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Leave No Stone Unturned: Defining Recurrence in Kidney Stone Formers

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Abstract

Purpose of review: Established guidelines provide recommendations on the management of kidney stones to prevent recurrence. However, clear and clinically useful terminology for recurrence of kidney stones is needed. This review describes the various manifestations of kidney stone recurrence and the reported rates of kidney stone recurrence in various clinical settings.

Recent findings: Kidney stone recurrence has a wide range of symptomatic and radiographic presentations. Symptomatic recurrence may include characteristic symptoms of stone passage via the ureter (renal colic and gross hematuria). This may be self-managed or result in clinical care, with or without confirmation of an obstructing stone on imaging. Radiographic recurrence has been variably defined as new stone formation, stone growth, or stone disappearance (from passage with or without symptoms). Studies have used inconsistent definitions of recurrence, and recurrence rates vary substantially. Stone free rates and residual stone fragment size after surgical interventions are useful predictors of symptomatic recurrence.

Summary: The recurrence rate of kidney stones has been assessed in stone formers from subspecialty clinics, the general community, and clinical trials. The definition of recurrence is quite heterogeneous between studies, but the rate of recurrence generally increases as more manifestations are included in the definition.

Keywords

nephrolithiasis; kidney stone; urinary stone; recurrence; outcomes

Introduction

The primary purpose of a kidney stone clinic is to provide personalized recommendations regarding, lifestyle, diet, and medications to reduce risk of recurrence of painful and expensive kidney stone episodes. There are known risk factors for kidney stone recurrence,

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Conflicts of Interest

None

as well as safe and effective preventative interventions. However, the incidence of kidney stones continues to rise in the United States and in the rest of the world.(1–3) There has also been a notable increase in the incidence of kidney stones among children, particularly adolescent girls.(4–6) This growing stone disease burden is associated with increasing healthcare utilization and lost productivity among sufferers.(7) Guidelines on the management of kidney stones have been developed to guide clinicians on the recommended evaluations and treatments that should be employed in order to prevent recurrence of kidney stones.(8–11) Despite these recommendations, there is a lack of consistency in the definition of kidney stone recurrence. Stone formers often present with pain, sometimes chronic, which may be attributed to a kidney stones without confirmatory imaging. These symptoms may resolve without visualized stone passage. Do symptoms in the absence of an imaging-confirmed stone or witnessed passage constitute recurrence? Alternatively, stone formers may have changes in their radiographic kidney stone burden with new stones, growth of old stones, or stone disappearance, but in the absence of symptoms. Do radiographic changes in kidney stone burden alone constitute recurrence? The goals of this review were to describe the different manifestations of kidney stone recurrence, and to assess how these various definitions of recurrence are utilized.

Symptomatic stone presentations and radiographic-defined recurrence

Symptomatic presentation of stone disease can be quite variable. Migration of a stone into the ureter may be heralded by back, flank, abdominal, urethral, or scrotal/ vulvar pain, with or without radiation between these sites. Pain may be accompanied by combinations of nausea, gross hematuria, and lower urinary tract symptoms including urinary frequency and urgency. Presence of a symptomatic stone can be confirmed by imaging to verify an obstructing stone in the ureter or renal pelvis.(1, 12–14) A mobile kidney stone (not yet migrated into the ureter) may also be symptomatic if it causes intermittent obstruction within the kidney itself. Once an obstructive stone is identified, management options may include trial of passage or surgical intervention including direct removal or fragmentation of the stone with anticipated subsequent passage of fragments. Such fragments may remain in situ, may pass asymptotically, or may cause symptomatic obstruction. Many stone formers are also identified by the incidental finding of an asymptomatic kidney stone on imaging. Asymptomatic stones are common and notably present by computed tomography (CT) in 11% of living kidney donors and 14% of patients undergoing a “virtual” CT colonography. (15, 16) Among patients presenting with a symptomatic kidney stone, the concurrent presence of an asymptomatic kidney stone may be considered a form of “recurrence”. As they are asymptomatic, such stones may be monitored and not surgically treated. Monitoring may reveal evidence of future “recurrence” manifest as growth or as passage with or without symptoms. Such monitoring may be useful to assess effectiveness of preventative interventions. Growth of an asymptomatic stone or new stone formation can be described as ‘metabolically active,’ due to a presumed higher risk for future symptomatic stone episodes. (8)

