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 now 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 conflict 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/. A 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. This 2024 Urolithiasis Guidelines present a limited update of the 2023 publication. The 2025 edition of the Urolithiasis Guidelines is a limited text update in which a new section on genetic factors and testing has been added. The Urolithiasis Guideline will be updated in full for 2026.

1.4.2 Summary of changes

Section 3.1.4 , a new section on Genetic factors and testing have been added.

2. METHODOLOGY

2.1 Methods

Recommendation 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 [5].

Additional information can be found in the general Methodology section online at the EAU website: http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at this address.

2.2 Review
The 2015 Urolithiasis Guidelines were subjected to peer review prior to publication. Chapter 6, detailing the treatment and follow-up of bladder stones was peer-reviewed in 2019.

3. GUIDELINES

3.1 Prevalence, aetiology, risk of recurrence
*3.1.1 **Introduction***
Stone 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 20% [6]. In countries with a high standard of life 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 [7-9]. There is emerging evidence linking nephrolithiasis to the risk of CKD [10].

Stones can be stratified into those caused by: infections, non-infectious causes, genetic defects [11, 12]; or adverse drug effects (drug stones) (Table 3.1). See also section 3.2.

Table 3.1: Stones classified by aetiology

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

**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. 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	$CaC_2O_4.H_2O$
Calcium oxalate dihydrate	Weddelite	$CaC_2O_4.2H_2O$
Basic calcium phosphate	Apatite	$Ca_{10}(PO_4)_6.(OH)_2$
Calcium hydroxyl phosphate	Carbonate apatite	$Ca_5(PO_4)_3(OH)$
b-tricalcium phosphate	Whitlockite	$Ca_3(PO_4)_2$
Carbonate apatite phosphate	Dahllite	$Ca_5(PO_4)_3OH$
Calcium hydrogen phosphate dihydrate	Brushite	$CaHPO_4.2H_2O$
Calcium carbonate	Aragonite	$CaCO_3$
Octacalcium phosphate	-	$Ca_8H_2(PO_4)_6.5H_2O$
Uric acid	Uricite	$C_5H4N_4O_3$

Uric acid dihydrate	Uricite	$C_5H_4O_3.2H_20$
Ammonium urate	-	$NH_4C_5H_3N_4O_3$
Sodium acid urate monohydrate	-	$NaC_5H_3N_4O_3.H_2O$
Magnesium ammonium phosphate hexahydrate	Struvite	$MgNH_4PO_4.6H_2O$
Magnesium acid phosphate trihydrate	Newberyite	
Magnesium ammonium phosphate monohydrate	Dittmarite	
Cystine	-	
Xanthine	-	-
2,8-Dihydroxyadenine	-	-
Proteins	-	-
Cholesterol	-	-
Calcite	-	-
Potassium urate	-	-
Trimagnesium phosphate	-	-
Melamine	-	-
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 [9, 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, 34]. 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]. 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 below.

Table 3.3: High-risk stone formers [16-32]

General factors
Early onset of urolithiasis (especially children and teenagers)
Familial stone formation
Recurrent stone formers
Short time since last stone episode
Brushite-containing stones ($CaHPO_4.2H_2O$)
Uric acid and urate-containing stones
Infection stones
Solitary kidney (the kidney itself does not particularly increase the risk of stone formation, but prevention of stone recurrence is of crucial importance to avoid acute renal failure)
Chronic Kidney Disease (CKD)

Diseases associated with stone formation
Hyperparathyroidism
Metabolic syndrome
Mineral Bone Disorder (MBD)
Nephrocalcinosis
Polycystic kidney disease (PKD)
Gastrointestinal diseases (i.e., enteric hyperoxaluria due to jejuno-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
Genetically determined stone formation
Cystinuria (type A, B and AB)
Primary hyperoxaluria (PH)
Renal tubular acidosis (RTA) type I
2,8-Dihydroxyadeninuria
Xanthinuria
Lesch-Nyhan syndrome
Cystic fibrosis
Drug-induced stone formation (see Table 4.11)
Anatomical abnormalities associated with stone formation
Medullary sponge kidney (tubular ectasia)
Ureteropelvic junction (UPJ) obstruction
Calyceal diverticulum, calyceal cyst
Ureteral stricture
Vesico-uretero-renal reflux
Horseshoe kidney
Ureterocele
Environmental and professional factors
High ambient temperatures
Chronic lead and cadmium exposure

Table 3.4 Risk factors for CKD and ESKD in stone formers

Risk factors for CKD/ESKD in stone formers
Female gender
Overweight
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 below.

Table 3.5 Risk factors for CKD and renal stones

Risk of chronic kidney disease and renal stones
• 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)
■ Neurological 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 ~45% [35] suggesting that genetic factors strongly influence this disease [36]. Monogenic forms of stones remain rare, and are seen in 12-21% [37, 38] of children/young adults and 1-11% [38, 39] of adults with KSD, but enable specific patient management [39]. 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 [39]. 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 ≤ 25 years and adults > 25 years if there is clinical suspicion of an inherited or metabolic disorder underlying the KSD. Features including recurrent (≥ 2 discrete episodes), bilateral disease or a strong family history [40] should prompt genetic testing. Genetic testing should be performed in combination with other metabolic testing (blood and 24 hour urine tests as detailed in tables 3.3, 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.

Table 3.7: Table of known pathogenic genes (adapted from Geraghty *et al.* 2024) [40]

Gene	Associated Conditions	Recommended Treatment
SLC7A9 ***SLC3A1***	Cystinuria, Cystine stones, Calcium containing Stones	Urinary alkalinisation; thiol-binding drugs; aggressive urinary dilution
CYP24A1	Idiopathic Infantile Hypercalcaemia, Calcium containing stones	Avoidance of excess vitamin D; Inhibition of vitamin D synthesis e.g. Fluconazole
AGXT ***GRHPR*** ***HOGA1***	Primary Hyperoxaluria, Calcium oxalate stones	Pyridoxine or Lumasiran for AGXT mutations. Potassium citrate, magnesium oxide and/or orthophosphate; aggressive urine dilution, limit oxalate intake
CLDN16 ***CLDN19***	Familial hypomagnesaemia, Calcium containing stones	Magnesium replacement; caution with vitamin D replacement; assess for ocular phenotypes with *CLDN19* variants
CASR	Autosomal Dominant Hypocalcaemia, Calcium containing stones	Avoid overzealous correction of hypocalcaemia
SLC34A3 ***SLC34A1*** ***PHEX***	Hypophosphataemic Rickets, Calcium containing stones	Screen for osteomalacia; phosphate replacement without vitamin D
CLCN5 ***OCRL***	Dent disease, Calcium containing stones	Screen for osteomalacia, vitamin D, phosphate and bicarbonate replacement if needed; thiazide diuretics
SLC22A12 ***SLC2A9***	Renal uric acid wasting, uric acid stones	Urinary alkalinisation; allopurinol or febuxostat
BSND ***CASR*** ***CLCN5*** ***CLCNKB*** ***KCNJ1*** ***SLC12A1***	Bartter Syndrome, Calcium containing stones	NSAIDs, aldosterone antagonists, electrolyte replacement as required
HNF4A	Fanconi Syndrome, Nephrocalcinosis	Refer to nephrology
XDH ***MOCOS***	Xanthinuria, Xanthine stones	Low purine diet
ATPV0A4 ***ATP6V1B1*** ***CA2*** ***SLC4A1*** ***WDR72***	Renal tubular acidosis, Calcium containing stones	Sodium bicarbonate or alkaline citrate; hearing screen; assessment for osteomalacia/ osteopetrosis
APRT	Adenine Phosphoribosyltransferase deficiency, 2,8 dihyroxyadenine 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, 9, 32].

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 < 5 mm, 5-10 mm, 10-20 mm, and > 20 mm for use in the treatment algorithm.

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 [41]. 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) [41, 42].

Table 3.7: X-ray characteristics

<table>
<tr><th>Radiopaque</th><th>Poor radiopacity</th><th>Radiolucent</th></tr>
<tr><td>Calcium oxalate dihydrate</td><td>Magnesium ammonium phosphate</td><td>Uric acid</td></tr>
<tr><td>Calcium oxalate monohydrate</td><td>Cystine</td><td>Ammonium urate</td></tr>
<tr><td colspan="2" rowspan="3">Calcium phosphate</td><td>Xanthine</td></tr>
<tr><td>2,8-Dihydroxyadenine</td></tr>
<tr><td>Drug-stones (Section 4.11)</td></tr>
</table>

3.3 Diagnostic evaluation
3.3.1 Diagnostic imaging
The most appropriate imaging modality will be determined by the clinical situation, which will differ depending on if 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 fever, but may also be asymptomatic [43]. Immediate evaluation is indicated in patients with solitary kidney, fever 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 pyeloureteric and vesico-ureteral 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 [44, 45].

The sensitivity and specificity of KUB is 44-77% [46]. Kidney-ureter-bladder radiography [47] is helpful in differentiating between radiolucent and radiopaque stones and could be used for comparison during follow-up.

3.3.1.1 Evaluation of patients with acute flank pain/suspected ureteral stones
Non-contrast-enhanced computed tomography has become the standard for diagnosing acute flank pain and has replaced intravenous urography (IVU). Non-contrast-enhanced CT 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 [48, 49].

Non-contrast-enhanced CT can detect uric acid and xanthine stones, which are radiolucent on plain films, but not indinavir stones [50]. 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 [51]. The advantage of non-contrast imaging must be balanced against the loss of information on renal function and urinary collecting system anatomy, as well as higher radiation dose [52-55].

Radiation risk can be reduced by low-dose CT, which may, however, be difficult to introduce in standard clinical practice [56-59]. 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 < 3 mm and 100% for calculi > 3 mm [60]. A meta-analysis (MA) of prospective studies [61] 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 [42].

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 assessed.	3

Recommendations	Strength rating
Immediate imaging is indicated with fever or solitary kidney, and when diagnosis is doubtful.	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 test. At this point, no distinction is made between high- and low-risk patients for stone formation.

3.3.2.1 Basic laboratory analysis - non-emergency urolithiasis patients

Biochemical work-up is similar for all stone patients (see 3.3.2.3). 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 3.3.2.3. Once the mineral composition is known, a potential metabolic disorder can be identified.

3.3.2.2 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;
- late recurrence after a prolonged stone-free period [62, 63].

Patients should be instructed to filter their urine to retrieve a concrement 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)[64, 65]. Equivalent results can be obtained by polarisation microscopy. Chemical analysis (wet chemistry) is generally deemed to be obsolete [64, 66].

3.3.2.3 Recommendations for laboratory examinations and stone analysis [17, 23, 67-69]

Recommendations	Strength rating
Urine	
Dipstick test of spot urine sample: • red cells; • white cells; • nitrites; • approximate urine pH; • urine microscopy and/or culture.	Weak

Blood	
Serum blood sample: • creatinine; • uric acid; • (ionised) calcium; • sodium; • potassium; • blood cell count; • C-reactive protein.	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 formers using a valid procedure (X-ray diffraction or infrared spectroscopy).	Strong
Repeat stone analysis in patients presenting with: • recurrent stones despite drug therapy; • early recurrence after complete stone clearance; • late recurrence after a long stone-free period because stone composition may change.	Strong

*3.3.3 **Diagnosis in special groups and conditions***

3.3.3.1 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 (< 50 mGy are considered as safe) and depend on the gestation age (minimum risk prior to the 8th week and after the 23rd week). Carcinogenesis (dose even < 10 mGy present a risk) and mutagenesis (500-1000 mGy 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 [70].

There is no imaging modality that should be routinely repeated in pregnant women. Scientific societies and organisations agree on the safety of the diagnostic evaluation when the US [71], X-ray imaging [72, 73], and MRI [74] are used as and when indicated [75-82]. 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 greater than 0.5 mGy 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 [78-80].

Magnetic resonance imaging can be used, as a second-line option [76], to define the level of urinary tract obstruction, and to visualise stones as a filling defect [83]. The use of gadolinium is not routinely recommended in pregnancy to avoid toxic effects on the embryo [78].

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 [84]. Although low-dose CT protocols reduce radiation exposure, judicious use is currently recommended in pregnant women as a last-line option [78].

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

3.3.3.2 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 nonmetabolic disorders facilitating stone formation are vesicoureteral reflux (VUR), UPJ obstruction, neurogenic bladder, and other voiding difficulties [85].

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 [86-90].

Ultrasound

Ultrasound is the primary imaging technique [91] 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 [86]. Colour Doppler US shows differences in the ureteral jet [92] and resistive index of the arciform arteries of both kidneys, which are indicative of the grade of obstruction [93]. Nevertheless, the US may fail to identify ureteral stones and provides limited information on renal function [94].

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 comparable to that for voiding cystourethrography (0.33 mSV) [95]. However, the need for contrast medium injection is a major drawback.

Non-contrast-enhanced computed tomography

Low-dose CT protocols have been shown to significantly reduce radiation exposure [96-98]. Sedation or anaesthesia is rarely needed with modern high-speed CT equipment.

Magnetic resonance urography

Magnetic resonance urography (MRU) cannot be used to detect urinary stones. 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 [99].

3.3.3.2.1 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 constitution 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 and compliance of the entire pelvic-calyceal system should be assessed for each patient. The design of therapeutic algorithms including all the above parameters is difficult mainly due to the great diversity of lithiasis disease per patient. Furthermore, there is a significant lack of comparative clinical studies to support 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 [100] and have better analgesic efficacy than opioids [101]. Ibuprofen compared to ketorolac is a more rapid-acting drug in controlling pain caused by renal colic with a similar side effect profile [102].

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 [103]. The addition of antispasmodics to NSAIDs does not result in better 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 [100, 101]. Oral diclofenac in the long-term increases the risk of cardiovascular events and upper GI bleeding [104]. 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 [105]. Non-steroidal anti-inflammatory drugs may affect renal function in those patients with pre-existing decreased GFR.

In an RCT including 150 patients, Intradermal sterile water injection (ISWI) and diclofenac (i.m.) were shown equally effective for pain relief in acute renal colic. Intradermal sterile water injection may be an alternative to NSAIDs in pregnant patients or others where NSAIDs are contra-indicated [106].

Opioids, particularly pethidine, are associated with a high rate of vomiting compared to NSAIDs and carry a greater likelihood of further analgesia being needed [100, 107]. If an opioid is used, it is recommended that it is not pethidine. Combination of opioids and NSAIDs increase analgetic effect compared to opioids alone [108]. Acupuncture seems to be effective in renal colic alone or in combination with analgetic drugs, but there is limited data [109, 110].

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 [111, 112]. Although NSAID can affect renal function in patients with already reduced function, it has no functional effect in patients with normal renal function [113].

The systematic review and MA by Hollingsworth *et al.,* [114] addressed pain reduction as a secondary outcome and concluded that medical expulsive therapy (MET) seems efficacious in reducing pain episodes of patients with ureteral stones.

If analgesia cannot be achieved medically, drainage, using stenting, percutaneous nephrostomy, or stone removal, is indicated [115].

3.4.1.1 Summary of evidence and recommendations for the management of renal colic

Summary of evidence	**LE**
Non-steroidal 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 non-steroidal anti-inflammatory as the first drug of choice; depending on cardiovascular risk factors and side effects.	Strong
Offer opiates (hydromorphine, pentazocine or tramadol) as a second choice.	Weak
Offer renal decompression or ureteroscopic stone removal in case of analgesic 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 [116]:

- placement of an indwelling ureteral stent
- 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 [116]. There appears to be no difference in success rate or complication rate of both procedures and there is not a 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 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 these patients experience [117, 118].

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; however, at the cost of longer hospital stay and higher analgesic requirements [119].

