Guidelines

Metabolic Evaluation and Recurrence Prevention for Urinary Stone Patients: EAU Guidelines

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Abstract

Context: An optimum metabolic evaluation strategy for urinary stone patients has not been clearly defined.
Objective: To evaluate the optimum strategy for metabolic stone evaluation and management to prevent recurrent urinary stones.
Evidence acquisition: Several databases were searched to identify studies on the metabolic evaluation and prevention of stone recurrence in urolithiasis patients. Special interest was given to the level of evidence in the existing literature.
Evidence synthesis: Reliable stone analysis and basic metabolic evaluation are highly recommended in all patients after stone passage (grade A). Every patient should be assigned to a low- or high-risk group for stone formation. It is highly recommended that low-risk stone formers follow general fluid and nutritional intake guidelines, as well as lifestyle-related preventative measures to reduce stone recurrences (grade A). High-risk stone formers should undergo specific metabolic evaluation with 24-h urine collection (grade A). More specifically, there is strong evidence to recommend pharmacological treatment of calcium oxalate stones in patients with specific abnormalities in urine composition (grades A and B). Treatment of calcium phosphate stones using thiazides is only highly recommended when hypercalciuria is present (grade A). In the presence of renal tubular acidosis (RTA), potassium citrate and/or thiazide are highly recommended based on the relative urinary risk factor (grade A or B). Recommendations for therapeutic measures for the remaining stone types are based on low evidence (grade C or B following panel consensus). Diagnostic and therapeutic algorithms are presented for all stone types based on the best level of existing evidence.
Conclusion: Metabolic stone evaluation is highly recommended to prevent stone recurrences.
Patient summary: In this report, we looked at how patients with urolithiasis should be evaluated and treated in order to prevent new stone formation. Stone type determination and specific blood and urine analysis are needed to guide patient treatment.
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1. Introduction

The lifetime risk of stone formation in an individual is estimated at 5–10% [1,2]. The recurrence rate after formation of an initial stone is reported to be as high as 50% at 5 yr and 80–90% at 10 yr [3]. People who form stones are more likely to have urinary metabolic abnormalities compared to a healthy population (level of evidence [LE] III/C) [4,5], while patients who form recurrent stones tend to have more significant metabolic abnormalities than those with a single stone episode (LE III/C) [5,6]. Because the removal of an existing calculus does not prevent further stone formation, patients should be thoroughly evaluated and educated on stone prevention. The aim of this review is to clarify the need and describe a method for evaluation of patients with first-time and recurrent stone formation. Diagnostic protocols for different etiologies of nephrolithiasis are provided. Specific therapeutic algorithms have been created to guide etiologic treatment of different stone types.

2. Evidence acquisition

A professional research librarian carried out literature searches for all sections of the urolithiasis guideline, covering the timeframe between 1976 until August 2013. Searches were carried out using the Cochrane Library Database of Systematic Reviews, the Cochrane Library of Controlled Clinical Trials, and Medline and Embase on the Dialog-Datastar platform. The searches used the controlled terminology of the respective databases. Both MesH and EMTREE were analyzed for relevant terms. In many cases, the use of free text ensured the sensitivity of the searches. The focus of the searches was identification of all level 1 scientific papers (systematic reviews and meta-analyses of randomized controlled trials). If sufficient data were identified to answer the clinical question, the search was not expanded to include lower-level literature. LE and/or grade of recommendation (GR) values were given according to the Oxford Centre for Evidence-based Medicine LEs [7]. In some cases, the link between LE is and GR is not directly obvious and recommendations have been up- or down-graded following expert panel discussion. These cases are clearly identifiable and marked in the recommendation section with an asterisk (*).

3. Evidence synthesis

3.1. General metabolic considerations for patient workup and recurrence prevention

3.1.1. Evaluation of patient risk
All patients should undergo stone analysis using infrared spectroscopy or X-ray diffraction prior to metabolic evaluation [8]. Stone analysis should be performed in recurrent stone formers during each stone episode, even if the initial stone composition is known, because changes in stone content have been reported in recurrent stone formers [9,10]. When stone analysis is not available, a

Table 1 – Investigating patients with stones of unknown composition

Investigation	Rationale for investigation
Medical history	Stone history (former stone events, family history) Dietary habits Medication chart
Diagnostic imaging	Ultrasound Unenhanced helical CT in cases of a suspected stone
Blood analysis	Creatinine Calcium (ionized calcium or total calcium + albumin) Uric acid
Urinalysis	Dipstick test: leukocytes, erythrocytes, nitrite, protein, urine pH, specific weight Urine culture Urine pH profile (measurement after each voiding, minimum four times daily) Microscopy of urinary sediment (morning urine) Cyanide nitroprusside test (exclusion of cystinuria)

CT = computed tomography.

specific workup of the patient should be performed (Table 1) [11].

After stone passage, every patient should undergo basic evaluation and be assigned to a group with low or high risk of stone recurrence (Tables 2 and 3; Fig. 1) [11].

Only high-risk stone formers require specific metabolic evaluation [12], which should be individualized based on different stone types. Specific metabolic evaluation requires collection of two consecutive 24-h urine samples [13,14]. Patients should remain on a self-selected diet [15]. The collection method should be chosen in close cooperation with the particular laboratory.

Spot urine samples are an alternative sampling method, particularly when 24-h urine collection is difficult, for example, in younger children. Spot urine studies normally link the excretion rates to creatinine [16]. Because the results may vary with collection time and patients' sex, body weight, and age, the value of spot urine studies is limited.

There is limited evidence to support the exact time to perform the specific metabolic evaluation and follow-up of stone patients (level III/grade C). For the initial specific metabolic workup, the patient should be stone-free. A minimum of 20 d is recommended between stone expulsion or removal and 24-h urine collection [17,18]. Follow-up

Table 2 – Basic evaluation of a stone former

Investigation	Rationale for investigation
Medical history and physical examination	Stone history (prior stone events, family history) Dietary habits Medication chart
Diagnostic imaging	Ultrasound
Blood analysis	Creatinine Calcium (ionized calcium or total calcium + albumin) Uric acid
Urinalysis	Dipstick test: leukocytes, erythrocytes, nitrite, protein, urine pH, specific weight Urine culture

Table 3 – High-risk stone formers

General factors

Early onset of urolithiasis (especially children and teenagers)

Familial stone formation

Brushite-containing stones (calcium hydrogen phosphate; $CaHPO_4 \cdot 2H_2O$)

Uric acid and urate-containing stones

Infection stones

Solitary kidney (the solitary kidney itself does not particularly increase risk of stone formation, but prevention of stone recurrence is of more importance)