Manifestations of stone recurrence can be conceptualized in terms of the underlying biology (Figure). Once formed, a stone can be detected if its size exceeds the spatial resolution of the imaging modality. Further growth of this stone can be detected by serial imaging. However,

there is tremendous variability in the sensitivity, specificity, and reproducibility of stone detection between different imaging modalities. The gold-standard method is CT imaging but at the cost of increased radiation exposure; roentgenography ("KUB") and ultrasound have reduced resolution to detect stones. Reproducibility of roentgenography may also be limited by overlying bowel contents and ultrasound is well recognized to have inter-user variability.(17) Furthermore, ultrasound has been demonstrated to overestimate the size of renal stones, complicating the accuracy of monitoring for stone growth with mixed imaging modalities.(18) Attempted passage occurs when the stone migrates into the ureter. This can result in three potential outcomes: stone passage will cause symptoms that lead to clinical care, symptoms from stone passage will be self-managed by the patient, or the stone will pass 'silently' with minimal or no symptoms (detected by stone disappearance on subsequent imaging). A symptomatic stone prompting clinical care may require surgical intervention. Some surgical interventions may result in stone fragments that can also cause symptoms with passage. Not shown on the diagram, asymptomatic stones can also prompt stone surgery. Surgical intervention on an asymptomatic kidney stone complicates the detection and interpretation of recurrence.

Referral-based cohort studies of recurrence

Many studies of recurrence are based on referral populations of stone formers seen in stone clinics or urology practices. Even after excluding rare stone types, inborn errors of metabolism, and renal tubular acidosis, the probability of symptomatic recurrence in pediatric stone clinic patients was 50% at 3 years.(4) A prospective cohort study of stone clinic patients found that 27% developed symptomatic recurrence during an average followup of 7.5 years; among those that were symptom free during follow-up, 28% were found to have a new stone on ultrasound.(19) Thus, radiographic recurrence is common, even among stone formers who do not have symptomatic recurrence.

Radiographic recurrence has myriad definitions. It has been studied more extensively in referral populations with asymptomatic kidney stones. A study of 347 patients with asymptomatic kidney stones (mean diameter of 4.4 mm) found that 54% developed a stone-related event during mean followup of 31 months.(20) These events include spontaneous asymptomatic kidney stone passage in 29 patients (15.6%) and 'disease progression' in 157 patients (45.2%). 'Disease progression' was defined as spontaneous symptomatic stone passage, stone growth, emergency room visit for stone-related symptoms or complications, and procedural intervention for symptomatic stones. Of those with disease progression, 46% developed a symptomatic episode with spontaneous passage while 54% underwent stone surgery. Another study of 160 asymptomatic kidney stones among 110 patients were followed in a urology practice for a mean of 41 months. During follow-up, 21% of stones grew by at least 50%; 28% of stones became symptomatic, of which 60% required a surgical intervention. Only 8% of the stones passed without symptoms or surgery, though the mean baseline diameter of stones in this study was 7 mm.(21) However, both studies were subject to the variability of multiple imaging methods used, as neither was based exclusively on CT imaging.

These studies show that radiographic changes are common, but do not directly link radiographic recurrence (stone growth or new stone formation) to symptomatic recurrence. This link was explored in a study of 550 stone clinic patients that had at least one CT scan obtained while asymptomatic. During a median followup of 4.7 years, 230 patients (42%) developed a symptomatic stone event. Automated total kidney stone volume at baseline was a stronger predictor than any other radiographic parameter – number of stones, largest stone diameter, and presence of bilateral stones. After adjustment for multiple risk factors, total stone volume was the only radiographic finding that predicted symptomatic recurrence. In those that had a follow-up CT scan, a rapid increase in total stone volume between scans was also associated with symptomatic recurrence.(13) A limitation of these referral-based studies is that the stone disease severity and likelihood of recurrence is much greater than in the average stone former.

