

NEW FRONTIERS ON NEPHROLITHIASIS: PATHOPHYSIOLOGY AND MANAGEMENT OF KIDNEY STONES

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ABSTRACT

Nephrolithiasis (also known as kidney stones, renal stones, urinary stones, urolithiasis, and renal calculi) affects a great number of patients worldwide. These can be of different types like calcium-oxalate, struvite, uric acid, cysteine. Larger stones in the urinary tract can cause extreme pain in the lower back or side. Urinary tract infections, kidney disorders and certain metabolic disorders such as hyperparathyroidism are also linked to stone formation. Cystinuria, hyperoxaluria, Hypercalciuria, drinking less water, consuming more salty food can cause stone formation in urinary tract. Various precautions and treatment are available includes life style changing (drinking more water or more fluid intake and reducing calcium rich diet intake), avoid junk food, Medical therapy (use of diuretics and other medicines), the over use of synthetic drugs which results in higher incidence of adverse drug reaction has motivated humans to return to nature for safe remedies and surgical treatment The present article revealed the update knowledge about remedy and treatment of nephrolithiasis for all those peoples who is having renal colic pain.

KEYWORDS: Nephrolithiasis, Herbal plants, Treatments, Precautions, latest technology.

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INTRODUCTION

The term nephrolithiasis often used synonymously with urolithiasis, refers to the formation of solid concretions consisting of both protein and crystalline materials in the lumen of the urinary tract attached to the uroepithelium. Kidney stones are the one of the most painful of the all urologic disorders and have been annoying continually humans for centuries. They vary considerably in size from small gravel like stones to large staghorn calculi. The calculi may stay in the position in which they formed or migrate down the urinary tract producing symptoms along the way. Each year, around almost 3 million people visits to health care providers and more than half a million people go to emergency rooms for kidney stone problems¹.

Men are more commonly affected than women with a male to female ration of 3:1. The peak age for developing stones is 30-50 years and recurrence is common. Geographic variations exist in stone prevalence, and regional stone belts have been identified and attributed to genetic and environmental factors such as hot climate (fluid loss) and sun exposure (vitamin D). Caucasians have more kidney stones than black at all

ages. Prevalence among Hispanics and Asians is intermediate between Caucasians and blacks. The risk of nephrolithiasis is higher in metabolic syndrome individuals and the gout patients. Higher body mass index or waist circumference is both positive associations with increased stone risk. The distribution of stone types is well distributed among individual to individual and different geographic variations. It can be well estimate by calcium oxalate (65%), calcium phosphate (15%), uric acid (10%), cystine (2%) and struvite (5%). Most kidney stones pass out of the body without any intervention by a physician. To treat the disorder, various drugs are used. Management of nephrolithiasis has been revolutionize not only by non-surgical methods such as lithotripsy, but also by improvements in fiber-optic technology and laser techniques, which also provide therapy alternatives to surgery². Other technologies, such as the use of electrical sparks, have been developed that effectively break up kidney stones but they are very expensive and many side effects especially loss of sexual desire^{3, 4, 5}. The safest and cheapest remedy for the treatment includes the use of various medicinal plants. For understanding how to

prevent this disorder, this is the hot topic in today scenario and for benefit of the public, this review article shows the various factors involved in it.

Mechanism of kidney stone formation

Stone formation is the end result of a multistep process in which the balance of factors that promote crystallization of urinary salts (promoters) and factors that inhibit crystallization (inhibitors) is perturbed⁶. When the urinary concentration of certain salts (e.g. calcium oxalate) exceeds their solubility product, the urine becomes supersaturated for that salt. In a state of supersaturation, nuclei of salt crystals are formed in a process called nucleation. Alkaline urine pH favors calcium phosphate crystallization and acid urine pH favors uric acid and cystine precipitation. Also, metabolic acidosis in humans induces hypercalciuria due to release of calcium from bone and decreased renal tubular calcium reabsorption, renal phosphate depletion and hypophosphataemia, and hypocitraturia⁷. Often there is another nidus of nucleation, such as the injured surface of renal tubular epithelial cells or a different solute (e.g. uric acid) that causes crystal formation (heterogeneous nucleation). There are certain sites also that promote crystal growth e.g. calcium phosphate deposits on external surface of papillae (Randall's plaques) and calcium oxalate receptors in collecting duct epithelium. The adhesion forces between the calcium oxalate monohydrate (COM, whewellite) crystal and the layer of the epithelial kidney cells can be directly measured under buffer solutions by using atomic force microscope (AFM)⁸.

Low concentrations of crystallization inhibitors (citrate, nephrocalcin, uropontin, Tamm-Horsfall protein, magnesium) may promote the nucleation of salts in saturated but stable solutions. If the nuclei begin to aggregate, crystals begin to form. These crystals continue to aggregate and eventually grow into stones.

Retention within the kidney appears to be important for the crystals to grow: If not retained, crystals are passed in the urine. Locations of prior injury, such as renal papillae, are hypothesized to be sites where crystals are retained. Low urine flow or stasis from genitourinary abnormalities or volume depletion also may promote crystallization. Stones tend to reside either at the area of prior injury or in gravity-dependent locations, such as the lower pole calices.

