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Review – Platinum priority – Editor's choice

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

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Abstract

Background and objective: The aim of this review was to define patients who are at high risk of recurrence of urolithiasis, to delineate diagnostic and therapeutic algorithms for each type of stone, and to clarify general guidelines and recommendations for prevention of recurrence.
Methods: A professional research librarian carried out literature searches for all sections of the urolithiasis guidelines, covering the timeframe between 1976 and June 2023.
Key findings and limitations: For every patient with urolithiasis, an attempt should be made to analyse the stone. Patients should be given general instructions on how to prevent recurrence, including adequate fluid and calcium intake, and low consumption of sodium and protein. Identifying and correcting the causative factors is a cornerstone in preventing the recurrence of urolithiasis. Diagnostic and therapeutic algorithms by stone composition are available. Every patient should undergo baseline metabolic screening, while patients with calcium stones, who are at high risk of relapse and complications, should undergo extensive metabolic screening with two 24-h urine collections and should receive targeted therapy. Patients with uric acid, infection, or cystine stones are at high risk of relapse. All patients at high risk of recurrence should be closely monitored, especially those not complying with therapy in the long term.
Conclusions and clinical implications: Metabolic stone evaluation and patient follow-up are highly recommended to prevent urolithiasis recurrence.

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ADVANCING PRACTICE

What does this study add?
Metabolic evaluation of stone formers, especially those at high risk for recurrence, is of vital importance for reducing recurrences and the long-term complications of urolithiasis such as chronic renal failure and infections. European Association of Urology Guidelines Panel on Urolithiasis perform a yearly update of published literature to update all recommendations given on metabolic evaluation of stone formers; the current manuscript represents an update of scientific evidence on this subject for the last eight years since the last update. In addition for the first time the risk of kidney function deterioration because of urolithiasis is addressed and those patients at risk are underlined.

Clinical Relevance
Metabolic evaluation and recurrence prevention for urinary stone patients: An EAU Guidelines update Using the EAU Guidelines robust methodology of combining a thorough literature review with expert recommendations including strength grading, the EAU Urolithiasis Guidelines Panel provides an overview on metabolic evaluation and follow-up of patients with urinary stones. In addition to general measures for stone prevention, including adequate fluid intake and dietary measures, the panel recommends patients with calcium stones and those at a high risk of relapse or chronic kidney disease, such as uric acid, infection, and cystine stones, should undergo extensive metabolic screening including two 24-hour urine collections and receive targeted therapy. The high-risk group can be determined using medical history and stone composition. These patients should receive close follow-up in addition to patients who are non-compliant with their medications. The panel also provides detailed diagnostic and therapeutic algorithms for each stone composition to guide clinical practice.
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Patient Summary
We reviewed the evidence for proper evaluation of patients with urinary and stones and the treatment options for preventing stone recurrence. It is essential to determine the type of stone and to carry out specific blood and urine tests for planning the best treatment course for each patient.

1. Introduction

The prevalence and incidence of urolithiasis have increased globally over the past decades [1–5]. The recurrence rate after stone formation is reported to be as high as 50% at 5 yr and 80–90% at 10 yr [6]. Surgical treatment of urolithiasis does not prevent recurrence of the disease. Recurrence of urolithaisis may compromise kidney function, increase the costs of treatment, reduce quality of life, and force patients to abstain from work, further increasing public and private health costs [7].

The aim of our review was to define which patients are at high risk of urolithiasis recurrence, to delineate diagnostic and therapeutic algorithms for each type of stone, to clarify general guidelines and recommendations for prevention of recurrence, and to recommend monitoring protocols for patients who are at high risk of relapse.

2. Methods

A professional research librarian carried out literature searches for all sections of the European Association of Urology (EAU) urolithiasis guidelines, covering the timeframe between 1976 and June 2023. Searches were conducted using the Cochrane Library Database of Systematic Reviews, the Cochrane Library of Controlled Clinical Trials, Medline, and Embase. Both MeSH and Emtree terms were used to search for relevant topics. In many cases, free text was used to ensure the sensitivity of the searches. The search strategy is available online (https://uroweb.org/guidelines/urolithiasis/ publications-appendices). The focus of the search was identification of all papers providing level 1 scientific evidence (randomised controlled trials [RCTs], systematic reviews, and meta-analyses). If sufficient data were identified to answer the clinical question, the search was not expanded to include lower-level literature, such as prospective nonrandomised comparative studies.

For every recommendation provided by the EAU Guidelines Panel, an online strength rating form is created to show the assessment of the ratio of benefits to harms and the patient preference for each recommendation. These forms follow the principles of the GRADE methodology, although they are not defined as being GRADE-compliant [8,9], and address the following key elements: overall quality of evidence based on the Oxford classification system (Oxford Centre for Evidence-Based Medicine Levels of Evidence); magnitude of the effect (individual or combined); certainty of results (precision, consistency, heterogeneity, and statistical or study-related factors); balance between desirable and undesirable outcomes; impact of patient preferences on the intervention; and certainty of the values. All of these elements were taken into consideration by the panel when rating each recommendation as strong or weak according to a standardised methodology [10].

3. Results

3.1. General metabolic considerations for patient work-up and recurrence prevention

3.1.1. Basic evaluation for all stone patients

For all patients with urolithiasis, stone analysis (when available), a basic metabolic investigation, and general prophylactic measures to avoid urolithiasis recurrence are recommended.

Stone analysis should be performed for all first-time stone formers. Patients should be instructed to filter their urine to retrieve a stone fragment. The preferred analytical procedures are infrared spectroscopy and X-ray diffraction [11,12]. Chemical analysis (wet chemistry) is generally deemed to be obsolete [13].

Basic evaluation of urolithiasis patients includes taking a medical history, physical examination, diagnostic imaging (ultrasound when the stone composition is known), blood analysis (creatinine, calcium, uric acid), and urinalysis. Helical computed tomography (CT) without contrast enhancement and specific urine testing (urine pH profile with measurement after each voiding, minimum 4 times daily; microscopy of urinary sediment in a morning urine sample; cyanide nitroprusside test) are also recommended when investigating patients with stones of unknown composition (Table 1). All patients should undergo a preoperative CT scan to delineate the anatomy and stone characteristics.

All stone formers should follow preventive measures involving normalisation of dietary habits and lifestyle risks to reduce the risk of urolithiasis recurrence (Table 2) [14–26].

3.1.2. Evaluating the risk of recurrence

After stone passage, the patient's risk of stone recurrence should be classified as low or high (Fig. 1). Stone composition, medical history, prescribed or over-the-counter medications, vitamin, and supplements, and disease severity determine the risk group for urolithiasis patients (Table 3) [26–42]. The risk status of a stone former should be determined in a holistic way, taking into consideration not only the probability of stone recurrence or regrowth but also the risk of chronic kidney disease, end-stage kidney disease, and metabolic bone disorder (Tables 4–6) [43,44].

Table 1 – Basic evaluation for a patient with a stone of known or unknown composition

Medical history	Stone history (former stone events, family history)
	Dietary habits
	Medication, vitamin supplements
Diagnostic imaging	Ultrasound, helical computed tomography without contrast enhancement [a]
Blood analysis	Creatinine
	Calcium (ionised 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) [a]
	Microscopy of urinary sediment (morning urine) [a]
	Cyanide nitroprusside test (exclusion of cystinuria) [a]

[a] When investigating patients with stones of unknown composition.

Table 2 – General preventive measures

Fluid intake (drinking advice)	Fluid amount: 2.5–3.0 l/d
	Water is the preferred fluid
	Diuresis: 2.0–2.5 l/d
	Specific weight of urine: <1.010 g/day
Nutritional advice for a balanced diet	Balanced diet [a]
	Rich in vegetables, fruits, and fibre
	Normal calcium content: 1–1.2 g/d
	Limited NaCl content: 4–5 g/d
	Limited animal protein content: 0.8–1.0 g/kg/d [b]
Lifestyle advice to normalise general risk factors	Retain a normal body mass index
	Adequate physical activity
	Balancing of excessive fluid loss
	Reduce the intake of alcohol-containing fluids
	Reduce the intake of sodas and calorie-containing fluids

[a] Avoid excessive consumption of vitamin supplements.
[b] Protein requirements are age-dependent; therefore, protein restriction in childhood should be handled carefully.

3.1.3. Specific metabolic evaluation

Only high-risk stone formers warrant specific metabolic evaluation. For calcium-based stones, this requires collection of two consecutive 24-h urine samples [45–47]. For the initial specific metabolic work-up, the patient should remain on a self-determined diet under normal daily conditions and should ideally be stone-free for at least 20 d [48]. The collection method should be chosen in close cooperation with the laboratory, while interpretation should be performed according to laboratory normal reference ranges and established clinical criteria [49,50].

A pH value of <5.5 for a 24-h urine sample indicates hyperacidic urine (acidic arrest) [51–53]. According to a consensus statement, renal tubular acidosis (RTA) is suspected if the pH of a 24-h urine sample is >6.2 in the absence of infection or if the pH of a spot urine sample from the second morning void is >5.8 [54,55]. Spot urine samples are an alternative sampling method, particularly when 24-h urine collection is difficult, such as in non–toilet-trained children [56]. Spot urine studies normally link the excretion rate to creatinine [57], but these are of limited use because the results may vary with collection time and the patient's sex, body weight, and age.

3.2. General considerations for pharmacological treatment

In some patients who are at high risk of urolithiasis recurrence and complications, pharmacological treatment is required. Table 7 lists drugs used to prevent recurrence, their dosage, characteristics, and side effects, and the type of stones for which they are indicated [14,23,58–109]. Patients receiving drug therapy should be monitored for its effectiveness and for side effects.

