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REVIEW

International Alliance of Urolithiasis (IAU) guidelines on the metabolic evaluation and medical management of urolithiasis

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Abstract

The aim of this study was to construct the fourth in a series of guidelines on the treatment of urolithiasis by the International Alliance of Urolithiasis (IAU) that by providing a clinical framework for the metabolic evaluation, prevention, and follow-up of patients with urolithiasis based on the best available published literature. All recommendations were summarized following a systematic review and assessment of the literature in the PubMed database from January 1976 to June 2022. Each generated recommendation was graded using a modified GRADE methodology. Guideline recommendations were developed that addressed the following topics: initial evaluation, metabolic testing, dietary measures, medical management, and follow-up of recurrent stone formers. It was emphasized by the Panel that prevention of new stone formation is as important as the surgical removal of the stones. Although general preventive measures may be effective in reducing stone recurrence rates in some patients, specific medical and dietary management should be well considered and eventually applied in an individualized manner based on the outcomes of metabolic work-up, stone analysis and some certain patient related factors. A detailed follow-up of each case is essential depending on the metabolic activity of each individual patient.

Keywords Urolithiasis · IAU · Kidney stone · Metabolic evaluation · Prevention · Follow-up

Introduction

Urolithiasis is a common condition that affects 5–10% of the world population [1, 2]. Despite technological advances in the surgical management of stones that have significantly increased the stone-free rates and reduced patient morbidity with quick recovery time, the natural history of stone disease remains undeterred. The increasing prevalence of obesity and type 2 diabetes, together with population growth, is projected to contribute to dramatic increases in the financial burden of urolithiasis on Health Authorities, with an additional cost in the USA estimated to be $1.24 billion by 2030 [3]. Based on further data from the USA, the predicted prevalence of the disease is estimated to increase 25% by 2050 [4].

Kidney stones recur in up to 50% of cases within 5 years and increasing to 90% within 10 years following the first stone episode [5, 6]. Since the removal of an existing stone only treats the symptoms of the disease without changing its clinical course (the underlying causes remain uncorrected), patients in the high-risk group, particularly the recurrent stone-formers, should be thoroughly evaluated and treated to reduce the recurrence of the disorder while, at the same time, providing each patient with an adequate education on stone prevention. These guidelines aim to clarify the need for the thorough screening of patients to outline their stone forming risk factors and to describe rational methods for the evaluation, medical prophylaxis and follow-up of first-time and recurrent stone formers. Diagnostic protocols for

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patients at increased risk of stone recurrence are proposed and up-to-date advice on the dietary and medical treatment protocols is provided to guide the urologist to the appropriate and effective treatment to prevent recurrence of stones based on their chemical composition previously formed when the patient concerned.

Methods

Data identification

All recommendations for these 2022 IAU guidelines on metabolic evaluation and medical management of urolithiasis have been based on a systematic review and assessment of the literature obtained from the PubMed database, followed by determination of consensus by the Panel. The comprehensive search covers all aspects of the metabolic evaluation and medical management of urolithiasis. The search terms included (but were not limited to) "urolithiasis," "nephrolithiasis," "kidney stone" and "urinary stone." The publication dates ranged from January 1976 to June 2022. The focus of the searches was identification of all level 1 scientific papers (systematic reviews and meta-analyses of randomized controlled trials). If no sufficient data were found to support the clinical recommendation, the search was expanded to include lower-level literatures. In total, 7256 article titles were reviewed and 1179 were identified as potential relevant for inclusion in the literature assessment for this guideline.

Recommendation

A modified GRADE methodology was used to assess the certainty in the evidence and formulate recommendations (GR) [7, 8]. The resulting recommendation was rated as strong ("the guideline panel recommends…") or conditional ("the guideline panel suggests"), based on four potential levels of evidence (high, moderate, low, or very low) (Tables 1 and 2). Recommendations are agreed upon by Panel Members following review and discussion of the evidence. The Panel Members deliberate on the interpretation of the clinical evidence, and vote on how the evidence should be incorporated into the existing guidelines.

Guidelines

Initial patient evaluation

- A patient diagnosed with kidney or ureteral stone should undergo a screening evaluation with a detailed dietary and medical history including serum laboratory tests and urinalysis *(1B)*

All stone patients should have a detailed medical history consisting of past and current medical conditions [9].

