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Kidney stones

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Abstract

Kidney stones are mineral deposits in the renal calyces and pelvis that are found free or attached to the renal papillae. They contain crystalline and organic components and are formed when the urine becomes supersaturated with respect to a mineral. Calcium oxalate is the main constituent of most stones, many of which form on a foundation of calcium phosphate called Randall's plaques, which are present on the renal papillary surface. Stone formation is highly prevalent, with rates of up to 14.8% and increasing, and a recurrence rate of up to 50% within the first 5 years of the initial stone episode. Obesity, diabetes, hypertension and metabolic syndrome are considered risk factors for stone formation, which, in turn, can lead to hypertension, chronic kidney disease and end-stage renal disease. Management of symptomatic kidney stones has evolved from open surgical lithotomy to minimally invasive endourological treatments leading to a reduction in patient morbidity, improved stone-free rates and better quality of life. Prevention of recurrence requires behavioural and nutritional interventions, as well as pharmacological treatments that are specific for the type of stone. There is a great need for recurrence prevention that requires a better

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understanding of the mechanisms involved in stone formation to facilitate the development of more-effective drugs.

Kidney stones (calculi) are mineral concretions in the renal calyces and pelvis (FIG. 1) that are found free or attached to the renal papillae. By contrast, diffuse renal parenchymal calcification is called nephrocalcinosis[1]. Stones that develop in the urinary tract (known as nephrolithiasis or urolithiasis) form when the urine becomes excessively supersaturated with respect to a mineral, leading to crystal formation, growth, aggregation and retention within the kidneys[2]. Globally, approximately 80% of kidney stones are composed of calcium oxalate (CaOx) mixed with calcium phosphate (CaP). Stones composed of uric acid, struvite and cystine are also common and account for approximately 9%, 10% and 1% of stones, respectively[3]. Urine can also become supersaturated with certain relatively insoluble drugs or their metabolites, leading to crystallization in the renal collecting ducts (iatrogenic stones). For example, patients with HIV who are treated with protease inhibitors such as indinavir and atazanavir are at risk for developing nephrolithiasis[4]. Both indinavir and atazanavir are metabolized by the liver, with a considerable proportion of the drug excreted in the urine unchanged, leading to their crystallization and the formation of kidney stones[5]. Even when given as part of a multiple drug regimen, atazanavir can crystallize in the urine and form kidney stones[6].

Poorly soluble dietary contaminants can also crystallize and form stones. For example, melamine has been implicated in the deaths of dogs and cats[7,8] and caused a major health emergency in China in 2008. Melamine adulteration of infant formula led to the development of stones and sand-like calculi in the urinary tracts of >294,000 infants[9,10], >50,000 of whom were hospitalized; six patients died as a result.

Stone formation is a common disease, with an estimated 5-year recurrence rate of up to 50%[11]. The prevalence of stones has been consistently increasing over the past 50 years and further increases are expected owing to changing lifestyle, dietary habits and global warming[12–14]. Obesity[15], diabetes[16–18], hypertension[13,17,19] and metabolic syndrome[20] are considered risk factors for stone formation; conversely, stone formers are at risk of hypertension[19,21], chronic kidney disease (CKD) and end-stage renal disease (ESRD)[22–25]. The costs associated with stone disease have also risen, increasing from an estimated US$2 billion in 2000 to over US$10 billion in 2006 in the United States alone[26].

Major advances have been made in the medical and surgical management of patients with kidney stones. Stones can be fragmented using shockwave lithotripsy (SWL) to enable them to pass in the urine, or surgically removed using percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS). PCNL involves direct endoscopic access into the kidney through an incision in the flank, whereas RIRS is performed using a flexible fibre-optic ureteroscope to access the upper urinary tract through natural passageways. Medical therapies are being used to ease stone passage, promote expulsion and reduce stone recurrence. Important advances have also been made in our understanding of stone pathogenesis. This Primer focuses on the medical and surgical management currently practiced, as well as the contemporary understanding of stone pathogenesis.

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Epidemiology

A recent review of epidemiological data from seven countries revealed incidence rates for kidney stones of 114–720 per 100,000 individuals and prevalence rates of 1.7–14.8%, and in nearly all countries, the rates seem to be rising[27]. According to data from the National Health and Nutrition Examination Survey (NHANES), the self-reported prevalence of kidney stones in the United States has increased nearly threefold, from 3.2% in the period 1976–1980 to 8.8% in 2007–2010 (REFS 12,28). The lifetime prevalence of kidney stones in the United Kingdom increased by 63% (7.14–11.62%) between 2000 and 2010 (REF. 29).

The propensity to form stones varies according to sex, ethnicity and geography. Although historically stones have been 2–3-times more common in men than in women, recent data indicate that this disparity is diminishing. For example, data from the US Nationwide Inpatient Sample revealed a decline in the male to female ratio for hospital discharges for stones, from 1.7 in 1997 to 1.3 in 2002 (REF. 30). The male to female ratio of incident kidney stones also declined in Rochester, Minnesota, USA, from 3.1 to 1.3, between 1970 and 2000 (REF. 31). In Florida (USA), analysis of resource use related to procedures for stones revealed that the increase in rates in women was greater than that in men between 1998 and 2004 (REF. 32). In Canada, a 48% increase in stone treatment between 1991 and 2010 was primarily accounted for by an increase in procedures among women[33]. The reason for the surge in stone disease in women is not precisely understood, but some have speculated that it might be attributable to changes in lifestyle and diet, resulting in increased obesity among women, a known risk factor for stone formation[30].

Racial and ethnic differences in stone prevalence have long been recognized. In the United States, non-Hispanic white individuals have the highest prevalence among racial and ethnic groups (10.3%), followed by Hispanics (6.4%) and non-Hispanic African Americans (4.3%)[12]. Comparison of NHANES II (1988–1994) with NHANES III (2007–2010) data has shown that the rise in kidney stone prevalence among Hispanics and African Americans was nearly double that of their white counterparts[12,28].

Geographical variation in stone disease typically reflects environmental risk factors, with higher stone prevalence in hot, arid climates. In the United States, kidney stones are most prevalent in the south and southeast regions and are lowest in the west of the country[28,34–37]. After controlling for other factors, ambient temperature and sunlight have been shown to be independently associated with stone prevalence[35].

Numerous systemic diseases and factors have been associated with an increased risk of kidney stones. Weight, weight gain, body mass index[15,38,39] and diabetes[18,40] have been shown in large prospective cohort studies to correlate with the risk of incident kidney stones, with a greater effect in women than in men in some cohorts. A multivariable model based on recent NHANES data showed that obesity and diabetes were associated with a 55% (95% CI: 1.25–1.94; $P < 0.001$) and a 59% (95 %CI: 1.22–2.07; $P < 0.001$) increased risk of kidney stones, respectively[12]. Metabolic syndrome has also been linked to risk of kidney stones, with NHANES data indicating that the number of metabolic traits correlates with the risk of stones[41]. Jeong and colleagues[42] detected a 25% higher rate of radiographically

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detected kidney stones among individuals with metabolic syndrome in a screened population in Asia, after adjusting for confounding variables (95% CI: 1.03–1.50; $P < 0.001$).

Finally, risk of cardiovascular disease has been associated with a history of kidney stones, although a cause and effect relationship has not been definitively established. Ferraro and colleagues[43] showed a modest increased risk of incident cardiovascular disease among women with a history of stones (an adjusted multivariable hazard ratio of 1.30; 95% CI: 1.04–1.62) but not in men in three large prospective cohorts. Similarly, among individuals registered in the Canadian health care system, a 63% higher risk of incident myocardial infarction was detected among stone formers (95% CI: 1.51–1.76), with a greater effect in women than in men[44]. A matched pair analysis, adjusted for confounding factors, revealed a 31% higher risk of myocardial infarction in stone formers than in the general population in Olmstead County, Minnesota, USA (95% CI: 1.02–1.69)[45].

Mechanisms/pathophysiology

Data from patients with stone disease provide visual and histological observations of the kidneys, microscopic and biochemical analyses of the urine and determination of the crystalline nature of the stones. Such observational data only produce a ‘snapshot’ at the end of a long process of the stone formation. To understand the mechanistic details theoretical, animal and cell culture models have been developed. Indeed, results obtained from such studies are providing a better understanding of the pathogenesis of stone formation and are described here.

Microstructure of kidney stones

Kidney stones are solid masses, ranging in size from a grain of sand to a pearl (or larger) — a stone does not have to cause symptoms. Depending on their composition, stones are either yellow or brown in colour and smooth or jagged in appearance. They are composed of crystals (FIG. 2) and a ubiquitous organic matrix (FIG. 3), which not only coats the crystals but is also present inside the crystals and the inter-crystalline spaces[46–48]. The matrix of calcific stones contains many macromolecules, including osteopontin (which also has a role in the biomineralization of bone), inter-α-inhibitor (which is a plasma protein) and urinary prothrombin fragment 1 (UPTF1) — all of which are normally present in the urine[49], albeit in small quantities[49–51]. The matrix also contains various forms of lipids, which have been shown to induce crystal nucleation[52–56]. The association between the crystals and the matrix seems to start early upon crystal nucleation and continues throughout the formative and growth phases of the developing stone. Although some urinary molecules, such as UPTF1, are considered crystallization inhibitors, others such as osteopontin can act as both inhibitors and promoters of crystallization[57]. These molecules seem to be produced as a protective response against mineralization. However, both CaOx and CaP crystals have been shown to induce the production of macromolecules that inhibit and/or modulate crystallization[51,58–60].

Calculi types—The four main types of stones are named after their major constituents. Calcium stones are the most common and occur as CaOx and CaP crystals, alone or in combination. Most kidney stones are partially or completely composed of CaOx, which exists as a monohydrate or dihydrate. Individual crystals of CaOx monohydrate (COM) are

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thin and plate-like, and generally acquire a ‘dumb-bell’ shape through twinning, as seen in urinary sediments. Inside the stones, COM crystals are arranged radially into fan-shaped profiles with distinct concentric laminations, showing outward growth of the crystals and stones. CaOx dihydrate (COD) crystals have characteristic tetragonal bipyramidal shape both in urinary sediment and in kidney stones. CaOx stones are small with shiny exteriors and generally contain both COM and COD crystals. COM stones are more common than the pure COD stones[61]. In mixed stones, COD crystals are predominantly present on the stone surface, which appears jagged. By contrast, pure COM stones have smooth surfaces. CaOx stone formation is a multistep process (see below). Hypercalciuria, hyperoxaluria and hypocitraturia are major risk factors.

CaP is mainly found as basic CaP (apatite), calcium hydrogen phosphate dihydrate (brushite) or tricalcium phosphate (whitlockite). Pure CaP stones are rare[62]. Apatite is the most common crystal in kidney stones and is often a powdery mass that fills the spaces in between other types of crystals, mainly CaOx crystals. Whitlokite is very rare in both kidney stones and urinary sediments. Brushite frequently occurs in kidney stones and is present as rosettes of radially arranged thin blade-like crystals. Hypercalciuria, hypocitraturia and increased urinary pH are major risk factors for CaP stone formation[63].

Uric acid stones comprise 8–10% of all kidney stones worldwide, with a disproportionate prevalence in stone formers who are obese and insulin resistant — two of the main components of metabolic syndrome. Unlike calcium stone types, overly acidic urine (a pH of <5.5) is recognized as the main abnormality responsible for uric acid nephrolithiasis[64]. In addition to the insolubility of uric acid at low urinary pH and dehydration, conditions that lead to excessive urinary uric acid excretion, known as hyperuricosuria, have also been associated with uric acid stone formation. These high levels might be due to excess dietary intake of purine-rich foods[65] or endogenous uric acid overproduction, as occurs in conditions such as gout (gouty diathesis). Increased purine catabolism (which can occur in those with myeloproliferative disorders or in those receiving chemotherapy) and the use of drugs that prevent renal reabsorption of uric acid are also contributing factors. Most uric acid stones are compact, appearing like pebbles, with a central core of loosely aggregated anhydrous uric acid crystals surrounded by radiating columnar anhydrous uric acid crystals organized in concentric laminations[66,67]. Some stones display a compact outer layer enclosing a porous friable interior consisting of anhydrous uric acid, uric acid dihydrate and COM crystals mixed with organic material.