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 [120, 121]. The regimen should be re-evaluated in the light of the culture-antibiogram results. Although clinically well accepted, the impact of a second antibiogram test on treatment outcome has not yet been evaluated [122]. Intensive care might become necessary.

3.4.2.1 *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 α-blockers, calcium channel inhibitors, and phosphodiesterase type 5 inhibitors (PDEI-5) are used for MET [123-126] A class effect of α-blockers in MET has been demonstrated in MAs although this is an off-label indication [127-129]. 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 α-blockers, besides some advantage for distal ureteral stones > 5 mm [130-134]. Based on studies with a limited number of patients [126, 127, 135, 136], no recommendation for the use of PDEI-5 or corticosteroids in combination with α-blockers in MET can be made. The Panel concludes that MET using α-blockers seems efficacious in the treatment of patients with distal ureteral stones > 5 mm who are amenable to conservative management. Medical expulsive therapy in special situations is addressed in the relevant chapters.

3.4.3.1 *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
Insufficient data exist to support the use of PDEI-5 or corticosteroids in combination with α-blockers as an accelerating adjunct.	2a
Alpha-blockers increase stone expulsion rates in distal ureteral stones > 5 mm.	1a
A class effect of α-blockers has been demonstrated.	1a

Recommendation	Strength rating
Offer α-blockers as medical expulsive therapy as one of the treatment options for (distal) ureteral stones > 5 mm.*	Strong

** Alpha-blockers are an off-label treatment*

3.4.4 ***Chemolysis***

Percutaneous irrigation chemolysis

Percutaneous chemolysis is rarely used nowadays, for practical reasons. 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 [137].

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 alkalising medication by self-monitoring the pH of their urine. A systematic review shows a complete or partial dissolution in 80.5%, discontinuation rate of 10.2% with 15.7% requiring further intervention [138].

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 > 5 mm [139]. Additional SWL might help to improve the results but evidence is weak [140].

3.4.4.1 *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 > 5mm 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 alkalising medication according to urine pH, as changes in urine pH are a direct consequence of such medication.	Strong
Carefully monitor patients during/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

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 3.4.9.3);
- patient's habitus (Section 3.4.10.3);
- 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 does not improve stone-free rates (SFRs), nor lowers the number of auxiliary treatments. It may, however, reduce the formation of steinstrasse [141-144].

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 [145].

Shock wave rate

Lowering shock wave frequency from 120 to 60-90 shock waves/min improves SFRs [146-154]. Ultraslow frequency of 30 shock waves/min may increase SFR [155]. Tissue damage increases with shock wave frequency [156-159].

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 [160]. Starting SWL on a lower energy setting with stepwise power (and SWL sequence) ramping can achieve vasoconstriction during treatment [156], which prevents renal injury [161-163]. Animal studies [164] and a prospective randomised study [165] 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 [166, 167].

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) [168].

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 [169]. Gentle swiping between the coupled therapy head and the patient skin helps remove air bubbles and improves the coupling [170]. Ultrasound gel is probably the most widely-used agent available as a lithotripsy coupling agent [171].

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 [172].

Pain Control

Careful control of pain during treatment is necessary to limit pain-induced movements and excessive respiratory excursions [173-176].

Antibiotic prophylaxis

No standard antibiotic prophylaxis before SWL is recommended. However, prophylaxis is recommended in the case of internal stent placement ahead of anticipated treatments and in the presence of increased bacterial burden (e.g., indwelling catheter, nephrostomy tube, or infectious stones) [68, 177, 178].

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 [179].

Post-treatment management

Mechanical percussion and diuretic therapy can significantly improve SFRs and accelerate stone passage after SWL [180].

Complications of extracorporeal shock wave lithotripsy

Compared to percutaneous nephrolithotomy (PCNL) and ureteroscopy (URS), there are fewer overall complications with SWL [181] (Table 3.9). In a MA of 115 RCT´s 18.43% of Clavien I–II complications and 2.48% of Clavien III–IV complications occurred [181]. The relationship between SWL and hypertension or diabetes is unclear. Published data are contradictory; however, no evidence exists supporting the hypothesis that SWL may cause long-term adverse effects [182-188].

Table 3.9: Shock wave lithotripsy-related complications

Complications			%	Reference
Related to stone fragments	Steinstrasse		4	[189-191]
	Macroscopic haematuria		17.2%	[181]
	Pain		12.1%	[181]
	Regrowth of residual fragments		21 – 59	[192, 193]
	Auxiliary procedure		6.9%	[181]
	Renal colic		2 – 4	[194]
Infectious	Bacteriuria in non-infection stones		7.7 – 23	[192-195]
	Sepsis		0.15%	[181]
Tissue effect	Renal	Haematoma, symptomatic	0.21%	[181]
		Haematoma, asymptomatic	1.2%	[181]
	Cardiovascular	Dysrhythmia	11 – 59	[192, 194]
		Morbid cardiac events	Case reports	[192, 194]
	Gastrointestinal	Bowel perforation	Case reports	[196]
		Liver, spleen haematoma	Case reports	[196-199]

3.4.5.1 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 to 1.5 Hz.	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 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
Antibiotic prophylaxis is recommended in the case of internal stent placement, infected stones, or bacteriuria.	1a

Recommendations	Strength rating
Ensure correct use of the coupling agent because this is crucial for effective shock wave transportation.	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
Prescribe antibiotics prior to SWL in the case of 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 (F). Rigid URS can be used for the whole ureter [182]. However, technical improvements, as well as the availability of digital scopes, also favour the use of flexible ureteroscopes in the ureter [200].

Percutaneous antegrade removal of ureteral stones is a consideration in selected cases, i.e. large (> 15 mm), impacted proximal ureteral calculi in a dilated renal collecting system [201, 202], or when the ureter is not amenable to retrograde manipulation [203].

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 > 2 cm showed a cumulative SFR of 91% with 1.45 procedures/patient; 4.5% of the complications were > Clavien 3 [204, 205]. Digital scopes demonstrate shorter operation times due to the improvement in image quality [206].

Stones that cannot be extracted directly must be disintegrated. If it is difficult to access stones within the lower renal pole that need disintegration it may help to displace them into a more accessible calyx [207].

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 [208]. Intravenous sedation is suitable for female patients with distal ureteral stones [209]. Smaller caliber (4.5/6 Fr) semi-rigid ureteroscope was associated with significantly higher SFR, lower rates of ureteric injury, and shorter hospital stay [210].

Antegrade URS is an option for large, impacted, proximal ureteral calculi [201, 211]. Reduction of flexible ureteroscope diameter may provide similar vision, deflection, and manoeuvrability to standard flexible ureteroscopes potentially with improved ureteric access [212]. Disposable ureteroscopes provide similar safety and clinical effectiveness to reusable scopes. Concerns regarding cost-effectiveness and environmental sustainability remain [210, 213-215].

Safety aspects

Fluoroscopic equipment must be available in the operating room. The Panel recommends placement of a safety wire, even though some groups have demonstrated that URS can be performed without it [216-220]. Balloon and plastic dilators should be available, if necessary.

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 [221]. 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) [222, 223].

Difficult lower pole anatomy such as steep infundibulopelvic angle predisposes to failure during RIRS [224]. A reusable flexible ureteroscope can be more helpful in reaching a difficult lower pole calyx [225]. Prolonged operative times are linked to increased complication rates in ureteroscopy, and efforts must be made to keep it below 90 minutes [226].

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 significantly facilitate URS. The use of ureteral access sheaths improves vision by establishing a continuous outflow, decreases intrarenal pressure, and potentially reduces operating time [227, 228].

The insertion of ureteral access sheaths may lead to ureteral damage, the risk is lowest in pre-stented systems [229]. No data on long-term side effects are available [204, 229]. Whilst larger cohort series showed no difference in SFRs and ureteral damage (stricture rates of about 1.8%), they did show lower post-operative infectious complications [230, 231]. Increasing sheath size directly determines higher grades of ureteral injury rates but there is no difference in long-term stricture rates [232]. The use of a ureteral access sheath is safe and can be useful for large and multiple renal stones or if long procedural time is expected [233].

Stone extraction
The aim of URS is complete stone removal. “Dust and go” strategies should be limited to the treatment of large (renal) stones [234]. Stones can be extracted by endoscopic forceps or baskets. Only baskets made of nitinol can be used for flexible URS [235].

Intracorporeal lithotripsy
The most effective lithotripsy system is the holmium: yttrium-aluminum-garnet (Ho: YAG) laser, which is currently the optimum standard for URS and flexible nephroscopy (Section 3.4.6), because it is effective in all stone types [236, 237]. 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 [238]. The only RCT to date shows no clinical difference regarding stone-free rate or operative time [239]. Although pulse-modulation in Ho: YAG lasers has demonstrated several *in vitro* benefits, a systematic review including eight comparative studies and only one RCT showed no difference in stone-free rate, complication rate, or operative time [240]. The two available RCTs on the subject both found a shorter operative time, without conferring a difference in success rate [241, 242]. 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 [243-245]. With the limited reports of clinical use available to date, a meta-analysis could not demonstrate the superiority of TFL over Ho: YAG, although the operative time to achieve this stone-free rate seems to be shorter with the use of TFL [246]. More comparative clinical studies are however needed between these two modalities. When a laser is not available, pneumatic and US systems can be used with high disintegration efficacy in rigid URS [247, 248]. However, stone migration into the kidney is a common problem, which can be prevented by the placement of special anti-migration tools proximal to the stone [249]. Medical expulsion therapy following Ho: YAG laser lithotripsy increases SFRs and reduces colic episodes [250].

Stenting before and after URS
Routine stenting is not necessary before URS. Despite a complete lack of RCTs on this subject, a meta-analysis has been performed, demonstrating that pre-stenting may improve the stone-free rate of ureteroscopic treatment of renal stones, but not of ureteral stones [251]. Although it may facilitate ureteroscopic management of stones and increase success in access sheath placement, intra-operative complications were not significantly different [251, 252]. 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.

Randomised prospective trials have found that routine stenting after uncomplicated URS (complete stone removal) is not necessary; stenting might be associated with higher post-operative morbidity and costs [253]. Smaller diameter ureteric stents may reduce urinary symptoms and patient-reported pain [254]. A ureteral catheter with a shorter indwelling time (one day) may also be used, with similar results [255].
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. Most urologists favour one to two weeks after URS. Alpha-blockers reduce the morbidity of ureteral stents and increase tolerability [256].

Medical expulsive therapy before and after ureteroscopy
Medical expulsion therapy before URS might reduce the risk for intra-operative ureteral dilatation, protect against ureteral injury when using access sheaths and increase stone-free rates four weeks after URS [257, 258].

Medical expulsion therapy following Ho: YAG laser lithotripsy accelerates the spontaneous passage of fragments and reduces episodes of colic [250].

Complications of ureteroscopy
The overall complication rate after URS is 4-25% [259, 260]. Most complications are minor and do not require intervention. There is evidence suggesting a risk of post-operative urosepsis of up to 5% [261, 262]. Ureteral avulsion and strictures are rare (< 1%). Previous perforations, pre-operative positive urine cultures, comorbidities, and longer operation time are the most important risk factor for complications [226, 263, 264]. Infectious complications following URS can be minimised using prophylactic antibiotics, limiting stent dwell and procedural time, identification and treatment of UTI, and planning in patients with large stone burden and multiple comorbidities [265].

High intrarenal pressure (IRP) predisposes to URS complications, and measures should be used to reduce IRP. Currently, there are no accurate ways to measure the intra-operative IRP [266].

3.4.6.1 *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.	
An α-blocker can reduce stent-related symptoms and colic episodes.	1a
The most effective lithotripsy system for flexible ureteroscopy is the Ho: YAG laser.	2a
Pneumatic and US 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
Pre-treatment of patients undergoing URS with an α-blocker one week prior to the procedure reduces the need for active dilatation and increases the stone free rate.	1a

Recommendations	Strength rating
Use holmium: yttrium-aluminum-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 Ho: YAG 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 > 2 cm) in cases where percutaneous nephrolithotomy or SWL are not an option. 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 reference. Standard access tracts are 24-30 F. Smaller access sheaths, < 18 F, were initially introduced for paediatric use, but are now increasingly utilised in the adult population [267, 268].

Contraindications
Patients receiving anticoagulant therapy must be monitored carefully pre-and post-operatively. Anti-coagulant therapy must be discontinued before PCNL [269].

Other important considerations include:
- untreated UTI;
- tumour in the presumptive access tract area;
- potential malignant kidney tumour;
- pregnancy (Section 3.4.14.1).

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 [270].

Pre-operative imaging
Pre-procedural 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).

Positioning of the patient
Both prone and supine positions are equally safe. A meta-analysis including twelve studies and a total of 1,290 patients treated, showed a similar SFR but a lower operative time for supine PCNL [271]. The supine position allows simultaneous retrograde access to the collecting system, using a flexible ureteroscope [272]. 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 [271, 273].

Puncture
Although fluoroscopy is still the most common intra-operative imaging method, the use of US as an additional or only means of puncture guidance provides advantages according to two meta-analyses including eight randomised controlled trials. Additional to the expected reduced radiation exposure with the use of US the meta-analyses also demonstrated a lower complication rate [274, 275]. Pre-operative CT or intra-operative 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 [276-278].

Dilatation
Dilatation of the percutaneous access tract can be achieved using a metallic telescopic, single (one-shot or serial) dilator, or balloon dilatator. During PCNL, safety and effectiveness are similar for different tract dilatation methods [279]. 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 [279, 280]. A meta-analysis 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 [281].

Choice of instruments
Several meta-analyses on mini-PCNL (12-22 F) vs. standard PCNL (> 22 F) 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 [268, 282-284]. 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 intra-renal pressure and increase stone-free rate [285].

Post-operative drainage
The decision on whether, or not, 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 intra-operative blood loss/ bleeding from the percutaneous tract;
- urine extravasation;
- ureteral obstruction;
- potential persistent bacteriuria due to infected stones;
- solitary kidney;
- bleeding diathesis;
- planned percutaneous chemolitholysis.

Small-bore nephrostomies seem to have advantages in terms of post-operative pain [268, 286, 287]. Tubeless PCNL is performed without a nephrostomy tube and is associated with reduced post-operative pain and hospital stay [288]. When neither a nephrostomy tube nor a ureteral stent is introduced, the procedure is known as a totally tubeless PCNL [289]. In uncomplicated cases, the latter procedure results in a shorter hospital stay, with no disadvantages reported [290].

As reported in the above section on the drainage of an infected or obstructed system [116-118] (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 [291].

Complications of percutaneous nephrolithotomy

A systematic 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% [292].

Peri-operative fever can occur, even with a sterile pre-operative urinary culture and peri-operative 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 post-operative SIRS or sepsis. Whenever possible a urine culture from the renal pelvis and/or stone culture should be taken at the time of PCL [293].

Intra-operative renal stone or renal pelvic urine culture may be more indicative of the causative organism for sepsis; therefore, helping to select the most suitable post-operative antibiotics [293-295]. Although this data is weak, there is limited retrospective data indicating that increased pressures during mPCNL may contribute to febrile complications [296-298]. This contrasts with the previously mentioned meta-analyses on mini vs standard PCNL that do not identify a difference in complication rate between the two procedures [268, 282-284]. 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 [299-301]. However, the transfusion rate in the control group of the meta-analyses was in the range of 10-12%.

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 post-operative complications including pleural damage, infections, and the need for transfusion [302].

To reduce post-operative 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 post-operative opioid analgesics [303, 304]. Current evidence shows that a quadratus lumborum block or infiltration of a local anaesthetic around the nephrostomy tube may reduce post-operative pain and opioid consumption after PCNL [305, 306].

