The Future of Stone Management

Reviewed by:
Dr Ajit Saxena
Pioneer, Urology Robotic Surgery
M.S., FRCS (Edin), FICS
MNAMS (Urol), Dipl. Urology (London)
Senior Consultant Urologist & Andrologist
Indraprastha Apollo Hospitals, Delhi

Prologue

There has been a substantial global increase in the prevalence of urolithiasis. It is one of the most pervasive diseases of the urinary system and recurrence of renal stones remains to be a serious problem in human health.[1] Around 50% patients suffer at least one recurrence in their life time, and 10 to 20% experience three or more further episodes of urolithiasis.[2] The increase in incidence of women affected by urolithiasis has outpaced that of men. Although it continues to be more common in men, the incidence rate ratio of men to women with urinary tract stones has narrowed from 3.4 to 1.3.[3] Estimatedly, about 12% of the Indian polulation is currently affected with urinary stones, half of which may end up with loss of kidney functions.[3]

The prevalence rate of urolithiasis is further expected to increase owing to lifestyle modifications, dietary habits and global warming. It is also noteworthy that there exist essential variations in the prevalence of urolithiasis across different geographical regions due to nutritional patterns, climate, environment, ethnicity, and heredity (Figure 1).[2,3]

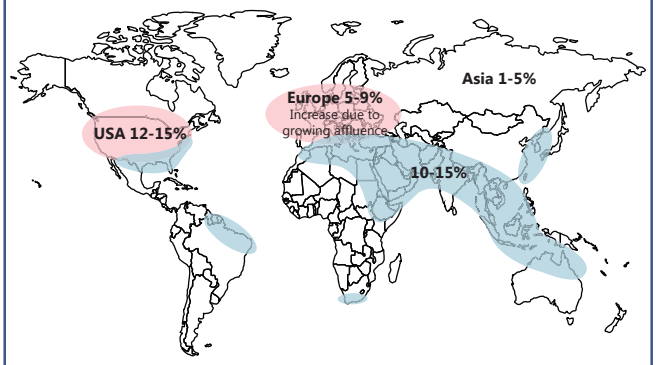
Obesity, diabetes, hypertension and metabolic syndrome are considered as important risk factors for stone formation; conversely, stone formers are also at risk of hypertension, chronic kidney disease (CKD) and end-stage renal disease (ESRD).[3,4]

Advancements in Diagnostic Investigations of Urolithiasis

Stone analysis

The most important factors influencing decisions regarding urologic interventions are stone location, size, composition, and patient symptoms.[5] (Figure 2 and Figure 3). Various chemical and physical analytical methods can be used for identification of stone components. Despite their low cost, chemical methods are often inadequate for accurately analyzing urinary calculi.

Figure 1: Urolithiasis: Prevalence belt



Source: Fisang C, Anding R, Müller SC, *et al*. Urolithiasis--an interdisciplinary diagnostic, therapeutic and secondary preventive challenge. *Dtsch Arztebl Int*. 2015;112(6):83–91.

Among physical methods, X-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FTIR) are currently the most popular techniques for stone analysis.[6]