Struvite stones, also known as ‘infection stones’, represent 7–8% of all stones worldwide and are typically caused by increased production of ammonia secondary to infection with urease-producing organisms, such as *Proteus* or *Klebsiella*. The subsequent alkaline urine leads to the formation of magnesium ammonium phosphate hexahydrate crystals[68]. Struvite and associated carbonate apatite crystals can grow quickly into large stones referred to as staghorn calculi, appropriately named for their horn-like projections that occupy the renal pelvis and renal calyces. Although historically feared for their association with high mortality, struvite stones and their association with urosepsis and infections are now treatable with surgical intervention and antibiotics. In the modern era, these stone types are better known for their preponderance for recurrence, particularly in immunocompromised

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individuals with incomplete stone removal. Struvite stones are large aggregates of orthorhombic ‘coffin-lid’-shaped struvite crystals covered with spherulitic carbonate apatite crystals and mixed with cellular debris, which often included bacteria[67].

Finally, cystine stones form as result of an autosomal recessive defect in the renal transporter of the amino acid cystine[69]. The lack of cystine reabsorption leads to increased urinary cystine excretion. At normal urinary pH, cystine is insoluble and forms cystine crystals that can aggregate to form recurrent kidney and bladder stones. Cystine stones are compact, amber coloured, slightly opaque and with homogenous interiors. Higher magnification of the stone and urinary deposits reveals a unique and characteristic hexagonal structure of the cystine crystals[62].

Chemistry of stone formation

Several models of kidney stone formation have been proposed; the two dominating mechanisms for the initiation of stones are commonly described by the terms ‘free particle’ (in which crystals form ‘Randall’s plugs’ in the tubule) and ‘fixed particle’ (in which stones grow on so-called Randall’s plaques; FIG. 1). Although these models encompass all the possible hypothetical models of how stones begin, no single model can rationalize the evidence observed from all patients with stones — many factors probably contribute. Regardless of the model, the chemical processes of nucleation and crystal growth are essential for the initiation and development of all stone types[70]. Stone formation is caused by an abnormal combination of factors that influence the thermodynamic driving force (supersaturation) and the kinetic (rate-controlling) processes involved in the crystallization of the various stone-forming minerals. The principal thermodynamic driving force for both stages is the degree of supersaturation of the fluid within which initiation occurs[70,71]. Whether this takes place intracellularly or extracellularly, the laws of crystallization chemistry must apply.

Crystal nucleation—Nucleation (in which solute molecules dispersed in a solvent begin to cluster) is the first stage in crystallization and can occur homogeneously or heterogeneously. Homogeneous nucleation requires a high degree of supersaturation with respect to the mineral concerned; *in vitro* this would normally take place in a pure solution containing no particulate matter and in a receptacle that is chemically inert. By contrast, heterogeneous nucleation is the much more likely mechanism through which crystal initiation occurs in the urine[71]. The process can occur in the presence of particulates consisting of proteins, other organic polymers or crystals of another mineral, and is contained within receptacles lined with chemically active cell surfaces. Heterogeneous nucleation requires a lower level of supersaturation than homogeneous nucleation for crystal initiation.

Supersaturation—Estimating the degree of supersaturation of urine with respect to each stone-forming mineral requires the measurement of 15 urinary constituents, including any crystals that may have precipitated before or after micturition (urination)[2,70–75]. Using an iterative ion speciation programme[2,72–75], these data can be used to calculate the concentrations of the various soluble complexes formed between these urinary constituents,

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the ionic strength of the urine and the activity coefficients of all the ions involved. From this information, the relative supersaturation (RSS) of the urine with respect to the mineral concerned can be calculated[73]; this is the theoretical RSS that would be achieved if all potential crystalline material in the urine remained in solution.

The RSS level at which nucleation occurs is known as the formation product of the mineral concerned; it is not a fixed thermodynamic constant, but covers a range of supersaturation values within which *de novo* crystal nucleation can take place. Its value depends on several factors. First, the length of time of incubation affects the RSS. The longer a given supersaturated solution is left to stand, the more likely it is to precipitate crystals. The higher the initial RSS, the shorter is the nucleation time[76]. Low initial levels of RSS generally require longer incubation times before nucleation takes place, which is important when considering the likelihood of crystal nucleation occurring during the short period when urine is forming in the kidneys[77,78]. The second factor that can affect the RSS value is the possible presence of nucleation inhibitors in the urine that could retard the process by 'poisoning' active growth sites on nascent crystals. Most studies on the effect of calcium salt nucleation inhibitors have been carried out using relatively long incubation periods (24–72 hours) and low RSS levels[79,80] that do not mirror the situation in the kidneys. However, many of these presumed inhibitors have been shown to have little effect on the nucleation of calcium salts under conditions that mimic urine crystallization (that is, high RSS levels and short incubation (3–4 minutes)). Furthermore, the RSS of tubular fluid with respect to calcium salts often exceeds their 3–4-minute formation product values[78,81]. Thus, the concept that inhibitors of nucleation play a part in preventing calcium-containing stones is questionable because their effect may be overwhelmed by high ambient levels of supersaturation.

Crystal growth and agglomeration—Once a crystal nucleus is established inside the kidneys[71], exposure to the urine enables the stone to grow by encrustation[82,83]. There are two basic pathways (free-particle and fixed-particle mechanisms) for the establishment of a stone nucleus, both of which can be active in any stone former, although stones from idiopathic stone formers are generally formed attached to plaques[84,85] (FIG. 1).

In the free-particle mechanism[71,77], crystals nucleate, grow and aggregate within the urine of the renal tubules. Once crystals aggregate to form large particles, they are retained inside the kidneys either by becoming too large to pass through the tubular lumens or by attaching themselves to the tubular epithelium[86]. In the presence of high supersaturation, crystal deposits occlude the collecting ducts[87] forming Randall's type 2 lesions or plugs[88], which protrude out into the renal pelvis and become exposed to the pelvic urine. Once tubular openings are blocked, stasis can promote the formation of small stones behind the plugs. Similarly, unattached stones in the renal calyces can also form through the free-particle mechanism.

Support for the free-particle mechanism comes from animal models and tissue culture studies. Experimentally induced hyperoxaluria or hypercalciuria leads to increased urinary supersaturation and the formation of CaOx or CaP crystals in the renal tubular lumen[1,89,90]. Crystals are retained at sites where urinary flow is impeded, either through a narrowing of the tubule as occurs where the proximal tubule meets the loop of Henle or at the papillary

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base where renal tubules bend[91]. Interestingly, the openings of the collecting ducts are slit-like and narrower than the luminal diameter of the duct, which hinders urinary passage and might play a part in ductal plugging[77,86]. Crystal retention is also accomplished by attaching to the renal epithelium, as well as the basement membrane, which has become exposed by epithelial sloughing[1,92].

This mechanism is probably involved in the formation of apatite, brushite and cystine stones, as well as CaOx stones associated with primary hyperoxaluria and hyperoxaluria after bariatric surgery[93–98]. Epithelial injury and sloughing is common in patients with brushite stones and in hyperoxaluric CaOx stone formers[96,99]. The plugs act as substrates for future crystal deposition and stone growth and can have the same or different crystalline composition[96,97].

The alternative mechanism for stone development is the fixed-particle mechanism in which stones form attached to calcific plaques on the papillary surface. The plaques, called Randall's plaques, start with CaP crystal formation and deposition in the renal interstitium[88,100]. A substantial number of idiopathic CaOx stones are formed attached to Randall's plaques[87,101,102]. The CaP deposits comprising the plaque seem to start deep in the renal interstitium, in the basement membrane of the loop of Henle[103,104], or are associated with the collecting ducts and vasa recta (the blood vessels that lie parallel to the loop of Henle)[105,106]. Haggitt and Pitcock[107] examined kidneys from 100 randomly selected cadavers and performed light microscopy and transmission electron microscopy (TEM) on selected specimens. They found alizarin red-positive (which stains for calcium) laminated spherulitic crystals in the interstitium, which, on closer examination by TEM, were shown to be associated with collagen fibres in the interstitium as well as the basement membrane of the collecting ducts. Furthermore, Cooke and colleagues[103,108] studied 62 normal kidneys and found calcification in four, all of which occurred in the basement membrane of the loop of Henle and extended into the medullary interstitium. Some collecting ducts and blood vessels were also involved.

High-resolution radiography of cadaveric kidneys was performed by Stoller *et al.*[105]. They reported that 57% of the kidneys had subepithelial Randall's plaques that extended deep within the papillae and were intimately associated with the collecting ducts and the vasa recta. Furthermore, von Kossa-positive (which stains for CaP) spherical CaP deposits were identified scattered in the interstitium as well as around the collecting ducts and blood vessels. Evan *et al.*[96] examined renal papillae from patients with various causes who form stones. They concluded that all idiopathic calcium stones develop attached to subepithelial Randall's plaques[109], and confirmed the earlier observations of Cooke *et al.*[103,108] about the involvement of the basement membrane of the loop of Henle in the development of Randall's plaques. Osteopontin[3,110], heavy chain of inter-α-inhibitor[111,112], collagen[103,104,107] and zinc[113] have been identified in these interstitial plaques. Interestingly, all Randall's plaques do not develop into stones — plaques have also been identified in the kidneys of non-stone formers[107].

Evan *et al.*[96,114] further hypothesized that deposits migrate from the basement membrane of the loop of Henle into the surrounding interstitium and become associated with type 1

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collagen, fusing into a synctium in which islands of mineral ‘float’ in an organic ‘sea’. Microscopic and analytical studies of plaques have shown that interstitial CaP deposition occurs in close association with cellular degradation products, membrane-bound vesicles, some unidentified fibrillary material and collagen fibres[100] (FIG. 4). Some vesicles contained needle-shaped crystals, presumably CaP[100]. Accordingly, crystal formation has been proposed to begin in membrane-bound vesicles, propagated through the mineralization of collagen, leading to the movement of a mineralization ‘front’ to the subepithelium of the renal papillae and the development of Randall’s plaques[100]. Thus, there are differences of opinions about the beginning of the Randall’s plaque. Does it start in the basement membrane of the loop of Henle, the vasa recta or the collecting ducts, or simply in the interstitium from where it grows outwards and in the process involves all components of the renal papillae? What provokes the formation of Randall’s plaques is unknown. It has been proposed that the formation of Randall’s plaques might be similar to vascular calcification[115,116] (see below).

One of the key differences between the free-particle and fixed-particle mechanisms is the location of the initial nidus (FIG. 1). Randall’s plugs (free particle) are tubular deposits — usually consisting of CaP — that are continuously exposed to the urine and grow accordingly. Conversely, Randall’s plaques (fixed particle) are subepithelial deposits that must have their surfaces breached before the crystalline mass is exposed to the urine for further growth (FIG. 5). Such a breach can happen with the involvement of matrix metalloproteinases and/or owing to the sheer force of the growing plaque[88,117]. Biological apatite is the main constituent of the plaques, whereas plugs can be made of any solid that can precipitate out into the supersaturated urine. However, both plugs and plaques are coated with an organic matrix, which (as mentioned earlier) is made of macromolecules produced by renal epithelial cells in response to their exposure to tubular deposition of crystals. Pelvic urine is normally metastable with respect to CaOx and would support heterogeneous nucleation and growth of CaOx. Animal model and tissue culture studies have shown that continuous exposure of epithelial cells to crystals leads to the production of large amounts of macromolecules. These molecules travel down with the urine and, when coating the crystal aggregates, promote further crystallization and stone growth. The formation and growth of CaOx crystals over plaques or plugs would eventually lead to the development of a calcific stone that is attached to the renal papillary tip. CaP by itself is also a good nucleator of CaOx[118] and has been shown to transform itself into CaOx through dissolution and recrystallization[119–121]. Thus, stone formation is the end product of a cascade of events (FIG. 6).

Rate of crystal growth—The rate of crystal growth of a particular mineral is mainly dependent on its RSS level in the urine but might also be influenced by certain modifiers of crystallization. Some modifiers have been shown to retard the rate of growth and/or agglomeration of crystals of calcium salts *in vitro*. These modifiers include magnesium[122], citrate[123], pyrophosphate[79,80], ADP[124], ATP[124], phosphopeptides[125], various glycosaminoglycans[126,127], non-polymerized Tamm–Horsfall protein (also known as uromodulin)[128,129], nephrocalcin[130,131], osteopontin[132,133], calgranulin[134], α1-microglobulin[135], β2-microglobulin[136], UPFT1 (REFS 137,138) and inter-α-inhibitor

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(bikunin light chain)[111,139]. However, only citrate and magnesium have been found to be excreted in lower amounts by some calcium stone formers than by non-stone formers[140].