Diseases associated with stone formation

Hyperparathyroidism

Nephrocalcinosis

Gastrointestinal diseases (ie, jejuno-ileal bypass, intestinal resection, Crohn's disease, malabsorptive conditions, enteric hyperoxaluria after urinary diversion) and bariatric surgery

Sarcoidosis

Genetically determined stone formation

Cystinuria (type A, B, AB)

Primary hyperoxaluria (PH)

Renal tubular acidosis (RTA) type I

2,8-Dihydroxyadenine

Xanthinuria

Lesch-Nyhan syndrome

Cystic fibrosis

Drugs associated with stone formation

Anatomical abnormalities associated with stone formation

Medullary sponge kidney (tubular ectasia)

Ureteropelvic junction obstruction

Calyceal diverticulum, calyceal cyst

Ureteral stricture

Vesico-uretero-renal reflux

Horseshoe kidney

Ureterocele

Table 4 – General preventive measures

Fluid intake (drinking advice)	Fluid amount: 2.5–3.0 l/d Circadian drinking Neutral pH beverages Diuresis: 2.0–2.5 l/d Specific weight of urine: <1.010
Nutritional advice for a balanced diet	Balanced diet[a] Rich in vegetable and fiber Normal calcium content: 1–1.2 g/d[b] Limited NaCl content: 4–5 g/d Limited animal protein content: 0.8–1.0 g/kg/d[c]
Lifestyle advice to normalize general risk factors	BMI: 18–25 kg/m^2 (target adult value, not applicable to children) Stress limitation measures Adequate physical activity Balancing of excessive fluid loss

BMI = body mass index; NaCl = sodium chloride.
[a] Avoid excessive consumption of vitamin supplements.
[b] Exception: patients with absorptive hypercalciuria, calcium excretion ≥8 mmol/d.
[c] Caution: the protein need is age-group–dependent; therefore, protein restriction in childhood should be handled carefully.

studies are necessary in patients receiving recurrent stone prophylaxis. The first follow-up 24-h urine measurements should be at 8–12 wk after starting pharmacological prevention of stone recurrence. This enables drug dosage to be adjusted if urinary risk factors have not normalized, with further 24-h urine measurements if necessary. Once urinary parameters have been normalized, it is sufficient to perform 24-h urine evaluation every 12 mo [17,18].

3.1.2. General considerations for recurrence prevention

All stone formers, independent of their individual risk, should follow the preventive measures presented in Table 4. The main focus of these measures is normalization of dietary habits and lifestyle risks, both of which are highly recommended for the prevention of stone formation (Table 5) [19–30].
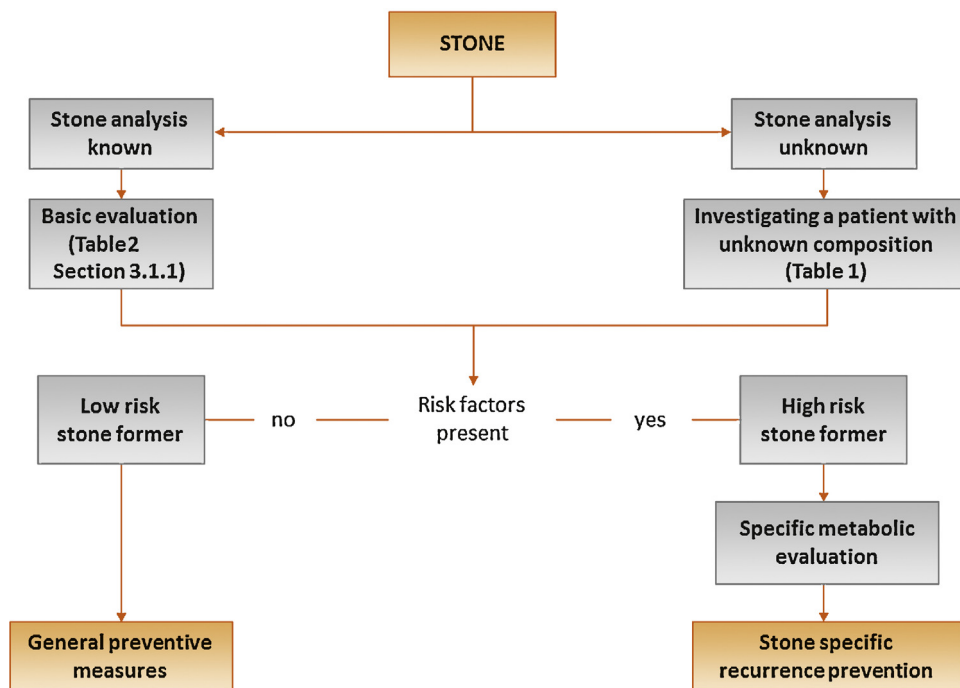

Fig. 1 – Assignment of patients to low- or high-risk groups of stone formers.

Table 5 – Recommendations for general preventative measures

		LE	GR
The aim should be to obtain a 24-h urine volume ≥2.5 l		1b	A
Hyperoxaluria	Oxalate restriction	2b	B
High sodium excretion	Restricted intake of salt	1b	A
Small urine volume	Increased fluid intake	1b	A
Urea level indicating a high intake of animal protein	Avoid excessive intake of animal protein	1b	A

GR = grade of recommendation; LE = level of evidence.

3.2. General considerations for pharmacological treatment

Pharmacological treatment is necessary in patients at high risk of recurrent stone formation and is normally used along with general preventive measures. The ideal drug should halt stone formation, have no side effects, and be easy to administer. Each of these aspects is important to achieve good compliance. Table 6 lists the pharmacological substances used for stone prevention [15,31–58].

3.3. Stone specific diagnostic and therapeutic algorithms

3.3.1. Calcium stones

3.3.1.1. Calcium oxalate stones. The criteria for identification of calcium oxalate stone formers with high recurrence risk are listed in Table 3.

3.3.1.1.1. Diagnosis. Blood analysis requires measurement of creatinine, sodium, potassium, chloride, ionized calcium (or total calcium + albumin), uric acid, and parathyroid hormone (PTH) in cases of increased calcium levels. Urinalysis requires measurement of urine volume, urine pH profile, specific weight, sodium, calcium, oxalate, uric acid, citrate, and magnesium [31,33,35,59].