Certain diuretics (e.g. loop diuretics), commonly called water pills, and calcium-based antacids may increase the risk of forming kidney stones by increasing the amount of calcium in the urine. Calcium oxalate stones may also form in people who have chronic inflammation of the

bowel or who have had an intestinal bypass operation, or ostomy surgery. People who take the protease inhibitor Indinavir, a medicine used to treat HIV infection, may also be at increased risk of developing kidney stones⁹. Indinavir is metabolized primarily through P450III A with 19% of the drug excreted in the urine. As a result, liver disease prolongs the half-life of the drug. Precipitation of Indinavir in the tubular lumen is a direct result of its low solubility at physiologic pH. Patients with reduced urinary volumes or higher circulating concentrations of the drug (higher filtered loads) would be expected to be at increased risk for intratubular precipitation and nephrolithiasis¹⁰.

Site of stone formation

The stone formation and store for long time can be in different sites of urinary system (figure 1).

Symptoms of kidney stones

- a strong gripping pain in the back below the ribs (also known as renal colic) and may also accompanied by pain in your side, groin and thigh.
- difficulty in passing urine,
- Blood in urine,
- Nausea and vomiting,
- Fever, shivers and sweating,
- Infection of kidney.

Risk factors

Anyone can have a kidney stone, but certain group of people is more likely to develop stones.

- Anatomic abnormalities: Ureteropelvic junction stenosis, polycystic renal disease
- Abnormalities of urinary pH: Renal tubular acidosis, Gouty diathesis
- Metabolic syndrome and obesity
- Low urine volume
- Hypercalcemic disorder
- Lithogenic drugs
- Inflammatory bowel disease

Disorder through genetically

There are certain genes which involved in the formation of kidney stone (Table 1). Kidney stones are most commonly associated with hypercalciuria. This hypercalciuric nephrolithiasis may also occur due to inherited diseases like: Dent's disease, X-linked recessive nephrolithiasis (XRN), and X-linked recessive hypophosphataemic rickets (XLRH). Cystinuria and hyperoxaluria are two other rare, inherited metabolic disorders that often cause kidney stones. Cystinuria is a rare but important cause of urinary stone disease. It is an autosomal recessive defect in amino acid transport¹¹. In cystinuria, too much of the amino acid cystine, which

does not dissolve in urine, is voided, leading to the formation of stones made of cystine. Two responsible genes have been identified: mutations in the SLC3A1 gene, located on the chromosome 2p, cause is cystinuria type I, while variants in SLC7A9 have been demonstrated in non type I cystinuria^{12, 13}. In patients with hyperoxaluria, the body produces too much oxalate, a salt. When the urine contains more oxalate than can be dissolved, the crystals settle out and form stones. In addition, more than 70 percent of people with a rare hereditary disease called renal tubular acidosis develop kidney stones¹⁴. In kidney stones, Medullary Nephrocalcinosis (calcification of renal parenchyma) may also occur due to primary hyperparathyroidism, distal renal tubular acidosis, Dent's disease, idiopathic hypercalciuria. Osteopenia is also found sometimes, due to hypercalciuria, high bone turnover, hyperparathyroidism¹⁵. Among dialysis patients, the prevalence of urinary tract lithiasis ranges from 3.6% to 8%¹⁶. Medullary sponge kidney (tiny stones form in kidney) which originates from congenital collecting duct dilatation and urinary stasis is also associated with nephrocalcinosis, hypercalciuria, primary hyperthyroidism and distal renal tubular acidosis¹⁷. Uric acid stones are associated with gout, chronic diarrheal disease, diabetes, and congenital disorders of purine metabolism (rare).

Different types of kidney stones

There are four main kinds of kidney stones. Each type has a different cause and may need a different kind of treatment or prevention. The four types are:-

- **Calcium-oxalate:** These are the most common kidney stones and also include calcium phosphate stones. They can be caused by eating too much calcium or vitamin D, some medicines, genetics and other kidney problems.
- **Struvite:** Struvite is a mixture of ammonium, calcium and phosphate¹⁸. These stones affect women more than men. They can grow very large and may harm the kidneys more than other stones. These may be staghorn like in shape. Having kidney infections may cause struvite stones.
- **Uric Acid:** These may be caused by eating too much animal protein or by genetics. Eating less red meat prevents occurrence of these stones.
- **Cystine:** These stones are very rare. They are caused by cystinuria, a genetic kidney disease.

Besides these stones, there are some other miscellaneous types of stones that may occur. These includes:-

- **Protein matrix stones:** occurs due to chronic infection (with struvite stones), end-stage renal disease

- **Ammonium urate stones:** These type of stones occurs mainly due to laxative abuse.

- **Xanthine and 2,8 dihydroxyadenine stones:**

Inherited metabolic disorders are the cause of such type of stones¹⁹.

- **Stones composed of drugs:** indinavir²⁰, sulfadiazine, triamterene.

Kidney stones may be of any shape (figure 2) e.g. staghorn, uric acid stone crystals are mostly in the rhomboid or football shaped forms, in cystinuria crystals are in hexagonal plate form. Also, the size of stones ranges from microscopic to stones the size of potatoes, with a smooth or jagged texture. Stones greater than 5mm of size are less likely to pass through urinary tract.