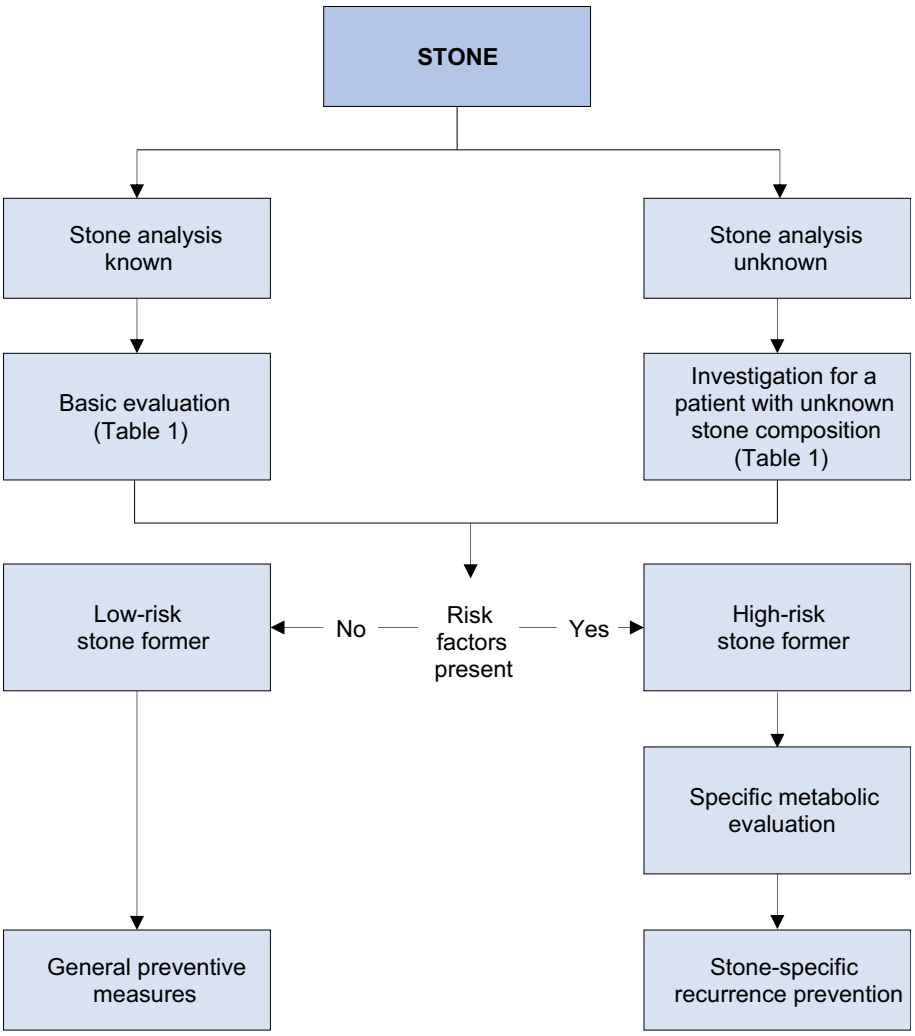


Fig. 1 – Assignment of patients to low- or high-risk groups for stone formation.

3.3. *Stone-specific diagnostic and therapeutic algorithms*

3.3.1. *Calcium oxalate stones*

3.3.1.1. Evaluation. Patients with calcium oxalate stones at high risk of recurrence (Table 3) or complications (Tables 5 and 6) should undergo basic and specific metabolic evaluation. Blood analysis is recommended for measurement of creatinine, sodium, potassium, chloride, ionised calcium (or total calcium corrected by the albumin concentration), phosphate, and uric acid, as well as parathyroid hormone (PTH) and vitamin D in cases with elevated calcium levels. Urinalysis of 24-h specimens should include measurement of urine volume, pH, specific weight, and calcium, citrate, oxalate, uric acid, and magnesium levels.

3.3.1.2. Diagnostic/aetiologic algorithm and interpretation of results. The most common metabolic abnormalities associated with calcium oxalate stone formation are hypercalciuria, which affects 30–60% of adult stone formers, and hyperoxaluria (26–67%), followed by hyperuricosuria (15–46%), hypocitraturia (5–29%), and hypomagnesuria (7–23%). However, ranges tend to differ by ethnicity [110]. Figure 2 summarises the diagnostic steps and the aetiology for calcium oxalate stones.

Hypercalciuria may be associated with normocalcaemia (idiopathic hypercalciuria, or granulomatous diseases) or hypercalcaemia (hyperparathyroidism [HPT], granulomatous diseases, vitamin D excess, or malignancy). Idiopathic hypercalciuria is the most common cause of elevated urinary calcium excretion. High levels of ionised calcium in serum (or total calcium corrected by the albumin concentration) require assessment of intact PTH to confirm or exclude suspected HPT [111]. A pH value >6.2 for a 24-h urine sample may indicate distal RTA provided that urinary tract infection (UTI) has been excluded. An ammonium chloride loading test can confirm distal RTA [112,113].

Hypocitraturia (males <1.7 mmol/d, females <1.9 mmol/d) may be idiopathic or secondary to metabolic acidosis or hypokalaemia [114].

Oxalate excretion >0.5 mmol/d in adults confirms hyperoxaluria. Primary hyperoxaluria (oxalate excretion mostly >1 mmol/d) occurs in three genetically determined forms.

Table 3 – High-risk stone formers

General factors
Early onset of urolithiasis (especially in children and teenagers)
Familial stone formation
Recurrent stone formers
Short time since last stone episode
Brushite-containing stones ($CaHPO_4{\cdot}2H_2O$)
Uric acid and urate-containing stones
Infection stones
Solitary kidney (the kidney itself does not particularly increase the risk of stone formation, but prevention of stone recurrence is of crucial importance to avoid acute renal failure)
Chronic kidney disease
Diseases associated with stone formation
Hyperparathyroidism
Metabolic syndrome
Metabolic bone disorder
Nephrocalcinosis
Polycystic kidney disease
Gastrointestinal diseases (enteric hyperoxaluria due to jejuno-ileal bypass, intestinal resection, Crohn's disease, malabsorptive conditions, urinary diversion, exocrine pancreatic insufficiency, and bariatric surgery)
Elevated levels of vitamin D
Sarcoidosis
Spinal cord injury, neurogenic bladder
Genetically determined stone formation
Cystinuria (types A, B, and AB)
Primary hyperoxaluria
Renal tubular acidosis type I
2,8-Dihydroxyadeninuria
Xanthinuria
Lesch-Nyhan syndrome
Cystic fibrosis
Drug-induced stone formation
Active compounds that crystallise in urine
Allopurinol/oxypurinol, amoxicillin/ampicillin, ceftriaxone, quinolones, ephedrine, indinavir and other HIV-protease inhibitors, magnesium trisilicate, sulfonamides, triamterene
Substances affecting urine composition
Acetazolamide, allopurinol, aluminium magnesium hydroxide, ascorbic acid, calcium, furosemide, laxatives, losartan, methoxyflurane, orlistat, vitamin D, topiramate, zonisamide
Anatomic abnormalities associated with stone formation
Medullary sponge kidney (tubular ectasia)
Ureteropelvic junction obstruction
Calyceal diverticulum, calyceal cyst
Ureteral stricture
Vesicoureterorenal reflux
Horseshoe kidney
Ureterocele
Environmental and professional factors
High ambient temperatures
Chronic lead and cadmium exposure
Drinking and micturition restrictions

HIV = human immunodeficiency virus.

Table 4 – Risk factors for chronic kidney disease and end-stage kidney disease in stone formers

Overweight
Frequent urinary tract infections
Struvite stones
Acquired single kidney
Neurogenic bladder
Previous obstructive nephropathy
Urinary diversion

Secondary hyperoxaluria (oxalate excretion >0.5 mmol/d and usually <1 mmol/d) occurs because of intestinal hyperabsorption of oxalate or extreme dietary intake of oxalate. Although mild hyperoxaluria (oxalate excretion 0.45–0.85 mmol/d) may be present in idiopathic calcium oxalate stone formers [85,115], secondary and primary hyperoxaluria should be considered in the differential diagnosis.

Hyperuricosuria may be associated with normouricaemia or with hyperuricaemia (gout, high dietary intake of purine, myeloproliferative disorders, haemolytic anaemia). The so-called acidic arrest (urine pH constantly <6) may promote co-crystallisation of uric acid and calcium oxalate. Similarly, elevated uric acid excretion (>4 mmol/d in adults or >12 mg/kg/d in children) can promote crystallisation [116].

3.3.1.3. Specific treatment. General preventive measures regarding fluid intake and diet are recommended for all patients with calcium oxalate stones, even in cases with normal metabolic results. Stone formers with hyperoxaluria should consume foods with low oxalate content, whereas those with hyperuricosuria benefit from a reduction in dietary purine [14]. Adequate urine dilution for patients with

Table 5 – Risk of chronic kidney disease and renal stones

Possible risk of chronic kidney disease
Xanthine stones
Indinavir stones
Distal renal tubular acidosis (incomplete)
Primary hyperparathyroidism
Eating disorders and laxative abuse
Medullary sponge kidney
Moderate risk of chronic kidney disease
Brushite stones
2,8-Dihydroxyadenine stones
Sarcoidosis
Pyeloureteral or ureteral strictures
High risk of chronic kidney disease
Cystine stones
Struvite stones
Stones in a single kidney
Distal renal tubular acidosis (complete)
Secondary hyperoxaluria (bariatric surgery, inflammatory bowel disease, bowel resection, and malabsorptive syndromes)
Other forms of nephrocalcinosis (often associated with genetic conditions with hypercalciuria)
Anatomic abnormalities of the kidney and urinary tract (eg, horseshoe kidney, ureterocele, and vesicoureteral reflux)
Neurogenic bladder
Very high risk of chronic kidney disease
Primary hyperoxaluria
Autosomal dominant polycystic kidney

Table 6 – Risk of metabolic bone disease and calcium renal stones

• Distal renal tubular acidosis(complete or incomplete)
Medullary sponge kidney
Primary hyperparathyroidism
Malabsorptive syndromes
Fasting hypercalciuria
Genetic disorders

primary hyperoxaluria is achieved by adjusting fluid intake to 3.5–4.0 l/d in adults (children 1.5 l/m^2 body surface area) according to a circadian drinking regimen [85].

Figure 2 summarises the pharmacological treatment for prevention of calcium oxalate stones. According to the evidence available, thiazides, alkaline citrate, oral calcium, allopurinol, and febuxostat when indicated are strongly recommended (Table 8) [58–65,68–71,75,76,80,81,83,86,94,97]. One recent RCT concluded that treatment with hydrochlorothiazide does not differ substantially from placebo in preventing stone recurrence in patients with marginal hypercalciuria [67].

Patients with primary hyperoxaluria benefit from alkaline citrate therapy (3.25–9.75 g/d in adults, 0.1–0.15 g/kg/d in children) and magnesium 200–400 mg/day (avoid magnesium in cases of renal insufficiency). Pyridoxine 5–20 mg/kg/d according to urinary oxalate excretion and patient tolerance is strongly recommended. Subcutaneous injection of lumasiran, with the dose and timing adjusted according to body weight and treatment duration, is strongly recommended in cases of pyridoxine unresponsiveness [85,89,117]. Nedosiran was also approved by the US Food and Drug Administration in 2023 for primary hyperoxaluria [118].

