Diagnosis and Management of Suspected Nephrolithiasis in Adults

Reviewed by:

Prof (Dr) Gokulnath
B.Sc., MD (Medicine) DM, DNB (Nephrology) FISN, FRCP (London)
Director Nephrology Services
Apollo Hospitals, Bangalore
Former Prof & Head, Dept of Nephrology
St Johns Medical College, Bangalore
Past President, Indian Society of Nephrology (Southern Chapter) &
Peritoneal Dialysis Society of India

Nephrolithiasis: An Insight

Renal and ureteral stones are commonly seen in clinical practice. The classical symptoms presented by patients with renal stones are renal colic and hematuria. Some patients may be asymptomatic or have atypical symptoms such as vague abdominal pain, acute abdominal or flank pain, nausea, urinary urgency or frequency, difficulty in urinating, penile pain, or testicular pain.[1] Clinicians need to be alert to decide upon a diagnostic approach considering the possibility of nephrolithiasis and its consequences.[2] Furthermore, stone formation is frequently associated with other diseases of affluence such as hypertension, osteoporosis, cardiovascular disease, metabolic syndrome, and insulin resistance.[3] This is changing the perspective of nephrolithiasis from an isolated disorder to a systemic disease that justifies further research in understanding the underlying mechanisms and elaborating diagnostic-therapeutic options.

Pathogenesis

The pathophysiology of urinary stone formation is complex, involving a combination of metabolic, genetic, and environmental factors. Over the past decades, remarkable advances have emerged in the understanding of the pathogenesis, diagnosis, and treatment of kidney calculi. Urinary calculi originate from the formation of crystals in the urine, which is a complex solution of various solutes. When the urine becomes supersaturated due to a low urine volume or excessive excretion of solutes, crystalline formation begins. The crystals may grow gradually or aggregate.[2] Eighty percent of patients with nephrolithiasis form calcium stones, most of which are composed primarily of calcium oxalate or, less often, calcium phosphate.[4] The other main types include uric acid, struvite (magnesium ammonium phosphate), and cystine stones. The same patient may have a stone that contains more than one crystal type (eg, calcium oxalate and uric acid).[1] The modes and putative sites of stone formation are depicted in Figure 1.[5]

Clinical Manifestations

The initial presentation of nephrolithiasis is often with renal colic - severe pain caused by stone passage - triggered by movement of a stone from the renal pelvis into the ureter, which leads to ureteral spasm and possibly obstruction. Pain starts in the flank area, and progresses downward and anteriorly into the genital region as the stone moves down the ureter. The pain is not usually aggravated or alleviated by change of position, and may be accompanied by nausea and vomiting. Hematuria is always present, but may be microscopic. If the stone is lodged at the uretero-vesical junction, it can cause a sensation of urinary frequency and urgency. All symptoms are relieved quite abruptly when the stone moves out of the ureter into the bladder, and passes. Symptoms in children can be similar, but may consist only of hematuria, generalized abdominal pain or urinary tract infection.[6]

