

# EAU Guidelines on Urolithiasis

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# 1. INTRODUCTION

## 1.1 Aims and scope

The European Association of Urology (EAU) Urolithiasis Guidelines Panel has prepared these guidelines to help urologists assess evidence-based management of stones/calculi in the urinary tract and incorporate recommendations into clinical practice. This document covers most aspects of the disease, which is still a cause of significant morbidity despite technological and scientific advances. The Panel is aware of the geographical variations in healthcare provision. In addition, information on the management of bladder stones is also included in these Guidelines.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients but rather help to focus decisions – also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

## 1.2 Panel composition

The EAU Urolithiasis Guidelines Panel consists of an international group of clinicians with expertise in this area. All experts involved in the production of this document have submitted potential conflicts of interest, which can be viewed on the EAU website Uroweb: <http://uroweb.org/guideline/urolithiasis/>.

## 1.3 Available publications

A quick reference document (Pocket Guidelines) is available in print. This is an abridged version which may require consultation together with the full text version. Several scientific publications are available [1-3], as are a number of translations of all versions of the EAU Urolithiasis Guidelines. All documents are accessible through the EAU website Uroweb: <http://www.uroweb.org/guideline/urolithiasis/>.

An EAU Guidelines App for iOS and Android devices is also available, containing the Pocket Guidelines, interactive algorithms and calculators, clinical decision support tools, guidelines cheat sheets, and links to extended guidelines.

## 1.4 Publication history and summary of changes

### 1.4.1 Publication history

The EAU Guidelines on Urolithiasis were first published in 2000. Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. These 2026 Urolithiasis Guidelines present a full update of the 2025 publication and have gone through a peer review process prior to publication. The Urolithiasis Guidelines will be updated in full for 2028.

### 1.4.2 Summary of changes

For the 2026 Urolithiasis Guidelines, new and relevant evidence was identified, collated and appraised through a structured assessment of the literature for all sections of the Guidelines. This resulted in the inclusion of 126 updated studies across the Guidelines. Key changes include:

- Revision of the summary of evidence and recommendations for the management of renal colic
- Revision of Section 3.4.3, on Medical expulsive therapy
- Revision of the information on antibiotic prophylaxis in Section 3.4.5, Extracorporeal shock wave lithotripsy
- Revision of the summary of evidence and recommendations for shockwave lithotripsy
- Revision of Section 3.4.6, Ureteroscopy (retrograde and antegrade)
- Revision of Section 3.4.7, Percutaneous nephrolithotomy
- Revision of the Section 3.4.8.b, Antithrombotic therapy and stone treatment
- Revision of Section 3.4.15.e, Endourological procedures – Rigid/semi-rigid ureteroscopy
- Revision of Section 3.5, Radiation exposure and protection during endourology
- Revision of Section 4.6, Disorders and diseases related to calcium stones
- Updates to Table 3.2, Stone composition
- Updates to Table 3.11, Suggested strategy for antithrombotic therapy in stone removal
- Updates to Table 4.2, Laboratory values for urinary parameters in adults
- Updates to Table 4.3, Normal values for spot urine samples: creatinine ratios (solute/creatinine) in children
- Updates to Table 4.6, Pharmacological substances used for stone prevention – characteristics, specifics and dosage
- Revised and updated references throughout the text

## 2. METHODOLOGY

### 2.1 Methods

Recommendations within the Guidelines are developed by the Panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms which accompany each Guideline statement, addresses a number of key elements:

1. the overall quality of the evidence which exists for the recommendation [4];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study-related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact and certainty of patient values and preferences on the intervention

Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower-quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference.

## 3. GUIDELINES

### 3.1 3.1 Prevalence, aetiology, risk of recurrence

#### 3.1.1 Introduction

Stone disease incidence depends on geographical, climatic, ethnic, dietary and genetic factors. The recurrence risk is basically determined by the disease or disorder causing the stone formation. Accordingly, the prevalence rates for urinary stones vary from 1% to 13% [5]. In developed countries such as Sweden, Canada or the USA, renal stone prevalence is notably high (> 10%). For some areas, an increase of more than 37% over the last 20 years has been reported [6-8]. There is emerging evidence linking nephrolithiasis to the risk of CKD [9].

Stones can be stratified into those caused by infections, non-infectious causes, genetic defects [10, 11], or adverse drug effects (drug stones) (Table 3.1). See also Section 3.2.

**Table 3.1: Stones classified by aetiology**

<b>Non-infection stones</b>		
• Calcium oxalate	• Calcium phosphate	• Uric acid • Ammonium urate*
<b>Infection stones</b>		
• Magnesium ammonium phosphate	• Highly carbonated apatite	• Ammonium urate
<b>Genetic causes</b>		
• Cystine	• Xanthine	• 2,8-Dihydroxyadenine
<b>Drug stones</b>		

\*In children in developing countries; in patients with anorexia or laxative abuse.

#### 3.1.2 Stone composition

Stone composition is the basis for further diagnostic and management decisions. Stones are often formed from a mixture of substances [12]. Table 3.2 lists the most clinically relevant substances and their mineral components.

**Table 3.2: Stone composition**

Chemical name	Mineral name [13]	Chemical formula
Calcium oxalate monohydrate	Whewellite	$\text{CaC}_2\text{O}_4 \cdot \text{H}_2\text{O}$
Calcium oxalate dihydrate	Weddelite	$\text{CaC}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$
Basic calcium phosphate	Non-stoichiometric hydroxyapatite	$\text{Ca}_x(\text{PO}_4)_y(\text{OH})_z$
Calcium hydroxyl phosphate	Hydroxyapatite	$\text{Ca}_5(\text{PO}_4)_3(\text{OH})$
$\beta$ -tricalcium phosphate	Whitlockite	$\text{Ca}_9\text{Mg}(\text{HPO}_4)(\text{PO}_4)_6$
Carbonate apatite phosphate	Dahllite	$\text{Ca}_{10}(\text{PO}_4)_6(\text{CO}_3)(\text{OH})_2$
Calcium hydrogen phosphate dihydrate	Brushite	$\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$
Calcium carbonate	Aragonite	$\text{CaCO}_3$
	Calcite	
Octacalcium phosphate	Octacalcium phosphate	$\text{Ca}_8\text{H}_2(\text{PO}_4)_6 \cdot 5\text{H}_2\text{O}$
Uric acid	Uricite	$\text{C}_5\text{H}_4\text{N}_4\text{O}_3$
Uric acid dihydrate	Tinnunculite	$\text{C}_5\text{H}_4\text{N}_4\text{O}_3 \cdot \text{C}_5\text{H}_4\text{N}_4\text{O}_3 \cdot 2\text{H}_2\text{O}$
Ammonium urate	-	$\text{NH}_4\text{C}_5\text{H}_3\text{N}_4\text{O}_3$
Sodium acid urate monohydrate	-	$\text{NaC}_5\text{H}_3\text{N}_4\text{O}_3 \cdot \text{H}_2\text{O}$
Magnesium ammonium phosphate hexahydrate	Struvite	$\text{MgNH}_4\text{PO}_4 \cdot 6\text{H}_2\text{O}$
Magnesium acid phosphate trihydrate	Newberyite	$\text{MgHPO}_4 \cdot 3\text{H}_2\text{O}$
Magnesium ammonium phosphate monohydrate	Dittmarite	$\text{MgHPO}_4 \cdot \text{H}_2\text{O}$
Cystine	-	$\text{C}_6\text{H}_{12}\text{N}_2\text{O}_4\text{S}_2$
Xanthine	-	$\text{C}_5\text{H}_4\text{N}_4\text{O}_2$
2,8-Dihydroxyadenine	-	$\text{C}_5\text{H}_4\text{N}_4\text{O}_2$
Proteins	-	-
Cholesterol	-	-
Calcite	-	-
Potassium urate	-	$\text{KC}_5\text{H}_3\text{N}_4\text{O}_3$
Trimagnesium phosphate	-	$\text{Mg}_3(\text{PO}_4)_2$
Melamine	-	$\text{C}_3\text{H}_6\text{N}_6$
Matrix	-	-
Drug stones	Active compounds crystallising in urine	-
Foreign body calculi	-	-

### 3.1.3 Risk groups for stone formation

Determination of the risk for stone formation is imperative for pharmacological treatment. Previous stone history (recurrence, regrowth, stone surgeries) is a fundamental element in determining risk for stone formation. About 50% of recurrent stone formers have just one-lifetime recurrence [8, 14]. A review of first-time stone formers calculated a recurrence rate of 26% in five years' time [15]. Highly recurrent disease is observed in slightly more than 10% of patients. Stone type and disease severity determine low- or high-risk stone formers (Table 3.3) [16-32].

However, the risk status of stone formers 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 (CKD), end-stage kidney disease (ESKD), and metabolic bone disorder (MBD) [33-35]. A comprehensive evaluation of stone risk in patients should also include the risk of developing CKD, ESKD, and MBD (Tables 3.4, 3.5, and 3.6) [33]. Although kidney stones are unlikely to be an independent, direct cause of CKD [36], urolithiasis can compromise renal function because of the renal stone (obstruction, infection), renal tissue damage due to the primary condition causing stone formation (some genetic diseases, nephrocalcinosis, enteric hyperoxaluria, etc.), or urological treatments for the condition [33]. Certain risk factors have been shown to be associated with such a risk in stone formers, as shown in Table 3.3.

**Table 3.3: High-risk stone formers [16-32, 37, 38]**

<b>General factors</b>
Early onset of urolithiasis (especially children and teenagers)
Familial stone formation
Recurrent stone formers
Short time since last stone episode
Brushite-containing stones (CaHPO <sub>4</sub> ·2H <sub>2</sub> O)
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 (CKD)
<b>Diseases associated with stone formation</b>
Hyperparathyroidism
Metabolic syndrome
Mineral Bone Disorder (MBD)
Nephrocalcinosis
Polycystic kidney disease (PKD)
Gastrointestinal diseases (i.e. enteric hyperoxaluria due to jejunio-ileal bypass, intestinal resection, Crohn's disease, malabsorptive conditions, urinary diversion, exocrine pancreatic insufficiency, and bariatric surgery).
Increased levels of vitamin D
Sarcoidosis
Spinal cord injury, neurogenic bladder
<b>Genetically determined stone formation</b>
Cystinuria (type A, B and AB)
Primary hyperoxaluria (PH)
Renal tubular acidosis (RTA) type I
2,8-Dihydroxyadeninuria
Xanthinuria
Lesch-Nyhan syndrome
Cystic fibrosis
<b>Drug-induced stone formation (see Table 4.11)</b>
<b>Anatomical abnormalities associated with stone formation</b>
Medullary sponge kidney (tubular ectasia)
Ureteropelvic junction (UPJ) obstruction
Calyceal diverticulum, calyceal cyst
Ureteral stricture
Vesico-uretero-renal reflux
Horseshoe kidney
Ureterocele
<b>Environmental and professional factors</b>
High ambient temperatures
Chronic lead and cadmium exposure

**Table 3.4: Risk factors for chronic kidney disease (CKD) and end-stage kidney disease (ESKD) in stone formers**

<b>Risk factors for CKD/ESKD in stone formers</b>
High ambient temperatures
Chronic lead and cadmium exposure
Female gender
Increased BMI
Frequent UTI
Struvite stones
Acquired single kidney
Neurogenic bladder
Previous obstructive nephropathy
Ileal conduit

Furthermore, some specific kinds of urolithiasis also carry a particular risk of developing CKD/ESKD, as shown in Table 3.5. below.

**Table 3.5: Risk factors for CKD and renal stones**

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

**Table 3.6: Risk factors for metabolic bone disease and calcium renal stones**

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

### 3.1.4 Genetic factors and testing

There are important genetic factors underlying kidney stone disease (KSD). Indeed, KSD has an estimated heritability of  $\pm 45\%$  [39], suggesting that genetic factors strongly influence this disease [40]. Monogenic forms of stones remain rare and are seen in 12–21% [41–43] of children/young adults and 1–11% [43, 44] of adults with KSD, but may enable specific patient management [43]. These figures should be taken in context, as there is substantial heterogeneity in how diagnostic variants are defined. Also, most reported studies examined selected KSD populations where a genetic diagnosis is suspected.

It is important to note that only one study has examined the differences in 24-hour urine findings between those with monogenic KSD and those without a genetic diagnosis of KSD [43]. There was no difference in 24-hour urine findings, except for urine cystine, which was significantly higher in the monogenic KSD group.

Genetic testing (in the form of a Next Generation Sequencing gene panel – see Table 3.7) should be considered in children, adults  $\leq 25$  years and adults  $> 25$  years if there is clinical suspicion of an inherited or metabolic disorder underlying the KSD. Features including recurrent ( $\geq 2$  discrete episodes), bilateral disease or a strong family history [44, 45] should prompt genetic testing. Positive genetic links between kidney stone disease and gastrointestinal diseases may implicate potential biological mechanisms in the pathogenesis of stone disease [46].

Genetic testing should be performed in combination with other metabolic testing (blood and 24-hour urine tests as detailed in Tables 4.1 and 4.2), and the patient should always have pre-genetic test counselling. Should a genetic diagnosis be made then family members should be offered screening. A nephrological consultation may also be needed.

**Table 3.7: Table of known pathogenic genes (adapted from Geraghty et al. 2024) [44]**

Gene	Associated Conditions	Recommended Treatment
<b>SLC7A9</b> <b>SLC3A1</b>	Cystinuria, cystine stones, calcium containing stones	Urinary alkalinisation; thiol-binding drugs; aggressive urinary dilution
<b>SLC7A9</b> <b>SLC3A1</b>	Cystinuria, cystine stones, calcium containing stones	Urinary alkalinisation; thiol-binding drugs; aggressive urinary dilution
<b>CYP24A1</b>	Idiopathic infantile hypercalcaemia, calcium containing stones	Avoidance of excess vitamin D; Inhibition of vitamin D synthesis e.g. Fluconazole
<b>AGXT GRHPR</b> <b>HOGA1</b>	Primary hyperoxaluria, calcium oxalate stones	Pyridoxine or lumasiran for AGXT mutations. Potassium citrate, aggressive urine dilution, limit oxalate intake
<b>CLDN16</b> <b>CLDN19</b>	Familial hypomagnesaemia, calcium containing stones	Magnesium replacement; caution with vitamin D replacement; assess for ocular phenotypes with CLDN19 variants
<b>CASR</b>	Autosomal dominant hypocalcaemia, calcium containing stones	Avoid overzealous correction of hypocalcaemia
<b>SLC34A3</b> <b>SLC34A1</b> <b>PHEX</b>	Hypophosphataemic rickets, calcium containing stones	Screen for osteomalacia; phosphate replacement without vitamin D
<b>CLCN5 OCRL</b>	Dent disease, calcium containing stones	Screen for osteomalacia, vitamin D, phosphate and bicarbonate replacement if needed; thiazide diuretics

<b>SLC22A12</b> <b>SLC2A9</b>	Renal uric acid wasting, uric acid stones	Urinary alkalinisation; allopurinol or febuxostat
<b>BSND CASR</b> <b>CLCN5</b> <b>CLCNKB</b> <b>KCNJ1</b> <b>SLC12A1</b>	Bartter syndrome, calcium containing stones	electrolyte replacement as required, NSAIDs, aldosterone antagonists,
<b>HNF4A</b>	Fanconi syndrome, nephrocalcinosis	Refer to nephrology
<b>XDH MOCOS</b>	Xanthinuria, xanthine stones	Low purine diet
<b>ATPV0A4</b> <b>ATP6V1B1</b> <b>CA2 SLC4A1</b> <b>WDR72</b>	Renal tubular acidosis, calcium containing stones	Sodium bicarbonate or alkaline citrate; hearing screen; assessment for osteomalacia/osteopetrosis
<b>APRT</b>	Adenine phosphoribosyl transferase deficiency, 2,8-dihydroxyadenine stones	Allopurinol or febuxostat

### 3.2 Classification of stones

Urinary stones can be classified according to size, location, X-ray characteristics, aetiology of formation, composition, and risk of recurrence [2, 8].

#### 3.2.1 Stone size

Stone size can be reported in a single, two or three dimensions. Currently, the guidelines still use the linear measurement of cumulative stone diameter to stratify stones in <5mm, 5–10mm, 10–20mm, and >20mm for use in the treatment algorithm. A systematic review (SR) and meta-analysis (MA) by the guidelines panel has demonstrated that volume is a better predictor of stone free status after stone surgery, several practical limitations such as accurate measurement, standardised reporting and the lack of cut-off values guiding treatment, currently prevent its clinical adoption [47].

#### 3.2.2 Stone location

Stones can be classified according to anatomical position: upper, middle, or lower calyx; renal pelvis; upper, middle, or distal ureter; and urinary bladder.

#### 3.2.3 X-ray characteristics

Stones can be classified according to plain X-ray appearance [kidney-ureter-bladder (KUB) radiography] (Table 3.8), which varies according to mineral composition [48]. Non-contrast-enhanced computed tomography (NCCT) can be used to classify stones according to density, inner structure, and composition, which can affect treatment decisions (Section 3.3) [49, 50].

**Table 3.8: X-ray characteristics**

<b>Radiopaque</b>	<b>Poor radiopacity</b>	<b>Radiolucent</b>
Calcium oxalate dihydrate	Magnesium ammonium phosphate	Uric acid
Calcium oxalate monohydrate	Cystine	Ammonium urate
Calcium phosphate		Xanthine
		2,8-Dihydroxyadenine
		Drug stones (Section 4.11)

### 3.3 Diagnostic evaluation

#### 3.3.1 Diagnostic imaging

The most appropriate imaging modality will be determined by the clinical scenario, which will differ depending on whether a ureteral or a renal stone is suspected.

Standard evaluation includes a detailed medical history and physical examination. Patients with ureteral stones usually present with loin pain, vomiting and sometimes pyrexia, but may also be asymptomatic [51]. Immediate evaluation is indicated in patients with a solitary kidney, pyrexia or when there is doubt regarding a diagnosis of renal colic. Ultrasound (US) should be used as the primary diagnostic imaging tool, although pain relief, or any other emergency measures, should not be delayed by imaging assessments. Ultrasound is safe (no risk of

radiation), reproducible and inexpensive. It can identify stones located in the calyces, pelvis, and ureteropelvic junction (UPJ) and vesicoureteral junctions (US with filled bladder), as well as in patients with upper urinary tract (UUT) dilatation. Ultrasound has a sensitivity of 45% and specificity of 94% for ureteral stones and a sensitivity of 45% and specificity of 88% for renal stones [52, 53].

The sensitivity and specificity of KUB is 44–77% [54]. Kidney-ureter-bladder radiography [55] is helpful in differentiating between radiolucent and radiopaque stones and could be used for comparison during follow-up.

### 3.3.1.a Evaluation of patients with acute flank pain/suspected ureteral stones

Non-contrast-enhanced computed tomography (NCCT) has become the standard for diagnosing acute flank pain and has replaced intravenous urography (IVU). Non-contrast-enhanced computed tomography (NCCT) can determine stone location, burden and density. When stones are absent, the cause of abdominal pain should be identified. In evaluating patients with suspected acute urolithiasis, NCCT is significantly more accurate than IVU or US [56].

Non-contrast-enhanced CT can detect uric acid and xanthine stones (which are radiolucent on plain films), but not indinavir stones [57]. Non-contrast-enhanced CT can determine stone density, the inner structure of the stone, skin-to-stone distance, and surrounding anatomy; all of which affect the selection of treatment modality [57-59]. The advantage of a lower radiation dose with non-contrast imaging versus contrast-enhanced CT scan must be balanced against the loss of information on renal function and urinary collecting system anatomy, but at a lower radiation dose and shorter scan time [60-63].

Radiation risk can be reduced by low-dose CT, which may, however, be difficult to implement in standard clinical practice [64-67]. In patients with a body mass index (BMI) < 30, low-dose CT has been shown to have a sensitivity of 86% for detecting ureteral stones < 3mm and 100% for calculi > 3mm [68]. An SR and MA of prospective studies [69] has shown that low-dose CT diagnosed urolithiasis with a pooled sensitivity of 93.1% (95% CI: 91.5–94.4) and a specificity of 96.6% (95% CI: 95.1–97.7%). Dual-energy CT can differentiate uric-acid-containing stones from calcium-containing stones [50].

Summary of evidence	LE
Non-contrast-enhanced CT is used to confirm stone diagnosis in patients with acute flank pain, as it is superior to IVU.	1a
CT imaging enables 3D reconstruction of the collecting system, as well as measurement of stone density and skin-to-stone distance.	2a
Consider a contrast study if stone removal is planned, and the anatomy of the renal collecting system needs to be delineated.	3

Recommendations	Strength rating
Immediate imaging is indicated with pyrexia or a solitary kidney, and when diagnosis is uncertain.	Strong
Use non-contrast-enhanced computed tomography to confirm stone diagnosis in patients with acute flank pain following initial ultrasound assessment.	Strong

### 3.3.2 Diagnostics: metabolism-related

Besides imaging, each emergency patient with urolithiasis needs a succinct biochemical work-up of urine and blood tests. At this point, no distinction is made between high- and low-risk patients for stone formation.

#### 3.3.2.a Laboratory analysis – non-emergency urolithiasis patients

Biochemical work-up is similar for all stone patients (see Section 3.3.2.c). However, if no intervention is planned, examination of sodium, potassium, C-reactive protein (CRP) and blood coagulation time can be omitted. Only patients at high risk for stone recurrence should undergo a more specific analytical programme [17]. Stone-specific metabolic evaluation is described in Chapter 4.

The easiest method for diagnosing stones is by analysis of a passed stone using a validated method as listed in Section 3.3.2.c. Once the mineral composition is known, a potential metabolic disorder can be identified.

### 3.3.2.b Analysis of stone composition

Stone analysis should be performed on all first-time stone formers.

In clinical practice, repeat stone analysis is needed in the case of:

- recurrence under pharmacological prevention;
- early recurrence after interventional therapy with complete stone clearance; and
- late recurrence after a prolonged stone-free period [70, 71].

Patients should be instructed to filter their urine to retrieve a stone fragment for analysis. Stone passage and restoration of baseline renal function should be confirmed.

The preferred analytical procedures are infrared spectroscopy (IRS) or X-ray diffraction (XRD) [72, 73]. Equivalent results can be obtained by polarisation microscopy. Chemical analysis (wet chemistry) is generally deemed to be obsolete [72-74].

### 3.3.2.c Recommendations for laboratory examinations and stone analysis [75-77]

Recommendations	Strength rating
<b>Urine</b>	
Dipstick test of spot urine sample: <ul style="list-style-type: none"><li>• red cells;</li><li>• white cells;</li><li>• nitrites;</li><li>• approximate urine pH; and</li><li>• urine microscopy and/or culture.</li></ul>	Weak
<b>Blood</b>	
Serum blood sample: <ul style="list-style-type: none"><li>• creatinine;</li><li>• uric acid;</li><li>• (ionised) calcium;</li><li>• sodium;</li><li>• potassium;</li><li>• blood cell count; and</li><li>• C-reactive protein.</li></ul>	Strong
Perform a coagulation test (partial thromboplastin time and international normalised ratio) if intervention is likely or planned.	Strong
Perform stone analysis in first-time stone formers using a valid procedure (X-ray diffraction or infrared spectroscopy).	Strong
Repeat stone analysis in patients presenting with: <ul style="list-style-type: none"><li>• recurrent stones despite drug therapy;</li><li>• early recurrence after complete stone clearance; and</li><li>• late recurrence after a long stone-free period because stone composition may change.</li></ul>	Strong

### 3.3.3 Diagnosis in special groups and conditions

#### 3.3.3.a Diagnostic imaging during pregnancy

In pregnant women, radiation exposure may cause non-stochastic (teratogenesis) or stochastic (carcinogenesis, mutagenesis) effects. Teratogenic effects are cumulative with increasing doses and require a threshold dose (< 50mGy is considered safe) and depend on the gestational age (minimum risk prior to the eighth week and after the 23<sup>rd</sup> week). Carcinogenesis (doses even < 10mGy present a risk) and mutagenesis (500–1,000mGy doses are required, far in excess of the doses in common radiographic studies) get worse with increasing dose, but they do not require a dose threshold and are not dependent on the gestational age [78].

There is no imaging modality that should be routinely used in pregnant women. Scientific societies and organisations agree on the safety of the diagnostic evaluation when US [79], X-ray imaging [80, 81] and MRI [82] are used as and when indicated [83-90]. A radiographic procedure should not be withheld from a pregnant woman if the procedure is clearly indicated and doing so will affect her medical care.

It is generally recommended that an investigation resulting in an absorbed dose to the foetus of > 0.5mGy requires justification.

Ultrasound (when necessary, using changes in the renal resistive index and transvaginal/transabdominal US with a full bladder) has become the primary radiological diagnostic tool when evaluating pregnant patients suspected of renal colic. However, normal physiological changes in pregnancy can mimic ureteral obstruction [83, 87, 88].

Magnetic resonance imaging can be used, as a second-line option [84], to define the level of urinary tract obstruction and to visualise stones as a signal void [91]. The use of gadolinium is not routinely recommended in pregnancy to avoid toxic effects on the embryo [83].

For the detection of urolithiasis during pregnancy, low-dose CT is associated with a higher positive predictive value (95.8%), compared to MRI (80%) and US (77%). As per White et al., low-dose CT offers improved diagnostic accuracy that can avoid negative interventions such as ureteroscopy [92]. Although low-dose CT protocols reduce radiation exposure, judicious use is currently recommended in pregnant women as a last-line option [83].

Summary of evidence	LE
Only low-level data exist for imaging in pregnant women supporting US and MRI.	3

Recommendations	Strength rating
Use ultrasound as the preferred method of imaging in pregnant women.	Strong
Use magnetic resonance imaging as a second-line imaging modality in pregnant women.	Strong
Use low-dose computed tomography as a last-line option in pregnant women.	Strong

### 3.3.3.b Diagnostic imaging in children

Children with urinary stones have a high risk of recurrence; therefore, standard diagnostic procedures for high-risk patients apply, including a valid stone analysis (Section 3.1.3 and Chapter 4). The most common non-metabolic disorders facilitating stone formation are vesicoureteral reflux (VUR), UPJ obstruction, neurogenic bladder and other voiding difficulties [93].

When selecting diagnostic procedures to identify urolithiasis in children, it should be remembered that these patients might be uncooperative, require anaesthesia and may be sensitive to ionising radiation. Again, the principle of ALARA (As Low As Reasonably Achievable) should be observed [94-97].

#### *Ultrasound*

Ultrasound is the primary imaging technique [98] in children. Its advantages are the absence of radiation and no need for anaesthesia. Imaging should include both the fluid-filled bladder with adjoining portion of the ureters, as well as the upper ureter [94]. Colour Doppler US shows differences in the ureteral jet [99] and resistive index of the arciform arteries of both kidneys, which are indicative of the grade of obstruction [100]. Nevertheless, US may fail to identify ureteral stones and provides limited information on renal function [101].

#### *Plain films (KUB radiography)*

Kidney-ureter-bladder radiography can help to identify stones and their radiopacity and facilitate follow-up.

#### *Intravenous urography*

The radiation dose for IVU is typically in the range of approximately 1–3 mSv, depending on patient age, size, and imaging protocol [102]. The need for intravenous contrast medium administration also represents an additional drawback.

#### *Non-contrast-enhanced computed tomography*

Low-dose CT protocols have been shown to significantly reduce radiation exposure [103-105]. Sedation or anaesthesia is rarely needed with modern high-speed CT equipment.

#### *Magnetic resonance urography*

Magnetic resonance urography (MRU) is generally not reliable for stone detection. However, it might provide detailed anatomical information about the urinary collecting system, the location of an obstruction or stenosis in the ureter, and renal parenchymal morphology [106].

### 3.3.3.c Summary of evidence and recommendations for diagnostic imaging in children

Summary of evidence	LE
Ultrasound is the first-line imaging modality in children when a stone is suspected. It should include the kidney, fluid-filled bladder and the ureter next to the kidney and the (filled) bladder.	2b
A kidney-ureter-bladder radiography (or low-dose NCCT) is an alternative investigation if US will not provide the required information.	2b

Recommendations	Strength rating
Complete a metabolic evaluation based on stone analysis in all children.	Strong
Collect stone material for analysis to classify the stone type.	Strong
Perform ultrasound as first-line imaging modality in children when a stone is suspected. It should include the kidney, fluid-filled bladder and the ureter.	Strong
Perform a kidney-ureter-bladder radiography (or low-dose non-contrast-enhanced computed tomography) if ultrasound will not provide the required information.	Strong

## 3.4 Disease management

The treatment of urolithiasis is based on many parameters and is individualised for each patient. Parameters such as the size, number, location and composition of the stones are the cornerstones for deciding the treatment. In addition, the morphology, shape, volume, mobility and hardness of the stone should be considered. Finally, the anatomy of the entire pelvicalyceal system should be assessed for each patient. The design of therapeutic algorithms including all the above parameters is difficult, mainly due to the great heterogeneity of stone disease between patients. Furthermore, there is a significant lack of comparative clinical studies to support the development of algorithms using parameters other than stone size and composition.

### 3.4.1 Renal colic

#### *Pain relief*

Non-steroidal anti-inflammatory drugs (NSAIDs) (including metamizole dipyrone) and paracetamol are effective in patients with acute stone colic [107] and have better analgesic efficacy than opioids [108]. Compared with ketorolac, ibuprofen is a more rapid-acting drug in controlling pain caused by renal colic, with a similar side effect profile [109].

Pain relief from intramuscular (i.m.) diclofenac compared favourably with those from intravenous (i.v.) ibuprofen and i.v. ketorolac; however, no recommendation can be given due to the way in which the results have been reported [110]. The addition of antispasmodics to NSAIDs does not result in improved pain control. Patients receiving NSAIDs are less likely to require further analgesia in the short-term. It should be taken into consideration that the use of diclofenac and ibuprofen increased major coronary events [107, 108]. Oral diclofenac in the long-term increases the risk of cardiovascular events and upper GI bleeding [111]. Patients with significant risk factors for cardiovascular events should be treated with diclofenac only after careful consideration. As risks increase with dose and duration, the lowest effective dose should be used for the shortest duration [112]. Nonsteroidal anti-inflammatory drugs may affect renal function in those patients with pre-existing decreased GFR.

Although a MA of three RCTs suggests that intradermal sterile water injections may provide effective analgesia for renal colic and could be considered in patients where NSAIDs are contraindicated (including pregnancy), it is important to emphasise that this technique is not part of current standard of care [113]. Intradermal sterile water injection may be an alternative to NSAIDs in pregnant patients or others where NSAIDs are contraindicated [114], nevertheless it is not standard treatment.

Opioids, especially pethidine, are associated with a high rate of vomiting compared to NSAIDs and carry a greater likelihood of further analgesia being required [107, 115]. If an opioid is used, it is recommended that an opioid other than pethidine be used. The combination of opioids and NSAIDs increases the analgesic effect compared to opioids alone [116]. Compared to opioids, ketamine use in the acute setting shows a longer duration of analgesia in renal colic with satisfactory safety profile [117]. Acupuncture seems to be effective in renal colic alone or in combination with analgesic drugs, but there is limited data [118, 119].

### Prevention of recurrent renal colic

Facilitation of passage of ureteral stones is discussed in Section 3.4.9. For patients with ureteral stones that are expected to pass spontaneously, NSAID tablets or suppositories (e.g. diclofenac sodium, 100–150 mg/day, 3–10 days) may help reduce inflammation and the risk of recurrent pain [120]. Although NSAIDs can affect renal function in patients with already reduced function, there is no functional effect in patients with normal renal function [121].