3.3.1.1.2. Interpretation of results and etiology. The diagnostic and therapeutic algorithm for calcium oxalate stones is shown in Figure 2 [31–44]. Elevated levels of ionized calcium in serum (or total calcium and albumin) require assessment of intact PTH to confirm or exclude suspected hyperparathyroidism (HPT) [60]. So-called acidic arrest (urine pH constantly <6) may promote cocrystallization of uric acid and calcium oxalate. Similarly, increased uric acid excretion

Table 6 – Pharmacological substances used for stone prevention: characteristics, specifics, and dosage

| Agent	Rationale	Dose	Specifics and side effects	Stone type
Alkaline citrates	Alkalinization Hypocitraturia Inhibition of calcium oxalate crystallization	5–12 g/d (14–36 mmol/d) Children: 0.1–0.15 g/kg bw/d	Daily dose for alkalinization depends on urine pH	Calcium oxalate Uric acid Cystine
Allopurinol	Hyperuricosuria Hyperuricemia	100–300 mg/d Children: 1–3 mg/kg bw/d	100 mg in isolated hyperuricosuria Renal insufficiency demands dose correction	Calcium oxalate Uric acid Ammonium urate 2,8-Dihydroxyadenine
Calcium	Enteric hyperoxaluria	500 mg/d	Intake 30 min before meals	Calcium oxalate
L-Methionine	Acidification	600–1500 mg/d		Infection stones Ammonium urate Calcium phosphate
Magnesium	Isolated hypomagnesiuria Enteric hyperoxaluria	200–400 mg/d Children: 6 mg/kg bw/d	Renal insufficiency demands dose correction	Calcium oxalate
Sodium bicarbonate	Alkalinization Hypocitraturia	4.5 g/d		Calcium oxalate Uric acid Cystine
Pyridoxine	Primary hyperoxaluria	Initial dose 5 mg/kg bw/d Maximum dose 20 mg/kg bw/d	Polyneuropathia	Calcium oxalate
Thiazide (hydrochlorothiazide)	Hypercalciuria	25–50 mg/d Children: 0.5–1 mg/kg bw/d	Hypotonic blood pressure Risk of agent-induced diabetes Risk of agent-induced hyperuricemia	Calcium oxalate Calcium phosphate
Tiopronin	Cystinuria Active decrease in urinary cystine levels	Initial dose 250 mg/d Maximum dose 2000 mg/d	Risk of tachyphylaxia and proteinuria	Cystine

bw = body weight.
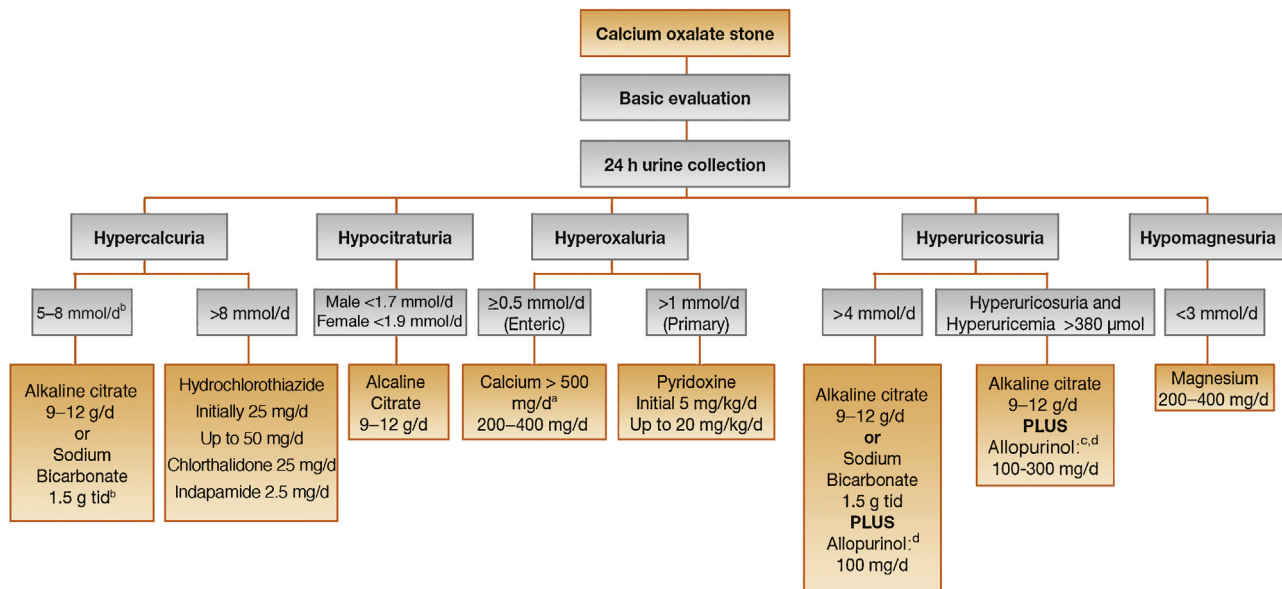
Fig. 2 – Diagnostic and therapeutic algorithm for calcium oxalate stones.
tid = 3 times daily.
[a] Be aware of excess calcium excretion.
[b] No magnesium therapy for patients with renal insufficiency.
[c] There is no evidence that combination therapy (thiazide + citrate) (thiazide + allopurinol) is superior to thiazide therapy alone.
[d] Febuxostat 80 mg/d.

(>4 mmol/d in adults or >12 mg/kg/d in children) can act as a promoter [61]. Urine pH levels constantly >5.8 in a daily profile indicate renal tubular acidosis (RTA), provided urinary tract infection (UTI) has been excluded. An ammonium chloride loading test confirms RTA and identifies the RTA subtype [57,58,62,63]. Oxalate excretion >0.5 mmol/d in adults (>0.37 mmol/1.73 m^2/d in children) confirms hyperoxaluria. Primary hyperoxaluria (oxalate excretion mostly ≥1 mmol/d) appears in three genetically determined forms, secondary hyperoxaluria (oxalate excretion ≥0.5 mmol/d, usually <1 mmol/d) occurs because of intestinal hyperabsorption of oxalate or extreme dietary oxalate intake, and mild hyperoxaluria (oxalate excretion 0.45–0.85 mmol/d) is commonly found in idiopathic calcium oxalate stone formers [57,58,64,65].

3.3.1.1.3. Specific treatment. Treatment for calcium oxalate stones includes general preventive measures, such as fluid intake and diet, thiazides and thiazide-like agents that

reduce calcium excretion, and alkalinizing agents that may inhibit growth and aggregation of calcium oxalate (Fig. 2, Table 7). Randomized controlled trials exist for all three strategies [15,22–44,66,67].