Table 1 Interpretation of strong and conditional recommendations

I	Implications		
Grade	Patients	Clinicians	Policy
Level 1 'Strong' "We recommend"	Most people in your situation would want the recommended course of action, and only a small proportion would not	Most patients should receive the recommended course of action	The recommendation can be evaluated as a candidate for developing a policy or a performance measure
Level 2 'Conditional' "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined

Table 2 Quality of evidence grades and their definitions

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect is close to the estimate of the effect
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
C	Low	The true effect may be substantially different from the estimate of the effect
D	Very low	The estimate of the effect is very uncertain, and often it will be far from the true effect

This should include the following as described in reference [9–11]:

- A detailed stone episode history.
- A medical history taking into account not only of stone episodes but also of other relevant medical disorders, past surgical history and anatomic predisposing conditions.
- A history of urinary tract infections
- Details of any anatomical abnormalities in the urinary tract.
- A history of past and current medications that might influence stone formation.
- A family history of stones
- A family history of other medical problems that may predispose to stone-formation, such as hypertension, type 2 diabetes, bowel disease including bariatric surgery, metabolic syndrome and any inborn errors of metabolism that are commonly associated with stone-formation.

In addition, all stone patients should provide a detailed lifestyle profile. This should include the following as described in reference [11]:

- Date of birth, gender, weight, height and body mass index (BMI)
- Ethnic origins, including details of cultural and religious dietary habits or practices
- A lifestyle questionnaire including details of occupation, working or living in a hot environment, night-time sweating, strenuous exercise that leads to excessive perspiration, and frequency of air travel (particularly long-haul flights).
- A history of extended stays in tropical countries.

A dietary history should focus on the average daily intake of fluids, foods with high potential renal acid load (such as meats, grains, eggs, cheeses), calcium, salt (sodium chloride), high oxalate-containing foods, fruits and vegetables and over-the-counter supplements [9]. Assistance from a registered dietitian nutritionist or other nutrition specialist may be helpful in eliciting a comprehensive assessment of the patient's diet. Serum laboratory analysis should include electrolytes, calcium, creatinine, and urate that may suggest underlying medical conditions associated with stone disease [12–15].

Metabolic evaluation

- High-risk stone-formers, rapid or frequent recurrent stone formers or interested first-time stone formers should be offered a comprehensive metabolic evaluation (*1B*)

Comprehensive metabolic screening is the second step in the evaluation of patients with complicated urolithiasis and no definite diagnosis after basic metabolic evaluation. High-risk stone-formers are likely to benefit from comprehensive metabolic evaluation and medical therapy based on the outcomes of this critical evaluation [16–18]. The Metabolic Screen consists of a blood and spot (random) urine sample taken at the patient's first appointment at the Stone Clinic. The blood sample should be analyzed for creatinine, urea, glucose, albumin, sodium, potassium, chloride, bicarbonate, calcium, corrected calcium, phosphate, magnesium, uric acid, alkaline phosphatase, parathyroid hormone (PTH) (if hypercalcinemia was found) and 25-hydroxyvitamin D3. The urine should be analyzed for urea, creatinine, osmolality, sodium, potassium, magnesium, phosphate, oxalate, citrate, cystine (in case cystinuria is suspected), urate and pH (measured by pH meter) [11].

The high-risk stone formers include, but are not limited to:

- Early onset of urolithiasis (< 18 years of age)
- Familial stone formation
- Bilateral or multiple stones
- Recurrent stones (that is two or more kidney stone episodes in the past)
- Uric acid and urate-containing stones
- Pure calcium phosphate stones (particularly brushite)
- Stone formation in a solitary kidney
- Systemic disease that increases the risk of kidney stones (e.g., gout, osteoporosis, bowel disorders, primary hyperparathyroidism, vitamin D deficiency, nephrocalcinosis, distal renal tubular acidosis)
- Genetically determined stone formation (e.g., cystinuria, primary hyperoxaluria, xanthinuria, cystic fibrosis)
- Drugs associated with iatrogenic stone-formation (acetazolamide, topiramate, triamterene, certain protease inhibitors).
- Patients with stones difficult to treat (e.g., urinary tract abnormalities/reconstruction).
- Occupation where public safety is at risk (e.g., pilots, air traffic controller, police officer, military personnel, firemen), those working in hot environment (workers in some industrial or factory settings, construction workers), and those with limited opportunities or access to toileting (teachers, bus and truck drivers, taxi drivers, frequent business travelers).

Urine is the medium in which all types of stones form. The composition of urine determines the types of stones for which the patient is at risk for stone formation. This can be influenced by diet, metabolic activity, lifestyle, and medical history. The primary objective in screening a patient with stones is to try to understand why his/her 24-hour urine has

the composition concerned. This is best accomplished by collecting one or two 24-hour samples from each patient on their regular free home diet. The recommendation is two collections, but this goal is sometimes difficult to reach and in those patients one collection might give sufficient information.

- For the initial metabolic evaluation, the patients should stay on their regular diet and should ideally be stone-free for at least 3 months *(2D)*

Currently, the evidence for the preferred time of 24-h urine collection in patients with urinary stones is limited. For the initial specific metabolic workup, ideally the patient should be stone-free [19]. Patients undergoing metabolic evaluation should continue their regular diet and fluid intakes without any obstruction and/or urinary tract infection to get on the right treatment plan. Numbers of detectable 24-h urine abnormalities increase with time after stone events [20, 21]. Therefore, a 3-months delay of metabolic evaluation after a stone event was recommended for these reasons.

