricted calcium diet increases enteric oxalate availability for absorption and results in increased urinary oxalate (85, 86). Patients with chronic diarrhea, pancreatic insufficiency, inflammatory bowel diseases, or small bowel resections may have malabsorption of bile acids and/or fatty acids which can complex with luminal calcium in the intestine, resulting in increased bioavailability of oxalate to be absorbed and subsequently excreted in the urine (89, 96). This is also termed enteric hyperoxaluria. Increased bioavailability of luminal oxalate can also result from decreased colonization by Oxalobacter formigenes which is a Gram-negative obligate anaerobe that utilizes oxalate as the sole energy source. O. formigenes also increases secretion of endogenous oxalate from plasma to the gut lumen which results in decreased urinary oxalate (126). Colonization by O. formigenes is associated with decreased bioavailability of intestinal oxalate for absorption, decreased urinary oxalate, and reduced risk of calcium oxalate stones (130, 131). Use of certain antibiotics to which O. formigenes are sensitive (macrolides, tetracyclines, chloramphenicol, rifampin and metronidazole) within the past 5 years is associated with a reduction in colonization when compared to non-users (132), and has been separately associated

with greater incidence of stone disease (133). Furthermore, patients with cystic fibrosis or inflammatory bowel disease who receive frequent antibiotic courses were found to have

lower prevalence of colonization by *O. formigenes*, which may contribute to their higher oxalate excretion and increased kidney stone formation (134, 135).

Table 14. Causes of Hyperoxaluria		
Primary hyperoxaluria		
Primary hyperoxaluria type 1 (mutations in AGXT gene)		
Primary hyperoxaluria type 2 (mutations in GRHPR gene)		
Primary hyperoxaluria type 3 (mutations in HOGA1 gene)		
Secondary hyperoxaluria		
High intake of oxalate rich foods (See Table 2)		
Vitamin C intake > 1,000 mg/day		
Low calcium intake		
Pancreatic insufficiency		
Inflammatory bowel disease (Crohn's disease)		
Small bowel surgeries		
Cystic fibrosis		
Decreased colonization by Oxalobacter formigenes		

Elevated Urine pH

Urine pH higher than 6.7 is a risk factor for calcium phosphate stones. The pKa for monohydrogen phosphate $(HPO4^{2-})$ is ~ 6.7. At a pH higher than the pKa, there is an

increased abundance of HPO4²⁻ which complexes with divalent cation calcium (Ca²⁺) to form brushite (CaHPO₄.2H₂O) and eventually to hydroxyapatite [Ca₁₀(PO₄)₆(OH)₂] (96). Table 15 summarizes potential causes of high urine pH.

Table 15. Causes of High Urine pH (89, 96)		
Distal renal tubular acidosis (RTA)		
Urinary tract infections		
Primary hyperparathyroidism		
Carbonic anhydrase inhibitors		
Alkali therapy		

Hyperuricosuria

Hyperuricosuria is defined as urinary uric acid greater than 800 mg/day in men and 750 mg/day in women (136). It is found in 40% of calcium stone formers and associated with increased risk of calcium oxalate stones (96). There are three main proposed mechanisms by which hyperuricosuria promotes calcium oxalate crystallization: 1) calcium oxalate precipitation on monosodium urate crystals through heterogeneous nucleation (137, 138), 2) removal of calcium oxalate crystallization inhibitors by colloidal urate particles (139), and 3) increased urate concentration decreases the solubility of calcium oxalate and leads to precipitation of calcium oxalate from solution by a salting-out mechanism (140). Hyperuricosuria is generally caused by increased purine intake, increased production of uric acid, or increased urinary excretion primarily from acquired conditions, although inherited causes of hyperuricosuria are also described (Table 16) (89, 136). Table 16. Causes of Hyperuricosuria (89, 136)Acquired Conditions:Increased intake:High purine rich diet (e.g. red meat, fish and poultry)Increased production:GoutMyeloproliferative and neoplastic disordersIncreased urinary excretion:Uricosuric drugsInherited Conditions (rare):Disorders of uric acid metabolism:Lesch-Nyhan syndromeChusene atoms of the part of th

Glycogen storage disease type 1A **Disorders of renal uric acid reabsorption:** Renal hypouricemia

MANAGEMENT OF CALCIUM STONES

Lifestyle Measures

A diet high in fluid (fluid intake of 2.3-3 liters per day or achieving urine volume of at least 2-2.5 liters per day), rich in fruits and vegetables, low in sodium (less than 2300 mg/day or 100 mmol/day), animal protein (limit to 0.8 to 1.0 g/kg body weight/day) and oxalate (less than 100 mg/day) and normal in calcium (1,000 to 1,200 mg/day preferably from dietary source) is recommended for calcium stone prevention (27-29, 95, 96). These were previously addressed in section "General measures for all patients with kidney stones" (Table 8).

Pharmacotherapy

Thiazide and thiazide-like diuretics:

Hypercalciuria is the most common risk factor for calcium stones. Thiazide (hydrochlorothiazide or HCTZ) and thiazide-like diuretics (indapamide and chlorthalidone) can reduce urinary calcium by two proposed mechanisms: 1) blockage of NaCl symporter in distal convoluted tubule leads to decreased distal sodium and water reabsorption and volume contraction, which results in increased sodium and water reabsorption in the renal proximal tubule, resulting in increased calcium reabsorption by passive transport (141), and 2) increased distal tubular calcium absorption by increased abundance of transport proteins TRVP5 and calbindins (142, 143). The hypocalciuric doseresponse to HCTZ has been studied in six healthy adults which demonstrated hypocalciuric effect at 12.5mg, 25mg, and 50mg daily; however, it was subtherapeutic for 12.5mg and 25mg daily when compared to 50mg daily (144). Several randomized controlled trials on thiazide diuretics with an average follow up of \sim 3 years showed reduction in the risk of recurrent stones in both hypercalciuric and normocalciuric stone formers (145). This underscores the lack of threshold effect of urinary calcium in predicting stone risk. Rather, the risk of stone formation increases progressively with increasing urinary calcium excretion even within the "normal range" (97). It also supports the empiric use of thiazide diuretics in recurrent calcium stone formers, even those with normocalciuria (27, 146). The doses used in these trials were HCTZ 25mg BID, 50mg and 100mg daily, indapamide 2.5mg daily and chlorthalidone 25mg and 50mg daily (145). A recent retrospective cohort study suggests lower doses of thiazide diuretics (HCTZ or chlorthalidone \leq 12.5 mg daily or indapamide \leq 1.25 mg daily) appear to have a similar protective effect against stone formation as higher doses in older adults (147).

Thiazide diuretics have also been shown to improve bone health. They reduce urinary calcium excretion resulting in positive calcium balance and reduced PTH which may

reduce bone turnover (96). They have also been shown to stimulate osteoblast differentiation and function and inhibit osteoclast differentiation in vitro (21, 115, 148). HCTZ 50mg daily improved cortical BMD in healthy postmenopausal women without baseline hypercalciuria (149, 150). In postmenopausal women with osteoporosis and hypercalciuria, addition of indapamide 2.5mg daily to alendronate 70mg weekly resulted in a reduction in urinary calcium and an additional increase in BMD at the lumbar spine over 12 months compared to alendronate single therapy (151). A meta-analysis of five observational cohort studies showed thiazide diuretics use was associated with a reduction in risk of hip fractures (152). Although there is no randomized placebo-controlled trial available, a secondary analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed a reduction in hip and pelvic fracture risk in patients on chlorthalidone 12.5mg to 25mg daily compared to those on lisinopril or amlodipine (153).