3.3.1.2. Calcium phosphate stones. Some calcium phosphate stone formers are at high risk of recurrence. Calcium phosphate mainly appears in two completely different minerals: carbonate apatite and brushite. Carbonate apatite crystallization occurs at pH ≥6.8 and may be associated with infection. Brushite crystallizes at an optimum pH of 6.5–6.8, and at high urinary concentrations of calcium (>8 mmol/d) and phosphate (>35 mmol/d). Its occurrence is not related to UTI. Possible causes of calcium phosphate stones include HPT, RTA, and UTI; each of which requires different therapy [31–38].

3.3.1.2.1. Diagnosis. Diagnosis requires blood analysis for creatinine, sodium, potassium, chloride, ionized calcium

Table 7 – Recommendations for the pharmacological treatment of patients with specific abnormalities in urine composition

Urinary risk factor	Suggested treatment	LE	GR
Hypercalciuria	Thiazide + potassium citrate	1a	A
Hyperoxaluria	Oxalate restriction	2b	A
Enteric hyperoxaluria	Potassium citrate	3–4	C
	Calcium supplement	2	B
	Oxalate absorption	3	B
Hypocitraturia	Potassium citrate	1b	A
High sodium excretion	Restricted intake of salt	1b	A
Small urine volume	Increased fluid intake	1b	A
Urea level indicating a high intake of animal protein	Avoid excessive intake of animal protein	1b	A
No abnormality identified	High fluid intake	2b	B

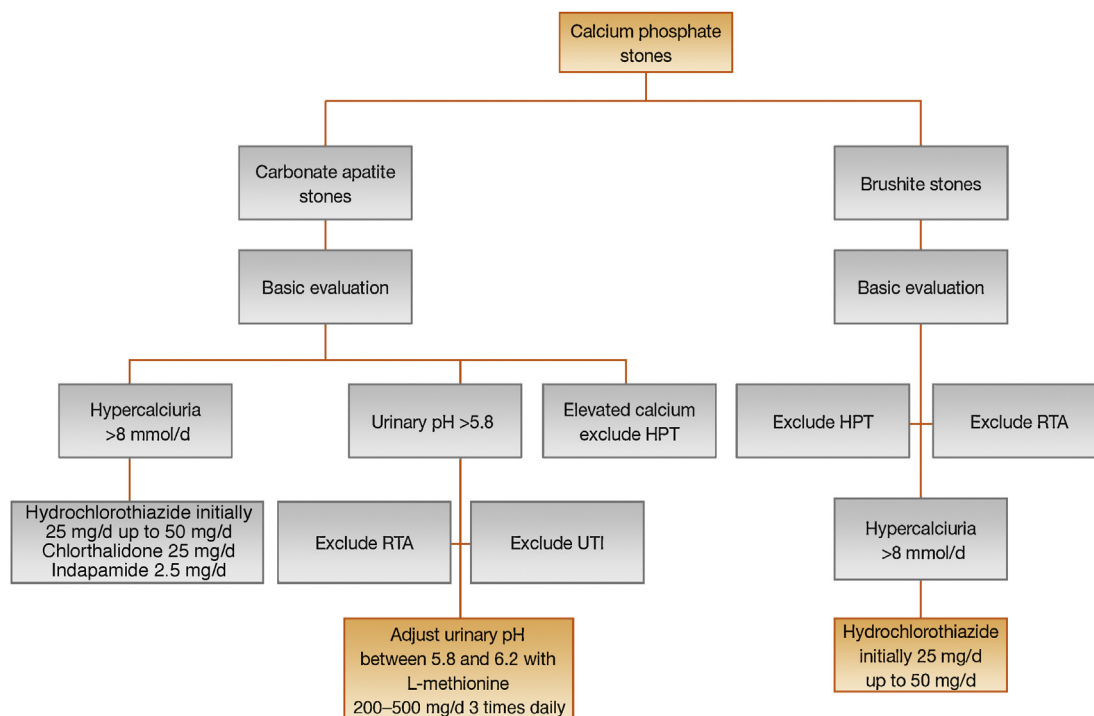GR = grade of recommendation; LE = level of evidence.

Fig. 3 – Diagnostic and etiologic algorithm for calcium phosphate stones.
HPT = hyperparathyroidism; RTA = renal tubular acidosis; UTI = urinary tract infection.

(or total calcium + albumin), and PTH (in cases of increased calcium levels). Urinalysis includes measurement of volume, urine pH profile, specific weight, calcium, phosphate, and citrate. A diagnostic and etiologic algorithm for calcium phosphate stones is provided in Figure 3 [31–38].

3.3.1.2.2. Specific treatment. General preventive measures involving fluid intake and diet are recommended.

3.3.1.2.3. Pharmacological therapy. HPT and RTA are common causes of calcium phosphate stone formation. Although most patients with primary HPT require surgery, RTA can be corrected pharmacologically. If primary HPT and RTA have been excluded, pharmacotherapy for calcium phosphate calculi depends on effective reduction of urinary calcium levels using thiazides. If urine pH remains constantly >6.2, urinary acidification with L-methionine may be helpful (Fig. 3, Table 8).

For infection-associated calcium phosphate stones, it is important to consider the guidance given for infection stones [31–38].

Table 8 – Recommendations for the treatment of calcium phosphate stones

Urinary risk factor	Suggested treatment	LE	GR
Hypercalciuria	Thiazide	1a	A
Inadequate urine pH	Acidification	3–4	C
Urinary tract infection	Antibiotics	3–4	C

GR = grade of recommendation; LE = level of evidence.

3.3.1.3. Disorders and diseases related to calcium stones

3.3.1.3.1. HPT. The stones of PTH patients may contain both calcium oxalate and calcium phosphate [68]. If HPT is suspected, neck exploration should be performed to confirm the diagnosis [69]. Primary HPT can only be cured by surgery. Treatment of granulomatous diseases may require steroids, hydroxychloroquine, or ketoconazole [70,71].

3.3.1.3.2. Hyperoxaluria. In approximately one-third of patients with primary hyperoxaluria type I, pyridoxine therapy normalizes or significantly reduces urinary oxalate excretion. The goal of adequate urine dilution is achieved by adjusting fluid intake to 3.5–4.0 l/d in adults (children 1.5 l/m^2 body surface area) and following a circadian drinking regimen. Therapeutic options for preventing calcium oxalate crystallization include hyperdiuresis, alkaline citrates, and magnesium. However, in end-stage renal failure, primary hyperoxaluria requires simultaneous liver-kidney transplantation (Table 9) [64,65].