The systematic review and MA by Hollingsworth *et al.* [122] addressed pain reduction as a secondary outcome and concluded that medical expulsive therapy (MET) seems efficacious in reducing pain episodes in patients with ureteral stones.

If analgesia cannot be achieved medically, drainage using stenting, percutaneous nephrostomy or stone removal is indicated [123].

#### 3.4.1.a Summary of evidence and recommendations for the management of renal colic

Summary of evidence	LE
Nonsteroidal anti-inflammatory drugs are very effective in treating renal colic and are superior to opioids.	1b
For symptomatic ureteral stones, stone removal as first-line treatment is a feasible option in selected patients.	1b

Recommendations	Strength rating
Offer a nonsteroidal, anti-inflammatory as the first drug of choice, depending on cardiovascular risk factors and side effects.	Strong
Offer opioids (hydromorphone, pentazocine or tramadol) or ketamine in the acute setting as second choice.	Weak
Offer renal decompression or ureteroscopic stone removal in case of analgesia-refractory colic pain.	Strong

#### 3.4.2 Management of sepsis and/or anuria in obstructed kidney

The obstructed kidney with all signs of urinary tract infection (UTI) and/or anuria is a urological emergency. Urgent decompression is often necessary to prevent further complications in infected hydronephrosis secondary to stone-induced, unilateral or bilateral, renal obstruction.

##### Decompression

There are two options for urgent decompression of obstructed collecting systems [124]:

- placement of an indwelling ureteral stent; or
- percutaneous placement of a nephrostomy tube.

Several systematic reviews on the subject have been published, all of which emphasise that the available literature comparing different drainage modalities for obstructing stones with or without infection is scarce, based on small cohorts and of medium to very low quality [124, 125]. There appears to be no difference in success rate or complication rate of both procedures and there is no difference in time to defervescence in the population presenting with fever. Both meta-analyses identified patients receiving a nephrostomy tube to have a longer stay in the hospital. Based on the available data, a double-J (DJ) stent has a more negative impact on the patients' quality of life (QoL) in comparison with a nephrostomy tube, which can be explained mainly by the stent-related symptoms that patients experience [125, 126].

Definitive stone removal should be delayed until the infection is cleared following a complete course of antimicrobial therapy. A small RCT showed the feasibility of immediate ureteroscopic stone removal combined with an appropriate antibiotic regimen at the cost of longer hospital stay and higher analgesic requirements [127].

##### Further measures

Along with urgent decompression of the obstructed and infected urinary collecting system, both urine and blood samples should be sent for culture-antibiogram sensitivity testing and antibiotics should be initiated immediately [128, 129]. The regimen should be re-evaluated in the light of the culture-antibiogram results. Although clinically well accepted, the impact of a repeat culture and antibiogram test on treatment outcome has not yet been evaluated [130]. Intensive care might become necessary.

### 3.4.2.a Summary of evidence and recommendations for the management of sepsis and anuria

Summary of evidence	LE
For decompression of the renal collecting system, ureteral stents and percutaneous nephrostomy catheters are equally effective.	1b

Recommendations	Strength rating
Urgently decompress the collecting system in case of sepsis with obstructing stones using percutaneous drainage or ureteral stenting.	Strong
Delay definitive treatment of the stone until sepsis is resolved.	Strong
Collect (again) urine for antibiogram test following decompression.	Strong
Start antibiotics immediately (+ intensive care, if necessary).	Strong
Re-evaluate antibiotic regimen following antibiogram findings.	Strong

### 3.4.3 Medical expulsive therapy

Several drug classes, including  $\alpha$ -blockers,  $\beta_3$  adrenergic receptor agonists, calcium-channel inhibitors and phosphodiesterase-5 inhibitors (PDE5Is), are used for MET [131-134]. However, these medications are used off label. A class effect of  $\alpha$ -blockers in MET has been demonstrated in MAs both in adults and children [135-138]. However, there is contradictory evidence between these studies and several well-designed, multicentre, placebo-controlled, double-blinded randomised studies showing limited, or no, benefit using  $\alpha$ -blockers, besides some advantage for distal ureteral stones > 5mm [139-142]. An SR has demonstrated that combination MET therapy of alpha blockers combined with PDEI-5, corticosteroids or phytotherapy may be more beneficial than alpha blockers alone for MET [143]. The Panel concludes that MET using  $\alpha$ -blockers seems efficacious in the treatment of patients with distal ureteral stones >5mm who are amenable to conservative management. Most recent studies show efficacy for MET for stones between 5–10mm. Medical expulsive therapy in special situations is addressed in the relevant chapters. Silodosin seems to be more effective than tamsulosin as MET [144, 145].

#### 3.4.3.a Summary of evidence and recommendations for medical expulsive therapy

Summary of evidence	LE
Medical expulsive therapy seems to be efficacious for treating patients with ureteral stones who are amenable to conservative management. The greatest benefit might be among those with > 5 mm (distal) ureteral stones.	1a
Combination of $\alpha$ -blockers with other agents (PDE5I, corticosteroids and phytotherapy) may be more effective than monotherapy alone.	1a
$\alpha$ -blockers increase stone expulsion rates in distal ureteral stones > 5mm.	1a
A class effect of $\alpha$ -blockers has been demonstrated.	1a

Recommendation	Strength rating
Offer $\alpha$ -blockers as medical expulsive therapy as one of the treatment options for distal ureteral stones 5–10mm.*	Strong

\*  $\alpha$ -blockers are an off-label treatment

### 3.4.4 Chemolysis

#### Percutaneous irrigation chemolysis

For practical reasons, percutaneous chemolysis is nowadays rarely used. Percutaneous irrigation chemolysis may be an option for infection stones and theoretically also for uric acid stones. For dissolution of struvite stones, Suby's G solution (10% hemiacidrin; pH 3.5–4) can be used. The method has been described in case series and literature reviews [146].

### Oral chemolysis

Stones composed of uric acid, but not sodium or ammonium urate stones, can be dissolved by oral chemolysis. Prior stone analysis may provide information on stone composition. Urinary pH measurement and X-ray characteristics can provide information on the type of stone.

Oral chemolysis is based on alkalinisation of urine by application of alkaline citrate or sodium bicarbonate. The pH should be adjusted to 7.0–7.2. Chemolysis is more effective at a higher pH, which might, however, promote calcium phosphate stone formation. Patients will need to adjust the dosage of alkalinising medication by self-monitoring the pH of their urine. A systematic review shows a complete or partial dissolution in 80.5%, a discontinuation rate of 10.2% and 15.7% requiring further intervention [147].

In the case of uric acid obstruction of the collecting system, oral chemolysis in combination with urinary drainage is indicated. A combination of alkalinisation with tamsulosin can increase the frequency of spontaneous passage of distal ureteral uric acid stones as shown in one RCT for stones > 5mm [148]. Additional SWL might help to improve the results, but evidence is weak [149].

#### 3.4.4.a Summary of evidence and recommendations for chemolysis

Summary of evidence	LE
Irrigation chemolysis has been used in limited clinical settings to dissolve struvite stones.	3
Uric acid stones can be dissolved based on oral alkalinisation of the urine above 7.0.	3
For obstructing uric acid stones, a combination of oral chemolysis with tamsulosin is more effective than each substance alone, particularly in stones > 8 mm.	1b

Recommendations (oral chemolysis of uric acid stones)	Strength rating
Inform the patient how to monitor urine pH by dipstick and to modify the dosage of alkalinising medication according to urine pH, as changes in urine pH are a direct consequence of such medication.	Strong
Carefully monitor patients during and after oral chemolysis of uric acid stones.	Strong
Combine oral chemolysis with tamsulosin* in case of (larger) ureteral stones (if active intervention is not indicated).	Weak

\*  $\alpha$ -blockers are an off-label treatment

#### 3.4.5 Extracorporeal shock wave lithotripsy (SWL)

The success of SWL depends on the efficacy of the lithotripter and the following factors:

- size, location (ureteral, pelvic or calyceal) and composition (hardness) of the stones (Section 3.4.8.d);
- patient's habitus (Section 3.4.10.c);
- performance of SWL (best practice, see below).
- 

Each of these factors significantly influences the retreatment rate and outcome of SWL.

#### Best clinical practice

##### Stenting

Routine use of internal stents before SWL neither improves stone-free rates (SFRs), nor lowers the number of auxiliary treatments. It may, however, reduce the formation of steinstrasse [150-152].

##### Pacemaker

Patients with a pacemaker can be treated with SWL, provided that appropriate technical precautions are taken. Patients with implanted cardioverter-defibrillators must be managed with special care (firing mode temporarily reprogrammed during SWL treatment). However, this might not be necessary with new-generation lithotripters [153].

##### Shock wave rate

Lowering shock wave frequency from 120 to 60–90 shock waves/min. improves SFRs [154-162]. Ultraslow frequency of 30 shock waves/min. may increase SFR [163]. Tissue damage increases with shock wave frequency [164-167].

#### *Number of shock waves, energy setting and repeat treatment sessions*

The number of shock waves that can be delivered at each session depends on the type of lithotripter and shock wave power. There is no consensus on the maximum number of shock waves [168]. Starting SWL on a lower energy setting with stepwise power (and SWL sequence) ramping can achieve vasoconstriction during treatment [164], which prevents renal injury [169-171]. Animal studies [172] and a prospective randomised study [173] have shown better SFRs (96% vs. 72%) using stepwise power ramping, but no difference has been found for fragmentation or evidence of complications after SWL, irrespective of whether ramping was used [174, 175].

There are no conclusive data on the intervals required between repeated SWL sessions. However, clinical experience indicates that repeat sessions are feasible (within one day for ureteral stones) [176].

#### *Improvement of acoustic coupling*

Proper acoustic coupling between the cushion of the treatment head and the patient's skin is important. Defects (air pockets) in the coupling gel deflect 99% of shock waves [177]. Gentle swiping between the coupled therapy head and the patient's skin helps remove air bubbles and improves the coupling [178]. Ultrasound gel is probably the most widely used lithotripsy coupling agent [179].

#### *Procedural control*

Results of treatment are operator-dependent, and experienced clinicians obtain better results. During the procedure, careful imaging control of localisation contributes to outcome quality [180].

#### *Pain Control*

Careful control of pain during treatment is necessary to limit pain-induced movements and excessive respiratory excursions [181-184].

#### *Antibiotic prophylaxis*

Standard antibiotic prophylaxis before SWL is not recommended in patients with preoperative sterile urine, even if a ureteral catheter or nephrostomy tube is present [76, 185, 186]. The results of the APPEAL trial, a large multi-centre, well-designed RCT on antibiotic prophylaxis for SWL that may provide more information, are eagerly awaited [187].

#### *Medical therapy after extracorporeal shock wave lithotripsy*

Despite conflicting results, most RCTs and several MAs support MET after SWL for ureteral or renal stones as an adjunct to expedite expulsion and increase SFRs. Medical expulsion therapy might also reduce analgesic requirements [188].

#### *Post-treatment management*

Mechanical percussion and diuretic therapy can significantly improve SFRs and accelerate stone passage after SWL [189].

#### *Complications of extracorporeal shock wave lithotripsy*

Compared to percutaneous nephrolithotomy (PCNL) and ureteroscopy (URS), there are fewer overall complications with SWL [190] (Table 3.9). In an MA of 115 RCTs 18.43% of Clavien I–II complications and 2.48% of Clavien III–IV complications occurred [190]. The relationship between SWL and hypertension or diabetes is unclear. Published data are contradictory, although no evidence exists supporting the hypothesis that SWL may cause long-term adverse effects [191-197].

**Table 3.9: Shock wave lithotripsy-related complications**

Complications		%	Reference
Related to stone fragments	Steinstrasse	4%	[198-200]
	Macroscopic haematuria	17.2%	[190]
	Pain	12.1%	[190]
	Regrowth of residual fragments	21–59	[201, 202]
	Auxiliary procedure	6.9%	[190]
	Renal colic	2–4%	[203]

Infectious	Bacteriuria in non-infection stones		7.7–23%	[201-204]
	Sepsis		0.15%	[190]
Tissue effect	Renal	Haematoma, symptomatic	0.21%	[190]
		Haematoma, asymptomatic	1.2%	[190]
	Cardiovascular	Dysrhythmia	11–59%	[201, 203]
		Morbid cardiac events	Case reports	[201, 203]
	Gastrointestinal	Bowel perforation	Case reports	[205]
		Liver, spleen haematoma	Case reports	[205-208]

### 3.4.5.a Summary of evidence and recommendations for shock wave lithotripsy

Summary of evidence	LE
Stepwise power ramping prevents renal injury.	1b
Clinical experience has shown that repeat sessions are feasible (within one day for ureteral stones).	4
Optimal shock wave frequency is 1.0–1.5Hz.	1a
Proper acoustic coupling between the cushion of the treatment head and the patient's skin is important.	2
Careful imaging control of localisation of the stone contributes to outcome of treatment.	2a
Careful control of pain during treatment is necessary to limit pain-induced movements and excessive respiratory excursions.	1a
An RCT found only small, mostly non-significant reductions in postoperative infections with a modest absolute decrease in pyelonephritis when using antibiotic prophylaxis for ESWL, the clinical relevance of which is limited by current EU fluoroquinolone restrictions.	1a

Recommendations	Strength rating
Ensure correct use of the coupling agent, because this is crucial for effective shock wave transmission.	Strong
Maintain careful fluoroscopic and/or ultrasonographic monitoring during shock wave lithotripsy (SWL).	Strong
Use proper analgesia, because it improves treatment results by limiting pain-induced movements and excessive respiratory excursions.	Strong
Do not use antibiotic prophylaxis for ESWL in patients with sterile urine. Prescribe antibiotic prophylaxis only in the case of suspected or diagnosed infected stones or bacteriuria.	Strong

### 3.4.6 Ureteroscopy (retrograde and antegrade)

The current standard for rigid ureteroscopes is a tip diameter of < 8 French (Fr). Rigid URS can be used for the whole ureter [191]. However, technical improvements, as well as the availability of digital scopes, also favour the use of flexible ureteroscopes in the ureter [209].

Percutaneous antegrade removal of ureteral stones is a consideration in selected cases, i.e. large (> 15mm), impacted proximal ureteral calculi in a dilated renal collecting system [210, 211], or when the ureter is not amenable to retrograde manipulation [212].

#### *Ureteroscopy for renal stones: Retrograde Intrarenal Surgery (RIRS)*

Technical improvements including endoscope miniaturisation, improved deflection mechanism, enhanced optical quality and tools, and introduction of disposables have led to an increased use of URS for both renal and ureteral stones. Major technological progress has been achieved for RIRS. A systematic review addressing renal stones > 2cm showed a cumulative SFR of 91% with 1.45 procedures/patient; 4.5% of the complications were > Clavien 3 [213, 214]. Digital scopes demonstrate shorter operation times due to the improvement in image quality [215].

Stones that cannot be extracted directly must be disintegrated. It can be difficult to access stones within the lower renal pole for disintegration [216]. An SR and MA found that relocation of lower pole stones <2cm to a more favourable position increased SFR[217].

#### *Best clinical practice in ureteroscopy*

##### *Access to the upper urinary tract*

Most interventions are performed under general anaesthesia, although local or spinal anaesthesia is possible [218]. Intervention under intravenous sedation is possible for female patients with distal ureteral stones [219]. Smaller calibre (4.5/6 Fr) semirigid ureteroscope was associated with significantly higher SFR, lower rates of ureteric injury and shorter hospital stay [220].

Patients are traditionally positioned in lithotomy position. SR and MA on the effect of 10–20 degrees anti-Trendelenburg position show that anti-Trendelenburg position is related to lower retropulsion and higher SFR in ureteric stone treatment [221] and Trendelenburg position is related to migration of stones to upper pole and facilitates/is related to high success rate in RIRS [222].

Antegrade URS is an option for large, impacted, proximal ureteral calculi [211, 223]. Reduction of flexible ureteroscope diameter may provide similar vision, deflection and manoeuvrability to standard flexible ureteroscopes potentially with improved ureteric access [224]. Disposable ureteroscopes provide similar safety and clinical effectiveness to reusable scopes [225]. Concerns regarding cost-effectiveness and environmental sustainability remain [220, 226-228].

##### *Safety aspects*

Although a MA has demonstrated that a fluoroscopy-free approach can achieve similar results in flexible ureteroscopy [229, 230] fluoroscopic equipment must be available in the operating room. The Panel recommends placement of a safety wire, even though some groups have demonstrated that ureteroscopy can be performed without it [231-233].

Prior rigid URS can be helpful for optical dilatation followed by flexible URS, if necessary. If ureteral access is not possible, insertion of a JJ stent followed by URS after seven to fourteen days offers an alternative [234]. Bilateral URS during the same session is feasible resulting in equivalent-to-lower SFRs, but slightly higher overall complication rates (mostly minor, Clavien 1 and 2) [235, 236].

Difficult lower pole anatomy such as steep infundibulopelvic angle predisposes to failure during RIRS [237].

While an *in vitro* study demonstrated that a single-use flexible ureteroscope can be more helpful in reaching a difficult lower pole calyx, several clinical case-control studies have shown that disposable flexible ureteroscopes are equally suitable for treating lower pole stones [238].

A fiberoptic reusable flexible ureteroscope can be more helpful in reaching a difficult lower pole calyx when compared with a single use flexible ureteroscope due to differences in flexibility and manoeuvrability to digital scopes [239].

Prolonged operative times are linked to increased complication rates in ureteroscopy, and efforts must be made to keep it below 90 minutes [240].

During ureteroscopy, intrarenal pressure (IRP) rises above physiologic levels ( $\pm 0-20$ cm H<sub>2</sub>O) due to irrigation and scope manipulation; sustained elevations near or above  $\pm 30$ mmHg ( $\pm 41$ cm H<sub>2</sub>O) are associated with pyelovenous backflow and infectious risk, with some data suggesting backflow can begin at even lower pressures, depending on papillary morphology [241, 242].

Real-time pressure-sensing ureteroscopes have shown how inflow rate, working-channel occupancy and device size dynamically drive IRP intraoperatively [243]. Ureteral access sheaths (UAS) improve outflow. Adding active suction (vacuum-assisted/flexible navigable suction UAS) can produce rapid pressure drops and reduce time spent above backflow pressure thresholds while simultaneously evacuating debris ('dust'), thereby improving visualisation [244, 245].

Several studies on stone treatment in selected patients show equal SFRs, but better perioperative outcome (shorter OR time, lower risk of postoperative fever, lower Hb drop) for the patients treated with active suction/negative-pressure UAS [246-254]. The results of suction assisted ureteroscopy are similar to mPCNL, despite a significantly longer operative time [253].

Laser lithotripsy converts most energy into heat, so intraluminal temperatures can surpass cytotoxic thresholds ( $\pm 43^{\circ}\text{C}$ ) within seconds if irrigation is inadequate. Higher power, longer activation and confined spaces are related to increased temperature. Adequate continuous irrigation mitigates thermal rise, but high inflow alone may raise IRP unless outflow is secured with UAS or suction [254-256].

Both Ho:YAG and thulium fiber lasers can generate injurious temperatures. *In vivo* monitoring confirms clinically relevant intrarenal temperature spikes during flexible URS, underscoring the need to balance laser settings with irrigation and outflow [257, 258].

In practice, pairing moderated inflow with an access sheath – preferably with controllable suction – helps keep IRP below  $\pm 30\text{mmHg}$  and intraluminal temperatures below injury thresholds while maintaining visibility and efficient fragment clearance [241, 243-249, 251, 252, 254-257, 259-261].

#### *Ureteral access sheaths*

Hydrophilic-coated ureteral access sheaths, which are available in different calibres (inner diameter from 9 F upwards), can be inserted (via a guide wire) with the tip placed in the proximal ureter.

Ureteral access sheaths allow easy multiple access to the UUT and therefore can significantly facilitate URS. The use of ureteral access sheaths improves vision by establishing a continuous outflow, decreases intrarenal pressure and potentially reduces operating time [262, 263].

The insertion of ureteral access sheaths may lead to ureteral damage. The risk is lowest in pre-stented systems [264]. No data on long-term side effects are available [213, 264]. Whilst larger cohort series showed no difference in SFRs and ureteral damage (stricture rates of about 1.8%), they did show lower postoperative infectious complications [265, 266]. Increasing sheath size directly determines higher grades of ureteral injury rates in patients who were not previously stented, but there is no difference in long-term stricture rates [267]. The use of a ureteral access sheath is safe when correctly used and applied and can be useful for large and multiple renal stones or if long procedural time is expected [268].

#### *Stone extraction*

The aim of URS is complete stone removal. ‘Dust and go’ strategies should be limited to the treatment of large (renal) stones [269]. Aside from that, stones or stone fragments can be extracted by active suction through the working channel in the ureteroscope or vacuum access sheath. Stones can also be extracted by endoscopic forceps or baskets. Only baskets made of nitinol can be used for flexible URS [270].

#### *Intracorporeal lithotripsy*

Historically, Ho:YAG has been the only laser technology for stones available and remained the gold standard for lithotripsy until newer technologies like thulium fiber laser and pulsed Thulium:YAG entered the market [271, 272]. Compared to low-power lasers, high-power laser reduces procedural time although the reported difference in clinical outcomes was non-significant and based on a low level of evidence [273, 274]. However, the only RCT to date shows no clinical difference regarding SFR or operative time [275]. One RCT comparing conventional (baskets + dusting) and Moses (pop-dusting) holmium lasers during flexible ureteroscopy (FURS) in the treatment of 2–3cm renal calculi found that an increase in stone volume can decrease the SFR and prolong the operation time, and use of a Moses laser can shorten the operation time [274, 276]. Thulium fiber laser (TFL) for stone disease has a promising role and offers good clinical outcomes, which seem to be comparable to Ho:YAG laser (holmium) laser [277-279]. A MA could not demonstrate the superiority of TFL over Ho:YAG, although the operative time to achieve this SFR seems to be shorter with the use of TFL [280]. Another SR and MA found higher SFR, shorter OR time and a shorter length of stay (LOS), but higher sepsis rates for TFL group [281]. When a laser is not available, pneumatic and ultrasonic systems can be used with high disintegration efficacy in rigid URS [282, 283]. However, stone migration into the kidney is a common problem, which can be prevented by the placement of special antimigration tools proximal to the stone [284]. Medical expulsion therapy following Ho:YAG laser lithotripsy increases SFRs and reduces colic episodes [285].

Pressurised fluid in ureteroscopy is needed for flow, to wash debris, turbid fluids and stone dust. But increased intrarenal pressure is also a risk for pyelovenous reflux inducing infections or mechanical damage. Several irrigation methods deliver irrigation fluid at different pressures, depending on different parameters to produce pressure as gravity, automated pressure, pressure bags, hand pumps, etc. A randomised trial found IRP during RIRS to be lower with pressure bag irrigation fluid compared to gravity combined with hand pump [286]. An RCT shows that higher pressure leads to more absorption of irrigation fluid [287].

Including suction in ureteroscopy and RIRS has rapidly expanded since 2020. Suction can be applied through the working channel of a rigid or flexible scope, or at the UAS. The design of the UAS has been adapted to facilitate a flexible distal part to be brought directly to the stone in every location in the kidney. Both suction techniques change the concept of retrograde ureteroscopy or RIRS. An SR and MA for several forms of suction in ureteroscopy combined found suction to be related to higher SFR, lower complication rates and shorter length of stay [288].

#### *Stenting before and after URS*

Routine stenting is not necessary before URS. Despite a lack of RCTs on this subject, a MA has been performed, demonstrating that pre-stenting may improve the SFR of ureteroscopic treatment of renal stones, but not of ureteral stones [289, 290]. Although it may facilitate ureteroscopic management of stones and increase success in access sheath placement, intraoperative complications were not significantly different [289, 291]. One should also consider that pre-stenting also causes the patient to experience stent-related symptoms during the time the stent is indwelling prior to a procedure. Several retrospective studies have found a relationship between longer preoperative stent indwelling time and postoperative infectious complications [292, 293].

Randomised prospective trials have found that routine stenting after uncomplicated URS (complete stone removal) is not necessary. Stenting might be associated with higher postoperative morbidity and costs [294, 295]. Smaller diameter ureteric stents may reduce urinary symptoms and patient-reported pain [296]. Stents on a string after uncomplicated URS result in shorter indwelling time and better patient-reported outcome measures (PROMS) than standard stents [297, 298]. A ureteral catheter with a shorter indwelling time (one day) may also be used, with similar results [299].

Stents should be inserted in patients who are at increased risk of complications (e.g. ureteral trauma, residual fragments, bleeding, perforation, UTIs or pregnancy), and in all doubtful cases, to avoid stressful emergencies. The ideal duration of stenting is not known and depends on the clinical context on which it was inserted. A shorter duration of three days compared to seven days leads to improved urinary, pain and general health scores [300].  $\alpha$ -blockers can reduce the morbidity of ureteral stents and increase tolerability [301].

#### *Medical expulsive therapy before and after ureteroscopy*

Medical expulsive therapy before URS might reduce the risk for intraoperative ureteral dilatation, protect against ureteral injury when using access sheaths and increase SFRs at four weeks after URS [302-304].

Medical expulsion therapy following Ho:YAG laser lithotripsy accelerates the spontaneous passage of fragments and reduces episodes of colic [285].

#### *Complications of ureteroscopy*

The overall complication rate after URS is 4–25% [305, 306]. Most complications are minor and do not require intervention. Urosepsis is a severe complication with a risk up to 5% [306-308]. Ureteral avulsion is a rare but severe complication with a risk of 0.04–0.9% [306, 308], with ureter stricture rate after URS found to be between 3% [308] and 4.9% [309]. Previous perforations, preoperative positive urine cultures, comorbidities and longer operation time are the most important risk factors for complications [240, 310, 311]. Infectious complications following URS can be minimised using prophylactic antibiotics, limiting stent dwell and procedural time, identification and treatment of UTI, and careful planning for patients with large stone burden and multiple comorbidities [312].

High intrarenal pressure (IRP) predisposes to URS complications, and measures should be used to reduce IRP [313].

### 3.4.6.a Summary of evidence and recommendations for retrograde URS, RIRS and antegrade ureteroscopy

Summary of evidence	LE
In uncomplicated URS, a post-procedure stent need not be inserted.	1a
In URS, pre-stenting has been shown to improve outcomes for renal stones.	2a
An $\alpha$ -blocker can reduce stent-related symptoms and colic episodes after URS.	1a
The most effective lithotripsy systems for flexible ureteroscopy are the Ho:YAG and the thulium fiber laser (TFL).	2a
Pneumatic and ultrasonic systems can be used with high disintegration efficacy in rigid URS.	2a
Percutaneous antegrade removal of proximal ureter stones or laparoscopic ureterolithotomy are feasible alternatives to retrograde ureteroscopy, in selected cases.	1b
Pretreatment of patients undergoing URS with an $\alpha$ -blocker one week prior to the procedure reduces the need for active dilatation and increases the SFR.	1a

Recommendations	Strength rating
Use holmium: yttrium-aluminium-garnet (Ho: YAG) or thulium fiber laser (TFL) laser lithotripsy for (flexible) ureteroscopy (URS).	Strong
Perform stone extraction only under direct endoscopic visualisation of the stone.	Strong
Do not insert a stent in uncomplicated cases.	Strong
Offer medical expulsive therapy for patients suffering from stent-related symptoms and after laser lithotripsy to facilitate the passage of fragments.	Strong
Use percutaneous antegrade removal of ureteral stones as an alternative when shock wave lithotripsy (SWL) is not indicated or has failed, and when the upper urinary tract is not amenable to retrograde URS.	Strong
Use flexible URS (even for stones > 2cm) in cases where percutaneous nephrolithotomy or SWL are not options. However, in this case, there is a higher risk that a follow-up procedure and placement of a ureteral stent may be needed.	Strong

### 3.4.7 Percutaneous nephrolithotomy

Percutaneous nephrolithotomy remains the standard procedure for large renal calculi. Different rigid and flexible endoscopes are available, and the selection is mainly based on the surgeon's own preference. Standard access tracts are 24–30Fr. Smaller access sheaths, < 18Fr, were initially introduced for paediatric use but are now increasingly utilised in the adult population [314, 315].

#### Contraindications

General recommendations on bleeding diathesis, anticoagulant therapy and bleeding risk are available in Section 3.4.8.b.

Other important considerations include:

- untreated UTI;
- tumour in the presumptive access tract area;
- potential malignant kidney tumour; and
- pregnancy (Section 3.4.14.a).

#### Best clinical practice

##### Intracorporeal lithotripsy

Several methods for intracorporeal lithotripsy during PCNL are available. Ultrasonic, pneumatic and combined systems are most commonly used for rigid nephroscopy, whilst the laser is increasingly used for miniaturised and flexible instruments [316].

##### Preoperative imaging

Preprocedural imaging evaluations are summarised in Section 3.3.1. In particular, US or CT of the kidney and the surrounding structures can provide information regarding interposed organs within the planned percutaneous path (e.g. spleen, liver, large bowel, pleura and lung). Developing 3D models from contrast-enhanced CT imaging for use in preoperative planning prior to PCNL may benefit the eventual procedure by reducing puncture time, surgical time and blood loss, while increasing the SFR [317, 318].

### *Positioning of the patient*

Both prone and supine positions are equally effective. An MA including 12 studies and a total of 1,290 patients treated showed a similar SFR but a lower operative time for supine PCNL [319]. An MA including 11,774 patients from 42 studies showed a similar SFR and hospital stay but a shorter operative time and lower major complication rate for supine PCNL [320]. The supine position allows simultaneous retrograde access to the collecting system, using a flexible ureteroscope [321]. The combination of PCNL and RIRS may be a good alternative for the treatment of complex renal stones compared to standard PCNL; however, the existing evidence is of low quality [322, 323].

### *Puncture*

Although fluoroscopy is still the most common intraoperative imaging method, the use of US as an additional or only means of puncture guidance is gaining importance. Three meta-analyses including up to 15 randomised controlled trials have demonstrated that US-guided PCNL is equally as effective and safe as fluoroscopy-guided PCNL, with the added benefit of reduced radiation exposure [229, 324, 325]. Preoperative CT or intraoperative US allows identification of the tissue between the skin and kidney and lowers the incidence of visceral injury. As an additional aid to increase puncture accuracy, the calyceal puncture may be done under direct visualisation using simultaneous flexible URS [326-328].

### *Dilatation*

Dilatation of the percutaneous access tract can be achieved using a metallic telescopic, single (one-shot or serial) dilatator, or balloon dilatator. During PCNL, safety and effectiveness are similar for different tract-dilatation methods [329]. Although there are papers demonstrating that single-step dilation is equally effective as other methods and that US only can be used for the dilatation, the difference in outcomes is most likely related to surgeon experience rather than to the technology used [329, 330]. An MA of the most commonly used tract dilation methods suggested that one-step dilation would allow for a shorter operative time and reduced complication rate, including haemoglobin loss and transfusion rate [331].

### *Choice of instruments*

Several meta-analyses on mini-PCNL (12-22 Fr) versus standard PCNL (>22Fr) have identified that both techniques allow for a similar SFR. Patients treated with mini-PCNL had reduced blood loss and transfusion rates, as well as a shorter hospital stay, without a significant difference in overall complication rates [315, 332-334]. However, it is important to note that the level of evidence was downgraded due to heterogeneity of data related to tract sizes used and types of stones treated. There is some evidence for using suction during PCNL to reduce operative time, reduce low-grade complications and increase SFR [335-337].