3.4.7.1 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 inter-positioned 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
Percutaneous nephrolithotomy performed with small instruments tends to be associated with significantly lower blood loss, but the duration of 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
Peri-operative 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 pre-operative midstream urine culture.	1a

Recommendations	**Strength rating**
Perform pre-procedural 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 time of PCNL, if possible.	Strong

3.4.8 General recommendations and precautions for stone removal

3.4.8.1 *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 [307].

Peri-operative antibiotic prophylaxis

The available evidence for prevention of infection following URS and percutaneous stone removal, remains limited [308]. Administration of a single dose of prophylactic antibiotics prior to ureteroscopy was found to be sufficient [308-310]. 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 [311]. Based on three meta-analyses, pooling data from small series with varying quality an extended course of pre-operative prophylactic antibiotics prior to PCNL compared to a single dose before anaesthesia significantly reduced post-operative sepsis and fever in patients with an a priori increased risk of infection [294, 312, 313]. In an RCT including only moderate to high-risk infection patients (patients with pre-operative stents/nephrostomy or positive urine culture), a 7-day course of pre-operative antibiotics reduced the risk of post-PCNL sepsis threefold in comparison to a two-day course [314]. 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 pre-operative course [313, 315]. In contrast to this, a prolonged course of post-operative antibiotics was not superior to a single dose pre-operatively [294, 313].

As national and regional antibiotic resistance patterns can differ significantly, the choice of antibiotic prophylaxis should be tailored to institutional or regional antimicrobial susceptibility [310].

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 peri-operative antibiotic prophylaxis to all patients undergoing endourological treatment.	Strong

3.4.8.2 *Antithrombotic therapy and stone treatment*

Patients with a bleeding disorder, or receiving antithrombotic therapy, should be referred to an internist for appropriate therapeutic measures before deciding on stone management [316-320]. 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 anti-coagulant/anti-platelet medication) [321]
- PCNL;
- percutaneous nephrostomy;
- laparoscopic surgery;
- open surgery [316].

Shock wave lithotripsy is feasible and safe after correction of the underlying coagulopathy [322, 323]. 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 [324-326]. Despite the appropriate cessation of anti-platelet agents, following standardised protocols, prolonged haematuria in tube drainage after PCNL has been reported [327]. Only data on flexible URS are available which support the superiority of URS in the treatment of proximal ureteral stones [328, 329]. Although URS is safe in patients with bleeding disorders or anticoagulation, an individualised patient approach is necessary [326].

Table 3.10: Risk stratification for bleeding [318-320, 330]

Low-risk bleeding procedures	• Cystoscopy • Flexible cystoscopy • Ureteral catheterisation • Extraction of ureteral stent • Ureteroscopy
High-risk bleeding procedures	• Shock wave lithotripsy • Percutaneous nephrostomy • Percutaneous nephrolithotomy

Table 3.11: Suggested strategy for antithrombotic therapy in stone removal [318-320]
(In collaboration with a cardiologist/internist weigh the risks and benefits of discontinuation of therapy, vs. 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	Elective surgery: postpone. Non-deferrable surgery: continue, if it is 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.	Continue	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.

3.4.8.2.1 Summary of evidence and recommendations for antithrombotic therapy and stone treatment

Summary of evidence	LE
Active surveillance is indicated in patients at high risk for thrombotic complications in the presence of an asymptomatic calyceal stone.	4
The temporary discontinuation, or bridging of antithrombotic therapy in high-risk patients, should be discussed with the internist.	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 internist.	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

3.4.8.3 Obesity

A high BMI can pose a higher anaesthetic risk and a lower success rate after SWL and PCNL and may influence the choice of treatment [331].

3.4.8.4 Stone composition

Stones composed of brushite, calcium oxalate monohydrate, or cystine are particularly hard, as well as homogeneous stones with a high density on NCCT [332, 333]. 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

3.4.8.5 Contraindications of procedures

Contraindications of extracorporeal SWL

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

- pregnancy, due to the potential effects on the foetus [334];
- bleeding disorders, which should be compensated for at least 24 hours before and 48 hours after treatment [335];
- uncontrolled UTIs;
- severe skeletal malformations and severe obesity, which prevent targeting of the stone;
- arterial aneurysm in the vicinity of the stone [336];
- anatomical obstruction distal to the stone.

Contraindications of 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 of PCNL

Patients receiving anti-coagulant therapy must be monitored carefully pre- and post-operatively. Anti-coagulant therapy must be discontinued before PCNL [326]. Other important contraindications include:

- untreated UTI;
- tumour in the presumptive access tract area;
- potential malignant kidney tumour;
- pregnancy (Section 3.4.14.1).

General contraindication for endourological procedures

Endourological interventions do not adversely affect renal function although care must be taken in those with poor pre-operative renal function, diabetes and hypertension [337]. However, a meta-analysis, 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 increase their renal function [338].

*3.4.9 **Specific stone management of ureteral stones***

3.4.9.1 Conservative treatment/observation

There are only limited data regarding spontaneous stone passage according to stone size [339, 340].

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 < 5 mm and 62% of stones ≥ 5 mm passed spontaneously, with an average time to stone expulsion about 17 days (range 6-29 days) [339, 341]. Considering both size and location, stones of < 5 mm in the distal ureteral have a 89% chance of spontaneous passage, while 71% of stones < 5 mm located in the upper ureter still pass spontaneously [339]. The Panel is aware of the fact that spontaneous stone expulsion decreases with increasing stone size and that there are differences between individual patients.

3.4.9.2 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.

3.4.9.3 Indications for treatment of ureteral stones

Indications for removal of ureteral stones are [182, 340, 342]:

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

3.4.9.4 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, and density, 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 this guideline, CT imaging can provide useful information that may influence the choice of treatment. A meta-analysis outlines that increasing stone density, stone burden, skin-to-stone distance, and hydronephrosis can negatively impact the success of the shockwave lithotripsy [343].

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

A large multi-centre non-inferiority trial compared URS to ESWL for ureteral stones. When excluding patients that had spontaneously passed their stone prior to treatment, ESWL could not be considered non-inferior to URS with only 12% of patients needing further intervention after URS in comparison to 26% in the SWL arm [259]. 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 [344].

The Panel performed a systematic review to assess the benefits and harms of URS compared to SWL [345]. 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 [346]. Clavien-Dindo grade complications were if reported, less frequent in patients treated with SWL [181].

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 [347], without however increasing the stone-free rate. These results however are based mainly on low level of evidence reports and should be interpreted with caution [347]. Similarly, ESWL can be performed in the acute setting or electively allowing a trial of spontaneous passage. In contrast to acute URS, ESWL in the acute setting does provide an increased stone-free rate and reduced need for auxiliary procedures [348].

For large proximal ureteral stones, a percutaneous antegrade approach may provide better stone-free results than a retrograde ureteroscopic approach [349].

Bleeding disorder
Ureteroscopy can be performed in patients with bleeding disorders, with a moderate increase in complications (see also Section 3.4.8.2) [326].

3.4.9.4.1 Summary of evidence and recommendations for selection of procedure for active removal of ureteral stones

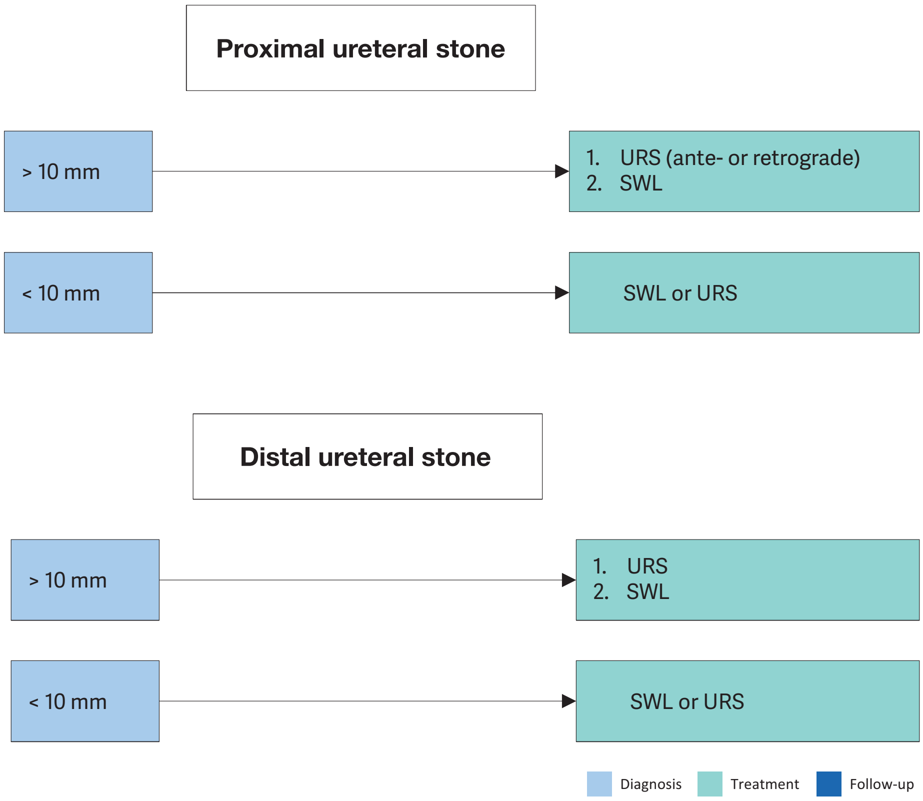
Summary of evidence	LE
Observation is feasible in informed patients who develop no complications (infection, refractory pain, deterioration of renal function).	2a
Medical expulsive therapy seems to be efficacious for treating patients with ureteral stones who are amenable to conservative management. The greatest benefit might be among those with > 5 mm (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 3.4.9.3) in patients with newly diagnosed small* ureteral stones, observe patient initially with periodic evaluation.	Strong
Offer α-blockers as medical expulsive therapy as one of the treatment options for (distal) ureteral stones > 5 mm**.	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 severe obesity.	Strong

**See stratification data [176].*

*** 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, non-obstructing 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 [350].

3.4.10.1 Conservative treatment (observation)

Observation of renal stones, especially in calyces, depends on their natural history (Section 3.4.10.3). The recommendations provided are not supported by high-level literature [351]. There is a prospective trial supporting annual observation for asymptomatic inferior calyceal stones, < 10 mm. In case stone growth is detected, the follow-up interval should be lowered [352]. Intervention is advised for growing stones > 5 mm [353]. 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%, surgical intervention from 7-26% [351].

3.4.10.2 Pharmacological treatment of renal stones

Dissolution therapy seems to be an option for uric acid stones. See sections 3.4.4. and 3.4.8.4.

3.4.10.3 Indications for stone 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) [354];
- patient preference;
- comorbidity;
- the social situation of the patient (e.g., profession or traveling).

3.4.10.4 Selection of procedure for active removal of renal stones
For general recommendations and precautions see Section 3.4.8.

3.4.10.4.1 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 [259, 355-361]. Although multiple treatments or sessions may be needed shock wave lithotripsy achieves good SFRs for stones up to 20 mm, except for those at the lower pole [357, 362, 363]. When SWL is considered, stones with density > 1,000 HU (and with high homogeneity) on non-contrast-enhanced CT are less likely to be disintegrated [49]. 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 > 10 mm, 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 [359, 361]. Stones > 20 mm 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) [364]. Retrograde renal surgery cannot be recommended as first-line treatment for stones > 20 mm in uncomplicated cases as SFRs decrease, and staged procedures will be required [365-367]. However, it may be a first-line option in patients where PCNL is not an option or contraindicated or in selected patients [368]. 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 [271].

3.4.10.4.2 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 intra-renal 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 < 1 cm [356, 358, 362, 364, 367, 369-376].

The following can impair successful stone treatment by SWL [377-383]:
- steep infundibular-pelvic angle;
- long calyx;
- long skin-to-stone distance;
- narrow infundibulum;
- 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 3.4.5 SWL) [180, 384, 385]. If there are negative predictors for SWL, PCNL and RIRS might be reasonable alternatives, even for smaller calculi [369]. Retrograde renal surgery seems to have comparable efficacy to SWL [356, 362, 364, 386]. 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 3 cm can be treated by RIRS [368, 387]. However, staged procedures are frequently required. Although mini-PCNL has the highest success rate for the treatment of lower pole stones up to 2 cm, it comes at the expense of a higher complication rate and longer hospital stay [361].

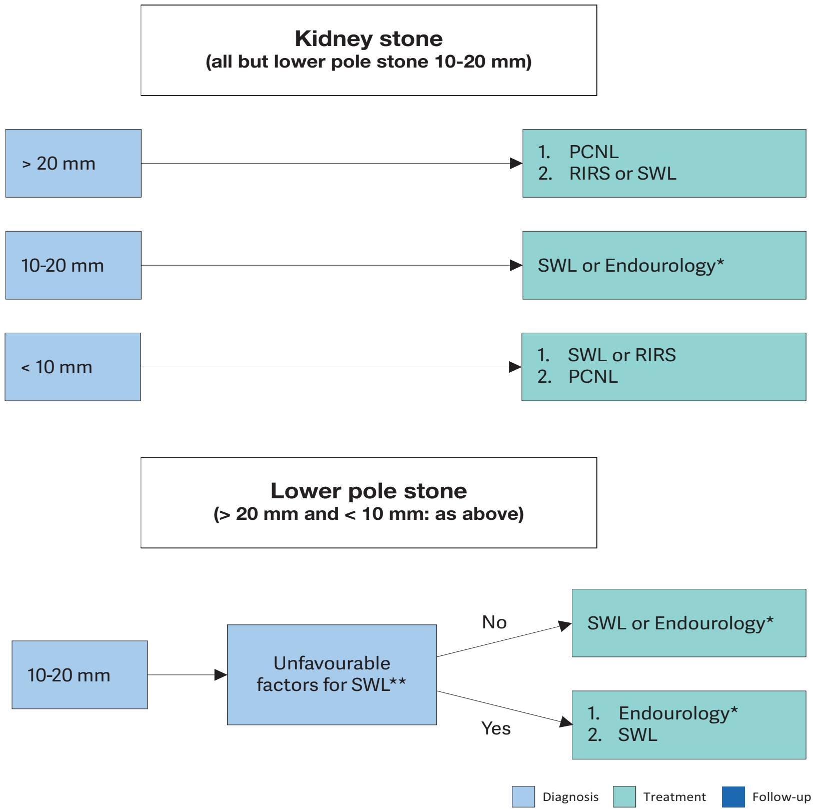
In complex stone cases, open or laparoscopic approaches are possible alternatives although they are infrequently used.

3.4.10.5 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, *de novo* obstruction, associated infection, and acute and/or chronic pain are indications for treatment.	3
Percutaneous nephrolithotomy is indicated in renal stones > 2 cm as primary option.	1a

Recommendations	Strength rating
Offer active treatment for renal stones in case of stone growth, *de novo* 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 > 2 cm.	Strong
Treat larger stones (> 2 cm) 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 > 1 cm, 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 [388-393]. 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 [394-398].

Few studies have reported laparoscopic stone removal. These procedures are usually reserved for special cases. When expertise is available, laparoscopic ureterolithotomy can be performed for large proximal ureteral stones as an alternative to URS or SWL [399, 400]. These more invasive procedures have yielded high SFRs and lower auxiliary procedure rates [202, 211, 395]. A systematic review showed no difference in the post-operative phase for stented or unstented laparoscopic ureterolithotomy [395].

Laparoscopic pyelolithotomy could be offered for solitary stones > 2 cm located in the renal pelvis as an alternative to PCNL [396]. In addition, in selected cases with an extrarenal and dilated pelvis, RLP can be considered as an alternative management of staghorn calculi [401].