Specific measures for enteric hyperoxaluria include restricted intake of oxalate-rich foods [119], restricted fat intake [119], calcium supplementation at mealtimes to facilitate calcium oxalate complex formation in the intestine (strong recommendations) [93,115], sufficient fluid intake to balance the intestinal loss of water caused by diarrhoea, and alkaline citrates to raise urinary pH and citrate.

3.3.2. *Calcium phosphate stones*

3.3.2.1. Evaluation. Patients with calcium phosphate stones at high risk of recurrence (Table 3) or complications (Tables 5 and 6) require a thorough evaluation. Diagnosis requires blood analysis of creatinine, sodium, potassium, chloride, ionised calcium (or total calcium corrected by the albumin concentration), phosphate, and PTH (in cases with elevated calcium levels). Urinalysis should include measurement of volume, urine pH, specific weight, calcium, phosphate, and citrate.

3.3.2.2. Diagnostic/aetiologic algorithm and interpretation of results. Calcium phosphate mainly occurs in two completely different mineral forms: carbonate apatite and brushite. Carbonate apatite crystallisation occurs at pH >6.8 and may be associated with infection, hypercalciuria, and HPT. Brushite crystallises at an optimum pH of 6.5–6.8 at high urinary concentrations of calcium (>8 mmol/day) and phosphate (>35 mmol/d). Its occurrence is related to RTA and HPT, but not to UTI (Fig. 3) [120].

RTA can be acquired or inherited. Type I RTA is related to urolithiasis and is diagnosed via an ammonium chloride loading test or a furosemide/fludrocortisone acidification test (Fig. 4) [121–124]. Causes of acquired RTA include chronic obstructive uropathy, recurrent pyelonephritis, acute tubular necrosis, renal transplantation, analgesic nephropathy, sarcoidosis, Sjögren syndrome and other autoimmune diseases, medullary sponge kidney, liver cirrhosis, sickle cell anaemia, idiopathic hypercalciuria, and primary HPT; RTA may also be drug-induced (eg, amphotericin B, foscarnet, lithium, zonisamide, and other carbonic anhydrase inhibitors).

3.3.2.3. Specific treatment. General preventive measures are recommended in terms of fluid intake and diet. Most patients with primary HPT require surgery. If primary HPT and RTA have been excluded, pharmacotherapy for calcium phosphate calculi depends on the effective reduction of urinary calcium levels using thiazides (strong recommendation). For infection-associated calcium phosphate stones, it is important to consider the guidance given for infection stones (Fig. 3) [76].

The main therapeutic aim of RTA treatment is to restore a normal acid-base equilibrium. Despite the alkaline pH of urine in RTA, alkalinisation using alkaline citrates or sodium bicarbonate is important for normalising the metabolic changes (intracellular acidosis) responsible for stone formation (Table 9) and bone demineralisation (strong recommendation). The alkali load reduces tubular reabsorption of citrate, which in turn normalises citrate excretion. Therapeutic success can be monitored via venous blood gas analysis (base excess: ±2.0 mmol/l) in complete RTA. If excessive calcium excretion (>8 mmol/d) persists after re-

Table 7 – Pharmacological agents used for stone prevention

Agent	Rationale	Dose	Specification and side effects	Stone type
Thiazide (hydrochlorothiazide) [a]	Calciuria >8 mmol/d	25–50 mg/d Children 0.5–1 mg/kg/d	Risk of hypotension diabetes, hyperuricaemia, hypokalaemia, hypocitraturia	Calcium oxalate Calcium phosphate
Alkaline citrates	Alkalinisation Hypocitraturia Inhibition of calcium oxalate crystallisation	3.25–9.75 g/d (10–30 mmol/d) Children 0.1–0.15 g/kg/d	Daily dose for alkalinisation depends on urine pH	Calcium oxalate Uric acid Cystine
Sodium bicarbonate	Alkalinisation Hypocitraturia	4.5 g/d	Daily dose for alkalinisation depends on urine pH	Calcium oxalate Uric acid Cystine
Allopurinol	Hyperuricosuria Hyperuricaemia	100–300 mg/d Children 1–3 mg/kg/d	100 mg in isolated hyperuricosuria Renal insufficiency requires dose correction Contraindicated in acute gout, pregnancy, and breastfeeding Allergies from trivial to very severe forms, xanthine stone formation	Calcium oxalate Uric acid Ammonium urate 2,8-Dihydroxyadenine
Febuxostat	Hyperuricosuria Hyperuricaemia	80–120 mg/d	Contraindicated in acute gout, pregnancy, and breastfeeding Xanthine stone formation	Calcium oxalate Uric acid
Calcium	Enteric hyperoxaluria	Up to 2000 mg/d depending on oxalate excretion	Intake 30 min before meals	Calcium oxalate
Magnesium	Isolated hypomagnesuria Enteric hyperoxaluria	200–400 mg/d Children 6 mg/kg/d	Renal insufficiency requires dose correction Diarrhoea, chronic alkali losses, hypocitraturia	Calcium oxalate
Pyridoxine	Primary hyperoxaluria	Initial dose 5 mg/kg/d Maximum 20 mg/kg/d	Sensory peripheral neuropathy	Calcium oxalate
Lumasiran	Primary Hyperoxaluria type I	Dose is adjusted according to body weight	Mainly at the site of subcutaneous injection	Calcium oxalate
L-Methionine	Acidification	600–1500 mg/d	Hypercalciuria, bone demineralisation, systemic acidosis No long-term therapy	Infection stones Ammonium urate Calcium phosphate
Captopril	Cystinuria Active decrease in urinary cystine levels	75–150 mg	Second-line option in cases with significant side effects of tiopronin	Cystine
D-Penicillamine	Cystinuria Chelating agent that binds with cystine to form a soluble disulfide complex	500 mg/d (start with 250 mg and increase gradually; maximum dose 4000 mg/d) Children 30 mg/kg/d in 2–3 doses	Second-line option in cases with significant side effects of tiopronin	Cystine
Tiopronin	Cystinuria Increase in solubility of cystine	Initial dose 800 mg/d Average dose 2000 mg/d Children Initial dose for patients >20 kg is 15 mg/kg/d. Avoid doss >50 mg/kg/d	Risk of proteinuria	Cystine

[a] Patients on hydrochlorothiazide should be advised to get their skin checked on a regular basis as they have a higher risk of developing a nonmelanoma skin cancer and some forms of melanoma. In patients with a history of skin cancer, the indication for treatment with hydrochlorothiazide should be thoroughly reviewed [107–109].

establishing acid-base equilibrium, thiazides may lower urinary calcium excretion (strong recommendation).

3.3.3. *Uric acid and ammonium urate stones*

3.3.3.1. Evaluation. All uric acid and ammonium urate stone formers are at high risk of recurrence [26]. Blood analysis should involve measurement of creatinine and uric acid levels; since acute inflammation might increase serum uric acid, in cases with a clinical suspicion of an inflammatory condition, measurement of uric acid levels should be repeated before initiation of pharmacotherapy. Urinalysis should involve measurement of urine volume, pH, and specific weight, as well as the uric acid level. A urine culture is needed in cases with ammonium urate stones.

3.3.3.2. Diagnostic/aetiologic algorithm and interpretation of results. Uric acid urolithaisis accounts for approximately 10% of renal stones [125] and is associated with hyperuricosuria and/or low urinary pH and/or low urine volume production. Hyperuricosuria may be a result of dietary excess,

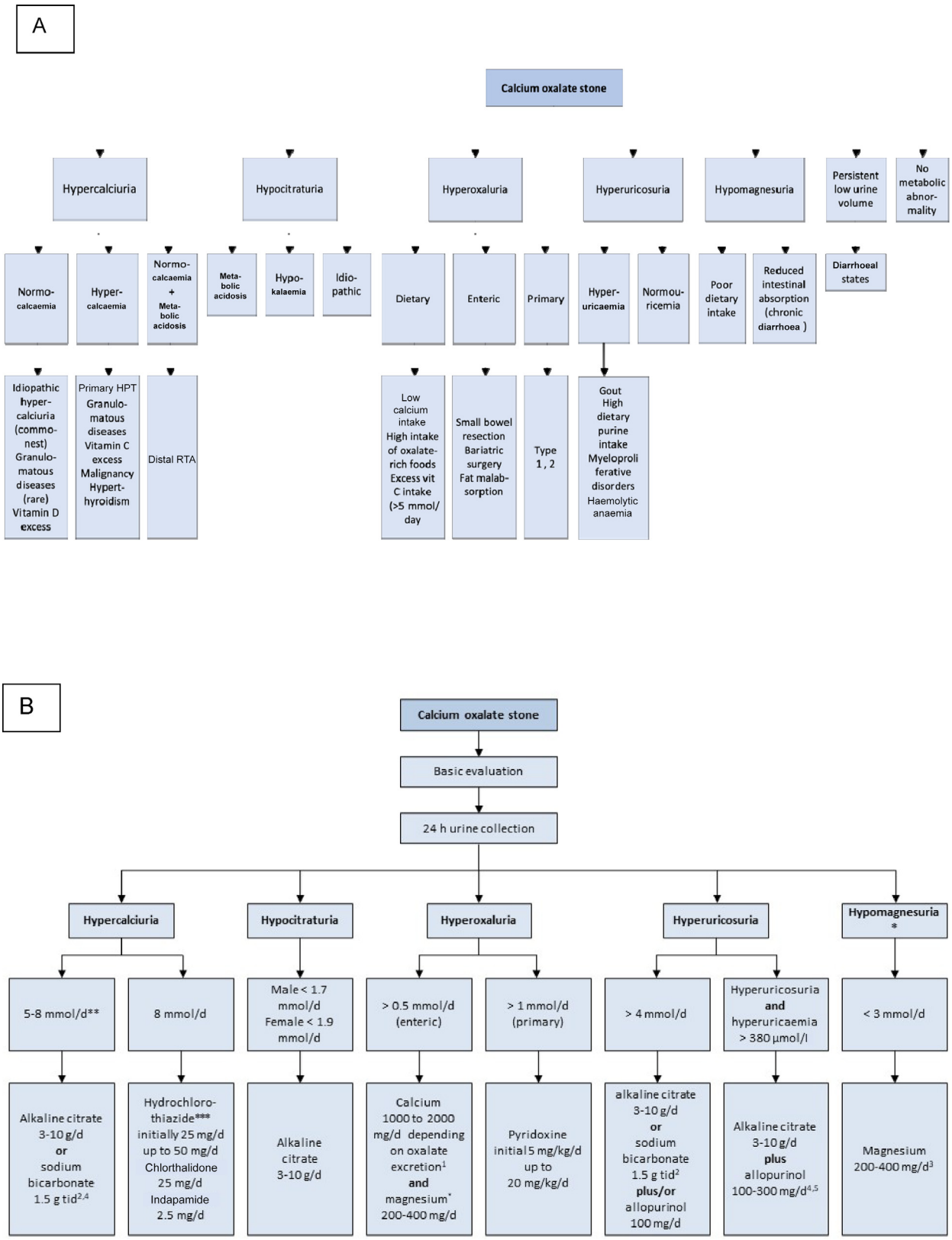


Fig. 2 – (A) Diagnostic/aetiologic algorithm and (B) therapeutic algorithm for calcium oxalate stones. HPT = hyperparathyroidism; RTA = renal tubular acidosis; vit = vitamin. [1] Be aware of excess calcium excretion. [2] tid = three times/d (24 h). [3] No magnesium therapy for patients with renal insufficiency. [4] There is no evidence that combination therapy (thiazide + citrate) or (thiazide + allopurinol) is superior to thiazide therapy alone. [5] Febuxostat 80 mg/d. * Low evidence. ** Calciuria is a continuous variable and treatment may be adjusted to the clinical need, even when below the threshold indicated. * Patients on hydrochlorothiazide should be advised to get their skin checked on a regular basis as they have a higher risk of developing nonmelanoma skin cancer and some forms of melanoma. In patients with a history of skin cancer, the indication for treatment with hydrochlorothiazide should be thoroughly reviewed.**