Thiazide diuretics use may be associated with hypokalemia which may induce hypocitraturia, thus potassium supplements are often needed. Potassium citrate is superior to potassium chloride given its ability to increase urinary citrate and pH and to further lower urine calcium excretion (154). Combination of thiazide diuretics with a potassium sparing diuretic (*e.g.* amiloride) can also be considered.

In summary, thiazide diuretics are recommended to patients with recurrent calcium stones with and without hypercalciuria (27).

Alkali therapy:

Potassium citrate treatment increases urine pH and urine citrate, decreases urine calcium, and decreases urinary supersaturation with respect to calcium oxalate (155). Several placebo-controlled randomized trials demonstrated potassium citrate and potassium magnesium citrate treatment reduced recurrent stone events in calcium stone formers with and without hypocitraturia (156-158).

Potassium citrate treatment may also prevent bone loss. Potassium citrate treatment increased BMD at the spine in idiopathic calcium stone formers (159) and increased BMD at the spine, femoral neck, and total hip in healthy elderly men and postmenopausal women without osteoporosis (160).

The proposed mechanisms by which potassium citrate improves BMD include systemic alkalization, increased osteoblastic activity, and reduced osteoclastic activity demonstrated by bone turnover markers, and positive calcium balance created by reduced urinary calcium excretion (21, 160, 161).

Currently, potassium citrate therapy is recommended for patients with recurrent calcium stones with and without hypocitraturia (27).

Xanthine oxidase inhibitors: Allopurinol and Febuxostat:

There is only one published randomized placebo-controlled trial on allopurinol in prevention of calcium nephrolithiasis. In this study, calcium oxalate stone formers with hyperuricosuria and normocalciuria treated with allopurinol 100mg TID had a lower rate of stone events than those treated with placebo over 24 months (162). Allopurinol is recommended for patients with recurrent calcium oxalate stones with hyperuricosuria and normocalciuria (27).

Febuxostat was studied in a randomized controlled trial comparing febuxostat 80mg daily with allopurinol 300mg daily or placebo on the effect of stone prevention in calcium stone formers (calcium oxalate and/or calcium phosphate) with hyperuricosuria and normocalciuria over 6 months (163). Febuxostat led to a greater reduction in urinary uric acid than allopurinol or placebo, but percent change in stone size was similar to allopurinol or placebo. This study was not powered to detect difference in stone events in the three groups. Currently, there is insufficient evidence to support the routine use of febuxostat for stone prevention in hyperuricosuric calcium stone patients, except in those who may be allopurinol-intolerant (29).

Pyridoxine:

Pyridoxine (vitamin B6) supplementation is helpful in primary hyperoxaluria type 1 (PH1) with specific mutations, namely Gly170Arg, Phe152lle and Ile244Thr. A trial of

pyridoxine for 3 months with a starting dose of 5 mg/kg body weight/day titrated to a maximum of 20 mg/kg body weight/day can be attempted in patients with suspected primary hyperoxaluria. Response to therapy is defined as more than 30% reduction in urinary oxalate from baseline (123).

Uric Acid Stones

Uric acid stones generally represent around 10% of all stones analyzed, although their prevalence has markedly increased in recent years, in parallel with the diabetes and obesity epidemics (164, 165). In a series of 2,464 calculi, the proportion of uric acid stones was 35.7% in patients with type 2 diabetes and 11.3% in patients without type 2 diabetes (166). Reciprocally, the proportion of patients with type 2 diabetes was significantly higher among uric acid than among calcium stone formers (27.8 versus 6.9%) In fact, several epidemiological and metabolic (166). studies have reported an association of uric acid stone disease with various features of the metabolic syndrome including obesity, type 2 diabetes, hypertension, dyslipidemia, hyperglycemia, hepatic steatosis, and greater visceral adiposity (167).

PATHOGENESIS AND RISK FACTORS

The three main factors implicated in the development of uric acid nephrolithiasis are low urine pH, hyperuricosuria, and low urine volume (Table 17) (168). Of these, low urine pH is the primary determinant of uric acid nephrolithiasis, as acidic urine favors the protonation of urate, forming relatively insoluble uric acid which precipitates in this overly acidic urinary environment. In fact, a decline in urine pH from 6.0 to 5.0 increases urinary uric acid concentration sixfold, whereas states of increased urate production typically increase urate excretion two-fold. Therefore, uric acid stone formation is more determined by pH than by urine volume or urine uric acid concentrations. Low urine pH may result intake of animal from excessive proteins (81), gastrointestinal alkali loss (from chronic diarrhea or laxative abuse), or may be idiopathic as frequently observed in patients with obesity, type 2 diabetes, and/or the metabolic syndrome (164, 168). Human metabolic studies have identified greater acid excretion and reduced urinary buffering by ammonia as the two culprits of aciduria in uric acid nephrolithiasis (169). Hyperuricosuria is less frequently encountered in patients with uric acid nephrolithiasis, and may result from inherited and/or acquired conditions (Tables 16 and 17). Finally, low urine volume due to extrarenal fluid losses contributes to increased urinary saturation with respect to uric acid, leading to stone formation.

Table 17. Risk Factors and Etiological Conditions Associated with Uric Acid Nephrolithiasis			
Urinary Risk Factor	Type of Abnormality	Etiological conditions	
Low urine pH	Inherited Conditions	Inherited uric acid lithiasis (unknown genetic abnormality)	
	Acquired Conditions	Metabolic syndrome, obesity, diabetes, CKD, high animal protein	
		intake, gastrointestinal alkali loss	
	Medications	Laxatives	
Hyperuricosuria	Inherited Conditions	Disorders of uric acid metabolism (e.g. Lesch-Nyhan);	
		Disorders of uric acid excretion (e.g. renal hypouricemia);	
		Glycogen storage disorder type 1A (glucose-6-phosphatase	
		deficiency)	
	Acquired Conditions	Gout, myeloproliferative disorders, hemolytic disorders, high	
		purine intake	
	Medications	Uricosuric agents: Losartan, Probenecid, Benzbromarone	
Low urine volume	Acquired Conditions	Chronic diarrhea, excessive perspiration, low fluid intake	
	Medications	Laxatives	



MANAGEMENT

Since uric acid stone formation is more determined by urine pH than by urine volume or urine uric acid concentrations, the cornerstone of therapy is urinary alkalinization.

Lifestyle Changes

Dietary restriction of animal protein intake is helpful in decreasing ingestion of proton sources, which reduces aciduria and aids with urinary alkalinization. At the same time, animal protein restriction also lowers uric acid excretion through a reduction in purine intake. Conversely, greater ingestion of alkali-rich fruits and vegetables aids in raising urine pH. Finally, higher fluid intake in general aids in raising urine volume, while intake of certain fruit juices such as orange juice can increase urine pH (along with the concomitant rise in urine volume). Still, one should be cautious about the sugar load imparted by fruit juices in uric acid stone formers with pre-diabetes or frank diabetes.