Based on limited evidence, regardless of a prone or supine position and the size of instruments used, performing flexible nephroscopy by an antegrade or retrograde approach may improve the success rate of PCNL for large and complex stones, while reducing the number of tracts needed [338, 339].

### *Postoperative drainage*

The decision to place a nephrostomy tube or a double J stent at the conclusion of the PCNL procedure depends on several factors, including:

- presence of residual stones;
- likelihood of a second-look procedure;
- significant intraoperative blood loss/bleeding from the percutaneous tract;
- urine extravasation;
- ureteral obstruction;
- potential persistent bacteriuria due to infected stones;
- solitary kidney;
- bleeding diathesis; and
- planned percutaneous chemolitholysis.

Small-bore nephrostomies seem to have advantages in terms of postoperative pain compared to large bore [315, 340, 341]. Tubeless PCNL is performed without a nephrostomy tube and is associated with reduced postoperative pain and hospital stay [342]. When neither a nephrostomy tube nor a ureteral stent is introduced, the procedure is known as a totally tubeless PCNL [343]. In uncomplicated cases, the latter procedure results in a shorter hospital stay, with no disadvantages reported [344]. An SR comparing standard PCNL to tubeless and totally tubeless PCNL could not identify significant differences regarding postoperative pain or complications for tubeless procedures. Totally tubeless procedures, however, may result in less postoperative pain and complications. It should be mentioned, however, that the certainty of evidence for these analyses was very low

[345]. Tubeless PCNL can be safely applied in paediatric patients, yielding outcomes comparable to standard PCNL, provided that indications are properly managed [346].

According to a systematic review, including six RCTs, in tubeless PCNL, an externalised ureteral catheter can be used as an alternative to a DJ stent providing reduced stent related symptoms, without influencing any other outcomes [347].

As reported in the above section on the drainage of an infected or obstructed system [124-126] (Section 3.4.2), the QoL may be slightly lower with a DJ stent in comparison to a short-term nephrostomy tube after PCNL. This should be weighed against the shorter hospital stay with a DJ stent [348].

#### *Complications of percutaneous nephrolithotomy*

A literature review of almost 12,000 patients shows the incidence of complications associated with PCNL: fever 10.8%, transfusion 7%, thoracic complication 1.5%, sepsis 0.5%, organ injury 0.4%, embolisation 0.4%, urinoma 0.2%, and death 0.05% [349].

Perioperative fever can occur, even with a sterile preoperative urinary culture and perioperative antibiotic prophylaxis, because the renal stones themselves may be a source of infection. The evidence demonstrates that a stone culture or urine culture taken directly from the renal pelvis is more predictive of postoperative SIRS or sepsis. Whenever possible a urine culture from the renal pelvis and/or stone culture should be taken at the time of PCNL [350].

Intraoperative renal stone or renal pelvic urine culture may be more indicative of the causative organism for sepsis; therefore, helping to select the most suitable postoperative antibiotics [350-352]. Although this data is weak, there is limited retrospective data indicating that increased pressures during mPCNL may contribute to febrile complications [353-355]. This contrasts with the previously mentioned meta-analyses on mini versus standard PCNL that do not identify a difference in complication rate between the two procedures [315, 332-334]. Bleeding after PCNL may be treated by briefly clamping the nephrostomy tube. Super-selective embolic occlusion of the arterial branch may become necessary in the case of severe bleeding. Several meta-analyses have demonstrated that the use of tranexamic acid reduces bleeding complications and the transfusion rate of PCNL [356-359].

Depending on the stone burden and the patient's anatomy, multiple tracts may be necessary to render the patient stone free in one session of PCNL. While this is a generally accepted practice, it should be highlighted that this comes with an increased risk of postoperative complications, including pleural damage, infections and the need for transfusion [360].

An SR including four small RCTs demonstrated that, when performing PCNL with use of a pneumatic lithotripter, using body temperature irrigation fluid has a lower risk of causing hypothermia than using room temperature or cooled irrigation fluid [361]. However, this may not be translatable to PCNL with the use of any other means of lithotripsy.

Two SRs, including mainly observational or comparative studies and only one RCT, concluded that carefully selected patients undergoing a PCNL procedure can be treated in an ambulatory setting without increasing the risk of complications [362, 363].

To reduce postoperative pain after PCNL, a peripheral nerve block can be performed at the intercostal nerve, paravertebral region, erector spinae or quadratus lumborum. Such a block may significantly reduce the need for postoperative opioid analgesics. Also, infiltration of a local anaesthetic around the nephrostomy tract may reduce postoperative pain and opioid consumption after PCNL [364-366].

### 3.4.7.a Summary of evidence and recommendations for endourology techniques for renal stone removal

Summary of evidence	LE
Imaging of the kidney with US or CT can provide information regarding interposed organs within the planned percutaneous path (e.g. spleen, liver, large bowel, pleura and lung).	3
Both prone and supine positions are equally safe with equivalent SFR.	1a
In selected patients, ambulatory PCNL can be performed without decreasing the SFR or increasing the complication rate.	2a
Both fluoroscopy-guided and US-guided PCNL are equally safe, with equivalent SFR and complication rates.	1a
Percutaneous nephrolithotomy performed with small instruments tends to be associated with significantly lower blood loss, but the duration of the procedure tended to be significantly longer. There are no significant differences in SFR or any other complications.	1a
In uncomplicated cases, a totally tubeless PCNL results in a shorter hospital stay, with no increase in complication rate.	1a
Perioperative use of tranexamic acid may reduce bleeding complications and transfusion rates.	1a
Urine cultures taken directly from the renal pelvis or a stone culture are more predictive of post-PCNL sepsis than a preoperative midstream urine culture.	1a

Recommendations	Strength rating
Perform preprocedural computed tomography imaging, including contrast medium when indicated or retrograde study when starting the procedure, to assess stone comprehensiveness and anatomy of the collecting system to ensure safe access to the renal stone.	Strong
Perform a tubeless (without nephrostomy tube) or totally tubeless (without nephrostomy tube and ureteral stent) percutaneous nephrolithotomy (PCNL) procedure, in uncomplicated cases.	Strong
Take a stone culture or urine culture directly from the renal pelvis at the time of PCNL, if possible.	Strong

### 3.4.8 General recommendations and precautions for stone removal

#### 3.4.8.a Antibiotic therapy

Urinary tract infections should always be treated if stone removal is planned. In patients with clinically significant infection and obstruction, drainage should be performed for several days before starting stone removal. A urine culture or urinary microscopy should be performed before treatment [367].

#### *Perioperative antibiotic prophylaxis*

The available evidence for prevention of infection following URS and percutaneous stone removal remains limited [368, 369]. Administration of a single dose of prophylactic antibiotics prior to ureteroscopy was found to be sufficient [368-371]. In a review of a large database of patients undergoing PCNL, it was found that in patients with negative baseline urine culture, antibiotic prophylaxis significantly reduced the rate of post-operative fever and other complications [372]. Based on three meta-analyses pooling data from small series with varying quality, an extended course of preoperative prophylactic antibiotics prior to PCNL compared to a single dose before anaesthesia significantly reduced postoperative sepsis and fever in patients with an *a priori* increased risk of infection [351, 373, 374]. In an RCT including only moderate to high-risk infection patients (patients with preoperative stents/nephrostomy or positive urine culture), a seven-day course of preoperative antibiotics reduced the risk of post-PCNL sepsis threefold in comparison to a two-day course [375]. In studies that did not specify the risk of the patient population, a single dose of antibiotic prophylaxis administered at induction was equivalent to an extended preoperative course [374, 376]. A prolonged course of postoperative antibiotics was not superior to a single dose preoperatively [351, 374, 377].

As national and regional antibiotic resistance patterns can differ significantly, the choice of antibiotic prophylaxis should be tailored to institutional or regional antimicrobial susceptibility [371].

Recommendations	Strength rating
Obtain a urine culture or perform urinary microscopy before any treatment is planned.	Strong
Exclude or treat urinary tract infections prior to stone removal.	Strong
Offer perioperative antibiotic prophylaxis to all patients undergoing endourological treatment.	Strong

### 3.4.8.b Antithrombotic therapy and stone treatment

Patients with a bleeding disorder, or receiving antithrombotic therapy should be referred to the appropriate physician for appropriate therapeutic measures before deciding on stone management [378-382]. In patients with an uncorrected bleeding disorder, the following are at elevated risk of haemorrhage or perinephric haematoma (PNH) (high-risk procedures):

- SWL (hazard ratio of PNH up to 4.2 during anticoagulant/antiplatelet medication) [383];
- PCNL;
- percutaneous nephrostomy;
- laparoscopic surgery; and
- open surgery [378].

Shock wave lithotripsy is feasible and safe after correction of the underlying coagulopathy [384, 385]. In the case of an uncorrected bleeding disorder or continued antithrombotic therapy, URS, in contrast to SWL and PCNL, might offer an alternative approach, since it is associated with less morbidity [386-389]. Despite the appropriate cessation of antiplatelet agents, following standardised protocols, prolonged haematuria in tube drainage after PCNL has been reported [390]. Only data on flexible URS are available, which supports the superiority of URS in the treatment of proximal ureteral stones [391, 392]. Although URS is safe in patients with bleeding disorders or anticoagulation, an individualised patient approach is necessary [388].

**Therapeutic anticoagulants** (warfarin, DOACs) are typically interrupted before PCNL; routine heparin “bridging” is not recommended for most patients. Resume after secure haemostasis [393, 394].

**Low-dose aspirin** ( $\pm 81$ mg/day) can usually be continued through PCNL without increased bleeding, based on multiple urologic series and a recent meta-analysis [394-398].

**P2Y12 inhibitors** (clopidogrel/prasugrel/ticagrelor) are typically interrupted at least five days before high-bleed-risk surgery like PCNL unless stent-thrombosis risk is prohibitive – coordinate with cardiology [393, 394].

If a patient **cannot interrupt** antithrombotic therapy, PCNL should be delayed or **ureteroscopy** can be performed as the first-line alternative for stone intervention if suitable [389].

**Stratify the thrombotic risk** (mechanical valve, recent VTE, CHA<sub>2</sub>DS<sub>2</sub>-VASc, etc.) and **plan holds** per drug above. Coordinate with prescribing physicians (cardiology/haematology/neurology) for high-risk patients [393]. Resume anticoagulant or antiplatelet therapy when bleeding risk has subsided, i.e. five days after the procedure or when haematuria has ceased, whichever comes last. In the event of continued haematuria reassess the patient for cause of bleeding and consult with the prescribing physician for further multidisciplinary management [389, 393, 395-398].

**Table 3.10: Risk stratification for bleeding** [380-382]

Low-risk bleeding procedures	<ul style="list-style-type: none"> <li>• Cystoscopy</li> <li>• Flexible cystoscopy</li> <li>• Ureteral catheterisation</li> <li>• Extraction of ureteral stent</li> <li>• Ureteroscopy</li> </ul>
High-risk bleeding procedures	<ul style="list-style-type: none"> <li>• Shock wave lithotripsy</li> <li>• Percutaneous nephrostomy</li> <li>• Percutaneous nephrolithotomy</li> </ul>

**Table 3.11: Suggested strategy for antithrombotic therapy in stone removal [380-382]**

(In collaboration with a cardiologist/internist, weigh the risks and benefits of discontinuation of therapy versus delaying elective surgical procedures).

Medication/agent	Bleeding risk of planned procedure	Risk of thromboembolism		
		Low risk	Intermediate risk	High risk
Warfarin dabigatran rivaroxaban apixaban	Low-risk procedure	May be continued	Bridging therapy	Bridging therapy
	High-risk procedure	May be temporarily discontinued at appropriate interval. Bridging therapy is strongly recommended.	Bridging therapy	Bridging therapy
Aspirin	Low-risk procedure	Continue	Continue	Elective surgery: postpone. Non-deferrable surgery: continue.
	High-risk procedure	Discontinue in case of primary prevention. Continue in case of secondary prevention.	Elective surgery: postpone. Non-deferrable surgery: continue if possible.	Elective surgery: postpone. Non-deferrable surgery: continue.
Thienopyridine agents (P2Y12 receptor inhibitors)	Low-risk procedure	Discontinue five days before intervention. Resume within 24–72 hours with a loading dose.	Discontinue five days before intervention.	Elective surgery: postpone. Non-deferrable surgery: continue.
	High-risk procedure	Discontinue five days before intervention and resume within 24–72 hours with a loading dose.	Elective surgery: postpone. Non-deferrable surgery: discontinue five days before procedure and resume within 24–72 hours with a loading dose. Bridging therapy-glycoprotein IIb/IIIa inhibitors if aspirin is discontinued.	Elective surgery: postpone. Non-deferrable surgery: discontinue five days before procedure and resume within 24–72 hours, with a loading dose. Bridging therapy-glycoprotein IIb/IIIa inhibitors.

**3.4.8.b.1 Summary of evidence and recommendations for antithrombotic therapy and stone treatment**

Summary of evidence	LE
The temporary discontinuation or bridging of antithrombotic therapy in high-risk patients should be discussed with the prescribing physician.	3
Retrograde (flexible) URS stone removal is associated with less morbidity in patients when antithrombotic therapy cannot be discontinued.	2a

Recommendations	Strength rating
Offer active surveillance to patients at high risk of thrombotic complications in the presence of an asymptomatic calyceal stone.	Weak
Decide on temporary discontinuation or bridging of antithrombotic therapy in high-risk patients, in consultation with the physician.	Strong
Retrograde (flexible) URS is the preferred intervention if stone removal is essential and antithrombotic therapy cannot be discontinued since it is associated with less morbidity.	Strong

#### 3.4.8.c Obesity

A high BMI can reduce the success rate after SWL [399] but can also pose a higher anaesthetic risk [400] and thus may influence the choice of treatment.

#### 3.4.8.d Stone composition

Stones composed of brushite, calcium oxalate monohydrate or cystine are particularly hard, as are homogeneous stones with a high density on NCCT [401, 402]. Percutaneous nephrolithotomy or RIRS and URS are alternatives for removal of large SWL-resistant stones.

Recommendations	Strength rating
Consider the stone composition before deciding on the method of removal, based on patient history, former stone analysis of the patient or Hounsfield unit on unenhanced computed tomography.	Strong
Attempt to dissolve radiolucent stones.	Strong

#### 3.4.8.e Contraindications to procedures

##### *Contraindications to extracorporeal SWL*

There are several contraindications to the use of extracorporeal SWL, including:

- pregnancy, due to the potential effects on the foetus [403];
- bleeding disorders, which should be compensated for at least 24 hours before and 48 hours after treatment [403];
- uncontrolled UTIs;
- severe skeletal malformations and severe obesity, which prevent targeting of the stone;
- arterial aneurysm in the vicinity of the stone [404]; and
- anatomical obstruction distal to the stone.

##### *Contraindications to URS*

Apart from general problems, for example, with general anaesthesia or untreated UTIs, URS can be performed in all patients without any specific contraindications.

##### *Contraindications to PCNL*

Patients receiving anticoagulant therapy must be monitored carefully pre- and postoperatively. Anticoagulant therapy must be discontinued before PCNL [388]. Other important contraindications include:

- untreated UTI;
- tumour in the presumptive access tract area;
- potential malignant kidney tumour; and
- pregnancy (Section 3.4.14.a).

##### *General contraindication to endourological procedures*

Endourological interventions do not adversely affect renal function, although care must be taken in those with poor preoperative renal function, diabetes and hypertension [405]. However, an MA, based on low-quality evidence, suggests that patients with impaired renal function and stone disease may in fact benefit from the procedure to preserve or improve their renal function [406].

#### 3.4.9 Specific stone management of ureteral stones

##### 3.4.9.a Conservative treatment/observation

There are only limited data regarding spontaneous stone passage according to stone size [407, 408]. Spontaneous stone passage was reported for 49–52% of upper ureteral stones, 58–70% of mid-ureteral stones and 68–83% of distal ureteral stones. Considering stone size almost 75% of stones < 5mm and 62% of stones

≥ 5mm passed spontaneously, with an average time to stone expulsion about 17 days (range 6–29 days) [407, 409]. Considering both size and location, stones of < 5mm in the distal ureter have an 89% chance of spontaneous passage, while 71% of stones < 5mm located in the upper ureter still pass spontaneously [407]. The Panel is aware that spontaneous stone expulsion decreases with increasing stone size, and that there are differences between individual patients.

#### 3.4.9.b Pharmacological treatment, medical expulsive therapy

Medical expulsive therapy should only be used in informed patients if active stone removal is not indicated. Treatment should be discontinued if complications develop (infection, refractory pain, deterioration of renal function). In the case of known uric acid stones in the distal ureter, a combination of alkalinisation with tamsulosin can increase the frequency of spontaneous passage. For details, see Sections 3.4.3 and 3.4.4.

#### 3.4.9.c Indications for treatment of ureteral stones

Indications for removal of ureteral stones are [191, 408, 410]:

- stones with a low likelihood of spontaneous passage;
- persistent pain despite adequate analgesic medication;
- persistent obstruction; and
- renal insufficiency (renal failure, bilateral obstruction, or single kidney).

#### 3.4.9.d Selection of procedure for removal of ureteral stones

The selection of the procedure depends on many factors, including stone-related factors, such as size, location, density and coexistence of ipsilateral renal stones, as well as patient-related factors, such as body habitus, urinary anatomy, bleeding disorders and other potential comorbidities. These and their influence on the outcomes of each of the procedures should be considered when counselling patients.

As previously mentioned in these Guidelines, CT imaging can provide useful information that may influence the choice of treatment. An MA outlines that increasing stone density, stone burden, skin-to-stone distance and hydronephrosis can negatively impact the success of the SWL [411].

Overall, SFRs after URS or SWL for ureteral stones are comparable. However, larger stones achieve earlier stone-free status with URS.

A large multicentre, noninferiority trial compared URS to SWL for ureteral stones. When excluding patients that had spontaneously passed their stone prior to treatment, SWL could not be considered noninferior to URS, with only 12% of patients needing further intervention after URS in comparison to 26% in the SWL arm [305]. In contrast to the success of shockwave lithotripsy, comparative data on the outcomes of URS depending on patients' BMI has shown URS to be as effective and safe in obese and morbidly obese patients as in non-obese patients [412].

The Panel performed an SR to assess the benefits and harms of URS compared to SWL [413]. Compared with SWL, URS was associated with a significantly greater SFR of up to four weeks, but the difference was not significant at three months in the included studies. Ureteroscopy was associated with fewer retreatments and the need for secondary procedures but with a higher need for adjunctive procedures, higher complication rates and longer hospital stay. Counterbalancing for URS's higher SFRs, SWL is associated with lower morbidity. Success rates and complications of URS are not impacted by previous unsuccessful SWL [414]. Clavien-Dindo grade complications were, if reported, less frequent in patients treated with SWL [190].

Apart from the treatment modality, the timing of treatment may also be of importance. Primary or emergent ureteroscopy appears to be a safe and feasible procedure for patients presenting with renal colic due to an obstructive ureteral stone [415], without, however, increasing the SFR. These results, however, are based mainly on low-level of evidence reports and should be interpreted with caution [415]. Similarly, SWL can be performed in the acute setting or electively allowing a trial of spontaneous passage. In contrast to acute URS, SWL in the acute setting does provide an increased SFR and reduced need for auxiliary procedures [416].

For large proximal ureteral stones, a percutaneous antegrade approach may provide better stone-free results than a retrograde ureteroscopic approach [417].

#### *Bleeding disorder*

Ureteroscopy can be performed in patients with bleeding disorders, with a moderate increase in complications (see also Section 3.4.8.b) [388].

3.4.9.d.1 **Summary of evidence and recommendations for selection of procedure for active removal of ureteral stones**

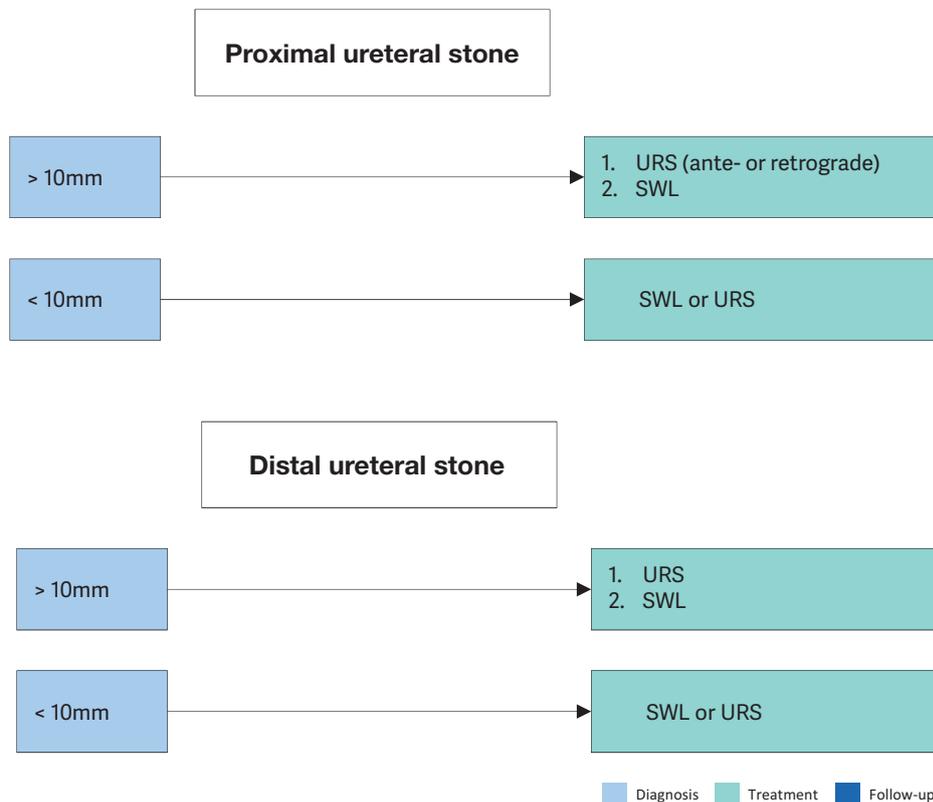
Summary of evidence	LE
Observation is feasible in informed patients who develop no complications (infection, refractory pain, deterioration of renal function).	2a
Medical expulsive therapy seems to be efficacious for treating patients with ureteral stones who are amenable to conservative management. The greatest benefit might be among those with > 5mm (distal) stones.	1a
Compared with SWL, URS was associated with significantly greater SFRs up to four weeks, but the difference was not significant at three months in the included studies.	1a
Ureteroscopy was associated with fewer retreatments and need for secondary procedures, but with a higher need for adjunctive procedures, greater complication rates and longer hospital stay.	1a
In the case of severe obesity, URS is a more promising therapeutic option than SWL.	2b

Recommendations	Strength rating
If active removal is not indicated (Section 3.4.9.c) in patients with newly diagnosed small* ureteral stones, observe patient initially with periodic evaluation.	Strong
Offer $\alpha$ -blockers as medical expulsive therapy as one of the treatment options for (distal) ureteral stones > 5mm**.	Strong
Inform patients that ureteroscopy (URS) has a better chance of achieving stone-free status with a single procedure.	Strong
Inform patients that URS has higher complication rates when compared to shock wave lithotripsy.	Strong
Use URS as first-line therapy for ureteral (and renal) stones in cases of morbid obesity.	Strong

\* See stratification data [184].

\*\* Alpha-blockers are an off-label treatment for this indication

**Figure 3.1: Treatment algorithm for ureteral stones (if stone removal is indicated)**



SWL = shock wave lithotripsy; URS = Ureteroscopy.

### 3.4.10 **Specific stone management of renal stones**

The natural history of small, nonobstructing asymptomatic calculi is not well defined, and the risk of progression is unclear. There is still no consensus on the follow-up duration, timing and type of intervention. In an RCT, patients with small asymptomatic renal stones who were not treated actively had a higher incidence of relapse [418].

#### 3.4.10.a **Conservative treatment (observation)**

Observation of renal stones, especially in calyces, depends on their natural history (see Section 3.4.10.c). The recommendations provided are not supported by high-level literature [419]. There is a prospective trial supporting annual observation for asymptomatic inferior calyceal stones <10mm. In case stone growth is detected, the follow-up interval should be lowered [420]. Intervention is advised for growing stones >5mm [421]. In a systematic review of patients with asymptomatic renal stones on active surveillance, spontaneous stone passage rates varied from 3–29%, symptom development from 7–77%, stone growth from 5–66%, and surgical intervention from 7–26% [419].

#### 3.4.10.b **Pharmacological treatment of renal stones**

Dissolution therapy seems to be an option for uric acid stones. See Sections 3.4.4. and 3.4.8.d.

#### 3.4.10.c **Indications for removal of renal stones**

Indications for the removal of renal stones include:

- stone growth;
- stones in high-risk patients for stone formation;
- obstruction caused by stones;
- infection;
- symptomatic stones (e.g. pain or haematuria) [422];
- patient preference;
- comorbidity; and
- the social situation of the patient (e.g. profession or travelling)

#### 3.4.10.d **Selection of procedure for active removal of renal stones**

For general recommendations and precautions, see Section 3.4.8.

##### 3.4.10.d.1 **Stones in the renal pelvis or upper/middle calyces**

Shock wave lithotripsy, PCNL and RIRS are available treatment modalities for renal calculi. While PCNL efficacy is hardly affected by the stone size, the SFRs after SWL or URS are inversely proportional to stone size [305, 423-429]. Although multiple treatments or sessions may be needed, SWL achieves good SFRs for stones up to 20mm, except for those at the lower pole [425, 430, 431]. When SWL is considered, stones with density >1,000HU (and with high homogeneity) on non-contrast-enhanced CT are less likely to be disintegrated [58]. Endourology is considered an alternative because of the reduced need for repeated procedures and consequently a shorter time until stone-free status is achieved. For stones >10mm and <20mm, mPCNL achieves a higher SFR than RIRS or SWL, but carries a higher risk of bleeding and is associated with a longer hospital stay, however, there is a high degree of heterogeneity among the included studies [427, 429, 432]. Stones >20mm should be treated primarily by PCNL, because SWL often requires multiple treatments, and is associated with an increased risk of ureteral obstruction (colic or steinstrasse) with a need for adjunctive procedures (Figure 3.2) [433]. Retrograde renal surgery cannot be recommended as first-line treatment for stones >20mm in uncomplicated cases as SFRs decrease, and staged procedures will be required [434-436].

However, it may be a first-line option in patients where PCNL is not an option or contraindicated or in selected patients [437]. The combination of PCNL and RIRS may be a good alternative for the treatment of complex renal stones compared to standard PCNL, however, the level of the existing evidence is low [322].

##### 3.4.10.d.2 **Stones in the lower renal pole**

The stone clearance rate after SWL seems to be lower for stones in the inferior calyx than for other intrarenal locations. Although the disintegration efficacy of SWL is not limited compared to other locations, the fragments often remain in the calyx and cause recurrent stone formation. The reported SFR of SWL for lower pole calculi is 25–95%. The preferential use of endoscopic procedures is supported by some current reports, even for stones <1cm [424, 426, 430, 435, 438-446]. One RCT found that there was no evidence of a difference in health status between FURS and ESWL for LPSs of ≤10mm, with FURS leading to a higher SFR. Shock wave lithotripsy was more cost effective than FURS [447].

The following can impair successful stone treatment by SWL [448-454]:

- steep infundibular-pelvic angle;
- long calyx;
- long skin-to-stone distance;
- narrow infundibulum; and
- shock wave-resistant stones (calcium oxalate monohydrate, brushite or cystine).

Further anatomical parameters cannot yet be established. Supportive measures such as inversion, vibration or hydration may facilitate stone clearance (See Section 3.4.5 SWL) [189, 455, 456]. There are negative predictors for SWL. PCNL and RIRS might be reasonable alternatives, even for smaller calculi [439]. Retrograde renal surgery seems to have comparable efficacy to SWL [424, 430, 438, 457]. Clinical experience has suggested a higher SFR of RIRS compared to SWL but at the expense of greater invasiveness. Depending on operator skills, stones up to 3cm can be treated by RIRS [437, 458]. However, staged procedures are frequently required. Although mini-PCNL has the highest success rate for the treatment of lower pole stones up to 2cm, it comes at the expense of a higher complication rate and longer hospital stay [429, 436].

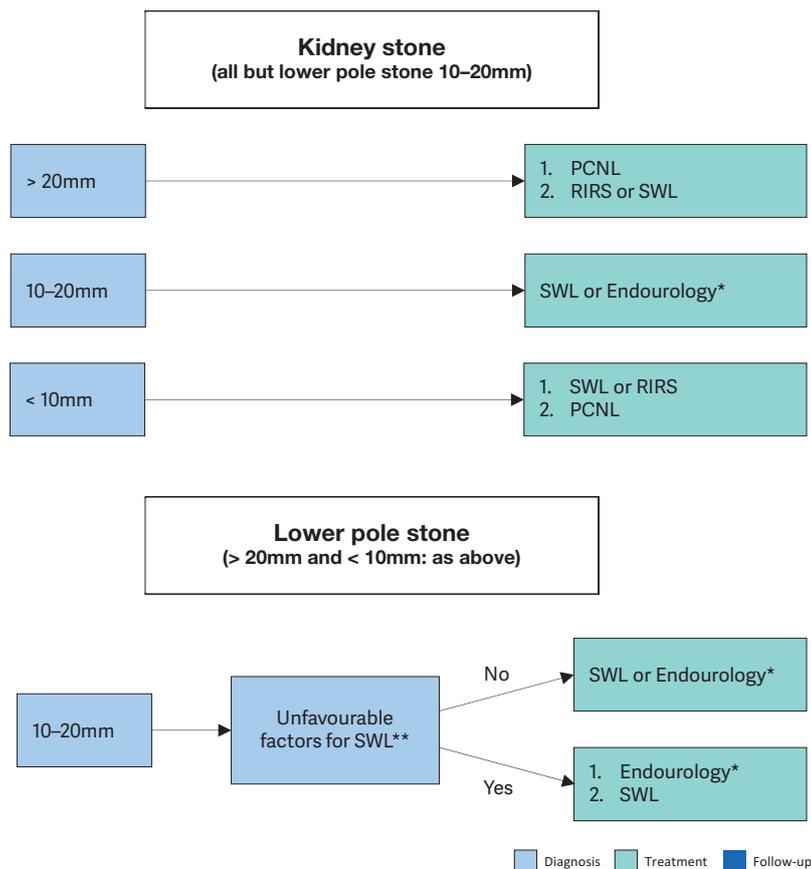
In complex stone cases, open or laparoscopic approaches are possible alternatives, although they are infrequently used.

#### 3.4.10.e Summary of evidence and recommendations for the management of renal stones

Summary of evidence	LE
It is still debatable whether renal stones should be treated, or whether annual follow-up is sufficient for asymptomatic calyceal stones that have remained stable for six months.	4
Although the question of whether asymptomatic calyceal stones should be treated is still unanswered. Stone growth, <i>de novo</i> obstruction, associated infection and acute and/or chronic pain are indications for treatment.	3
Percutaneous nephrolithotomy is indicated in renal stones > 2cm as primary option.	1a

Recommendations	Strength rating
Offer active treatment for renal stones in case of stone growth, <i>de novo</i> obstruction, associated infection and acute and/or chronic pain.	Weak
Evaluate stone composition before deciding on the method of removal based on patient history, former stone analysis of the patient or Hounsfield unit (HU) on unenhanced CT.	Strong
Perform percutaneous nephrolithotomy (PCNL) as first-line treatment of larger stones > 2cm.	Strong
Treat larger stones (> 2cm) with flexible ureteroscopy or shock wave lithotripsy (SWL) in cases where PCNL is not an option. However, in such instances there is a higher risk that a follow-up procedure and placement of a ureteral stent may be needed.	Strong
Perform PCNL or retrograde intrarenal surgery for the lower pole, even for stones > 1cm, as the efficacy of SWL is limited (depending on favourable and unfavourable factors for SWL).	Strong

Figure 3.2: Treatment algorithm for renal stones (if/when active treatment is indicated)



\* The term 'Endourology' encompasses all PCNL and URS interventions.

