REVIEW ARTICLE

# Nephrolithiasis

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Nephrolithiasis is a common, costly, condition that occurs most frequently in Caucasian adult males but can be seen in all ages and demographics.[1] Nephrolithiasis often reoccur without proper management and are associated with the development of systemic disorders such as coronary artery disease, diabetes and chronic kidney disease.[2,3] This article serves to review common pathophysiology of stone formation, clinical presentation, work-up and management. Patients must be educated about their condition and encouraged to implement preventative measures such as adequate intake of fluids and regular physician visits.[4] These practices increase awareness and understanding of the disease while decreasing recurrence rate, risk of complication and cost of care.[5]

## INTRODUCTION

Nephrolithiasis and renal or kidney stones are interchangeable terms for a common affliction affecting humans for ages. It can be seen across all age ranges, but tends to have a peak incidence in males aged 20-30.[1] The treatment of nephrolithiasis has an annual expenditure of over $5 billion with a reoccurrence rate of nearly 50% in a ten-year period if not properly managed.[2] However, despite an incidence of 3-5% and association with significant cost, morbidity and impact on quality of life, significant research on stone disease has largely been ignored.[1] A more efficient approach to treating this disorder has the potential to reduce cost and reoccurrence.

## METHODS

The National Center for Biotechnology Information PubMed database was used as the primary source of references used to complete this review. Keywords and phrases searched include nephrolithiasis, nephrolithiasis management review, kidney stones, kidney stone management, OMM nephrolithiasis, medical expulsive therapy, Medscape, Google, and OVID journal database were also used to access reference information. Material published in 2001 or later was included in the compilation of this review.

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## EPIDEMIOLOGY

The incidence of nephrolithiasis has been on the rise in several areas of the world, doubling over the past three decades.[6] Studies in areas such as the United States, Southeast Asia, Australia and many parts of Europe have attributed this dramatic rise in nephrolithiasis disease to factors such as gender, ethnicity, geography, fluid intake, diet, obesity, bowel disease and an increasing prevalence with higher socioeconomic classification. It has been seen that the lower the economic status, the lower the likelihood of renal stones. Stone disease primarily affects young white males.[1] In many medical circles, nephrolithiasis has become recognized as a systemic disorder that is associated with an increased risk of developing common systemic diseases such as coronary artery disease, diabetes and chronic kidney disease.[3]

## PATHOGENESIS AND RISK FACTORS

Calcium based calculi represent 80% of all kidney stones. The most common calcium stones are calcium oxalate.[1] Calcium oxalate stones tend to grow from an interstitial mineral plaque (Randall's plaque) on the renal papillary surface while calcium phosphate stones tend to form from apatite crystal formation in the inner medullary collecting duct.[6,4] Intracellular nanobacteria are also thought to play a role in stone formation as they are present in 97% of nephrolithiasis and in Randall's plaques.[4] Low urinary volume increases the risk of forming renal calculi by increasing the likelihood of crystal formation.[1] Stone development is also significantly contributed to by endogenous conditions and factors discussed below.

Calcium stones can develop a number of different ways. The most frequently occurring contributing factor in calcium stone formers is hypercalciuria which is defined as calcium excretion greater than 200-250 milligrams in 24 hours.[1,6] Hypercalciuria is found in 30-60% of adults with

**Table 1: Conditions contributing to calcium renal stones**

| Hypercalciuria | Hyperuricosuria | Hypocitruria | Hyperoxaluria | Urinary pH |
|---|---|---|---|---|
| Increased intestinal calcium absorption | High purine diet | Metabolic acidosis | Increased intestinal oxalate absorption | pH<5.5 |
| Decreased renal calcium reabsorption | | Distal renal tubular acidosis | Increased oxalate in diet | pH>6.7 |
| Increased bone resorption | | Thiazides causing hypokalemia | Increased oxalate production | |
| Increase in 1, 25 (OH)2 concentration | | Carbonic anhydrase inhibitors | | |
| | | Increase in protein or salt consumption | | |

nephrolithiasis. Hypercalciuria is most commonly caused by increased intestinal calcium absorption in renal stone formers. Calcium stones can also occur as a result of increased bone resorption, most commonly by primary hyperparathyroidism, among other processes. Additional contributing factors to calcium stone formation include hypocitruria, hyperoxaluria and hyperuricosuria which can be caused by low extracellular fluid pH, intestinal hyperabsorption of oxalate and a purine-rich diet, respectively (Table 1). Hyperoxaluria caused by increased intestinal absorption of oxalate is common clinically in the form of intestinal malabsorptive disorders. 10-50% of calcium stone formers have detectable hyperoxaluria. Acidic urine precipitates uric acid formation which facilitates calcium oxalate crystal formation. Alkaline urine ultimately contributes to a buildup of hydroxyapatite. Patients with first degree relatives and family members with a history of renal calculi are also at an increased risk of developing calcium stones.[6]