Pharmacological Therapy

Medical dissolution therapy of uric acid stones with alkali therapy (potassium citrate, to raise 24-hour urine pH to 6.0 to 6.5) is the cornerstone of uric acid management. Alkali therapy is well-tolerated by most uric acid stone formers and effectively dissolves stones, potentially avoiding the morbidity of urological interventions (170, 171). In patients who cannot tolerate potassium citrate, alternative alkali regimens include sodium bicarbonate and potassium bicarbonate. Occasionally, xanthine oxidase inhibitors (allopurinol or febuxostat) are added to potassium citrate in patients with hyperuricosuria whose uric acid stones recur despite alkali therapy. A recent study has suggested that the thiazolidinedione pioglitazone may aid in raising urine pH in uric acid stone formers (172), although the risk/benefit ratio of this medication needs to be considered.

Cystine Stones

PATHOGENESIS AND RISK FACTORS

Cystine represent around 1-2% of stones in adult patients, but account for 5-8% of stones in pediatric patients. Cystine stones result from inactivating mutations in genes that encode renal tubular transporters that reabsorb the amino acid cysteine (173). The complexation of two molecules of the dibasic amino acid cysteine results in the formation of cystine which is relatively insoluble. Cystine normally appears in urine in small amounts that are insufficient to cause supersaturation, crystalluria, or stone formation. Due to defects in renal cysteine reabsorption, patients with cystinuria exhibit greater than a 10-fold increase in urine cystine excretion (as well as greater excretion of the other dibasic amino acids lysine, ornithine, and arginine). As a result, the solubility limit of cystine in the urine (250 mg/L) is exceeded. Homozygous inheritance results in more severe phenotype, whereas heterozygous inheritance is associated with variable increases in amino acid excretion and an intermediate increase in cystinuria. Cystine stones form in the upper urinary tract as early as the first decade of life, and tend to be large, staghorn, bilateral, and highly recurrent (173). Stone formation may manifest as obstruction, infection, hematuria, and renal failure. Cystine stones are visible on standard abdominal radiographs because of the relative density of the sulfur constituent of cysteine (Table 6).

MANAGEMENT

The goal of therapy in cystinuria is to reduce cystine excretion and increase urinary cystine solubility (173, 174). This is accomplished using a combination of lifestyle changes and pharmacological interventions.

Lifestyle Changes

Large urine volumes of 3-4 liters per day may be effective at reducing cystine concentration and reducing stone recurrence in some patients, although this is difficult to institute in children and even adult patients. Dietary protein restriction to around 1 g protein/kg body weight/day reduces cysteine intake, and may cause small decreases in cystine synthesis (175), although this should be avoided in growing children and adolescents. A low sodium intake can also contribute to reduced cystine excretion (176).

Pharmacological Therapy

When fluid and dietary therapy fail, then pharmacologic therapy may be effective. Alkaline pH in the 7.0-7.5 range will reduce cystine solubility and can be achieved by the addition of alkali therapy such as potassium citrate (177). Tiopronin (Thiola®) and D-penicillamine reduce cystine formation in urine by preventing cysteine-cysteine complexation and the formation of more soluble thiol-cysteine disulfides that are more readily excreted in the urine. Both agents however have potentially serious side effects (proteinuria, abnormal LFTs, others) and therefore they are not used as first-line treatment (174).

Struvite (Infection) Stones

PATHOGENESIS AND RISK FACTORS

Struvite (magnesium ammonium phosphate) stones form only in the presence of bacteria that produce urease. Common urease-producing bacteria that may populate the urinary tract are proteus, klebsiella, pseudomonas, and enterococci. Urease-mediated splitting of urea and the generation of ammonium results in an alkaline urine. Urine pH above 7.0 normally is associated with very low urine ammonium levels of less than 10 mEg/day. However, urine ammonium excretion exceeding 30 mEg/day along with 24-hour urine pH > 7.0 virtually make the diagnosis of struvite stones. Other constituents of the stone may include calcium carbonate and brushite (calcium phosphate), which form crystals in the very alkaline urine. Patients who form struvite stones do not pass them spontaneously, but rather are at high risk for bleeding, obstruction, and decreased renal function. Some infection stones begin as calcium oxalate stones that become

REFERENCES

1. Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC. Time trends in reported prevalence of kidney infected with a urease-producing bacterium. Spread of infection to the contralateral kidney may occur.

MANAGEMENT

untreated staghorn calculi will Because require nephrectomy in 50% of patients, definitive treatment is indicated (178). Growth of infection stones and their progressive damage to kidney tissue may be limited by shockwave lithotripsy and percutaneous nephrolithotomy (PCNL); however definitive treatment of struvite stones is surgical removal. Extended antibiotic therapy has proven ineffective in eradicating the infection and does not substitute for complete removal of even the smallest particulate of the stone (178). Management with PCNL followed by careful follow-up and medical management minimizes stone recurrence and maintains kidney function in the majority of patients (179). Larger stone burden preoperatively, residual stones after surgery, and presence of medical comorbidities are independent risk factors for stone recurrence or residual stone-related events (179). Acetohydroxamic acid inhibits urease produced by the bacteria and has been shown to be effective in eradicating chronic infection of struvite stones (180). Use of the drug has been limited, however, as it is associated with potentially serious side effects such as hemolytic anemia and venous thromboembolic disease.

CONCLUSIONS

In conclusion, urinary stones are common, morbid, and highly recurrent. The pathophysiology of kidney stone formation is diverse, and includes a combination of genetic and environmental factors. Several endocrinological disorders increase the risk of stone formation. Metabolic evaluation of patients with kidney stones helps to identify the underlying etiological factors and provides an opportunity to institute preventive lifestyle and/or pharmacologic measures to reduce stone recurrence risk.

stones in the United States: 1976-1994. Kidney Int. 2003;63(5):1817-23.

- Scales CD, Jr., Smith AC, Hanley JM, Saigal CS. Prevalence of kidney stones in the United States. Eur Urol. 2012;62(1):160-5.
- 3. Ziemba JB, Matlaga BR. Epidemiology and economics of nephrolithiasis. Investig Clin Urol. 2017;58(5):299-306.
- Kittanamongkolchai W, Vaughan LE, Enders FT, Dhondup T, Mehta RA, Krambeck AE, et al. The Changing Incidence and Presentation of Urinary Stones Over 3 Decades. Mayo Clin Proc. 2018;93(3):291-9.
- Soucie JM, Coates RJ, McClellan W, Austin H, Thun M. Relation between geographic variability in kidney stones prevalence and risk factors for stones. Am J Epidemiol. 1996;143(5):487-95.
- Brikowski TH, Lotan Y, Pearle MS. Climate-related increase in the prevalence of urolithiasis in the United States. Proc Natl Acad Sci U S A. 2008;105(28):9841-6.
- 7. Pearle MS, Calhoun EA, Curhan GC. Urologic diseases in America project: urolithiasis. J Urol. 2005;173(3):848-57.
- Antonelli JA, Maalouf NM, Pearle MS, Lotan Y. Use of the National Health and Nutrition Examination Survey to calculate the impact of obesity and diabetes on cost and prevalence of urolithiasis in 2030. Eur Urol. 2014;66(4):724-9.
- Rule AD, Lieske JC, Li X, Melton LJ, 3rd, Krambeck AE, Bergstralh EJ. The ROKS nomogram for predicting a second symptomatic stone episode. J Am Soc Nephrol. 2014;25(12):2878-86.
- Vaughan LE, Enders FT, Lieske JC, Pais VM, Rivera ME, Mehta RA, et al. Predictors of Symptomatic Kidney Stone Recurrence After the First and Subsequent Episodes. Mayo Clin Proc. 2019;94(2):202-10.
- Yongzhi L, Shi Y, Jia L, Yili L, Xingwang Z, Xue G. Risk factors for urinary tract infection in patients with urolithiasisprimary report of a single center cohort. BMC Urol. 2018;18(1):45.
- Lotan Y, Daudon M, Bruyere F, Talaska G, Strippoli G, Johnson RJ, et al. Impact of fluid intake in the prevention of urinary system diseases: a brief review. Curr Opin Nephrol Hypertens. 2013;22 Suppl 1:S1-10.
- Rocha H, Santos LC. Relapse of urinary tract infection in the presence of urinary tract calculi: the role of bacteria within the calculi. J Med Microbiol. 1969;2(3):372-6.
- Barr-Beare E, Saxena V, Hilt EE, Thomas-White K, Schober M, Li B, et al. The Interaction between Enterobacteriaceae and Calcium Oxalate Deposits. PLoS One. 2015;10(10):e0139575.
- Agarwal DK, Krambeck AE, Sharma V, Maldonado FJ, Westerman ME, Knoedler JJ, et al. Treatment of nonobstructive, non-struvite urolithiasis is effective in treatment of recurrent urinary tract infections. World J Urol. 2019.
- 16. Keddis MT, Rule AD. Nephrolithiasis and loss of kidney function. Curr Opin Nephrol Hypertens. 2013;22(4):390-6.