A few studies with limited numbers of patients have reported using robotic surgery in the treatment of urinary stones [397]. Open surgery should be considered as the last treatment option after all other possibilities have been explored.

Studies on laparoscopy should be interpreted with caution due to their low design and quality of evidence.

3.4.11.1 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 [402]. Steinstrasse occurs in 4% of cases of SWL [181, 189], and the major factor in the development of steinstrasse formation is stone size [403].

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 [142]. When steinstrasse is asymptomatic, conservative treatment is an initial option. Medical expulsion therapy increases stone expulsion and reduces the need for endoscopic intervention [404, 405]. Ureteroscopy and SWL are effective in the treatment of steinstrasse [191, 406]. In the event of UTI or fever, the urinary system should be decompressed, preferably by percutaneous nephrostomy [119, 407].

3.4.12.1 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 [353, 408-411]. 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, that will pass spontaneously without causing any stone-related event, might lead to over-treatment. Therefore, imaging at four weeks seems most appropriate [412-414]. 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 [415, 416].

A systematic review and meta-analysis examining residual fragments following any treatment has demonstrated that around a third of patients with either dust or fragments </= 4mm experience disease progression and re-intervention 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 [417].

Although NCCT has the highest sensitivity to detect residual fragments, this must be balanced to 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 [418].

3.4.13.1 Recommendation for management of patients with residual stones

Recommendation	Strength rating
Treat residual fragments > 4 mm.	Weak

*3.4.14 **Management of specific patient groups***

3.4.14.1 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 [70]. For diagnostic imaging see Section 3.3.1. Patients with urolithiasis may be at increased risk of developing adverse maternal or neonatal outcomes [419].

Conservative approaches for symptomatic hydronephrosis as well as for ureteric calculi are the preferred initial management option in pregnant patients [420, 421].

If spontaneous passage does not occur, or if complications develop (e.g., intractable symptoms, severe hydronephrosis, spontaneous renal fornix rupture [422] 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 [423-425].

In the treatment of renal stones during pregnancy, when a stent 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 [426].

Ureteroscopy has become a reasonable alternative in these situations [414, 427]. 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 [428, 429].

Non-urgent ureteroscopy in pregnant women is best performed during the second trimester, by an experienced urologist. Counselling of the patient should include access to neonatal and obstetric services [78].

Although feasible, percutaneous removal of renal stones during pregnancy remains an individual decision and should be performed only in experienced centres [430]. Pregnancy remains an absolute contraindication for SWL.

3.4.14.1.1 Summary of evidence and recommendation for the management of urinary stones and related problems during pregnancy

Summary of evidence	LE
Stent insertion seems to be more effective than conservative treatment in the management of symptomatic 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

3.4.14.2 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 [431, 432]. Metabolic factors (hypercalciuria, hyperoxaluria and hypocitraturia), infection with urease-producing bacteria, foreign bodies, mucus secretion, and urinary stasis are responsible for stone formation [433] (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 [434].

Management
Smaller upper-tract stones can be treated effectively with SWL [435, 436]. In most cases, endourological techniques are necessary to achieve stone-free status [437]. In individuals with long, tortuous conduits or with invisible ureter orifices, a retrograde endoscopic approach might be difficult or impossible [438].

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 [439].

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 [440], and if present, a surgical approach should be considered.

Prevention
Recurrence risk is high in patients with urinary diversion [434]. 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 [441].

3.4.14.2.1 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

3.4.14.3 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 [442, 443]. The most common causes are urinary stasis and infection (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 [444, 445].

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 [446]. The risk of stone formation after augmentation cystoplasty in immobile patients with sensory impairment can be significantly reduced by irrigation protocols [441].

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.

3.4.14.3.1 Summary of evidence and recommendation 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

3.4.14.4 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 [447].

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% [447]. Risk factors for *de novo* stone formation in these patients are multi-fold:

- Immunosuppression increases the infection risk, resulting in recurrent UTIs.
- Hyper-filtration, excessively alkaline urine, renal tubular acidosis (RTA), and increased serum calcium caused by persistent tertiary hyperparathyroidism [448] are biochemical risk factors.

Management

Selecting the appropriate technique for stone removal in a transplanted kidney is difficult, although management principles are like those applied in other single renal units [449-451]. Additional factors such as transplant function, coagulative status, and anatomical alterations due to the iliac position of the organ, directly influence the surgical strategy.

For large or ureteral stones, careful percutaneous access and subsequent antegrade endoscopy are more favourable. The introduction of small flexible ureteroscopes and the holmium laser has made URS a valid treatment option for transplant calculi; however, one must be aware of potential injury to adjacent organs [450, 452, 453]. Retrograde access to transplanted kidneys can be difficult due to the anterior location of the ureteral anastomosis, and ureteral tortuosity [454-456]. Treatment of donor stones may be needed pre-transplant and increases the pool available for renal transplants. Post-transplant stone disease may also need treatment to maintain the allograft function. A systematic review evaluating the outcomes of pre- vs. post-transplant URS demonstrated a 100% SFR with an overall 7.5% complication rate, compared to an SFR of 60-100% with an overall complication rate of 12.9% for post-transplant URS; most complications were Clavien 1 [457]. 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% [458].

3.4.14.4.1 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 absolutely 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

3.4.14.5 Special problems in stone removal

Table 3.12: Special problems in stone removal [459]

Calyceal diverticulum stones	• SWL, PCNL [460] (if possible) or RIRS [460, 461]. • Can also be removed using laparoscopic retroperitoneal surgery [462, 463]. • Patients may become asymptomatic due to stone disintegration (SWL), whilst well-disintegrated stone material remains in the original position due • to narrow calyceal neck.
Horseshoe kidneys	• Can be treated in line with the options described above [464-466]. • Passage of fragments after SWL might be poor. • Acceptable SFRs (up to 76%) with low major complication rates (2.4%) can be achieved with flexible ureteroscopy [464-466].
Stones in pelvic kidneys	• SWL, RIRS, PCNL or laparoscopic surgery [467].
Stones formed in a continent reservoir	• Each stone must be considered and treated individually.
Patients with obstruction of the UPJ	• When outflow abnormality requires correction, stones can be removed by PCNL together with percutaneous endopyelotomy or open/laparoscopic reconstructive surgery. • URS together with endopyelotomy with Ho:YAG laser [468].

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 different counties worldwide [469] and large-scale databases [470, 471] 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 [472] the greatest increase in incidence has been seen in older female adolescents [469].

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 [473-475]. Hypocitraturia, low urine volume and hypercalciuria predominate [90, 473-475]. 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 [475]. 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 identifying causes [473, 476]. 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 [477-479].

For diagnostic procedures see Section 3.3.3.2, for acute decompression see Section 3.4.2. and for metabolic evaluation see Chapter 4.

3.4.15.1 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 [480] while in older children flank pain, micro or gross haematuria and recurrent UTIs are more common [481].

3.4.15.2 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 [482, 483] or residual fragments remained after SWL, RIRS or PCNL [484]. 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, non-cystine stones < 7 mm, with no anatomic abnormalities [482]. Intervention may be needed for stones located elsewhere independently of their size [482-484].

3.4.15.3 Medical expulsive therapy in children
There are limited studies on MET as off-label expulsive therapy for children with ureteral stones up to 10 mm which show conflicting outcomes. Several systematic reviews and meta-analyses, including 6 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 [485-487]. The use of alpha-blockers also reduces the stone expulsion time and decreases pain episodes and analgesia demand with the disadvantage of more side-effects such as headache and nasal congestion [486, 487].

3.4.15.4 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 > 10 mm in diameter, impacted stones, calcium oxalate monohydrate or cystine stones, or for stones in children with unfavourable anatomy and in whom localisation is difficult [488].

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 [489-493]. A MA of fourteen studies reporting on 1,842 paediatric patients treated with SWL found significantly higher SFR for stones < 10 mm than for stones > 10 mm and higher retreatment rates as the stone size increased [488]. For best clinical practice see Section 3.4.5. A MA on slow SWL vs. 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 [485]. 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 [494].

Based on the results of a meta-analysis which compared SWL to dissolution therapy for intra-renal 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 [485]. When SWL was compared to mini-percutaneous nephrolithotomy for lower pole renal stones 1-2 cm 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) [495].

3.4.15.5 Endourological procedures
Rigid/semi-rigid ureteroscopy
In recent years ureteroscopy is increasingly used in children with ureteral stones [496]. Ureteroscopy proved to be effective with SFR of 81-98% [497-499], retreatment rates of 6.3%-10% [500] and complication rates of 1.9-23% [497-499, 501]. Similar to adults, routine stenting is not necessary before URS. Pre-stenting may facilitate URS, increase SFR and decrease complication rates [502, 503].

Flexible ureteroscopy/retrograde intrarenal surgery
Retrograde intra-renal 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% [504-507]. Younger age, cystine composition [508], large stone diameter [507] and lack of pre-stenting predispose to FURS failure in children [502]. 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 [509].

Although high-level evidence is lacking to support a strong recommendation [485], FURS may be a particularly effective treatment option for lower calyceal stones in the presence of unfavourable factors for SWL [499, 505, 510].

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 [511]. Similarly, retrospective data indicate that RIRS may achieve lower SFRs compared to micro percutaneous surgery in favour of shorter operative time, shorter fluoroscopy time, and less hospitalisation time [512, 513]. A published meta-analysis confirmed these results [514].

Percutaneous nephrolithotomy
Indications for PCNL in children are like those in adults and include renal stones > 2 cm, or smaller stones resistant to SWL and ureteroscopic treatment. Reported SFRs with paediatric PCNL are 71.4-95% after a single session [511-513, 515, 516] with an overall complication rate of 20% [517]. A high degree of hydronephrosis, increased number of tracts and operative time [518], and large tract size [516, 519-521] are associated with

increased blood loss. Child age [520] and stone burden [516] 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 post-operative pain [522, 523]. 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% [509].

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 [524]. Using pre- and post-PCNL dimercaptosuccinic acid (DMSA) scans, Cicekbilek *et al.* demonstrated that PCNL tracts between 12-24 Charrière in size did not cause significant harm to paediatric kidneys [515].

3.4.15.6 Open and laparoscopic/robot-assisted stone surgery

With the advances in ESWL, 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 USA 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 [525]. 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 ≥ 1 cm single stone located in an extra-renal pelvis [526], or when laparoscopic ureterolithotomy was applied to impacted ureteric stones ≥ 1.5 cm, or to ureteric stones that were refractory to SWL or URS [527]. There are extremely limited data available on the efficacy and complications of robot-assisted laparoscopic management of paediatric urolithiasis [528].

3.4.15.7 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).

3.4.15.8 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 (~300 mm^2) are ideal candidates for SWL.	1b
Ureteroscopy has become the treatment of choice for larger distal ureteral stones in children.	1a
In children, the indications for PCNL are similar to those in adults.	1a
Mini-PCNL is safe and effective in children.	

Recommendations	Strength rating
Offer children with single ureteral stones less than 10 mm 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 20 mm (~300 mm^2) SWL.	Strong
Offer children with renal pelvic or calyceal stones with a diameter > 20 mm (~300 mm^2) percutaneous nephrolithotomy.	Strong
Retrograde renal surgery is a feasible alternative for renal stones smaller than 20 mm in all locations.	Weak

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 [529, 530]. 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 [531-533].

Current evidence from atomic bomb patients [534, 535], retrospective epidemiological data on medical exposure [536, 537], and modelling studies [538, 539] suggest an age and dose-dependent risk of secondary malignancy from ionising radiation.

The International Commission on Radiological Protection (ICRP) recommends a maximum annual occupational exposure of 50mSv [540]. 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 recommended protection methods to reduce radiation exposure to patients, surgical, anaesthesiologic, and nursing staff.

Table 3.13 Radiation protection measures

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: • Reducing fluoroscopy time; • Limiting time adjacent to patient; • Using low-dose radiation; • Irradiating only to observe motion; • Intra-operative use of pulsed fluoroscopy; • Reduced fluoroscopy pulse rate; • Collimated fields; • Avoid digital image acquisition and rely on last image hold and instant replay technology.
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 fluoroless and fluoroscopy-free operations in urology. Several RCTs have been published showing a good outcome in means of stone-free and complication rates [172, 276, 541-543]. These trials have been limited to non-complex cases and they were not sufficiently powered to show the non-inferiority of fluoroscopy in PCNL [276, 531] or the superiority of ultrasound in URS [219, 220].

4. METABOLIC EVALUATION AND RECURRENCE PREVENTION

4.1 General metabolic considerations for patient work-up

4.1.1 Evaluation of patient risk

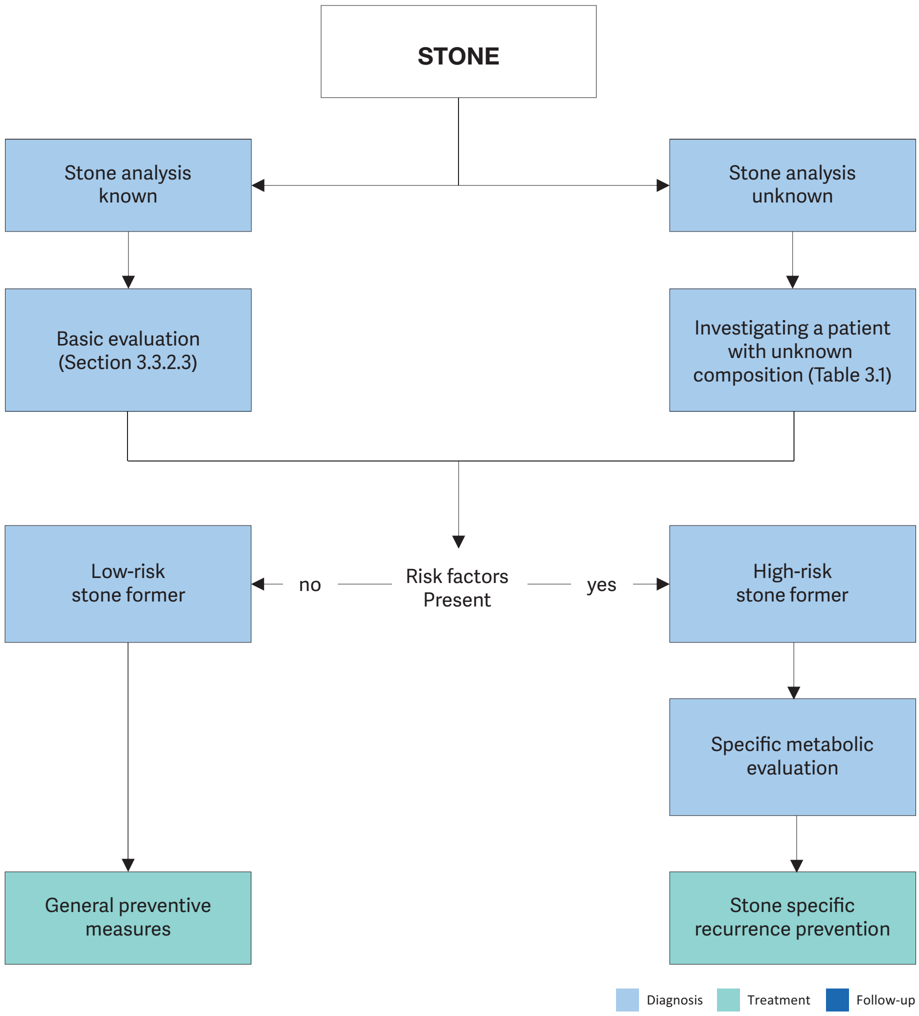
After stone passage, every patient should be assigned to a low- or high-risk group (Table 3.3) for stone formation (Figure 4.1).