Table 8 – Recommendations for pharmacological treatment for calcium oxalate stones in patients with specific abnormalities in urine composition in 24-h urine samples

Recommendation	Strengthrating
Prescribe thiazide or alkaline citrates or both in cases of hypercalciuria. [a]	Strong
Advise oxalate restriction if hyperoxaluria is present.	Weak
Offer alkaline citrates in enteric hyperoxaluria.	Weak
Offer calcium supplements in enteric hyperoxaluria.	Strong
Advise reduction in dietary fat and oxalate in enteric hyperoxaluria.	Weak
Prescribe alkaline citrates or sodium bicarbonate in cases of hypocitraturia.	Strong
Prescribe allopurinol in cases of hyperuricosuria.	Strong
Offer febuxostat as a second-line treatment for hyperuricosuria.	Strong
Avoid excessive intake of animal protein in hyperuricosuria.	Strong
Advise restricted intake of salt if there is high urinary sodium excretion.	Strong

[a] Patients on hydrochlorothiazide should be advised to get their skin checked on a regular basis as they have a higher risk of developing nonmelanoma skin cancer and some forms of melanoma. In patients with a history of skin cancer, the indication for treatment with hydrochlorothiazide should be thoroughly reviewed.

endogenous overproduction (enzyme defects), myeloproliferative disorders, chemotherapy drugs, gout, or catabolism [51]. Low urinary pH may be caused by a decrease in urinary ammonium excretion (insulin resistance, gout, autosomal dominant polycystic kidney disease), elevated endogenous acid production (insulin resistance, metabolic syndrome, or exercise-induced lactic acidosis), greater acid intake (high animal protein intake), or an increase in base loss (diarrhoea) [51]. Low urine volume may be the outcome of chronic dehydration, excessive respiration, exercise, or chronic diarrhoea (Fig. 5).

Hyperuricosuria is defined as uric acid excretion, defined as >4 mmol/d in adult females, >5 mmol/d in adult males, and >0.12 mmol/kg/d in children. Hyperuricaemia may be present, but there is only weak evidence for an association with stone formation [126].

Hyperuricosuric calcium oxalate stone formation can be distinguished from uric acid stone formation by urinary pH, which is usually >5.5 for calcium oxalate stone formation and <5.5 for uric acid stone formation; occasionally, hyperuricosuria is absent in patients with pure uric acid stones [127,128].

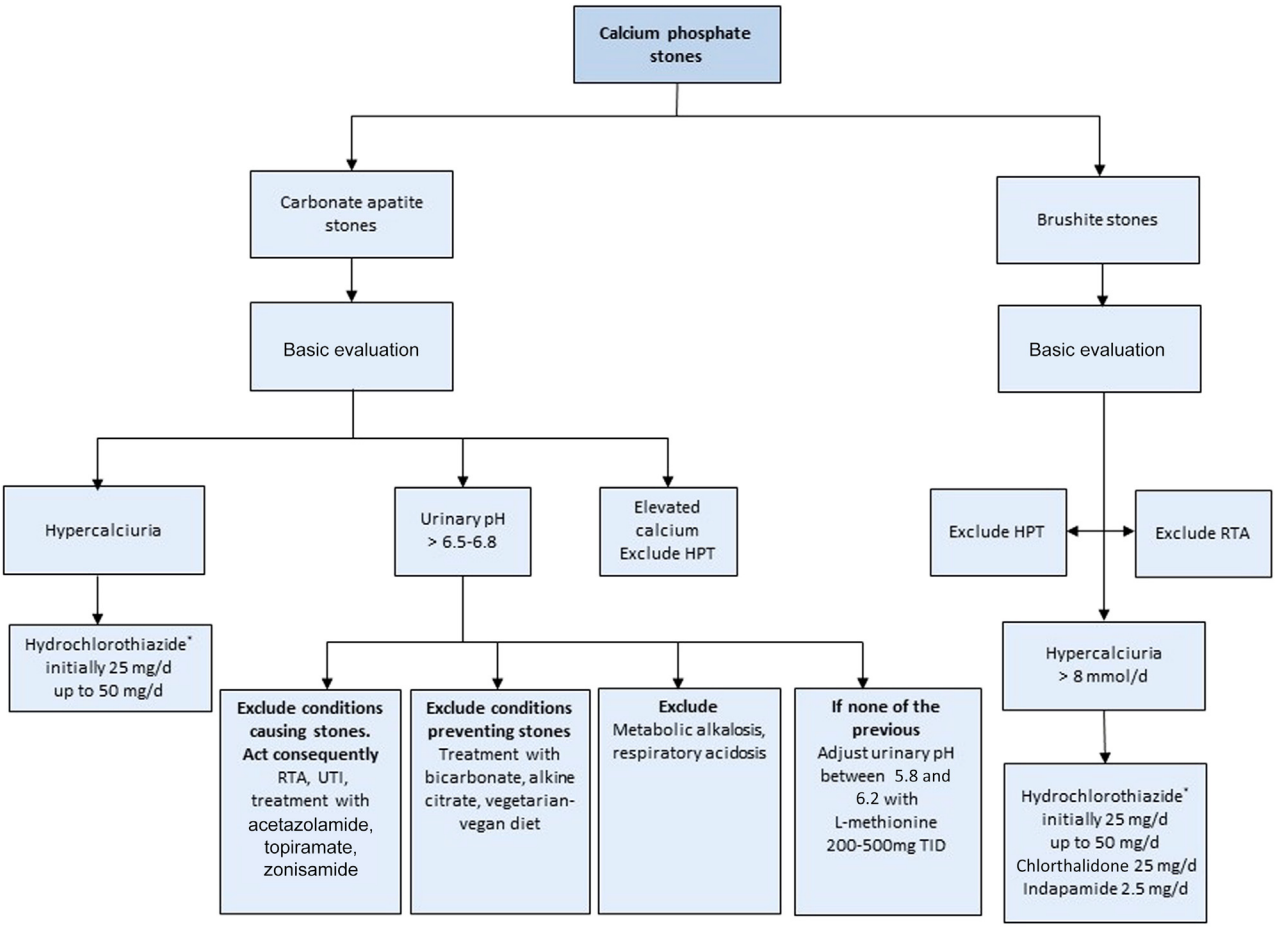


Fig. 3 – Diagnostic and therapeutic algorithm for calcium phosphate stones. HPT = hyperparathyroidism; RTA = renal tubular acidosis; UTI = urinary tract infection. * Patients on hydrochlorothiazide should be advised to get their skin checked on a regular basis as they have a higher risk of developing nonmelanoma skin cancer and some forms of melanoma. In patients with a history of skin cancer, the indication for treatment with hydrochlorothiazide should be thoroughly reviewed.

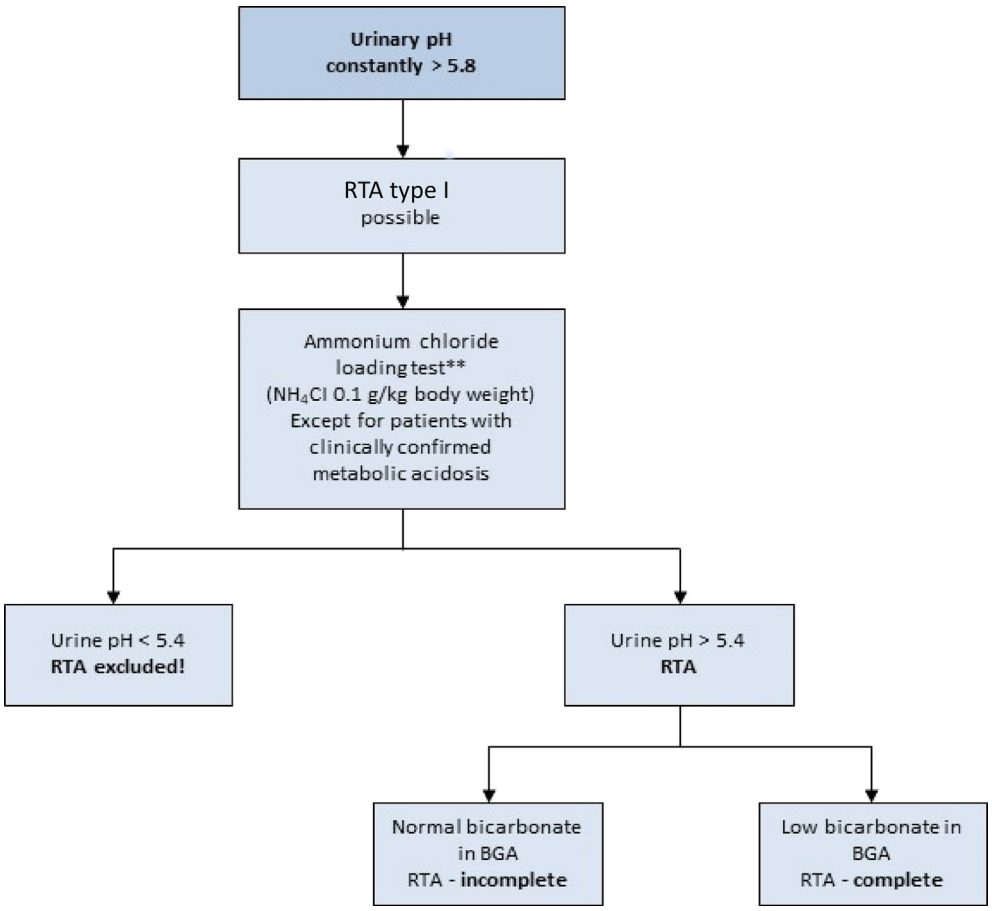


Fig. 4 – Diagnosis of renal tubular acidosis. BGA = blood gas analysis; RTA = renal tubular acidosis. ** An alternative ammonium chloride loading test using a 1-d NH_4Cl load at 0.05 g/kg body weight might provide similar results and may be better tolerated by the patient. A second alternative in these cases could be the furosemide/fludrocortisone acidification test.