DIAGNOSIS

If the stones are small, they will often pass out of the body unnoticed. Often, kidney stones are found on an x-ray or ultrasound taken of someone who complains of blood in the urine or sudden pain. These diagnostic images give the doctor valuable information about the stone's size and location. There are some parameters which are used to tell about the biochemical changes in urine after stone formation (Table 2). Blood and urine tests help detect any abnormal substance that might promote stone formation e.g. levels of calcium and uric acid in the blood will be examined.

Plain x-ray has traditionally been the standard by which stone size is measured. Recently non contrast spiral computerized tomography (CT) has been established as a highly sensitive and specific tool for assessing ureteral calculi in patients with flank pain²¹. It is more sensitive than plain x-ray for detecting calculi regardless of size, location or chemical composition. Plain x-rays do not 'see' stones not made of calcium, like those containing uric acid. Small stones and those in front of bones do not show up either. Intravenous pyelogram (IVP)/Intravenous urography (IVU) is an older test that may be used for stones that X-ray cannot show. Dye is injected into a vein and X-ray studies are taken as it passes through the kidneys. Any problems with the passage of urine out of the body can be found. According to previous studies, the sensitivity of IVU for the diagnosis of ureter stone is only around 60%²².

The doctor may decide to scan the urinary system using a special test called a computerized tomography (CT) scan or an intravenous pyelogram (IVP). CT scanning shows all stones well and have relative diagnostic sensitivity of 100%. Abdominal plain film are used (have relative diagnostic sensitivity of 60%-65%) to determine if stone is radiopaque and thus likely not uric acid (uric acid stones appears radiolucent on plain abdominal film).

Ultrasound scanning (have relative diagnostic sensitivity of 10%-25%) is less good at seeing stones but can show if a blockage is present²³. It is an option in pregnancy.

Where people repeatedly form stones there will be:

- A full metabolic evaluation and measurement of certain substances in the urine and blood
- And a dietary assessment

PREVENTION

If someone has kidney stones before, there are more chances that kidney stones will occur again. To avoid reoccurrence of kidney stones, following preventive measures can be used:-

- Drink 6 to 8 glasses (i.e. near about 2 litres) of water each day. If your urine is dark yellow than you are not drinking enough water.
- Visit your doctor for blood and urine test, to determine the type of stone, cause of stone formation and hence the appropriate treatment that should be used.
- After concerning the doctor, limit your eating habits e.g. eat less salt (sodium), meat and eggs.
- Patients may be told to avoid food with added vitamin D and certain types of antacids that have a calcium base. Someone who has highly acidic urine may need to eat less meat, fish, and poultry. These foods increase the amount of acid in the urine.
- Persons with calcium oxalate stones are told to avoid certain food which contains high oxalate contents such as: spinach, peanuts, rhubarb, and chocolate.
- To prevent cystine stones, a person should drink enough water each day to dilute the concentration of cystine that escapes into the urine. Benefits of specific beverages like: wine, beer, coffee, tea, lemonade should not be ignored.
- Herbal tea can be an alternative to regular tea in case of those patients who have calcium oxalate stones. Also, risk of certain beverages like: grapefruit juice should be kept in mind.
- Salt and protein rich diet should be restricted in many cases of hypercalciuria. In a similar manner, low-purine diet is preferred during hyperuricosuria.

DRUG INTERACTION STUDIES

Prescribing certain medications may help prevent calcium and uric acid stones. These medicines control the amount of acid or alkali in the urine, key factors in crystal formation. The medicine allopurinol may also be useful in some cases of hyperuricosuria. Allopurinol interferes with the liver's production of uric acid²⁴. Hyperuricosuria is too much uric acid in the urine, is a risk factor for calcium stones. Allopurinol reduces calcium stone formation in such patients. Anthraquinone derivatives like: ruberythric acid, alizarin, quinizarin,

purpuric acid, rubiadin, purpurin present in *R. tinctorum* L. possess the ability to dissolve kidney stones as well as to prevent their deposition in the urinary tract. Hypercalciuria can be controlled by use of certain diuretics, such as Hydrochlorothiazide²⁵. These thiazide diuretics act by increasing renal calcium absorption in proximal tubule (volume depletion) and early distal convoluted tubule (sodium chloride cotransporter).

Crystallization of calcium oxalate (CaOx) appears to be reduced by molecules in the urine that retard the formation, growth, aggregation, and renal cell adherence of calcium oxalate. By purifying urine using salt precipitation, preparative isoelectric focusing, and sizing chromatography, some researchers have found that the molecule calgranulin is able to inhibit calcium oxalate crystal growth²⁶. Calgranulin is a protein formed in the kidney.

Rarely, patients with hypercalciuria are given the medicine sodium cellulose phosphate, which binds calcium in the intestines and prevent it from leaking into the urine. Thiola and cuprimine may be prescribed for cystine stones when these are not controlled by drinking more fluids. Potassium forms of alkali are preferred to decrease uric acid and increase urate concentration in patients with uric acid stones. Besides these, antibiotics and urease inhibitors like: acetohydroxamic acid, are used for treatment of stones with infections²⁷. For struvite stones that have been totally removed, the first line of prevention is to keep the urine free of bacteria that can cause infection. If struvite stones cannot be removed, a doctor may prescribe Acetohydroxamic acid (AHA). AHA is used with long-term antibiotic medicines to prevent the infection that leads to stone growth.

TREATMENT

Various treatments for nephrolithiasis can be summarized under this figure 3.