After calcium oxalate stones, comprising approximately 56-61% of renal calculi, calcium phosphate stones, 8-18%, are the next most common. Uric acid stones have an incidence of 9-17% while struvite or magnesium ammonium phosphate stones constitute 10-20% of nephrolithiasis. Cysteine stones have an approximate incidence of 1%.[3] Uric acid stones are prone to form in patients with low urine volume, hyperuricosuria and acidic urine.[6] Struvite stones are more likely to form in those with urease producing bacterial urinary infections such as those caused by the Serratia and Klebsiella species.[1,4]

## CLINICAL PRESENTATION

The presentation of acute nephrolithiasis has many classic symptoms. Typically, individuals complain of cramping and intermittent bouts of abdominal and flank pain, or renal colic, that worsens as pressure and ureteral smooth muscle spasm are precipitated by stone obstruction.[3,5] Gross or microscopic hematuria, nausea and vomiting not associated with an acute abdomen or peritonitis are symptoms that most likely indicate nephrolithiasis caused by an acute ureteral or renal pelvic obstruction from a calculus.[5] Patients with chronic nephrolithiasis can be asymptomatic or present with recurring symptoms as noted above.

## HISTORY AND PHYSICAL EXAM

To properly diagnose a patient with nephrolithiasis, systemic, environmental influences and prior history must be carefully identified.

Determining the location and characteristic of pain will help guide the practitioner as to the position of the stone in the urinary tract, degree of obstruction, presence of ureteral spasm and presence of any associated infection. The differential diagnosis can vary depending on the location of the pain. For example, a stone in the distal ureter can refer pain to the groin or genitals and be confused with prostatitis in men or pelvic inflammatory disease in women.

Pain attacks generally occur in three phases, tend to last between 2-4 hours and follow dermatomes T10 to S4.[7] The first phase begins acutely in the mornings, has a slow and insidious onset and will intermittently dissipate in 30-minute intervals. The second phase is constant pain that reaches maximum intensity. This pain will remain until successful treatment of the underlying disorder, or in some patients, will spontaneously resolve. The final phase of stone pain is the relief phase.[5] One of the most important considerations when examining an individual with expected nephrolithiasis is ruling out more serious conditions such as an acute abdomen.[7] Patients with conditions associated with peritonitis have fever, abdominal tenderness, guarding and rebound.[8] In patients with renal colic, the abdominal exam is usually unremarkable. Bowel sounds will be normal or slightly hypoactive, peritoneal signs will be absent and unlike patients with an acute abdomen, patients with nephrolithiasis tend to move constantly trying to find a comfortable position.[5]

Special attention should be given to the osteopathic portion of the exam. Checking for tissue texture changes in the thoracic region, a positive Lloyd sign, or the presence of both anterior and posterior Chapman's points can give important clues in the diagnosis of renal stone disease. Anterior Chapman's points for the kidney and bladder are located just supralateral to the umbilicus and over the umbilicus, respectively. The posterior points are noted to be just lateral to the L1 spinous process for the kidney and over the transverse processes of L2 or L3 for the bladder and urethra. Taking a calculated approach to the physical exam can efficiently aid the practitioner in arriving at a correct diagnosis.