- Dhondup T, Kittanamongkolchai W, Vaughan LE, Mehta RA, Chhina JK, Enders FT, et al. Risk of ESRD and Mortality in Kidney and Bladder Stone Formers. Am J Kidney Dis. 2018;72(6):790-7.
- 18. Semins MJ, Matlaga BR. Kidney stones during pregnancy. Nat Rev Urol. 2014;11(3):163-8.
- Swartz MA, Lydon-Rochelle MT, Simon D, Wright JL, Porter MP. Admission for nephrolithiasis in pregnancy and risk of adverse birth outcomes. Obstet Gynecol. 2007;109(5):1099-104.
- 20. Ross AE, Handa S, Lingeman JE, Matlaga BR. Kidney stones during pregnancy: an investigation into stone composition. Urol Res. 2008;36(2):99-102.
- Sakhaee K, Maalouf NM, Kumar R, Pasch A, Moe OW. Nephrolithiasis-associated bone disease: pathogenesis and treatment options. Kidney Int. 2011;79(4):393-403.
- Sakhaee K. Nephrolithiasis as a systemic disorder. Curr Opin Nephrol Hypertens. 2008;17(3):304-9.
- Devarajan A. Cross-talk between renal lithogenesis and atherosclerosis: an unveiled link between kidney stone formation and cardiovascular diseases. Clin Sci (Lond). 2018;132(6):615-26.
- 24. Oxalate contents of foods 2017 [Available from: https://regepi.bwh.harvard.edu/health/Oxalate/files.
- 25. Daudon M, Frochot V, Bazin D, Jungers P. Drug-Induced Kidney Stones and Crystalline Nephropathy: Pathophysiology, Prevention and Treatment. Drugs. 2018;78(2):163-201.
- 26. Matlaga BR, Shah OD, Assimos DG. Drug-induced urinary calculi. Rev Urol. 2003;5(4):227-31.
- Pearle MS, Goldfarb DS, Assimos DG, Curhan G, Denu-Ciocca CJ, Matlaga BR, et al. Medical management of kidney stones: AUA guideline. J Urol. 2014;192(2):316-24.
- Turk C, Petrik A, Sarica K, Seitz C, Skolarikos A, Straub M, et al. EAU Guidelines on Diagnosis and Conservative Management of Urolithiasis. Eur Urol. 2016;69(3):468-74.
- Dion M, Ankawi G, Chew B, Paterson R, Sultan N, Hoddinott P, et al. CUA guideline on the evaluation and medical management of the kidney stone patient - 2016 update. Can Urol Assoc J. 2016;10(11-12):E347-E58.
- Healy KA, Hubosky SG, Bagley DH. 24-hour urine collection in the metabolic evaluation of stone formers: is one study adequate? J Endourol. 2013;27(3):374-8.
- Nayan M, Elkoushy MA, Andonian S. Variations between two 24-hour urine collections in patients presenting to a tertiary stone clinic. Can Urol Assoc J. 2012;6(1):30-3.
- Pak CY, Peterson R, Poindexter JR. Adequacy of a single stone risk analysis in the medical evaluation of urolithiasis. J Urol. 2001;165(2):378-81.
- Parks JH, Goldfisher E, Asplin JR, Coe FL. A single 24hour urine collection is inadequate for the medical evaluation of nephrolithiasis. J Urol. 2002;167(4):1607-12.

- Castle SM, Cooperberg MR, Sadetsky N, Eisner BH, Stoller ML. Adequacy of a single 24-hour urine collection for metabolic evaluation of recurrent nephrolithiasis. J Urol. 2010;184(2):579-83.
- Werness PG, Brown CM, Smith LH, Finlayson B. EQUIL2: a BASIC computer program for the calculation of urinary saturation. The Journal of urology. 1985;134(6):1242-4.
- Parks JH, Coward M, Coe FL. Correspondence between stone composition and urine supersaturation in nephrolithiasis. Kidney Int. 1997;51(3):894-900.
- Prochaska M, Taylor E, Ferraro PM, Curhan G. Relative Supersaturation of 24-Hour Urine and Likelihood of Kidney Stones. J Urol. 2018;199(5):1262-6.
- Assimos D, Krambeck A, Miller NL, Monga M, Murad MH, Nelson CP, et al. Surgical Management of Stones: American Urological Association/Endourological Society Guideline, PART II. J Urol. 2016;196(4):1161-9.
- Pak CY, Poindexter JR, Adams-Huet B, Pearle MS. Predictive value of kidney stone composition in the detection of metabolic abnormalities. Am J Med. 2003;115(1):26-32.
- Lee TT, Elkoushy MA, Andonian S. Are stone analysis results different with repeated sampling? Can Urol Assoc J. 2014;8(5-6):E317-22.
- Mandel N, Mandel I, Fryjoff K, Rejniak T, Mandel G. Conversion of calcium oxalate to calcium phosphate with recurrent stone episodes. The Journal of urology. 2003;169(6):2026-9.
- Kadlec AO, Fridirici ZC, Acosta-Miranda AM, Will TH, Sakamoto K, Turk TM. Bilateral urinary calculi with discordant stone composition. World J Urol. 2014;32(1):281-5.
- Rivera ME, Nottingham CU, Borofsky MS, Kissel SM, Maniar V, Dauw CA, et al. Variability in stone composition and metabolic correlation between kidneys in patients with bilateral nephrolithiasis. Int Urol Nephrol. 2019.
- 44. Hesse A, Kruse R, Geilenkeuser WJ, Schmidt M. Quality control in urinary stone analysis: results of 44 ring trials (1980-2001). Clin Chem Lab Med. 2005;43(3):298-303.
- 45. Basiri A, Taheri M, Taheri F. What is the state of the stone analysis techniques in urolithiasis? Urol J. 2012;9(2):445-54.
- 46. Mandel NS, Mandel IC, Kolbach-Mandel AM. Accurate stone analysis: the impact on disease diagnosis and treatment. Urolithiasis. 2017;45(1):3-9.
- Siener R, Buchholz N, Daudon M, Hess B, Knoll T, Osther PJ, et al. Quality Assessment of Urinary Stone Analysis: Results of a Multicenter Study of Laboratories in Europe. PLoS One. 2016;11(6):e0156606.
- Krambeck AE, Khan NF, Jackson ME, Lingeman JE, McAteer JA, Williams JC, Jr. Inaccurate reporting of mineral composition by commercial stone analysis

laboratories: implications for infection and metabolic stones. J Urol. 2010;184(4):1543-9.