A second group of modifiers is postulated to stimulate the crystallization of calcium salts. Known as crystallization promoters, they include matrix substance A[135], various uncharacterized urinary proteins and glycoproteins[141–143] and the polymerized form of Tamm–Horsfall protein (uromucoid)[144–146]. So far, stone formers have not been shown to excrete an excess of any of these macromolecules, but some researchers still believe that they might have a role in the growth phase of many stones and research continues on their possible role in promoting the development of stones.

Stone formation and vascular calcification

Several analyses have suggested a link between vascular calcification and the formation of idiopathic kidney stones[147–151]. Deposition of CaP in association with collagen is similar to what is seen at sites of vascular calcification, which is currently considered to be an active process in which vascular smooth muscle cells acquire an osteogenic phenotype[152–154]. Exposure of vascular smooth muscle cells to high levels of calcium and phosphate triggers this transformation[154,155], which activates bone morphogenetic proteins (BMPs) and WNT signalling pathways via upregulation of Runt-related transcription factor 2 (RUNX2) and msh homeobox 2 (MSX2) transcription factors[156]. Transformation is also mediated by reactive oxygen species[157,158]; the transformed cells produce matrix proteins[154,159]. Some evidence supports the theory that renal epithelial cells have the capacity to become osteogenic[116]. Basal levels of BMP2, RUNX2 and osterix (also known as Sp7; another transcription factor) are higher in genetic hypercalciuric rats that produce intrarenal CaP deposits[160]. Indeed, Madin–Darby canine kidney cells produce CaP microliths on the basal side when grown in monolayers[161,162], and exposure of these cells to high oxalate levels, as well as CaOx and CaP crystals, leads to the activation of NADPH oxidase and the production of reactive oxygen species[60,163–167], resulting in an osteogenic phenotype. Evidence has shown that genes considered to be involved in epithelial transformation and bone morphogenesis — including those that encode RUNX2, osterix, BMP2, BMP7, BMP receptor type 2, collagen, osteocalcin, osteonectin, osteopontin, matrix-gla-protein, osteoprotegrin, cadherin, fibronectin and vimentin — are upregulated in hyperoxaluric rats[168], all of which are markers of the osteogenic phenotype. Overall, some evidence supports that the abnormal urinary conditions of hyperoxaluria, hypercalciuria, hypocitraturia and renal oxidative stress trigger the transformation of renal epithelial cells into osteoblastic phenotypes. The dedifferentiation promotes the deposition of CaP crystals and the formation of Randall's plaques[88].

Diagnosis, screening and prevention

Patients with urinary stones generally present with the typical reno-ureteral colic and less frequently with loin pain; associated manifestations could be gross haematuria, vomiting and sometimes fever. However, patients can also be asymptomatic. A diagnosis of nephrolithiasis is only confirmed when a stone has been passed, has been extracted or destroyed, or has

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been identified in the urinary tract by imaging studies or surgery. Otherwise, other possible causes of the above manifestations should be investigated.

Symptoms of nephrolithiasis in children are often unclear. The only manifestations are microhaematuria or recurrent episodes of macrohaematuria; pollachiuria–dysuria; acute or subacute episodes of recurrent abdominal pain, located in the flank in older patients or diffuse in the abdomen in younger (<8 years of age) patients; urinary tract infections; or, finally, nonspecific manifestations such as irritability, vomiting, unmotivated crying and motor agitation in those <2 years of age. In the absence of a clear demonstration of a stone, the only clue that these manifestations are due to urinary stones could be the observation of concurrent hypercalciuria or hyperuricosuria.

A detailed medical history and physical examination is part of the evaluation of patients with a suspected stone. Clinical diagnosis generally needs to be supported by appropriate imaging. Renal and urinary tract ultrasonography can identify stones that are situated in the calices, the pelvis and the pyeloureteric and vesicoureteric junctions; it may also identify indirect signs of a stone such as pyeloureteric dilation and a perirenal film of extravasated urine. Indeed, ultrasonography has been shown to identify renal stones with a sensitivity of 70% and a specificity of 94%[169]. For ureteral stones, the sensitivity and specificity of ultrasonography is lower at 57.3% and 97.5%, respectively[170]. Plain abdominal X-ray imaging is generally not used anymore in the evaluation of a flank pain given its modest diagnostic performance (sensitivity and specificity of 44–77% and 80–87%, respectively)[171]. However, plain abdominal X-ray imaging might still have a role in distinguishing between radiopaque and radiolucent stones and in follow-up care[172].

Intravenous urography, which was the historical gold-standard imaging technique for urolithiasis, has been replaced by non-contrast-enhanced CT (NCCT) owing to its higher sensitivity and specificity for identifying ureteral stones regardless of location, size and composition; its lack of contrast agents; and because it can recognize extraurinary causes of renal colic in 30% of patients[173]. Moreover, NCCT can determine the stone density and inner structure, as well as the skin-to-stone distance, which are useful ahead of extracorporeal SWL[174].

Categories of stone formers

Patients with kidney stones are generally classified in different categories according to the composition of stones and the history of previous stone episodes. This classification influences the diagnostic work up and preventive treatment. However, both of these aspects have limitations. For example, classification according to stone composition has the caveat that chemical methods are imprecise and do not distinguish the crystalline forms[175]; infrared spectroscopy or X-ray diffraction are the preferred methods.

Classification according to a history of previous stone episodes is easier because a single stone former is defined as one who seeks advice for a single kidney stone episode; by contrast, a recurrent stone former is a patient who has passed many temporally spaced stones. Given that no metabolic markers are available to distinguish between single and recurrent stone formers, a long observation period is required to determine whether a patient

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is a single or a recurrent stone former. The majority of stone formers will pass only a single stone in their lifetime or over a long observation period[176]. Furthermore, recurrence of stone formation in most first-time calcium stone formers occurs in a period that could be as long as 5 years, and only 15–20% of calcium stone formers recur ≥4 times[176]. Accordingly, the term recurrent calcium stone former has been proposed to describe a patient who has experienced three or more episodes of passing stones in a 5-year period[176]. Other patients with some stone recurrence can be identified as occasionally recurrent or sporadic stone formers.

Although the number of stones formed by a patient denotes the clinical activity of the stone disease, the concept of metabolic activity of the stone disease is different. Metabolic activity in stone disease refers to an ongoing crystallization-driving process that will probably lead to new stones or to the growth of the existing stones. It is this concept that should ideally drive the clinician's decision on how to treat the patient. Unfortunately, we do not have reliable metabolic markers. Patients with their first (and most likely only) stone might have the same metabolic urine abnormalities observed in those with recurrent stones[177]; the same is probably the case for the occasional recurrent stone former. Thus, we must rely on a surrogate marker of metabolic activity: clinical activity, which has limitations. A recurrent calcium stone former, who has passed many new stones in a relatively short period of time, should be considered as metabolically active, as should a patient who exhibits stone growth on serial imaging even if it is their first stone. By contrast, a patient with multiple kidney stones discovered on the same occasion could not be clinically active because the cluster of stones could have formed previously in a short time-frame as a result of time-concentrated, non-long-lasting and unique metabolic derangements. Thus, when the stones formed, the patient was metabolically active but might not be at the moment of diagnosis.

We suggest that stone disease should not be evaluated only in reference to stone composition and clinical activity, but the risk of complications should also be appraised in the diagnostic process and patient categorization (BOX 1).

Box 1

Categories of patients with renal stones

Non-calcium stones

- Struvite stones
- Matrix stones
- Uric acid stones
- Other purine stones (such as xanthine and 2,8-dihydroxyadenine)
- Cystine stones
- Drug stones

Calcium stones

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- Single and sporadic stone formers who are not at risk of chronic kidney disease and/or metabolic bone disease
- Single and sporadic stone formers who are at risk of chronic kidney disease and/or metabolic bone disease
- Recurrent stone formers

Diagnosis

Diagnosing and developing effective prevention strategies requires both understanding the metabolic background that promotes lithogenesis and assessing the patient's risk of CKD and metabolic bone disease (MBD). Metabolic evaluation of patients with stones aims to estimate the propensity of the urine to crystallize, investigate the metabolic mechanisms of nephrolithiasis, diagnose underlying systemic causes of nephrolithiasis, determine the risk of CKD and MBD and to achieve insights on nutritional habits.

Specific software for estimating the urine propensity for crystallization have been proposed (for example, the EQUIL and JESS programs)[73,178]. These programs calculate the urinary supersaturation of numerous salts by considering the concentration in the urine of different ionic species. The probability of stone formation can also be evaluated by algorithms based on urine excretion of a limited number of parameters[140]. Although these methods can be of help, they are not compulsory for a successful metabolic assessment and follow-up.

Risk factors of CKD and MBD—The categorization of first-time or sporadic stone formers, according to CKD or MBD risk, aims to identify those who require pharmacological prevention and/or special attention during follow-up care. Risk factors for MBD in stone formers include distal renal tubular acidosis (complete or incomplete), medullary sponge kidney, primary hyperparathyroidism, malabsorptive syndromes, fasting hypercalciuria and genetic disorders (for example, sodium-phosphate transporter disorders)[179]. In calcium stone formers, the risk of developing CKD is increased as a result of systemic or renal tubular disorders, high recurrence rates or in those with MBD. All patients with non-calcium nephrolithiasis are at risk of developing CKD and recurrent stones. In first-time or sporadic stone formers, stone composition, family and personal recall, imaging and laboratory data would suggest that these individuals have disorders that put them at a higher risk of CKD (BOX 2). Children (and young adults) should be considered at high risk of developing CKD and MBD[180].

Box 2

Stones and risk of chronic kidney disease

The conditions reported in this box complicate more or less frequently with chronic kidney disease (CKD). The different categories of CKD risk are arbitrarily attributed by the author (G.G.) on the basis of personal experience and the literature. No or very few studies have investigated the prevalence or incidence of CKD in the listed conditions; for some of the rarest stones, the risk attribution was based on few case reports.

Possible risk of CKD

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- Xanthine stones
- Indinavir stones
- Distal renal tubular acidosis (incomplete)
- Primary hyperparathyroidism
- Eating disorders and laxative abuse
- Medullary sponge kidney

Moderate risk of CKD

- Brushite stones
- 2,8-Dihydroxyadenine stones
- Sarcoidosis
- Pyelo-ureteral or ureteral strictures

High risk of CKD

- Cystine stones
- Struvite stones
- Stones in a single kidney
- Distal renal tubular acidosis (complete)
- Secondary hyperoxaluria (bariatric surgery, inflammatory bowel disease, bowel resection and malabsorptive syndromes)
- Other forms of nephrocalcinosis (often associated with genetic conditions with hypercalciuria)
- Anatomical abnormalities of the kidney and urinary tract (for example, horseshoe kidney, ureterocele and vesicoureteral reflux)
- Neurological bladder

Very high risk of CKD

- Primary hyperoxaluria
- Autosomal dominant polycystic kidney

CKD can also result from whatever has caused stones to precipitate, renal damage from stone complications (pyelonephritis and obstructive nephropathy) or can be the result of urological treatment[181]. Referral to a nephrologist is highly recommended in patients with stones and CKD.

Stone analysis—Knowledge of stone composition is fundamental in non-calcium stone formers; in these cases, it is a formidable pathway to diagnosis. For instance, finding that a stone is pure cystine or contains even a small percentage of cystine is diagnostic of cystinuria (an inherited autosomal recessive disease). Furthermore, discovering a composite

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stone of struvite and CaOx is a strong hint of the existence of a metabolic disorder[182]. In calcium stones, the precise recognition of the mineral components is much less relevant. The identification of apatite as a major component of a stone could suggest renal tubular acidosis or primary hyperparathyroidism, but this is not always the case. Finding brushite, another crystalline form of CaP, suggests more-active stone disease that is less amenable to preventive treatments and increases the risk of CKD[183]. Most calcium stones have mixed composition; this is believed to depend on the pathogenetic mechanisms involved in lithogenesis (that is, low levels of apatite in a CaOx stone suggests lithogenesis on Randall's plaques) and/or on the superimposition of a different form of lithogenesis (for example, a mixed CaOx and uric acid stone). The calcium composition of a stone can be deduced by the plain abdominal X-ray imaging of radiopaque stones. Dual-energy CT shows promise as a diagnostic tool for uric acid stones[184].