Population-based studies of recurrence in symptomatic stone formers

Several recent studies on kidney stone incidence and recurrence have used the comprehensive linked medical records of the Rochester Epidemiology Project (REP) to study the clinical care of all stone formers in the general community.(1, 12, 14, 22, 23) Recurrence of confirmed symptomatic kidney stone episodes resulting in clinical care among first-time symptomatic stone formers were 11%, 20%, 31%, and 39% at 2, 5, 10, and 15 years, respectively.(14) Risk factors for recurrence were younger age, male gender, white race, family history of stones, gross hematuria, prior asymptomatic stone on imaging, prior suspected stone episode (symptoms but no documented seen stone), a concurrent nonobstructing kidney stone, symptomatic pelvic or lower pole kidney stone, no ureterovesical junction stone, and uric acid stone composition. These symptomatic recurrence rates are lower, likely due to less selection bias compared to referral-based studies of patients seen in stone clinics or urology clinics. Also, a strict definition of symptomatic recurrence likely decreases the recurrence rate by requiring both a confirmed obstructing stone (on imaging or from passage) and symptoms. However, a strict definition ensures that symptomatic kidney stone recurrence was indeed valid. Radiographic recurrence without symptoms is of unclear clinical relevance and symptoms without a confirmed stone may be due to other disease processes.

More recently, the 5-year symptomatic recurrence rate after the first, second, third, and fourth or higher stone episodes was identified as 17%, 32%, 47%, and 60%, respectively. (23) The risk of recurrence was highest right after each stone episode and then decreased with the passage of time. The revised nomogram identified additional predictors of symptomatic recurrence including high BMI, pregnancy, number of stones in both kidneys, diameter of largest kidney stone, no history of calcium oxalate stone, and history of a brushite/struvite/uric acid stone.(23) In the general community, 93% of kidney stones are common calcium stones (calcium oxalate and/or calcium phosphate), 5% are uric acid stones, and everything else is rare.(22) Notably, stone compositions of uric acid, brushite, and struvite are more likely to recur than common calcium stones. Rare genetic stone diseases including cystinuria, primary hyperoxaluria, adenine phosphoribosyltransferase (APRT) deficiency, and Dent disease are well known to be highly recurrent. The general pattern seems to be that the rarer the stone type, the higher the risk of recurrence. For

example, untreated cystinuria, a disorder that affects only 0.1% of adult stone formers,(22) can lead to new stones every year in affected patients.(24) Nonetheless, patients who have less common or rare stone composition types are more likely to have more common stone composition types on follow-up than vice versa.(22)

Population-based studies of recurrence in asymptomatic stone formers

Community-based studies of radiographic kidney stones and their outcomes using the most accurate imaging modality, CT, are lacking. However, ultrasound based studies in China of employees undergoing annual health screening visits with abdominal ultrasounds have studied outcomes of asymptomatic kidney stones.(25) Among a cohort of asymptomatic stone formers (mean stone 4.7mm; range 2–10mm), followed for a mean 4.2 years, 60% experienced at least one stone event. The 5-year stone event rate was 28% for a symptomatic stone passage with renal colic or hematuria, 22% for asymptomatic stone passage, 17% for stone growth, and 4% for stone surgery.(25) Risk factors for these stone events included stone size >5mm, diabetes mellitus, hyperuricemia, and non-lower pole stone, some of which were reported in prior studies.(20, 21)

Recurrence in Clinical Trials

Clinical trials best inform stone prevention efforts, but strict criteria for identifying kidney stone recurrence are often not used. The use of various combinations of symptomatic and radiographic recurrence as a composite endpoint helps increase the event rate in clinical trials.(26, 27) Even surgery to remove an asymptomatic stone may be considered an acceptable endpoint in clinical trials.(26, 27) A recent review reported the recurrence rates from clinical trials of idiopathic calcium stone formers.(26) The rates of recurrence from 21 clinical trials averaged 6 per 100 person-years for first-time stone formers to 15 per 100 person-years in recurrent stone formers.(26) Of the 21 studies included in the review, 2 assessed for symptomatic recurrence, 4 assessed for radiographic recurrence, and 16 assessed for symptomatic or radiographic recurrence. Some defined symptomatic recurrence as either symptomatic stone passage or surgery on an asymptomatic kidney stone. Radiographic recurrence was defined by new stone formation, but by varying degrees of stone growth and by non-standardized imaging modalities over differing time intervals. With these differing definitions of recurrence, recurrence rates ranged from 6 to 110 per 100 person-years in the control arms of different clinical trials. Despite superior imaging resolution (17, 28, 29), CT was typically not used. The significant heterogeneity of recurrence definitions and wide range of recurrence hinders comparison between clinical trials.