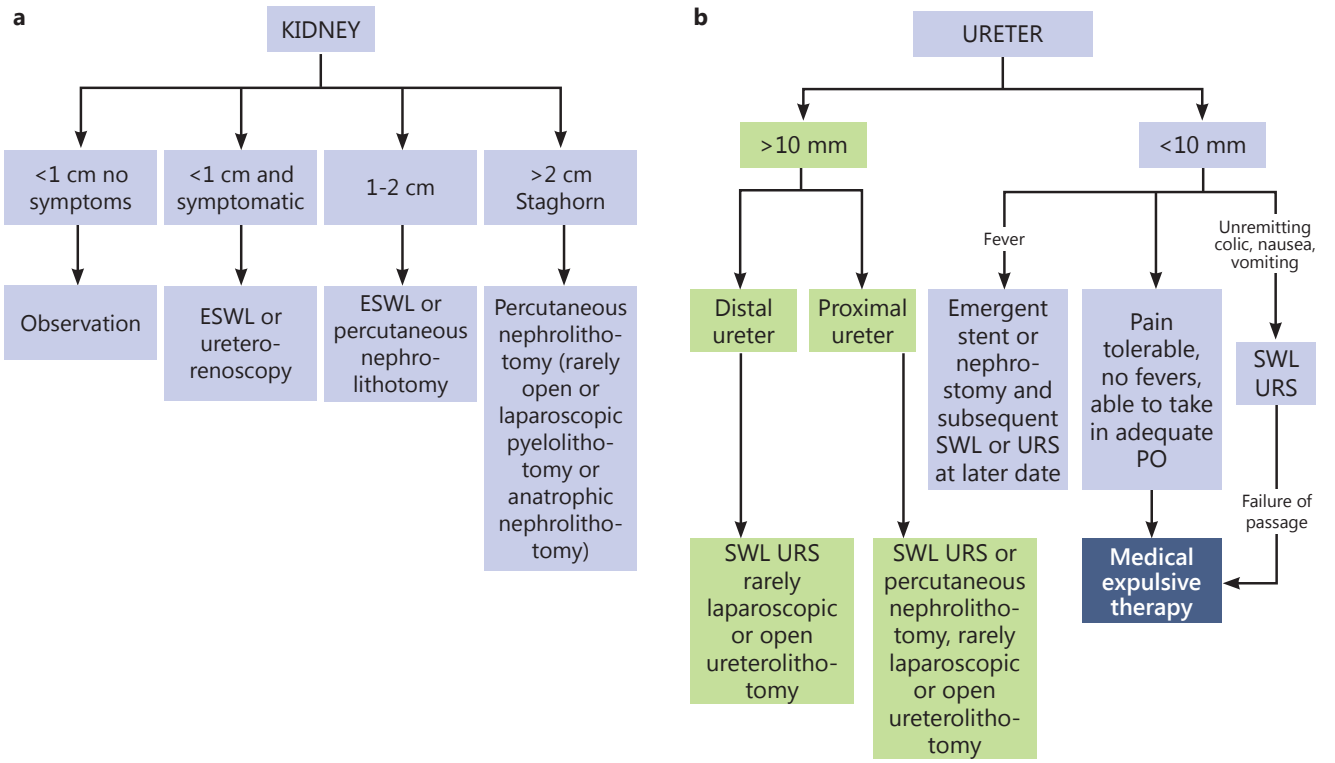
These methods are able to identify non-calcium stones such as cystine, 2,8-dihydroxyadenine, xanthine, uric acid, urates, methyl-1 uric acid, struvite, proteins, lipids or drugs, as well as calcium oxalate (CaOx) and/or calcium phosphate (CaPh) stones.

Moving forwards, new technology and innovations are currently being designed and tested to enhnace the accuracy of stone analysis as it is paramount in assessing the environmental factors behind the process of stone formation and also in identification of other underlying lithogenic processes.[7]

Nanoscale Flow Cytometry

A new non-invasive and high throughput method of evaluating stone burden and subtype, currently underway is the nanoscale flow cytometry which involves analyzing urine samples for the presence of nanocrystals that bind fluorescent alendronate probes. Nanoscale flow cytometry

Figure 2: Investigations based treatment options for stone management



Abbreviations: ESWL = extracorporeal shock wave lithotripsy, PO = per os [by mouth (ie, nutrition)], URS = ureteroscopy.

Source: Kambadakone AR, Eisner BH, Catalano OA, Sahani DV. New and evolving concepts in the imaging and management of urolithiasis: urologists' perspective. Radiographics. 2010 May 4;30(3):603-23

can be used to infer calculi composition and burden in a quantitative manner with greater accuracy. It can be performed to enhance clinical follow-up for patients making lifestyle changes and also assessing response to treatments such as shock wave lithotripsy.[8]

Petrographic Thin Sectioning of Calculi

Another method known as petrographic thin sectioning of calculi, currently under research can prove highly beneficial due to its ability to examine the calculi in their entirety; its a very accurate method of determining composition of calculi and should be adopted as part of the full clinical workup of calculi analysis.[8]