PCNL = percutaneous nephrolithotomy; RIRS = retrograde intrarenal surgery; SWL = shock wave lithotripsy; URS = ureteroscopy.

### 3.4.11 Laparoscopy and open surgery

Advances in SWL and endourological surgery (URS and PCNL) have significantly decreased the indications for open or laparoscopic stone surgery [459-464]. There is a consensus that most complex stones, including partial and complete staghorn stones, should be approached primarily with PCNL. Additionally, a combined approach with PCNL and RIRS may also be an appropriate alternative. However, if percutaneous approaches are not likely to be successful, or if multiple endourological approaches have been performed unsuccessfully, open or laparoscopic surgery may be a valid treatment option [465-469].

When expertise is available, laparoscopic ureterolithotomy can be performed for large proximal ureteral stones as an alternative to URS or SWL [470, 471]. These more invasive procedures have yielded high SFRs and lower auxiliary procedure rates [211, 223, 466]. An RCT shows that retroperitoneal laparoscopic urethral lithotomy for large proximal ureteric stones is not superior to flexible ureteroscopy [472].

A systematic review showed no difference in the postoperative phase for stented or unstented laparoscopic ureterolithotomy [466]. Laparoscopic pyelolithotomy could be offered for solitary stones > 2cm located in the renal pelvis as an alternative to PCNL [467]. In addition, in selected cases with an extrarenal and dilated pelvis, retroperitoneal laparoscopic pyelotomy (RLP) can be considered as an alternative management of staghorn calculi [473].

A few studies with limited numbers of patients have reported using robotic surgery in the treatment of urinary stones [468]. Open surgery should be considered as the last treatment option after all other possibilities have been explored.

### 3.4.11.a Recommendation for laparoscopy and open surgery

Recommendation	Strength rating
Offer laparoscopic or open surgical stone removal in rare cases in which shock wave lithotripsy, retrograde or antegrade ureteroscopy and percutaneous nephrolithotomy fail or are unlikely to be successful.	Strong

### 3.4.12 Steinstrasse

Steinstrasse is an accumulation of stone fragments or stone gravel in the ureter and may interfere with the passage of urine [474]. Steinstrasse occurs in 4% of cases of SWL [190, 198], and the major factor in the development of steinstrasse formation after SWL is stone size [475].

A major problem of steinstrasse is ureteral obstruction, which may be silent in up to 23% of cases. A MA including eight RCTs (n = 876) suggested a benefit of stenting before SWL in terms of steinstrasse formation but did not result in a benefit on SFRs or less auxiliary treatments [151]. When steinstrasse is asymptomatic, conservative treatment is an initial option. Medical expulsion therapy increases stone expulsion and reduces the need for endoscopic intervention [476, 477]. Ureteroscopy and SWL are effective in the treatment of steinstrasse [200, 478]. One prospective randomised study based on a low volume of patients shows better treatment outcome of ureteroscopy [479]. In the event of UTI or fever, the urinary system should be decompressed, preferably by percutaneous nephrostomy [127, 480].

### 3.4.12.a Summary of evidence and recommendations for steinstrasse

Summary of evidence	LE
Medical expulsion therapy increases the stone expulsion rate of steinstrasse.	1b
Ureteroscopy is effective for the treatment of steinstrasse.	3
Only low-level evidence is available supporting SWL or URS for the treatment of steinstrasse.	4

Recommendations	Strength rating
Treat steinstrasse associated with urinary tract infection (UTI)/fever preferably with percutaneous nephrostomy.	Weak
Treat steinstrasse when large stone fragments are present with shock wave lithotripsy or ureteroscopy (in absence of signs of UTI).	Weak

### 3.4.13 Management of patients with residual stones

Following initial treatment with SWL, URS or PCNL, residual fragments may remain and require additional intervention [421, 481-484], however, there is no consistent definition of residual fragments [479]. Most of these studies indicate that initial imaging is performed on the first day or the first week after treatment. However, false positive results from dust or residual fragments, which will pass spontaneously without causing any stone-related event, might lead to overtreatment. Therefore, imaging at four weeks seems most appropriate [485-487]. Compared to US, KUB and IVU, NCCT scan has a higher sensitivity to detect small residual fragments after definitive treatment of ureteral or kidney stones [488, 489].

An SR and MA examining residual fragments following any treatment has demonstrated that around a third of patients with either dust or fragments  $\leq 4$ mm experience disease progression and reintervention within three years, whilst a third have spontaneous passage within two years, regardless of imaging modality follow-up. For fragments  $> 4$ mm, there are fewer studies, but these suggest low spontaneous passage rates and high intervention rates [490].

Although NCCT has the highest sensitivity to detect residual fragments, this must be balanced against the exposure to ionising radiation when compared with KUB and US. Recurrence risk in patients with residual fragments after treatment of infection stones is higher than for other stones [491].

### 3.4.13.a Recommendation for management of patients with residual stones

Recommendation	Strength rating
Treat residual fragments > 4mm.	Weak

#### 3.4.14 Management of specific patient groups

##### 3.4.14.a Management of urinary stones and related problems during pregnancy

Clinical management of a pregnant patient with urolithiasis is complex and demands close collaboration between the patient, radiologist, obstetrician and urologist [78]. For diagnostic imaging, see Section 3.3.1. Patients with urolithiasis may be at increased risk of developing adverse maternal or neonatal outcomes [492].

Conservative approaches for symptomatic hydronephrosis, as well as for ureteric calculi, are the preferred initial management option in pregnant patients [493, 494].

If spontaneous passage does not occur, or if complications develop (e.g. intractable symptoms, severe hydronephrosis, spontaneous renal fornix rupture [495] or induction of premature labour), placement of a ureteral stent or a percutaneous nephrostomy tube is necessary, as it is more effective than conservative treatment for symptom relief [496-498].

In the treatment of renal stones during pregnancy, when drainage is necessary, PCN versus ureteral stent placement does not confer a significant difference in rates of adverse pregnancy events. However, ureteral stent placement was associated with a lower incidence of hospital admissions, emergency department visits, exchange procedures, and new UTIs or pyelonephritis [499].

Ureteroscopy has become a reasonable alternative in these situations [487, 500, 501]. When compared to temporary ureteral JJ stenting until after delivery, ureteroscopy resulted in fewer needs for stent exchanges, less irritative LUTS and better patient satisfaction [502, 503].

Non-urgent ureteroscopy in pregnant women is best performed during the second trimester by an experienced urologist [504]. Counselling of the patient should include access to neonatal and obstetric services [83].

Although feasible, percutaneous removal of renal stones during pregnancy remains an individual decision and should be performed only in experienced centres [505]. Pregnancy remains an absolute contraindication for SWL.

##### 3.4.14.a.1 Summary of evidence and recommendation for the management of urinary stones and relationship problems during pregnancy

Summary of evidence	LE
Stent insertion seems to be more effective than conservative treatment in the management of symptomatic ureteral stones causing moderate-to-severe hydronephrosis during pregnancy.	1a
Ureteroscopy is a reasonable alternative to avoid long-term stenting/drainage.	1b
There is a higher tendency for stent encrustation during pregnancy.	3

Recommendation	Strength rating
Treat all uncomplicated cases of urolithiasis in pregnancy conservatively (except when there are clinical indications for intervention).	Strong

##### 3.4.14.b Management of stones in patients with urinary diversion

###### Aetiology

Patients with urinary diversion are at high risk for stone formation in the renal collecting system and ureter or in the conduit or continent reservoir [506, 507]. Metabolic factors (hypercalciuria, hyperoxaluria and hypocitraturia), infection with urease-producing bacteria, foreign bodies, mucus secretion, and urinary stasis are responsible for stone formation [508] (see Section 3.1.3). One study has shown that the risk for recurrent upper tract stones in patients with urinary diversion subjected to PCNL was 63% at five years [509].

### Management

Smaller upper-tract stones can be treated effectively with SWL [510, 511]. In most cases, endourological techniques are necessary to achieve stone-free status [512]. In individuals with long, tortuous conduits or with invisible ureter orifices, a retrograde endoscopic approach might be difficult or impossible [513].

For stones in the conduit, a trans-stomal approach can be used to remove all stone material (along with the foreign body) using standard techniques, including intracorporeal lithotripsy and flexible endoscopes. Trans-stomal manipulations in continent urinary diversion must be performed carefully to avoid disturbance of the continence mechanism [514].

Before considering any percutaneous approach in these cases, CT should be undertaken to assess the presence of overlying bowel, which could make this approach unsafe [515], and if present, a surgical approach should be considered.

### Prevention

Recurrence risk is high in patients with urinary diversion [509]. Metabolic evaluation and close follow-up are necessary to obtain the risk parameters for effective long-term prevention. Preventive measures include medical management of metabolic abnormalities, appropriate therapy of urinary infections, and hyper-diuresis or regular irrigation of continent reservoirs [516].

#### 3.4.14.b.1 Summary of evidence and recommendation for the management of stones in patients with urinary diversion

Summary of evidence	LE
The choice of access depends on the feasibility of orifice identification in the conduit or bowel reservoir. Whenever a retrograde approach is impossible, percutaneous access with antegrade ureteroscopy is the alternative.	4

Recommendation	Strength rating
Perform percutaneous lithotomy to remove large renal stones in patients with urinary diversion, as well as for ureteral stones that cannot be accessed via a retrograde approach, or that are not amenable to shock wave lithotripsy.	Strong

#### 3.4.14.c Management of stones in patients with neurogenic bladder

##### *Aetiology, clinical presentation and diagnosis*

Patients with neurogenic bladder develop urinary calculi because of additional risk factors such as bacteriuria, hydronephrosis, VUR, renal scarring and lower urinary tract reconstruction [517-519]. The most common causes are urinary stasis and infection (see Section 3.1.3). Indwelling catheters and surgical interposition of bowel segments for treatment of bladder dysfunction both facilitate UTI. Although calculi can form at any level of the urinary tract, they occur more frequently in the bladder; especially if bladder augmentation has been performed [520, 521].

Diagnosis of stones may be difficult and delayed in the absence of clinical symptoms due to sensory impairment and vesicourethral dysfunction. Difficulties in self-catheterisation should lead to suspicion of bladder calculi. Imaging studies are needed (US, CT) to confirm the clinical diagnosis prior to surgical intervention.

### Management

Management of calculi in patients with neurogenic bladder is similar to that described in Section 3.3. Any surgery in these patients must be performed under general anaesthesia because of the impossibility of using spinal anaesthesia. Bone deformities often complicate positioning on the operating table [522]. Individuals with spinal cord injury are at higher risk for minor, major and infectious complications after PCNL, with similar stone-free rates [523]. The risk of stone formation after augmentation cystoplasty in immobile patients with sensory impairment can be significantly reduced by irrigation protocols [520].

For efficient long-term stone prevention in patients with neurogenic bladder, correction of the metabolic disorder, appropriate infection control and restoration of normal storing/voiding function of the bladder are needed.

### 3.4.14.c.1 Summary of evidence for the management of stones in patients with neurogenic bladder

Summary of evidence	LE
Patients undergoing urinary diversion and/or suffering from neurogenic bladder dysfunction are at risk for recurrent stone formation.	3

### 3.4.14.d Management of stones in patients with transplanted kidneys

Stones in transplanted kidneys can either be transplanted or present *de novo* allograft stones. Usually, they are detected by routine US examination, followed by NCCT in cases of unclear diagnosis [524].

#### Aetiology

Transplant patients depend on their solitary kidneys for renal function. Impairment causing urinary stasis/obstruction, therefore, requires immediate intervention or drainage of the transplanted kidney. Stones in kidney allografts have an incidence of 2% [524]. Risk factors for *de novo* stone formation in these patients are multifold:

- Immunosuppression increases the infection risk, resulting in recurrent UTIs.
- Hyperfiltration, excessively alkaline urine, renal tubular acidosis (RTA) and increased serum calcium caused by persistent tertiary hyperparathyroidism [525] are biochemical risk factors.

#### Management

Selecting the appropriate technique for stone removal in a transplanted kidney is difficult, although management principles are similar to those applied in other single renal units [526-528]. Additional factors, such as transplant function, coagulative status and anatomical alterations due to the iliac position of the organ, directly influence the surgical strategy.

Retrograde access to transplanted kidneys can be difficult due to the anterior location of the ureteral anastomosis and ureteral tortuosity [529-531]. The introduction of small flexible ureteroscopes and the holmium laser has made URS a valid treatment option for transplant calculi [537]. For large or ureteral stones, careful percutaneous access and subsequent antegrade endoscopy are more favourable, however, one must be aware of potential injury to adjacent organs [527, 532-534]. Treatment of donor stones may be needed pretransplant and increases the pool available for renal transplants. Posttransplant stone disease may also need treatment to maintain the allograft function [535]. A systematic review evaluating the outcomes of pre- versus posttransplant URS demonstrated a 100% SFR with an overall 7.5% complication rate for pretransplant URS, compared to an SFR of 60–100% with an overall complication rate of 12.9% for posttransplant URS; most complications were Clavien 1 [536]. A systematic review shows that SWL is also a safe and effective option for *de novo* stones after transplantation, with an overall SFR of 81% and a complication rate of 17.2% [537].

Although feasible, percutaneous removal of renal stones in transplant kidneys can be difficult and high risk of complications and should be performed only in experienced centres [538].

### 3.4.14.d.1 Summary of evidence and recommendation for the management of stones in patients with transplanted kidneys

Summary of evidence	LE
Conservative treatment for small asymptomatic stones is only possible under close surveillance and in compliant patients.	3
Shock wave lithotripsy for small calyceal stones is an option with minimal risk of complication, but localisation of the stone can be challenging.	3

Recommendation	Strength rating
Offer patients with transplanted kidneys any of the contemporary management options, including shock wave lithotripsy, flexible ureteroscopy and percutaneous nephrolithotomy.	Strong

### 3.4.14.e Special problems in stone removal

**Table 3.12: Special problems in stone removal [539]**

Calyceal diverticulum stones	<ul style="list-style-type: none"> <li>• SWL, PCNL [540] (if possible) or RIRS [540-542].</li> <li>• Can also be removed using laparoscopic retroperitoneal surgery [543, 544].</li> <li>• Patients may become asymptomatic due to stone disintegration (SWL), whilst well-disintegrated stone material remains in the original position due to narrow calyceal neck.</li> </ul>
Horseshoe kidneys	<ul style="list-style-type: none"> <li>• Can be treated in line with the options described above [545-547].</li> <li>• Passage of fragments after SWL or fragmentation of stones might be poor.</li> <li>• Acceptable SFRs (up to 76%) with low major complication rates (2.4%) can be achieved with flexible ureteroscopy [545-547].</li> </ul>
Stones in pelvic kidneys	<ul style="list-style-type: none"> <li>• SWL, RIRS, PCNL or laparoscopic surgery [548].</li> </ul>
Stones formed in a continent reservoir	<ul style="list-style-type: none"> <li>• Each stone must be considered and treated individually.</li> </ul>
Patients with obstruction of the UPJ	<ul style="list-style-type: none"> <li>• When outflow abnormality requires correction, stones can be removed by PCNL together with percutaneous endopyelotomy or open/laparoscopic reconstructive surgery.</li> <li>• URS together with endopyelotomy with Ho:YAG laser [549].</li> </ul>

### 3.4.15 Management of stones in children

The true incidence of nephrolithiasis in children remains unclear due to the global lack of large epidemiological studies. Data derived from nationwide epidemiological studies, studies performed in various counties worldwide [550] and large-scale databases [551, 552], indicate that the incidence and prevalence of paediatric urinary stone disease have increased over the last few decades. Although boys are most commonly affected in the first decade of life [553], the greatest increase in incidence has been seen in older female adolescents [550].

Stone composition is similar in children as in adults, with a predominance of calcium oxalate stones. Compared to historical data, metabolic abnormalities responsible for stone formation are less commonly identified in children nowadays [554-556]. Hypocitraturia, low urine volume and hypercalciuria predominate [554-557]. Age may affect the predominant metabolic abnormality with hypercalciuria and hypocitraturia being the most common disorder present in children < 10 and > 10 years old, respectively [556]. Genetic or systemic diseases (e.g. cystinuria or nephrocalcinosis) contributing to stone formation are relatively frequent in children, accounting for less than 17% of the identified cases [554, 558]. The role of diet remains unclear in children, although there is some evidence that children are drinking less water and taking greater daily amounts of sodium than is recommended [559-561].

For diagnostic procedures, see Section 3.3.3.b; for acute decompression, see Section 3.4.2; and for metabolic evaluation, see Chapter 4.

#### 3.4.15.a Clinical presentation

Children with urinary stones can be asymptomatic or present with non-specific symptoms that necessitate a high index of suspicion for proper diagnosis. Symptoms are age-dependent with infants presenting with crying, irritability and vomiting in 40% of cases [562], while in older children, flank pain, micro or gross haematuria and recurrent UTIs are more common [563].

#### 3.4.15.b Conservative management

There is a lack of evidence on conservative management of paediatric stones with evidence for ureteric calculi coming from the placebo arms of medical expulsive trials, while evidence for renal stones comes from small cohort studies, either on primary stones [564, 565] or residual fragments after SWL, RIRS or PCNL [566]. Expectant management for single, asymptomatic lower-pole renal stones could be the initial approach, with increased odds of stone passage, especially in patients with non-struvite, noncystine stones < 7mm, with no anatomic abnormalities [564]. Intervention may be needed for stones located elsewhere independently of their size [564-567].

#### 3.4.15.c Medical expulsive therapy in children

There are limited studies on MET as off-label expulsive therapy for children with ureteral stones up to 10mm which show conflicting outcomes. Several systematic reviews and meta-analyses, including six RCTs and one conference abstract of an RCT, have been performed, all unanimously reporting that the use of  $\alpha$ -blockers for distal ureteric stones increases the stone-free or stone expulsion rate [138, 567, 568]. The use of  $\alpha$ -blockers also reduces the stone expulsion time and decreases the number of pain episodes and the need for analgesia, with the disadvantage of more side-effects such as headache and nasal congestion [138, 568].

#### 3.4.15.d Extracorporeal shock wave lithotripsy

Shock wave lithotripsy is still the first-line treatment for most ureteral stones in children. However, it is less likely to be successful for stones >10mm in diameter, impacted stones, calcium oxalate monohydrate or cystine stones, or for stones in children with unfavourable anatomy and in whom localisation is difficult [569].

Studies on extracorporeal SWL in children suggest an overall SFR of 70–90%, retreatment rate of 4–50% and need for auxiliary procedures in 4–12.5% of cases [570-574]. A MA of 14 studies reporting on 1,842 paediatric patients treated with SWL found significantly higher SFR for stones < 10mm than for stones 10mm, and higher retreatment rates as the stone size increased [569]. For best clinical practice, see Section 3.4.5. An MA on slow SWL versus rapid SWL for renal stones revealed very low-quality evidence about the effects of SWL on SFRs, serious adverse events or complications of treatment, and secondary procedures for residual fragments [567]. Shock wave lithotripsy is well tolerated; however, good treatment outcomes are more likely to require the administration of general anaesthesia to children. With improvements in modern (second- and third-generation) lithotripters, successful treatment using intravenous sedation, patient-controlled analgesia or no medication at all has been increasingly performed in a select population of older, co-operative children [575].

Based on the results of an MA which compared SWL to dissolution therapy for intrarenal stones, and SWL to ureteroscopy with holmium laser or pneumatic lithotripsy for renal and distal ureteric stones, no firm conclusions can be drawn about the effects of SWL on SFR, serious adverse events or complications of treatment and secondary procedures for residual fragments [567]. When SWL was compared to mini-percutaneous nephrolithotomy for lower pole renal stones 1–2cm in size, SWL resulted in lower SFRs (RR: 0.88, 95% CI: 0.80–0.97; moderate-quality evidence) and higher rates of secondary procedures (RR: 2.50, 95% CI: 1.01–6.20; low-quality evidence); however, SWL showed less severe adverse events (RR: 0.13, 95% CI: 0.02–0.98; low-quality evidence) [576]. Shock wave lithotripsy has shown equivalent outcomes using US only, as it reduces radiation exposure to children [577].

#### 3.4.15.e Endourological procedures – Rigid/semi-rigid ureteroscopy

In recent years ureteroscopy has increasingly been used in children with ureteral stones [578]. Ureteroscopy proved to be effective with SFR of 81–98% [579-581], retreatment rates of 6.3%–10% [582] and complication rates of 1.9–23% [579-581, 583]. Similar to adults, routine stenting is not necessary before URS. Pre-stenting may facilitate URS, increase SFR and decrease complication rates [584, 585].

##### *Flexible ureteroscopy/retrograde intrarenal surgery*

Retrograde intrarenal surgery with flexible ureteroscopes (FURS) has become an efficacious treatment modality for paediatric renal stones. Studies report SFRs of 76–100%, retreatment rates of 0–19% and complication rates of 0–28% [586-589]. Younger age, cystine composition [590], large stone diameter [589] and lack of pre-stenting predispose to FURS failure in children [584]. A large global study across eight centres shows an SFR of 75.5%; although complications were minor, they were higher in patients < 5 years of age [591].

An SR by the panel based on limited evidence demonstrated that flexible ureteroscopy has a better SFR than SWL for renal stones in paediatric patients; however, with an increased operative time and length of stay [592]. Although high-level evidence is lacking to support a strong recommendation [567], FURS may be a particularly effective treatment option for lower calyceal stones in the presence of unfavourable factors for SWL [581, 587, 593].

One RCT including 60 patients has shown equivalent outcomes of RIRS to mini-PCNL for stones between 1 and 2.5cm [594]. For large and complex kidney stones, RIRS has a significantly lower SFR compared to PCNL (71% vs. 95%), but is associated with less radiation exposure, lower complication rates and a shorter hospital stay [595]. Similarly, retrospective data indicate that RIRS may achieve lower SFRs compared to micropercutaneous surgery in favour of shorter operative time, shorter fluoroscopy time and less hospitalisation time [596, 597]. A published MA confirmed these results [598].

### *Percutaneous nephrolithotomy*

Indications for PCNL in children are like those in adults and include renal stones >2cm, or smaller stones resistant to SWL and ureteroscopic treatment. Reported SFRs with paediatric PCNL are 71.4–95% after a single session [595-597, 599, 600] with an overall complication rate of 20% [601]. A high degree of hydronephrosis, increased number of tracts and operative time [602], and large tract sizes [600, 603-605] are associated with increased blood loss. Child age [604] and stone burden [600] predispose to the use of larger instruments during PCNL in children. The miniaturisation of equipment increases the opportunity to perform tubeless PCNL in appropriately selected children, which can reduce the length of hospital stay and postoperative pain [606, 607]. A systematic review on the role of mini-PCNL showed an initial and overall SFR of 87.9% and 97%, respectively, with no conversions to standard PCNL and a complication rate of 19%, with a mean transfusion rate of 3.3% [591]. As in adults, supine PCNL in children has similar outcomes regarding SFR as prone PCNL. Two meta-analyses including very few RCTs and a small number of patients suggest that supine PCNL has additional advantages of reduced operative time and length of stay [608, 609]. A retrospective study has shown equivalent outcomes for ECIRS compared to prone or supine PCNL [610].

Concerns have been raised regarding the possible adverse effects of PCNL on the renal parenchyma of the developing child. However, focal damage is only reported in 5% of cases [611]. Using pre- and post-PCNL dimercaptosuccinic acid (DMSA) scans, Cicekbilek *et al.* demonstrated that PCNL tracts between 12 and 24Fr in size did not cause significant harm to paediatric kidneys [599].

#### 3.4.15.f Open and laparoscopic/robot-assisted stone surgery

With the advances in SWL, PCNL and RIRS, very few cases of paediatric urolithiasis require open surgery. Data extracted from the National Inpatient Sample (NIS) databases for 2001–2014 showed that, in the United States, incisional procedures (mainly nephrolithotomy, pyelolithotomy and ureterotomy) were performed in 2.6% of hospitalised patients (52% aged 15–17 years) who required surgical intervention for urinary stones [612]. Laparoscopy for the management of paediatric renal and ureteric stones is a safe and effective procedure when specific indications are followed. Stone-free rates of 100% were reported when laparoscopic pyelolithotomy was applied for a  $\geq 1$ cm single stone located in an extrarenal pelvis [613], or when laparoscopic ureterolithotomy was applied to impacted ureteric stones  $\geq 1.5$ cm, or to ureteric stones that were refractory to SWL or URS [614]. There are extremely limited data available on the efficacy and complications of robot-assisted laparoscopic management of paediatric urolithiasis [615, 616].

#### 3.4.15.g Special considerations on recurrence prevention

All paediatric stone formers need metabolic evaluation and recurrence prevention with respect to the detected stone type. Children are in the high-risk group for stone recurrence (see Chapter 4).

#### 3.4.15.h Summary of evidence and recommendations for the management of stones in children

Summary of evidence	LE
In children, MET could increase the rate of stone expulsion, reduce the stone expulsion time and decrease pain episodes/analgesia demand, but it has a higher incidence of side effects.	1b
In children, the indications for SWL, URS and PCNL are similar to those in adults.	1b
Children with renal stones of a diameter up to 20 mm ( $\sim 300$ mm <sup>2</sup> ) are ideal candidates for SWL.	1b
Ureteroscopy has become the treatment of choice for larger distal ureteral stones in children.	1a
Mini-PCNL is safe and effective in children.	1b

Recommendations	Strength rating
Offer children with single ureteral stones less than 10mm shock wave lithotripsy (SWL) if localisation is possible or ureteroscopy as first-line option.	Strong
Ureteroscopy is a feasible alternative for ureteral stones not amenable to SWL.	Strong
Offer children with renal stones with a diameter of up to 20mm ( $\pm 300$ mm <sup>2</sup> ) SWL.	Strong
Offer children with renal pelvic or calyceal stones with a diameter > 20mm ( $\pm 300$ mm <sup>2</sup> ) percutaneous nephrolithotomy.	Strong

### 3.5 Radiation exposure and protection during endourology

The diagnosis and treatment of nephrolithiasis are associated with high levels of ionising radiation exposure to patients [617, 618]. Currently, there are no studies estimating the lifetime radiation exposure of stone formers or the subsequent risk of malignancy development. The radiation exposure of endourologists has been extensively studied. Still, there are no studies assessing the risk of radiation-induced malignancies in urologists or operating theatre staff members [619-621].

Current evidence from atomic bomb patients [622, 623], retrospective epidemiological data on medical exposure [624, 625], and modelling studies [626, 627] suggest an age- and dose-dependent risk of secondary malignancy from ionising radiation. Radiation exposure of patients generally is higher during PCNL, followed by SWL and URS [628].

The International Commission on Radiological Protection (ICRP) recommends a maximum annual occupational exposure of 50mSv [629]. However, the risk of radiation-induced malignancy follows a stochastic model having no known safe threshold of exposure. Taking this into consideration, as well as the length of a urologist's career, the upper limit of 50mSv is still highly concerning.

Table 3.13 shows the EAU Urolithiasis Guidelines Panel's recommended protection methods to reduce radiation exposure to patients, surgical, anaesthesiologic, and nursing staff.

**Table 3.13: Radiation protection measures [630]**

Limit studies or intervention involving radiation exposure to those that are strictly medically necessary.
Implement a patient electronic record of medical imaging.
Make use of imaging studies with lower radiation doses (US, KUB, digital tomosynthesis, low-dose and ultra-low-dose CT scan).
Create and follow a precise radiation exposure protection protocol in your department.
Act in accordance with the As Low As Reasonably Achievable (ALARA) principle.
Measure and report fluoroscopy time to the operative surgeon (use dosimeters and perform monthly calculations).
Technical measures to reduce radiation exposure include: <ul style="list-style-type: none"> <li>• Reducing fluoroscopy time;</li> <li>• Limiting time adjacent to patient;</li> <li>• Using low-dose radiation;</li> <li>• Irradiating only to observe motion;</li> <li>• Intraoperative use of pulsed fluoroscopy;</li> <li>• Reduced fluoroscopy pulse rate;</li> <li>• Collimated fields; and</li> <li>• Avoid digital image acquisition and rely on last image hold and instant replay technology.</li> </ul>
Use radiation protection instruments (chest, pelvic and thyroid shields, lead or lead-free gloves, protective glasses, lead protection under the operating table between the X-ray source and the surgeon).
The radiation protection instruments must be cared for appropriately, as any damage decreases effectiveness and increases exposure risk. They should be monitored and measured regularly to ensure integrity.
Proper surgeon and operating room setup should be observed (follow the inverse square law, use the X-ray source underneath the patient's body, decrease the X-ray source to patient distance, reduce magnification, avoid field overlap by not turning the C-arm in extreme angles, operate in the standing rather than the seated position).

The availability of fluoroscopy is mandatory for endourological procedures. There is an increasing interest in fluoroleless and fluoroscopy-free operations in urology.

A systematic review by the panel has demonstrated that fluoroscopy-free procedures can be performed without significantly influencing the outcomes such as SFR, operative time and complications. However, many trials included in the MA excluded patients with complex stone loads or anatomic abnormalities [229].

## 4. METABOLIC EVALUATION AND RECURRENCE PREVENTION

### 4.1 General metabolic considerations for patient work-up

#### 4.1.1 Evaluation of patient risk

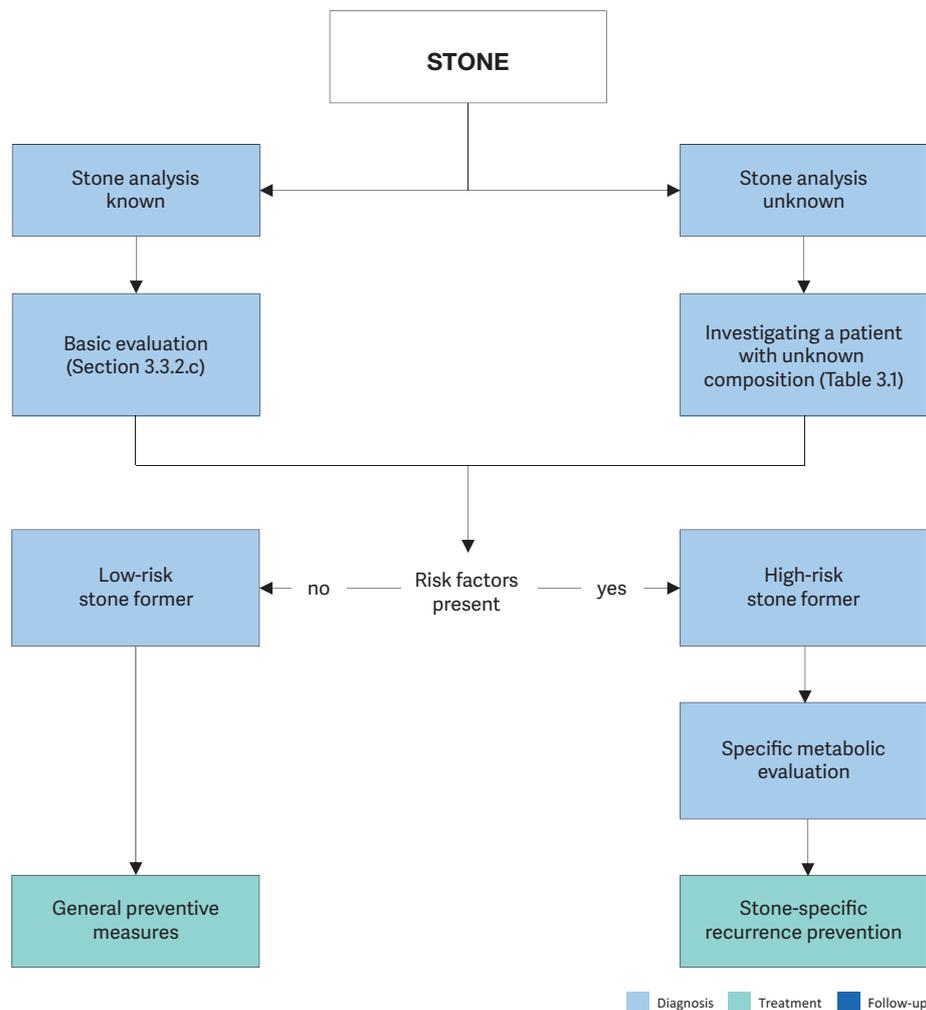
After stone passage, every patient should be assigned to a low- or high-risk group (Table 3.3) for stone formation (Figure 4.1).