Enteric hyperoxaluria is a particularly problematic condition in patients with intestinal malabsorption of fat. This abnormality is associated with a high risk of stone formation, and is seen after intestinal resection and malabsorptive bariatric surgical procedures, and in Crohn's disease and pancreas insufficiency. Specific preventive measures include restricted intake of oxalate-rich foods, restricted fat intake and calcium supplementation at meal times to enable calcium oxalate complex formation in the intestine, sufficient fluid intake to balance intestinal loss of

Table 9 – Recommendations for dietary and pharmacological treatment of hyperoxaluria

Urinary risk factor	Suggested treatment	LE	GR
Primary hyperoxaluria (PH)	Pyridoxine in PH type I	3	B
	Alkaline citrate 9–12 g/day in adults; 0.1–0.15 meq/kg/day in children	3–4	C
	Magnesium: 200–400 mg/day (no magnesium in case of renal insufficiency)	3	C
Enteric hyperoxaluria	Potassium citrate 9–12 g/day in adults	3–4	C
	Calcium supplement	2	B
	Oxalate absorption	3	B
Small urine volume	Increased fluid intake	1b	A
GR = grade of recommendation; LE = level of evidence.			

water caused by diarrhea, and alkaline citrates to raise urinary pH and citrate (Table 9) [65,72,73].

3.3.1.3.3. Distal RTA. Patients with distal RTA type I are prone to stone formation. Figure 4 outlines the diagnosis of RTA [62,63]. The main therapeutic aim is to restore a normal acid-base equilibrium. Despite the alkaline pH of urine in RTA, alkalinization using alkaline citrates or sodium bicarbonate is the key to normalizing the metabolic changes (intracellular acidosis) responsible for stone formation (Tables 10 and 11). The alkali load reduces tubular reabsorption of citrate, which in turn normalizes citrate excretion and simultaneously reduces calcium turnover (LE 2b; GR B) [62,63]. Therapeutic success can be monitored by venous blood gas analysis (base excess ±2.0) in complete RTA. If excessive calcium excretion (>8 mmol/d) persists after re-establishing acid-base equilibrium, thiazides may lower urinary calcium excretion (LE 1a; GR A) [15,62,63].

3.3.1.3.4. Nephrocalcinosis. Nephrocalcinosis is associated with several metabolic risk factors such as HPT, primary hyperoxaluria, RTA, vitamin D metabolic disorders, idiopathic hypercalciuria and hypocitraturia, and genetic disorders, including Dent's disease and Bartter's syndrome [73,74]. Diagnostically, patients require the following blood analysis: PTH (in cases of increased calcium levels), vitamin D and metabolites, vitamin A, sodium, potassium, magnesium, chloride, and blood gas analysis. Urinalysis should investigate the urine pH profile (minimum four times/d), daily urine volume, specific weight of urine, and levels of calcium, oxalate, phosphate, uric acid, magnesium, and citrate [73,74]. Therapeutic attention must focus on the underlying metabolic or genetic disease, while minimizing the biochemical risk factors.

3.3.2. Uric acid and ammonium urate stones

All uric acid and ammonium urate stone formers are considered to be at high risk of stone recurrence [18]. Hyperuricosuria may be a result of dietary excess, endogenous overproduction (enzyme defects), myeloproliferative disorders, tumor lysis syndrome, drugs, gout, or catabolism [75].

Ammonium urate stones are associated with UTI, malabsorption (inflammatory bowel disease and ileostomy diversion or laxative abuse), and malnutrition. They form in urine at pH >6.5 and high uric acid concentrations. They are common in the urinary bladder [76–78].

3.3.2.1. Diagnosis. Figure 5 shows the diagnostic and therapeutic algorithm for uric acid nephrolithiasis.
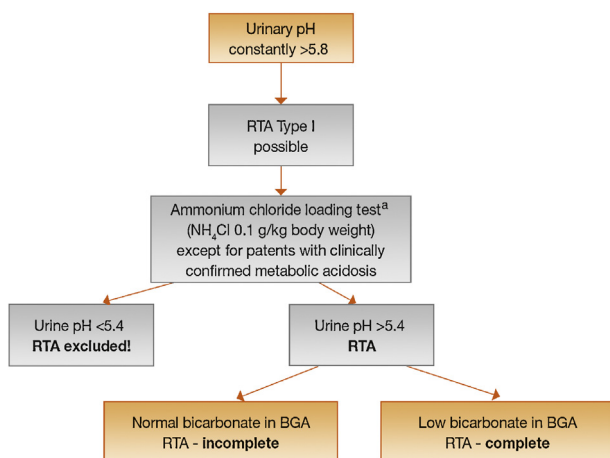

Fig. 4 – Diagnostic algorithm for renal tubular acidosis (RTA).
BGA = blood gas analysis.
[a] An alternative ammonium chloride loading test using NH₄Cl load with 0.05 g/kg body weight over 3 d might provide similar results and may be better tolerated by the patient.

Table 10 – Pharmacological treatment of renal tubular acidosis

Biochemical risk factor	Rationale for pharmacological therapy	Medication
Hypercalciuria	Calcium excretion >8 mmol/d	Hydrochlorothiazide • Adults: 25 mg/d initially, up to 50 mg/d • Children: 0.5–1 mg/kg/d
Inadequate urine pH	Intracellular acidosis in nephron	Alkaline citrate, 9–12 g/d **OR** Sodium bicarbonate, 1.5 g tid
tid = 3 times daily.		