Passage of stone fragments after stone surgery

The increase in kidney stone disease has led to increased utilization of surgical intervention. (7, 30) Stones can be fragmented in situ with shockwave lithotripsy, or removed by ureteroscopy, percutaneous nephrolithotomy, or rarely open nephrolithotomy. After surgery, patients can develop symptoms from subsequent passage of postoperative residual stone fragments. Clinical trials and cohort studies have identified that stone-free states (complete

stone clearance after the procedure) and residual stone fragment size 4mm lower the risk of symptomatic recurrence.(31–34) A New Zealand study of 9,538 patients that underwent shockwave lithotripsy for symptomatic stones achieved a 45% postprocedural stone-free rate, 14% had residual stone fragments of 4 mm, and 41% still had residual stone fragments >4mm.(31) These residual stone fragments led to a 6.8% hospitalization rate for stone related complications and a 4% rate of stent placement during follow-up.(31) Shockwave lithotripsy is particularly ineffective at clearing and preventing recurrence of lower pole kidney stones.(32) A landmark randomized trial comparing shockwave lithotripsy vs percutaneous nephrolithotomy for lower pole stones demonstrated inferior stone free rates for shockwave lithotripsy among stones with a mean size of 14mm (37% vs 95%).(35) A follow up trial comparing shockwave lithotripsy vs ureteroscopy for lower pole stones <10mm did not identify a difference in stone clearance rates.(36)

Percutaneous nephrolithotomy is the treatment of choice for large stone burden. A study of 658 patients that underwent percutaneous nephrolithotomy found that 83% of patients became stone free or had residual stone fragments 4mm. (33) Those with residual fragments > 4mm versus 4mm were more likely to undergo a reintervention (28% versus 17%) during an average follow-up of 13 months. Ureteroscopic procedures had shorter operation times, length of stay, and fluoroscopic time and lower complication rates than percutaneous nephrolithotomy.

Conclusion

There is significant variability among recurrence definitions in the literature. Symptomatic recurrence can range from minimal discomfort with self-managed stone passage to severe pain and high healthcare costs including emergency room visits, hospitalizations, and surgeries. Radiographic recurrence, including new stone formation and stone growth, is perhaps not a patient-centered outcome, but may be a useful and practical surrogate for symptomatic recurrence. This is supported by asymptomatic kidney stone growth and larger size being predictive of symptomatic stone recurrence.(13, 20, 21, 25) Having more consistent definitions and terminology for describing and discussing kidney stone recurrence may aid advances in this field. Recent Kidney Disease Improving Global Outcomes (KDIGO) guidelines addressed the challenges of clinical trials in nephrology and recommended consistency across studies with selection of outcomes that are relevant to patients and providers.(37)

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Key Points

- Kidney stones may recur with symptomatic or radiographic manifestations and the definition of recurrence is highly variable across different studies.
- Some patients may pass kidney stones without symptoms; some patients may have symptoms attributed to a stone but without a confirmed stone ever being seen.
- Radiographic recurrence often exceeds symptomatic recurrence making it useful for clinical trials. However, the relationship between radiographic recurrence and symptomatic recurrence is poorly understood.
- The success of stone procedures includes the absence of residual stone fragments or fragments ≤ 4 mm in diameter, since passage of stone fragments can lead to symptomatic recurrence.

Figure.

A conceptual model for the biology of kidney stone recurrence and its detection by symptoms or imaging. Dashed boxes show the biological changes and solid boxes show how these changes may be detected.