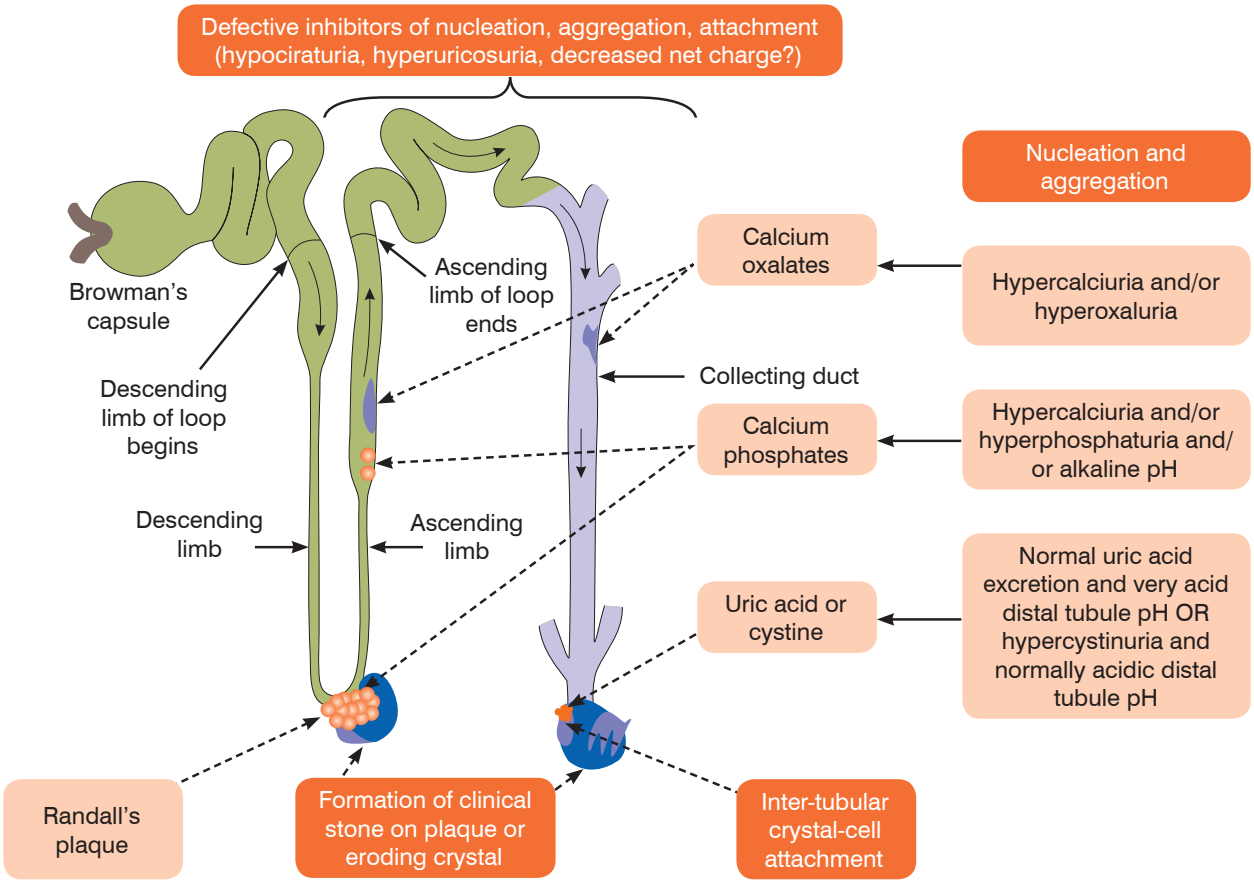
Differential Diagnosis

The differential diagnosis for flank pain and hematuria includes papillary necrosis with passage of a sloughed papilla, renal emboli, renal tumor and sometimes urinary tract infection.[6]

Diagnosis

In the diagnosis of patients with nephrolithiasis, systemic and environmental influences must be carefully identified. Systemic abnormalities include intestinal disease, disorders of calcium homeostasis such as primary hyperparathyroidism, conditions accompanied by extra renal $1,25(OH)_2D$

Figure 1: Modes and putative sites of stone formation



Adapted from: Ratkalkar VN, Kleinman JG. Mechanisms of Stone Formation. *Clin Rev Bone Miner Metab.* 2011;9(3-4):187-197.