Table 11 – Recommendations for renal tubular acidosis (RTA) treatment

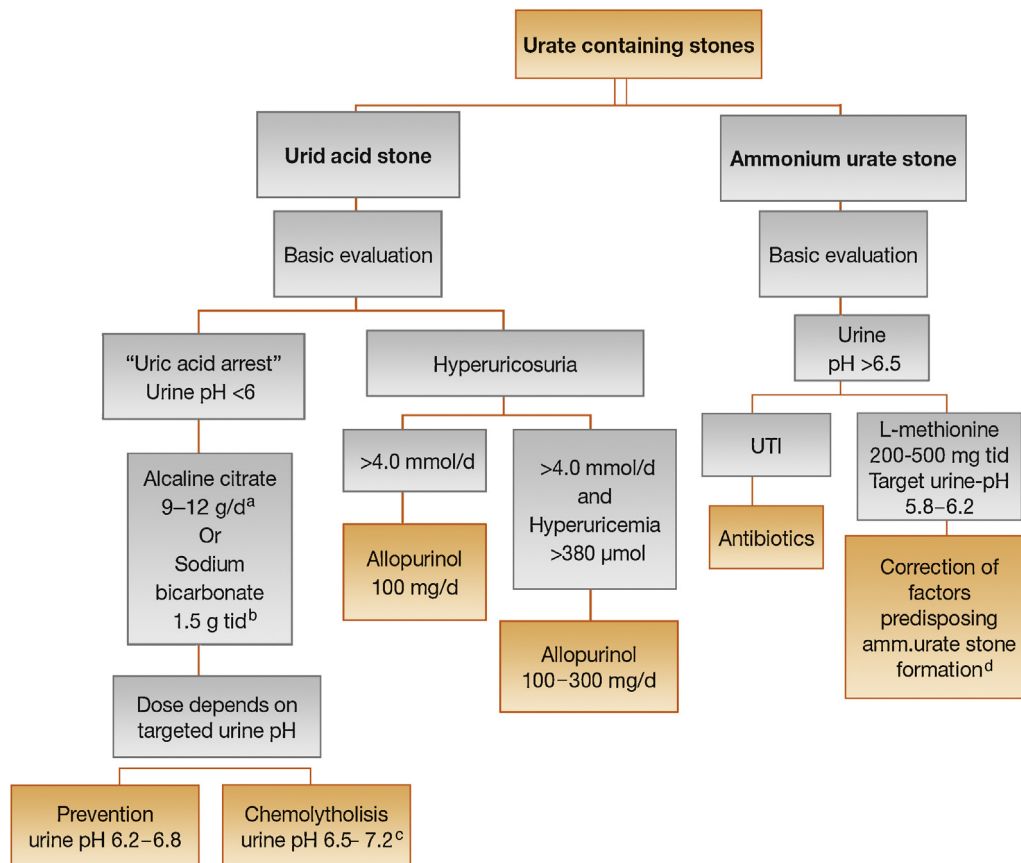| Urinary risk factor	Suggested treatment	LE	GR
Distal RTA	Potassium citrate	2b	B
Hypercalciuria	Thiazide + potassium citrate	1a	A
GR = grade of recommendation; LE = level of evidence.			

Fig. 5 – Diagnostic and therapeutic algorithm for uric acid and ammonium urate stones. tid = three times daily.
[a] d: day.
[b] tid: three times a day.
[c] A higher pH may lead to calcium phosphate stone formation.
[d] In patients with high uric acid excretion Allopurinol may be helpful.

Blood analysis requires measurement of creatinine and uric acid levels. Urinalysis requires measurement of urine volume, urine pH profile, specific weight of urine, and uric acid [75–79].

3.3.2.2. Interpretation of results. Uric acid and ammonium urate stones form under completely different biochemical conditions. Acidic arrest (urine pH constantly <6) promotes uric acid crystallization.

Hyperuricosuria is defined as uric acid excretion ≥4 mmol/d in adults or >0.12 mmol/kg/d in children. Hyperuricemia may be present, but there is only weak evidence of its association with stone formation.

Hyperuricosuric calcium oxalate stone formation can be distinguished from uric acid stone formation by two ways: urinary pH, which is usually above 5.5 in calcium oxalate stone formation and below in uric acid stone formation; and occasional absence of hyperuricosuria in patients with pure uric acid stones [80,81]. Ammonium urate crystals form in urine at pH >6.5, at high uric acid concentration, and in the presence of cations.

3.3.2.3. Specific treatment. General preventive measures involving fluid intake and diet are recommended. Hyperuricosuric

stone formers benefit from purine reduction in their daily diet. Figure 5 shows the therapeutic algorithm for urate-containing stones.
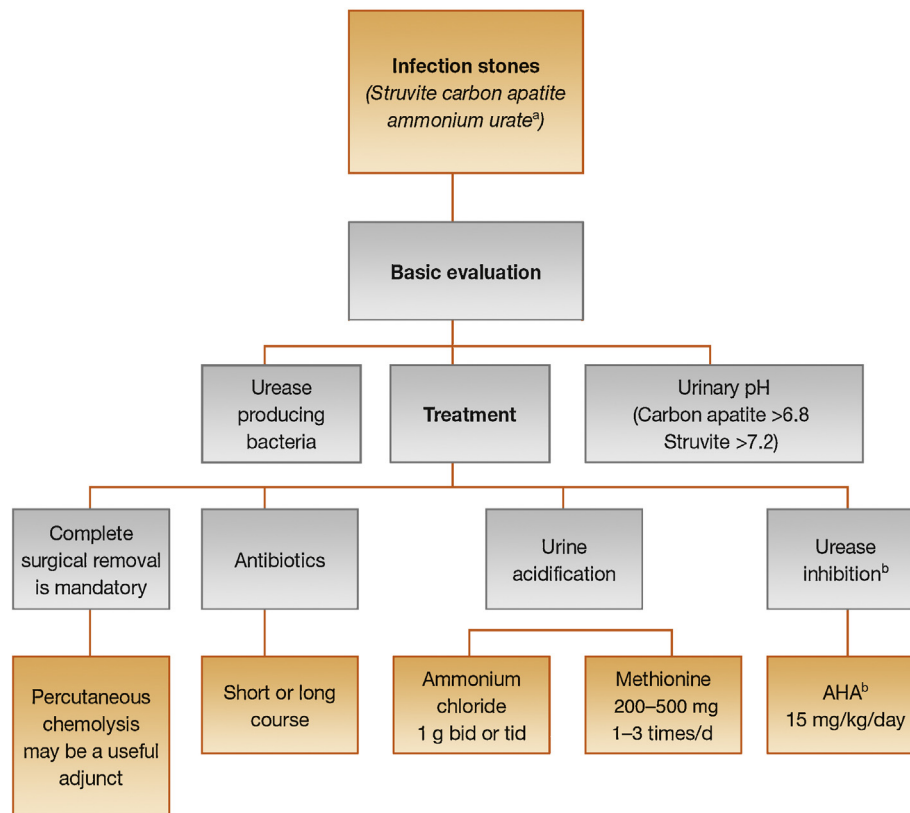
3.3.3. Struvite and infection stones
All infection stone formers are deemed at high risk of recurrence. The diagnostic and therapeutic algorithm for infection stones is shown in Figure 6 [82].

3.3.3.1. Diagnosis. Blood analysis requires measurement of creatinine, and urinalysis requires a urine pH profile and urine culture.

3.3.3.2. Interpretation. Infection stones contain the following minerals: struvite and/or carbonate apatite and/or ammonium urate. Urine culture typically provides evidence of urease-producing bacteria that increase ammonia ions and lead to alkaline urine. Carbonate apatite starts to crystallize at a urine pH of 6.8. Struvite precipitates only at pH >7.2 [83–85]. *Proteus mirabilis* accounts for more than half of all urease-positive infections [86,87].

3.3.3.3. Specific treatment. General preventive measures are recommended, including fluid intake and diet. Specific

AHA = acetohydroxamic acid; bid = twice daily; tid = 3 times/d.