- 24-h urine sample should be collected with preservatives or stored at 4 °C to prevent the risk of spontaneous crystallization and bacterial growth *(2C)*

Thymol, toluene, boric acid, hydrochloric acid, sodium azide and alkalinizing agents are all recommended as preservatives for 24-h urine sample [21–23]. Although we believe the storage of urine at 4 °C might be optimal, it is very unlikely that patients can store urine in that way and it is, moreover, necessary to carefully make sure that any precipitates formed during storage are dissolved before analysis. Urinalysis should be carried out immediately after collection. Acidification of urine is recommended for patients with calcium oxalate and calcium phosphate stones for whom information on urine calcium, oxalate and phosphate is fundamental. In patients with uric acid stones for whom information on urate excretion is important the preservative should be alkaline. Spot urine samples for pH measurement must be obtained after overnight fasting [24, 25].

The suggested added volumes and quantities are approximately adapted for 24 h urine samples with volumes between approximately 1500 and 2000 mL. For larger urine volumes it is necessary to increase the added volume accordingly. Acidification of the urine for analysis of calcium and oxalate may require a pH as low as 1.0. Sodium azide preservation can be used for the analysis of urate.

- Two 24-h urine collections are recommended to correct and reliable identification of metabolic abnormalities *(2C)*

Although performing a single 24-hour urine collection could reduce the overall cost and increase patient compliance, it is generally recommended that two 24-hour urine collection and evaluation should be done on 2 non-consecutive days to complete a comprehensive metabolic evaluation. There are a series of retrospective studies indicating the significant differences in urinary parameters between two separate samples [26–28]. Accordingly, single 24-hour urine collection is not optimal and may lead to misdiagnosis of the patient's underlying metabolic defect. In patients reluctant to collect two samples, valuable information nevertheless can be obtained from one sample, provided the collection has been carried out in a correct way. But it can be decided to add repeated collections based on borderline data in one or two collections before starting medical treatment.

- Urinary supersaturation levels for the individual stone components are useful measures of the risk of stone formation *(2C)*

Supersaturation is the presence of a material in solution at a concentration above its own solubility product. Supersaturation is the driving force for crystal formation in urine. Urine supersaturation for most kidney stones includes calcium oxalate, calcium phosphate, and uric acid. Supersaturation is calculated using an iterative approximation computer program taking the physiochemical interactions of multiple factors (including certain promoters and inhibitors) into account [29, 30]. Available programs that estimate urine supersaturation calculation programs include EQUIL2, JESS and LithoRisk [31]. Several studies demonstrated that the urine supersaturation is correlated with the risk of recurrent stone formation and can be used to assess the effectiveness of dietary and drug therapy [29, 32]. Not all Stone Clinics have access to the computer programs listed above and simplified expressions of the ion-activity products of calcium oxalate and calcium phosphate such as AP(CaOx) [33] index and AP(CaP) [34] index are very helpful.

During the review of 24-hour urine studies, physicians should be aware that patients often increase their fluid intake or alter their diet temporarily in an attempt to achieve better results (i.e., the "stone clinic effect" [35]) and interpret it accordingly [36].

- A spot (random) urine is not suitable to be used interchangeably in place of the 24-h urine collections in the evaluation of urinary metabolic abnormalities in stone-formers *(2C)*

Despite conflicting results, most studies have reported that the value of spot urine studies is limited in clinical practice as the results may vary with collection time and the patients' gender, body weight, and age [37–40]. Spot

urine samples may be the alternative sampling method only for those patients in whom 24-hour urine collection is impractical or not possible (such as children). In addition, spot urine evaluation can be useful for monitoring – especially if quoted as a ratio against creatinine, to allow some calibration for the concentration of the urine at the time the spot test was taken. Moreover, this can be useful for patients on specific treatment – e.g., an oxalate: creatinine ratio for patients who have made dietary adjustments.

- Fasting crystalluria can provide evidence of the propensity of the urine to form stones *(2D)*.

Studies of repeated crystalluria evaluated under microscope have shown that large and aggregated crystals correlate with calcium oxalate stone recurrence, the volume of cystine crystals predicts the risk of new stones formation and crystals of 2,8 dihydroxyadenine is pathognomonic of an autosomal recessive metabolic disorder, the adenine phosphoribosyltransferase deficiency (APRTD), caused by a mutation in the adenine phosphoribosyltransferase gene encoding on chromosome 16q24 [41–43].

- Whenever possible, stone analysis should be performed at each episode *(1B)*.