- Poletti PA, Platon A, Rutschmann OT, Schmidlin FR, Iselin CE, Becker CD. Low-dose versus standard-dose CT protocol in patients with clinically suspected renal colic. AJR Am J Roentgenol. 2007;188(4):927-33.
- Wilhelm K, Schoenthaler M, Hein S, Adams F, Schlager D, Kuehhas FE, et al. Focused Dual-energy CT Maintains Diagnostic and Compositional Accuracy for Urolithiasis Using Ultralow-dose Noncontrast CT. Urology. 2015;86(6):1097-102.
- Smith-Bindman R, Aubin C, Bailitz J, Bengiamin RN, Camargo CA, Jr., Corbo J, et al. Ultrasonography versus computed tomography for suspected nephrolithiasis. N Engl J Med. 2014;371(12):1100-10.
- Hubner WA, Irby P, Stoller ML. Natural history and current concepts for the treatment of small ureteral calculi. Eur Urol. 1993;24(2):172-6.
- Miller OF, Kane CJ. Time to stone passage for observed ureteral calculi: a guide for patient education. J Urol. 1999;162(3 Pt 1):688-90; discussion 90-1.
- NICE Guideline Renal and ureteric stones: assessment and management: NICE (2019) Renal and ureteric stones: assessment and management. BJU Int. 2019;123(2):220-32.
- 55. Parmar MS. Kidney stones. BMJ. 2004;328(7453):1420-4.
- Segura JW, Preminger GM, Assimos DG, Dretler SP, Kahn RI, Lingeman JE, et al. Ureteral Stones Clinical Guidelines Panel summary report on the management of ureteral calculi. The American Urological Association. J Urol. 1997;158(5):1915-21.
- Afshar K, Jafari S, Marks AJ, Eftekhari A, MacNeily AE. Nonsteroidal anti-inflammatory drugs (NSAIDs) and nonopioids for acute renal colic. Cochrane Database Syst Rev. 2015(6):CD006027.
- Gottlieb M, Long B, Koyfman A. The evaluation and management of urolithiasis in the ED: A review of the literature. Am J Emerg Med. 2018;36(4):699-706.
- Minhaj FS, Hoang-Nguyen M, Tenney A, Bragg A, Zhang W, Foster J, et al. Evaluation of opioid requirements in the management of renal colic after guideline implementation in the emergency department. Am J Emerg Med. 2019.
- Soleimanpour H, Hassanzadeh K, Vaezi H, Golzari SE, Esfanjani RM, Soleimanpour M. Effectiveness of intravenous lidocaine versus intravenous morphine for patients with renal colic in the emergency department. BMC Urol. 2012;12:13.
- 61. Sterrett SP, Nakada SY. Medical expulsive therapy. Curr Opin Urol. 2008;18(2):210-3.
- 62. Campschroer T, Zhu X, Vernooij RW, Lock MT. Alphablockers as medical expulsive therapy for ureteral stones. Cochrane Database Syst Rev. 2018;4:CD008509.

- Meltzer AC, Burrows PK, Wolfson AB, Hollander JE, Kurz M, Kirkali Z, et al. Effect of Tamsulosin on Passage of Symptomatic Ureteral Stones: A Randomized Clinical Trial. JAMA Intern Med. 2018;178(8):1051-7.
- 64. Ziemba JB, Matlaga BR. Guideline of guidelines: kidney stones. BJU Int. 2015;116(2):184-9.
- Pak CY, Sakhaee K, Crowther C, Brinkley L. Evidence justifying a high fluid intake in treatment of nephrolithiasis. Ann Intern Med. 1980;93(1):36-9.
- Borghi L, Meschi T, Maggiore U, Prati B. Dietary therapy in idiopathic nephrolithiasis. Nutr Rev. 2006;64(7 Pt 1):301-12.
- Borghi L, Meschi T, Amato F, Briganti A, Novarini A, Giannini A. Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: a 5-year randomized prospective study. J Urol. 1996;155(3):839-43.
- Littlejohns TJ, Neal NL, Bradbury KE, Heers H, Allen NE, Turney BW. Fluid Intake and Dietary Factors and the Risk of Incident Kidney Stones in UK Biobank: A Populationbased Prospective Cohort Study. Eur Urol Focus. 2019.
- Curhan GC, Willett WC, Rimm EB, Stampfer MJ. A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. N Engl J Med. 1993;328(12):833-8.
- Curhan GC, Willett WC, Rimm EB, Spiegelman D, Stampfer MJ. Prospective study of beverage use and the risk of kidney stones. Am J Epidemiol. 1996;143(3):240-7.
- Kang DE, Sur RL, Haleblian GE, Fitzsimons NJ, Borawski KM, Preminger GM. Long-term lemonade based dietary manipulation in patients with hypocitraturic nephrolithiasis. J Urol. 2007;177(4):1358-62; discussion 62; quiz 591.
- 72. Wabner CL, Pak CY. Effect of orange juice consumption on urinary stone risk factors. J Urol. 1993;149(6):1405-8.
- Sorensen MD, Kahn AJ, Reiner AP, Tseng TY, Shikany JM, Wallace RB, et al. Impact of nutritional factors on incident kidney stone formation: a report from the WHI OS. J Urol. 2012;187(5):1645-9.
- Sakhaee K, Harvey JA, Padalino PK, Whitson P, Pak CY. The potential role of salt abuse on the risk for kidney stone formation. J Urol. 1993;150(2 Pt 1):310-2.
- Worcester EM, Coe FL. New insights into the pathogenesis of idiopathic hypercalciuria. Semin Nephrol. 2008;28(2):120-32.
- 76. Nouvenne A, Meschi T, Prati B, Guerra A, Allegri F, Vezzoli G, et al. Effects of a low-salt diet on idiopathic hypercalciuria in calcium-oxalate stone formers: a 3-mo randomized controlled trial. Am J Clin Nutr. 2010;91(3):565-70.
- Borghi L, Schianchi T, Meschi T, Guerra A, Allegri F, Maggiore U, et al. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. N Engl J Med. 2002;346(2):77-84.