Fig. 6 – Diagnostic and therapeutic algorithm for infection stones. AHA = acetohydroxamic acid; bid = twice daily; tid = three times daily.
[a] Discussed for uric acid stones.
[b] When nationally available.

measures include complete surgical stone removal [11], short- or long-term antibiotic treatment [88], urinary acidification using methionine [49] or ammonium chloride [50], and urease inhibition [51,52]. For severe infections, acetohydroxamic acid (Lithostat) may be an option (Table 12).

3.3.4. Cystine stones

All cystine stone formers are deemed at high risk of stone recurrence.

Table 12 – Recommendations for therapeutic measures for struvite stones

	LE	GR
Surgical removal of the stone material as completely as possible		
Short-term antibiotic course	3	B
Long-term antibiotic course	3	B
Urinary acidification: ammonium chloride, 1 g bid/tid	3	B
Urinary acidification: methionine, 200–500 mg, 1–3 times/d	3	B
Urease inhibition	1b	A

bid = twice daily; tid = three times daily; GR = grade of recommendation; LE = level of evidence.

3.3.4.1. Diagnosis. Blood analysis includes measurement of creatinine, and urinalysis includes measurement of urine volume, pH profile, specific weight, and cystine.

3.3.4.2. Interpretation. Cystine is poorly soluble in urine and crystallizes spontaneously within the physiological pH range of urine. Cystine solubility depends strongly on urine pH; at pH 6.0, the limit of solubility is 1.33 mmol/l. Routine analysis of cystine is not suitable for therapeutic monitoring. Regardless of the phenotype or genotype of the cystinuric patient, the clinical manifestations are the same [53]. There is no role for genotyping of patients in the routine management of cystinuria [89–91]. Reductive therapy targets the disulfide bond in the cysteine molecule. For therapy monitoring, it is essential to differentiate between cystine, cysteine, and drug-cysteine complexes. Only high performance liquid chromatography (HPLC)-based analysis differentiates between the different complexes formed after therapy. Diagnosis is established by stone analysis. The typical hexagonal crystals are detectable in only 20–25% of urine specimens from cystinuric patients [92]. The cyanide nitroprusside colorimetric qualitative test detects the presence of cystine at a threshold concentration of 75 mg/l with sensitivity of 72% and specificity of 95%. False-positive results may occur

in patients with Fanconi's syndrome or homocystinuria, or in patients taking various medications, including ampicillin and sulfa-containing medications [93,94]. Quantitative 24-h urinary cystine excretion confirms the diagnosis in the absence of stone analysis. Levels >30 mg/d are considered abnormal [95].

3.3.4.3. Specific treatment. General preventative measures involving fluid intake and diet are recommended. Although a diet low in methionine may theoretically reduce urinary excretion of cystine, patients are unlikely to comply sufficiently with such a diet. However, a restricted sodium intake is more easily achieved and is more effective in reducing urinary cystine. Patients are usually advised to avoid sodium consumption >2 g/d [96]. A high diuresis rate is of fundamental importance, with the aim being a 24-h urine volume of ≥3 l [96]. A considerable fluid intake evenly distributed during the day is necessary.

3.3.4.4. Pharmacological treatment of cystine stones. The main therapeutic option for avoiding cystine crystallization is to maintain urine pH >7.5 to improve cystine solubility and to ensure appropriate hydration, with a minimum of 3.5 l/d in adults, or 1.5 l/m^2 body surface area in children. Free cystine concentrations can be decreased using reductive substances, which act by splitting the disulfide bond in cystine.

Tiopronin is currently the best choice for cystine reduction. However, side effects often lead to treatment termination, for example, when nephrotic syndrome develops or in the case of poor compliance, especially with long-term use. After carefully considering the risk of early tachyphylaxis and of recurrence, and putting in place a dose-escape phenomenon for long-term use, tiopronin is recommended for cystine levels >3.0 mmol/d or in the case of troublesome disease.

Ascorbic acid is used when cystine excretion is <3.0 mmol/d. However, it has limited reductive power and is estimated to lower urinary cystine levels by ~20% [96]. The effectiveness and use of ascorbic acid as a standard therapeutic regimen are controversial [11]. Results for the angiotensin-converting enzyme inhibitor captopril are also controversial. Captopril remains a second-line option, for use when tiopronin is not feasible or is unsuccessful (Fig. 7, Table 13) [55].
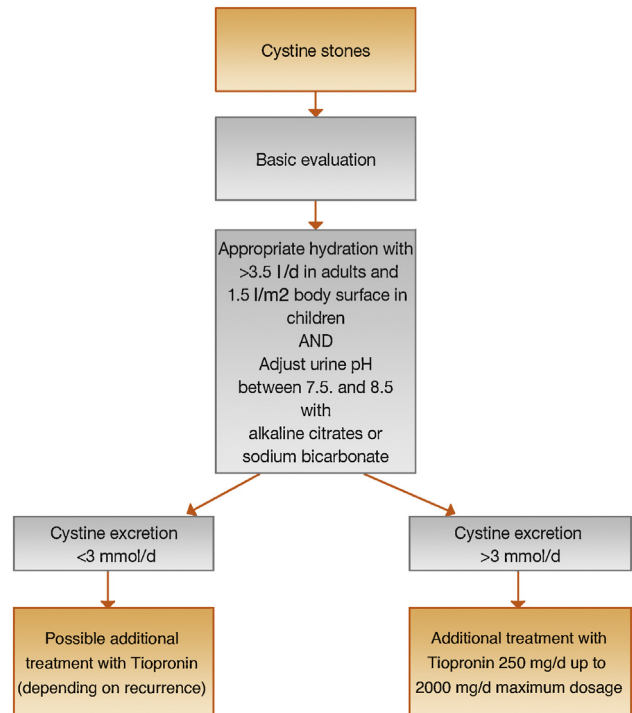

Fig. 7 – Metabolic management of cystine stones.

3.4. Discussion

The prevalence of urolithiasis and the high recurrence rate for first-time symptomatic stone former strongly support proper patient evaluation and appropriate management to prevent stone reformation (Grade of Recommendation A*).