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 different stone types include:

- calcium oxalate;
- calcium phosphate;
- uric acid;
- ammonium urate;
- struvite (and infection stones);
- cystine;
- xanthine;
- 2,8-Dihydroxyadenine;
- drug stones;
- 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 [69, 544, 545]. The collecting bottles should be prepared with 1 g thymol per litre or stored at < 8°C during collection to reduce bacterial proliferation [69]. Pre-analytical errors can be minimised by carrying out urinalysis immediately after collection. Alternatively, boric acid (10 g powder per urine container) can also be used, but this prevents the correct determination of pH [69]. The collecting method should be chosen in close cooperation with the laboratory. A pH < 5.5 in a 24-hour urine indicates hyper acidic urine (acidic arrest) [546-548]. 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, 69, 549]. 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 [550, 551].

Spot urine samples are an alternative sampling method, particularly when 24-hour urine collection is difficult, for example, in non-toilet-trained children [552]. Spot urine studies normally link the excretion rates to the creatinine [553], 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*

For the initial specific metabolic work-up, the patient should stay on a self-determined diet under normal daily conditions and should ideally be stone-free for at least twenty days [554]. Follow-up studies are necessary for patients taking medication for recurrence prevention [555]. The first follow-up 24-hour urine measurement is suggested eight to twelve 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 different laboratory values in serum and urine.

Table 4.1: Normal laboratory values for blood parameters in adults [23, 555]

Blood parameter	Reference range	
Creatinine	50-100 μmol/L	
Sodium	135-145 mmol/L	
Potassium	3.5-5.5 mmol/L	
Calcium	2.0-2.5 mmol/L (total calcium)	
	1.12-1.32 mmol/L (ionised calcium)	
Uric acid	119-380 μmol/L	
Chloride	98-112 mmol/L	
Phosphate	0.81-1.29 mmol/L	
Blood gas analysis	pH	7.35-7.45
	pO_2	80-90 mmHg
	pCO_2	35-45 mmHg
	HCO_3	22-26 mmol/L
	BE	BE ± 2 mmol/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 [556-559]. However, clinical validation of these risk indices for recurrence prediction or therapy improvement is ongoing.

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) [550, 551]
	Consistently > 7.0 (suspicious of infection)
	Consistently < 5.5 in morning urine and in 24-hr collection (suspicious of acidic arrest) [546, 560]
Specific weight	Specific weight > 1.010
Creatinine	7-13 mmol/day (females), 13-18 mmol/day (males)
Calcium	> 5.0 mmol/day (see Fig. 4.2)
	> 8.0 mmol/day (see Fig. 4.2)
Oxalate	> 0.5 mmol/day (suspicious of enteric hyperoxaluria)
	>1.0 mmol/day (suspicious of primary hyperoxaluria)
Uric acid	> 4.0 mmol/day (females), 5 mmol/day (males)
Citrate	< male < 1.7 mmol/day, female < 1.9 mmol/day
Magnesium	< 3.0 mmol/day
Inorganic phosphate	> 35 mmol/day
Ammonium	> 50 mmol/day
Cystine	> 0.8 mmol/day

Table 4.3: Normal values for spot urine samples: creatinine ratios (solute/creatinine) in children [561]

Parameter/Patient age	Ratio of solute to creatinine	Units
Calcium	**mol/mol**	**mg/mg**
< 12 months	< 2.0	0.81
1-3 years	< 1.5	0.53
1-5 years	< 1.1	0.39
5-7 years	< 0.8	0.28
> 7 years	< 0.6	0.21
Oxalate	**mol/mol**	**mg/mg**
0-6 months	< 325-360	288-260
7-24 months	< 132-174	110-139
2-5 years	< 98-101	80
5-14 years	< 70-82	60-65
> 16 years	< 40	32
Citrate	**mol/mol**	**g/g**
0-5 years	> 0.25	0.42
> 5 years	> 0.15	0.25
Magnesium*	**mol/mol**	**g/g**
	> 0.63	> 0.13
Uric acid		
> 2 years	< 0.56 mg/dL (33 μmol/L) per GFR (ratio x plasma creatinine)	

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

Table 4.4: Solute excretion in 24-hour urine samples in children [562, 563]*

Calcium/24	Citrate/24 hour		Cystine/24 hour		Oxalate/24 hour		Urate/24 hour	
All age groups	Boys	Girls	< 10 years	> 10 years	All age groups	< 1 year	1-5 years	> 5 years
< 0.1 mmol/kg/ 24 h	> 1.9 mmol/ 1.73 m2/24 h	> 1.6 mmol/ 1.73 m2/24 h	< 55 μmol/ 1.73 m2/24 h	< 200 μmol/ 1.73 m2/24 h	< 0.5 mmol/ 1.73 m2/24 h	< 70 μmol/ kg/24 h	< 65 mμmol/ kg/24 h	< 55 μmol/ kg/24 h
< 4 mg/kg/24 h	> 365 mg/ 1.73 m2/24 h	> 310 mg/ 1.73 m2/24 h	< 13 mg/ 1.73 m2/24 h	< 48 mg/ 1.73 m2/24 h	< 45 mg / 1.73 m2/24 h	< 13 mg/ kg/24 h	< 11 mg/ kg/24 h	< 9.3 mg/ kg/24 h

**24 h 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: 2.5-3.0 L/day
	Water is the preferred fluid
	Diuresis: 2.0-2.5 L/day
	Specific weight of urine: < 1,010 g/day
Nutritional advice for a balanced diet	Balanced diet*
	Rich in vegetables and fibre
	Normal calcium content: 1-1.2 g/day
	Limited NaCl content: 4-5 g/day
	Limited animal protein content: 0.8-1.0 g/kg/day
Lifestyle advise 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 [562-566]. The beneficial effect of fruit juices is mainly determined by the presence of citrate or bicarbonate [567]. Citrus fruit juices seem to protect against stone disease either by increasing urinary citrate levels or by having an alkalinising effect on it [568]. However, if potassium is present, both pH and citrate are increased [569, 570]. 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 160 mL/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 [571]. An analysis of 3 Channing's 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 [572], whereas consumption of tea and coffee does not seem to increase the risk of stones disease [573]. 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 [563, 574, 575]. Sufficient calcium intake is needed especially in vegetarian and vegan diets [576].

Fruit, vegetables, and fiber: Fruit and vegetable intake should be encouraged because of the beneficial effects of fiber, although the role of the latter in preventing stone recurrences is debatable [577-580]. 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 [581], 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 [582]. However, it seems wise to advise calcium oxalate stone formers to avoid excessive intake.

Animal protein: Animal protein should not be consumed in excess [583, 584] and limited to 0.8-1.0 g/kg body weight. Excessive consumption of animal protein has several effects that favour stone formation, including hypocitraturia, low urine pH, hyperoxaluria, and hyperuricosuria.

Calcium 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 [578, 585]. The daily requirement for calcium is 1,000 to 1,200 mg [23]. Calcium supplements are not recommended except in enteric hyperoxaluria when additional calcium should be taken with meals to bind intestinal oxalate [563, 581, 583, 586]. 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 stones formation associated with calcium supplement use [587].

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

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

Calcium stone formation can be reduced by restricting sodium and animal protein [583, 584]. A positive correlation between sodium consumption and the risk of first-time stone formation has been confirmed only in women [585]. 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 [588, 589] and uric acid stones. Intake should not exceed 500 mg/day [23].

4.2.3 *Lifestyle*

Lifestyle factors may influence the risk of stone formation, for example, those causing obesity [590], diabetes mellitus [591], and metabolic syndrome [592].

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 > 2.5 L.	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	3.25-9.75 g/d (10-30 mmol/d) Children: 0.1-0.15 g/kg/d	Daily dose for alkalinisation depends on urine pH.	Calcium oxalate Uric acid Cystine	[593-598]
Allopurinol	Hyperuricosuria Hyperuricaemia	100-300 mg/d Children: 1-3 mg/kg/d	100 mg 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-Dihydroxyadenine	[563, 599-602]
Calcium	Enteric hyperoxaluria	Up to 2,000 mg/d depending on oxalate excretion	Intake 30 min before meals.	Calcium oxalate	[583, 585, 586, 603]
Captopril	Cystinuria Active decrease of urinary cystine levels	75-150 mg	Second-line option in case of significant side effects of tiopronin.	Cystine	[604, 605]
Febuxostat	Hyperuricosuria Hyperuricaemia	80-120 mg/d	Contraindicated in acute gout, pregnancy and breastfeeding. Xanthine stone formation.	Calcium oxalate Uric acid	[606, 607]
L-Methionine	Acidification	600-1,500 mg/d	Hypercalciuria, bone demineralisation, systemic acidosis. No long-term therapy.	Infection stones Ammonium urate Calcium phosphate	[593, 608]
Magnesium	Isolated Hypomagnesuria Enteric hyperoxaluria	200-400 mg/d Children: 6 mg/kg/d	Renal insufficiency demands dose correction. Diarrhoea, chronic alkali losses, hypocitraturia.	Calcium oxalate	[609, 610] (Low level of evidence)
Sodium bicarbonate	Alkalinisation Hypocitraturia	4.5 g/d	Daily dose for alkalinisation depends on urine pH	Calcium oxalate Uric acid, Cystine	[611]
Pyridoxine	Primary hyperoxaluria	Initial dose 5 mg/kg/d Max. 20 mg/kg/d	Sensory peripheral neuropathy	Calcium oxalate	[612]

Thiazide (Hydro-chlorothiazide*)	Hypercalciuria	25-50 mg/d Children: 0.5-1 mg/kg/d	Risk for hypotension diabetes, hyperuricaemia, hypokalaemia, hypocitraturia.	Calcium oxalate Calcium phosphate	[589, 593-602, 604-622]
Tiopronin	Cystinuria Increase in solubility of levels	Initial dose 800 mg/d Avg. 2,000 mg/d** Children: Initial dose in patients > 20kg is 15 mg/kg/day. Avoid dosages > 50mg/kg/day	Risk for proteinuria.	Cystine	[623-626]

* *Patients on hydrochlorothiazide should be advised to get their skin checked on a regular basis as 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 [627-629].*

** *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*

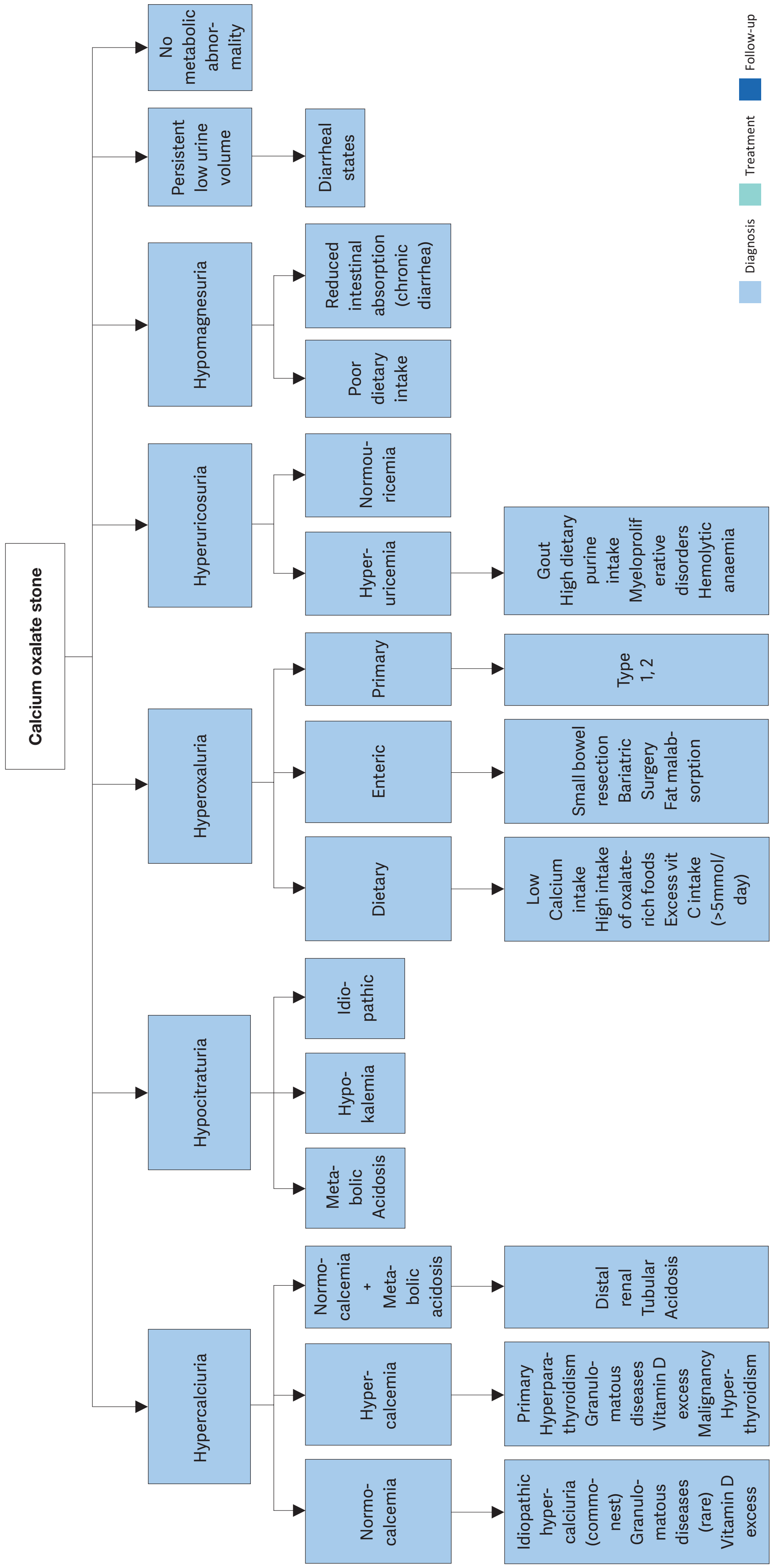
4.4 Calcium oxalate stones

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

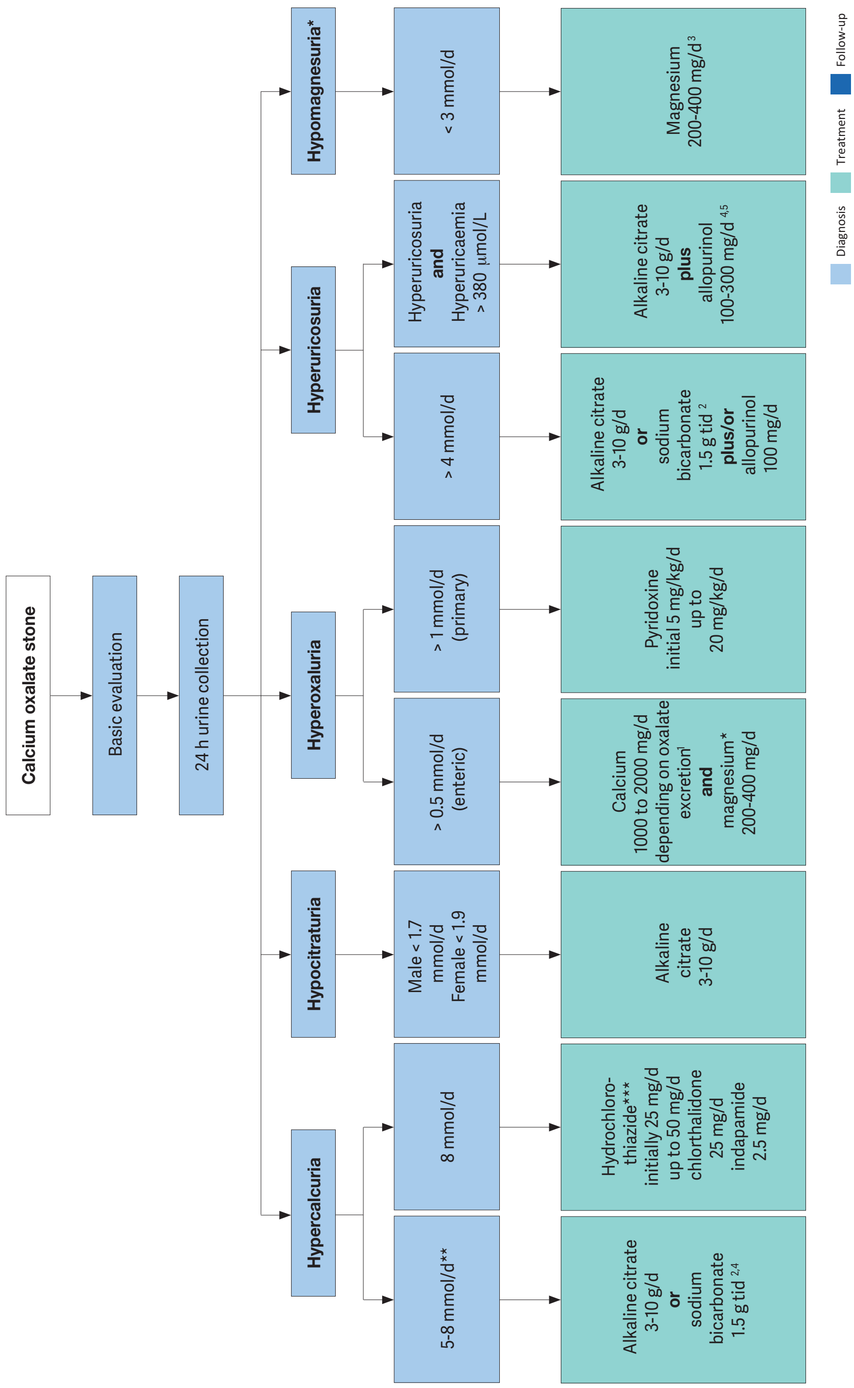


4.4.2 ***Interpretation of results and aetiology***

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 [630].