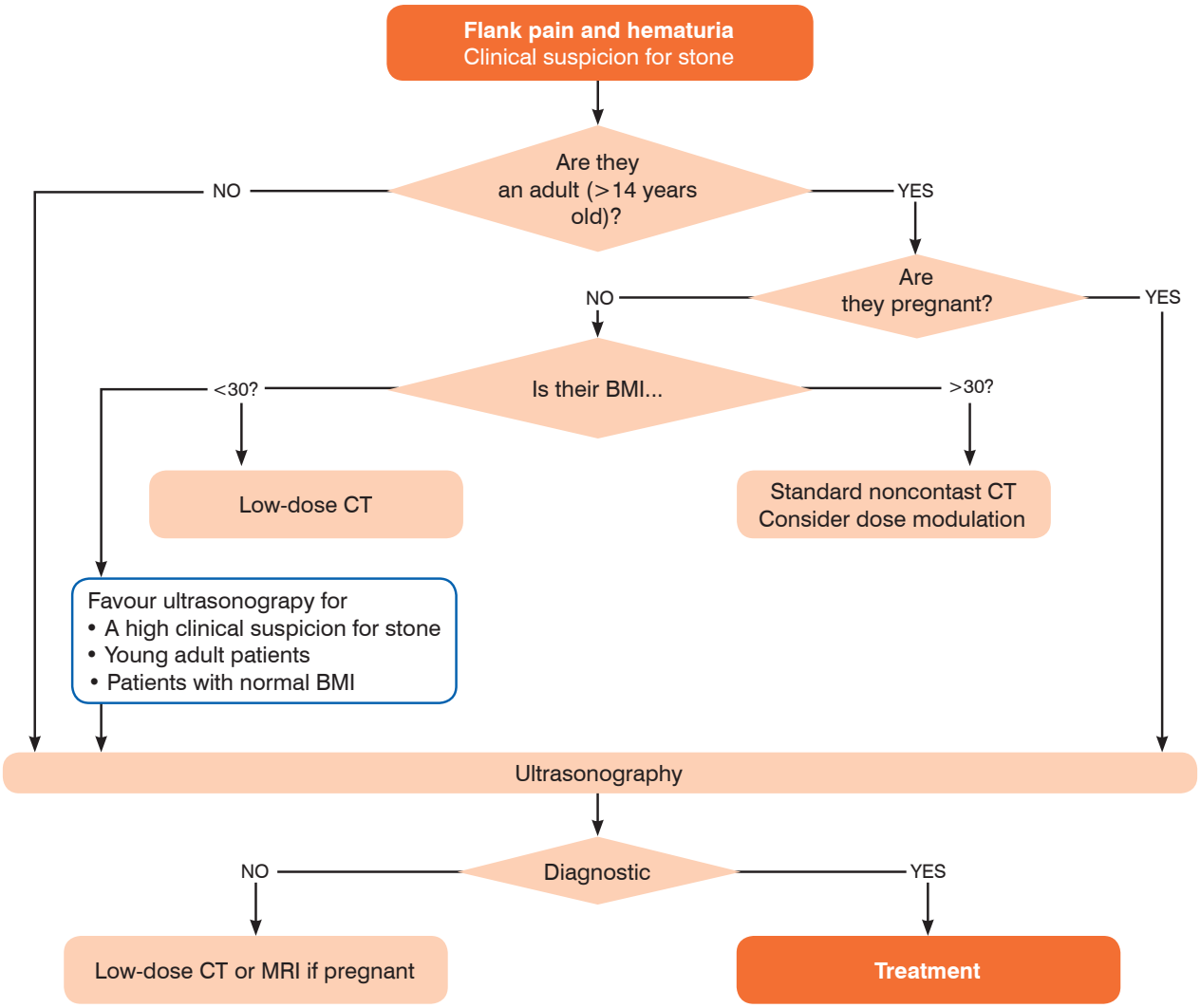
production such as granulomatous diseases, obesity, type II diabetes, recurrent urinary tract infection, bariatric surgery, medullary sponge kidney, and various drug treatments.[7]

Furthermore, diet plays a crucial role in the formation of kidney stones. High dietary salt and protein consumption are the two most common dietary aberrations that increase the risk of nephrolithiasis. Aside from dietary risk factors, it has been suggested that kidney stone risk increases in hot climates as well as with frequent and/or intense exercise, largely due to extra renal fluid loss as a result of perspiration, resulting in a significant fall in urine volume.[7]

Importantly, laboratory diagnosis plays a valuable role in the diagnosis of kidney stone patients. It includes stone analysis, imaging studies, blood profiles, and a urine metabolic evaluation. Stone analysis of patients with nephrolithiasis specifically reports the infrequently encountered kidney stones such as uric acid, cystine, infection-induced, drug-induced, and NH4+ urate stones.[7] In addition to stone analysis, blood and metabolic profiling are incumbent upon patients with nephrolithiasis. High fasting blood calcium, low phosphorus, and elevated PTH are suggestive of primary hyperparathyroidism. In that case, the patient must be considered for a noninvasive localization study followed by parathyroidectomy. Normal serum calcium, low serum phosphorus, elevated $1,25(OH)_2D$, and normal PTH are suggestive of renal phosphorus leak. The finding of low serum potassium and low serum bicarbonate is suggestive of distal renal tubular acidosis. Hyperuricemia and high serum triglycerides are encountered in patients with uric acid stones.[7]