Quantitative analysis of the stone (obtained or passed) is an essential part of the metabolic evaluation [44, 45]. It is a crucial prerequisite for an effective treatment and recurrence prevention. Fourier Transform Infrared (FTIR) spectroscopy and X-ray diffraction are both reliable methods for stone analysis. Chemical analysis (wet chemistry) is insufficient and generally deemed to be obsolete [46, 47]. According to the expert and key opinion leaders description of stone morphology and classification of stones in the light of Daudon's morpho-constitutional classification is a valuable approach to the etiology of stones; it was suggested to apply this method to all retrieved stones [48].

- Genetic testing can aid in the diagnosis of monogenic urinary stone diseases *(2C)*.

Identifying genetic predisposition may lead to new prevention strategies for urolithiasis [49]. Genetic screening is important for the diagnosis of the rare monogenic urinary stone diseases (such as primary hyperoxaluria, Dent's disease, hereditary distal renal tubular acidosis, cystinuria, and 2,8-dihydroxyadeninuria) because the clinical phenotype may not identify the precise cause of the disease. Sequencing approaches include targeted gene panels and whole exome sequencing [50].

Management

Fluid intake

- High fluid intake has a beneficial effect on prevention of stone recurrence. Daily fluid intake should be high enough to reach at least 2.2–2.5 L of urine per 24 h under all circumstances (1A)
- Most fluids are equally protective. However, sugar-added beverages, such as fruit punch and soft drinks, are associated with a higher risk of kidney stone disease *(2C)*.

Of all dietary interventions aimed to reduce the risk of kidney stones, urine dilution by increasing fluid intake is one of the most important factors [51]. For every additional drink (200 ml) consumed per day of total fluid, the risk of kidney stones has been shown to decline by 13% [52, 53]. Some drinks are associated with a higher risk of stone disease including tea and wine. Carbonated, sugar-added, soft drinks frequently contain fructose. Fructose may increase the urinary excretion of calcium, oxalate, and urate, and is associated with a higher risk of kidney stone formation [54].

Diet therapy

A balanced dietary calcium intake (1.2 g per day) has protective effects against kidney stone-formation *(1B)*.
Oxalate is present in many foods (particularly fruits and vegetables), so it is difficult to significantly limit their intake. Dietary manipulation might be useful only in case of excessive intake of high oxalate containing vegetables, such as spinach, rhubarb, chocolate, and nuts, and when concomitant calcium intake is insufficient *(1B)*
Animal protein restriction has a favorable effect on the metabolic risk factors for nephrolithiasis *(2C)*
In the case of high urinary calcium excretion with a high estimated dietary salt (sodium chloride), it is always advisable to introduce a low-sodium diet *(1C)*
Vitamin D, in routinely consumed amounts, is not statistically associated with risk of kidney stone formation in its routinely consumed amounts *(1B)*
Vitamin C intake in typical amounts (< 1 g per day) is not statistically associated with increased risk of kidney stone formation *(2C)*
A low-calcium diet leads to an increased intestinal absorption of free oxalate, resulting in oxaluria and urinary supersaturation with calcium oxalate, favoring the nucleation process and crystal growth [55, 56]. Further-

more, balanced dietary calcium intake seems to have protective effects on kidney stone events independent of its origin, from both dairy and nondairy sources [57]. Oxalate is widely present in many foods, so it is difficult to limit its intake significantly [58]. To appreciate the intestinal oxalate absorption for a specific food stuff the following formula is useful:

$$(\text{Oxalate (mg/100g)}/\ \text{Calcium (mg/100g)}) \times 0.44.$$

Foodstuffs with index < 0.8 are considered to contain enough calcium to prevent oxalate intestinal absorption. On the contrary, if the ratio is > 0.8 the quantity of calcium is insufficient to bind oxalate and those aliments are recommended to be avoided [59].

Vegetable proteins were not found to be associated with the risk of kidney stones, while dairy proteins were inversely associated with incident kidney stones. Nondairy animal proteins are thought to pose the greatest risk for the occurrence of kidney stones [60, 61]. Protein intake should be limited to 1 g protein/kg normal body weight/day. Daily protein intake can be calculated from the 24-h urine excretion of urea as follows: $[\text{UUrea (mmol/day)} \times 0.18 + 13 = \text{grams protein/day}]$ [62].

High sodium intake increases urinary calcium excretion. Admittedly, a low-sodium diet is challenging with the availability and popularity of processed foods, as sodium is added to virtually any industrial-transformed food. Vitamin D intake in typical amounts was not found to increase mean urinary excretion of calcium significantly. However, increased risk with higher doses of Vitamin D cannot be excluded [63].

In some large cohort studies, supplemental or diet vitamin C intakes were not associated with risk of incident kidney stones [64]. However, in male patients with ascorbic acid intake of approximately 1000 mg recruited from a population of 48 850 and followed for 11 years, the relative risk of stone formation was approximately doubled compared with that in patients only taking multivitamin doses [65]. A small metabolic study in normal volunteers and stone formers found that vitamin C in doses of 2 g daily increased urinary oxalate by 20–30% [66].