Herbal Treatment

Recent studies have shown that foods high in calcium, including dairy products, may help prevent calcium stones. Taking calcium in pill form, however, may increase the risk of developing stones. To treat this, there are the few herbal treatments available for kidney stones (Table 3).

LATEST TECHNOLOGY USED TO TREAT KIDNEY STONES

Extracorporeal shock wave lithotripsy

Extracorporeal shock wave lithotripsy (SWL) has revolutionized treatment (figure 4) for most patients with urolithiasis since its introduction in the early 1980s. However, uric acid stones were once regarded as a relative contraindication for SWL with the Dornier HM3

lithotripter because of the difficulty in localizing the radiolucent stones with fluoroscopy³⁴. Today, the second generation ultrasound-guided lithotripters with alkali therapy are used which allow more accurate and harmless localization of radiolucent stones. Nowadays, this is the most frequently used treatment for Kidney stones. In ESWL, shock waves that are created outside the body travel through the skin and body tissues until they hit the denser stones³⁵. The stones break down into small particles and are easily passed through the urinary tract in the urine.

A rare direct side effect of ESWL is cardiac arrhythmia and a rare direct complication is a renal hematoma. Also lack of disintegration may be regarded as a direct complication. The most frequent problems after ESWL are secondary complications such as: hampered fragment passage, obstruction, colic, hydronephrosis (partial/complete), infection, sepsis.

Percutaneous Nephrolithotomy

This treatment is often used when the stone is quite large or in a location that does not allow effective use of ESWL. In this procedure, the surgeon makes a tiny incision in the back and creates a tunnel directly into the kidney. Using an instrument called a nephroscope, the surgeon locates and removes the stone. For large stones, some type of energy probe—ultrasonic or electrohydraulic—may be needed to break the stone into small pieces. Often, patients stay in the hospital for several days and may have a small tube called a nephrostomy tube left in the kidney during the healing process.

Technique Of PNL (Figure 5)

The entire procedure, particularly the initial puncture, is performed in the urology department with the patient under general anaesthesia. Prior to the procedure, a retrograde study is performed and a ureteral balloon catheter placed at the ureteropelvic junction. The collecting system is moderately filled with contrast dye (i.e., with addition of methylene blue). PNL is carried out with the patient placed in the prone position. One may use a specially designed cushion enabling a deflected position to place the patient flat on the fluoroscopic table.

For the puncture of the collecting system, we use a combination of ultrasound (freehand technique, fully guided system) and fluoroscopy. Based on sonographic imaging, the puncture is carried out to the desired calyx. The final placement of the needle is mostly performed under fluoroscopic control. A peripheral puncture to transverse a minimum of cortical tissue has to be accomplished, to avoid injury to major intrarenal vessels,

to avoid fistula injury, to establish the shortest tract between the skin and calyx, and to minimize radiation exposure. Afterwards, a 0.97-mm floppy-tipped guidewire is passed through the needle into the collecting system. A working channel is then established using the Alken telescope metal dilators system (Storz, Tuttlingen, Germany) under X-ray control to 24–26F³⁶. Then, a standard 26F nephroscope is placed directly into the kidney over the established tract.

Alternatively, a dilatation balloon system together with an Amplatz sheath can be used. The number and type of access depend on the treated stone size (i.e., staghorn stone) and localisation (upper pole, lower pole) as well as on the treatment strategy (single session PNL vs. combination with ESWL).

For stone disintegration preference is given to the use of an ultrasound lithotripsy probe. Except for very hard stones (i.e., calcium oxalate monohydrate) it enables fragmentation with simultaneous evacuation of the gravel. Other alternatives include the use of ballistic devices or holmium/yttrium-aluminum garnet laser³⁷. Flexible nephroscopy is used when stone fragments migrate into other calyces or in case of additional stone burden in other calyces not accessible by the rigid nephroscope. At the end of the procedure, a 22F Foley catheter is used as a nephrostomy tube and blocked with 1–2 ml in the renal pelvis. Alternatively, a red rubber catheter or a detachable silicone balloon catheter can be placed. An antegrade nephrogram is taken 24–28 h after the procedure (depending on the clarity of urine). The tube is removed if no extravasation or retained calculi are present.

However some complications during or, after PNL may be present with an overall high complication rate including extravasation, transfusion and fever whereas major complications such as septicaemia and colonic or, pleural injury are rare.

PNL usually ends with the placement of a nephrostomy tube to allow for drainage, tamponade of bleeding and delayed second-look nephroscopy. Placement of a postoperative temporary nephrostomy tube and urinary leakage that persists after its removal, however, remains a significant inconvenience for both patient and medical personnel, increase the analgesic requirement, and prolong the hospitalization. In an attempt to avoid this problematic feature, a tubeless approach has been successfully used nowadays known as tubeless percutaneous nephrolithotomy.