Laboratory evaluations—In all stone formers, the initial metabolic work up is best performed ≥3 weeks after the acute episode, such as renal colic with or without stone passage, obstruction, stone removal or concomitant urinary tract infection. In calcium stone formers, the diagnostic algorithm differs according to the history of previous stones and/or co-morbidities (TABLE 1). Conversely, the diagnostic algorithm for individuals with non-calcium stones (TABLE 2) is dependent on stone composition only because many of these conditions are recurrent and/or have a high risk of CKD and ESRD. If the stone is not analysed or its composition is unknown, the patient should be investigated as a calcium stone former (TABLE 1). Children who have passed stones with calcium or of unknown composition should be evaluated intensively as recurrent stone formers. However, in these patients, 24-hour urine collection and MBD-related evaluations could be difficult to undertake; thus, analyses of the spot urine might be sufficient.

Genetic investigations—A recent study has concluded that in up to 11.4% of adult and 20.8% of paediatric patients with renal stones and nephrocalcinosis, previously unsuspected monogenic disorders such as cystinuria were eventually diagnosed[185]. This finding is at odds with several investigations that did not find carriers of mutated genes in large series of patients with renal stones and/or hypercalciuria[186]. Accordingly, a systematic investigation of patients with stones for genetic mutations is probably not warranted. Instead, these findings implicitly suggest that patients should be thoroughly investigated for the clinical manifestations of inherited disorders[180].

Prevention

Stone formation can be a recurring disease that may have severe consequences, such as CKD, MBD and ESRD. Thus, the aim of preventive strategies should also focus on CKD, MBD and ESRD. Examples that such an approach is possible, at least with respect to MBD, have been reported[187,188]. Comprehensive metabolic evaluation is followed by a range of preventive measures, including specific pharmacological interventions in addition to advice for a change in lifestyle and nutritional habits.

Recurrent calcium stones—Although prevention of new calcium stones is possible, there is no pharmacological treatment that can dissolve existing calcium stones. In non-

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idiopathic calcium nephrolithiasis, the primary conditions should be addressed with specific treatments. In these cases, preventive measures are supportive. In the majority of patients with idiopathic stone disease, behavioural and nutritional interventions are potentially helpful and should be the first step of stone prevention[189]. Nutritional advice for patients with calcium stones include increased water intake (>2 l per day and >3 l per day in the summer) to provide 24-hour diuresis of >2 l[190], and maintenance of a balanced diet with calcium intake not <800–1,000 mg per day, reduced meat and poultry intake (≤0.8 g per kg of body weight)[191], reduced salt intake (<2 g per day, which is equivalent to 5 g of table salt (sodium chloride)), avoidance of excess food intake, increased vegetable consumption[192] and avoidance of soda beverages[193].

Low calcium diets should be avoided in the majority of patients because they increase intestinal absorption and urinary excretion of oxalate, thereby increasing lithogenesis[194]; furthermore, such diets can cause or worsen MBD in calcium stone formers. Low oxalate diets are difficult to attain because of the presence of oxalate in many common foods. Only foods with very high oxalate content should be limited or avoided (see https://regepi.bwh.harvard.edu/health/Oxalate/files). The concomitant consumption of foods that are rich in oxalate and calcium is a possible strategy to decrease the absorption of oxalate[195].

Drug treatment could be considered if stones continue to recur despite the above measures, or if the CKD and/or MBD risks are considerable, or in certain groups of people (for example, flying airline personnel) and in those who have severe urine metabolic abnormalities. For example, thiazides reduce calciuria and might improve bone mineral density[179] and should be considered in patients with high or relatively high urine calcium levels and recurrent calcium stones. However, thiazides have also been shown to decrease stone activity in individuals with normocalciuria[196]. Indeed, the American Urological Association guidelines[195] suggest that lowering calciuria with thiazides might be effective regardless of the absolute rate of calcium excretion. Thiazides are appropriate for both CaOx and CaP stones when dietary measures and increased fluid intake have not been successful in preventing stone recurrence. Allopurinol or febuxostat could be useful in patients with calcium stones who are hyperuricosuric[195]; the former was shown to be effective in reducing urinary uric acid and stone recurrence in hyperuricosuric CaOx stone formers without other metabolic abnormalities[197]. Although no data support its use, the hypouricosuric effect of febuxostat suggests that this drug could be effective in stone formers who cannot tolerate allopurinol[198].

Citrate (generally potassium citrate) use to increase citraturia, which raises the inhibitory activity against calcium crystallization[199], has been shown to be effective in two randomized trials[200,201]. Citrate is indicated in those with recurrent CaOx stones with decreased urinary citrate excretion; in patients with complete or incomplete distal renal tubular acidosis, chronic diarrhoeal states, drug-induced or diet-induced hypocitraturia; and in patients with MBD who form stones. In general, potassium citrate is preferred to sodium citrate because it attenuates calciuria and, therefore, is likely to be more effective in preventing calcium stones[202]. However, some concern pertains to overtreatment with citrate, which in theory might increase the risk of forming new CaP stones because it raises urinary pH (via its metabolism to bicarbonate by the liver). However, in patients with medullary sponge kidney

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and/or distal renal tubular acidosis and pre-existing high urinary pH, kidney stone recurrence rate is decreased rather than increased after treatment with citrate[203,204].

Uric acid stones—To prevent frequently occurring uric acid stones, uric acid supersaturation in the urine must be decreased. This can be achieved by increasing urinary volume (>2 l per day), increasing urinary pH to approximately 7.0, decreasing uricosuria and administering sodium bicarbonate or potassium citrate. Although not supported by data from clinical trials, allopurinol or febuxostat can be used if the patient has hyperuricosuria and dietary measures fail to normalize urinary uric acid[205].

Cystine stones—Reducing the concentration of cystine in the urine and increasing its solubility will prevent stone formation in this highly recurrent stone disease. The preventive strategy involves increasing water intake to >3 l per day and the administration of sodium bicarbonate or potassium citrate to raise urinary pH and increase the solubility of cystine. Early in the treatment course, urinary pH should be checked multiple times per day to titrate the quantity of alkali; at a later stage of treatment, the urinary pH should be monitored less frequently. The target pH is 7.0–8.0 (REF. 195). If cystinuria is >300 μmol per mmol of creatinine (>2,600 μmol per g of creatinine) or if the aforementioned measures fail to prevent new stones, 6-mercaptopropionyl glycine can be administered, with d-penicillamine as an alternative treatment[195]. Given that both drugs can cause proteinuric glomerular diseases, urine should be periodically monitored for proteinuria. Ideally, cystine solubility should be assessed; numerous methods have been proposed[206–208], but few laboratories have this capacity. Thus, generally, treatment is guided by cystine stone formation and/or growth.

Patients with cystine stones require close follow-up because of the high metabolic activity of the disease (with a very high risk of stone recurrence, the rapid growth of these stones, staghorn stone formation, need of surgical procedures and CKD occurrence) and because of the possible adverse effects of treatment. Indeed, a French cohort study of 442 patients showed that 26.7% had CKD and only 22.5% had a (normal) estimated glomerular filtration rate (eGFR) of >90 ml/min/1.73 m^2; a history of staghorn stones and multiple open surgical stone procedures constituted a relevant risk factor for CKD and nephrectomy[209]. Accordingly, patients should be monitored for urinary pH and volume.

Struvite stones—The risk of recurrence of struvite stones is high. Particularly in men, these ‘infection stones’ are a complication of common calcium stones[182]; thus, it is important to look for and treat the metabolic abnormalities that are typical of calcium nephrolithiasis in these patients. Complete removal of struvite stones is a prerequisite for successful recurrence prevention. Indeed, it is almost impossible to cure infection in the presence of the stone because it represents a microorganism reservoir. After clearing the stones, long-term (several months) targeted antibiotic treatment might be necessary to keep urine sterile and prevent new stone formation[205].

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Management

Surgical management

Over the past 30 years, the management of paediatric and adult patients with symptomatic kidney stones has evolved from open surgical lithotomy to minimally invasive endourological approaches. The three most common treatment modalities for renal stones include extracorporeal SWL (40–50% worldwide use), rigid or flexible retrograde ureteroscopic stone fragmentation and retrieval (30–40%) and PCNL (5–10%). Each of these therapies has its own particular adverse-effect profile and expected success rate depending on the experience of the treating physician, stone factors (size, location and composition) and patient characteristics (body habitus, medical co-morbidities and anatomy). With appropriate counselling and proper procedure selection, patients should expect high stone clearance rates, low associated morbidity and quick recovery times. A general decision-tree algorithm of the most common of these approaches, stratified by stone location, stone size and stone density, is presented in FIG. 7.

Shockwave lithotripsy—SWL involves the non-invasive delivery of high-energy acoustic waves that fragment a kidney stone. The shockwave, created by electrohydraulic, electromagnetic or other types of energy sources, travels through the patient and is focused on the stone using an acoustic lens. When these shockwaves approach and pass through the calculus, energy is released resulting in internal structure disruption and stone fragmentation. Fluoroscopic or ultrasonographic guidance is routinely used during SWL to aid in calculus targeting and for precise acoustic-wave focusing. Deep sedation or general anaesthesia is commonly used for intra-operative analgesia, as well as to control respiratory renal movement. Although recent Canadian and US medical claims data have demonstrated a marked decrease in use over the past decade, SWL remains the most commonly performed endourological kidney stone procedure worldwide[210,211].

The success of SWL is typically determined 1–3 months after the procedure by plain abdominal X-ray with or without renal ultrasonography. As small residual fragments of <4 mm in size within the kidney are considered to be passable, patients with these clinically insignificant stones are often referred to as stone free by most classification systems[212]. This misnomer becomes confusing when comparing stone-free rates among studies using plain abdominal X-ray versus CT imaging because CT is more sensitive than X-ray or renal ultrasonography for assessing residual kidney stones. Despite these discrepancies, stone-free rates for SWL are considered equivalent to those of ureteroscopic retrieval (50–80% success) for small radiopaque stones (<2 cm in size) located in non-dependent portions of the kidney (upper pole, middle pole or renal pelvis; TABLE 3). Stones located in the lower pole of the kidney remain the most daunting clinical challenge for endourologists performing SWL. Multiple explanations have been offered for the poor stone-free rates for lower-pole stones, including anatomical factors (long, narrow lower-pole infundibulum) and the dependent position of the calculi limiting the passage of fragments[213]. Owing to these factors and the poor stone passage rates for larger stones, most clinicians do not perform SWL for lower-pole stones that are >1 cm in size[214,215].

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In addition to lower-pole limitations, SWL might require repeated treatments to match the efficacies of PCNL and ureteroscopic retrieval[211,216]. This retreatment risk is associated with obesity (a body mass index of >30) and with extremely dense stones. Patients who are obese are believed to have lower SWL success rates because their kidneys — and, accordingly, stone depth — exceed the lithotripter focal length (shockwaves only penetrate 12–14 cm) and/or their body habitus prevents adequate stone visualization at the time of lithotripsy[217,218]. Dense stones, such as cystine, brushite or COM, are more resistant to SWL fragmentation. As stone composition is usually unknown before surgery, CT stone attenuation values in Hounsfield units (HUs) are commonly used as preoperative surrogates for stone density. Although variable, most urologists use high attenuation values of >1,000 HU as a predictor of renal stone disintegration failure that should be considered before undertaking SWL[219].

Overall, most of the SWL shortcomings are surmounted by the excellent quality-of-life (QOL) measures and low morbidity associated with the procedure. Patients who undergo SWL have repeatedly been shown to have faster return to work, shorter recovery times and higher satisfaction scores than those who undergo ureteroscopic retrieval, especially if SWL occurs without stenting[215]. SWL also has a low complication profile, including a 5% rate of steinstrasse (that is, stone fragment build-up within the ureter) and a 2% rate of urinary tract infection (TABLE 3). Major complications such as sepsis or profound haemorrhage are rare but deserve mention. The development of sepsis following SWL is low in absolute terms (<1% of patients), but is considerably higher in the presence of staghorn or colonized stones (up to 10% of patients)[220]. To mitigate this risk, patients with urinary obstruction or positive urine cultures before SWL should be completely treated. The majority of patients who undergo SWL develop transient haematuria that resolves within days, and imaging studies in asymptomatic patients post-procedure have shown a haematoma rate of 25%[221]. However, symptomatic fluid collections (perirenal, subcapsular or intrarenal haematomas) are rare (<1% of patients), and the rate of post-SWL blood transfusions are very low (<0.2% of patients).