- 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 mmol/day in adults or > 12 mg/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 (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 < 1.7 mmol/d, female < 1.9 mmol/d) may be idiopathic or secondary to metabolic acidosis or hypokalaemia.
- Oxalate excretion > 0.5 mmol/day in adults confirms hyperoxaluria (see Table 4.3 for the values in children).
    - primary hyperoxaluria (oxalate excretion mostly > 1 mmol/day), appears in three genetically determined forms;
    - secondary hyperoxaluria (oxalate excretion > 0.5 mmol/day, usually < 1 mmol/day), occurs due to intestinal hyperabsorption of oxalate or extreme dietary oxalate intake;
    - mild hyperoxaluria (oxalate excretion 0.45-0.85 mmol/day), commonly found in idiopathic calcium oxalate stone formers.
- Hypomagnesuria (< 3.0 mmol/day) may be related to poor dietary intake or to reduced intestinal absorption (chronic diarrhoea).

Figure 4.3: Therapeutic algorithm for calcium oxalate stones



1 *Be aware of excess calcium excretion.*

2 *tid = three times/day (24h).*

3 *No magnesium therapy for patients with renal insufficiency.*

4 *There is no evidence that combination therapy (thiazide + citrate) or (thiazide + allopurinol) is superior to thiazide therapy alone [594, 631].*

5 *Febuxostat 80 mg/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 [627-629].*

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 [563, 570, 593-596, 599, 600, 602, 606, 609-611, 615-622, 630, 632-635]. There is only low-level evidence for the efficacy of preventing stone recurrence based on pre-treatment stone composition examination and biochemistry measures, or on-treatment biochemistry measures [563]. 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 [636]. However, the study was not powered to show any difference of HCTZ over placebo [637]. In fact, the study's main objective based on the author's protocol [637], was to investigate the existence of a dose-response relationship, i.e., a linear trend for three different doses of HCTZ (12.5, 25 mg, and 50 mg/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).

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 reduces 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 [627-629].*

4.5 **Calcium phosphate stones** [563, 593, 602, 615, 616, 620, 638]

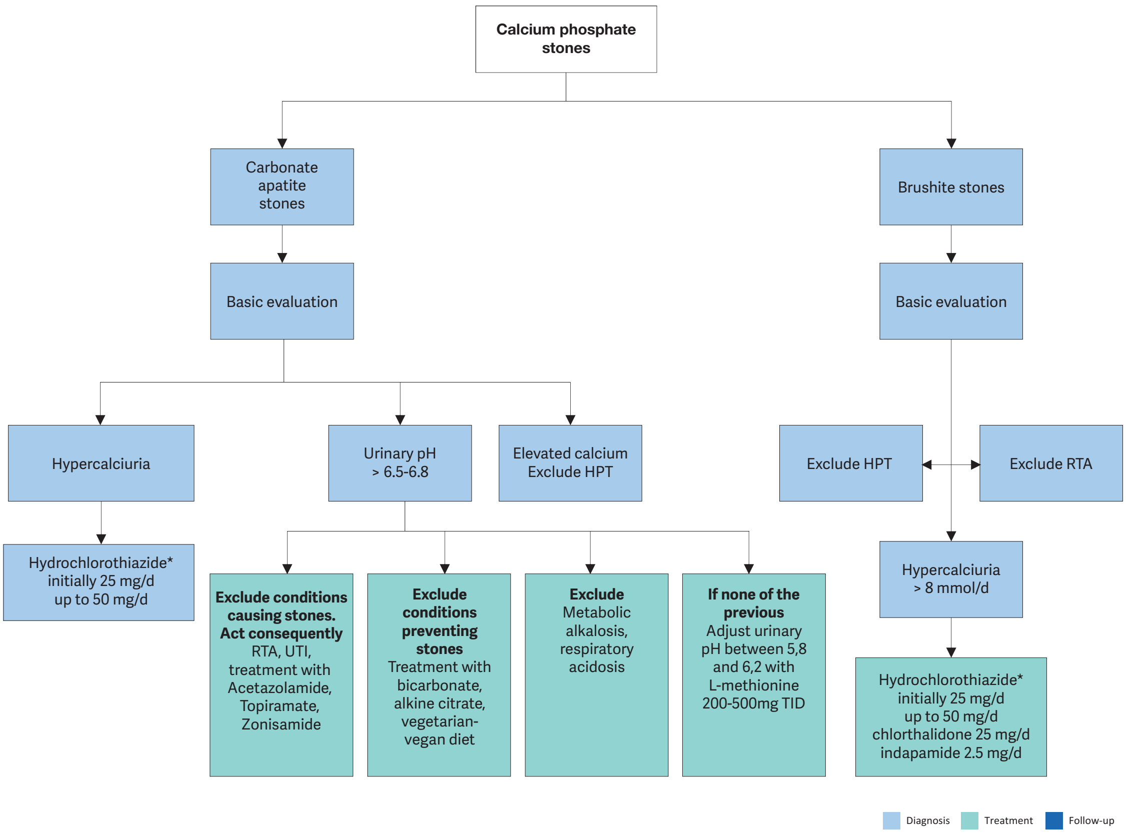
Some calcium phosphate stone formers are at high risk of recurrence. Further information on identifying high-risk patients is provided in section 3.1.3.

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 (> 8 mmol/day) and phosphate (> 35 mmol/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 [627-629].*

4.5.3 ***Pharmacological therapy [563, 593, 602, 615, 616, 620, 638]***
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 > 8 mmol/24 hours.	Strong

4.6 Disorders and diseases related to calcium stones

4.6.1 Hyperparathyroidism [639-642]

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.

If HPT is suspected, neck exploration should be performed to confirm the diagnosis. If surgery is contraindicated, primary HPT can be treated with cinacalcet.

4.6.2 Granulomatous Diseases [643]

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 [612]

Patients with primary hyperoxaluria (PH) should be referred to a specialised center, 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 3.5-4.0 L/day in adults (children 1.5 L/m2 body surface area) and following a circadian drinking regimen.

Therapeutic options for preventing calcium oxalate crystallisation include hyper-diuresis, alkaline citrates, magnesium, and Lumasiran, an RNAi agent, a new treatment for reducing the synthesis of oxalate of PH type 1 [644].

Treatment regimens are:

- pyridoxine in PH type I: 5-20 mg/kg/day according to urinary oxalate excretion and patient tolerance;
- alkaline citrate: 3.25-9.75 g/day in adults, 0.1-0.15 mq/kg/day in children;
- magnesium: 200-400 mg/day (no magnesium in the case of renal insufficiency).
- Lumasiran: Subcutaneous injection with dose and timing adjusted according to body weight and duration of treatment:
    - Initial Dose: Bodyweight < 10 kg: 6 mg/kg; Bodyweight 10-20 kg: 6 mg/kg; Bodyweight > 20 kg: 3 mg/kg; once per month for 3 months subcutaneous injection.
    - Maintenance starting one month after initial doses: Bodyweight < 10 kg: 3 mg/kg 1-mal monthly; Bodyweight 10-20 kg: 6 mg/kg every 3 months, Bodyweight > 20 kg: 3 mg/kg [645].

4.6.3.1 *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 can reduce the urinary oxalate excretion 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

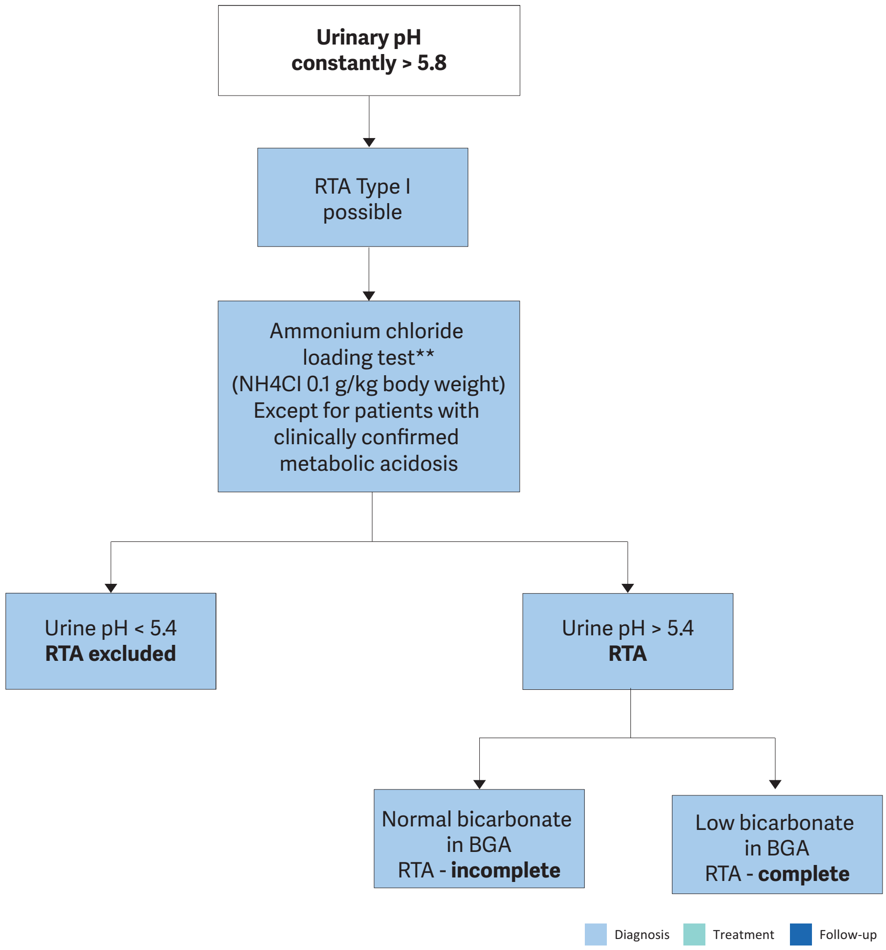
4.6.4 ***Enteric hyperoxaluria [581, 586, 646-648]***
Enteric hyperoxaluria is a particularly problematic condition in patients with intestinal malabsorption of fat. This abnormality is associated with a high risk of stone formation and is seen after intestinal resection and malabsorptive bariatric surgery, as well as in Crohn's disease and pancreas 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 [581];
- restricted fat intake [581];
- calcium supplementation at mealtimes to enable calcium oxalate complex formation in the intestine [586, 646-648];
- sufficient fluid intake to balance the intestinal loss of water caused by diarrhoea;
- 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 oxalate content.	Weak

4.6.5 ***Renal tubular acidosis*** [563, 602, 649, 650]
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 1-day NH_4Cl load with 0.05 g/kg body weight might provide similar results and may be better tolerated by the patient [651]. A second alternative in these cases could be the furosemide/fludrocortisone acidification test [652].*

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 re-absorption of citrate, which in turn normalises citrate excretion. Therapeutic success can be monitored by venous blood gas analysis (base excess: ± 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: 25 mg/day initially, up to 50 mg/day - in children: 0.5-1 mg/kg/day Alternatives in adults: Chlorthalidone 25 mg/d Indapamide 2.5 mg/d
Inadequate urine pH	Citrate excretion male < 1.7 mmol/day, female < 1.9 mmol/day	Alkaline citrate, 3.25-9.75 g/day divided in three doses *OR* Sodium bicarbonate, 1.5 g, 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 treatment with hydrochlorothiazide should be thoroughly reviewed [627-629].*

4.6.5.1 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	2b
Thiazides are beneficial for hypercalciuria.	1a

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

*4.6.6 **Nephrocalcinosis** [653]*

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.

4.6.6.1 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 [551].

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 [654] 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 [548]. 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, or exercise-induced lactic acidosis), increased acid intake (high animal protein intake), or increased base loss (diarrhoea) [548].

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, hypokalemia, 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.