Ureteroscopic Stone Removal

This technique of ureteroscopy (figure 6) (or simply “stone basketting”) may be needed for mid- and lower-

ureter stones³⁸. No incision is required in this procedure. Instead, the surgeon passes a small fiberoptic instrument called an ureteroscope through the urethra and bladder into the ureter. The surgeon then locates the stone and either removes it with a cage-like device or shatters it with a special instrument that produces a form of shock wave. A small tube or stent may be left in the ureter for a few days to help urine flow. Patients received spinal or general anesthesia at the beginning of the procedure based on patient and anesthesiologist preference. All patients underwent rigid cystoscopy with placement of a guide wire into the renal collecting system under fluoroscopic guidance. Another safety guide wire was also placed based on surgeon preference. Flexible or rigid ureteroscopes were used depending on stone location and patient gender. When the ureteroscope did not pass easily into the ureter, the ureteral orifice was balloon dilated to 15 mm. Calculi were extracted with graspers or baskets when feasible, or fragmented using a holmium:YAG laser or electrohydraulic lithotripter³⁹. A stent was placed postoperatively according to attending surgeon judgment. All ureteral perforations noted intraoperatively were treated with stent placement. Recently, the miniaturization of ureteroscopes, together with the introduction of the holmium laser, has improved stone-free rates and decreased the complication rates, widening the indications for ureteroscopy.

DISCUSSION

Nephrolithiasis has afflicted humans since the earliest recorded history and has been observed in wide range of animals. Nephrolithiasis is largely a recurrent disease with a relapse rate of 50% in 5–10 years and 75% in 20 years⁴⁰. The occurrence of kidney stones increases in rural than urban population. Numerous defense mechanisms contribute to keeping crystals from forming and adhering to the uroepithelium but physiology is not perfect and failure in this task presents itself as nephrolithiasis. The purpose of this review is to provide an update about the most common risk factors or medical conditions associated with kidney stone formation, the current medical treatments are available but there are more side effects shown, so to overcome this we can strict on precautions and the use of herbal plants extracts in daily life which leads to non occurrence of kidney stone formation. The majority of patients, the symptoms and consequences are not life threatening, but stones in the urinary tract are a major cause of morbidity, hospitalization and days lost from work. The correction of metabolic changes in body is the basic tool for prevention and reoccurrence of stone.

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Table 1: Monogenic causes of Nephrolithiasis

<i>Disease</i>	<i>Gene and Inheritance</i>	<i>Protein</i>	<i>Features other than Stones</i>
Distal renal tubular acidosis	ATP6V1B1 (AR)	B1 subunit V type H ⁺ ATPase	Deafness
	ATP6V0A4 (AR)	a4 subunit of V type H ⁺ ATPase	Normal hearing
	SLC4A1 (AR)	Anion exchanger (AE) 1	Ovalocytosis, hemolytic anemia
	SLC4A1 (AD)	Anion exchanger (AE) 1	No red cell defects
Dent disease	CLCN5 (XL)	Chloride channel CLC-5	Fanconi syndrome
Oculocerebral syndrome of Lowe	OCRL1 (XL)	Phosphatidylinositol-4,5-bisphosphate 5-phosphatase	Fanconi syndrome, rickets, cataracts, mental retardation
Bartter syndrome	NKCC2 (AR)	Sodium potassium chloride cotransporter (NKCC)	Classic (less severe presentation in childhood) <i>or</i> antenatal (hydraninos, salt wasting)
	KCNJ1 (AR)	Renal outer medullary potassium (ROMK) channel	Classic or antenatal Bartter syndrome
	CLCNKb (AR)	Chloride channel, CLC-Kb	Usually classic (milder); can present without nephrocalcinosis
	BSND (AR)	Barttin, subunit of CLC-Kb	Associated with deafness
	CASR (AD)	Calcium-sensing receptor (activating mutation)	Hypocalcemia; also known as autosomal dominant hypocalcemia
Hereditary hypophosphatemic rickets	SLC34A3 (AD/R)	Sodium phosphate cotransporter type 2C (NaPi-2c)	Hyperphosphaturia, rickets, hypervitaminosis D
Familial isolated Hypoparathyroidism	CASR (AD)	Calcium-sensing receptor (activating mutation)	Hypocalcemia
	PTH (AR or AD)	Parathyroid hormone	Hypocalcemia, hyperphosphatemia
	GCMB	Glial cells missing B transcription factor	Hypocalcemia, hyperphosphatemia
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis	PCLN1 (AR)	Paracellin 1	Hypomagnesemia, hyperuricemia, polyuria, ocular abnormalities
Cystinuria	SLC3A2 (AR)	Amino acid transporter rBAT	Cystinuria
	SLC7A9 (AR)	Amino acid transporter b ⁰⁺ AT	
Primary hyperoxaluria	AGXT (AR)	Alanine/glyoxylate aminotransferase	Hyperoxaluria, nephrocalcinosis, systemic oxalosis
	GRHPR (AR)	Glyoxylate reductase/hydroxypyruvate reductase	
Lesch-Nyhan syndrome, Kelly-seegmiller syndrome	HPRT (XL)	Hypoxanthine-guanine phosphoribosyltransferase	Hyperuricosuria, gout, neurologic syndrome
Renal hypouricemia	SLC22A12 (AR)	URAT1 uric acid transporter	Hypouricemia Nephrolithiasis, and acute kidney injury from exercise
	SLC2A9 (AR)	GLUT9 uric acid transporter	

AD=autosomal dominant; AR=autosomal recessive; XL=X-linked.