Reliable stone analysis by infrared spectroscopy or X-ray diffraction and basic metabolic evaluation is mandatory for all stone formers.

Only high-risk stone formers require specific metabolic evaluation. Stone type is the deciding factor for further diagnostic tests. The various stone types include:

- calcium oxalate;
- calcium phosphate;
- uric acid;
- ammonium urate;
- struvite (and infection stones);
- cystine;
- xanthine;
- 2,8-Dihydroxyadenine;
- drug stones; and
- stones of unknown composition.

Figure 4.1: Assignment of patients to low- or high-risk groups for stone formation



#### 4.1.2 Urine sampling

Specific metabolic evaluation requires the collection of two consecutive 24-hour urine samples [77, 631, 632]. The collecting bottles should be prepared with 1g thymol per litre or stored at < 8°C during collection to reduce bacterial proliferation [77]. Preanalytical errors can be minimised by carrying out urinalysis immediately after collection. Alternatively, boric acid (10g powder per urine container) can also be used, but this prevents the correct determination of pH [77]. The collecting method should be chosen in close cooperation with the laboratory. A pH < 5.5 in a 24-hour urine indicates hyperacidic urine (acidic arrest) [633-635]. In the course of alkalinising therapy for cystinuria and uric acid stones, urine pH should be assessed during the collection of freshly voided urine at different times throughout the day using sensitive pH dipsticks or a pH-meter [23, 77, 636]. A consensus statement stated that RTA is suspected if 24-hour urine pH is > 6.2 and fasting second-morning spot urine pH is > 5.8 [637, 638].

Spot urine samples are an alternative sampling method, particularly when 24-hour urine collection is difficult, for example, in non-toilet-trained children [639]. Spot urine studies normally link the excretion rates to the creatinine [640], but these are of limited use because the results may vary with collection time and patients' sex, body weight and age.

#### 4.1.3 Timing of specific metabolic work-up

After an acute stone episode, metabolic evaluation should be performed no earlier than 20 days – and preferably around three months – once the patient is stable, free of infection and on their usual diet and fluid intake. Follow-up studies are necessary for patients taking medication for recurrence prevention [641]. The first follow-up 24-hour urine measurement is suggested eight to 12 weeks after starting pharmacological prevention of stone recurrence. This enables diet and/or drug dosage to be adjusted if urinary risk factors have not normalised, with further 24-hour urine measurements, if necessary. Once urinary parameters have been normalised, it is sufficient to perform a 24-hour urine evaluation every twelve months. On this issue, the Panel realises that there is only very limited published evidence.

#### 4.1.4 Reference ranges of laboratory values

Tables 4.1–4.4 provide the internationally accepted reference ranges for the various laboratory values in serum and urine.

**Table 4.1: Normal laboratory values for blood parameters in adults [23, 641]**

Blood parameter	Reference range	
Creatinine	50–100µmol/L	
Sodium	135–145mmol/L	
Potassium	3.5–5.5mmol/L	
Calcium	2.0–2.5mmol/L (total calcium)	
	1.12–1.32mmol/L (ionised calcium)	
Uric acid	119–380µmol/L	
Chloride	98–112mmol/L	
Phosphate	0.81–1.29mmol/L	
Blood gas analysis	pH	7.35–7.45
	pO <sub>2</sub>	80–90mmHg
	pCO <sub>2</sub>	35–45mmHg
	HCO <sub>3</sub>	22–26mmol/L
	BE	BE ±2mmol/L

BE = base excess (loss of buffer base to neutralise acid); HCO = bicarbonate; pCO = partial pressure of carbon dioxide; PO = partial pressure of oxygen.

#### 4.1.5 Risk indices and additional diagnostic tools

Several risk indices have been developed to describe the crystallisation risk for calcium oxalate or calcium phosphate in the urine [642-645]. Several tools for predicting stone recurrence have also been developed, including those based on artificial intelligence and machine-learning algorithms. However, their overall predictive performance remains moderate [908-911]. These models rely on heterogeneous combinations of clinical and

biochemical variables, and most lack robust external validation. Consequently, their current applicability in guiding individualised prevention strategies in clinical practice is limited.

**Table 4.2: Laboratory values for urinary parameters in adults**

Urinary Parameters	Reference ranges and limits for medical attention
pH	Consistently fasting morning spot urine pH > 5.8 and 6.2 in 24-hr collection (suspicious of renal tubular acidosis) [637, 638]
	Consistently > 7.0 (suspicious of infection)
	Consistently < 5.5 in morning urine and in 24-hr collection (suspicious of acidic arrest) [633, 646]
Specific weight	Specific weight > 1.010
Creatinine	15 to 20mg/kg/day (females), 18 to 25mg/kg/day (males)
Calcium	5.0mmol/day (see Figure 4.2)
	> 8.0mmol/day (see Figure 4.2)
Oxalate	> 0.5mmol/day (suspicious of enteric hyperoxaluria)
	> 1.0mmol/day (suspicious of primary hyperoxaluria)
Uric acid	4.0mmol/day (females), 5mmol/day (males)
Citrate	male < 1.7mmol/day, female < 1.9mmol/day
Magnesium	< 3.0mmol/day
Inorganic phosphate	35mmol/day
Ammonium	50mmol/day
Cystine	70µmol/mmol creatinine

**Table 4.3: Normal values for spot urine samples: creatinine ratios (solute/creatinine) in children [48, 647]**

Parameter/Patient age	Ratio of solute to creatinine	Units
<b>Calcium</b>	<b>mol/mol</b>	<b>mg/mg</b>
< 12 months	< 2.2	< 0.8
1–3 years	< 1.5	< 0.53
3–5 years	< 1.1	< 0.4
5–7 years	< 0.8	< 0.3
> 7 years	< 0.6	< 0.21
<b>Oxalate</b>	<b>mol/mol</b>	<b>mg/mg</b>
0–6 months	325–360	288–260
17–24 months	132–174	110–139
2–5 years	98–101	80
5–14 years	70–82	60–65
> 16 years	< 40	< 32
<b>Citrate</b>	<b>mol/mol</b>	<b>g/g</b>
0–5 years	0.12–0.25	0.20–0.42
0.25 years	0.08–0.15	0.14–0.25

Magnesium*	mol/mol	g/g
<1 year	0.4–2.2	0.10–0.48
1–2 years	0.4–1.7	0.09–0.37
2–3 years	0.3–1.6	0.07–0.34
3–5 years	0.3–1.3	0.07–0.29
5–7 years	0.3–1.0	0.06–0.21
7–10 years	0.3–0.9	0.05–0.18
10–14 years	0.2–0.7	0.05–0.15
14–17 years	0.2–0.66	0.05–0.13
Uric acid	mol/mol	g/g
< 1 year	< 1.5	< 2.2
1-3 years	< 1.3	< 1.9
3-5 years	< 1.0	< 1.5
5-10 years	< 0.6	< 0.9
>10 years	< 0.4	< 0.6

\* There is low-level evidence regarding the importance of magnesium.

**Table 4.4: Solute excretion in 24-hour urine samples in children [648, 649]\***

Calcium/ 24 hour	Citrate/24 hour		Cystine/24 hour		Oxalate/24 hour		Urate/24 hour	
	Boys	Girls	< 10 years	10 years	All age groups	< 1 year	1–5 years	5 years
< 0.1mmol/ kg/24h	> 1.9mmol/ 1.73m <sup>2</sup> /24h	> 1.6mmol/ 1.73m <sup>2</sup> /24h	< 55µmol/ 1.73m <sup>2</sup> /24h	< 200µmol/ 1.73m <sup>2</sup> /24h	< 0.5mmol/ 1.73m <sup>2</sup> /24h	< 70µmol/ kg/24h	< 65µmol/ kg/24h	< 55µmol/ kg/24h
< 4mg/kg/24h	> 365 mg/ 1.73m <sup>2</sup> /24h	> 310mg/ 1.73m <sup>2</sup> /24h	< 13 mg/ 1.73m <sup>2</sup> /24h	< 48mg/ 1.73m <sup>2</sup> /24h	< 45mg/ 1.73m <sup>2</sup> /24h	< 13mg/ kg/24h	< 11mg/ kg/24h	< 9.3mg/ kg/24h

\* 24h urine parameters are diet- and gender-dependent and may vary geographically.

## 4.2 General considerations for recurrence prevention

All stone formers, independent of their individual risk, should follow the preventive measures in Table 4.5. The main focus is the normalisation of dietary habits and lifestyle risks. Stone formers at high risk need specific prophylaxis for recurrence, which is usually pharmacological treatment based on stone analysis and urinary risk profile.

**Table 4.5: General preventive measures**

Fluid intake (drinking advice)	Fluid amount: 2.5–3.0L/day
	Water is the preferred fluid
	Diuresis: 2.0–2.5L/day
	Specific weight of urine: < 1,010g/day
Nutritional advice for a balanced diet	Balanced diet*
	Rich in vegetables and fibre
	Normal calcium content: 1–1.2g/day
	Limited NaCl content: 4–5g/day
	Limited animal protein content: 0.8–1.0g/kg/day
Lifestyle advice to normalise general risk factors	Retain a normal BMI level
	Adequate physical activity
	Balancing of excessive fluid loss
	Reduce the intake of alcohol containing fluids
	Reduce the intake of sodas and calorie-containing fluids

Caution: Protein requirements are age-dependent. Therefore, protein restriction in childhood should be handled carefully.

\* Avoid excessive consumption of vitamin supplements.

#### 4.2.1 **Fluid intake**

An inverse relationship between high fluid intake and stone formation has been repeatedly demonstrated [648-652]. Consuming additional water was associated with greater weight loss (range 44–100% more than control conditions) and fewer nephrolithiasis events (15 fewer events per 100 participants over five years) [653]. The beneficial effect of fruit juices is mainly determined by the presence of citrate or bicarbonate [654]. Citrus fruit juices seem to protect against stone disease either by increasing urinary citrate levels or by having an alkalinising effect on urine [655]. However, if potassium is present, both pH and citrate are increased [656, 657]. One large moderate-quality RCT randomly assigned men with more than one past renal stone of any type and soft drink consumption of at least 160mL/day to reduced soft drink intake or no treatment. Although the intervention significantly reduced the risk for symptomatic recurrent stones (RR: 0.83; CI: 0.71–0.98), the level of evidence for this outcome is low because the results were from only one trial [658]. An analysis of three Channing cohorts (194,095 participants) over a median follow-up of more than eight years has shown that consumption of sugar-sweetened soda and punch is associated with a higher risk of stone formation, whereas consumption of coffee, tea, beer, wine and orange juice is associated with a lower risk [659]. However, the intake of fluids should be considered within a holistic approach to health. Some of them contain calories or alcohol that may be detrimental to health. Therefore, water should be the preferred fluid.

#### 4.2.2 **Diet**

A common-sense approach to diet should be taken, that is, a mixed, balanced diet with contributions from all food groups, without any excesses [649, 660, 661]. Sufficient calcium intake is needed especially in vegetarian and vegan diets [662].

*Fruit, vegetables and fibre:* Fruit and vegetable intake should be encouraged because of the beneficial effects of fibre, although the role of the latter in preventing stone recurrences is debatable [663-666]. The alkaline content of a vegetarian diet also increases urinary pH. In addition, fruits and vegetables have a high-water content and can significantly contribute to fluid intake.

*Oxalate:* Excessive intake of oxalate-rich products should be limited or avoided to prevent high oxalate load [667], particularly in patients who have high oxalate excretion.

*Vitamin C:* Although vitamin C is a precursor of oxalate, its role as a risk factor in calcium oxalate stone formation remains controversial [668]. However, it seems wise to advise calcium oxalate stone formers to avoid excessive intake.

*Animal protein:* Animal protein should not be consumed in excess [669, 670] and limited to 0.8–1.0g/kg body weight. Excessive consumption of animal protein has several effects that favour stone formation, including hypocitraturia, low urine pH, hyperoxaluria, and hyperuricosuria.

*Calcium intake:* Calcium should not be restricted, unless there are strong reasons for doing so, due to the inverse relationship between dietary calcium and stone formation [664, 671]. The daily requirement for calcium is 1,000 to 1,200mg [23]. Calcium supplements are not recommended, except in enteric hyperoxaluria when additional calcium should be taken with meals to bind intestinal oxalate [649, 667, 669, 672]. Older adults who do not have a history of renal stones but who take calcium supplements should ensure adequate fluid intake, since it may prevent increases in urine calcium concentration, and thereby reduce or eliminate any increased risk of renal stone formation associated with calcium supplement use [673].

*Sodium:* Daily sodium (NaCl) intake should not exceed 4–5g [23]. High intake adversely affects urine composition:

- Calcium excretion is increased by reduced tubular reabsorption;
- urinary citrate is reduced due to loss of bicarbonate; and
- increased risk of sodium urate crystal formation.

Calcium stone formation can be reduced by restricting sodium and animal protein [669, 670]. A positive correlation between sodium consumption and the risk of first-time stone formation has been confirmed only in women [671]. There have been no prospective clinical trials on the role of sodium restriction as an independent variable in reducing the risk of stone formation.

*Urate:* Intake of purine-rich food should be restricted in patients with hyperuricosuric calcium oxalate [674, 675] and uric acid stones. Intake should not exceed 500mg/day [23].

### 4.2.3 Lifestyle

Lifestyle factors may influence the risk of stone formation, for example, those causing obesity [676], diabetes mellitus [677] and metabolic syndrome [678].

### 4.2.4 Summary of evidence and recommendation for recurrence prevention

Summary of evidence	LE
Increasing water intake reduces the risk of stone recurrence.	1a

Recommendation	Strength rating
Advise patients that a generous intake of fluids, preferably water, is to be maintained, allowing for a 24-hour urine volume > 2.5L.	Strong

## 4.3 Stone-specific metabolic evaluation and pharmacological recurrence prevention

### 4.3.1 Introduction

Pharmacological treatment is necessary in patients at high risk for stone formation or for associated systemic conditions. 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 4.6 highlights the most important characteristics of commonly used medication.

**Table 4.6: Pharmacological substances used for stone prevention – characteristics, specifics and dosage**

Agent	Rationale	Dose	Specifics and side effects	Stone type	Ref
Alkaline citrates	Alkalinisation Hypocitraturia Inhibition of calcium oxalate crystallisation	3.25–9.75g/d (10–30mmol/d) Children: 0.1–0.15g/kg/d	Daily dose for alkalinisation depends on urine pH	Calcium oxalate uric acid cystine	[679-683]
Allopurinol	Hyperuricosuria Hyperuricaemia	100–300mg/d Children: 1–3mg/kg/d	100mg in isolated hyperuricosuria. Renal insufficiency demands 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-Dihydroxy-adenine	[649, 684-687]
Calcium	Enteric hyperoxaluria	Up to 2,000mg/d depending on oxalate excretion	Intake 30 min. before meals	Calcium oxalate	[669, 671, 672, 688]
Magnesium	Isolated hypomagnesuria Enteric hyperoxaluria	200–400mg/d Children: 6mg/kg/d	Renal insufficiency demands dose correction. Diarrhoea, chronic alkali losses, hypocitraturia	Calcium oxalate	[689, 690] (Low-level of evidence)
Sodium bicarbonate	Alkalinisation hypocitraturia	4.5g/d	Daily dose for alkalinisation depends on urine pH	Calcium oxalate Uric acid cystine	[691]
Pyridoxine	Primary hyperoxaluria	Initial dose 5mg/kg/d Max. 20mg/kg/d	Sensory peripheral neuropathy	Calcium oxalate	[692]
Thiazide (Hydrochlorothiazide*)	Hypercalciuria	25–50mg/d Children: 0.5–1mg/kg/d	Risk for hypotension diabetes, hyperuricaemia, hypokalaemia, hypocitraturia	Calcium oxalate Calcium phosphate	[675-679, 687, 689-707]

Tiopronin	Cystinuria Increase in solubility of levels	Initial dose 800mg/d Avg. 2,000mg/d** Children: Initial dose in patients > 20kg is 15mg/kg/day. Avoid dosages > 50 mg/kg/day	Risk for proteinuria, occasional rash or gastrointestinal disturbances; autoimmune reaction	Cystine	[708-710]
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\* Patients on hydrochlorothiazide should be advised to get their skin checked on a regular basis, because they have a higher risk of developing a non-melanoma skin cancer (NMSC) and some forms of melanoma. In patients with a history of skin cancer, the indication for treatment with hydrochlorothiazide should be thoroughly reviewed [708-714].

\*\* No information is available on maximum dose and patients may be initiated on a very low dose if they have previously had reactions to tiopronin or penicillamine. For all patients, dosage should be titrated according to the frequency of stone episodes, side effects and renal function under expert supervision with close monitoring.

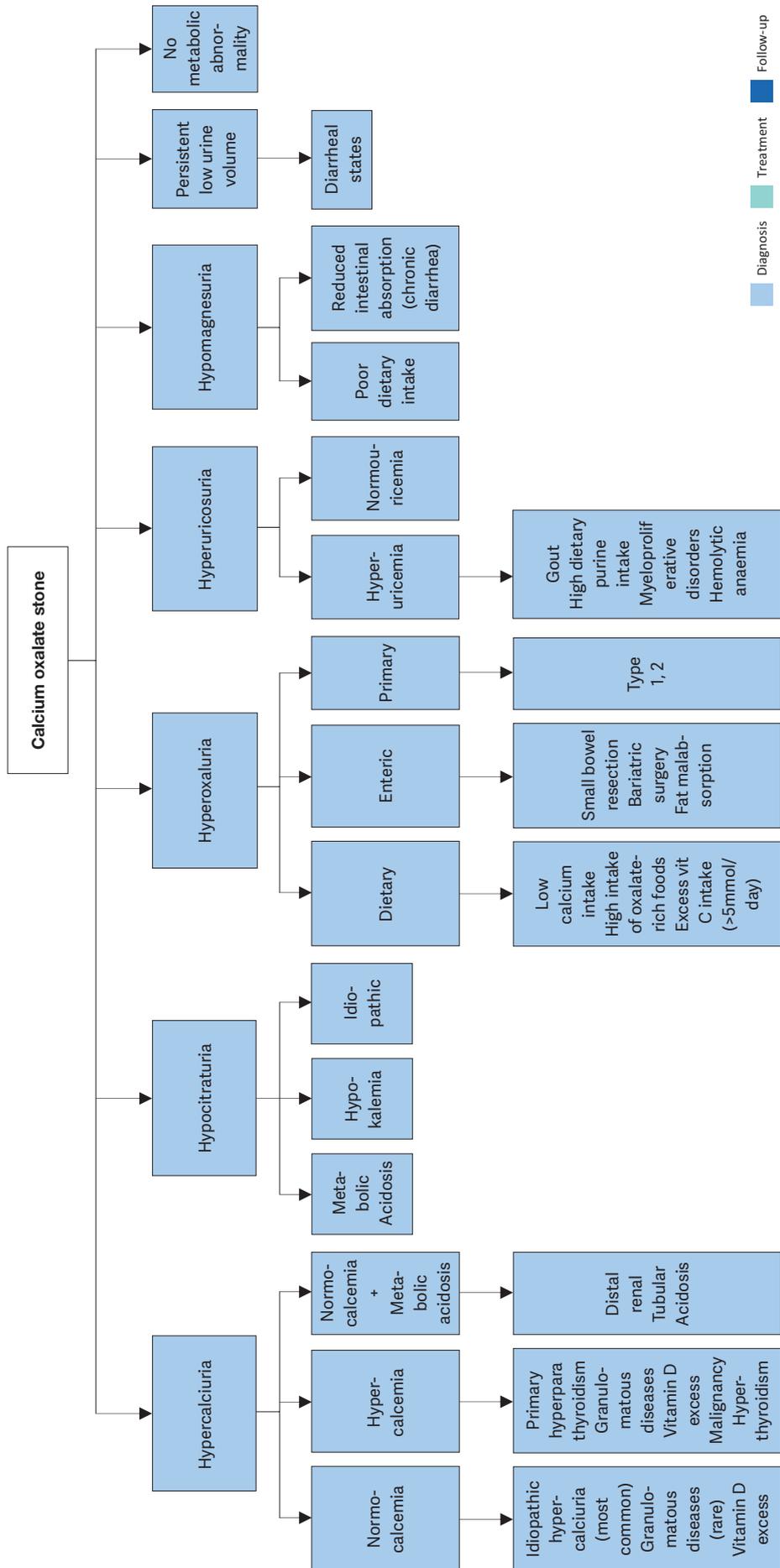
#### 4.4 Calcium oxalate stones

The criteria for identification of calcium oxalate stone formers with a high risk of recurrences and comorbidities are listed in Section 3.1.3.

##### 4.4.1 Diagnosis

Blood analysis requires measurement of creatinine, sodium, potassium, chloride, ionised calcium (or total calcium + albumin), phosphate, uric acid and, in the case of increased calcium levels, parathyroid hormone (PTH) and vitamin D. Urinalysis requires measurement of urine volume, urine pH, specific weight, calcium, oxalate, uric acid, citrate, sodium and magnesium. Figure 4.2 summarises the diagnostic steps for calcium oxalate stones.

Figure 4.2 Diagnostic algorithm for Calcium Oxalate stones

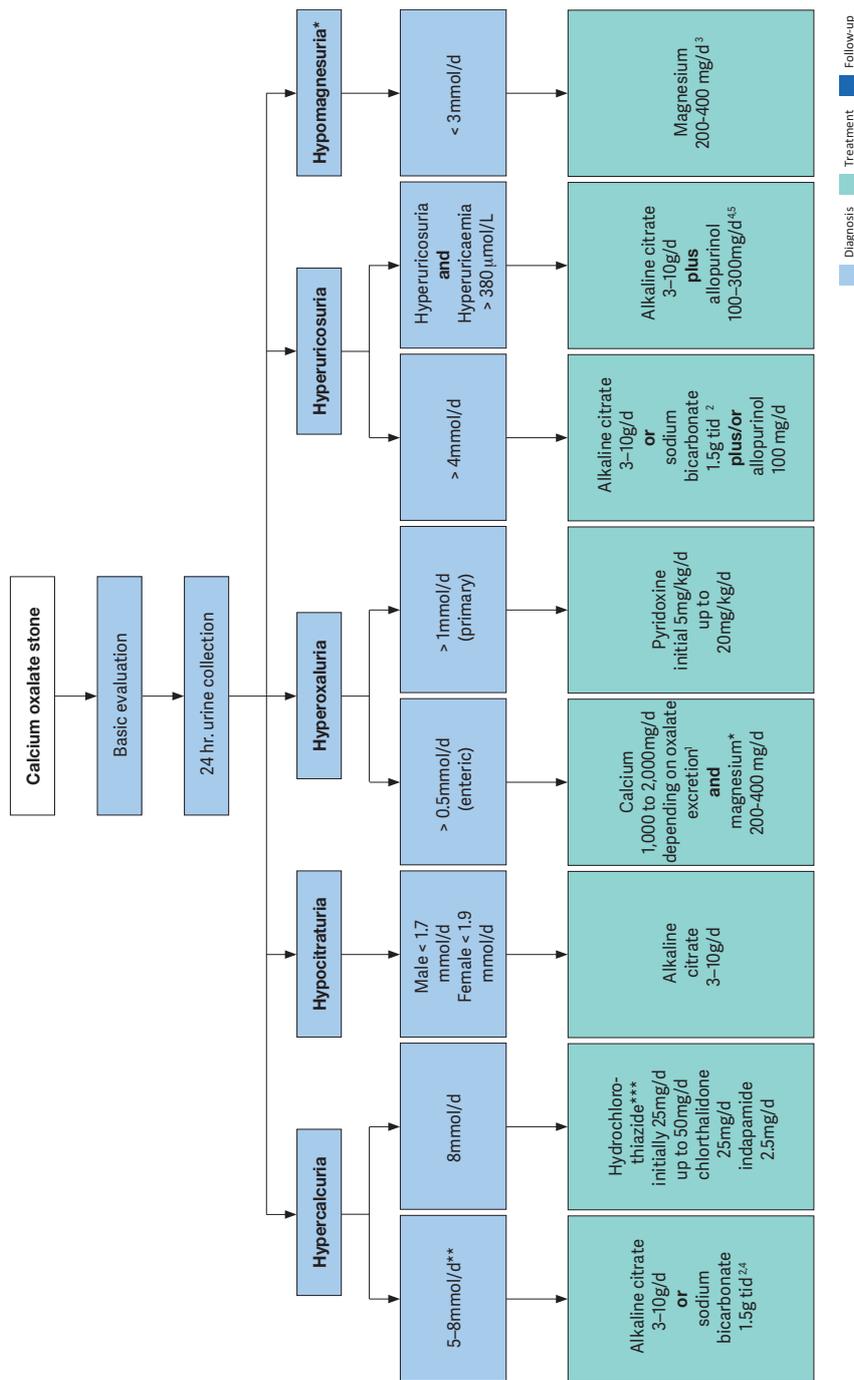


#### 4.4.2 Interpretation of results and aetiology

The most common metabolic abnormalities associated with calcium stone formation are hypercalciuria, – which affects 30–60% of adult stone formers – and hyperoxaluria (26–67%), followed by hyperuricosuria (15–46%), hypomagnesuria (7–23%), and hypocitraturia (5–29%). However, ranges tend to differ based on ethnicity [715].

- Elevated levels of ionised calcium in serum (or total calcium and albumin) require assessment of intact PTH to confirm or exclude suspected hyperparathyroidism (HPT).
- Consistently low pH (< 5.5) or 24-hour urine pH < 5.5 may promote co-crystallisation of uric acid and calcium oxalate.
- Similarly, increased uric acid excretion (> 4.5mmol/day and > 4.7mmol/day in adult women and men, respectively, or > 12mg/kg/day in children) can act as a promoter.
- A pH > 6.2 in a 24-hour urine collection may indicate RTA provided UTI has been excluded. An ammonium chloride loading test confirms distal RTA (see Section 4.6.5).
- Hypercalciuria may be associated with normocalcemia (idiopathic hypercalciuria or granulomatous diseases) or hypercalcemia (hyperparathyroidism, granulomatous diseases, vitamin D excess or malignancy).
- Hypocitraturia (male < 1.7mmol/d, female < 1.9mmol/d) may be idiopathic or secondary to metabolic acidosis or hypokalaemia.
- Oxalate excretion > 0.40mmol/day in adults confirms hyperoxaluria (see Table 4.3 for the values in children).
  - o primary hyperoxaluria (oxalate excretion mostly > 1mmol/day), appears in three genetically determined forms;
  - o secondary hyperoxaluria (oxalate excretion > 0.5mmol/day, usually < 1mmol/day), occurs due to intestinal hyperabsorption of oxalate or extreme dietary oxalate intake;
  - o mild hyperoxaluria (oxalate excretion 0.40–0.50mmol/day), commonly found in idiopathic calcium oxalate stone formers.
- Hypomagnesuria (< 3.0mmol/day) may be related to poor dietary intake or to reduced intestinal absorption (chronic diarrhoea) [716].

Figure 4.3: Therapeutic algorithm for calcium oxalate stones



<sup>1</sup> Be aware of excess calcium excretion.

<sup>2</sup> tid = three times/day (24h).

<sup>3</sup> No magnesium therapy for patients with renal insufficiency.

<sup>4</sup> There is no evidence that combination therapy (thiazide + citrate) or (thiazide + allopurinol) is superior to thiazide therapy alone [680, 717].

<sup>5</sup> Febuxostat 80mg/d.

\* Low evidence (see text)

\*\* Calciuria is a continuous variable, and treatment may be adjusted to 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 NMSC and some forms of melanoma. In patients with a history of skin cancer, the indication for treatment with hydrochlorothiazide should be thoroughly reviewed [712-714].

#### 4.4.3 Specific treatment

General preventive measures are recommended for fluid intake and diet. Hyperoxaluric stone formers should consume foods with low oxalate content, whereas hyperuricosuric stone formers benefit from daily dietary reduction of purine. Figure 4.3 summarises the pharmacological treatment of calcium oxalate stones [649, 657, 679-682, 684, 685, 687, 689-691, 695, 700-707, 715, 718-721]. There is only low-level evidence for the efficacy of preventing stone recurrence based on pretreatment stone composition examination and biochemistry measures, or on-treatment biochemistry measures [649]. One RCT concluded that treatment with hydrochlorothiazide (HCTZ) does not differ substantially from placebo in the prevention of stone recurrence of kidney stones in patients at high risk for recurrence [722]. However, the study was not powered to show any difference of HCTZ over placebo [723]. In fact, the study's main objective based on the author's protocol [723], was to investigate the existence of a dose-response relationship, i.e. a linear trend for three different doses of HCTZ (12.5, 25mg, and 50mg/day) on stone recurrence, and this was shown. In addition, the hypercalciuria levels in the population enrolled in the study were significantly lower than the threshold the EAU Guidelines recommend being administered to patients (Figure 4.3) Magnesium citrate supplements were shown to decrease the 24-hour urine calcium oxalate supersaturation [716].

#### 4.4.4 Summary of evidence and recommendations for pharmacological treatments for patients with specific abnormalities in urine composition (based on 24-hour urine samples)

Summary of evidence	LE
Alkaline citrates can reduce stone formation.	1a
Thiazides reduce calciuria.	1a
Oxalate restriction is beneficial if hyperoxaluria is present.	2b
Alkaline citrates can reduce stone formation in enteric hyperoxaluria.	4
Calcium supplement can reduce stone formation in enteric hyperoxaluria.	2
A diet reduced in fat and oxalate can be beneficial in reducing stone formation.	3
Alkaline citrates and sodium bicarbonate can be used if hypocitraturia is present.	1b
Allopurinol is first-line treatment of hyperuricosuria.	1a
Febuxostat is second-line treatment of hyperuricosuria.	1b
Avoid excessive intake of animal protein in hyperuricosuria.	1b
Restricted intake of salt is beneficial if there is high urinary sodium excretion.	1b

Recommendations	Strength rating
Prescribe thiazide or alkaline citrates or both in case of hypercalciuria.*	Strong
Advise oxalate restriction if hyperoxaluria is present.	Weak
Offer alkaline citrates in enteric hyperoxaluria.	Weak
Offer calcium supplement in enteric hyperoxaluria.	Strong
Advise reduced dietary fat and oxalate in enteric hyperoxaluria.	Weak
Prescribe alkaline citrates or sodium bicarbonate in case of hypocitraturia.	Strong
Prescribe allopurinol in case of hyperuricosuria.	Strong
Offer febuxostat as second-line treatment of hyperuricosuria.	Strong
Avoid excessive intake of animal protein in hyperuricosuria.	Strong
Advise restricted intake of salt if there is high urinary sodium excretion.	Strong

\* Patients on hydrochlorothiazide should be advised to get their skin checked on a regular basis, as they have a higher risk of developing an NMSC and some forms of melanoma. In patients with a history of skin cancer, the indication for treatment with hydrochlorothiazide should be thoroughly reviewed [712-714].