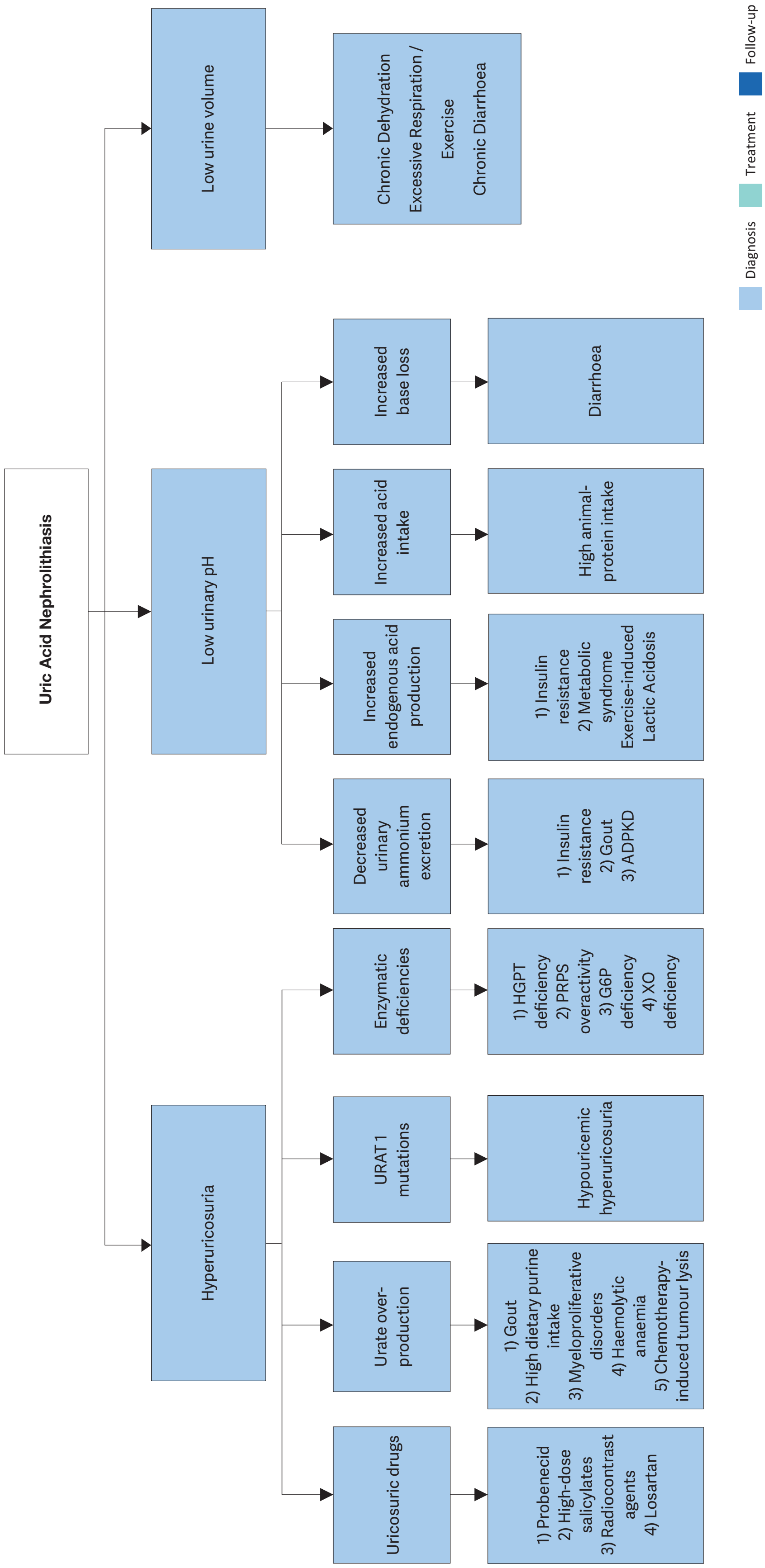
Hyperuricosuria is defined as uric acid excretion > 4 mmol/day and day and > 5 mmol/day in adult females and males, respectively, or > 0.12 mmol/kg/day in children. Hyperuricaemia may be present, but there is only weak evidence for its association with stone formation [655].

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 [656, 657]. Ammonium urate crystals form in urine at pH > 6.5, high uric acid concentration in urine when ammonium is present [658, 659].

4.7.3 ***Specific treatment***

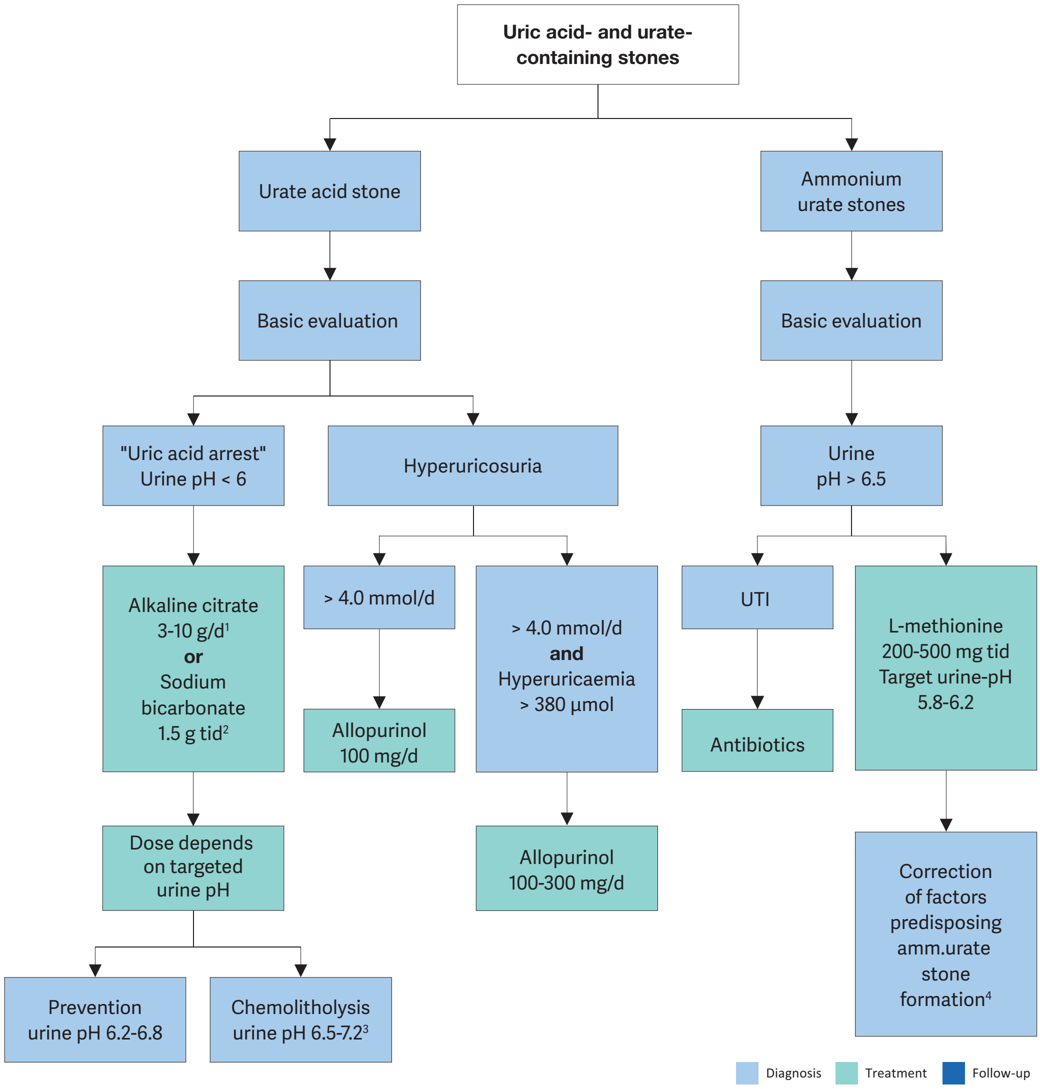
General preventive measures are recommended for fluid intake and diet. Hyperuricosuric stone formers benefit from purine reduction in their daily diet. Figure 4.6 describes pharmacological treatment [23, 654, 656-666]. For uric acid stones, allopurinol may change the stone composition distribution in patients with gout to a pattern similar to that in stone formers without gout [667].

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 stones



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

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 [668]. There are several factors predisposing patients to struvite stone formation (Table 4.9) [669]. Several studies have reported that urinary metabolic alterations can be disclosed in 36-81% of patients with mixed struvite stones [670-675].

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 [676, 677]. 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 [675]. Proteus mirabilis accounts for more than half of all urease positive UTIs [678, 679].

4.8.3 Specific treatment
General preventive measures are recommended for fluid intake and diet. Specific measures include complete surgical stone removal [669], short- or long-term antibiotic treatment [680], and urinary acidification using methionine [608] or ammonium chloride [681]. For persistent infections/colonisation, acetohydroxamic acid may be an option [682, 683] (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, 1 g, two or three times daily, can ensure urinary acidification to prevent recurrent infection.	3
Methionine, 200-500 mg, 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, 1 g, two or three times daily to ensure urinary acidification.	Weak
Prescribe methionine, 200-500 mg, one to three times daily, as an alternative, to ensure urinary acidification.	Weak

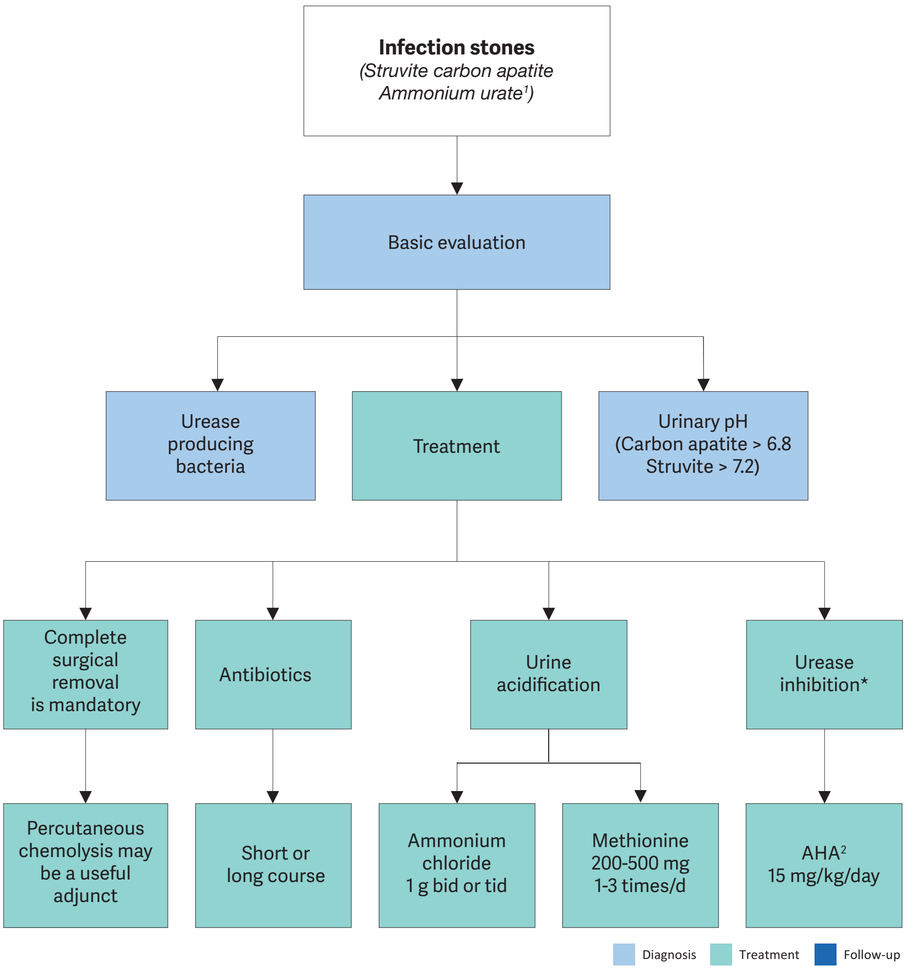
Table 4.9: Factors predisposing to struvite stone formation.

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

Table 4.10: Most important species of urease-producing bacteria

Obligate urease-producing bacteria (> 98%)
• *Proteus spp.* • *Providencia rettgeri* • *Morganella morganii* • *Corynebacterium urealyticum* • *Ureaplasma urealyticum*
Facultative urease-producing bacteria
• *Enterobacter gergoviae* • *Klebsiella spp.* • *Providencia stuartii* • *Serratia marcescens* • *Staphylococcus spp.*
CAUTION: *0-5% of Escherichia coli, Enterococcus spp. and Pseudomonas aeruginosa strains may produce urease.*

Figure 4.8: Diagnostic and therapeutic algorithm for infection stones.



[1] Discussed with uric acid stones.
[2] 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 [684, 685]. All cystine stone formers are deemed at high risk of recurrence and CKD [686, 687].

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 [688].

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 1.33 mmol/L.
- Routine analysis of cystine is not suitable for therapeutic monitoring.
- Regardless of the phenotype or genotype of the cystinuric patient, the clinical manifestations are the same [689].
- There is no role for genotyping patients in the routine management of cystinuria [690, 691].
- 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 different complexes formed by therapy are cumbersome [692, 693] non accurate, including high-performance liquid chromatography (HPLC) [69].
- Quantitative 24-hour urinary cystine excretion confirms the diagnosis in the absence of stone analysis.
- Levels above 0.125 mmol/day (30 mg/day) are considered abnormal [694, 695].

4.9.2 *Specific treatment*

General preventative measures for fluid intake and diet are recommended. A diet low in methionine may theoretically reduce urinary excretion of cystine; however, patients are unlikely to comply sufficiently with such a diet. A restricted intake of sodium is more easily achieved and is more effective in reducing urinary cystine. Patients are usually advised to avoid sodium consumption > 2 g/day (5 g NaCl) [696]. A high level of diuresis is of fundamental importance, aiming for a 24-hour urine volume of > 3 L [689, 696-698]. A considerable fluid intake evenly distributed throughout the day is necessary.

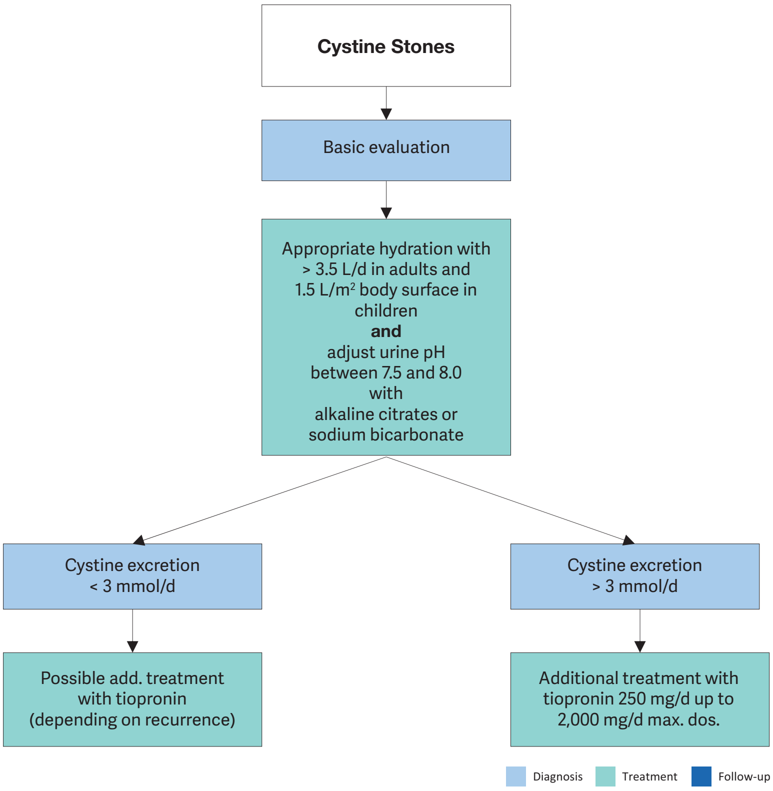
4.9.2.1 Pharmacological treatment of cystine stones

The main therapeutic option for avoiding cystine crystallisation is to maintain urine pH > 7.5, to improve cysteine solubility, and ensure appropriate hydration with a minimum of >3 L/day in adults, or 1.5 L/m^2 body surface area in children [689, 696-698]. Home monitoring of the urine pH is suggested because of the possibility of self-adjusting alkaline treatment keeping the urine pH within range [69].

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

Tiopronin is currently the best choice for cystine reduction. However, side effects often lead to treatment termination, for example when nephrotic syndrome develops or when there is poor compliance, especially with long-term use. After carefully considering the risk of early tachyphylaxis, putting into place a dose-escape phenomenon for long-term use, and recurrence risk, tiopronin is recommended at cystine levels > 3.0 mmol/day (720 mg/day) or in the case of recurring stone formation, notwithstanding other preventive measures [689, 696-698]. Spot measurement of urine protein should be performed at baseline and during follow-up.

Figure 4.9: Metabolic management of cystine stones [699]



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 3 L is used to dilute the cystine.	3
Alkaline citrates 3-10 mmol two or three times daily can be used to achieve pH > 7.5.	3
Tiopronin, 250-2,000 mg/day can be used to reduce stone formation in patients with cysteine excretion, > 3 mmol/day, or when other measures are insufficient.	3

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

4.10 2,8-Dihydroxyandenine 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 [700]. High-dose allopurinol or febuxostat are important options but should be given with regular monitoring [701].