Table 2: Interpretation of urinary biochemical profiles

Parameter	Expected Daily Values	Interpretation
Total Volume	≥ 2.5 L	Diminishes with low fluid intake, sweating, and diarrhea
pH	5.8-6.2	<5.5 increase risk of uric acid precipitation commonly found in uric acid stone patients, subjects with intestinal disease and diarrhea, and those with intestinal bypass surgery >6.7 increase risk of calcium phosphate precipitation seen in patients with dRTA, primary hyperparathyroidism, alkali overtreatment, repeated shock wave lithotripsy >7.0-7.5 indicates a urinary tract infection as a result of urease-producing bacteria
Creatinine	15-25 mg/kg body weight	Gauges adequacy of collection. 15-20 mg/kg body weight in females and 20-25 mg/kg body weight in males
Sodium	100 mEq	Reflective of dietary sodium intake in the absence of excessive sweating and/or diarrhea; can cause secondary hypercalciuria
Potassium	40-60 mEq	Reflective of dietary potassium intake in the absence of excessive diarrhea; a marker of dietary alkali intake
Calcium	≤250-300 mg	Direct risk factor and precipitating solute for calcium stones; possible differences between male and female subjects (higher value in males)
Magnesium	≥ 80 mg	Low urinary magnesium reflects low magnesium intake, intestinal malabsorption (small bowel disease), and following bariatric surgery; role as inhibitor is controversial
Oxalate	≤ 45 mg	Direct risk factor and precipitating solute for calcium oxalate stones; seen in intestinal fat malabsorption and sometimes following bariatric surgery; values higher than 100mg/day are suspicious of primary hyperoxaluria
Phosphorous	≤ 1,100 mg	Indicative of dietary phosphorous intake and absorption; high excretion rate may increase the risk of calcium phosphate stone; conditions of renal phosphate leak can also lead to hypercalciuria
Uric acid	600-800 mg	Can contribute to uric acid stones when urinary pH is low; can also increase risk of calcium oxalate stones; encountered with the overindulgence of purine-rich foods; values > 1,000 mg may indicate rare enzyme deficiencies
Sulfate	≤25-30 mmol	Sulfate is a marker of the acid content in the diet; dietary acid intake is important to guide interpretation of urine pH, citrate, ammonium excretion
Citrate	≥ 320 mg	Principal inhibitor of calcium stone formation; hypocitraturia is encountered in states with intracellular acidosis such as metabolic acidosis, dRTA, chronic diarrhea, excessive protein ingestion, frequent strenuous physical exercise, potassium deficiency, carbonic anhydrase inhibitors, and, rarely, ACE inhibitors
Ammonium	30-40 mEq	Ammonia is a major buffer that carries protons in the form of ammonium; its excretion usually corresponds with dietary acid load (marked by urinary sulfate); a high ammonium-to-sulfate ratio indicates nondietary acid load such as GI alkali loss or high endogenous acid production
Chloride	100 mEq	Usually corresponds with sodium intake and excretion; renal sodium bicarbonate loss may lead to discrepancies in urine sodium and chloride
Cystine	≤ 30-60 mg	Limited urinary solubility at 250 mg/L

ACE=Angiotensin-Converting Enzyme; dRTA=distal renal tubular acidosis; GI=gastrointestinal.

These limits are mean ± 2 standard deviations (for calcium, oxalate, uric acid, pH, sodium sulfate, and phosphorus) or mean -2 standard deviations (for citrate, pH, and magnesium) from normal.

Table 3: Medicinal plants used in treatment of urinary tract and kidney stones

Plant name/family/local name	Mode of intake and use
<i>Medicago sativa</i> , (Fabaceae), Alfalfa	An alfalfa juice concentrate can dramatically improve the kidney function. Increase kidney function helps to rid the body of toxins and increases the flow of urine.
<i>Vaccinium myrtillus</i> , (Ericaceae), Blueberry	The dried berries and leaves of the bilberry (Blueberry) plant have been shown to be successful in curing and preventing urinary tract infections. Acting as an antiinflammatory, blueberry extracts can eliminate and/or inhibit the spread of UTI Bacteria ^{28,29} .
<i>Echinacea</i> , (Asteraceae)	Echinacea is often referred to as the "wonder drug" of herbs. Used to treat everything from the common cold to the flu, this herb also helps fight off urinary tract infections. Echinacea helps strengthen the immune system and fight off bacterial infections.
<i>Bryophyllum pinnatum</i> (Lamk.) Oken. (Crassulaceae), <i>Patharchata</i> , <i>Ajuba</i> , <i>Ghavpatta</i> , <i>Parnbeej</i>	Fresh leaf juice along with 2-3 <i>Kalimirch</i> (<i>Piper nigrum</i> Linn.) powder is taken twice a day for 15 days.
<i>Crataeva nurvala</i> Buch-Ham. (Capparaceae), <i>Barna</i> , <i>Varuna</i>	Bark decoction twice daily for seven days is given in urinary tract infection (UTI) and for stone removal.
<i>Hydrastis Canadensis</i> , (Ranunculaceae), Goldenseal Root	It can be taken several times per day in the form of a tea or in capsule or tincture form. Because it can cause premature contractions of the uterus, Goldenseal is not recommended for women who are pregnant ³⁰ .
<i>Daucus carota</i> Linn. (Apiaceae), <i>Gajar</i>	One glass <i>Gajar</i> juice is taken regularly for a fortnight to expel stones from urinary bladder and kidney.
<i>Equisetum debile</i> Roxb. (Equisetaceae), <i>Jode tode ki ghas</i>	Whole plant juice is given along with 1 gm <i>Piper nigrum</i> Linn. Twice a day for 7 days for removal of stones.
<i>Gomphrena celosoides</i> Martius (Amaranthaceae), <i>Kasia</i>	Whole plant juice along with 4 <i>Piper nigrum</i> Linn. And lemon juice taken twice a day for 10 days to cure urolithiasis.