- Robertson WG, Peacock M, Marshall DH. Prevalence of urinary stone disease in vegetarians. Eur Urol. 1982;8(6):334-9.
- Breslau NA, Brinkley L, Hill KD, Pak CY. Relationship of animal protein-rich diet to kidney stone formation and calcium metabolism. J Clin Endocrinol Metab. 1988;66(1):140-6.
- Kerstetter JE, O'Brien KO, Insogna KL. Low protein intake: the impact on calcium and bone homeostasis in humans. J Nutr. 2003;133(3):855S-61S.
- Maalouf NM, Moe OW, Adams-Huet B, Sakhaee K. Hypercalciuria associated with high dietary protein intake is not due to acid load. J Clin Endocrinol Metab. 2011;96(12):3733-40.
- Monsen ER. The 10th edition of the Recommended Dietary Allowances: what's new in the 1989 RDAs? J Am Diet Assoc. 1989;89(12):1748-52.
- Bleich HL, Moore MJ, Lemann J, Jr., Adams ND, Gray RW. Urinary calcium excretion in human beings. N Engl J Med. 1979;301(10):535-41.
- Taylor EN, Stampfer MJ, Curhan GC. Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. J Am Soc Nephrol. 2004;15(12):3225-32.
- von Unruh GE, Voss S, Sauerbruch T, Hesse A. Dependence of oxalate absorption on the daily calcium intake. J Am Soc Nephrol. 2004;15(6):1567-73.
- Zarembski PM, Hodgkinson A. Some factors influencing the urinary excretion of oxalic acid in man. Clin Chim Acta. 1969;25(1):1-10.
- Sorensen MD, Hsi RS, Chi T, Shara N, Wactawski-Wende J, Kahn AJ, et al. Dietary intake of fiber, fruit and vegetables decreases the risk of incident kidney stones in women: a Women's Health Initiative report. J Urol. 2014;192(6):1694-9.
- Meschi T, Maggiore U, Fiaccadori E, Schianchi T, Bosi S, Adorni G, et al. The effect of fruits and vegetables on urinary stone risk factors. Kidney Int. 2004;66(6):2402-10.
- 89. Maalouf N. Approach to the Adult Kidney Stone Former. Clin Rev Bone Miner Metab. 2012;10(1):38-49.
- Bird VY, Khan SR. How do stones form? Is unification of theories on stone formation possible? Arch Esp Urol. 2017;70(1):12-27.
- 91. Bushinsky DA. Nephrolithiasis: site of the initial solid phase. J Clin Invest. 2003;111(5):602-5.
- Evan AP. Physiopathology and etiology of stone formation in the kidney and the urinary tract. Pediatr Nephrol. 2010;25(5):831-41.
- Evan AP, Lingeman JE, Coe FL, Parks JH, Bledsoe SB, Shao Y, et al. Randall's plaque of patients with nephrolithiasis begins in basement membranes of thin loops of Henle. J Clin Invest. 2003;111(5):607-16.

- Linnes MP, Krambeck AE, Cornell L, Williams JC, Jr., Korinek M, Bergstralh EJ, et al. Phenotypic characterization of kidney stone formers by endoscopic and histological quantification of intrarenal calcification. Kidney Int. 2013;84(4):818-25.
- 95. Worcester EM, Coe FL. Clinical practice. Calcium kidney stones. N Engl J Med. 2010;363(10):954-63.
- Sakhaee K, Maalouf NM, Sinnott B. Clinical review. Kidney stones 2012: pathogenesis, diagnosis, and management. J Clin Endocrinol Metab. 2012;97(6):1847-60.
- Parvin M, Shakhssalim N, Basiri A, Miladipour AH, Golestan B, Mohammadi Torbati P, et al. The most important metabolic risk factors in recurrent urinary stone formers. Urol J. 2011;8(2):99-106.
- Coe FL, Worcester EM, Evan AP. Idiopathic hypercalciuria and formation of calcium renal stones. Nat Rev Nephrol. 2016;12(9):519-33.
- 99. Coe FL, Parks JH, Moore ES. Familial idiopathic hypercalciuria. N Engl J Med. 1979;300(7):337-40.
- 100. Pak CY, Oata M, Lawrence EC, Snyder W. The hypercalciurias. Causes, parathyroid functions, and diagnostic criteria. J Clin Invest. 1974;54(2):387-400.
- Insogna KL, Broadus AE, Dreyer BE, Ellison AF, Gertner JM. Elevated production rate of 1,25-dihydroxyvitamin D in patients with absorptive hypercalciuria. J Clin Endocrinol Metab. 1985;61(3):490-5.
- 102. D.E. Barilla JEZ, C.Y.C. Pak A critical evaluation of the role of phosphate in the pathogenesis of absorptive hypercalciuria. Mineral and Electrolyte Metabolism. 1979;2(6):302-9.
- 103. Van Den Berg CJ, Kumar R, Wilson DM, Heath H, 3rd, Smith LH. Orthophosphate therapy decreases urinary calcium excretion and serum 1,25-dihydroxyvitamin D concentrations in idiopathic hypercalciuria. J Clin Endocrinol Metab. 1980;51(5):998-1001.
- Dhayat NA, Luthi D, Schneider L, Mattmann C, Vogt B, Fuster DG. Distinct phenotype of kidney stone formers with renal phosphate leak. Nephrol Dial Transplant. 2019;34(1):129-37.
- 105. Negri AL, Spivacow R, Del Valle E, Fradinger E, Marino A, Zanchetta JR. Renal phosphate leak in patients with idiopathic hypercalciuria and calcium nephrolithiasis. Urol Res. 2003;31(6):378-81.
- 106. Karnauskas AJ, van Leeuwen JP, van den Bemd GJ, Kathpalia PP, DeLuca HF, Bushinsky DA, et al. Mechanism and function of high vitamin D receptor levels in genetic hypercalciuric stone-forming rats. J Bone Miner Res. 2005;20(3):447-54.
- 107. Li XQ, Tembe V, Horwitz GM, Bushinsky DA, Favus MJ. Increased intestinal vitamin D receptor in genetic hypercalciuric rats. A cause of intestinal calcium hyperabsorption. J Clin Invest. 1993;91(2):661-7.

- Favus MJ, Karnauskas AJ, Parks JH, Coe FL. Peripheral blood monocyte vitamin D receptor levels are elevated in patients with idiopathic hypercalciuria. J Clin Endocrinol Metab. 2004;89(10):4937-43.
- Worcester EM, Gillen DL, Evan AP, Parks JH, Wright K, Trumbore L, et al. Evidence that postprandial reduction of renal calcium reabsorption mediates hypercalciuria of patients with calcium nephrolithiasis. Am J Physiol Renal Physiol. 2007;292(1):F66-75.
- 110. Sakhaee K, Nicar MJ, Brater DC, Pak CY. Exaggerated natriuretic and calciuric responses to hydrochlorothiazide in renal hypercalciuria but not in absorptive hypercalciuria. J Clin Endocrinol Metab. 1985;61(5):825-9.
- 111. Sutton RA, Walker VR. Responses to hydrochlorothiazide and acetazolamide in patients with calcium stones. Evidence suggesting a defect in renal tubular function. N Engl J Med. 1980;302(13):709-13.
- 112. Worcester EM, Coe FL, Evan AP, Bergsland KJ, Parks JH, Willis LR, et al. Evidence for increased postprandial distal nephron calcium delivery in hypercalciuric stone-forming patients. Am J Physiol Renal Physiol. 2008;295(5):F1286-94.
- 113. Zerwekh JE. Bone disease and idiopathic hypercalciuria. Semin Nephrol. 2008;28(2):133-42.
- 114. Melton LJ, 3rd, Crowson CS, Khosla S, Wilson DM, O'Fallon WM. Fracture risk among patients with urolithiasis: a population-based cohort study. Kidney Int. 1998;53(2):459-64.
- 115. Lauderdale DS, Thisted RA, Wen M, Favus MJ. Bone mineral density and fracture among prevalent kidney stone cases in the Third National Health and Nutrition Examination Survey. J Bone Miner Res. 2001;16(10):1893-8.
- 116. Fuss M, Pepersack T, Bergman P, Hurard T, Simon J, Corvilain J. Low calcium diet in idiopathic urolithiasis: a risk factor for osteopenia as great as in primary hyperparathyroidism. Br J Urol. 1990;65(6):560-3.
- Hess B. Low calcium diet in hypercalciuric calcium nephrolithiasis: first do no harm. Scanning Microsc. 1996;10(2):547-54; discussion 54-6.
- 118. Frings-Meuthen P, Baecker N, Heer M. Low-grade metabolic acidosis may be the cause of sodium chlorideinduced exaggerated bone resorption. J Bone Miner Res. 2008;23(4):517-24.
- Gomes SA, dos Reis LM, Noronha IL, Jorgetti V, Heilberg IP. RANKL is a mediator of bone resorption in idiopathic hypercalciuria. Clin J Am Soc Nephrol. 2008;3(5):1446-52.
- 120. Zuckerman JM, Assimos DG. Hypocitraturia: pathophysiology and medical management. Rev Urol. 2009;11(3):134-44.
- 121. Sakhaee K. Recent advances in the pathophysiology of nephrolithiasis. Kidney Int. 2009;75(6):585-95.