Ureteroscopic fragmentation and retrieval—Ureteroscopy consists of retrograde passage of an endoscope from the urethra proximally towards the affected ureter and kidney, enabling access to the stone as well as delivery of other instruments, such as guidewires, balloon dilators, laser fibres and baskets. Although fairly non-invasive, ureteroscopy requires spinal or general anaesthesia to minimize pain and the visceral response to ureteral and renal dilation. Rigid ureteroscopes are reserved for distal ureteral stones, whereas flexible ureteroscopes, with their deflection ability, are used to reach the extremes of the renal collecting system and negotiate access to anatomically difficult renal calyceal variants. Some urologists place ureteral access sheaths (long reinforced hollow tubes) from the urethra to the renal pelvis to enable repetitive passage of the ureteroscope while minimizing urothelial trauma. These sheaths also enable the continuous flow of irrigation fluid, improving stone visualization and facilitating a low-pressure system. Although flexible electrohydraulic lithotripters are available, the holmium yttrium-aluminium-garnet (Ho:YAG) laser remains the preferred method of lithotripsy in most centres in developed countries owing to its rapid absorption in water and minimal tissue penetration[213].

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A recent meta-analysis of seven large randomized controlled trials totalling >1,200 patients demonstrated that ureteroscopic retrieval achieved a higher ureteral and kidney stone-free rate and a lower need for retreatment than did SWL[222]. As such, for ureteral stones <10 mm in size, SWL and ureteroscopy are considered first-line therapy. For ureteral stones >10 mm in size, ureteroscopic fragmentation results in higher stone-free rates and fewer procedures[223]. For renal stones in non-dependent locations such as the lower pole, ureteroscopy stone-free rates are comparable to those of SWL, if not slightly better (TABLE 3). Like SWL, ureteroscopic management of lower-pole stones is frequently more challenging than for stones located elsewhere in the kidney. Not only can acute infundibular angles make deflection and manoeuvring of the scope difficult but also the passage of the accessory instruments through the ureteroscope working channel reduces the ability of the surgeon to actively deflect the ureteroscope, creating a scenario in which a lower-pole stone can be visualized but not manipulated[213]. With the advent of smaller flexible endoscopes and tipless stone baskets, many endourologists relocate lower-pole stones into a more-favourable upper-pole location before fragmentation[224].

Compared with SWL, ureteroscopy is associated with higher procedure-related complication rates and longer hospital stays (TABLE 3). Many of the symptoms that raise complication rates are secondary to the ureteral stent that is left in place following the procedure[213]. These small, hollow polyurethane tubes are designed with proximal and distal coils to maintain their position within the kidney and the bladder. Unfortunately, the distal bladder coil can be felt by the majority of patients, causing haematuria and irritative voiding symptoms that range from mild to intolerable[215]. Ureteroscopy is favoured over SWL in the setting of multiple or radiolucent stones (stones that are not visible on plain film), hydronephrosis, obesity or high-density stones (holmium lasers are able to fragment all stone types). Ureteroscopy for renal stones during pregnancy or in patients with bleeding diathesis is unusual but would be considered the safest approach, if necessary (TABLE 3).

Percutaneous nephrolithotomy—PCNL involves the direct passage of an endoscope percutaneously through skin, muscle and perirenal fat, and into the kidney and is generally performed for stones >2 cm in size. With the patient under general anaesthesia in either the prone or supine position, the kidney is located using anatomical markings. Renal access is achieved under fluoroscopic and/or ultrasonographic guidance and can be combined with endoscopic or radiographic imaging techniques. For the posterior approach, renal access below the 12th rib is preferred to avoid the pleural cavity and intercostal vessels and nerves. A needle puncture into a posterior calyx rather than the renal pelvis is also recommended to avoid posterior renal artery or vein branch injury. This ‘access’ can be performed preoperatively as an outpatient procedure in an angiography suite (percutaneous nephrostomy tube placement) or preferably during the same setting as PCNL.

Worldwide, approximately 70% of all renal access for PCNL occurs in the lower-pole calyx, and prior cystoscopic placement of a ureteral catheter for retrograde injection of a contrast has been shown to dramatically improve targeting and access to the kidney[225]. Once entry into the kidney has been achieved, a guidewire is then advanced antegrade to the bladder to maintain access and enable passage of either sequential or balloon dilators to expand the tract. After dilation and placement of a working sheath, both rigid and flexible nephroscopes

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can be passed into the kidney for stone removal and lithotripsy. After the procedure, nephrostomy tubes with or without a ureteral catheter or a ureteral stent by itself ('tubeless' stents) are left in place to facilitate maximal renal drainage[226].

PCNL generally offers very high stone-free rates in the 80–90% range, which can be attributed to the shorter working distance, the introduction of relatively large working sheaths (30 French or 10 mm) and more-effective instruments for the removal of larger stone fragments (TABLE 3). For patients with a stone burden of >2 cm or staghorn calculi, PCNL is considered the standard of care, mirroring the successes of open surgery while decreasing the length of hospital stay by 75%[227]. PCNL is regarded as being more effective than ureteroscopic procedures or SWL for most stones, but is more invasive. For ureteral stones, antegrade access to the ureter can also be achieved with high success depending on the ureteral diameter. However, ureteral stone management is typically reserved for less-invasive approaches and smaller stones.

Owing to its more-invasive nature, especially for larger and branched stones, PCNL has a greater complication profile than less-invasive endoscopic techniques, including a 2% sepsis risk and a 5% risk of requiring blood transfusion[228]. Other complications are also reported with varying frequency, such as pneumothorax (1% of patients, usually with upper-pole access), arterial injury requiring embolization (0.3% of patients) and colonic perforation (rare)[213]. As stone clearance relies on visibility, nuisance bleeding can obstruct visibility, requiring procedure termination, placement of a nephrostomy tube and a return operating room appointment at a later date. Anatomical limitations, such as narrow infundibulum or entrances at acute angles to the tract, can also make it difficult to access the entire calyceal system through one tract. In these cases, a second or even third access tract is required to obtain complete stone clearance, occasionally even requiring a combined retrograde approach.

Medical management

Treatment of renal colic and medical expulsive therapy—Treatment of the pain associated with kidney stones (renal colic) is based on the use of NSAIDs as a first choice in the absence of contraindications[229,230] and, in case of failure in relieving pain, opioids. Intravenous paracetamol (acetaminophen) also seems to be as effective as morphine[231]. The use of antispasmodics does not seem to have a significant effect[229,232]. If analgesia cannot be achieved with the previous measures, drainage of the renal pelvis through percutaneous nephrostomy or ureteral stenting and eventually stone removal should be performed.

Hydration should be normal and intravenous fluids are only indicated in the case of protracted vomiting because it does not favour stone expulsion but instead increases pain and the risk of complications (renal pelvic rupture and urine extravasation)[233]. α-Adrenergic receptor antagonists (mainly tamsulosin)[234,235] and calcium channel blockers[234] have been demonstrated to be an effective medical expulsive therapy, believed to be due to their ability to dilate the distal ureter and increase the probability of spontaneous stone passage. The efficacy of these agents in promoting the passage of small distal ureteral stones (<5 mm in size) has recently been decried by two well-designed, randomized, placebo-controlled trials,

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one of which found efficacy only for larger stones (≥5 mm in size) and the other found no efficacy for stones of any size[236,237].

Oral and percutaneous dissolution therapy of stones—Oral dissolution of existing stones is generally effective only with uric acid stones. Two-thirds of these stones can be at least partially dissolved by following the same rules suggested for their prevention: modulating the pH of urine to 7.0, increasing urinary volume and decreasing uricosuria with allopurinol or febuxostat[238,239]. Few observations also suggest that cystine stones might be amenable to oral chemolysis with 6-mercaptopropionyl glycine, high urine output and alkalinization[240]. Finally, the use of percutaneous solutions, such as 10% hemiacidrin or Suby's solution, to turn insoluble kidney stones into more-water-soluble forms was popularized in the 1960s but is rarely used today. Although somewhat effective for infection, uric acid, cystine and brushite stones, percutaneous dissolution of kidney stones is labour intensive and considerably less effective than contemporary minimally invasive removal techniques[241].

Quality of life

As indicated earlier, the prevalence of urolithiasis and nephrolithiasis has increased over the past decades and affects approximately 9% of the American adult population[12]. Although many kidney stones remain asymptomatic for long periods, the incidence of stone episodes, such as pain, infection or obstruction, has increased[27]. Furthermore, following an initial stone event, >50% of patients experience a recurrent stone in the following 5 years[242]. Thus, for these patients, treatment (both medical and surgical) and implementation of lifestyle modifications can significantly affect patient QOL.

The most commonly used QOL questionnaire in the literature is the 36-Item Short-Form Health Survey (SF-36) questionnaire, which consists of self-administered questions (a total of 36) divided into eight domains including: physical function, role limitations due to physical health problems, bodily pain, general health perception, vitality, social function, role limitations due to emotional problems and mental health[243]. The eight domains are scored from 0 (worst) to 100 (optimal). Three US studies using this questionnaire compared stone formers to healthy adults and found lower scores in stone formers in two (general health perception and bodily pain), five (physical function, role limitations due to physical health problems, general health perception, social function and role limitations due to emotional problems) and six (all except role limitations due to emotional problems and mental health) of the eight domains, respectively[244–246]. Among stone formers, one study reported that cystine stone formers had the worst QOL owing to role limitations caused by emotional problems[247]. When comparing scores between men and women, most of the studies reported lower QOL in female stone formers[244–247]. However, these results have to be interpreted with caution because the timing of the questionnaire in relation to the last stone event has a significant effect on the SF-36 score. When adjusting results according to the interval from the last stone episode, patients with a recent stone event (within the past month) had lower scores (role limitations due to physical health problems, bodily pain, general health perception and social function) than the general American population,

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whereas patients with a remote stone event (>1 month ago) had scores similar to the general population with the exception of general health perception[244,245].

In addition to QOL evaluation for urolithiasis, it is also important to evaluate QOL in regard to management because some patients might require surgical treatment. The current guidelines for the management of urolithiasis are based on the stone-free rates between the different surgical modalities but do not incorporate QOL as an additional end point. One study directly compared SWL, ureteroscopy and PCNL a few months after surgery to a control group using the SF-36 questionnaire[248]. The global score after treatment was higher in the patients undergoing surgery than in controls for physical function, role limitations due to physical health problems, vitality, role limitations due to emotional problems and mental health; the only exception to this finding was for bodily pain, which was lower after treatment[248]. Two other studies did not find differences between patients who underwent surgical treatment and controls[249,250]. When comparing the different surgical modalities, patients who underwent PCNL had worse scores in all QOL domains, except for bodily pain, whereas the patients who underwent SWL reported the highest QOL scores[248]. Furthermore, increasing numbers of surgical procedures were associated with lower QOL[244,248]. Stent placement, often used at the end of the surgical procedure, has also been reported to impair QOL without a difference between ureteral and nephrostomy stents[244,251–253]. In the case of residual fragments, one study found that fragments of >4 mm in size might affect QOL[254]. Finally, dietary changes and medical therapy have not been reported to affect QOL except for alkali therapy[244,245].

Outlook

John Wickham (a pioneer of stone surgery) once said at an early SWL congress — when he realized the consequences of the procedure — that we had made an almost unbelievable journey from open surgery via minimally invasive techniques to non-invasive stone removal. Although this development reflected a giant step in stone treatment, his vision was that the final goal would be entirely medical. Three decades later, it is obvious that we still have a long way to go before that dream comes true.