Lastly, kidney stone imaging is an important diagnostic tool and initial step in deciding which therapeutic options to use for the management of kidney stones. Selection of optimal initial imaging modality is important to evaluate patients with suspected obstructive nephrolithiasis. Noncontrast CT of the abdomen and pelvis consistently provides the most accurate diagnosis but also exposes patients to ionizing radiation. Traditionally, ultrasonography has a lower sensitivity and specificity than CT, but does not require use of radiation. Both modalities have advantages and disadvantages. Kidney, ureter, bladder (KUB) plain film radiography is most helpful in evaluating for interval stone growth in patients with

Figure 2: A proposed algorithm for imaging patients with acute stone disease



Adapted from: Brisbane W, Bailey MR, Sorensen MD. An overview of kidney stone imaging techniques. *Nat Rev Urol.* 2016;13(11):654-662.

known stone disease, and is less useful in the setting of acute stones. MRI provides the possibility of 3D imaging without exposure to radiation, but it is costly and currently stones are difficult to visualize. A proposed algorithm for imaging patients with acute stones in light of the current guidelines and a randomized controlled trial could aid clinicians (Figure 2). Further developments are expected to enhance each imaging modality for the evaluation and treatment of kidney stones.[8]

Management

The methods of stone removal from the urinary tract have benefited from technological innovations that have revolutionized the treatment of the disease and reduced its morbidity. Medical treatment of kidney stones includes dietary management, disease-specific therapies, and medical expulsion therapy (MET) of stones.[9]

Dietary Management

Fluid intake and dietary changes are important measures in preventing recurrence of kidney stones. Many trials have shown that increasing urine volume to at least 2 L/day can reduce the recurrence of stone disease by up to 40-50%.[10]

Oral potassium citrate has been shown to be useful in reducing the stone recurrence. Hypocitraturia is a proven risk factor for stone formation and is found in about 16–63% of calcium stone formers. Oral citrate therapy increases the urinary citrate levels, which in turn binds with calcium and inhibits the crystallisation thus reduces stone formation.[9] A

recent review[11] determined the efficacy and adverse events associated with citrate salts for the treatment and prevention of calcium containing kidney stones. The investigators concluded that citrate salts prevent new stone formation and reduce further stone growth in patients with residual stones that predominantly contain oxalate.

Stone-expulsive therapies

Medical expulsive therapy (MET) is treatment with combination of drugs which facilitates the spontaneous passage of ureteric calculi.[9] The two most important factors in predicting the ureteral stone passage are stone size and location. Distal ureteral stones 5mm or smaller in size have about a 50-70% probability of passing spontaneously. Stones between 5-10 mm have less than 50% of chance. The American Urology Association Nephrolithiasis Clinical Guidelines panel in its recent guidelines have said, MET facilitates and accelerates the spontaneous passage of ureteric stones and the stone fragments generated by shock wave lithotripsy. Calcium-channel blockers and α-1 blockers have emerged as the most promising agents for MET. Calcium-channel blockers (such as nifedipine) suppress smooth muscle contraction and reduce ureteral spasm, whereas α-1D adrenergic receptor antagonists (e.g. tamsulosin) decrease ureteral smooth muscle tone, frequency, and force of peristalsis.[12]

Role of alpha blockers: Focus on Tamsulosin

Alpha adrenergic receptors are densely located in the smooth muscles of ureter. Alpha-1a-receptors predominate in bladder outlet, prostate, and proximal urethra, whereas alpha-1d-receptors are seen in lower ureter and detrussor muscle of bladder. Drugs which block these receptors cause smooth muscle relaxation and inhibit peristalsis and relieve spasm.[9]

Tamsulosin, an alpha-1 blocker, is effective in expulsion therapy as it increases the passage rate and reduces the passage time for stones up to 10 mm. In a study[13] of tamsulosin in renal colic, 100% expulsion rate was seen in the treatment group and 70% in the control group. The mean expulsion time in the treatment group was 65.7 h (range 2–288 h) compared with 111.1 h for the control group (range 12–240 h). In this study, the mean stone size was 6.7 (SD 2.1) mm in the treatment group, compared with 5.8 mm in control subjects (P=0.047). Thus, it can be concluded that tamsulosin alone as MET for ureteral calculi had excellent expulsive effectiveness. In addition, when appropriately used it may have substantial fiscal benefits by reducing the number of interventional procedures and the acute attacks too.[14]