## LABORATORY AND IMAGING

Nephrolithiasis may be suspected based on the history and physical examination, but diagnostic imaging and lab work are essential to confirm or exclude a diagnosis of nephrolithiasis.[9] Urinalysis should be performed to check for the presence of blood, urine pH and crystals that can help identify the composition of the stone.[3] Determining the stone composition will help direct the medical therapy for the patient. In addition, a 24-hour urine collection can be used to identify dietary and individual risk factors for recurrent nephrolithiasis.[1] In the past, several imaging modalities have been used in the work up of nephrolithiasis. Abdominal ultrasound has limited use in the diagnosis and management of nephrolithiasis unless the patient is pregnant or has additional factors that contradict better imaging modalities.[9] Plain-film radiography of the kidneys, ureters and bladder (KUB) has had some success in identifying the size and location of stones that contain calcium phosphate or calcium oxalate. However, radiolucent calculi are frequently missed and the sensitivity (45-59%) and specificity (71-77%) of KUB radiography alone remains poor.[3,9] The intravenous pyelogram (IVP) provides useful information in determining stone location and size. This imaging modality is widely available, generally inexpensive and easily distinguishes ureteral from non-ureteral pathology. Compared with ultrasound and KUB radiography, IVP has greater sensitivity (64-87%) and specificity (92-94%).[9] Unfortunately, obtaining the IVP is very labor intensive and may provoke a contrast induced allergic reaction or renal failure. Currently, the gold standard imaging modality in the diagnosis of nephrolithiasis is a non-contrast helical CT. CT scans are readily available in most hospitals and can be performed and read in a few minutes. Numerous studies have demonstrated that CT has a sensitivity of 95-100% and superior specificity as compared to IVP.[5]

## MANAGEMENT

The management of stone disease can be divided into emergent and non-emergent approaches.

In emergent settings where the concern primarily revolves around renal function, the focus of treatment should be on correcting dehydration, treating urinary infections, preventing scarring, and reducing the risk of acute renal failure.[5]

The treatment should begin by addressing pain with the administration of either narcotics or a non-steroidal anti-inflammatory agent. Both have been shown to be highly effective for analgesia in nephrolithiasis. The parenteral route should be used in patient unable to take oral medications.[5]

Next, an agent should be given to alleviate nausea and vomiting. Metoclopramide (Reglan) is the only antiemetic that has been specifically studied in the treatment of nephrolithiasis and has been shown to relieve pain as well as nausea.[5] Usual dosing is 10 mg IV or IM every 4-6 hours as needed.

Desmopressin (DDAVP) can be administered as it has been shown to reduce pain in many patients with nephrolithiasis. It is thought to act by reducing intraurethral pressure and may have some direct relaxing effect on the renal pelvic musculature. It is an off-label use with the dosage being 40 micrograms intranasally or 4 micrograms intravenously.[5,16] Noted side effects could include headache, nausea, flushing or fatigue.

The usage of antibiotics remains controversial in the treatment of renal stones.[9] Overuse of antibiotic therapy may lead to highly resistant bacteria causing UTIs, but failure to adequately treat could lead to potentially life-threatening urosepsis.[5] Antibiotics should be prescribed if there is any evidence of infection noted.

Intravenous hydration should be administered if there are signs of dehydration. There is some debate whether this hydration can worsen nephrolithiasis pain because of additional back pressure versus the fluids hastening the passage of stones.[5]

If the patient fails to respond to medical therapy, surgical intervention such as ureteral stents, percutaneous nephrostomy, laser lithotripsy or shock wave lithotripsy may be indicated.

In non-emergent settings the stone size, shape and chemical composition are important predictors of prognosis and treatment. Stones less than 4 mm in diameter have an 80% chance of spontaneous passage; this falls to 20% for stones larger than 8 mm in diameter.[5] It has been shown that aggressive medical therapy, directed by stone size and composition, has increased spontaneous stone passage

rate and relieving discomfort while minimizing narcotic usage. In addition, aggressive medical treatment avoids the development of a potentially dangerous urosepsis.[9]

Medical expulsive therapy (MET) could include any of the following medications: Corticosteroids, NSAIDs, calcium-channel blockers and α-adrenergic blockers. However, the use of calcium-channel blockers and α-adrenergic blockers has shown the most promising results as agents for MET.[10] Both calcium-channel blockers α-adrenergic blockers are smooth muscle relaxants thought to help facilitate passage of the stone.[5] Studies have shown that combination therapy with an α-1 blocker like tamsulosin (Flomax) and corticosteroids have been more efficacious than other medical treatment combinations improving stone passage time and decreasing the need for analgesics.[11]