Table 9 – Pharmacological treatment of renal tubular acidosis

Biochemical risk factor	Indication for pharmacological therapy	Medication
Hypercalciuria	Calcium excretion >8 mmol/d	Hydrochlorothiazide [a] – Adults: 25 mg/d initially, up to 50 mg/d – Children: 0.5–1 mg/kg/d Alternatives in adults: Chlorthalidone 25 mg/d Indapamide 2.5 mg/d
Systemic acidosis, low citraturia	Serum bicarbonate <20 mEq/l Citrate excretion: males <1.7 mmol/d, females <1.9 mmol/d	Alkaline citrate 3.25–9.75 g/d in three doses OR Sodium bicarbonate 1.5 g, three times daily

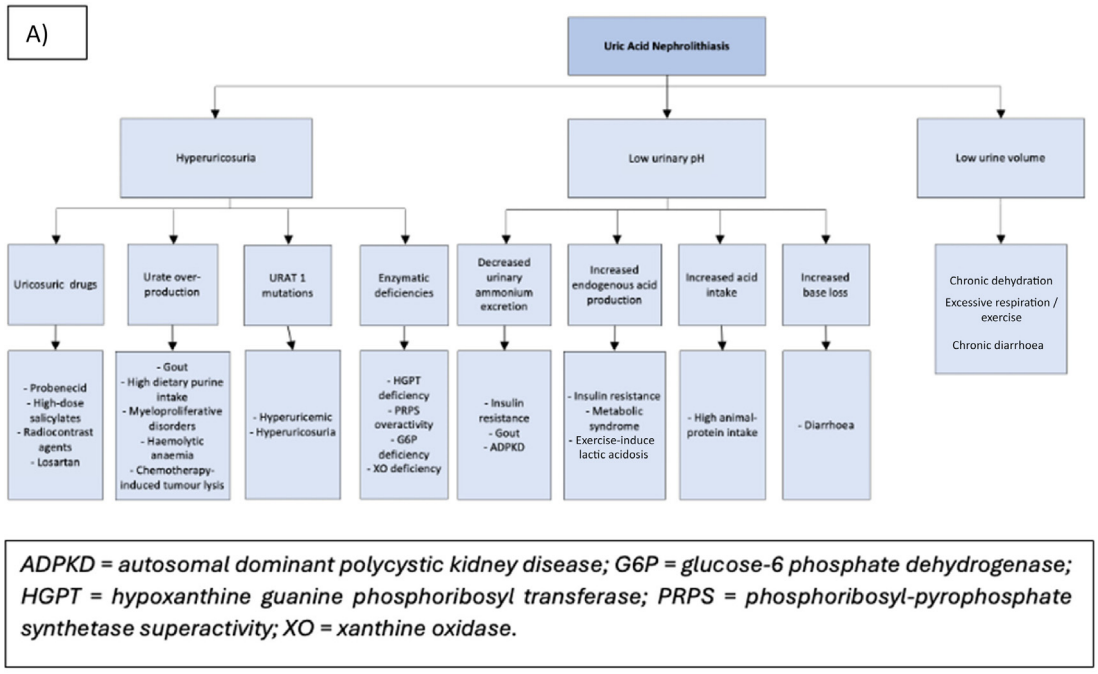
[a] Patients on hydrochlorothiazide should be advised to get their skin checked on a regular basis as they have a higher risk of developing nonmelanoma skin cancer and some forms of melanoma. In patients with a history of skin cancer, the indication for treatment with hydrochlorothiazide should be thoroughly reviewed.

Ammonium urate stones are extremely rare, comprising <1% of all urinary stones. They are associated with UTI, malabsorption (inflammatory bowel disease and ileostomy diversion or laxative abuse), phosphate deficiency, hypokalaemia, and malnutrition. Chronic kidney disease is frequently observed. Ammonium urate crystals form in urine at pH levels >6.5 when the concentration of uric acid is high and ammonium is present [129,130].

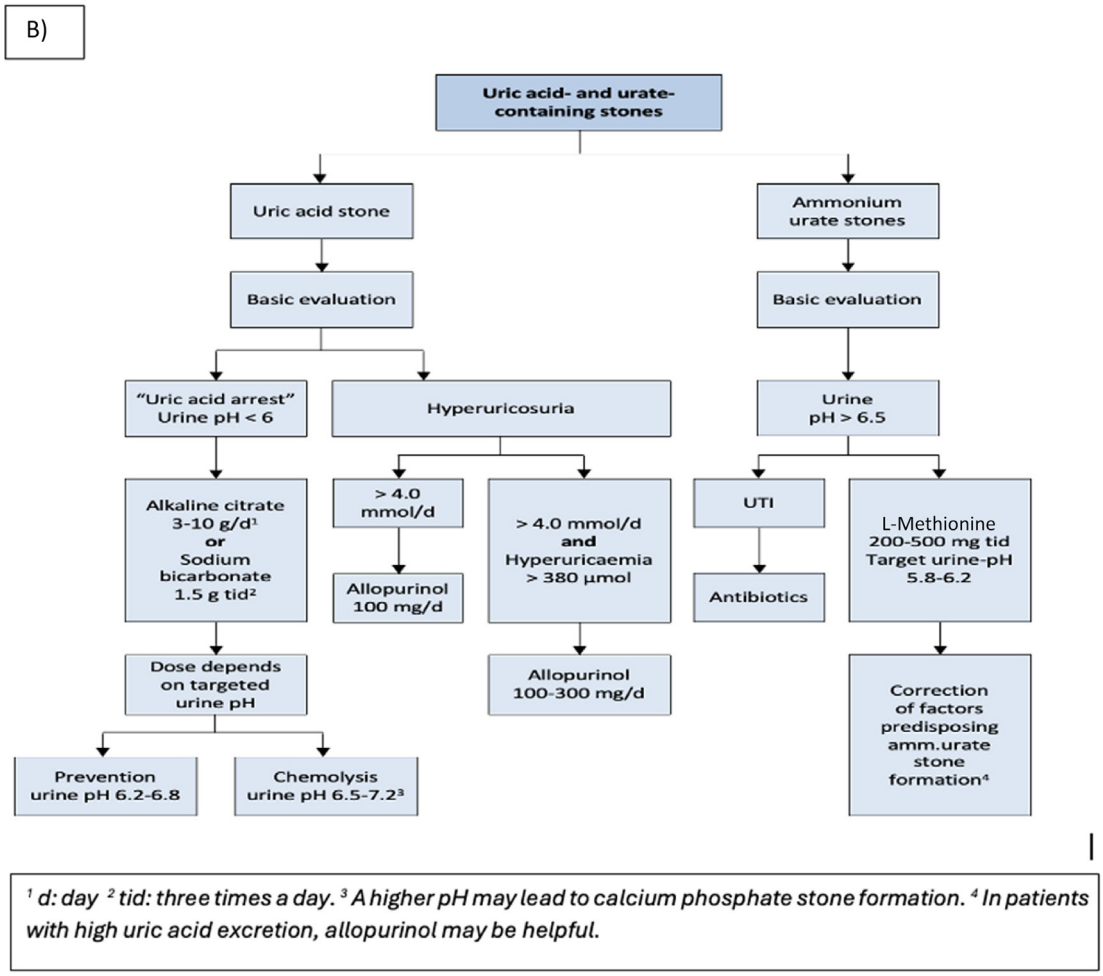
3.3.3.3. Specific treatment. General preventive measures regarding fluid intake and diet are recommended. Stone formers with hyperuricosuria benefit from a reduction in dietary purine. Figure 5 provides an overview of pharmacological treatment [26,125,127–136]. For uric acid stones, alkaline citrate and allopurinol, when indicated, are strongly recommended. Allopurinol may change the stone composition distribution in patients with gout to a pattern like that in stone formers without gout [137]. Antibiotics, L-methionine, and correction of predisposing factors can help in preventing the formation of ammonium urate stones.

3.3.4. Struvite and infection stones

3.3.4.1. Evaluation. All patients with an infection stone are at high risk of recurrence. Blood analysis should involve



ADPKD = autosomal dominant polycystic kidney disease; G6P = glucose-6 phosphate dehydrogenase; HGPT = hypoxanthine guanine phosphoribosyl transferase; PRPS = phosphoribosyl-pyrophosphate synthetase superactivity; XO = xanthine oxidase.



[1] d: day [2] tid: three times a day. [3] A higher pH may lead to calcium phosphate stone formation. [4] In patients with high uric acid excretion, allopurinol may be helpful.

Fig. 5 – (A) Diagnostic and (B) therapeutic algorithm for uric acid stones. UTI = urinary tract infection; amm. urate = ammonium urate.

measurement of creatinine, and urinalysis should include repeat urinary pH measurements and urine cultures. In cases with mixed struvite stones, measurement of metabolic abnormalities in 24-h urine after stone removal and infection control is recommended.

3.3.4.2. Diagnostic/aetiologic algorithm and interpretation of results. Struvite stones account for 2–15% of urolithiasis cases and may originate de novo or grow on pre-existing stones infected with urea-splitting bacteria [138]. Several factors predispose patients to struvite stone formation (Table 10) [139]. Several studies have reported that urinary metabolic alterations can be identified in 36–81% of patients with mixed struvite stones [140–145].

Infection stones contain struvite and/or carbonate apatite and/or ammonium urate. A urine culture typically provides evidence of urease-producing bacteria, which increase ammonia ions leading to alkaline urine (Table 11). Carbonate apatite starts to crystallise at a urine pH level of 6.8. Struvite only precipitates at pH >7.2 [146,147]. A mixed struvite stone (ie, containing a high percentage of calcium oxalate and carbonate apatite) suggests over-infection of a "metabolic" calcium oxalate or calcium phosphate stone [145]. *Proteus mirabilis* accounts for more than half of all urease-positive UTIs [148,149].