Finally, food culture is completely different from country to country. Clinicians in each country should analyze their diet carefully and determine what diet is appropriate to prevent stone formation.

Lifestyle

- Excessive fluid loss through chronic diarrhea or sweating should be compensated by an increased fluid intake *(1A)*
- Adequate exercise to achieve weight reduction can be helpful in decreasing the risk of new stone formation/regrowth *(2D)*

Chronic dehydration (due to exposure to excessive heat or a consequence of poor drinking) is a confirmed risk factor for kidney stones. Overweight and obese patients are at increased risk of kidney stones [17]. A positive correlation between BMI and urinary excretions of calcium, oxalate and urate has been demonstrated [67]. Mild to moderate amounts of weekly physical activity are associated with a decreased risk of development of kidney stones [68].

Calcium-containing stones

Hypercalciuria

- Thiazide diuretics can decrease urinary calcium excretion and reduce the rate of stone recurrence *(1B)*

A diet with a low potential of renal acid load (meats, grains, eggs, cheeses) and salt (sodium chloride) is recommended. After that, a repeat 24-h urine analysis can be carried out to determine the response. If hypercalciuria persists, pharmacological treatment (such as administration of thiazides) may be of value. Thiazides can reduce recurrence rate by 30% in idiopathic calcium stone formers [69]. The mechanism whereby thiazides reduce stone recurrences remains unresolved, in that the success of thiazide therapy was not associated with any urinary chemical parameter, including calcinuria [70]. A further problem is that randomized thiazide trials applied doses of 50–100 mg/day, whereas nowadays – influenced by treatment data from cardiovascular trials—65% of thiazide doses given to stone patients are below 50 mg/day [71]. Thiazides can induce a positive calcium balance and reduce urinary calcium by up to 50% [72–74]. Medication with thiazide is ineffective unless dietary salt intake is restricted, because dietary sodium counteracts the hypocalciuric effect of thiazides [73]. It is estimated that for every gram reduction in daily salt intake, the 24-h urine calcium excretion will decrease by 5.5 mg [72]. Thiazides also reduce serum potassium, increase urate levels, and reduce urinary citrate excretion [75]. Therefore, addition of potassium citrate is often useful when starting treatment with thiazides. Potassium citrate not only increases the level of citrate in urine, but may also increase the renal reabsorption of calcium, leading to additional reduction of hypercalciuria.

Hypocitraturia

- Alkali citrates are effective to increase urinary citrate concentration, raise the urinary pH, and limit stone recurrence in calcium stone-formers *(1B)*

Potassium citrate or other alkali supplements constitutes the treatment of choice in patients with hypocitraturia because it increases urinary citrate and therefore increased urinary inhibitory activity. In one study of stone formers with hypocitraturia, potassium citrate therapy additionally reduced urinary calcium excretion by 30% [76]. If the patient develops hyperkalemia, additional potassium should not be given, but that problem is unusual. Sodium citrate as well as sodium bicarbonate also increase urinary citrate and significantly increases pH, but excessive sodium intake can increase blood pressure as well as urinary calcium and uric acid excretion [77, 78]. Currently, these agents are reserved for patients in whom potassium citrate is contraindicated or poorly tolerated. The dose of potassium citrate should be adjusted to obtain the optimal effect on the urinary citrate and pH levels. Follow-up analysis of 24-h urine is recommended for all patients treated with potassium citrate to assess the response to therapy and to titrate the dose to effect. For calcium-stone formation, the optimal urine pH should be 6—6.5. Moreover, a high sodium intake can decrease urinary citrate by 20%, therefore, limited dietary salt is recommended.

Acid–base status determines urinary citrate excretion: acidosis decreases urinary citrate excretion and alkalosis promotes a citraturic response. Many experimental and clinical studies have shown a significant role of the nutritional status, caloric and carbohydrate intake, daily sodium intake, negative potassium balance and various hormones. Acidosis, acid loads, chronic diarrhea and/or malabsorption, starvation, and some drugs, such as acetazolamide, ethacrynic acid and angiotensin converting enzyme (ACE) inhibitors seem to work in the same way, by decreasing urinary citrate excretion [79]. In addition, approximately 20% of patients with hypocitraturia appear to be relatively resistant to citrate complementary therapy [80, 81].

Hyperoxaluria

- If dietary oxalate intake is high and not appropriately countered by dietary calcium, oxalate restriction is beneficial in cases with hyperoxaluria *(1B)*
- Limiting fat intake and fatty acids may reduce oxalate absorption in patients with enteric hyperoxaluria *(2D)*
- Magnesium and calcium supplements can reduce stone formation in enteric hyperoxaluria *(1C)*
- Pyridoxine or vitamin B6 administration can significantly reduce urinary oxalate excretion if vitamin B6 status is deficient or insufficient *(2C)*

If excessive urinary oxalate is of intestinal origin (enteric hyperoxaluria), the first therapeutic step should aim to reduce the bioavailability (absorption) of dietary oxalate intake. High fluid intake is also recommended to reduce urinary saturation of calcium oxalate. One therapeutic obstacle to dietary oxalate reduction is the lack of accurate information about the oxalate content of various foodstuffs, because food manufacturers do not detail the oxalate content of their products on the product labels.