<i>Musa balbisiana</i> Colla. (Musaceae), <i>Kela</i>	Decoction of <i>Musa</i> roots and <i>gulli</i> (axis of maize cob, <i>Zea mays</i> Linn.) is given twice daily for 7 days in complaints of kidney and urinary tract stones and severe pain.
<i>Achras zapota</i> , (Sapotaceae) Chikku fruit	2. Juices of chiku fruit have also shown ability of dissolving urinary stones ³¹ .
<i>Solanum surattense</i> Burm (Solanaceae), <i>Ber Kateli</i> , <i>Neeli Kateli</i>	Root powder along with <i>Bari Kateli</i> (<i>Solanum indicum</i> Linn.) root powder is given with curd daily for two weeks.
<i>Arctostaphylos uva-ursi</i> , (Ericaceae), Bearberry	<i>Uva ursi</i> is an herb with antiseptic and diuretic properties that helps soothe the urinary tract as well as strengthens it. It can also be ingested in the form of a tea several times per day ³² .
<i>Tribulus terrestris</i> Linn. (Zygophyllaceae), <i>Gokhuru</i> , <i>Chhota gokhuru</i>	Fruits and root decoction thrice a day is taken regularly for a fortnight to help in expelling kidney stones.
<i>Zea mays</i> Linn. (Poaceae), <i>Makka</i> , <i>Makki</i>	Decoction of styles obtained from female inflorescence or immature cobs are given twice daily for 7 days.
<i>Aerva lanata</i> (Linn.) juss. (Amaranthaceae), <i>Chaya</i>	Whole plant decoction of <i>Chaya</i> , along with Castor (<i>Ricinus communis</i> root) and <i>Gokhuru</i> (<i>Tribulus terrestris</i> Linn.) fruit is given twice a day for two weeks to cure stones. Root decoction is also used.
<i>Cynodon dactylon</i> (Linn.) Person (Poaceae), <i>Doobghas</i> , <i>Doobra</i> , <i>Hari Doob</i>	Root decoction is given with honey or <i>misri</i> (Clarified and crystallised sugar) twice daily for 3 weeks to cure urolithiasis.
<i>Urtica dioica</i> , (Urticaceae), Nettle	Drinking one cup of nettle leaf tea up to six times per day can help to flush your system and help relieve the symptoms of a urinary tract infection. Nettle acts as an anti-inflammatory and can help reduce pain and swelling that often accompanies a urinary tract infection. It also works as a diuretic, so it increases the flow of urine helping to flush out bad bacteria. It also helps reduce bloating. Nettle is also rich in minerals, which naturally help combat UTIs ³³ .
<i>Abutilon indicum</i> (Linn.) sweet (Malvaceae), <i>Kanghi</i>	Leaf juice taken twice daily for two weeks is efficacious for the treatment stones.
<i>Trianthema portulacastrum</i> Linn. (Ficoideae), <i>Saunthi</i> , <i>Lalsubni Patharchata</i> , <i>Bishkapra</i>	Fresh leaf juice is given twice a day for a week in case of stone problem.
<i>Ricinus communis</i> Linn. (Euphorbiaceae), <i>Arandi</i> , <i>Arand andi</i> , <i>Chian</i>	Root decoction along with half a gram <i>sunthi</i> (dried and powdered rhizomes of <i>Zinziber officinale</i> Rosc.), one pinch of <i>Heeng</i> (<i>Ferula asfoetida</i> Linn.) and common salt is taken twice daily for 7 days to treat kidney stones.
<i>Boerhaavia diffusa</i> Linn. (Nyctaginaceae), <i>Bishkapra</i> , <i>Punarnava</i>	Root decoction is taken daily for one month.