Residual fragments in the kidney are frequently encountered, not only following SWL[255–257] but also after other minimally invasive procedures[258–262]. The course of residual fragments is variable, but their presence is problematic for both the patient and the treating physician and requires careful follow-up or, often, repeated intervention. Given that most residual fragments are composed of CaOx, will it be possible to accomplish fragment elimination by enzymatic dissolution with oxalate decarboxylase and formate dehydrogenase[262]? Although such an approach certainly can be carried out by percutaneous irrigation in selected patients, the question is whether or not it might be possible to incorporate the enzymes in stents or other intracorporeal devices with a slow-release function. Furthermore, the medical advances of managing patients with stone disease have remained behind the times. The literature currently indicates a faint awakening interest in factors that are responsible for stone formation and recurrence prevention[242,263–265]. However, the enthusiasm among urologists to deal with metabolic and medical aspects of stone disease, nevertheless, is too weak.

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Another therapy is that of inversion (head down) therapy, which is a procedure carried out after stone disintegration with the aim of favourably changing the position of the lower calyces. This step would facilitate fragment elimination by gravitation. The altered position of the kidneys is often combined with vibration on the body surface to add some kinetic energy. This treatment approach can be used in patients with residual fragments in the lower pole of the kidneys[266–269], although the results have been conflicting[270].

In another recently published report, ultrasonic propulsion was used successfully to facilitate fragment elimination, which is a new and interesting concept[271]. Although promising, this technology is not US FDA approved and is being performed in patients only in experimental protocols. To facilitate fragment elimination, a pharmacological agent could be used to promote muscle contraction in the calyx. Poor local smooth muscle activity might, hypothetically, be associated with poor clearance of fragments. Whereas fragments from small disintegrated stones are relatively easily eliminated, fragments from large stones are not. A possible explanation for this discrepancy is that the large stone in the calyx has hindered muscle contraction. This research area has not been addressed hitherto[272].

It is interesting to note that present treatment trends comprise relatively aggressive, albeit minimally invasive, methods for fragment removal. Such a step is of course necessary in patients with infection stones and stones composed of uric acid, cystine and brushite, but the question is whether such procedures are necessary in asymptomatic patients with minor residual fragments composed of CaOx. Given the high recurrence risk that these patients experience despite meticulous stone clearance, this is a pertinent question regarding overtreatment. In an epidemiological study[273], a 10-year recurrence risk of about 25% was shown for patients who had formed only one stone at the start of follow-up, but was approximately 70% for patients with more than one stone at the same point in time. The average recurrence risk for patients with calcium stones was estimated to be approximately 50% during a 10-year period after their first stone episode[273].

Recent research has revived the role of Randall's plaques and plugs[88]. In the final process of CaOx stone formation, high supersaturation with CaOx and low pH seem to be important factors that need to be corrected[121]. The goal, therefore, should be to reduce the risk of precipitation or growth of CaOx on the surface of CaP[3,274–276] (FIG. 8). The formation of CaOx stones requires a complex interaction of nucleation of both CaP and CaOx, with subsequent growth and aggregation. Interference with the precipitation of these two essential crystal phases at different levels of the nephron seems necessary to arrest or counteract the formation of the most commonly encountered stones in patients.

Numerous recurrence preventive efforts for calcium stone formation have been described and tested, but none have shown the capacity to definitely arrest stone formation. One contributing factor to insufficient success is the lack of long-term patient compliance[264]. Another important explanation is the shortage of means to counteract the initial precipitation of CaP[54]. With current treatment options, we are only addressing the final steps in the chain of abnormal crystallization events in idiopathic patients who form calcium stones. Whereas recurrence prevention in patients who are stone free can be accomplished by reducing supersaturation of CaOx in the final urine; how can we approach the remaining CaP

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deposits? Would it be possible to decrease CaP supersaturation in the nephron urine and interstitial tissues with a short-term intensive treatment and hope for natural elimination of CaP by the action of, for example, macrophages[49,277]? Or can we interfere with any other step in CaP precipitation that would eliminate this risk factor? In this regard, radiological improvements might enable the detection and quantification of papillary CaP deposits[278].

The initiation of stone formation in most patients is an occasional event. Accordingly, optimal compliance can only be expected with regimens based on strictly individualized analysis of risk factors and risk periods. The information obtained from 24-hour urine collections and other long-term urine collections gives only rough average information on specific risk variables during the period. Indeed, imprecise data on urinary pH are the rule rather than the exception. Better analytical focus on periods assumed to represent particularly high risk is necessary. Such information can be obtained by combining a careful medical history with analysis of risk factors during periods when supersaturation with CaOx occurs simultaneously with low urinary pH. Such an approach might enable the design of individualized recurrence prevention[279].

Today, it is very attractive to remove kidney stones with flexible ureteroscopy[265] and, if that is not optimal, to use smaller and smaller instruments for percutaneous removal of smaller and smaller stones. However, it seems logical that for each treatment decision a balance is reached between the intention of the treatment and the efforts required to reach that goal. Active or pharmacological removal of residual fragments should be considered in view of the risk of the procedures and of the recurrence rate. There is no doubt that recurrence preventions need to be further developed, fine-tuned and used in an individually designed manner. With further increased understanding of the mechanisms behind stone formation, it is possible that some general treatment can be prescribed for many patients with idiopathic calcium stone disease.

It stands to reason, however, that further progress in the management of patients who form stones cannot be made without a genuine interest and responsibility by urologists who regularly see these patients. The need for close interaction between stone removing and recurrence preventive procedures are absolute prerequisites for success. Basic as well as clinical research must have its focus on both aspects. In this regard, the urologist, during various endoscopic procedures, has a unique possibility to visually observe and record the clinical features of the pathology involved in stone formation. It cannot be too strongly emphasized that the optimal care of patients with stone disease is not only surgical, in its widest sense, but also medical.

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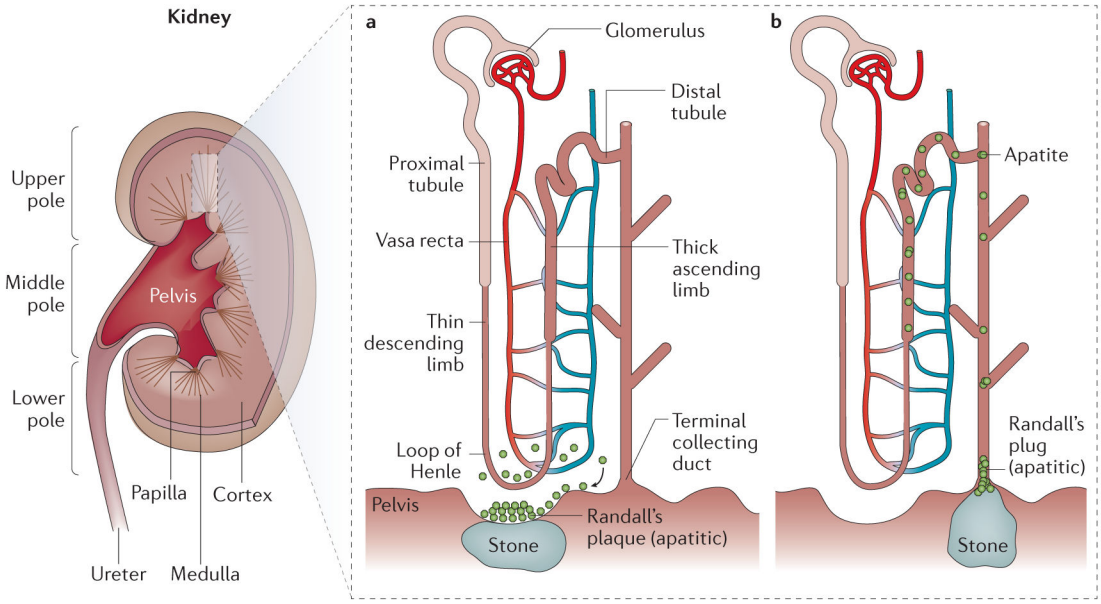

Figure 1. Macroscopic and microscopic morphology of human kidneys and location of stones

a | According to the fixed-particle mechanism, stones begin as depositions of calcium phosphate (CaP) in the interstitium (apatite), grow outwards reaching the renal papillary surface, become exposed to the pelvic urine and establish a nucleus for the deposition of calcium oxalate (CaOx), leading to the formation of CaOx stones attached to a CaP base, known as Randall's plaques. **b** | By contrast, in the free-particle mechanism, for example, CaP, uric acid or cystine crystals form in the renal tubules, move with the urine, aggregate and plug the terminal collecting ducts. These plugs, called Randall's plugs or lesions, are exposed to the pelvic urine. Deposition of CaOx crystals on the CaP plugs leads to the formation of CaOx kidney stones.

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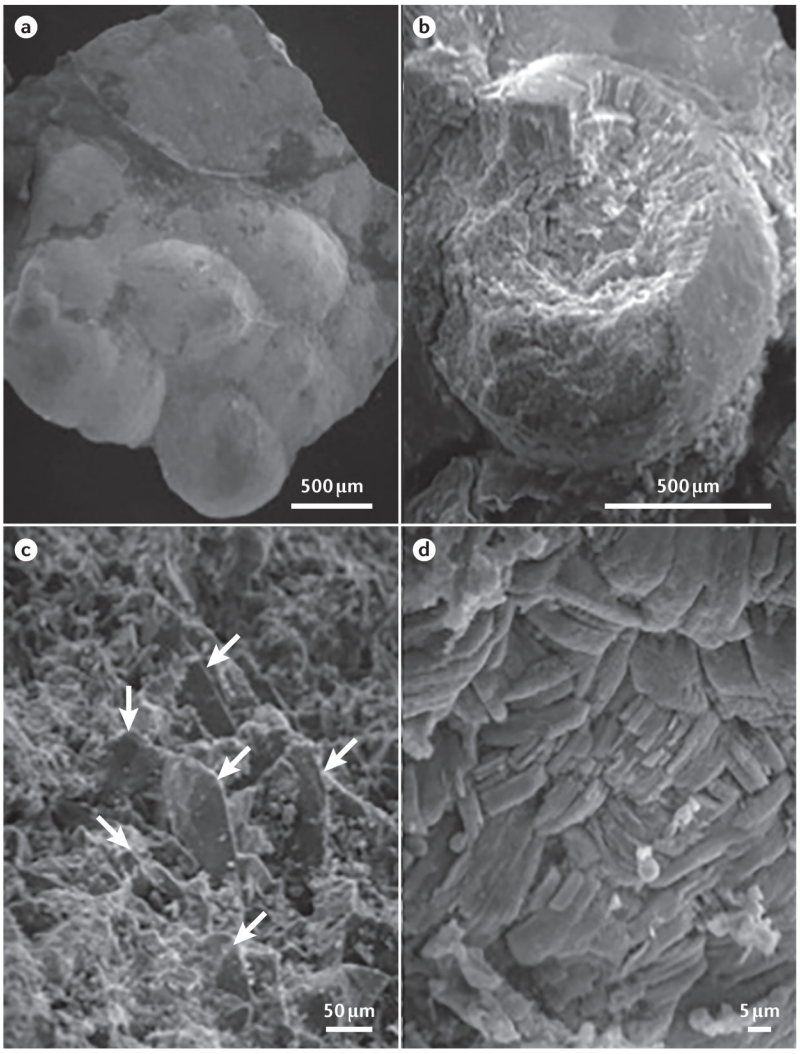

Figure 2. Calcium oxalate kidney stones examined using scanning electron microscopy

a | A low magnification image showing the outer nodular appearance of a calcium oxalate (CaOx) monohydrate stone. **b** | The fractured surface showing CaOx monohydrate crystals organized in concentric laminations and radial striations. **c** | The surface of a stone with an outer layer of CaOx dihydrate crystals. Bipyramidal CaOx dihydrate crystals protruding on the surface are shown (arrows) and are powdered with tiny calcium phosphate crystals. **d** | The surface of a CaOx monohydrate stone. The tabular morphology of CaOx monohydrate crystals is clearly visible.