It is important to consider the use of OMM in the treatment of acute nephrolithiasis. The goals of treatment may include balancing parasympathetic tone, reducing hypersympathetic tone to the kidneys and ureters, maintaining venous and lymphatic drainage through the pelvic diaphragm and improving thoracic diaphragm and cage movements. Utilizing modalities such as rib raising, psoas muscle spasm treatment, cranial base decompression and release, Still technique for thoracolumbar and thoracodiaphragm, paraspinal inhibition T-10 to L-2 and treatment of anterior Chapman's points may augment the above treatments and help combat the long term complications of renal stone disease by balancing the autonomic nervous system.[12]

## SPECIAL CONSIDERATIONS

Pregnant women are at an increased risk of developing renal stones as compared to age-matched non-pregnant women.[3,9] They are twice as likely to have calcium phosphate stones and are two to three times more likely to develop calcium phosphate stones than oxalate stones.[3] Nephrolithiasis in these patients predispose them to a higher risk of UTIs and pre-term delivery. Ultrasound is the imaging modality of choice.[13]

An increase in the development of childhood nephrolithiasis has been attributed to the corresponding rise in diabetes, obesity and hypertension.[9,13,14] These patients are more likely to have metabolic and anatomic abnormalities,[14] as well as higher urinary calcium oxalate saturation.[2] Studies have also shown that children who generate stones due to hereditary conditions are at a much greater risk of long term renal impairment compared with age-matched controls.[9]

## PREVENTION

Measures to prevent nephrolithiasis should be discussed with patients who have a history of or are at risk for stone formation. Drinking adequate fluids, 2-3 liters per day, is the most important patient factor to minimize the risk of stone recurrence in renal stone formers. Other general measures for decreasing the likelihood of stone formation include limiting protein, salt and oxalate consumption, as well as normalizing calcium intake and drinking cranberry juice to decrease oxalate excretion.[4] Patients should also work to maintain a healthy weight and control blood sugar, if applicable. Overall, however, preventative measures should be targeted towards limiting risk factors specific to each patient's stone forming history. Other interventions may be recommended based on the patient's stone classification and diagnostic lab results.[3] Pertinent medical history and prescription medications known to contribute to formation of renal calculi should be monitored closely.

**Table 2: Treatment for prevention of stones**

| Type of Stones | Treatment Options |
|---|---|
| **Calcium Stones** | |
| • Normal urine calcium | Potassium citrate |
| • High urine calcium | Thiazide diuretics, potassium magnesium citrate, potassium phosphate |
| • High serum uric acid | Allopurinol, potassium citrate |
| • High urine oxalate | Pyridoxine, Vitamin B6, calcium, Cholestyramine |
| • Low urine citrate | Potassium citrate |
| **Struvite Stones** | Acetohydroxamic acid, treat infection |
| **Cystine Stones** | Potassium citrate, D-penicillamine |

Encouraging patients to regularly see their physician and increasing fluids has been estimated to decrease stone recurrence by up to 60%.[5] However, it is still very likely that an individual with at least one renal stone will have a recurrence at some point in their lifetime.[1] Recurrence rates after an initial episode have been reported as 14%, 35%, and 52% at 1, 5, and 10 years, respectively. Serious complications may result from renal stones including but not limited to abscess or fistula formation, ureteral perforation, extravasation, urosepsis, kidney infection and renal loss. Infected hydronephrosis is the most dangerous complication.[5] Multiple stone episodes are also a significant risk factor for chronic kidney disease, end stage renal disease and significant scarring. Recurrences unilaterally could be attributable to sleep position.[1]

## CONCLUSION / DISCUSSION

Nephrolithiasis primarily affects Caucasian adults and predisposes them to an increased risk of developing systemic diseases.[1,3] A proper history and physical is crucial in the management of nephrolithiasis. Patients presenting with flank pain, hematuria, nausea and vomiting should be evaluated for nephrolithiasis. Urinalysis and non-contrast helical CT are the gold standard diagnostic studies in the work up of this disorder.[3,5] After proper diagnosis, guidelines have been established to help aid the practitioner in the treatment of nephrolithiasis. Appropriate management prevents the likelihood of complications in both emergent and non-emergent cases of renal stone disease. Medical expulsive therapy directed by stone size and composition increases passage rate, decreases pain and lowers the risk of stone-related complications.[9,11] Management should also be directed at correcting any endogenous conditions that facilitates the formation of calculi. Patients must be educated about their condition and encouraged to implement preventative measures such as adequate intake of fluids and regular physician visits.[4] These practices increase awareness and understanding of the disease while decreasing recurrence rate, risk of complication and cost of care.[5]

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