3.3.4.3. Specific treatment. General preventive measures involving fluid intake and diet are recommended. Specific measures include complete surgical removal of the stone when feasible (strong recommendation) [139], short- or long-term antibiotic treatment (strong recommendation) [150], and urinary acidification using methionine [96] or ammonium chloride [95] (weak recommendation). For persistent infections/colonisation, acetohydroxamic acid may be an option [98,99] (Fig. 6); however, this agent is not licensed or available in all European countries. Eradication of infection after complete stone removal is desirable. Evidence regarding the duration of postoperative antibiotic administration is inconclusive, so treating physicians could adjust the antibiotic duration on the basis of repeated urine cultures as clinically indicated.

Percutaneous chemolysis is rarely used now for practical reasons, but may be an option for infection stones. Suby's G solution (10% hemiacidrin; pH 3.5–4) can be used to dissolve struvite stones. The method has been described in case series and literature reviews [151,152].

Table 10 – Factors predisposing to struvite stone formation.

• Neurogenic bladder
• Spinal cord injury/paralysis
• Continent urinary diversion
• Ileal conduit
• Foreign body
• Stone disease
• Indwelling urinary catheter
• Urethral stricture
• Benign prostatic hyperplasia
• Bladder diverticulum
• Cystocele
• Calyceal diverticulum Ureteropelvic junction obstruction

3.3.5. Cystine stones

3.3.5.1. Evaluation. All cystine stone formers are at high risk of recurrence and chronic kidney disease [153,154]. Blood analysis should include measurement of creatinine, and urinalysis should include measurement of urine volume, pH profile, specific weight, and cystine. Since the disease may be asymptomatic, siblings of cystinuric patients should be investigated for cystinuria [155].

3.3.5.2. Diagnostic/aetiologic algorithm and interpretation of results. Cystine stones account for 1–2% of all adult urolithiasis cases and 6–8% of paediatric cases [156,157]. Cystine is poorly soluble in urine and crystallises spontaneously within the physiological urinary pH range. Cystine solubility strongly depends on urine pH: at pH 6.0, the solubility limit is 1.33 mmol/l. Routine analysis of cystine is not suitable for therapeutic monitoring. Regardless of the phenotype or genotype of patients with cystinuria, clinical manifestations are the same [158]. There is no role for patient genotyping in the routine management of cystinuria [159,160]. Reductive therapy targets the disulfide bond in the cystine molecule. For therapy monitoring, it is important to differentiate between cystine, cysteine, and drug-cysteine complexes. However, methods for monitoring cystinuria treatment that may be able to differentiate between the different complexes formed with the therapeutic agent are not accurate [106,161], including high-performance liquid chromatography [45]. Quantitative measurement of 24-h urinary cystine excretion confirms the diagnosis in the absence of stone analysis. Levels >0.125 mmol/d (30 mg/d) are considered abnormal [162,163]. Stone analysis, identification of a pathognomonic cystine crystal shape (hexagonal plates with even sides), and a sodium nitroprusside test are other methods for confirming the diagnosis.

3.3.5.3. Specific treatment. General preventive measures in terms of fluid intake and diet are recommended. A diet low in methionine may theoretically reduce urinary excretion of cystine; however, patients are unlikely to comply sufficiently with this dietary advice. A restricted intake of sodium is more easily achieved and is more effective in reducing urinary cystine. Patients are usually advised to avoid sodium consumption >2 g/d (5 g of NaCl) [164]. A high level of diuresis is of fundamental importance, with a 24-h urine volume target of >3 l (strong recommendation) [158,164–166]. A considerable fluid intake evenly distributed throughout the day is necessary.

The main therapeutic option for avoiding cystine crystallisation is to maintain urinary pH >7.5 to improve cystine solubility and ensure appropriate hydration, at a minimum of >3 l/d in adults or 1.5 l/m^2 body surface area in children (strong recommendation) [158,164–166]. Home monitoring of urinary pH is suggested because of the possibility of self-adjusting alkaline treatment to keep the pH level within the therapeutic range [45].

Free cystine concentrations can be decreased by reductive substances, which act by splitting the disulfide bond of cystine (strong recommendation; Fig. 7). Tiopronin is currently the best choice for cystine reduction. However, side

Table 11 – Most important species of urease-producing bacteria [a]

• **Obligate urease-producing bacteria (>98%)**
• *Proteus* spp.
Providencia rettgeri
Morganella morganii
Corynebacterium urealyticum
Ureaplasma urealyticum
Facultative urease-producing bacteria
• *Enterobacter gergoviae*
Klebsiella spp.
Providencia stuartii
Serratia marcescens
Staphylococcus spp.

[a] Note that 0–5% of *Escherichia coli*, *Enterococcus* spp., and *Pseudomonas aeruginosa* strains may produce urease.

effects often lead to treatment termination, for example, when proteinuria develops or when there is poor compliance, especially with long-term use. Tiopronin is recommended at cystinuria levels >3.0 mmol/d (720 mg/d) and in cases with recurring stone formation despite other preventive measures [158,164–166]. For cases in which tiopronin cannot be used (eg, patients with unbearable side effects), D-penicillamine is another chelating agent; captopril and α-lipoic acid have also been tested, with the latter showing promising results [167]. Spot measurement of urinary protein should be performed at baseline and during follow-up.

3.4. *Follow-up for patients at high risk of recurrence*

The EAU Urolithiasis Guidelines Panel performed a systematic review of the benefits and harms of scheduled imaging and metabolic follow-up for patients who underwent definitive treatment for upper urinary tract stone disease [168]. There are insufficient data for high-risk patients, but the current literature indicates that patients who adhere to targeted medical treatment seem to experience less stone growth or regrowth of residual fragments and may be discharged after 36–48 mo of nonprogressive disease on imaging. However, as <40% of patients with metabolic abnormalities not on medication remained

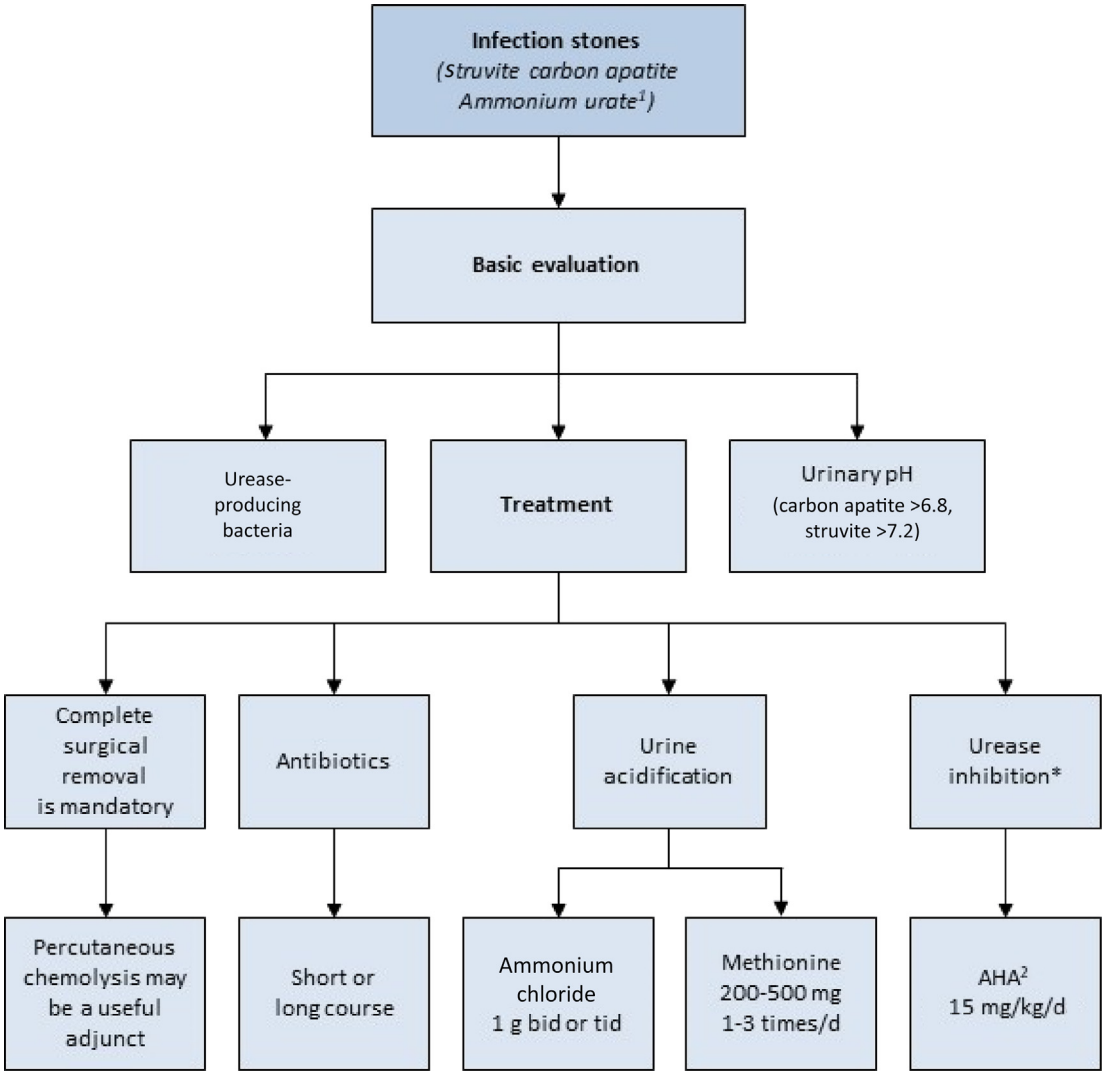


Fig. 6 – Diagnostic and therapeutic algorithm for infection stones. bid = twice a day; tid = three times a day; AHA = acetohydroxamic acid. [1] Discussed for uric acid stones. [2] Acetohydroxamic acid. * When nationally available.

stone-free after 3 yr of follow-up, more extensive follow-up is recommended (Figs. 8 and 9). Owing to the paucity of high-level evidence and a consensus-derived follow-up algorithm, the panel can make no recommendations on follow-up.

4. Discussion

Follow-up for urolithiasis patients depends on the metabolic profile of each patient, the risk of chronic kidney disease, and the risk of osteoporosis/osteopenia. The great diversity of urolithiasis patients makes it difficult to classify them into groups regarding the risk of recurrence, while design of high-quality studies with strong and sufficient data to support clinical guidelines is cumbersome. For these reasons, as well as cost-effectiveness issues, international societies such as the National Institute for Health and Care Excellence, despite providing similar recommendations to the EAU guidelines regarding metabolic testing and prevention of recurrences, do not give the same strength of recommendation for specific areas [169].