Imaging Techniques

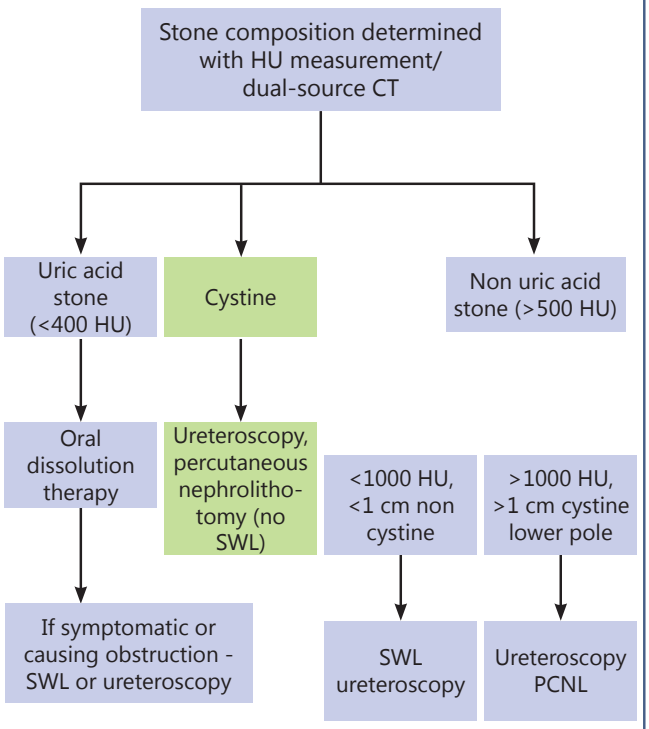
Imaging is the most important diagnostic tool that offers confirmation of the diagnosis made on behalf of the familial history, physical examination and laboratory tests.[6] Conventional abdominal (kidney, ureter, bladder [KUB]) radiography as the sole imaging modality for the evaluation of nephrolithiasis is limited by several factors, including bowel gas, extrarenal calcification, and large patient habitus. These factors diminish the sensitivity of KUB radiography.[5]

Real-time ultrasound is now being used as a first-line imaging technique for urolithiasis during pregnancy, as it does not involve risks of radiation exposure like teratogenicity, mutagenicity and carcinogenicity to the foetus. It is also the imaging tool of choice for detecting and locating renal stones in children. The technique is very cost effective and can detect all types of stones except for its incapability of detecting ureteral calculi.[6,9]

Intravenous pyelography is much more sensitive than KUB and ultrasound. However, it is not recommended due to potential adverse effects associated with the contrast media that range from nausea, flushing, bradycardia to nephrotoxicity and anaphylactic reactions.[6]

The specificity of magnetic resonance imaging (MRI) for stone visualization is as high at 98.3%. A major advantage of

Figure 3: Possible stone treatment options based on CT investigations



Abbreviations: CT = computed tomography, SWL = shock wave lithotripsy, PCNL = percutaneous nephrolithotomy, HU= hounsfield unit.

Source: Kambadakone AR, Eisner BH, Catalano OA, Sahani DV. New and evolving concepts in the imaging and management of urolithiasis: urologists' perspective. Radiographics. 2010 May 4;30(3):603-23.

MRI is the ability to provide 3D imaging without radiation. Unfortunately, the drawbacks of MRI prevent it from widespread use in stone imaging. MRI costs about three times more than a CT scan and has lower accuracy and much longer image acquisition times.[6,9]

Noncontrast helical computed tomography (non helical CT) has become increasingly popular owing to its speed, accuracy and its efficiency in detecting all types of stones at any location with the exception of some stones that are caused by the precipitation of protease-inhibitor medications in the urine. It is known to have sensitivity and specificity of 96-100% and accuracy of 96-98%.[6,9] The only drawback of this technique is the high amount of ionising radiations required for imaging because of which, it cannot be used in pregnant women and children.[6]

The shortfalls of regular CT are overcome by new age advancements such as low dose CT, dual energy CT.[6]

Low-dose Computed Tomography

Low-dose CT is a method of reducing radiation exposure by lowering the tube current to the radiation source. A traditional noncontrast CT might use a tube current of 100 mAs, whereas in low-dose CT the tube current decreases to 30 mAs or lower. In comparison with standard CT, the sensitivity of low-dose CT is excellent, at 99% with a specificity of 94%. However, image quality and accuracy tends to decrease with reduced tube current.[5,6,9]

Dual Energy Computed Tomography

Dual energy CT (DECT) is a recent exciting innovation to overcome the shortfalls of non helical CT. DECT possesses two X-ray sources and two detector units and utilizes differences in X-ray attenuation properties of the constituents of stones for determining the mineral composition of stones. When viewed with DECT, stones appear in varied colors depending upon their type.[6] With DECT, the *in vivo* composition of urinary stones may be separated into three distinct groups: uric acid, cystine, and calcium. A single DECT examination may contribute to not only the identification but also the chemical characterization of stones in the urinary tract, and it may contribute to surgical and medical treatment decisions.[10]

Despite the fact that renal calculi has high intensity values in the CT images, many bright spots also exist in kidney regions due to image noise that can yield false positive results.[11] Two accurate and novel strategies have been designed to address this issue that are currently in experimental stages ; total variation (TV) flow to reduce image noise and maximally stable extremal region (MSER) to robustly extract renal calculi from smoothed images by choosing image blobs with stable volume adaptable to a range of intensity thresholds.[11]

These imaging modalities are currently experimental but may come up with more benefits and wider acceptance.[6,9]