Dietary intervention targeting the pathophysiology of intestinal (enteric) hyperoxaluria is to reduce the fat intake. Fatty acids in the intestinal lumen reduce the intraluminal content of free calcium and cause increased oxalate absorption and excretion [82, 83].

Addition of dietary calcium results in calcium binding to oxalate in the intestinal lumen, reducing intraluminal oxalate and intestinal oxalate absorption. Dietary calcium or supplemental calcium increases intestinal calcium oxalate complex formation thereby reducing absorption of oxalate. In idiopathic calcium oxalate stone formers, simultaneous intake of calcium (calcium-rich mineral waters, dairy products) with any snack or meal lowered urinary oxalate as well as urinary calcium oxalate supersaturation by 21% [84, 85]. Magnesium can also bind oxalate in the intestine and reduce oxalate absorption; however, magnesium may cause diarrhea, further exacerbating hyperoxaluria [86, 87].

The gut microbiome contains bacteria that metabolize oxalate as an energy source. Oxalate-degrading bacteria might thus be used for treating hyperoxaluria. However, not only does the correct strain of bacteria need to be identified, but optimal treatment protocols developed [88]. Pyridoxine (vitamin B6) administration may significantly reduce urinary oxalate excretion [89, 90]. However, the benefits may be limited to those patients who are vitamin B6-deficient or insufficient and, therefore, with suboptimal cofactor capacity for the enzyme alanine:glyoxylate aminotransferase (AGT). Lower AGT activity increases oxalate biosynthesis and, ultimately, urinary oxalate excretion. However, large RCTs examining the effect of pyridoxine administration on stone recurrence are lacking.

No abnormalities in the 24-h collection

- Bullet Thiazide and alkaline citrates/bicarbonates alone or both can reduce stone formation (1B)

If a patient develops recurrent stones despite an adequate increase in urinary output and a repeat 24-h urine still shows no specific abnormality, empirical therapy can be given with

a thiazide diuretic, potassium citrates/bicarbonates or both. This will force a mandatory increase in urinary volume but can cause mineral and salt imbalance in the blood and several other complications. Failure to increase oral fluid intake while taking a diuretic can lead to dehydration. Thiazide or alkaline citrates or both can limit stone-formation by reducing urinary calcium excretion and increasing urinary citrates, respectively [74, 76]. Recent evidence showed that bisphosphonate, an inhibitor of bone resorption, could reduce the calcium-containing stone formation [91].

Uric acid stones

- Patients with uric acid stones can benefit well from urinary alkalinization *(1B)*
- Allopurinol can be beneficial as an adjunctive therapy in patients with hyperuricaemia or hyperuricosuria, but is not sufficient for prevention of uric acid stones *(2B)*.

Low urinary pH is the predominant risk factor for uric acid stone-formation. Hyperuricosuria may be important for the formation of urate stones in a few patients when urine pH is above 7.0 [92, 93]. Increased fluid intake and urinary alkalinization is therefore the first-line of therapy for patients with uric acid stones [94]. Urine pH values should aimed to be 6–6.5 [95]. Sodium citrate or potassium citrate, and/or other alkalis are generally used for uric acid stone patients. Uric acid stones are often associated with metabolic syndrome, and low urine pH has been demonstrated to be the consequence of renal tubular insulin resistance with reduced urine buffering of hydrogen ions [96]. In case of insufficient urine pH elevation with alkalinization alone, pioglitazone which directly addresses insulin resistance, has been shown to significantly raise urine pH [97].

Because allopurinol is not effective in preventing stone recurrence in patients with normal urinary urate [98], it should not be routinely prescribed as the first-line therapy for patients with uric acid stones. There is some evidence that allopurinol reduces the recurrence of calcium oxalate stones in patients with hyperuricosuria and normocalciuria [99].

Cystine stones

- Urinary alkalinization is the initial step in medical therapy for cystine stones *(2C)*

Prior to pharmacological therapy, patients with cystine stones should be advised to substantially increase their fluid intake, and restrict sodium intake, and in adults, foods rich in methionine and cysteine in adults [100]. Restriction of these amino acids in children is not recommended because they are essential for growth. As the solubility of cystine is increased at higher urinary pH values, alkalinization of the urine targeting a urine pH above 7 helps to reduce cystine crystallization [101]. Acetazolamide may be used as an adjunct to urinary alkalinization when potassium citrate alone is ineffective.