- Fargue S, Milliner DS, Knight J, Olson JB, Lowther WT, Holmes RP. Hydroxyproline Metabolism and Oxalate Synthesis in Primary Hyperoxaluria. J Am Soc Nephrol. 2018;29(6):1615-23.
- 123. Cochat P, Rumsby G. Primary hyperoxaluria. N Engl J Med. 2013;369(7):649-58.
- 124. Riedel TJ, Knight J, Murray MS, Milliner DS, Holmes RP, Lowther WT. 4-Hydroxy-2-oxoglutarate aldolase inactivity in primary hyperoxaluria type 3 and glyoxylate reductase inhibition. Biochim Biophys Acta. 2012;1822(10):1544-52.
- 125. Hoppe B. An update on primary hyperoxaluria. Nat Rev Nephrol. 2012;8(8):467-75.
- 126. Mitchell T, Kumar P, Reddy T, Wood KD, Knight J, Assimos DG, et al. Dietary oxalate and kidney stone formation. Am J Physiol Renal Physiol. 2019;316(3):F409-F13.
- 127. Attalla K, De S, Monga M. Oxalate content of food: a tangled web. Urology. 2014;84(3):555-60.
- 128. Baxmann AC, De OGMC, Heilberg IP. Effect of vitamin C supplements on urinary oxalate and pH in calcium stone-forming patients. Kidney Int. 2003;63(3):1066-71.
- Traxer O, Huet B, Poindexter J, Pak CY, Pearle MS. Effect of ascorbic acid consumption on urinary stone risk factors. J Urol. 2003;170(2 Pt 1):397-401.
- Kaufman DW, Kelly JP, Curhan GC, Anderson TE, Dretler SP, Preminger GM, et al. Oxalobacter formigenes may reduce the risk of calcium oxalate kidney stones. J Am Soc Nephrol. 2008;19(6):1197-203.
- Siener R, Bangen U, Sidhu H, Honow R, von Unruh G, Hesse A. The role of Oxalobacter formigenes colonization in calcium oxalate stone disease. Kidney Int. 2013;83(6):1144-9.
- Kelly JP, Curhan GC, Cave DR, Anderson TE, Kaufman DW. Factors related to colonization with Oxalobacter formigenes in U.S. adults. J Endourol. 2011;25(4):673-9.
- Tasian GE, Jemielita T, Goldfarb DS, Copelovitch L, Gerber JS, Wu Q, et al. Oral Antibiotic Exposure and Kidney Stone Disease. J Am Soc Nephrol. 2018;29(6):1731-40.
- Kumar R, Ghoshal UC, Singh G, Mittal RD. Infrequency of colonization with Oxalobacter formigenes in inflammatory bowel disease: possible role in renal stone formation. J Gastroenterol Hepatol. 2004;19(12):1403-9.
- 135. Sidhu H, Hoppe B, Hesse A, Tenbrock K, Bromme S, Rietschel E, et al. Absence of Oxalobacter formigenes in cystic fibrosis patients: a risk factor for hyperoxaluria. Lancet. 1998;352(9133):1026-9.
- Wiederkehr MR, Moe OW. Uric Acid Nephrolithiasis: A Systemic Metabolic Disorder. Clin Rev Bone Miner Metab. 2011;9(3-4):207-17.
- Coe FL, Lawton RL, Goldstein RB, Tembe V. Sodium urate accelerates precipitation of calcium oxalate in vitro. Proc Soc Exp Biol Med. 1975;149(4):926-9.

- Pak CY, Arnold LH. Heterogeneous nucleation of calcium oxalate by seeds of monosodium urate. Proc Soc Exp Biol Med. 1975;149(4):930-2.
- 139. Zerwekh JE, Holt K, Pak CY. Natural urinary macromolecular inhibitors: attenuation of inhibitory activity by urate salts. Kidney Int. 1983;23(6):838-41.
- Grover PK, Marshall VR, Ryall RL. Dissolved urate salts out calcium oxalate in undiluted human urine in vitro: implications for calcium oxalate stone genesis. Chem Biol. 2003;10(3):271-8.
- 141. Nijenhuis T, Vallon V, van der Kemp AW, Loffing J, Hoenderop JG, Bindels RJ. Enhanced passive Ca2+ reabsorption and reduced Mg2+ channel abundance explains thiazide-induced hypocalciuria and hypomagnesemia. J Clin Invest. 2005;115(6):1651-8.
- 142. Jang HR, Kim S, Heo NJ, Lee JH, Kim HS, Nielsen S, et al. Effects of thiazide on the expression of TRPV5, calbindin-D28K, and sodium transporters in hypercalciuric rats. J Korean Med Sci. 2009;24 Suppl:S161-9.
- Lee CT, Shang S, Lai LW, Yong KC, Lien YH. Effect of thiazide on renal gene expression of apical calcium channels and calbindins. Am J Physiol Renal Physiol. 2004;287(6):F1164-70.
- 144. Martins MC, Meyers AM, Whalley NA, Margolius LP, Buys ME. Indapamide (Natrilix): the agent of choice in the treatment of recurrent renal calculi associated with idiopathic hypercalciuria. Br J Urol. 1996;78(2):176-80.
- Reilly RF, Peixoto AJ, Desir GV. The evidence-based use of thiazide diuretics in hypertension and nephrolithiasis. Clin J Am Soc Nephrol. 2010;5(10):1893-903.
- 146. Goldfarb DS. Empiric therapy for kidney stones. Urolithiasis. 2019;47(1):107-13.
- 147. Alexander RT, McArthur E, Jandoc R, Welk B, Fuster DG, Garg AX, et al. Thiazide Diuretic Dose and Risk of Kidney Stones in Older Adults: A Retrospective Cohort Study. Can J Kidney Health Dis. 2018;5:2054358118787480.
- 148. Dvorak MM, De Joussineau C, Carter DH, Pisitkun T, Knepper MA, Gamba G, et al. Thiazide diuretics directly induce osteoblast differentiation and mineralized nodule formation by interacting with a sodium chloride cotransporter in bone. J Am Soc Nephrol. 2007;18(9):2509-16.
- 149. Bolland MJ, Ames RW, Horne AM, Orr-Walker BJ, Gamble GD, Reid IR. The effect of treatment with a thiazide diuretic for 4 years on bone density in normal postmenopausal women. Osteoporos Int. 2007;18(4):479-86.
- Reid IR, Ames RW, Orr-Walker BJ, Clearwater JM, Horne AM, Evans MC, et al. Hydrochlorothiazide reduces loss of cortical bone in normal postmenopausal women: a randomized controlled trial. Am J Med. 2000;109(5):362-70.
- 151. Giusti A, Barone A, Pioli G, Girasole G, Siccardi V, Palummeri E, et al. Alendronate and indapamide alone or

in combination in the management of hypercalciuria associated with osteoporosis: a randomized controlled trial of two drugs and three treatments. Nephrol Dial Transplant. 2009;24(5):1472-7.