All patients should undergo stone analysis and a basic evaluation after having passed a stone or having been treated for a urinary stone. Stone patients at high risk of recurrence should undergo specific metabolic evaluation with 24-h urine collection to identify altered urinary factors that could be corrected with specific treatment. Whether this correction will ultimately lead to an overall lower recurrence rate is a matter of debate. This is mainly because of the lack of randomized controlled trials (RCTs) supporting the idea that pretreatment stone composition and biochemistry measurements predict treatment efficacy in preventing stone recurrence. Only baseline uric acid levels

Table 13 – Recommendations for the treatment of cysteine stones

Therapeutic measures	LE	GR
Urine dilution High fluid intake recommended so that 24-h urine volume exceeds 3 l Intake should be ≥150 ml/h	3	B
Alkalinization For cystine excretion <3 mmol/day: potassium citrate 3–10 mmol bid/tid, to achieve pH >7.5	3	B
Complex formation with cystine For patients with cystine excretion >3 mmol/d, or when other measures are insufficient: Tiopronin, 250–2000 mg/d Captopril, 75–150 mg/d, remains a second-line option if tiopronin is not feasible or is unsuccessful	3	B
bid = twice daily; tid = three times daily; GR = grade of recommendation; LE = level of evidence.		

predicted the efficacy of treatment. Moreover, there is a lack of RCTs supporting the suggestion that biochemistry measurements during treatment can predict the treatment efficacy in preventing stone recurrence [97].

Two RCTs, one on high water intake and stone recurrence after the first idiopathic calcium stone episode, and one on high water intake and stone recurrence after extracorporeal shockwave lithotripsy (ESWL), as well as large epidemiologic studies, have indicated an inverse relationship between high fluid intake and stone formation [23,24]. The role of beverages is controversial in the literature. This is mainly because urinary levels of lithogenic risk factors were used as surrogate end points instead of the onset or relapse of stones. According to literature results, beverages that alter urinary pH (freshly squeezed/industrially produced orange or lemon juice, coffee, green tea, beer, and wine), increase oxalate (eg, tea, grapefruit, apple juice, cola), or are rich in fructose, sucrose, phosphoric acid (eg, soft drinks), sodium, carbohydrates, or caffeine (energy/sport drinks) should be used cautiously on a long-term basis [25,26].

There is level 1b/a evidence indicating that the combination of extensive metabolic evaluation and a tailored diet results in fewer stone recurrences compared to limited metabolic evaluation and general diet recommendations. However, results are reported collectively and not separately for any metabolic or tailored diet subgroup [19]. There are no RCTs examining the independent effect of altering dietary intake of calcium, sodium, animal protein, fruit and fiber, purine, oxalate, or any other individual dietary element on the risk of stone recurrence [20,21]. A commonsense approach to diet should be taken, that is, a mixed balanced diet with contributions from all food groups, but without consumption of excess oxalate, vitamin C, animal protein, sodium, and urate-rich foods [27–29]. Lifestyle factors may influence the risk of stone formation. Large epidemiologic studies have documented an increase in the risk of kidney stones for overweight and obese individuals. However, it is not clear whether weight loss will lead to a reduction in risk [30].

Calcium salts are the most common constituents of kidney stones in the industrialized world. Untreated first-time calcium stone formers have been found to have a 27% chance of recurrence within 5 yr, 50% within 8–9 yr, and approximately 75% within 20 yr [23,98]. When a recurrence has already occurred, it is estimated that future new stone formation will occur in up of 43–48% of patients within a 3-yr follow-up period [31,33,35].

RCTs have been carried out for all preventive measures, including general measures for fluid intake and diet, thiazides and thiazide-like agents that reduce calcium excretion, and alkalinizing agents that may inhibit growth and aggregation of calcium oxalate [23–44,66,67].

Many of the subjects in these trials had idiopathic hypercalciuria, sometimes combined with other mild metabolic abnormalities. However, in many of the trials, treatment was nonselective. In first-time calcium oxalate stone formers who were followed up for 5 yr, increased fluid intake to keep urine volume >2 l/d resulted in a 15% absolute recurrence reduction compared to usual fluid intake (LE 1b) [23]. In recurrent calcium stone formers who were followed for 5 yr, adequate calcium intake (1200 mg/d), along with sodium (50 mmol/d) and protein (52 g/d) restriction, resulted in an 18% absolute recurrence reduction compared to restricted calcium intake (400 mg/d) (LE 1b) [29]. Good evidence from RCTs has proven that thiazides are effective in decreasing calciuria [36,38] and in preventing calcium stone recurrence [31,33,35,36]. Trials with at least 3 yr of follow-up showed a higher benefit for thiazide therapy. The patients in these studies were a mixture of hypercalciuric and normocalciuric stone formers, so it is difficult to discern whether the treatment is more beneficial in one group. The negative outcome regarding thiazide therapy in two RCTs [32,38] may be due, in part, to smaller sample size, shorter duration of treatment, and a lack of control of fluid intake and dietary restrictions. A meta-analysis of eight RCTs on thiazide therapy revealed a 57% posttreatment stone risk reduction for the treatment arms compared to the placebo arms (LE 1a) [15]. There is some evidence (LE 1b) supporting the use of alkaline citrate in the form of potassium magnesium citrate for the treatment of nonselective calcium oxalate stone formers [42]. However, although alkaline citrate inhibits the growth and aggregation of calcium oxalate, it is commonly used for pure hypercalciuric stone patients. Patients with hypocitraturia can be treated with oral alkali in order to increase urinary citrate excretion [40–42]. Of three trials, two were conducted in populations with normal or low normal urinary citrate, and showed a significant reduction in recurrent calcium oxalate stone formation [40,42]. Half of the population in the third study had low urinary citrate. This latter study did not show any advantage of sodium-potassium citrate use compared to a high fluid intake and dietary restrictions [41]. The differences between these studies may be due to the small size and higher alkali treatment dosages in the latter study. In addition, the use of sodium may halt the positive effect of potassium used in these preparations.

Two RCTs have shown that for hyperuricosuric calcium oxalate stone formers without other metabolic abnormalities, such as hypercalcemia, hypercalciuria, hyperoxaluria, or hypocitraturia, allopurinol (300 mg/d) is effective in reducing urinary uric acid and stone recurrence compared with no treatment [43,44]. In hyperuricosuric calcium oxalate stone formers with multiple metabolic abnormalities, the benefit of reduction of hyperuricosuria alone by allopurinol is less evident [99].

The LE supporting preventive measures in patients suffering from uric acid, struvite, and cystine nephrolithiasis is low. The panel recognizes the need for further RCTs to increase the power of the proposed preventive and therapeutic measures for these stone patients.

4. Conclusions

After stone passage, every patient should be assigned to a group with low or high risk of stone formation. For correct classification, reliable stone analysis and basic evaluation of every patient are required. Low-risk stone formers may

benefit by adopting general preventive measures regarding fluid and nutritional intake, as well as lifestyle improvements. For high-risk stone formers, a specific metabolic evaluation is required to guide individual treatment and prevent stone recurrence.

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