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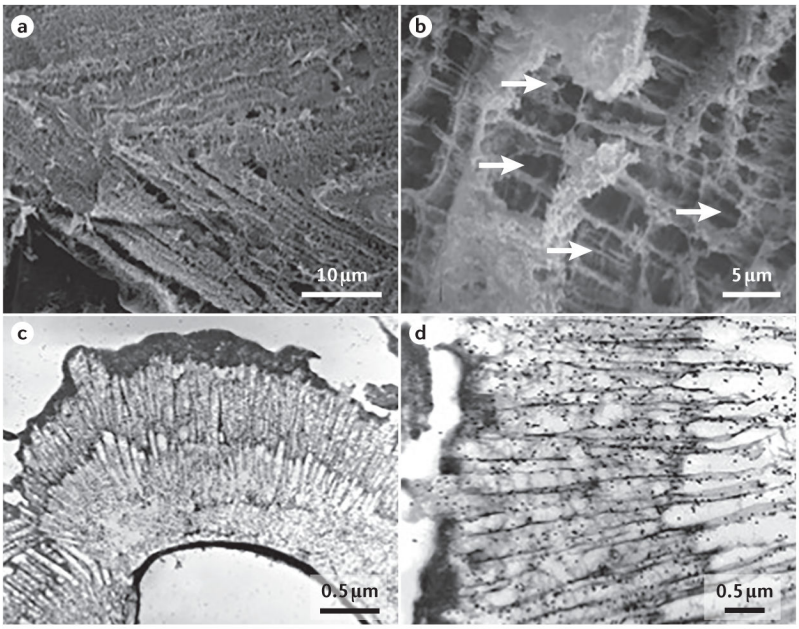

Figure 3. Scanning electron microscopy and transmission electron microscopy of kidney stones

These images demonstrate the ubiquitous nature of the organic matrix, and its intimate association with the crystalline components of the stone. Stone fragments were demineralized and then processed for electron microscopy. The stone and crystals maintained their architecture even after the removal of the crystalline components. **a** | A scanning electron microscopy image of the organic matrix of calcium oxalate (CaOx) dihydrate crystals in a CaOx stone. The organic matrix is organized in layers, but the overall bipyramidal architecture of the CaOx dihydrate crystal is maintained even after demineralization. **b** | The fractured surface of CaOx monohydrate crystal ‘ghosts’ showing internal spaces (arrows) created by a loss of plate-like CaOx monohydrate crystals. **c** | A transmission electron microscopy image of the organic matrix, showing at least two layers of radially organized CaOx monohydrate crystal ghosts. **d** | A higher magnification of the CaOx monohydrate crystal ghosts from part **c** stained with antibodies against osteopontin (black dots), demonstrating its substantial presence in the matrix.

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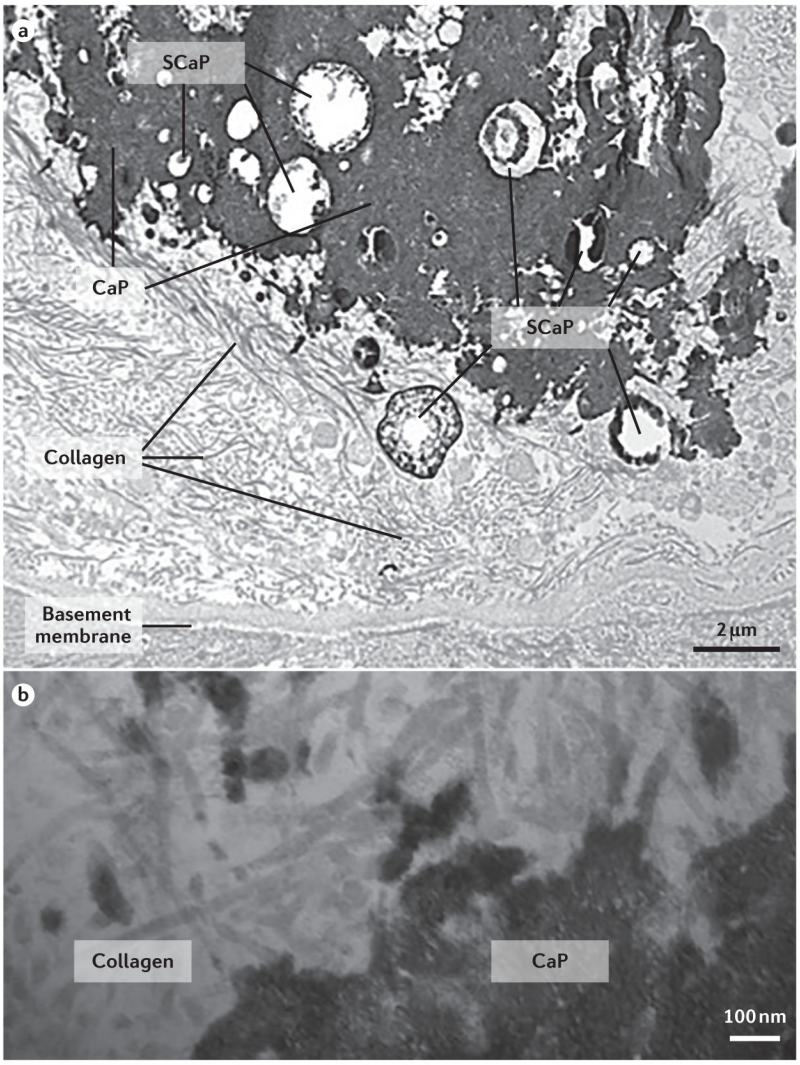

Figure 4. The renal interstitium of a calcium oxalate stone former with Randall's plaque

a | The tubular epithelium is separated from the interstitium by the basement membrane. The interstitium contains collagen fibres, spherulitic calcium phosphate (SCaP) reminiscent of membrane-bound vesicles with crystals, as well as dense and compacted calcium phosphate (CaP) crystals. There is a close association between collagen and dense CaP. **b** | A portion of the image in part **a**, but at a higher magnification. Collagen fibres are intimately associated with dense deposits of CaP.

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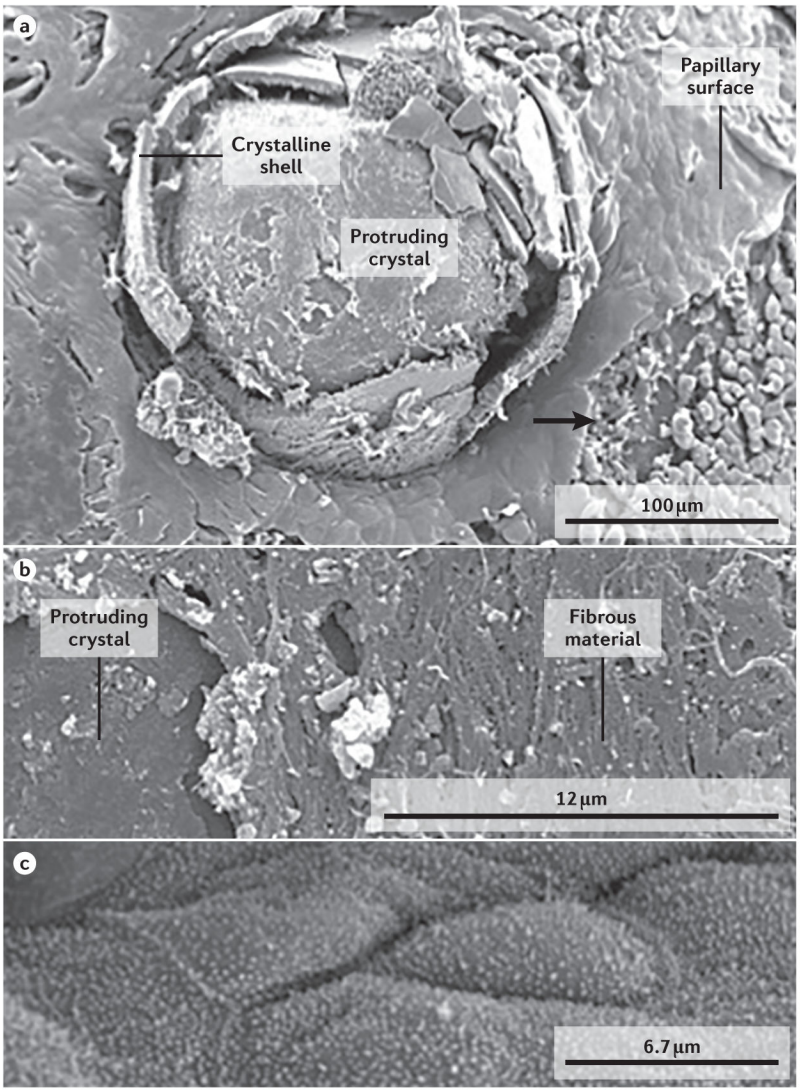

Figure 5. The renal papillary surface of a calcium oxalate monohydrate stone former examined using scanning electron microscopy

a | A crystalline entity is protruding through the papillary surface, causing epithelial cells to be pushed apart (arrow). The protrusion is covered with fibrous material and surrounded by a layer of crystalline shell. **b** | Fibrous material covering the protrusion. **c** | An intact portion of the papillary surface epithelium.

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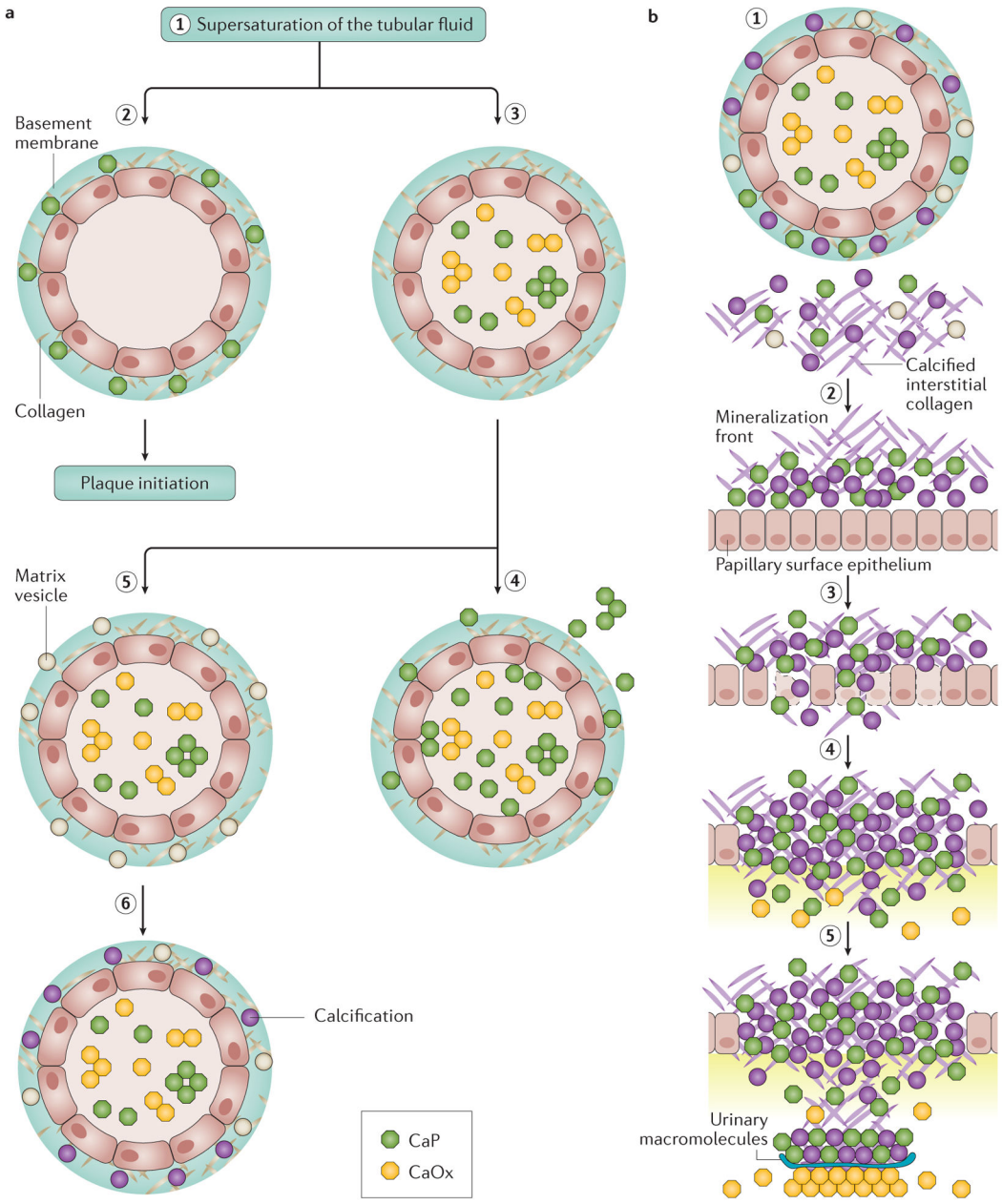