#### 4.5 Calcium phosphate stones [649, 679, 687, 700, 701, 705, 724]

Some calcium phosphate stone formers are at high risk of recurrence. Further information on identifying high-risk patients is provided in Section 3.1.3.

Calcium phosphate mainly appears in two completely different minerals: carbonate apatite and brushite. Carbonate apatite crystallisation occurs at a pH > 6.8 and may be associated with infection. Brushite crystallises at an optimum pH of 6.5–6.8 at high urinary concentrations of calcium (>8mmol/day) and phosphate (>35mmol/day). Its occurrence is not related to UTI. Possible causes of calcium phosphate stones include HPT, RTA and UTI, each of which requires different therapy.

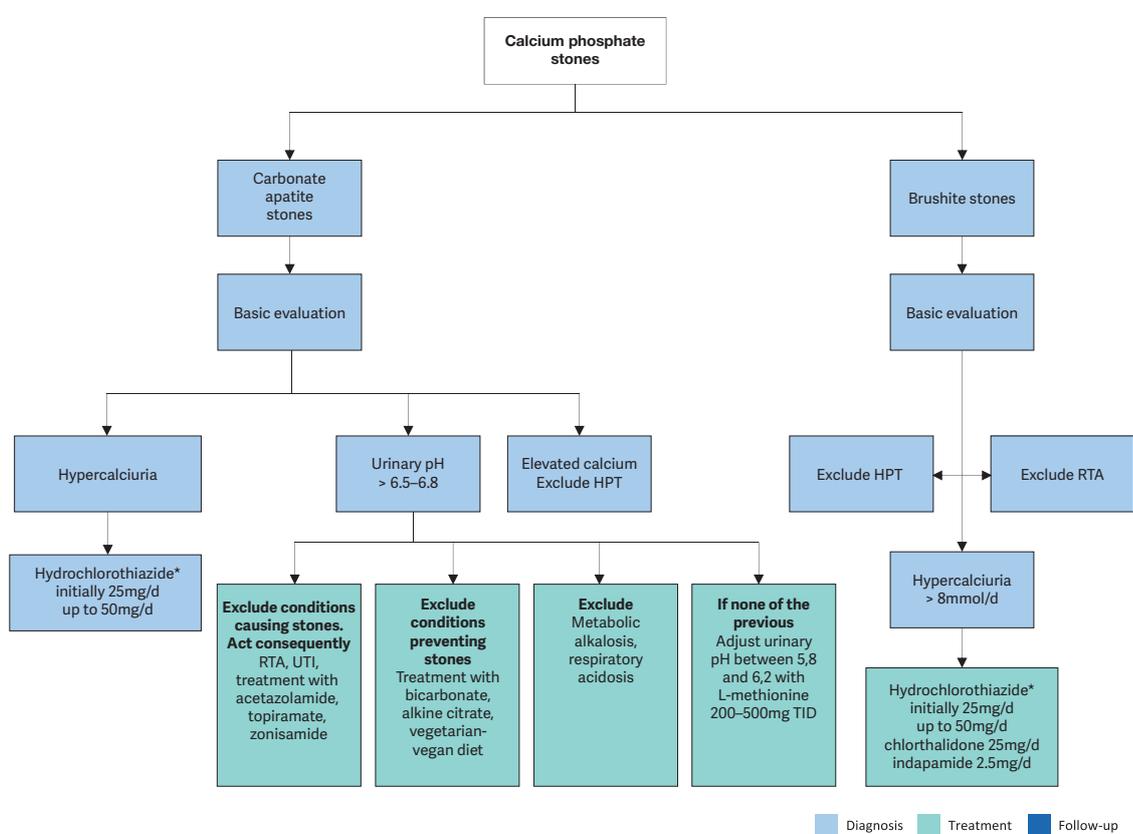
#### 4.5.1 Diagnosis

Diagnosis requires blood analysis for creatinine, sodium, potassium, chloride, ionised calcium (or total calcium + albumin), phosphate and PTH (in the case of increased calcium levels). Urinalysis includes measurement of volume, urine pH, specific weight, calcium, phosphate and citrate.

#### 4.5.2 Interpretation of results and aetiology

General preventive measures are recommended for fluid intake and diet. The diagnostic and therapeutic algorithm for calcium phosphate stones is shown in Figure 4.4.

Figure 4.4: 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 NMSC and some forms of melanoma. In patients with a history of skin cancer, the indication for treatment with hydrochlorothiazide should be thoroughly reviewed [712-714].

#### 4.5.3 Pharmacological therapy [649, 679, 687, 700, 701, 705, 724]

Hyperparathyroidism and RTA are common causes of calcium phosphate stone formation. Most patients with primary HPT require surgery. Renal tubular acidosis can be corrected pharmacologically, including with bicarbonate or alkaline citrate therapy. If primary HPT and RTA have been excluded, pharmacotherapy for calcium phosphate calculi depends on the effective reduction of urinary calcium levels using thiazides. For infection-associated calcium phosphate stones, it is important to consider the guidance given for infection stones.

#### 4.5.4 Summary of evidence and recommendation for the management of calcium phosphate stones

Summary of evidence	LE
Thiazide decreases calciuria.	1a

Recommendation	Strength rating
Prescribe thiazide in case of hypercalciuria > 8mmol/24 hours.	Strong

## 4.6 Disorders and diseases related to calcium stones

### 4.6.1 Hyperparathyroidism [725-730]

Primary HPT is responsible for an estimated 5% of all calcium stone formation. Renal stones occur in approximately 20% of patients with primary HPT. Elevated levels of PTH significantly increase calcium turnover, leading to hypercalcemia, hypercalciuria and bone disease. Serum calcium may be mildly elevated and serum PTH may be within the upper normal limits, therefore, repeated measurements may be needed; preferably with the patient fasting. Stones of HPT patients may contain both calcium oxalate and calcium phosphate. Nephrocalcinosis and CKD may also occur.

Although the effect on stone relapses is uncertain if primary HPT is diagnosed [731], parathyroidectomy is generally suggested to prevent or cure other complications. If surgery is contraindicated, primary HPT can be treated with cinacalcet.

### 4.6.2 Granulomatous Diseases [732]

Granulomatous diseases, such as sarcoidosis, may be complicated by hypercalcemia and hypercalciuria secondary to increased calcitriol production. The latter is independent of PTH control, leading to increased calcium absorption in the gastrointestinal tract and suppression of PTH. Treatment focuses on the activity of the granulomatous diseases and may require steroids, hydroxychloroquine or ketoconazole. Treatment should be reserved for a specialist.

### 4.6.3 Primary Hyperoxaluria [692]

Patients with primary hyperoxaluria (PH) should be referred to a specialised centre, as successful management requires an experienced interdisciplinary team. The main therapeutic aim is to reduce endogenous oxalate production, which is increased in patients with PH. In approximately one-third of patients with PH type I, pyridoxine therapy normalises or significantly reduces urinary oxalate excretion. The goal of adequate urine dilution is achieved by adjusting fluid intake to 3.5–4.0L/day in adults (children 1.5L/m<sup>2</sup> body surface area) and following a circadian drinking regimen.

Therapeutic options for preventing calcium oxalate crystallisation include hyper-diuresis, alkaline citrates, magnesium and RNAi agents, Lumasiran and Nedosiran (the latter not yet approved for use by EMA). These are new treatments for reducing the synthesis of oxalate of PH type 1 [733]. Lumasiran has been shown to decrease oxaluria, oxalaemia and stone recurrences. It stabilises GFR and may improve nephrocalcinosis [734, 735].

Treatment regimens are:

- pyridoxine in PH type I: 5–20mg/kg/day according to urinary oxalate excretion and patient tolerance;
- alkaline citrate: 3.25–9.75g/day in adults, 0.1–0.15mg/kg/day in children;
- Lumasiran: subcutaneous injection with dose and timing adjusted according to body weight and duration of treatment:
  - o Initial dose: bodyweight < 10kg: 6mg/kg; bodyweight 10–20kg: 6mg/kg; bodyweight > 20kg: 3mg/kg; once per month for three months subcutaneous injection.
  - o Maintenance starting one month after initial doses: bodyweight < 10kg: 3mg/kg once monthly; bodyweight 10–20kg: 6mg/kg every three months, bodyweight > 20kg: 3mg/kg every three months [644].

#### 4.6.3.a Summary of evidence and recommendation for the management of primary hyperoxaluria

Summary of evidence	LE
Pyridoxine can reduce the urinary oxalate excretion in primary hyperoxaluria type 1.	3
Lumasiran reduces the urinary oxalate excretion and stone recurrences in primary hyperoxaluria type 1.	1b

Recommendations	Strength rating
Prescribe pyridoxine for primary hyperoxaluria type 1.	Strong
Prescribe Lumasiran for primary hyperoxaluria type 1 if not responsive to pyridoxine.	Strong

#### 4.6.4 **Enteric hyperoxaluria** [667, 672, 736-738]

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 surgery, as well as in Crohn's disease and pancreatic insufficiency. In addition to hyperoxaluria, these patients usually present with hypocitraturia due to loss of alkali. Urine pH is usually low, as are urinary calcium and urine volume. All these abnormalities contribute to high levels of supersaturation with calcium oxalate, crystalluria, stone formation and, less frequently, to nephrocalcinosis and CKD. Specific preventive measures are:

- restricted intake of oxalate-rich foods [667];
- restricted fat intake [667];
- calcium supplementation at mealtimes to enable calcium oxalate complex formation in the intestine [672, 736-738];
- sufficient fluid intake to balance the intestinal loss of water caused by diarrhoea; and
- alkaline citrates to raise urinary pH and citrate.

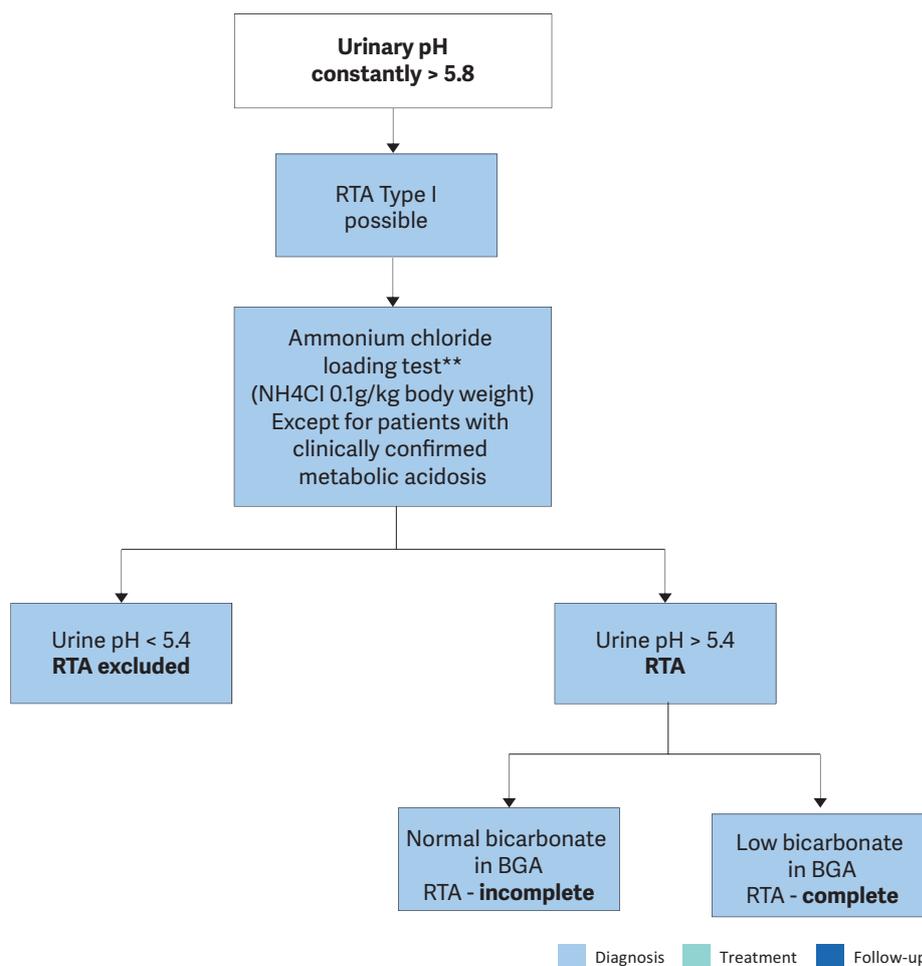
Summary of evidence	LE
Alkaline citrates can be beneficial to replace citrate loss and raise urine pH.	3
Calcium supplements with meals enable calcium oxalate complex formation in the intestine.	2b
Reduction in dietary fat and oxalate can be beneficial in intestinal malabsorption.	3

Recommendations	Strength rating
Prescribe alkaline citrates for enteric hyperoxaluria.	Weak
Advise patients to take calcium supplements with meals.	Strong
Advise patients to follow a diet with a low-fat and low-oxalate content.	Weak

#### 4.6.5 **Renal tubular acidosis** [649, 687, 739, 740]

Renal tubular acidosis is caused by severe impairment of proton (type I) or bicarbonate handling (type II) along the nephron. Kidney stone formation occurs in patients with distal RTA type I. Figure 4.5 outlines the diagnosis of RTA type I. Table 4.7 shows acquired and inherited causes of RTA.

Figure 4.5: Diagnosis of renal tubular acidosis



BGA = blood gas analysis; RTA = renal tubular acidosis.

\*\* An alternative ammonium chloride loading test using one-day NH<sub>4</sub>Cl load with 0.05g/kg bodyweight might provide similar results and may be better tolerated by the patient [741]. A second alternative in these cases could be the furosemide/fludrocortisone acidification test [722].

Renal tubular acidosis can be acquired or inherited. Reasons for acquired RTA can be 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 parathyroidism. It may also be drug-induced (e.g. amphotericin B, foscarnet, lithium, zonisamide and other carbonic anhydrase inhibitors).

Table 4.7: Inherited causes of renal tubular acidosis

Type - inheritance	Gene/gene product/function	Phenotype
Autosomal dominant	SLC4A1/AE1/Cl-bicarbonate exchanger	Hypercalciuria, hypokalaemia, rickets/osteomalacia
Autosomal recessive with hearing loss	ATP6V1B1/B1 sub-unit of vacuolar H-ATPase / proton secretion	Hypercalciuria, hypokalaemia, rickets/osteomalacia
Autosomal recessive	ATP6V0A4 / A4 sub-unit of vacuolar H-ATPase / proton secretion	Hypercalciuria, hypokalaemia, rickets/osteomalacia

Very rarely, biallelic causative variants in FOXI1 and WDR72 genes have also been identified. The main therapeutic aim of RTA treatment is restoring 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 4.8) and bone demineralisation. The alkali load reduces tubular reabsorption of citrate, which in turn normalises citrate excretion. Therapeutic

success can be monitored by venous blood gas analysis (base excess:  $\pm 2.0$ mmol/L) in complete RTA. If excessive calcium excretion ( $> 8$ mmol/day) persists after re-establishing acid-base equilibrium, thiazides may lower urinary calcium excretion.

**Table 4.8: Pharmacological treatment of renal tubular acidosis**

Biochemical risk factor	Indication for pharmacological therapy	Medication
Hypercalciuria	Calcium excretion $> 8$ mmol/day	Hydrochlorothiazide*, in adults: 25mg/day initially, up to 50mg/day in children: 0.5–1mg/kg/day Alternatives in adults: Chlorthalidone 25mg/d Indapamide 2.5mg/d
Inadequate urine pH	Citrate excretion male $< 1.7$ mmol/day, female $< 1.9$ mmol/day	Alkaline citrate, 3.25–9.75g/day divided in three doses OR Sodium bicarbonate, 1.5g, three times daily

\* Patients on hydrochlorothiazide should be advised to get their skin checked on a regular basis as they have a higher risk of developing NMSC and some forms of melanoma. In patients with a history of skin cancer, the indication for treatment with hydrochlorothiazide should be thoroughly reviewed [712-714].

#### 4.6.5.a Summary of evidence and recommendations for the management of tubular acidosis

Summary of evidence	LE
Alkaline citrates can be beneficial in distal renal tubular acidosis to correct metabolic acidosis.	2b
Thiazides are beneficial for hypercalciuria.	1a

Recommendations	Strength rating
Prescribe alkaline citrates for distal renal tubular acidosis.	Strong
Address normalisation of bicarbonatemia and citraturia with alkaline citrate.	Strong
Prescribe thiazides for hypercalciuria.	Strong

#### 4.6.6 Nephrocalcinosis [742]

Nephrocalcinosis (NC) refers to increased calcium crystal deposition within the renal cortex or medulla and occurs alone or in combination with renal stones. There are various metabolic causes. The main causes are HPT, primary and enteric hyperoxalurias, genetic and acquired RTA, medullary sponge kidney, vitamin D metabolic disorders, sarcoidosis, idiopathic hypercalciuria and hypocitraturia, and genetic disorders, including Dent's disease and Bartter's syndrome. The many causes of NC mean there is no single standard therapy. Therapeutic attention must focus on the underlying metabolic or genetic disease, on the frequent association with CKD while minimising the biochemical risk factors.

##### 4.6.6.a Diagnosis

Diagnosis requires the following blood analysis: PTH (in the case of increased calcium levels), vitamin D and metabolites, vitamin A, sodium, potassium, magnesium, chloride and bicarbonate. Urinalysis should investigate urine pH profile at different times of the day, daily urine volume, specific weight of urine, and levels of calcium, oxalate, phosphate, uric acid, magnesium and citrate [638].

#### 4.7 Uric acid and ammonium urate stones

All uric acid and ammonium urate stone formers are considered to be at high risk of recurrence [23]. Uric acid nephrolithiasis is responsible for approximately 10% of renal stones [743, 744] and is associated with hyperuricosuria or low urinary pH. Hyperuricosuria may be a result of dietary excess, endogenous overproduction (enzyme defects), myeloproliferative disorders, chemotherapy drugs, gout or catabolism [635]. Low urinary pH may be caused by decreased urinary ammonium excretion (insulin resistance, gout, autosomal

dominant polycystic kidney disease [ADPKD]). Increased endogenous acid production (insulin resistance, metabolic syndrome, exercise-induced lactic acidosis), increased acid intake (high animal protein intake), or increased base loss (diarrhoea) [635].

Ammonium urate stones are extremely rare, comprising < 1% of all types of urinary stones. They are associated with UTI, malabsorption (inflammatory bowel disease and ileostomy diversion or laxative abuse), phosphate deficiency, hypokalaemia and malnutrition. Suggestions on uric acid and ammonium urate nephrolithiasis are based on level 3 and 4 evidence. Chronic kidney disease is frequently observed.

#### 4.7.1 **Diagnosis**

Figure 4.6 shows the diagnostic algorithm for uric acid stones and Figure 4.7 shows the therapeutic algorithm for uric acid and ammonium urate stones. Blood analysis requires measurement of creatinine and uric acid levels. Urinalysis requires measurement of urine volume, urine pH, specific weight of urine and uric acid level. Urine culture is needed in the case of ammonium urate stones.

#### 4.7.2 **Interpretation of results**

Uric acid and ammonium urate stones form under completely different biochemical conditions. Low urine pH promotes uric acid crystallisation.

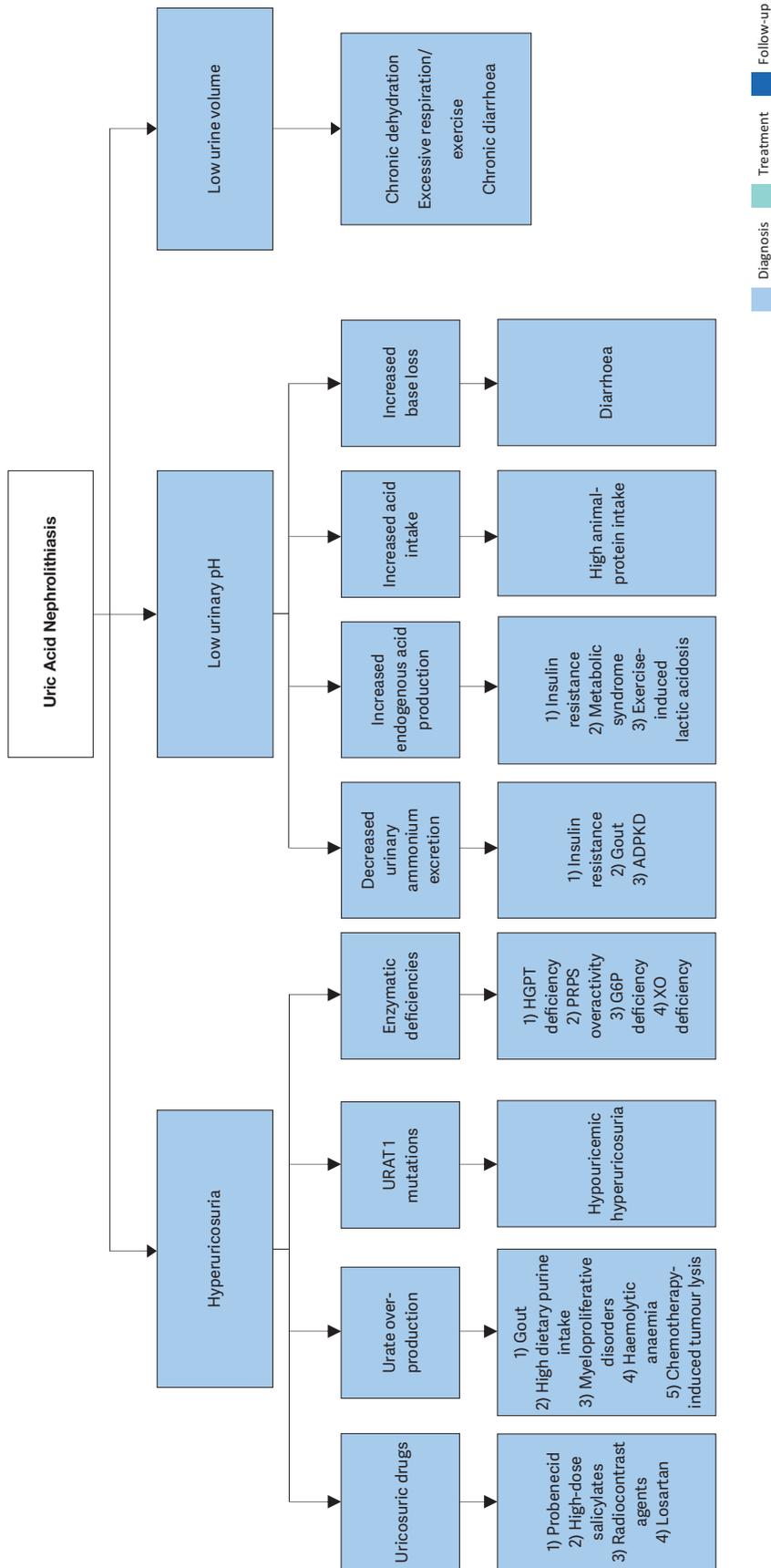
Hyperuricosuria is defined as uric acid excretion > 4mmol/day and > 5mmol/day in adult females and males, respectively, or > 0.12mmol/kg/day in children. Hyperuricaemia may be present, but there is only weak evidence for its association with stone formation [745].

Hyperuricosuric calcium oxalate stone formation can be distinguished from uric acid stone formation by urinary pH, which is usually > 5.5 in calcium oxalate stone formation and < 5.5 in uric acid stone formation and occasional absence of hyperuricosuria in patients with pure uric acid stones [746, 747]. Ammonium urate crystals form in urine at pH > 6.5 and high uric acid concentration in urine in the presence of ammonium [748, 749].

#### 4.7.3 **Specific treatment**

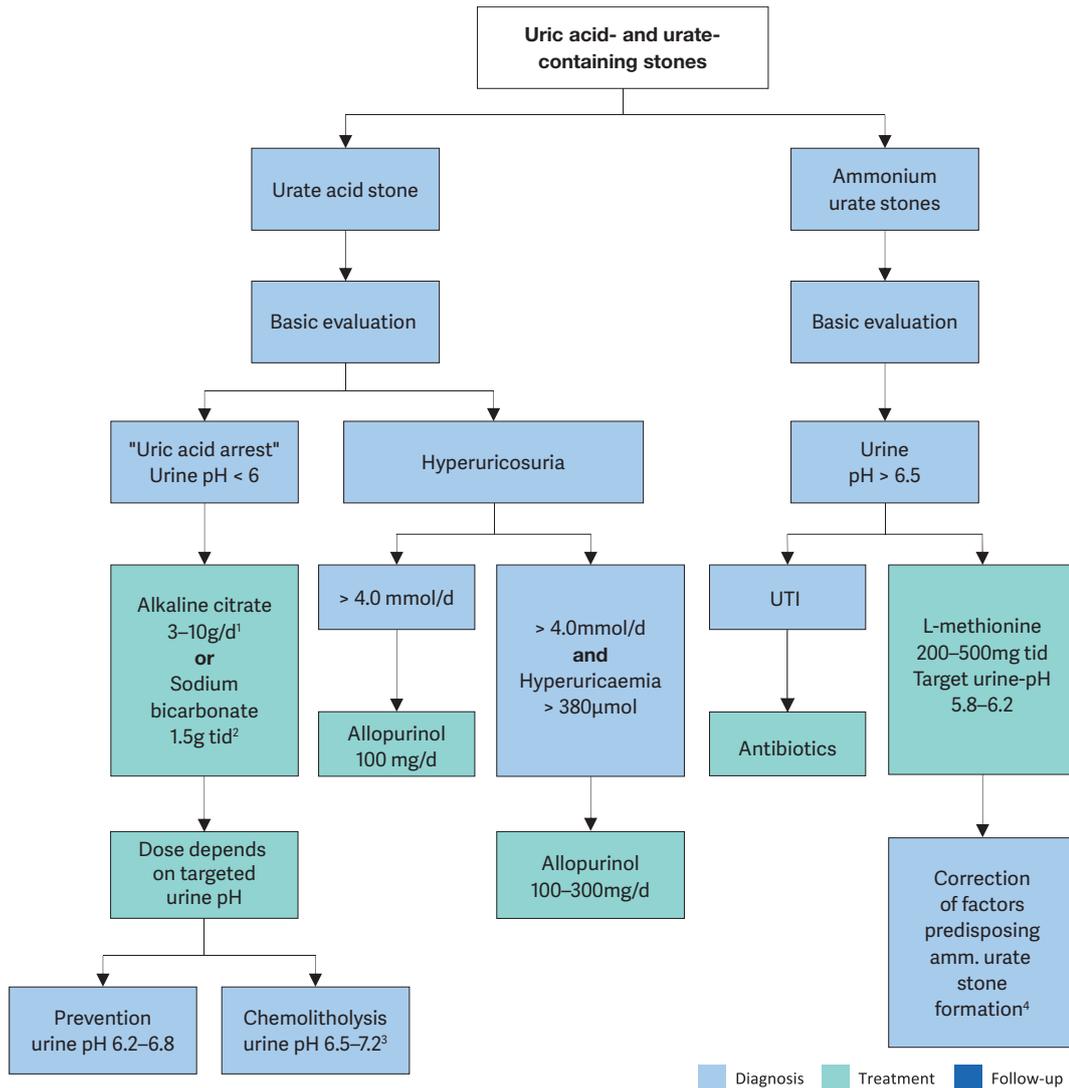
General preventive measures are recommended for fluid intake and diet. Hyperuricosuric stone formers benefit from purine reduction in their daily diet. Figure 4.6 describes pharmacological treatment [23, 743, 746, 747]. For uric acid stones, allopurinol may change the stone composition distribution in patients with gout to a pattern similar to that in stone formers without gout [750].

Figure 4.6: Diagnostic algorithm for uric acid stones



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

Figure 4.7: Therapeutic algorithm for uric acid and ammonium urate stone



<sup>1</sup> d: day.

<sup>2</sup> tid: three times a day.

<sup>3</sup> A higher pH may lead to calcium phosphate stone formation.

<sup>4</sup> In patients with high uric acid excretion, allopurinol may be helpful.

4.7.4 Summary of evidence and recommendations for the management of uric acid and ammonium urate stones

Summary of evidence	LE
Alkaline citrates can be beneficial to alkalinise the urine in uric acid stone formers.	3
Allopurinol can be beneficial in hyperuricosuric urate stone formers.	1b

Recommendations	Strength rating
Prescribe alkaline citrates to alkalinise the urine in uric acid stone formers.	Strong
Prescribe allopurinol in hyperuricosuric urate stone formers.	Strong

4.8 Struvite and infection stones

All infection-stone formers are deemed at high risk of recurrence. Struvite stones represent 2–15% of the stones sent for analysis. Stones that contain struvite may originate *de novo* or grow on pre-existing stones, which are infected with urea-splitting bacteria [751]. There are several factors predisposing patients to struvite stone formation (Table 4.9) [752]. Several studies have reported that urinary metabolic alterations can be disclosed in 36–81% of patients with mixed struvite stones [753-758].

#### 4.8.1 **Diagnosis**

Blood analysis requires measurement of creatinine, and urinalysis requires repeat urine pH measurements and urine culture. In cases of mixed struvite stones, the search for metabolic abnormalities in 24-hour urine after stone removal and infection control is suggested.

#### 4.8.2 **Interpretation**

Infection stones contain the following minerals: struvite and/or carbonate apatite and/or ammonium urate. Urine culture typically provides evidence for urease-producing bacteria, which increase ammonia ions and develop alkaline urine (Table 4.10). Carbonate apatite starts to crystallise at a urine pH level of 6.8. Struvite only precipitates at pH > 7.2 [759, 760]. A mixed struvite stone, i.e. containing a high percentage of calcium oxalate and carbonate apatite, suggests the over-infection of a 'metabolic' calcium oxalate or calcium phosphate stone [758]. *Proteus mirabilis* accounts for more than half of all urease-positive UTIs [761, 762].

#### 4.8.3 **Specific treatment**

General preventive measures are recommended for fluid intake and diet. Specific measures include complete surgical stone removal [752], short- or long-term antibiotic treatment [763], and urinary acidification using methionine [697] or ammonium chloride [764]. For persistent infections/colonisation, acetohydroxamic acid may be an option [765, 766] (Figure 4.8), however, it is not licensed/available in all European countries.

Eradication of infection after complete stone removal is desirable. The evidence regarding the duration of post-operative antibiotic administration is inconclusive.