- Cystine-binding thiol drugs should be used if alkalinizing agents fail to adequately control cystine stone-formation *(2C)*

Cystine-binding thiol drugs constitute the next line of therapy [102]. D-Penicillamine (1–2 g) or Tiopronin (800–1200 mg in daily divided doses). Tiopronin is possibly more effective and associated with fewer adverse side effects than D-Penicillamine and should be considered when rich fluid intake and alkali have insufficient effect on cystine stone formation [103].

Struvite and infection stones

- Antibiotics for long-term treatment after operation are helpful for inhibiting the growth of infection stones *(1C)*

Infection stones are mainly composed of magnesium ammonium phosphate, carbonate apatite and ammonium urate [104]. Magnesium ammonium phosphate and carbonate apatite are the main components of struvite. Struvite formation is caused by urease producing bacteria in the urinary tract, the most common of which are Proteus, followed by Klebsiella, Pseudomonas, mycoplasma (Ureaplasma urealyticum) and Staphylococcus [105]. It has been shown that antibiotics can be used for long-term treatment after surgical stone clearance to inhibit growth of infection stone fragments [106]. Culture-specific antibiotics should be used for long-term treatment. Although the optimal antibiotic regimen with regard to dosage, agent and duration of treatment has not been established, some advocate reducing the dose of antibiotics to half after one to two weeks of treatment, and then continuing suppressive antibiotics for about 3 months [106]. Urine cultures should be carried out every month during three consecutive months after stopping antibiotic treatment, and routine urine culture should be carried out at all follow-up visits [107]. In case of recurrence 6 weeks of antibotic treatment regimens might be offered following surgical interventions.

- Urine acidification is recommended for patients with residual fragments after surgery *(2D)*

The main mechanism of infection stone formation is that urease produced by bacteria catalyze urea into ammonia and carbon dioxide, after which ammonia and water form ammonium hydroxide. Ammonium hydroxide is an alkaline agent,

which significantly increases urinary pH. When urine pH reaches 7.2, ionic ammonium can combine with magnesium and phosphate to form magnesium ammonium phosphate. It is suggested that infection stones should be treated by surgery. If there are residual fragments after surgery, urine acidification should be considered. Urine acidification can not only ease the passage of residual fragments, but also prevent formation of a new stone. Commonly used agent acidifying agents include ascorbic acid, ammonium chloride, ammonium sulfate, ammonium nitrite and L-methionine [108]. Among them, ammonium chloride is suitable for short-term treatment, while ammonium sulfate is the rational choice for long-term treatment [107]. The target pH of urine acidification is 6.2, which also helps to control urinary infection [109]. It has been suggested that intermittent treatment with large doses of ammonium chloride might be efficient while circumventing the physiological buffering effect.

- Acetohydroxamic acid can reduce the growth of infection stones *(2C)*

In view of the key role of urease in the formation of struvite, urease inhibitors can be used to reduce the growth rate of stones [110]. Acetohydroxamic acid is an irreversible urease inhibitor that is the most frequently utilized agent. Several randomized trials have shown that acetohydroxamic acid can reduce the growth of infection stones [111, 112]. However, 20% of treated patients have been reported to experience neurological, dermatological and hematological side-effects, thereby limiting its clinical use. In patients with impaired renal function the acetohydroxamic acid effect is reduced [113]. Therefore, acetohydroxamic acid is prohibited for patients with creatinine levels greater than 2.5 mg/dl^2 (220 umol/L), pregnant women and women of childbearing age not utilizing taken birth control measures [114].

Primary hyperoxaluria

- Pyridoxine can reduce the urinary oxalate excretion in primary hyperoxaluria type 1 *(1C)*

Primary hyperoxaluria type 1 involves functional loss of the enzyme AGT, encoded by the AGXT gene, which leads to accumulation of glyoxylate in the cytosol and its LDH-mediated conversion to oxalate [115]. Pyridoxine, which is metabolized to pyridoxal-5′-phosphate (PLP, the essential cofactor of AGT), leads to a decrease in urine oxalate in approximately 50% of patients with primary hyperoxaluria type 1, particularly those with the Gly170Arg or Phe152Ile genotypes [115, 116]. The mechanism of action of pyridoxine in primary hyperoxaluria involves multifactorial activity on AGT: pyridoxine has been shown to increase expression, catalytic activity and peroxisomal import of AGT, restoring the function of the enzyme lost in primary hyperoxaluria type [115].

- Lumasiran can reduce the urinary oxalate excretion in primary hyperoxaluria type 1 *(2C)*

Subcutaneously administered Lumasiran is a small interfering RNA targeting the mRNA for hydroxyacid oxidase 1 gene (HAO1; encodes glycolate oxidase) that is administered subcutaneously for the treatment of primary hyperoxaluria type 1 [117]. By silencing the gene encoding glycolate oxidase, Lumasiran depletes glycolate oxidase and thereby inhibits the synthesis of oxalate, which is the toxic metabolite that is directly associated with the clinical manifestations of primary hyperoxaluria type 1. A Phase 3 study showed that treatment with Lumasiran resulted in a clinically significant (53.5 percent) reduction in 24-h urinary oxalate excretion from baseline to month 6 compared with placebo [118].