The literature has not yet addressed the substantial differences between patients with a single episode of urolithiasis and patients with recurrent disease, or between metabolically active and inactive patients; therefore, we cannot justify different screening and follow-up approaches for these groups. There is a lack of sufficient data to argue that universal screening on initial presentation is cost-effective, can decrease recurrence and intervention rates, or improve the quality of life of patients. Furthermore, there is very limited clinical evidence to support the interpretation of abnormalities in urinary parameters as a guide to assess the effectiveness of dietary or pharmacological interventions [76,170]. The ideal scenario of practising precision medicine by evaluating urine chemistry and the genotype of all urolithiasis patients lies far beyond reality, mainly because of health care resource constraints, difficulties in explaining the proper procedure for 24-h urine collection to patients, and variability in urine biochemistry according to diet, exercise, activity levels, and occupation [171]. Even hypercalciuria, one of the commonest risk factors for urolithiasis, does not follow a clearly dichotomised pattern of normal versus abnormal, although higher values are more commonly related to stone recurrence in comparison to lower values [172]. For all these reasons, there is paucity of data indicating superiority of selecting treatment on the basis of 24-h urine results over empiric treatment; thus, in cases for which 24-h urine results cannot be obtained, patients may be counselled empirically on the basis of their phenotype characteristics.

Several urine-based risk indices have been proposed for prediction of stone recurrence, but they are not supported by adequate clinical trials to establish any of them as a standard tool [45]. We recommend basic metabolic screening for all urolithiasis patients, and specific metabolic screening involving measurement of urinary abnormalities in two 24-h urine samples for patients at high risk of recurrence or complications, although there are data supporting the position that even one 24-h urine sample might be adequate [173]. Our opinion is mainly based on studies that have shown that 10-yr and 15-yr urolithiasis rate does not exceed 50% [174]. In addition, retrospective studies have shown that targeted therapy for metabolically active urolithiasis patients leads to a significant reduction in the risk of new stone formation [175,176]. We also note that carrying out a specific metabolic evaluation for patients with a first episode of urolithiasis who are interested in knowing the cause of their problem will not cause harm [177].

Many societies recommend an evaluation the based on the patient's individual risk factors and comorbidities [178]. Patient evaluation begins with a detailed medical history and a physical examination. Equally important is an assessment of the patient's dietary habits and fluid intake, as well as medication use. The aim of all of these steps is to identify any risk factors predisposing to urolithiasis recurrence. Stone analysis is recommended for all patients before baseline and extended metabolic screening. The stone composition may mean that further extensive screening can be avoided, as patients with non-calcium stones have a specific metabolic profile and do not require a 24-h urinalysis. Furthermore, among patients with calcium stones, which are associated with a heterogeneous metabolic profile, those with calcium phosphate stones have a specific aetiological pathology, namely RTA or primary HPT, and may not benefit from a complete metabolic evaluation [179]. The stone should initially be examined under a stereomicroscope to assess which parts should be sent for analysis via either infrared spectroscopy or X-ray diffraction [180,181]. Examination of the whole stone provides information about its morphology and composition, as well as how the stone developed initially via inspection of the nucleus. A patient with a calcium oxalate stone that formed initially as a dihydrate, indicative of hyperoxaluria, is at high risk of recurrence even if the composition has transformed over time to the monohydrate form of the mineral [182]. Analysis of collections of fragments is likely to lead to a better-quality result in comparison to analysis of just one fragment [183].

Basic metabolic assessment is easy, fast, and cost-effective in comparison to extended metabolic evaluation [184] and should be performed in all urolithiasis patients. Measurement of intact PTH is recommended if there is a strong suspicion of primary HPT because of elevated blood calcium levels. However, hypercalcaemia may be intermittent within the course of a day, and PTH may need to be measured along with ionised calcium as a routine procedure [185]. Crystalluria analysis is not routinely recommended to provide evidence of the propensity for stone formation, as some non–stone formers have crystals in their urine [186,187]. However, the formation of large and aggregated crystals and persistent crystalluria in >50% of the urine samples tested may be predictive of stone recurrence [188,189]. Examination of crystals can reveal rare stone types such as cystine and 2,8-dihydroxyadenine stones [182,190].

Analysis of a 24-h urine sample is important in guiding selection of an appropriate treatment, advice on dietary adjustments, and the follow-up regimen for patients with high-risk calcium-containing stones [18,172]. A significant

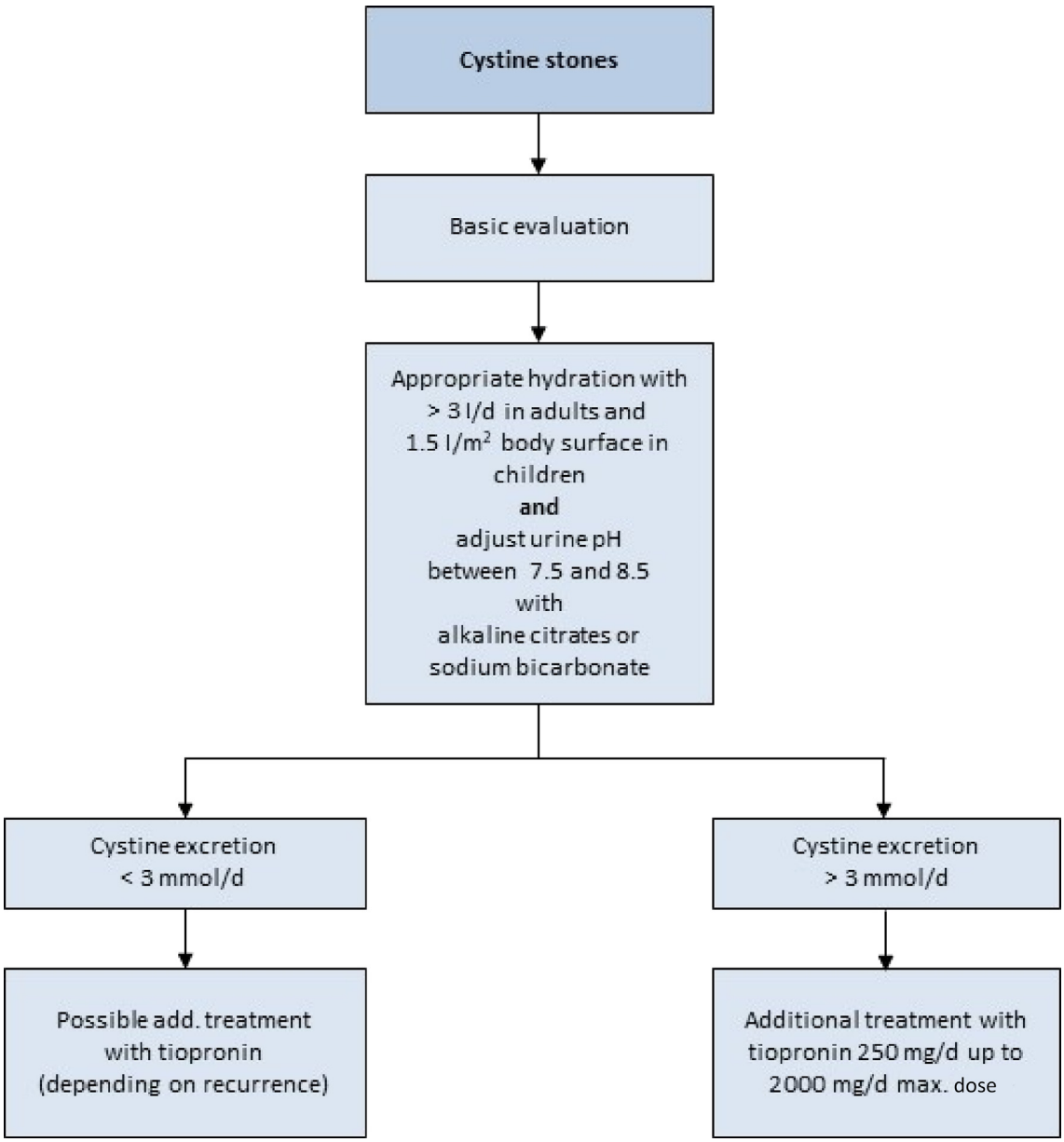


Fig. 7 – Metabolic management of cystine stones. add. = additional; max. = maximum.

number of patients might have been prescribed different medical therapies on the basis of results for just one 24-h urine sample [46,191,192]. Patients should remain on their regular diet without any restrictions during the urine collection period. All 24-h urine specimens should be collected in a vessel containing a preservative [45]. Urine volume and creatinine levels are useful parameters for assessing the completeness of a patient's 24-h collection [193]. Spot urine analysis, including a morning fasting sample or other urine collections over part of a day, can be valuable, but there are few studies to allow identification of best practices for urine analysis outside the standard 24-h collection [45]. Obtaining a 24-h urine sample is impractical in children and an afternoon specimen may be sufficient [194]. Empirical prescribing of drugs without 24-h urinalysis results may result in a just a small number of patients receiving appropriate treatment, while other patients may receive treatment they do not need [171,195].