Summary of evidence	LE
Removing the stone material as completely as possible with surgery can reduce ongoing infection.	3
Antibiotics are beneficial after complete stone removal.	3
Ammonium chloride, 1g two or three times daily, can ensure urinary acidification to prevent recurrent infection.	3
Methionine, 200–500mg, one to three times daily, can be used as an alternative to ammonium chloride, to ensure urinary acidification.	3
Treatment of underlying metabolic abnormalities reduces recurrence of mixed struvite stones.	3
Urease inhibitors in case of severe infection are occasionally used (if licensed).	1b

Recommendations	Strength rating
Surgically remove the stone material as completely as possible.	Strong
Prescribe antibiotics in case of persistent bacteriuria.	Strong
Prescribe ammonium chloride, 1g two or three times daily to ensure urinary acidification.	Weak
Prescribe methionine, 200–500mg, one to three times daily, as an alternative, to ensure urinary acidification.	Weak

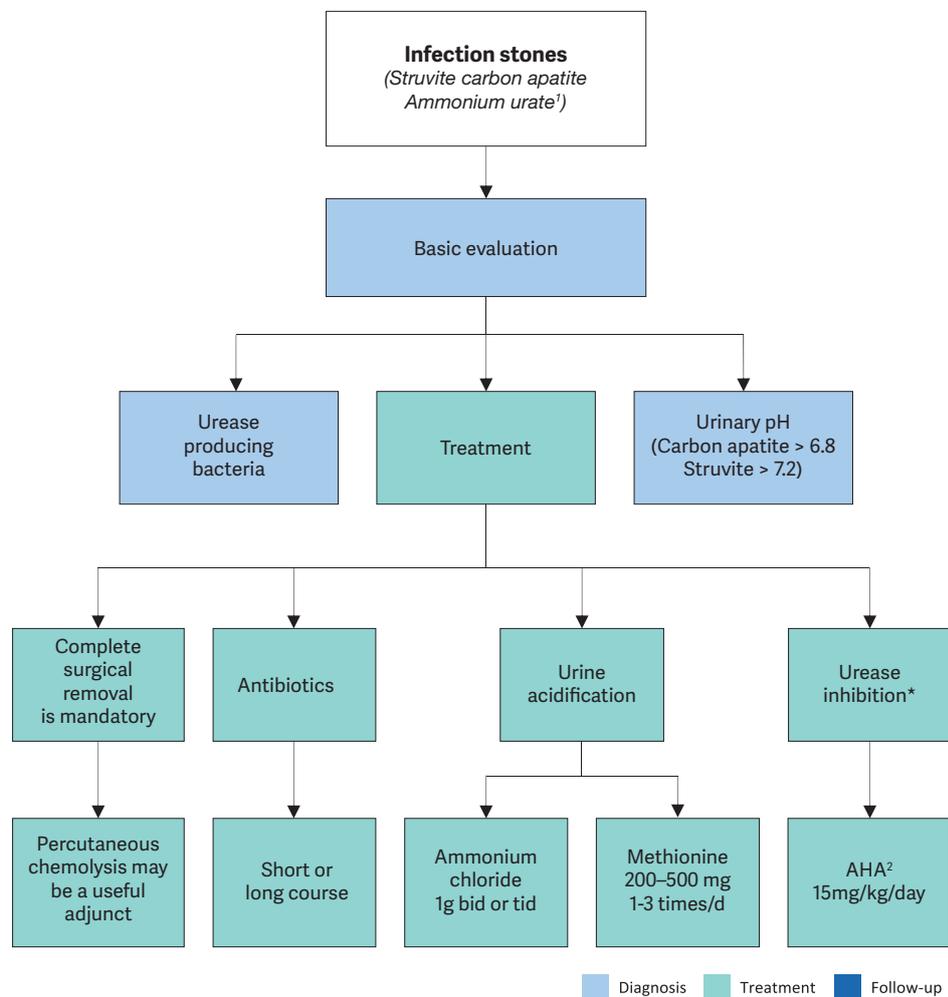
**Table 4.9: Factors predisposing to struvite stone formation.**

<ul style="list-style-type: none"> <li>• Neurogenic bladder</li> <li>• Spinal cord injury/paralysis</li> <li>• Continent urinary diversion</li> <li>• Ileal conduit</li> <li>• Foreign body</li> <li>• Stone disease</li> <li>• Indwelling urinary catheter</li> </ul>	<ul style="list-style-type: none"> <li>• Urethral stricture</li> <li>• Benign prostatic hyperplasia</li> <li>• Bladder diverticulum</li> <li>• Cystocele</li> <li>• Calyceal diverticulum</li> <li>• UPJ obstruction</li> </ul>
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**Table 4.10: Most important species of urease-producing bacteria**

Obligate urease-producing bacteria (> 98%)
<ul style="list-style-type: none"> <li>• <i>Proteus</i> spp.</li> <li>• <i>Providencia rettgeri</i></li> <li>• <i>Morganella morganii</i></li> <li>• <i>Corynebacterium urealyticum</i></li> <li>• <i>Ureaplasma urealyticum</i></li> </ul>
Facultative urease-producing bacteria
<ul style="list-style-type: none"> <li>• <i>Enterobacter gergoviae</i></li> <li>• <i>Klebsiella</i> spp.</li> <li>• <i>Providencia stuartii</i></li> <li>• <i>Serratia marcescens</i></li> <li>• <i>Staphylococcus</i> spp.</li> </ul>
<p><b>CAUTION:</b> 0–5% of <i>Escherichia coli</i>, <i>Enterococcus</i> spp. and <i>Pseudomonas aeruginosa</i> strains may produce urease.</p>

**Figure 4.8: Diagnostic and therapeutic algorithm for infection stones**



<sup>1</sup> Discussed with uric acid stones.

<sup>2</sup> Acetohydroxamic acid.

\* When nationally available.

bid = twice a day; tid = three times a day; AHA = acetohydroxamic acid.

## 4.9 Cystine stones

Cystine stones account for 1–2% of all urinary stones in adults and 6–8% of the stones reported in paediatric studies [767, 768]. All cystine stone formers are deemed at high risk of recurrence and CKD [769, 770].

### 4.9.1 Diagnosis

Blood analysis includes measurement of creatinine, and urinalysis includes 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 [771].

#### Interpretation

- Cystine is poorly soluble in urine and crystallises spontaneously within the physiological urinary pH range.
- Cystine solubility depends strongly on urine pH: at pH 6.0, the limit of solubility is 1.33mmol/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 [772].
- There is no role for genotyping patients in the routine management of cystinuria [773, 774].
- Reductive therapy targets the disulphide binding in the cystine molecule. For therapy monitoring, it is important to differentiate between cystine, cysteine, and drug-cysteine complexes. However, available methods to monitor cystinuria treatment which may be able to differentiate between the various complexes formed by therapy are cumbersome [775, 776] and/or inaccurate. This includes high-performance liquid chromatography (HPLC) [77]. Quantitative 24-hour urinary cystine excretion confirms the diagnosis in the absence of stone analysis.
- Levels above 0.125mmol/day (30mg/day) are considered abnormal [777, 778].

### 4.9.2 Specific treatment

General preventative measures for fluid intake and diet are recommended. A diet low in methionine (poor in meat, especially red meat and poultry, fish, eggs and dairy products, cheese in particular) may theoretically reduce urinary excretion of cystine. However, patients may not comply with such a diet. A restricted intake of sodium is more easily achieved and is more effective in reducing urinary cystine [779]. Patients are usually advised to avoid sodium consumption > 2g/day (5g NaCl) [780]. A high level of diuresis is of fundamental importance, aiming for a 24-hour urine volume of > 3L [772, 780-782]. A considerable fluid intake evenly distributed throughout the day is necessary.

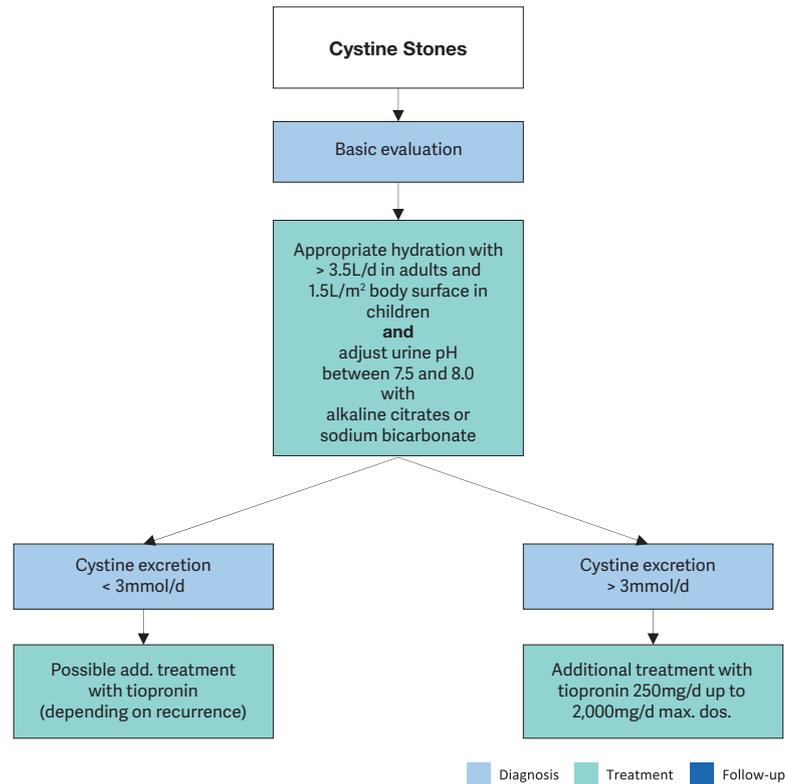
#### 4.9.2.a Pharmacological treatment of cystine stones

The main therapeutic option for avoiding cystine crystallisation is to maintain urine pH > 7.5, to improve cystine solubility, and ensure appropriate hydration with a minimum of > 3L/day in adults or 1.5L/m<sup>2</sup> body surface area in children [772, 780-782]. Home monitoring of the urine pH is suggested because of the possibility of self-adjusting alkaline treatment keeping the urine pH within range and to avoid excess alkalinisation [77, 783].

Free cystine concentration can be decreased by reductive substances, which act by splitting the disulphide binding of cystine.

The thiol-binders tiopronin and penicillamine are currently the best choice for cystine reduction. However, side effects often lead to treatment termination or to switching to the other thiol-binder, for example, when nephrotic syndrome develops or when there is poor compliance, especially with long-term use. Tiopronin is recommended at cystine levels  $\geq$  3.0mmol/day (720 mg/day) or in the case of recurring stone formation, notwithstanding other preventive measures [772, 780-782]. Spot measurements of urine protein should be performed at baseline and during follow-up along with specific blood monitoring.

Figure 4.9: Metabolic management of cystine stones [784]



4.9.3 Summary of evidence and recommendations for the management of cystine stones

Summary of evidence	LE
Increasing fluid intake so that 24-hour urine volume exceeds 3L is used to dilute the cystine.	3
Alkaline citrates 3–10mmol two or three times daily can be used to achieve pH > 7.5.	3
Tiopronin, 250–2,000mg/day can be used to reduce stone formation in patients with cystine excretion ≥ 3mmol/day, or when other measures are insufficient.	3

Recommendations	Strength rating
<b>Therapeutic measures</b>	
<b>Urine dilution</b> Advise patients to increase their fluid intake so that 24-hour urine volume exceeds 3L.	Strong
<b>Alkalinisation</b> Prescribe potassium citrate 3–10mmol two or three times daily, to achieve pH > 7.5	Strong
<b>Complex formation with cystine</b> For patients with cystine excretion, > 3mmol/day, or when other measures are insufficient: prescribe in addition to other measures tiopronin, 250–2,000mg/day.	Strong

4.10 2,8-Dihydroxyadenine stones and xanthine stones

All 2,8-Dihydroxyadenine and xanthine stone formers are at high risk of recurrence. Both stone types are rare. Diagnosis and specific prevention are similar to those for uric acid stones [23].

4.10.1 2,8-Dihydroxyadenine stones

A genetically determined defect of adenine phosphoribosyl transferase causes high urinary excretion of poorly soluble 2,8-Dihydroxyadenine [785]. High-dose allopurinol or febuxostat are important options but should be given with regular monitoring [786].

#### 4.10.2 Xanthine stones

Patients who form xanthine stones usually show decreased levels of serum uric acid. There is no available pharmacological intervention.

#### 4.10.3 Fluid intake and diet

Recommendations for general preventive measures apply. Pharmacological intervention is difficult; therefore, high fluid intake ensures optimal specific weight levels of urine < 1.010 (urine specific gravity). A purine-reduced diet decreases the risk of spontaneous crystallisation in urine.

### 4.11 Drug-induced stones

Drug stones are induced by pharmacological treatment [787] (Table 4.10). Two types exist:

- stones formed by crystallised compounds of the drug; and
- stones formed due to unfavourable changes in urine composition under drug therapy.

**Table 4.11: Compounds that cause drug stones**

Active compounds crystallising in urine	Substances impairing urine composition
<ul style="list-style-type: none"><li>• Allopurinol/oxypurinol</li><li>• Amoxicillin/ampicillin</li><li>• Ceftriaxone</li><li>• Quinolones</li><li>• Ephedrine</li><li>• Indinavir and other HIV-protease inhibitors</li><li>• Magnesium trisilicate</li><li>• Sulphonamides</li><li>• Triamterene</li></ul>	<ul style="list-style-type: none"><li>• Acetazolamide</li><li>• Aluminium magnesium hydroxide</li><li>• Ascorbic acid</li><li>• Calcium</li><li>• Laxatives</li><li>• Losartan</li><li>• Methoxyflurane</li><li>• Orlistat</li><li>• Vitamin D</li><li>• Topiramate</li><li>• Zonisamide</li></ul>

### 4.12 Matrix stones

Pure matrix stones are extremely rare, with fewer than 70 cases described in the literature, and are more prevalent in females. The main risk factors are recurrent UTIs, especially due to *P. mirabilis* or *E. coli*, previous surgery for stone disease, chronic renal failure, and haemodialysis. Complete endourological removal, frequently via the percutaneous approach, is critical. Given the rarity of matrix calculi, a specific prophylactic regimen to minimise recurrence cannot be recommended. Eliminating infections and prophylactic use of antibiotics are most commonly proposed [788].

### 4.13 Unknown stone composition [16]

An accurate medical history is the first step towards identifying risk factors as summarised in Section 3.1.3 and Figure 4.1.

Diagnostic imaging begins with a US examination of both kidneys to establish whether the patient is stone-free. Stone detection by the US should be followed by KUB and unenhanced multislice CT in adults to differentiate between calcium-containing and non-calcium stones.

Blood analysis may demonstrate severe metabolic and organic disorders, such as renal insufficiency, HPT or other hypercalcaemic states and hyperuricaemia. In children with GFR lower than 30ml/min., oxalaemia should also be checked.

Urinalysis is performed routinely with a dipstick test as described above. A urine culture is required if there are signs of infection. Urine pH < 5.5 in 24-hour urine collection indicates hyperacidic urine, which could promote uric acid crystallisation. Urine pH > 6.2 in 24-hour urine collection may indicate RTA if UTI is excluded [738, 740].

Microscopy of urinary sediment can help to discover rare stone types, because crystals of 2,8-dihydroxyadenine, cystine and xanthine are pathognomonic for the corresponding disease. In cases in which the presence of cystine is doubtful, a cyanide nitroprusside colorimetric qualitative test can be used to detect the presence of cystine in urine, with a sensitivity of 72% and specificity of 95%. False-positive results are possible in patients with Fanconi's syndrome or homocystinuria or in those taking various drugs, including ampicillin or sulfa-containing medication [789, 790].

Following this programme, the most probable stone type can be assumed, and specific patient evaluation can follow. Further metabolic investigations will depend on the presence of risk factors (see Section 3.1.3) and on the results of previous investigations. However, if any expelled stone material is available, it should be analysed for diagnostic confirmation or correction.

**4.13.1 Recommendations for investigations for the assessment of patients with stones of unknown composition** [17, 23, 76, 679]

Recommendations		Strength rating
Investigation	Rationale for investigation	
Take a medical history	<ul style="list-style-type: none"> <li>Stone history (former stone events, family history)</li> <li>Dietary habits</li> <li>Medication chart</li> </ul>	Strong
Perform diagnostic imaging	<ul style="list-style-type: none"> <li>Ultrasound in the case of a suspected stone</li> <li>Unenhanced helical computed tomography</li> <li>Determination of Hounsfield units provides information about the possible stone composition</li> </ul>	Strong
Perform a blood analysis	<ul style="list-style-type: none"> <li>Creatinine</li> <li>Calcium (ionised calcium or total calcium + albumin)</li> <li>Uric acid</li> </ul>	Strong
Perform a urinalysis	<ul style="list-style-type: none"> <li>pH measurement</li> <li>Dipstick test: leukocytes, erythrocytes, nitrites</li> <li>Protein, specific weight</li> <li>Urine cultures</li> <li>Microscopy of urinary sediment (morning urine)</li> <li>Cyanide nitroprusside test (cystine exclusion)</li> </ul> <p>Further examinations depend on the results of the investigations listed above.</p>	Strong

## 5. FOLLOW-UP OF URINARY STONES

There is no consensus in the urological literature on whether, when, how or the frequency with which stone patients should be followed up after definitive treatment (extracorporeal SWL, URS, PCNL, medical chemoprophylaxis). This is mainly attributed to the high heterogeneity of stone disease among patients and to the lack of comparative studies regarding follow-up versus no follow-up.

The EAU Urolithiasis Guidelines Panel performed a systematic review questioning the benefits and harms of scheduled imaging and metabolic follow-up for patients who underwent definitive treatment for upper urinary tract stone disease [490]. Based on the results a consensus was reached regarding the frequency of the follow-up for stone-free patients (the general population and the high-risk patients), patients with residual fragments  $\leq 4$ mm, and patients with residual fragments  $> 4$ mm (Figures 5.1 and 5.2).

Stone-free patients could be discharged after two years (radiopaque stones) or after three years (radiolucent stones) as 80% of them will remain stone-free thereafter. Increasing the safety margin for remaining stone-free up to 90%, the patients should be followed up to five years. Most stone-free patients in the general population remained stone-free during the first year, while  $< 40\%$  of patients with metabolic abnormalities not on medication remained stone-free after three years of follow-up. Therefore, a more extensive follow-up is proposed for patients with metabolic abnormalities.

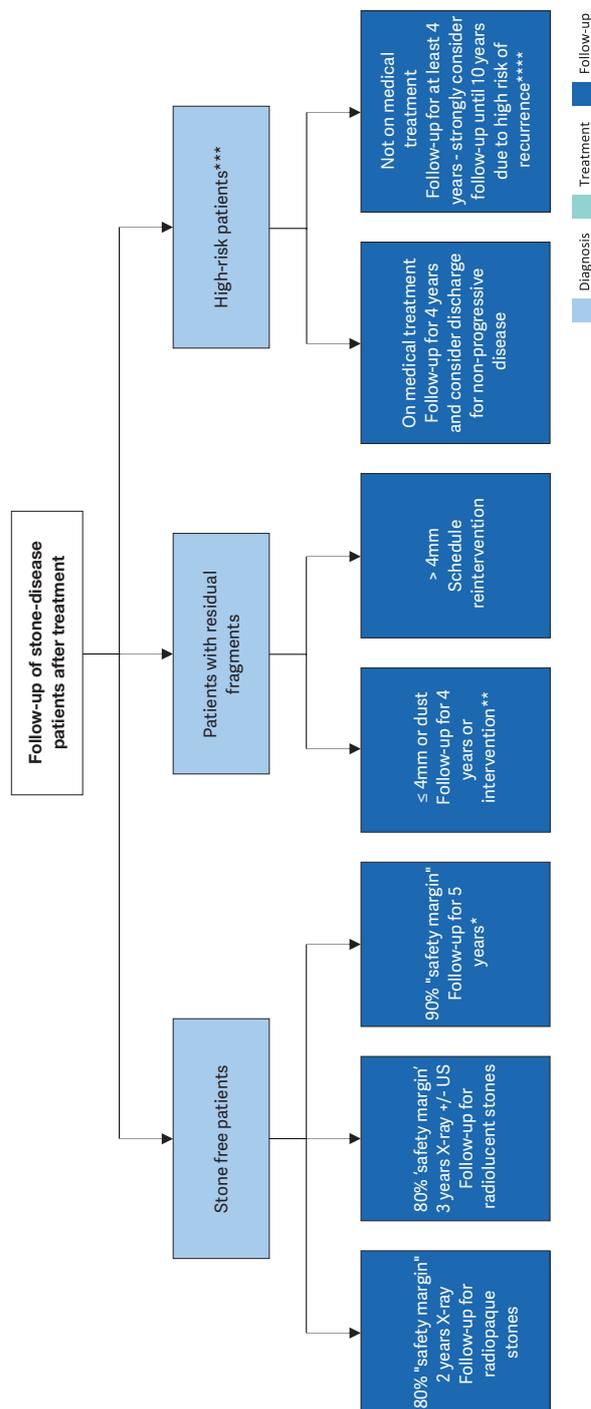
Patients with fragments  $\leq 4$ mm showed a spontaneous expulsion rate of 17.9–46.5% during the first year. At 49-months follow-up, disease progression rate was 9–34%, the intervention rate 17–29%, and the spontaneous passage rate 21–34%.

Patients with residual stone fragments >4mm had only a 9% spontaneous expulsion rate at three years. These patients should be offered further definitive treatment since intervention rates are high (24–100%). For those on follow-up, close surveillance is needed. Insufficient data exist for high-risk patients, but current literature dictates that patients who are adherent to targeted medical treatment seem to experience less stone growth or re-growth of residual fragments and may be discharged after 36–48 months of non-progressive disease on imaging (Figure 5.1).

Proposed imaging consists of plain X-ray KUB and/or US, based on stone characteristics and clinicians' preferences. Computed tomography scan should be reserved for symptomatic disease or preoperative imaging, to avoid extensive radiation exposure [490].

The information on stone composition can be used to counsel patients to set expectations and help plan the need for follow-up and medical stone management [791].

**Figure 5.1: Follow-up duration of urinary stone patients after treatment.**



Stone-free = No stone fragments on postoperative imaging (i.e. no stone fragments on CT/KUB/US).

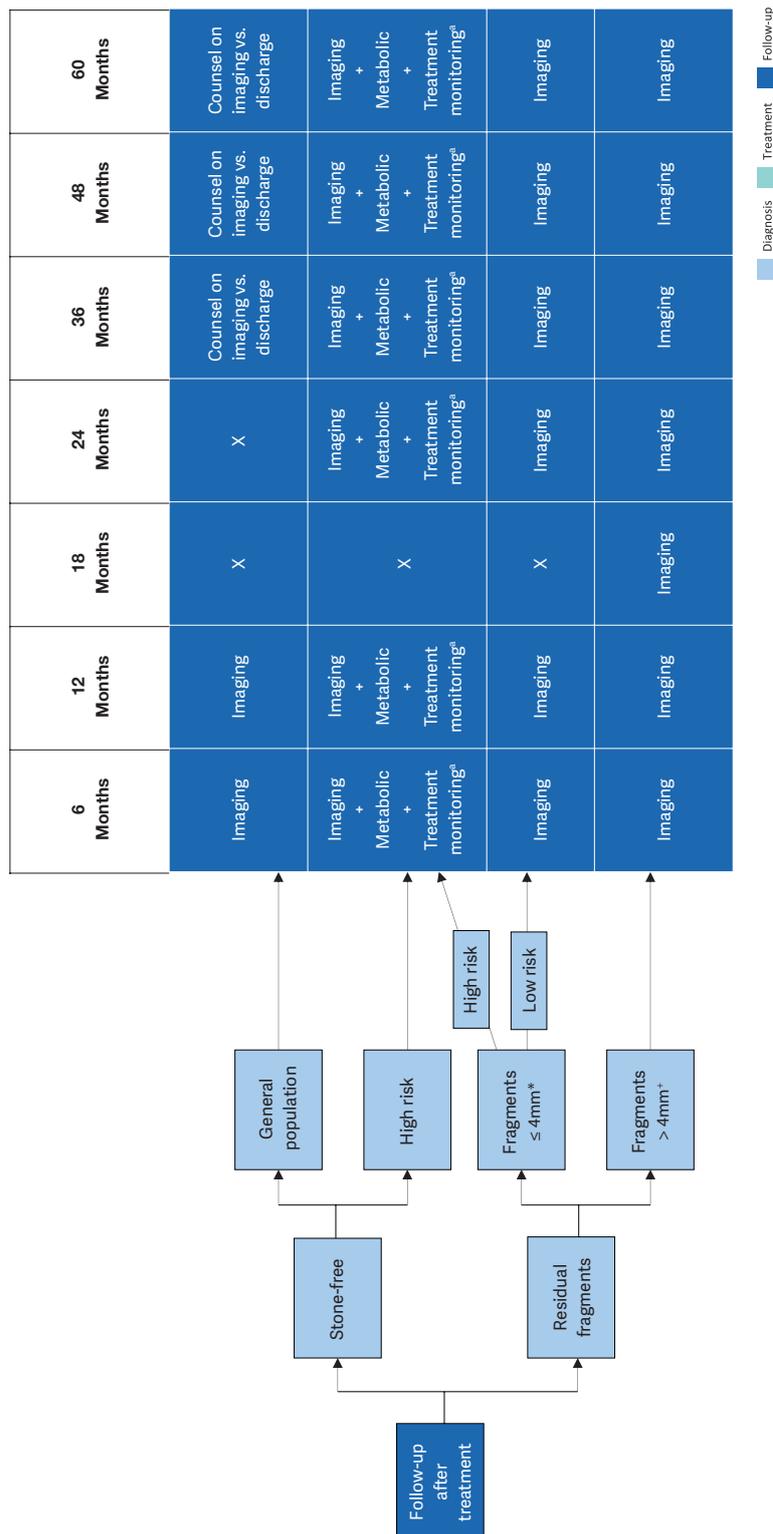
High-Risk = Known biochemical abnormality (i.e. hypercalciuria, hypocitraturia, hyperuricosuria, RTA or high-risk stone type such as struvite [See Table 3.3]).

Imaging = plain film KUB &/or kidney ultrasonography (KUS) based on clinicians' preference and stone characteristics. Consider CT if the patient is symptomatic or if intervention is planned.

\* Clinicians may choose the imaging-only pathway in patients with fragments  $\leq 2\text{mm}$ . 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 for reintervention based on clinicians' preference.

Figure 5.2: Consensus on follow-up frequency and imaging modality to use after treatment



Stone free = No stone fragments on postoperative imaging (i.e. no stone fragments on CT/KUB/US).

High-Risk = Known biochemical abnormality (i.e. hypercalciuria, hypocitraturia, hyperuricosuria, RTA or high-risk stone type, such as struvite [See table 3.6]).

Imaging = plain film KUB &/or kidney ultrasonography (KUS) based on clinicians' preference and stone characteristics. Consider CT if the patient is symptomatic or if intervention is planned.

\* Clinicians may choose the imaging-only pathway in patients with fragments  $\leq 2$ mm.

a Treatment monitoring for side effects, intolerance, and compliance.

+ Panel recommends reintervention; however, close follow up may be considered for some patients at high risk for reintervention based on clinicians' preference.

## 6. BLADDER STONES

### 6.1 Prevalence, aetiology and risk factors of bladder stones

Bladder stones constitute only approximately 5% of all urinary tract stones [792] yet are responsible for 8% of urolithiasis-related mortalities in developed nations [793]. The incidence is higher in developing countries [794]. The prevalence of bladder stones is higher in males, with a reported male-to-female ratio between 10:1 and 4:1 [795, 796]. The age distribution is bimodal: incidence peaks at three years in children in developing countries [795, 797] and 60 years in adulthood [796].

The aetiology of bladder stones is typically multifactorial [796]. Bladder stones can be classified as primary, secondary or migratory [798].

Primary or endemic bladder stones occur in the absence of other urinary tract pathology, typically seen in children in areas with poor hydration, recurrent diarrhoea and a diet deficient in animal protein [799].

Secondary bladder stones occur in the presence of other urinary tract abnormalities, which include bladder outlet obstruction (BOO), neurogenic bladder dysfunction, chronic bacteriuria, foreign bodies (including catheters), bladder diverticula, and bladder augmentation or urinary diversion. In adults, BOO is the most common predisposing factor for bladder stone formation and accounts for 45–79% of vesical calculi [796, 800-803].

Migratory bladder stones are those that have passed from the upper urinary tract where they formed and may then serve as a nidus for bladder stone growth. Patients with bladder calculi are more likely to have a history of upper tract stones and risk factors for their formation [804].

A wide range of metabolic urinary abnormalities can predispose to calculi anywhere in the urinary tract, which is covered in more detail in Section 4. Metabolic Evaluation and Recurrence Prevention. There is a paucity of studies on the specific metabolic abnormalities that predispose to bladder stones.

Bladder stones will form in 3–4.7% of men undergoing surgery for benign prostatic obstruction (BPO) [805, 806], 19–39% and 36–67% of motor-incomplete and motor-complete spinal cord injury patients, respectively [807], and 2.2% of patients with long-term catheters [808]. Two research groups have identified that a larger intravesical protrusion of the prostate is an independent risk factor for bladder stone formation in patients with benign prostatic hyperplasia (BPH) undergoing transurethral resection of the prostate (TURP) [809, 810]. Kim and colleagues additionally found older age and a lower  $Q_{\max}$  to be predictive of bladder stones [809].

In men with chronic urinary retention secondary to BPO, the 24-hour urine of 27 men with bladder stones had a higher uric acid supersaturation (2.2 vs. 0.6mmol/L,  $p < 0.01$ ), lower magnesium (106 vs. 167mmol/L,  $p = 0.01$ ) and lower pH (5.9 vs. 6.4,  $p = 0.02$ ) than the 21 men without bladder stones [804]. It is therefore likely that patients with these conditions who form bladder stones also have an abnormal urine composition which predisposes them to bladder stone formation.

The metabolic abnormalities which predispose patients to form secondary bladder stones are poorly understood. Stone analysis of 86 men with a BPO-related bladder stone demonstrated that 42% had calcium-based stones (oxalate, phosphate), 33% had magnesium ammonium phosphate, 10% had mixed stones and 14% had urate stones [796]. Similar findings were reported in more recent studies [811-813], and it is therefore likely that multiple metabolic factors predispose patients to secondary bladder stone formation.

Low urine volume (poor hydration) is the most consistently demonstrable abnormality in children [814-816].

As an outlet obstruction is more often absent in children than in adults, the aetiology is most likely quite different in this population. Twenty-four-hour urine analysis in children with endemic bladder stones is reported in two studies. Of 57 children in Pakistan, 89.5% had hypocitraturia, 49% had a low urine volume, 44% had hyperoxaluria and 42% had hypocalciuria [814]. Of 61 children in India, stone formers had higher urine calcium and uromucoid concentrations than controls [815]. One study from Thailand compared 24-hour urine analyses from children from a rural area with a high prevalence of bladder stones with those from an urban area: rural children had lower urine volumes and, despite equal calcium, oxalate and uric acid concentrations, crystalluria with uric acid and calcium oxalate crystals was more prevalent in rural children [816].

**Table 6.1: Bladder stones classified by aetiology**

Type of bladder stone	Primary	Secondary	Migratory
Cause/Associations	Occur in the absence of other urinary tract pathology, typically in children in areas with poor hydration, recurrent diarrhoea, and a diet deficient in animal protein	BOO (e.g. BPO, urethral stricture)	Form in the upper urinary tract, then passed into the bladder where they may be a nidus for stone growth
		Neurogenic bladder dysfunction	
		Chronic bacteriuria	
		Foreign bodies (including catheters)	
		Bladder diverticula	
		Bladder augmentation	
		Urinary diversion	

BOO = Bladder Outlet Obstruction; BPO = Benign Prostatic Obstruction.

## 6.2 Presentation

The symptoms most associated with bladder stones are urinary frequency, haematuria (which is typically terminal), and dysuria or suprapubic pain, which are worst towards the end of micturition. Sudden movement and exercise may exacerbate these symptoms. Detrusor overactivity is found in over two-thirds of adult male patients with vesical calculi and is significantly more common in patients with larger stones (> 4cm). However, recurrent urinary tract infections (UTIs) may be the only symptom [801, 802].