Digital Tomosynthesis

Digital tomosynthesis combines KUB radiography with computer integration of the image data from an opposed detector. This procedure assists in visualization of stones from multiple angles rather than simply anterior to posterior. For patients with kidney stones, imaging at multiple angles improves sensitivity and specificity with scant increases in radiation exposure.[10]

Recent Advancements In The Treatment Options of Urinary Stone Disease:

Medical Expulsive Therapy

The most frequent strategy for treatment of urolithiasis presenting with acute renal colic is conservative management with the aim of achieving spontaneous passage of the urinary stone.[2] Current guidelines endorse the use of alpha-blockers to facilitate passage of ureteral stones less than 10 mm in diameter in appropriately selected patients. Alpha-blockers promote spontaneous passage and reduce episodes of colic. However, caution should be taken in case of elevated parameters of retention or infection parameters. Moreover, conservative treatment is not appropriate if despite adequate analgesia the patient continues to suffer pain or symptoms such as nausea and vomiting.[12]

Surgical Intervention

Extracorporeal shock wave lithotripsy (ESWL) uses high–energy shock waves to fragment the stone; the patients subsequently pass out the fragments.[12] Recent technical innovations have taken place in ESWL machines to overcome shortfall of the conventional machines.

Flexible ureteroscopy (fURS) has also been through significant technological and technical advancements. The first combined rigid and flexible ureteroscope "the Sun's ureteroscope" possesses a retractable rigid shaft and flexible tip that enables the operator to treat ureteral and intrarenal stones efficiently without the need to exchange from one endoscope to another. The Sun's ureteroscope has resulted in short operative time with an overall stone-free rate (SFR) of 83%.[13]

Standard Percutaneous Nephrolithotripsy (PCNL) is usually performed through 24- to 30-Fr percutaneous tracts. Recently, several reports have indicated towards the risk of bleeding with conventional PCNL.

Recent studies have also evaluated the validity of retrograde intrarenal surgery (RIRS) as a fist-line therapy for stones larger than 2 cm. The benefit of using this technique in stones >20 mm is the smaller rate of complications in comparison with PCNL and the shorter hospitalization time.[15]

The techniques described above are being currently used in practice. Though they are helpful in alleviation of urolithiasis to a large extent, certain risks (postoperative pain, potential renal damage, and bleeding) and inconveniences are associated with them.[14] For this reason, newer modified techniques like miniperc/ultraperc have evolved (Table 1). Therefore, the following furtherance and explorations have been made for the management of patients with kidney stones.

Table 1: Summary of the advances or technical aspects of laser lithotripsy

	Advancement or technical aspect	Benefit
Laser lithotripters	Long pulse length (pulse duration or pulse width)	• Less fiber tip degradation • Less stone retropulsion • Smaller residual fragments • Ideal for "dusting"
	Moses effect (modulated laser pulse)	• More ablative (in vitro) • Less retropulsion
	Burst laser lithotripsy	• Greater ablation volume
	Thulium laser (pulsed)	• More ablative than Ho:YAG • Less retropulsion
Laser fibers	Ball tip fiber	• Easier insertion in deflected scope
	Tip cleaving tools	• All were equivalent
	Leaving fibers coated	• Greater stone ablation • Easier to pass in the scope • Safer than stripped fiber
	Stripping of fibers	• Debatable higher stone ablation
Laser settings and technique	Fragmentation technique	• Faster ablation of primary stone
	Dusting technique	• No fragments (dust) • No basketing • Decreased ureteral access sheath use
	Pop-corning	• Ideal for multiple smaller stone fragments in an enclosed space • Avoids endless chase of fragments
	Pop-dusting	• Similar to pop-corning, but creating more dust

Mini Percutaneous Nephrolithotripsy

Mini-PCNL can be the first-line treatment for renal stones with a diameter larger than 2 cm in children, and general indications for mini-PCNL in adults may include renal stones less than 2 or 2.5 cm in size with previous failure of ESWL.[14]

Laser Lithotripsy Using Holmium

YAG laser has become the standard for stone lithotripsy due to its efficacy and safety. The holmium laser is effective for any composition of stones. Stones are ablated via a photothermal effect, the laser radiation being absorbed by residual water in the stone, creating a vapour pressure that breaks the stone.[16]

Recently, a novel Ho:YAG laser lithotripsy mode has been developed called as burst laser lithotripsy. Each burst consists of three individual laser pulses, the first one being more energy intense while the last one the least energy intense, having successive increasing pulse lengths and which are emitted in a rapid succession after one another. The novel burst mode is significantly more ablative, achieving 60% higher ablation volumes than standard lithotripsy at similar power and energy settings.[16]