Renal tubular acidosis (RTA)

- Alkaline citrates and/or bicarbonates can be beneficial in distal RTA to correct the intracellular acidosis *(2C)*

Distal RTA is characterized by inability of the distal renal tubule to appropriately excrete excess acid, leading to metabolic acidosis. Distal RTA mostly occurs in its incomplete form [119]. The prevalence is high in idiopathic calcium stone formers, between 13.7% and 16.6% [25, 120], and higher in female [25]. Intrarenal calcifications (nephrocalcinosis) and calcium stones are commonly observed in patients with distal RTA. The mechanisms for development of nephrocalcinosis and renal stones in RTA are not completely understood, but hypocitraturia and in some cases hypercalciuria, are considered the primary risk factors for stone formation [121]. Systemic and/or intracellular acidosis leads to increased citrate reabsorption in the proximal tubule and reduced urinary citrate excretion. Long-term alkali therapy not only corrects the acid retention and normalizes urinary citrate and calcium, but also reduces clinical stone recurrences by more than fivefold [25, 122].

Follow-up

- X-ray KUB or ultrasonography is recommended for monitoring metabolic stone activity *(1C)*

X-ray KUB or ultrasonography should be periodically obtained to identify stone recurrence, defined as stone regrowth or new stone formation. KUB and ultrasonography have the advantages of being both practical and cost-effective. The first follow-up of imaging study should be

carried out within 6 months, with subsequent yearly follow-up examinations thereafter depending on the aggressiveness of stone disease [123, 124].

- Blood analyses are recommended to assess the possible adverse effects of pharmacological therapy *(2C)*

Pharmacological agents used in stone prevention may be associated with potential adverse effects. For example, potassium citrate occasionally may result in hyperkalemia whereas thiazide diuretics may result in hypokalemia. Allopurinol may cause liver enzyme abnormalities and tiopronin may cause hematological abnormalities. D-penicillamine is recognized to induce glomerular disease. Therefore, periodic blood analysis should be performed to detect any potential side effects of all prescribed pharmacological agents [125, 126].

- Urologists/clinicians should obtain a single 24-h urine analysis within six months after start of treatment and then annually or with higher frequency to evaluate the response to dietary and/or medical therapy *(2C)*

Urinary supersaturation with stone-forming salts and acids has been shown to correlate with stone formation. Consequently, urine supersaturation obtained from a 24-h urine analysis may be used to follow response to treatment [29, 127]. High-risk stone formers are likely to benefit from 24-h urine testing to guide their daily dietary treatment and/or pharmacotherapy [100].

- Urologists/clinicians should obtain a single 24-h urine analysis within six months to assess the response to dietary and/or medical therapy once treatment has been initiated [9]. After the initial follow-up, it is also recommended to obtain a single 24-h urine sample for annual analysis or more frequently, depending on stone activity and kind of treatment. The purpose is to determine each patients' adherence to the treatment and metabolic response, and to enable adjustment of the prevention and/or medical therapy protocols for individuals with active stone-formation [9]. If patients remain stone free for an extended period, the frequency of follow-up 24-h urine analysis can be reduced.

Urologists/clinicians should repeat stone analysis, when possible, especially in patients with observed stone recurrences or with high risk of recurrences *(2D)*.

Stones composed of uric acid, cystine or struvite indicates specific metabolic or genetic abnormalities. Identification of such stones can directly provide the basis for decisions on pharmacological recurrence prevention and other therapeutic options [128]. Therefore, stone analysis is always a direct and important part of recurrence prevention [10]. It is of note, however, that 32.9% of patients in one study demonstrated changing in stone composition with other components in two successive recurrent stone episodes [129]. Therefore, accurate and repeated stone analysis throughout the follow-up is highly important and beneficial. Efforts should, therefore, be made to ask patients to collect all stones that pass spontaneously or are removed by surgery [9, 10].

Conclusions

The prevention of new stone-formation is as important as the surgical removal of the stones. The urologists, who successfully treat urolithiasis, also play an important role in establishing optimal strategies to prevent recurrence of the disorder. Based on an assessment of the risk for stone recurrence and metabolic activity, stone formers should be evaluated in a comprehensive manner. A fully comprehensive protocol containing a screening program and database (LITHOSCREEN) for the assessment and management of patients with kidney stones has recently been published [11]. Although general preventive measures may be effective in all stone-forming patients, medical and dietary management should be applied in an individualized manner based on the outcomes of metabolic work-up, stone analysis and some certain patient related factors. A careful and close follow-up of stone formers should be performed depending on the level of metabolic activity of each individual patient.

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Declarations

Conflict of Interest The authors declare no conflict of interest.

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