Summary

Nephrolithiasis is a common health problem across the globe with a prevalence of 15%-20%. Idiopathic hypercalciuria is the most common cause of nephrolithiasis, and calcium oxalate stones are the most common type of stones in idiopathic hypercalciuric patients. Calcium phosphate stones are frequently associated with other diseases such as renal tubular acidosis type 1, urinary tract infections, and hyperparathyroidism. High fluid intake to >2 L/day coupled with reduced salt and protein intake are considered the cornerstone of prevention of all forms of stone formation. Attacks of renal colic can be managed with analgesics to relieve the pain and increased fluid intake at first. Oral alkalinizing medications such as potassium citrate are generally safe and aid in dissolving and preventing renal stones. Furthermore, medical treatment to promote spontaneous expulsion of ureteric stones may potentially diminish health care expenditures associated with shock wave lithotripsy and ureteroscopy. Tamsulosin has been found to increase and hasten stone expulsion rates, decrease acute attacks by acting as a spasmolytic, reduces mean days to stone expulsion and decreases analgesic dose usage. Medical therapy, when used judiciously in conjunction with dietary measures, can help in preventing recurrence and in expulsion of small size (<10 mm) stones.

References

1. Curhan GC, Aronson SD, Preminger GM. Diagnosis and acute management of suspected nephrolithiasis in adults. UptoDate. 2018. Available at: https://www.uptodate.com/contents/diagnosis-and-acute-management-of-suspected-nephrolithiasis-in-adults.
2. Gambaro G, Trinchieri A. Recent advances in managing and understanding nephrolithiasis/nephrocalcinosis. *F1000Res.* 2016;5:F1000 Faculty Rev-695.
3. Shadman A, Bastani B. Kidney Calculi: Pathophysiology and as a Systemic Disorder. *Iran J Kidney Dis.* 2017;11(3):180-191.
4. Singh P, Enders FT, Vaughan LE, *et al*. Stone Composition Among First-Time Symptomatic Kidney Stone Formers in the Community. *Mayo Clin Proc.* 2015; 90:1356.
5. Ratkalkar VN, Kleinman JG. Mechanisms of Stone Formation. *Clin Rev Bone Miner Metab.* 2011;9(3-4):187-197.
6. Worcester EM, Coe FL. Nephrolithiasis. *Prim care.* 2008;35(2):369-vii.
7. Sakhaee K, Maalouf NM, Sinnott B. Kidney Stones 2012: Pathogenesis, Diagnosis, and Management. *J Clin Endocrinol Metab.* 2012;97(6):1847-60.
8. Brisbane W, Bailey MR, Sorensen MD. An overview of kidney stone imaging techniques. *Nat Rev Urol.* 2016;13(11):654-62.
9. Barnela SR, Soni SS, Saboo SS, Bhansali AS. Medical management of renal stone. *Indian J Endocrinol Metab.* 2012;16(2):236–9.
10. Borghi L, Meschi T, Amato F, Briganti A, Novarini A, Giannini. Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: a 5-year randomized prospective study. *J Urol.* 1996;155(3):839-43.
11. Phillips R, Hanchanale VS, Myatt A, Somani B, Nabi G, Biyani CS. Citrate salts for preventing and treating calcium containing kidney stones in adults. *Cochrane Database Syst Rev.* 2015;(10):CD010057.
12. Pachaly MA, Baena CP, Carvalho Md. Therapy of nephrolithiasis: where is the evidence from clinical trials? *J Bras Nefrol.* 2016;38(1):99-106.
13. Dellabella M, Milanese G, Muzzonigro G. Efficacy of tamsulosin in the medical management of juxtavesical ureteral stones. *J Urol.* 2003;170(6 Pt 1):2202-5.
14. Griwan MS, Singh SK, Paul H, Pawar DS, Verma M. The efficacy of tamsulosin in lower ureteral calculi. *Urol Ann.* 2010;2(2):63-66.