In children, symptoms may also include pulling of the penis, difficulties in micturition, urinary retention, enuresis and rectal prolapse (resulting from straining due to bladder spasms). Bladder stones may also be an incidental finding in 10% of cases [799, 817].

## 6.3 Diagnostic evaluation

### 6.3.1 Diagnostic investigations for bladder stones

Plain X-ray of KUB has a reported sensitivity of 21–78% for cystoscopically detected bladder stones in adults [801, 818]. Larger (> 2.0cm) stones are more likely to be radiopaque [818]. However, plain X-ray provides information on radio-opacity which may guide treatment and follow-up (see Section 3.2.3).

Ultrasound has a reported sensitivity and specificity of 20–83% and 98–100%, respectively, for the detection of bladder stones in adults [819, 820]. Computed tomography and cystoscopy have a higher sensitivity for detecting bladder stones than US or X-ray in adults [819, 820]. No study compares cystoscopy and CT for the diagnosis of bladder stones. Cystoscopy has the advantage of detecting other potential causes for a patient's symptoms (e.g. bladder cancer), whilst CT can also assess upper tract urolithiasis (see also Section 3.2.3) [821].

There is a paucity of evidence for the investigation of bladder stones, particularly in children [97, 822]. See also Section 3.3, for further information on diagnostic imaging for urolithiasis. The principle of ALARA should be applied, especially in children [823].

#### 6.3.2 **Diagnosing the cause of bladder stones**

The cause of the bladder stone should be considered prior to bladder stone treatment, as eliminating the underlying cause will reduce recurrence rates [824]. The following should be performed where possible prior to (or at the time of) bladder stone treatment:

- physical examination of external genitalia and peripheral nervous system (including digital rectal examination, peri-anal tone and sensation in men);
- uroflowmetry and post-void residual urine assessment;
- urine dipstick to include pH ± culture;
- metabolic assessment (see also Section 3.3.2.c) including: serum (creatinine, [ionised] calcium, uric acid, sodium, potassium, blood cell count);
- urine pH;
- stone analysis: in first-time formers using a valid procedure (X-ray diffraction or infrared spectroscopy).

The following investigations should also be considered for selected patients:

- upper tract imaging (in patients with a history of urolithiasis or loin pain);
- cystourethroscopy or urethrogram.

## 6.4 **Disease management**

### 6.4.1 **Conservative treatment and indications for active stone removal**

Migratory bladder stones in adults may typically be left untreated, especially asymptomatic small stones. Rates of spontaneous stone passage are unknown, but data on ureteric stones suggest stones <1cm are likely to pass in the absence of BOO, bladder dysfunction or long-term catheterisation (see Section 3.4.9). Primary and secondary bladder stones are usually symptomatic and are unlikely to pass spontaneously: active treatment of such stones is therefore indicated.

### 6.4.2 **Medical management of bladder stones**

There is a paucity of evidence on chemolitholysis of bladder stones. However, guidance on the medical management of urinary tract stones in Section 3.4.9, can be applied to urinary stones in all locations. Uric acid stones can be dissolved by oral urinary alkalinisation when a PH >6.5 is consistently achieved, typically using alkaline citrate or sodium bicarbonate. Regular monitoring is required during therapy (see Section 3.4.4). Irrigation chemolysis is also possible using a catheter, however, this is time-consuming, may cause chemical cystitis and is therefore not commonly employed [825, 826].

### 6.4.3 **Bladder stone interventions**

Minimally invasive techniques for the removal of bladder stones have been widely adopted to reduce the risk of complications and shorten hospital stay and convalescence. Bladder stones can be treated with open, laparoscopic, robotic-assisted laparoscopic, endoscopic (transurethral or percutaneous) surgery or SWL [827].

#### 6.4.3.a **Suprapubic cystolithotomy**

Open suprapubic cystolithotomy is very effective but is associated with a need for catheterisation and longer hospital stay in both adults and children compared to all other stone removal modalities [827]. In children, a non-randomised study found that, when the bladder was closed meticulously in two layers, 'tubeless' (drain-less and catheter-less) cystolithotomy was associated with a significantly shorter hospital stay compared with traditional cystolithotomy. This was achieved without significant differences in late or intraoperative complications, provided that children with prior UTI, recurrent stones, or previous anorectal malformation surgery (or other relevant surgery) were excluded [828].

#### 6.4.3.b **Transurethral cystolithotripsy**

In both adults and children, transurethral cystolithotripsy provides high SFRs and appears to be safe, with a very low risk of unplanned procedures and major postoperative and late complications [827].

##### 6.4.3.b.1 **Transurethral cystolithotripsy in adults**

In adults, an MA of four RCTs including 409 patients demonstrated that transurethral cystolithotripsy has a shorter hospital stay and convalescence with less pain, but equivalent SFR and complications compared to percutaneous cystolithotripsy [827]. Transurethral cystolithotripsy with a nephroscope was quicker than percutaneous cystolithotripsy in three RCTs, although transurethral cystolithotripsy with a cystoscope was slower than percutaneous cystolithotripsy [827].

Rates of urethral strictures following transurethral procedures were not robustly reported: studies report rates between 2.9% and 19.6% during a follow-up period of 12–24 months [811, 827, 829]. One small RCT demonstrated a shorter duration of catheterisation, hospital stay and procedure with transurethral cystolithotripsy than open cystolithotomy with similar SFR [827]. Meta-analysis of five RCTs found significantly shorter procedure duration for transurethral cystolithotripsy using a nephroscope versus cystoscope with similar SFRs, hospital stay, convalescence, pain and complications [830]. Two retrospective studies (n = 188) reported that using a resectoscope or nephroscope was associated with a shorter procedure duration ( $p < 0.05$ ) than a cystoscope for transurethral cystolithotripsy [831, 832]. This suggests that transurethral cystolithotripsy is quicker when using a continuous flow instrument.

#### 6.4.3.b.1.a Lithotripsy modalities used during transurethral cystolithotripsy in adults

When considering lithotripsy modalities for transurethral cystolithotripsy, the Panel's systematic review found very low-quality evidence from five non-randomised studies (n = 385) which found no difference in SFR between modalities (mechanical, laser, pneumatic, ultrasonic, electrohydraulic lithotripsy [EHL] or washout alone) [827]. Unplanned procedures and major postoperative complications were low-rate events and were not significantly different between lithotripsy modalities, although one non-randomised study (NRS) suggested these might be higher with EHL or mechanical lithotripsy than pneumatic or ultrasonic lithotripsy [833]. All outcomes had very low-quality evidence (GRADE) [827]. High-powered lasers seem to reduce lithotripsy time. Laser lithotripsy was faster than pneumatic lithotripsy (MD 16.6 minutes; CI: 23.51–9.69,  $p < 0.0001$ ) in one NRS (n = 62); however, a laser was used with a resectoscope and the pneumatic device with a cystoscope [834]. The same conclusion was stated in an MA of ten RCTs with high heterogeneity and small sample sizes in some of the included RCTs [835]. An SR states post-laser lithotripsy SFR of 96% [836]. Continuous versus intermittent irrigating instruments may affect the operation time more significantly than the choice of lithotripsy device [827].

#### 6.4.3.b.1.b Transurethral cystolithotripsy in children

In children, three NRS suggest that transurethral cystolithotripsy has a shorter hospital stay and catheterisation time than open cystolithotomy, but similar stone-free and complication rates [837-839]. One small quasi-RCT found a shorter procedure time using laser versus pneumatic lithotripsy for <1.5cm bladder stones with no difference in SFR or other outcomes [838]. Another RCT (n = 73) found shorter procedure time using pneumatic versus laser therapy for bladder stones  $\leq 1.5$ cm with similar SFRs and higher (minor) complication rates for pneumatic lithotripsy [839]. An SR showed that open cystolithotomy offers a shorter procedure duration than endourological management, whereas a percutaneous approach features a shorter procedure duration than transurethral approach. In terms of length of stay, transurethral and percutaneous approaches were superior to open, while a transurethral was better than a percutaneous approach [840].

#### 6.4.3.c Percutaneous cystolithotripsy

##### 6.4.3.c.1 Percutaneous cystolithotripsy in adults

One NRS found a shorter duration of procedure and catheterisation and less blood loss for percutaneous, compared with open surgery in adult male patients with urethral strictures; all patients in both groups were rendered stone-free [813].

Meta-analysis of four RCTs comparing transurethral and percutaneous cystolithotripsy found a shorter hospital stay for transurethral cystolithotripsy over percutaneous surgery. Transurethral cystolithotripsy was quicker when using a nephroscope. There were no significant differences in SFRs, major postoperative complications, or retreatment [827].

##### 6.4.3.c.2 Percutaneous cystolithotripsy in children

In children, three NRS suggest that percutaneous cystolithotripsy has a shorter hospital stay and catheterisation time, but a longer procedure duration and more perioperative complications than open cystolithotripsy, SFRs were similar [817, 827, 837, 841].

A systematic review identified four non-randomised studies comparing percutaneous and transurethral cystolithotripsy and found similar SFRs, but that transurethral surgery offers shorter duration of catheterisation and hospital stay [817, 837]. In contrast, a transurethral approach may need a longer operative time and shows a higher postoperative stricture rate [841]. One small NRS found a nonsignificant increased risk of unplanned procedures (within 30 days of primary procedure) and major post-operative complications for percutaneous operations compared with transurethral procedures. However, age and stone size determined which intervention children underwent and all patients were rendered stone-free [817]. One RCT compared 48 boys <14 years undergoing transurethral lithotripsy versus 49 boys undergoing percutaneous lithotripsy with comparable success and complication rates. However, PCCL had a shorter operative time and less need for stone disintegration [842].

#### 6.4.3.d Extracorporeal shock wave lithotripsy

Extracorporeal SWL is the least invasive therapeutic procedure [827].

##### 6.4.3.d.1 Shock wave lithotripsy in adults

In adults, one RCT compared SWL with transurethral cystolithotripsy in 100 patients with  $\leq 2$ cm bladder stones presenting with acute urinary retention. Stone-free rate after one SWL session favoured transurethral cystolithotripsy (86% vs. 98%,  $p = 0.03$ ); however, following up to three sessions of SWL, there was no significant difference in SFR (94% vs. 98%,  $p = 0.3$ ) [827, 843].

Two NRS compared transurethral cystolithotripsy versus SWL and found no significant difference in SFR (97.0% vs. 93.9%,  $p = 0.99$ ; 97.7% vs. 89.7%,  $p = 0.07$ ) despite larger stones in transurethral cystolithotripsy patients (4.2 vs. 2.5cm,  $p = 0.014$ ; and 3.6 vs. 2.6cm [p value not reported]) [844, 845].

Length of hospital stay appeared to favour SWL in all three studies (0 vs. 1 day, 4.8 vs. 0 days,  $p = 0.02$ , 0.8 vs. 2.4 days, respectively) [843-845]. No significant differences in major postoperative or intraoperative complications were reported in any study [843-845].

#### 6.4.3.e Shock wave lithotripsy in children

One large NRS found lower SFR for SWL than both transurethral cystolithotripsy and open cystolithotomy, despite treating smaller stones with SWL. However, the length of hospital stays favoured SWL over open cystolithotomy, although this appeared to be comparable between SWL and transurethral cystolithotripsy [846].

#### 6.4.3.f Laparoscopic cystolithotomy

Laparoscopic cystolithotomy has been described in adults and is typically performed in combination with simple prostatectomy using either traditional laparoscopy or with robotic assistance [847, 848]. A systematic review found no studies comparing laparoscopic surgery with other procedures [827].

#### 6.4.4 Treatment for bladder stones secondary to bladder outlet obstruction in adult men

Bladder stones in men aged over 40 years may be caused by BPO, the management of which should also be considered. Bladder stones were traditionally an indication for a surgical intervention for BPO – a doctrine that has been questioned by studies. One prospective study reports urodynamics (cystometrogram) findings in 46 men aged  $> 60$  years before and after bladder stone treatment [802]. Only 51% of men had BOO while 10% had detrusor underactivity. Eighteen percent of men had a completely normal urodynamic study and 68% had detrusor overactivity. There was no significant difference between pre- and post-bladder-stone-removal urodynamic findings [802].

One NRS compared 64 men undergoing transurethral cystolithotripsy with either transurethral resection of the prostate (TURP) or medical management for BPO ( $\alpha$ -blocker with or without 5-alpha-reductase inhibitor). After 28 months of follow-up, no men on medication had had a recurrence, but 34% underwent TURP – a high post-void residual urine volume predicted the need for subsequent TURP [849]. Another observational study of 23 men undergoing cystolithotripsy and commencing medical management for BPO found 22% developed a BPO-related complication, including 17% who had recurrent stones [824]. One RCT comparing cystolithotripsy with concomitant TURP to cystolithotripsy with medical management of bladder outlet obstruction with tamsulosin and finasteride demonstrated that both groups had a significantly improved  $Q_{max}$ , IPSS and PVR at follow-up, although the TURP group had a longer procedure and catheterisation time [850]. Large prostates ( $> 54$ gr) and a high PVR ( $> 190$ ml) were predictive of needing a TURP over time in the medical management cohort, although this was based on only a small number of patients.

Large studies support the safety of performing BPO and bladder stone procedures during the same operation with no difference in major complications compared to a BPO procedure alone [851-853]. An observational study on 2,271 patients undergoing TURP found no difference in complications except UTIs, which occurred slightly more frequently in patients with simultaneously treated bladder stones: 0% vs. 0.6%,  $p = 0.044$  [851]. An observational study of 320 men undergoing Holmium laser enucleation of the prostate (HoLEP) found a higher rate of early postoperative incontinence (26.8% vs. 12.5%,  $p = 0.03$ ) in men having concomitant transurethral cystolithotripsy, but no difference in long-term continence rates [853]. Another larger multicentre observational study of 963 patients undergoing HoLEP found no significant differences in the frequency of complications in patients with ( $n = 54$  [5.6%]) or without concomitant transurethral cystolithotripsy [854].

#### 6.4.5 **Special situations**

##### 6.4.5.a **Neurogenic bladder and stone formation**

Patients with a neurogenic bladder secondary to spinal cord injury or myelomeningocele are at increased risk of forming bladder stones. Within eight to ten years, 15–36% of patients with spinal cord injury will develop a bladder stone [855-857]. According to a systematic review, the prevalence of stone formation depends on the level of the spinal cord injury with 19–39% and 36–67% of motor-incomplete and motor-complete spinal cord injury patients developing bladder stones over time, respectively [807]. The absolute annual risk of stone formation in spinal cord injury patients with an indwelling catheter is 4%, compared with 0.2% for those voiding with clean intermittent self-catheterisation (CISC) [858].

A study of 2,825 spinal cord injury patients over eight years found a 3.3% incidence of bladder stones: 2% with CISC, 6.6% with an indwelling urethral catheter, 11% with a suprapubic catheter, and 1.1% in patients voiding using reflex micturition [859]. However, another study of 457 spinal cord injury patients for six months found no difference in bladder stones between urethral and suprapubic catheterisation [858]. Spinal cord injury patients with an indwelling urethral catheter are six times more likely to develop bladder stones than patients with normal micturition [857, 859].

The risk of stone recurrence after complete removal in spinal cord injury patients is 16% per year [858]. An RCT of 78 spinal cord injury patients who perform CISC found a significant reduction in bladder stone formation when twice weekly manual bladder irrigations were performed for six months (49% vs. 0%,  $p < 0.0001$ ), as well as less symptomatic UTIs (41% vs. 8%;  $p = 0.001$ ) [860]. However, this study excluded patients who developed autonomic dysreflexia during bladder irrigations. The irrigation volume used was not reported.

##### 6.4.5.b **Bladder augmentation**

The incidence of vesical calculus formation after bladder augmentation is 2–44% in adults [861-870] and 4–53% in children [870-885]. Following cystoplasty, stones form after 24–31 months in adults [862, 864, 869] and after 25–68 months in children [875, 878, 879, 883, 886-888]. The reported cumulative incidence of bladder stone formation after 10 years is 28–36% and after twenty years is 41% [870, 889].

Risk factors for bladder stone formation after augmentation include excess mucus production, incomplete bladder emptying, noncompliance with CIC or bladder irrigations, bacteriuria or urinary tract infections (due to urease-producing bacteria), foreign bodies (including staples, mesh, non-absorbable sutures), drainage by vesico-entero-cystostomy (Mitrofanoff or Monti) [516, 862, 865, 867, 868, 875, 879, 882, 889]. Stone formation is also more common in patients voiding by CISC compared with those voiding spontaneously [866]. Gastric segment augmentation confers a lower risk of bladder stones than ileal or colonic segment cystoplasty [871, 875, 879, 882].

In previous stone formers, the rate of recurrence is 15–44% in adults [862-864, 866, 869] and 19–56% in children [516, 871, 875, 877-880, 882, 888]. The risk of recurrence is greatest during the first two years, at approximately 12% per patient per year, with the risk decreasing with time [888].

Daily or three-times-weekly bladder irrigations reduce the incidence of bladder stones following bladder augmentation or continent urinary diversion [516, 865]. A randomised study found that daily bladder irrigation with 240mL of saline reduced stone recurrences ( $p < 0.0002$ ,  $p = 0.0152$ ) and symptomatic UTIs ( $p < 0.0001$ ,  $p < 0.0001$ ) compared to 60mL or 120mL [865]. The frequency of bladder irrigations required is unclear.

##### 6.4.5.c **Urinary diversion**

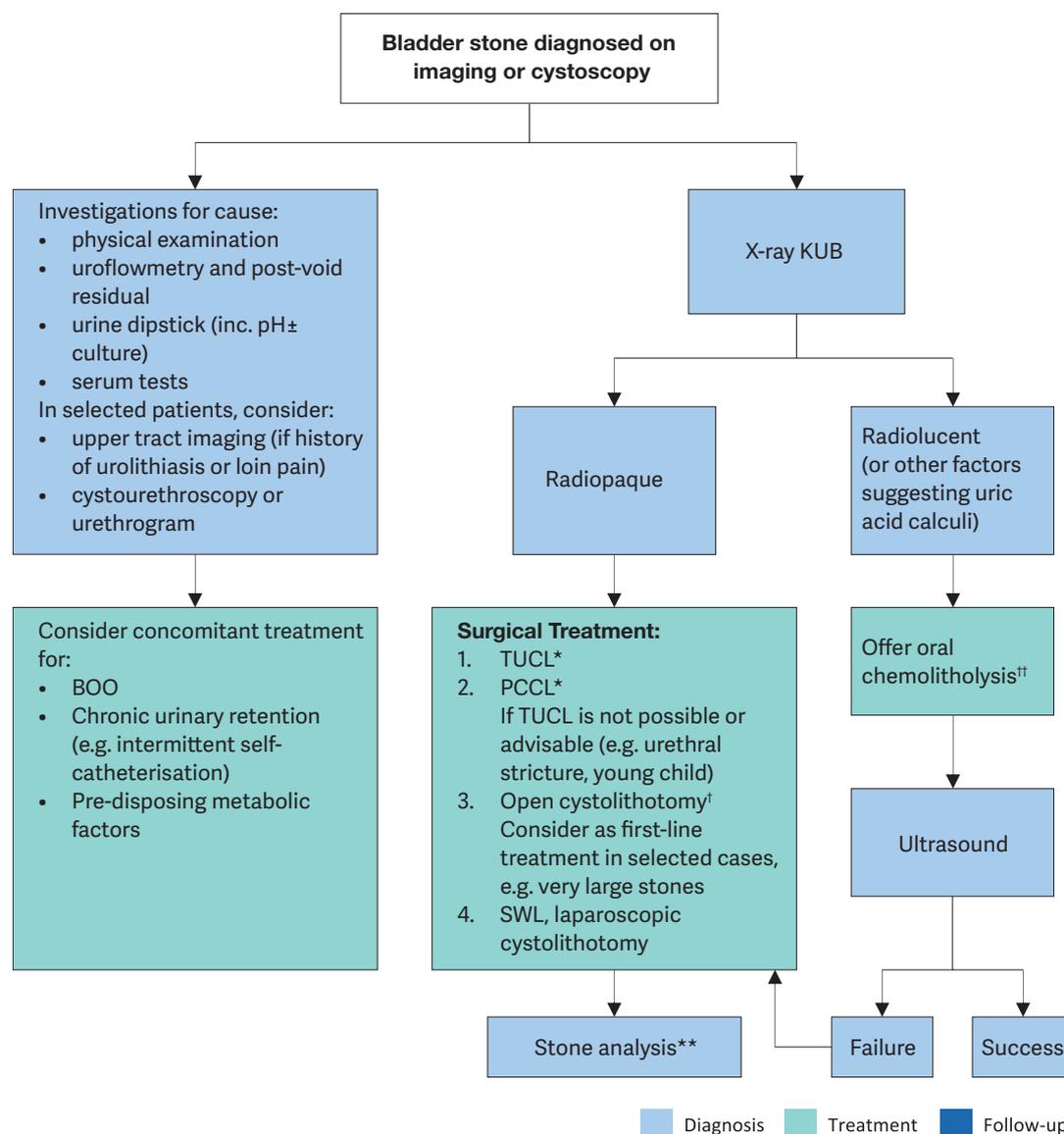
The incidence of stone formation after urinary diversion with an ileal or colon conduit is 0–3% [890, 891]. The incidence of stone formation is 0–34% in orthotopic ileal neobladders (Hautmann, hemi-Kock, Studer, T-pouch or w-neobladder) [514, 866, 891-898] and 4–6% in orthotopic sigmoid neobladders (Reddy) [896, 899]. The risk of pouch stone formation is 4–43% in adults with an ileocaecal continent cutaneous urinary diversion (Indiana, modified Indiana, Kock, or Mainz I) [506, 866, 890, 891, 900, 901]. The average interval from construction of the urinary diversion to stone detection is 71–99 months [895, 902]. In children, the incidence of neobladder stone formation is 30% after Mainz II diversion (rectosigmoid reservoir) [872] and 27% after Kock ileal reservoir construction [884].

#### 6.4.5.d Treatment of stones in patients with bladder augmentation or urinary diversion

Stones may be removed by open or endoscopic surgery in patients with bladder augmentation or diversion [877]. However, access often cannot be obtained through a continent vesico-entero-cystostomy without damaging the continence apparatus; hence a percutaneous or open approach is typically preferred [877].

No studies comparing outcomes following procedures for stones in reconstructed or augmented bladders were found. Two observational studies indicate that percutaneous lithotomy can be safely performed with US or CT guidance in patients with reconstructed or augmented bladders [903, 904] and is proposed to offer similar advantages over open surgery to those for percutaneous native bladder surgery. Stone recurrence after successful removal has been reported to be 10–42% [903, 904], but appears to be unrelated to the modality used for stone removal [869, 875, 879, 880, 882, 888].

**Figure 6.1: Management of bladder stones**



\* Lithotripsy modality at surgeon's discretion (e.g. mechanical, laser, pneumatic, ultrasonic).

† Prefer 'tubeless' procedure (without placing a catheter or drain) for children with primary bladder stones and no prior infection, surgery or bladder dysfunction where open cystolithotomy is indicated.

\*\* Stone analysis should be sent for all first-time stone formers and in patients who develop a recurrence under pharmacological prevention, early recurrence after interventional therapy with complete stone clearance, or late recurrence after a prolonged stone-free period (see main Urolithiasis Guidelines).

†† Use an alkaline citrate or sodium bicarbonate with frequent urine pH monitoring and dose titration to achieve a consistent pH > 6.5.

BOO = Bladder outlet obstruction; TUCL = Transurethral cystolithotripsy, PCCL = Percutaneous cystolithotripsy, SWL = Shock-wave lithotripsy.

## 6.5 Bladder stones follow-up

There are no studies examining the merits of differing follow-up modalities or frequencies following conservative, medical or operative treatment of bladder stones in adults or children. Identification and prevention of the cause of bladder stone formation will be crucial to prevent recurrence (see Section 6.3.2).

In adults, there is a paucity of evidence on dietary modification or medical treatment for the prevention of bladder stone recurrence. Recommendations in the EAU Guidelines on Urolithiasis, based on evidence from upper tract stones, constitute the best available recommendations, especially for migratory bladder stones (see Chapter 4).

Where it is possible to address the cause of secondary bladder stones (e.g. treatment of BPO), it is unclear whether metabolic intervention would offer any significant additional benefit in preventing stone recurrence. However, especially where the secondary cause cannot be addressed (e.g. indwelling catheter, neuropathic bladder, bladder augmentation, urinary diversion), metabolic interventions are likely to reduce bladder stone recurrence rates.

Regular bladder irrigation reduces the chances of bladder stone recurrence in adults and children with bladder augmentation or continent cutaneous urinary diversion and adults with spinal cord injury who perform CISC (see Section 6.4.5) [860, 865, 891].

In children with primary (endemic) bladder stones, maintenance of hydration, avoidance of diarrhoea and a mixed cereal diet with milk and vitamins A and B supplements, with the addition of eggs, meat and boiled cow's milk after one year of age are recommended to prevent a recurrence [814].

Finally, there are contradictory reports on a possible association between bladder calculi and the future development of bladder cancer [905-907]. The need for follow-up with regular cystoscopy therefore remains controversial.

## 6.6 Summary of evidence and recommendations for the treatment of bladder stones

Summary of evidence	LE
The incidence of bladder stones peaks at three years in children (endemic/primary stones in developing countries) and 60 years in adults.	2c
In adults, BOO is the most common predisposing factor for bladder stone formation.	2c
Of men undergoing surgery for BPO, 3–4.7% form bladder stones.	2b
Primary (endemic) bladder stones typically occur in children in areas with poor hydration, recurrent diarrhoea and a diet deficient in animal protein. The following measures are proposed to reduce their incidence: maintenance of hydration, avoidance of diarrhoea, and a mixed cereal diet with milk and Vitamins A and B supplements, with the addition of eggs, meat and boiled cows' milk after one year of age.	5
Endoscopic bladder stone treatments (transurethral or percutaneous) are associated with comparable SFRs, but a shorter length of hospital stay, duration of procedure and duration of catheterisation compared to open cystolithotomy in adults.	1a
Stone-free rates are lower in patients treated with SWL than those treated with open or endoscopic procedures in both adults and children.	2a
Transurethral cystolithotripsy is associated with a shorter length of hospital stay, less pain and a shorter convalescence period than percutaneous cystolithotripsy in adults.	1b
Transurethral cystolithotripsy with a nephroscope is quicker than when using a cystoscope with no difference in SFR in adults.	1a
Mechanical, pneumatic and laser appear equivalent lithotripsy modalities for use in endoscopic bladder stone treatments in adults and children.	2a
Open cystolithotomy without a retropubic drain or urethral catheter ('tubeless') is associated with a shorter length of hospital stay than traditional cystolithotomy and can be performed safely in children with primary stones and no prior bladder surgery or infections.	2b

Bladder stone removal with concomitant treatment for BOO is associated with no significant difference in major postoperative complications when compared to BOO treatment alone in adults. However, concomitant bladder stone treatment does increase the rates of short-term postoperative incontinence and UTI.	2b
The incidence of bladder stone formation in spinal cord injury patients is 19–67% over time. The absolute annual risk of stone formation in spinal cord injury patients is significantly higher with an indwelling catheter compared to those voiding with CISC or spontaneously.	2b
The incidence of bladder stone formation after bladder augmentation or vesico-entero-cystostomy is between 2–53% in adults and children.	2b
The risk of bladder stone formation in spinal cord injury, bladder augmentation or continent urinary diversion patients is reduced by performing regular bladder irrigation.	2b

Recommendations	Strength rating
Use ultrasound as first-line imaging with symptoms suggestive of a bladder stone.	Strong
Use cystoscopy or computed tomography, or kidney-ureter-bladder X-Ray (KUB) to investigate adults with persistent symptoms suggestive of a bladder stone if US is negative.	Strong
All patients with bladder stones should be examined and investigated for the cause of bladder stone formation, including: <ul style="list-style-type: none"> <li>• uroflowmetry and post-void residual;</li> <li>• urine dipstick, pH, ± culture; and</li> <li>• metabolic assessment and stone analysis (see sections 3.3.2.c and 4.1 of the Urolithiasis Guidelines for further details).</li> </ul> In selected patients, consider: <ul style="list-style-type: none"> <li>• upper tract imaging (in patients with a history of urolithiasis or loin pain); and</li> <li>• cystourethroscopy or urethrogram.</li> </ul>	Weak
Offer oral chemolitholysis for radiolucent or known uric acid bladder stones in adults.	Weak
Offer adults with bladder stones transurethral cystolithotripsy where possible.	Strong
Perform transurethral cystolithotripsy with a continuous flow instrument in adults (e.g. nephroscope or resectoscope) where possible.	Weak
Offer adults percutaneous cystolithotripsy where transurethral cystolithotripsy is not possible or advisable.	Strong
Suggest open cystolithotomy as an option for very large bladder stones in adults and children.	Weak
Offer children with bladder stones transurethral cystolithotripsy where possible.	Weak
Offer children percutaneous cystolithotripsy where transurethral cystolithotripsy is not possible or is associated with a high risk of urethral stricture (e.g. young children, previous urethral reconstruction and spinal cord injury).	Weak
Open, laparoscopic and extracorporeal shock wave lithotripsy are alternative treatments where endoscopic treatment is not advisable in adults and children.	Weak
Prefer 'tubeless' procedure (without placing a catheter or drain) for children with primary bladder stones and no prior infection, surgery or bladder dysfunction where open cystolithotomy is indicated.	Weak
Individualise imaging follow-up for each patient as there is a paucity of evidence. Factors affecting follow-up will include: <ul style="list-style-type: none"> <li>• whether the underlying functional predisposition to stone formation can be treated (e.g. TURP); and</li> <li>• metabolic risk.</li> </ul>	Weak
Recommend regular irrigation therapy with saline solution to adults and children with bladder augmentation, continent cutaneous urinary reservoir or neuropathic bladder dysfunction, and no history of autonomic dysreflexia to reduce the risk of stone recurrence.	Weak

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## 8. CONFLICT OF INTEREST

All members of the Urolithiasis guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is provided below and is also publicly available on the EAU website: <https://uroweb.org/guidelines/urolithiasis/panel>.

This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative and travel and meeting expenses. No honoraria or other reimbursements have been provided.

Disclosures: The EAU Guidelines Office certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (e.g., employment/ affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: H.U. Jung reported serving as company consultant for AMBU A/S, AMBU, and receiving company speaker honoraria from Boston Scientific. G. Kamphuis reported serving as a company consultant for Olympus and Boston Scientific, Coloplast Porges and AMBU A/S, AMBU, and Company speaker honorarium from Alnylam Pharmaceuticals. A. Neisius reported receiving honoraria or consultation fees from Boston Scientific Europe and Desitin Arzneimittel GmbH, and receiving company speaker honoraria from Recordati Pharma GmbH, Aristo, Johnson & Johnson, and Merck. A. Petřík reported receiving company speaker honoraria from Olympus Czech Group, S.R.O. and Surgicare. B. Somani reported receiving honoraria or consultation fees from Zhuhai Pusen Medical Technology Co., Ltd., Boston Scientific, CJ Medical, GlaxoSmithKline, Novo Nordisk and Coloplast. T. Taily reported working as a company consultant for Ambu GmbH, Cook Medical, Stroz Medical AG, BD and Dornier Med Tech GmbH, and receiving company speaker honorarium from Boston Scientific. S. Croghan, F. Esperto, N. Davis, G. Gambaro, R. Geraghty, L. Lardas, R. Lombardo, I. Manolitsis, A. Skolarikos and L. Tzelves have nothing to declare.

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