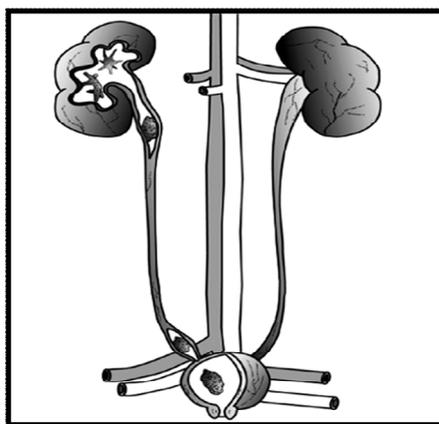


Figure 1: Kidney stones in the kidney, ureter, and bladder

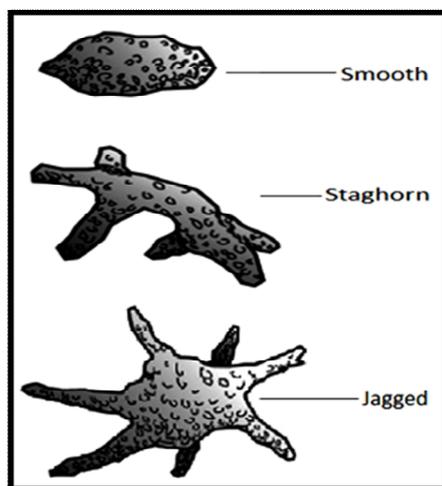


Figure 2: Shapes of various stones

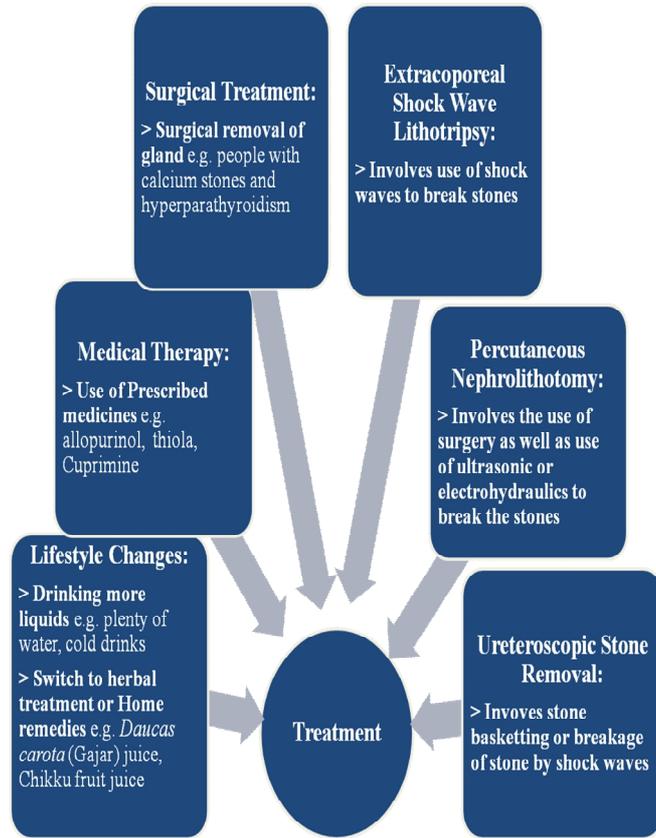


Figure 3: Various treatments of arthritis

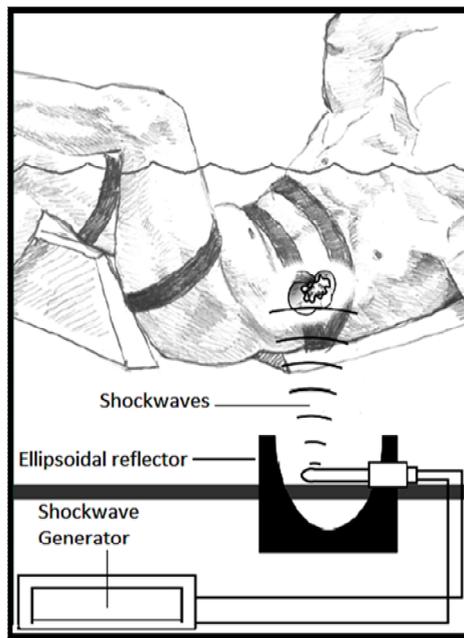


Figure 4: Extracorporeal shock wave lithotripsy

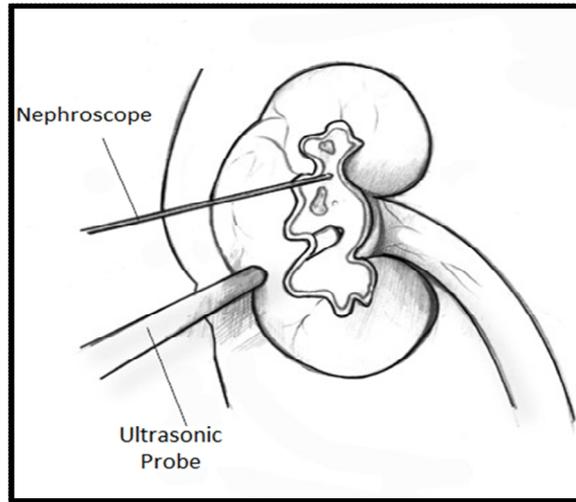


Figure 5: Percutaneous Nephrolithotomy(PNL)

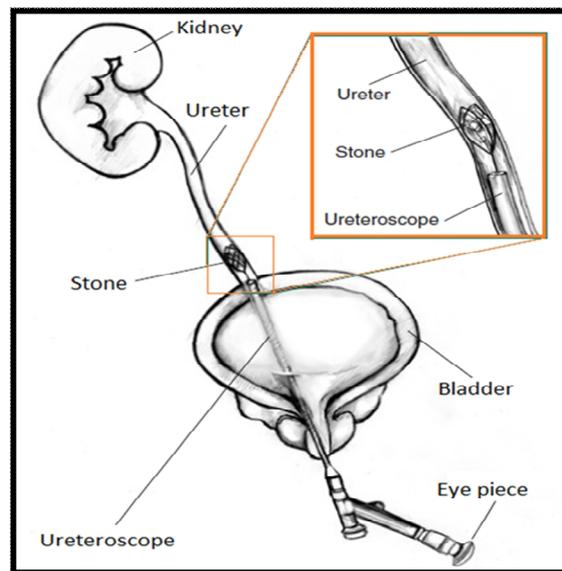


Figure 6: Ureteroscopic Stone Removal