- Aung K, Htay T. Thiazide diuretics and the risk of hip fracture. Cochrane Database Syst Rev. 2011(10):CD005185.
- 153. Puttnam R, Davis BR, Pressel SL, Whelton PK, Cushman WC, Louis GT, et al. Association of 3 Different Antihypertensive Medications With Hip and Pelvic Fracture Risk in Older Adults: Secondary Analysis of a Randomized Clinical Trial. JAMA Intern Med. 2017;177(1):67-76.
- 154. Nicar MJ, Peterson R, Pak CY. Use of potassium citrate as potassium supplement during thiazide therapy of calcium nephrolithiasis. The Journal of urology. 1984;131(3):430-3.
- Sakhaee K, Nicar M, Hill K, Pak CY. Contrasting effects of potassium citrate and sodium citrate therapies on urinary chemistries and crystallization of stone-forming salts. Kidney Int. 1983;24(3):348-52.
- 156. Barcelo P, Wuhl O, Servitge E, Rousaud A, Pak CY. Randomized double-blind study of potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. J Urol. 1993;150(6):1761-4.
- 157. Ettinger B, Pak CY, Citron JT, Thomas C, Adams-Huet B, Vangessel A. Potassium-magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. J Urol. 1997;158(6):2069-73.
- 158. Soygur T, Akbay A, Kupeli S. Effect of potassium citrate therapy on stone recurrence and residual fragments after shockwave lithotripsy in lower caliceal calcium oxalate urolithiasis: a randomized controlled trial. J Endourol. 2002;16(3):149-52.
- 159. Pak CY, Peterson RD, Poindexter J. Prevention of spinal bone loss by potassium citrate in cases of calcium urolithiasis. J Urol. 2002;168(1):31-4.
- 160. Jehle S, Hulter HN, Krapf R. Effect of potassium citrate on bone density, microarchitecture, and fracture risk in healthy older adults without osteoporosis: a randomized controlled trial. J Clin Endocrinol Metab. 2013;98(1):207-17.
- Moseley KF, Weaver CM, Appel L, Sebastian A, Sellmeyer DE. Potassium citrate supplementation results in sustained improvement in calcium balance in older men and women. J Bone Miner Res. 2013;28(3):497-504.
- Ettinger B, Tang A, Citron JT, Livermore B, Williams T. Randomized trial of allopurinol in the prevention of calcium oxalate calculi. N Engl J Med. 1986;315(22):1386-9.
- 163. Goldfarb DS, MacDonald PA, Gunawardhana L, Chefo S, McLean L. Randomized controlled trial of febuxostat versus allopurinol or placebo in individuals with higher urinary uric acid excretion and calcium stones. Clin J Am Soc Nephrol. 2013;8(11):1960-7.
- 164. Sakhaee K, Maalouf NM. Metabolic syndrome and uric acid nephrolithiasis. Semin Nephrol. 2008;28(2):174-80.

- 165. Xu LHR, Adams-Huet B, Poindexter JR, Maalouf NM, Moe OW, Sakhaee K. Temporal Changes in Kidney Stone Composition and in Risk Factors Predisposing to Stone Formation. J Urol. 2017;197(6):1465-71.
- 166. Daudon M, Traxer O, Conort P, Lacour B, Jungers P. Type 2 diabetes increases the risk for uric acid stones. Journal of the American Society of Nephrology : JASN. 2006;17(7):2026-33.
- Tran TVMM, N.M. Uric Acid Stone Disease: Lessons from Recent Human Physiologic Studies. Curr Opin Nephrol Hypertens. 2020;29(4):in press.
- Maalouf NM, Sakhaee K, Parks JH, Coe FL, Adams-Huet B, Pak CY. Association of urinary pH with body weight in nephrolithiasis. Kidney Int. 2004;65(4):1422-5.
- 169. Bobulescu IA, Park SK, Xu LHR, Blanco F, Poindexter J, Adams-Huet B, et al. Net Acid Excretion and Urinary Organic Anions in Idiopathic Uric Acid Nephrolithiasis. Clin J Am Soc Nephrol. 2019;14(3):411-20.
- 170. Gridley CM, Sourial MW, Lehman A, Knudsen BE. Medical dissolution therapy for the treatment of uric acid nephrolithiasis. World J Urol. 2019.
- 171. Canales BK, Sharma N, Yuzhakov SV, Bozorgmehri S, Otto BJ, Bird VG. Long-term Recurrence Rates in Uric Acid Stone Formers With or Without Medical Management. Urology. 2019;131:46-52.
- 172. Maalouf NM, Poindexter JR, Adams-Huet B, Moe OW, Sakhaee K. Increased production and reduced urinary buffering of acid in uric acid stone formers is ameliorated by pioglitazone. Kidney Int. 2019;95(5):1262-8.
- 173. Sakhaee K. Pathogenesis and medical management of cystinuria. Semin Nephrol. 1996;16(5):435-47.
- 174. Andreassen KH, Pedersen KV, Osther SS, Jung HU, Lildal SK, Osther PJ. How should patients with cystine stone disease be evaluated and treated in the twenty-first century? Urolithiasis. 2016;44(1):65-76.
- 175. Rodman JS, Blackburn P, Williams JJ, Brown A, Pospischil MA, Peterson CM. The effect of dietary protein on cystine excretion in patients with cystinuria. Clin Nephrol. 1984;22(6):273-8.
- Jaeger P, Portmann L, Saunders A, Rosenberg LE, Thier SO. Anticystinuric effects of glutamine and of dietary sodium restriction. N Engl J Med. 1986;315(18):1120-3.
- 177. Fjellstedt E, Denneberg T, Jeppsson JO, Tiselius HG. A comparison of the effects of potassium citrate and sodium bicarbonate in the alkalinization of urine in homozygous cystinuria. Urol Res. 2001;29(5):295-302.
- 178. Preminger GM, Assimos DG, Lingeman JE, Nakada SY, Pearle MS, Wolf JS, Jr. Chapter 1: AUA guideline on management of staghorn calculi: diagnosis and treatment recommendations. J Urol. 2005;173(6):1991-2000.
- 179. Iqbal MW, Youssef RF, Neisius A, Kuntz N, Hanna J, Ferrandino MN, et al. Contemporary Management of Struvite Stones Using Combined Endourologic and

Medical Treatment: Predictors of Unfavorable Clinical Outcome. J Endourol. 2016;30(7):771-7.

 Silverman DE, Stamey TA. Management of infection stones: the Stanford experience. Medicine (Baltimore). 1983;62(1):44-51.