Wide Focal Zone Shock Wave Generators

Wide focal zone shock wave generators have come into picture, which are basically lithotripters, differing in their acoustic output (i.e. the dimensions and pressures of the focal zone (wide focal zone provide more efficient fragmentation).[17] Recently, an intensity focused ultrasound (histotripsy) with an electrohydraulic lithotripter has also demonstrated a significant reduction in fragmentation time *in vitro*.[17]

Conclusion

Despite considerable improvements in the development of new therapies for the management of urinary stones, the incidence of urolithiasis is increasing worldwide. It is certain that renal cell injury, crystal retention, cell apoptosis, Randall's plaque, and associated stone inhibitors or promoters play important roles for kidney stone formation. These should be the critical targets that lead to developing a novel strategy to prevent kidney stone disease and drugs against kidney stones. Identification of novel treatment targets on the basis of molecular and cellular alterations in relation to stone formation can also help in discovery of newer more efficacious drugs and strategies to manage urolithiasis in the near future.

Reference

1. Alelign T, Petros B. Kidney Stone Disease: An Update on Current Concepts. *Adv Urol.* 2018;2018:3068365. Published 2018 Feb 4.
2. Fisang C, Anding R, Müller SC, Latz S, Laube N. Urolithiasis--an interdisciplinary diagnostic, therapeutic and secondary preventive challenge. *Dtsch Arztebl Int.* 2015;112(6):83–91.
3. Roudakova K, Monga M. The evolving epidemiology of stone disease. *Indian J Urol.* 2014;30(1):44–48.
4. Khan SR, Pearle MS, Robertson WG, *et al.* Kidney stones. *Nat Rev Dis Primers.* 2016;2:16008. Published 2016 Feb 25.
5. Kambadakone AR, Eisner BH, Catalano OA, Sahani DV. New and evolving concepts in the imaging and management of urolithiasis: urologists' perspective. *Radiographics.* 2010 May 4;30(3):603-23.
6. Bawari S, Sah AN, Tewari D. Urolithiasis: An Update on Diagnostic Modalities and Treatment Protocols. *Indian J Pharm Sci.* 2017 Apr 30;79(2):164-74.
7. Cloutier J, Villa L, Traxer O, Daudon M. Kidney stone analysis: "Give me your stone, I will tell you who you are!". *World J Urol.* 2014;33(2):157–169.
8. Gavin, Carson T., et al. "Novel methods of determining urinary calculi composition: petrographic thin sectioning of calculi and nanoscale flow cytometry urinalysis." *Scientific reports* 6 (2016):19328.
9. Andrabi Y, Patino M, Das CJ, Eisner B, Sahani DV, Kambadakone A. Advances in CT imaging for urolithiasis. *Indian J Urol.* 2015;31(3):185–193.
10. Hidas G, Eliahou R, Duvdevani M, Coulon P, Lemaitre L, Gofrit ON, Pode D, Sosna J. Determination of renal stone composition with dual-energy CT: in vivo analysis and comparison with x-ray diffraction. *Radiology.* 2010 Nov;257(2):394-401.
11. Liu J, Wang S, Turkbey EB, Linguraru MG, Yao J, Summers RM. Computer-aided detection of renal calculi from noncontrast CT images using TV-flow and MSER features. *Med Phys.* 2014;42(1):144–153.
12. Scales CD Jr, Tasian GE, Schwaderer AL, Goldfarb DS, Star RA, Kirkali Z. Urinary Stone Disease: Advancing Knowledge, Patient Care, and Population Health. *Clin J Am Soc Nephrol.* 2016;11(7):1305–1312.
13. Alenezi H, Denstedt JD. Flexible ureteroscopy: Technological advancements, current indications and outcomes in the treatment of urolithiasis. *Asian J Urol.* 2015;2(3):133–141.
14. Kim BS. Recent advancement or less invasive treatment of percutaneous nephrolithotomy. *Korean J Urol.* 2015;56(9):614–623.
15. Rodríguez-Monsalve Herrero M, Doizi S, Keller EX, De Coninck V, Traxer O. Retrograde intrarenal surgery: An expanding role in treatment of urolithiasis. *Asian J Urol.* 2018;5(4):264–273.
16. Kronenberg P, Somani B. Advances in Lasers for the Treatment of Stones-a Systematic Review. *Curr Urol Rep.* 2018;19(6):45. Published 2018 May 17.
17. Elmansy HE, Lingeman JE. Recent advances in lithotripsy technology and treatment strategies: A systematic review update. *Int J Surg.* 2016;36(Pt D):676–680.