A prospective randomised study showed that dietary recommendations tailored based on 24-hour urinalysis results were more effective than general dietary recommendations in preventing the formation of a second stone [18]. The role of fluid intake in reducing the recurrence of urolithiasis has been extensively studied and is perhaps the most important prevention method that urologists should recommend to their patients. In a previous publication, the EAU Urolithiasis Guidelines Panel recommended fluid intake of 2.5–3 l/d [196]. We recommend that the primary fluid should be water, as both prospective randomised trials and large epidemiological studies have shown a negative association between water intake and lithogenesis [15–17,76]. Studies have revealed a controversial role of

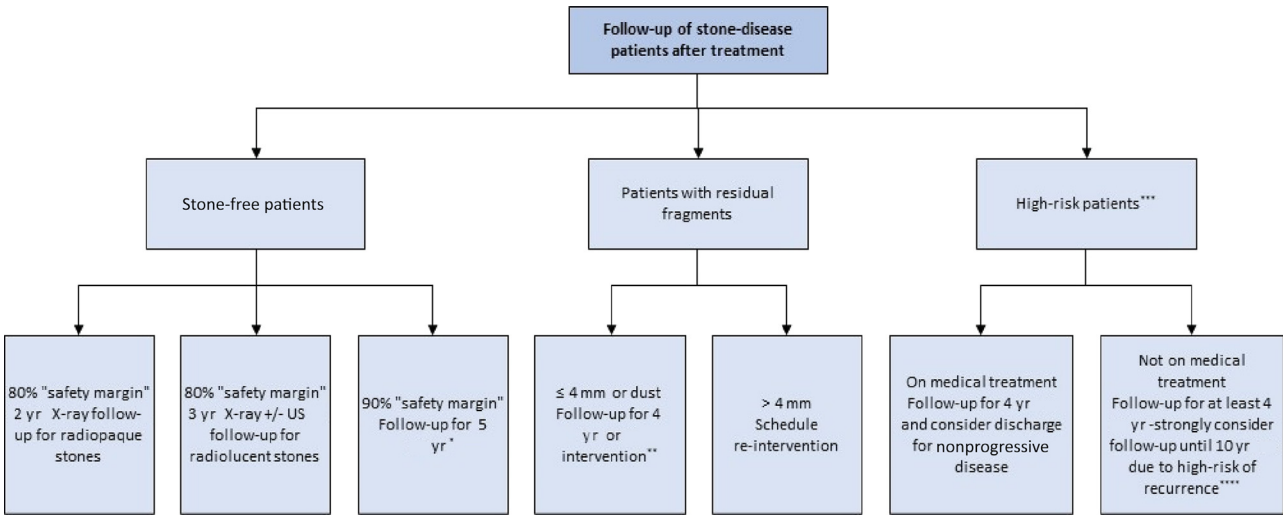


Fig. 8 – Follow-up duration after treatment of urinary stones. US = ultrasonography. * Not enough data for subgroup analysis of radiolucent versus radiopaque stones. ** According to patient preference or symptomatic disease. * Patients diagnosed with metabolic abnormalities. **** Lifelong follow-up is advised but data are available for up to 10 yr.**

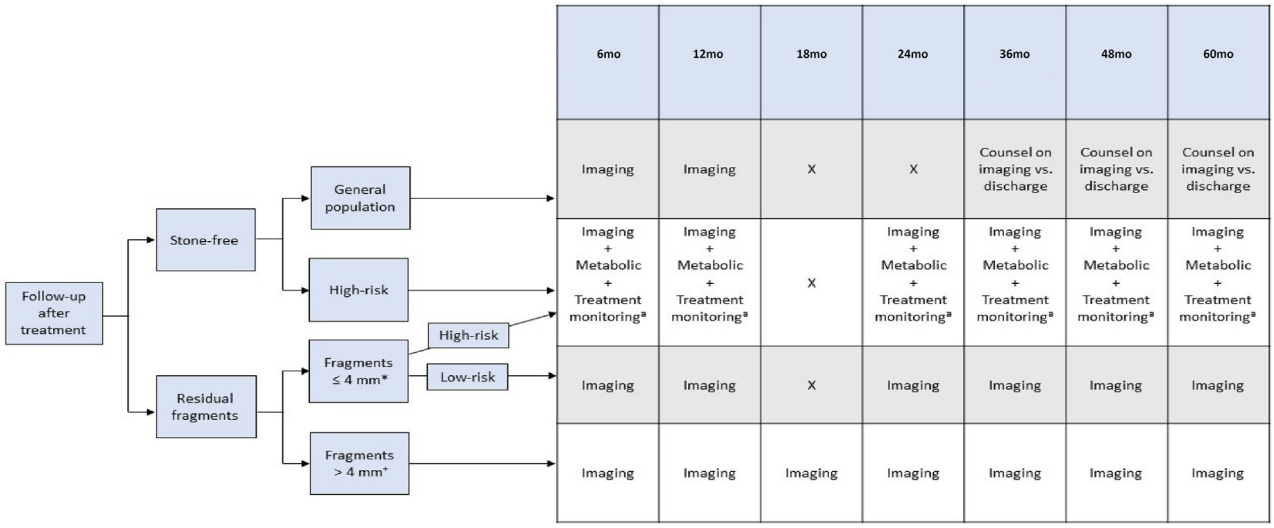


Fig. 9 – Consensus on the follow-up frequency and imaging modality to use after treatment. Stone free = no stone fragments on postoperative imaging (computed tomography, kidney-ureter-bladder X-ray, or ultrasonography). High-risk = known biochemical abnormality (hypercalciuria, hypocitraturia, hyperuricosuria, renal tubular acidosis) or a high-risk stone type such as struvite. Imaging = plain film kidney-ureter-bladder X-ray and/or kidney ultrasonography according to the clinician's preference and the stone characteristics. Consider computed tomography if the patient is symptomatic or if an intervention is planned. * Clinicians may choose the imaging-only pathway in patients with fragments ≤2 mm. [a] Treatment monitoring for side effects, intolerance, and compliance. + The panel recommends reintervention; however close follow-up may be considered for some patients at high risk of reintervention according to the clinician's preference.

beverages, and the conflicting results may be related to the fact that urinary levels of lithogenic risk factors were used as surrogate endpoints instead of stone onset or relapse [197,198]. The beneficial effect of fruit juices is mainly determined by the level of citrate or bicarbonate. An analysis of three Channing cohorts (194 095 participants) over median follow-up of >8 yr showed that consumption of sugar-sweetened soda and punch was associated with a higher risk of stone formation, whereas consumption of coffee, tea, beer, wine, and orange juice was associated with a lower risk [199,200].

A common-sense approach to diet should be taken, involving consumption of a mixed, balanced diet with contributions from all food groups, without any excesses [18,19,76]. Sufficient calcium intake is needed, especially for individuals on a vegetarian or vegan diet [20]. Animal protein should not be consumed in excess [14,201] and limited to 0.8–1.0 g/kg body weight. Excessive consumption of animal protein has several effects that favour stone formation, including hypocitraturia, low urine pH, hyperoxaluria, and hyperuricosuria.

Calcium stones are the most common stones in the modern era. The longer a patient is followed after a first episode, the greater is the chance of a stone forming again, with incidence rates of approximately 30%, 50%, and 75% at 5, 10, and 15 yr, respectively, from the initial diagnosis [15,202]. Once

a patient has experienced recurrence, the likelihood of a new episode increases, with an incidence of approximately 43–48% at 3 yr [59,61,63]. The level of evidence of studies on the treatment of calcium stones is high, as prospective randomised studies have been published for each treatment [15,19,21,59,61–65,69–71,81,197,198,201]. Many of the subjects in these trials had idiopathic hypercalciuria, sometimes concomitant to other mild metabolic abnormalities. However, treatment was nonselective in many of the trials. In patients with new-onset lithiasis followed over a 5-yr period, water intake to achieve a target of daily production of more >2 l of urine, resulted in an absolute 15% reduction in recurrence in comparison to usual fluid intake[15]. In a group of patients with recurrent calcium urolithiasis who consumed a diet with normal calcium intake (1200 mg/d) and restricted sodium (50 mmol/d) and protein intake (52 g/d) for 5 yr, the recurrence rate was 18% lower than in a group in which patients with the same profile consumed a diet limited only in calcium (400 mg/d) for the same period [201]. Drug treatment of calcium stones is also supported by RCTs. Patients with calcium oxalate stones and hypercalciuria, hypocitraturia, and hyperuricosuria benefit from urine alkalisation [69–71]. One RCT showed that for calcium oxalate stone formers with hyperuricosuria and no other metabolic abnormalities, allopurinol was effective in reducing urinary uric acid and stone recurrence in comparison to no treatment [81]. Febuxostat is strongly recommended as a second-line treatment for hyperuricosuria.

As mentioned, isolation of a single parameter for monitoring of changes in this parameter after targeted therapy and in the subsequent risk of stone recurrence is extremely difficult to achieve. This difficulty, as well as the diversity of urolithiasis patients and poor study designs, often leads to conflicting results. One study [70], in contrast to others [69,71] showed no benefit from the use of sodium potassium citrate in patients with hypocitraturia, particularly when compared with ample fluid intake and dietary restrictions. In this study, the total population sample was small, only 50% of patients had low baseline urinary citrate levels, and the sodium used in the preparations may have inhibited the energising effect of potassium.

Thiazides are a group of drugs that have been studied extensively in the treatment and prevention of calcium urolithiasis whose value has recently been questioned. A meta-analysis of eight RCTs demonstrated that the use of thiazides resulted in a 57% reduction in the rate of stone recurrence [58]. The result is mainly driven by randomised studies that showed that thiazides reduced hypercalciuria [64,65] and prevented recurrences in patients with calcium urolithiasis [59,61,63,64]. The patients in these studies were a mixed population of hypercalciuric and normocalciuric stone formers, so it is difficult to discern whether the treatment is more beneficial in one group. Two randomised trials failed to show a benefit with thiazide use [60,65]. This negative result may be because of the shorter treatment duration and shorter follow-up, as studies with follow-up and treatment duration longer than 3 yr have shown an advantage with this medication class. One recent RCT concluded that hydrochlorothiazide does not differ substantially from placebo in preventing the recurrence of kidney stones in patients at high risk of recurrence [67]. However, the study was not powered to show any difference between hydrochlorothiazide and placebo [203]. According to the protocol [203], the objective was to investigate the existence of a dose-response relationship, and the study results did show a linear trend for the effect of three different hydrochlorothiazide doses (12.5, 25, and 50 mg/d) on stone recurrence. In addition, hypercalciuria levels in the study population were significantly lower than the threshold recommended in the EAU guidelines for hydrochlorothiazide administration (Fig. 3).

5. Conclusions

The patient's medical history and the stone composition will determine the risk group for the recurrence of urolithiasis to which a patient is assigned after their initial treatment. For every patient with urolithiasis, an attempt to analyse the stone and general instructions on the prevention of recurrence are recommended. Identifying and correcting causative factors are a cornerstone in preventing the recurrence of urolithiasis.

Every patient should undergo baseline metabolic screening, while patients at high risk of recurrence and complications should undergo extensive metabolic screening and receive targeted therapy. Patients at high risk of relapse and complications, especially those who do not comply with their medication, should be closely monitored.

Author contributions: Andreas Skolarikos had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Skolarikos, Somani, Neisius, Jung, Petřík, Tailly, Davis, Tzelves, Geraghty, Lombardo, Gambaro.
Acquisition of data: Skolarikos, Gambaro.
Analysis and interpretation of data: Skolarikos, Gambaro.
Drafting of the manuscript: Skolarikos, Gambaro.
Critical revision of the manuscript for important intellectual content: Skolarikos, Somani, Neisius, Jung, Petřík, Tailly, Davis, Tzelves, Geraghty, Lombardo, Gambaro.
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Supplementary material

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