Figure 6. Randall's plaque and calcium oxalate stone formation

On the basis of experimental and available clinical data, one can surmise that stone formation is a multistep process, probably involving the formation of Randall's plugs and plaques. For simplicity, we have separated out these steps, but a combination of factors probably contributes to stone formation and growth. **a** | In Randall's plaque formation, supersaturation of tubular fluid with respect to calcium phosphate (CaP) and/or calcium oxalate (CaOx) occurs in renal tubules at the end of the loop of Henle and at the beginning of the colleting duct system (step 1). From here, two alternate pathways have been suggested. Supersaturation with respect to CaP leads to the deposition of CaP in the basement membrane of the loop of Henle (step 2), initiating the process of plaque

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formation[104] (FIG. 1). Alternatively, crystal formation occurs in the renal tubules (step 3). CaP crystals translocate into the interstitium (step 4) or are internalized by the cells, dissolved and re-precipitated in the tubular basement membrane[121]. Another possibility is that renal epithelial cells, when exposed to CaP and/or CaOx, produce reactive oxygen species and, probably, a range of factors associated with osteogenesis, such as Runt-related transcription factor 2 (RUNX2), osterix (also known as Sp7), bone morphogenetic protein 2 (BMP2), BMP7, BMP receptor type 2 (BMPR2), collagen and osteopontin. Epithelial cells produce matrix vesicles on the basal side (step 5) followed by their calcification (step 6; REFS 88,168). **b** | Once CaP crystals have been deposited in the basement membrane of the loop of Henle and/or collecting ducts, mineralization continues. Collagen fibres and membranous vesicles become calcified (step 1). The mineralization front reaches the renal papillary surface and a subepithelial plaque is established (step 2). The papillary surface epithelium is disrupted (step 3) and plaques rupture, exposing the CaP crystals to the pelvic urine metastable with respect to CaOx (step 4). Urinary macromolecules are deposited over the exposed CaP crystals, promoting the deposition of CaOx crystals on the CaP base (step 5).

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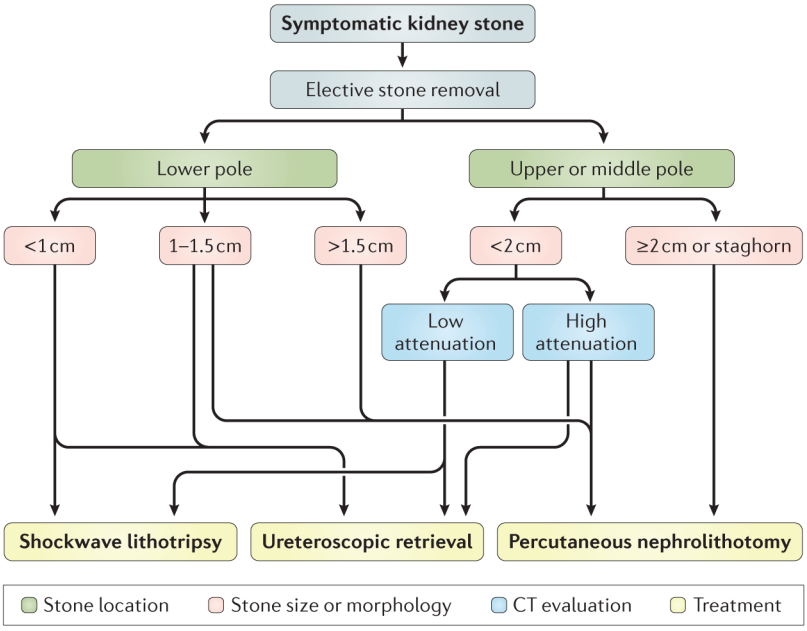

Figure 7. Algorithm for the most common approaches to surgical treatment of kidney stones

The decision of which surgical strategy to use is dictated by the location of the stone (with lower-pole stones being more difficult to treat), stone size and stone density.

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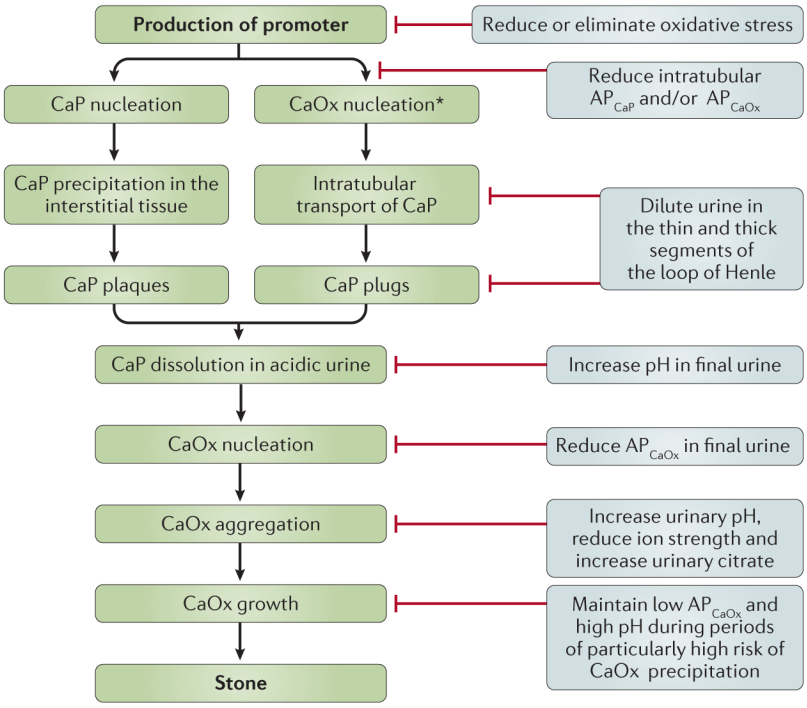

Figure 8. Potential methods to interfere with abnormal crystallization and stone formation

Oxidative stress in the proximal tubules might induce lipid peroxidation and damage to the brush border membrane at this level of the nephron. Released membrane fragments and vesicles containing phospholipids are considered important as promoters for both calcium phosphate (CaP) and calcium oxalate (CaOx) precipitation at supersaturation levels lower than those otherwise required for crystallization. Precipitation of CaOx higher in the nephron is only expected when very high concentrations of oxalate are available. Dilution of the urine at all levels of the nephron is most certainly associated with a reduced risk of intratubular, as well as interstitial, precipitation of CaP and CaOx. *Indicates that precipitation of CaOx at high nephron levels only occurs when very high concentrations of oxalate are available. AP, ion-activity product.

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Table 1

Laboratory assessment of calcium stones

Patient category	Stone analysis*	Blood‡	24-hour urine collection§	First morning spot urine	Others
First-time or sporadic stone former	Yes	Creatinine, calcium, phosphate and potassium levels and eGFR	Not suggested	pH, routine urinalysis and urine culture	According to the blood findings
First-time or sporadic stone former at risk of CKD and/or MBD	Yes	Creatinine, calcium, phosphate, potassium and bicarbonate levels and eGFR	Oxalate, calcium and citrate levels and volume	Calcium to creatinine ratio//	Renal acidification test¶, bone turnover markers# and bone densitometry
Recurrent stone former	Yes	Creatinine, calcium, phosphate, potassium, bicarbonate and uric acid levels and eGFR	Oxalate, calcium, phosphate, citrate, uric acid, urea, sodium and potassium ** levels and volume	pH, routine urinalysis, urine culture, cystine (qualitative) levels and calcium to creatinine ratio//	Renal acidification test¶, parathyroid hormone levels‡‡, bone turnover markers#,§§ and bone densitometry

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MBD, metabolic bone disease.

*Stone (and stone fragment) analysis should be performed on all available stones.

‡The determination of ion concentrations aims to recognize secondary forms of urolithiasis and risk of CKD and MBD. High calcium and/or low phosphate levels suggest hyperparathyroidism; low or marginally low potassium levels suggest renal tubular acidosis. Low bicarbonate levels suggest renal tubular acidosis.

§Data from at least two 24-hour urine collections in the usual conditions of diet and fluid intake should be obtained. Collections should be performed in plastic bottles following laboratory instructions. The accuracy of the collection could be checked by evaluating creatininuria.

//The urinary calcium to creatinine ratio in a morning (fasting) spot urine sample is performed in patients with hypercalciuria; it is a marker of the obligatory urinary loss of calcium. Values of >0.25 mg per mg suggest an increased bone turnover.

¶The test is optional to confirm renal tubular acidosis, which should be suspected in patients with or without systemic acidosis and recurrent nephrolithiasis of pure calcium phosphate (CaP) stones or stones mainly composed of CaP. Renal tubular acidosis should also be considered in recurrent calcium stone formers (both calcium oxalate and CaP) with hypocitraturia and a urinary pH of >5.8 and in patients with nephrocalcinosis.

#Urinary hydroxyproline, or urinary or serum deoxypyridinoline crosslinks. Assessment can help to monitor the effects of treatment on MBD[280].

**The 24-hour urinary excretion of sodium, potassium, phosphate and urea provide important information on the nutritional habits of the patient, and the daily protein intake can be estimated.

‡‡When blood tests suggest hyperparathyroidism, serum parathyroid hormone levels should be measured and parathyroid imaging should be performed.

§§In patients with hypercalciuria.

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Table 2

Laboratory assessment of non-calcium stones

Stone type	Stone analysis	Blood	24-hour urine collection*	Spot urine
Struvite stone‡	Yes, stone culture	Creatinine, bicarbonate, calcium, potassium and inorganic phosphate levels and eGFR	Calcium and oxalate levels, pH and volume	pH, routine urinalysis§ and urine culture
Matrix stone‖	N/A	Creatinine levels and eGFR	Volume and pH	pH, routine urinalysis and urine culture
Uric acid stone	Yes	Creatinine and uric acid levels and eGFR	Uric acid levels, pH and volume	pH and routine urinalysis§
Cystine stone	Yes	Creatinine levels and eGFR	Cystine levels (quantitative), proteinuria¶, pH and volume	pH# and routine urinalysis§
Other purine stones (such as xanthine and 2,8-dihydroxyadenine)	Yes	Creatinine and uric acid levels and eGFR	Uric acid levels and volume	pH and routine urinalysis§
Drug stones	Yes	Creatinine levels and eGFR	pH and volume	pH and routine urinalysis§

eGFR, estimated glomerular filtration rate; N/A, not applicable.

*Data from at least two 24-hour urine collections in the usual conditions of diet and fluid intake should be obtained. Collections should be performed in plastic bottles following laboratory instructions. The accuracy of the collection could be checked by evaluating creatinine levels in the urine.

‡Given that struvite stones could be a complication of common calcium stones, especially in men, the common metabolic risk factors for calcium stones should be examined.

§Typical crystals of the corresponding condition can be observed.

‖It has the same background conditions of infection stones.

¶Total proteinuria has to be checked in patients who are treated or are going to be treated with 6-mercaptopropionyl glycine or d-penicillamine.

#The determination of pH in spot urine during the day is useful for treatment guidance.

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Table 3

Indications, success rates, risks and contraindications for renal stone procedures

Location	Stone size	Success rate	Risks	Absolute and relative contraindications
Shockwave lithotripsy				
Upper pole, middle pole and renal pelvis	≤2 cm	50–70%	• >15% require retreatment • 2–5% experience steinstrasse • <2% experience obstructions • 2% experience urinary tract infections, haematomas and sepsis	Coagulopathy, pregnancy, obesity, multiple or radiolucent stones, obstruction, cystine composition and dense stones *
Lower pole	≤1 cm	50%		
Ureteroscopy				
Upper pole, middle pole and renal pelvis	<2 cm	60–80%	• >25% experience stent pain • 5% experience urinary tract infections, ureter injuries or require retreatment • <1% experience sepsis or avulsion	Bladder reconstruction, ileal conduit, renal transplantation, large median prostate lobes, ureteral stricture, re-implantation or pathology
Lower pole	≤1.5 cm	50–60%		
Percutaneous nephrolithotomy				
Upper pole, middle pole and renal pelvis	>2 cm	80–95%	• 2–5% experience sepsis or require blood transfusion • 1% require intubation and 0.3% experience arterial embolization	Coagulopathy, pregnancy, high pulmonary risk, bowel overlying renal access and an inability to tolerate prone position
Lower pole	≥1.5 cm	70–80%		

* Defined as stones of >1,000 HU on CT.