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 [593, 702] (Table 4.10). Two types exist:
- stones formed by crystallised compounds of the drug;
- 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
• Allopurinol/oxypurinol • Amoxicillin/ampicillin • Ceftriaxone • Quinolones • Ephedrine • Indinavir and other HIV-protease inhibitors • Magnesium trisilicate • Sulphonamides • Triamterene	• Acetazolamide • Aluminium magnesium hydroxide • Ascorbic acid • Calcium • Laxatives • Losartan • Methoxyflurane • Orlistat • Vitamin D • Topiramate • Zonisamide

4.12 Matrix Stones
Pure matrix stones are extremely rare with less than 70 cases described in the literature. They 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 [703].

4.13 Unknown stone composition [16]
An accurate medical history is the first step towards identifying risk factors as summarised in sections 3.1.3 and 4.13.1 and Fig. 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 30 ml/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 hyper-acidic urine, which could promote uric acid crystallisation. Urine pH > 6.2 in 24-hour urine collection may indicate RTA if UTI is excluded [648, 650].

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 [704, 705].

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 expulsed 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, 68, 593]

Recommendations		**Strength rating**
Investigation	**Rationale for investigation**	
Take a medical history	• Stone history (former stone events, family history) • Dietary habits • Medication chart	Strong
Perform diagnostic imaging	• Ultrasound in the case of a suspected stone • Un-enhanced helical computed tomography • Determination of Hounsfield units provides information about the possible stone composition	Strong
Perform a blood analysis	• Creatinine • Calcium (ionised calcium or total calcium + albumin) • Uric acid	Strong
Perform a urinalysis	• pH measurement • Dipstick test: leukocytes, erythrocytes, nitrites • Protein, specific weight • Urine cultures • Microscopy of urinary sediment (morning urine) • Cyanide nitroprusside test (cystine exclusion) Further examinations depend on the results of the investigations listed above.	Strong

5. FOLLOW-UP OF URINARY STONES

There is no consensus in the urological literature on whether, when, how, and how often stone patients should be followed up after definitive treatment (extracorporeal shock wave lithotripsy, ureteroscopy, percutaneous nephrolithotripsy, 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 [417]. 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 ≤ 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 ≤ 4 mm showed a spontaneous expulsion rate of 17.9-46.5% during the first year. At 49 months of follow-up disease progression rate was 9-34%, the intervention rate 17-29%, and the spontaneous passage rate 21-34%.

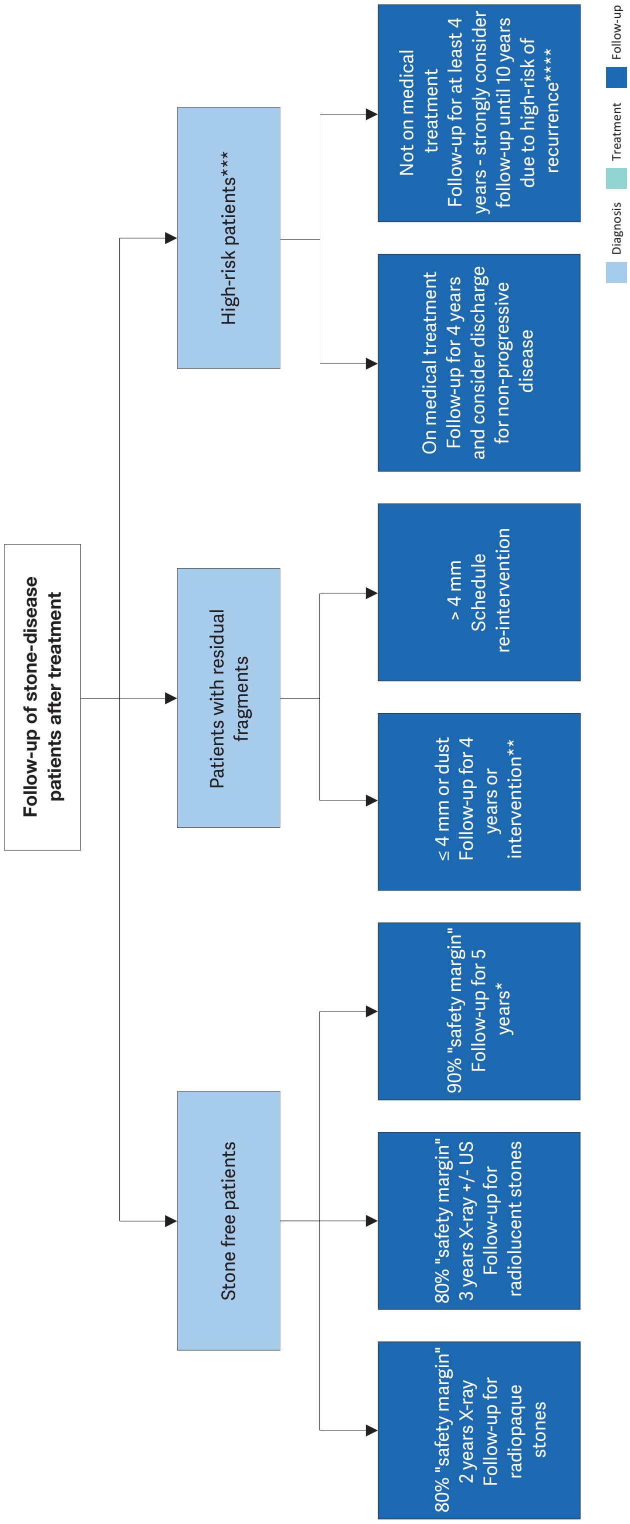
Patients with residual stone fragments > 4 mm had only 9% of spontaneous expulsion at three years. These patients should be offered further definitive treatment since intervention rates are high (24-100%). For those on follow-up close surveillance is needed.

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 pre-operative imaging, to avoid extensive radiation exposure [417].

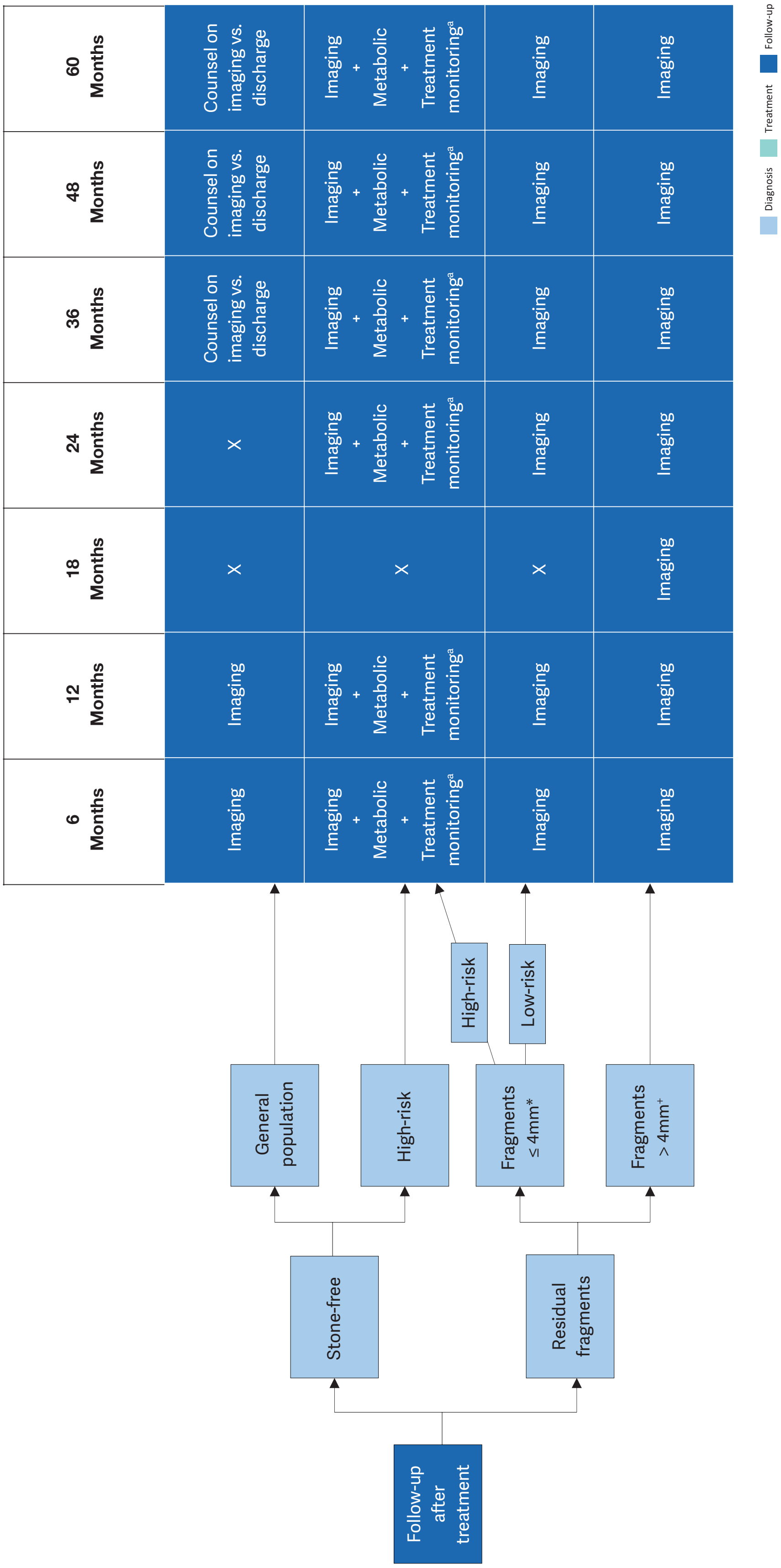
The information on stone composition can be used to counsel patients to set expectations and help plan the need for follow up and medical stone management [706].

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



* Not enough data about subgroup analysis of radiolucent and radiopaque stones.
**According to patient preference or symptomatic disease.
***Patients with diagnosed metabolic abnormalities.
****Lifelong follow-up is advised but data are available for up to ten years.

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 ≤ 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 [707] yet are responsible for 8% of urolithiasis-related mortalities in developed nations [708]. The incidence is higher in developing countries [709]. The prevalence of bladder stones is higher in males, with a reported male-to-female ratio between 10:1 and 4:1 [710, 711]. The age distribution is bimodal: incidence peaks at three years in children in developing countries [710, 712], and 60 years in adulthood [711].

The aetiology of bladder stones is typically multi-factorial [711]. Bladder stones can be classified as primary, secondary, or migratory [713].

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 [714].

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 [711, 715-718].

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 [719].

A wide range of metabolic urinary abnormalities can pre-dispose 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) [720, 721], 19-39% and 36-67% of motor-incomplete and motor-complete spinal cord injury patients, respectively [722], and 2.2% of patients with long-term catheters [723]. Two research groups have identified that a larger intravesical protrusion of the prostrate is an independent risk factor for bladder stone formation in patients with benign prostatic hyperplasia (BPH) undergoing transurethral resection of the prostate (TURP) [724, 725]. Kim and colleagues additionally found older age and a lower Q_{max} to be predictive of bladder stones [724].

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. 0.6 mmol/L, $p < 0.01$), lower magnesium (106 vs. 167 mmol/L, $p = 0.01$) and lower pH (5.9 vs. 6.4, $p = 0.02$) than the 21 men without bladder stones [719]. 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 [711]. Similar findings were reported in more recent studies [726-728] 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 [729-731].

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 [729]. Of 61 children in India, stone formers had higher urine calcium and uromucoid concentrations than controls [730]. 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 [731].

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 are 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 over-activity is found in over two-thirds of adult male patients with vesical calculi and is significantly more common in patients with larger stones (> 4 cm). However, recurrent urinary tract infections (UTIs) may be the only symptom [716, 717].

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 [714, 732].

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 [716, 733]. Larger (> 2.0 cm) stones are more likely to be radiopaque [733]. However, plain X-ray provides information on radio-opacity which may guide treatment and follow-up (see Section 3.2.3 X-ray characteristics, for further information).

Ultrasound has a reported sensitivity and specificity of 20-83% and 98-100%, respectively for the detection of bladder stones in adults [734, 735]. Computed tomography and cystoscopy have a higher sensitivity for detecting bladder stones than US or X-ray in adults [734, 735]. 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 X-ray characteristics) [736].

There is a paucity of evidence for the investigation of bladder stones, particularly in children [89, 737]. See also Section 3.3 Diagnostic evaluation, for further information on diagnostic imaging for urolithiasis. The principle of ALARA should be applied, especially in children [738].

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 [739]. 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 3.3.2.3) 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);
- cysto-urethroscopy 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 < 1 cm are likely to pass in the absence of BOO, bladder dysfunction, or long-term catheterisation (see section 3.4.9 Specific stone management of ureteral stones).

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 Specific stone management of ureteral stones, 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 Chemolysis). Irrigation chemolysis is also possible using a catheter; however, this is time-consuming may cause chemical cystitis and is therefore not commonly employed [740, 741].

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 ESWL [742].

6.4.3.1 *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 [742]. In children, a non-randomised study found that, if the bladder was closed meticulously in two layers, "tubeless" (drain-less and catheter-less) cystolithotomy was associated with a significantly shorter length of hospital stay compared with traditional cystolithotomy, without significant differences regarding late or intra-operative complications provided that children with prior UTI, recurrent stones, or with previous surgery for anorectal malformation (or other relevant surgery) were excluded [743].

6.4.3.2 *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 post-operative and late complications [742].

6.4.3.2.1 Transurethral cystolithotripsy in adults

In adults, a meta-analysis 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 [742]. Transurethral cystolithotripsy with a nephroscope was quicker than percutaneous cystolithotripsy in three RCTs, although transurethral cystolithotripsy with a cystoscope was slower than percutaneous cystolithotripsy [742].

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 [726, 742, 744].

One small RCT demonstrated a shorter duration of catheterisation, hospital stay and procedure with transurethral cystolithotripsy than open cystolithotomy with similar SFR [742]. Meta-analysis of five RCTs found significantly shorter procedure duration for transurethral cystolithotripsy using a nephroscope vs. cystoscope with similar SFRs, hospital stay, convalescence, pain, and complications [745]. 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 [746, 747]. This suggests that transurethral cystolithotripsy is quicker when using a continuous flow instrument.

6.4.3.2.1.1 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) [742]. Unplanned procedures and major post-operative 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 [748]. All outcomes had very low-quality evidence (GRADE) [742]. 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 [749]. The same conclusion was stated in a meta-analysis of ten RCTs with high heterogeneity and small sample sizes in some of the included RCTs [750]. Continuous vs. intermittent irrigating instruments may affect the operation time more significantly than the choice of lithotripsy device [742].

6.4.3.2.1.2 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 [751]. One small quasi-RCT found a shorter procedure time using laser vs. pneumatic lithotripsy for < 1.5 cm bladder stones with no difference in SFR or other outcomes [752]. Another RCT (n=73) found shorter procedure time using pneumatic vs. laser therapy for bladder stones ≤ 1.5 cm with similar SFRs and higher (minor) complication rates for pneumatic lithotripsy [753].

6.4.3.3 Percutaneous cystolithotripsy

6.4.3.3.1 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 [728].

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 post-operative complications, or re-treatment [742].

6.4.3.3.2 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 peri-operative complications than open cystolithotripsy; SFRs were similar [732, 742, 751, 754].

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 [732, 751] in contrast, a transurethral approach may need a longer operative time and shows a higher post-operative stricture rate [754]. One small NRS found a non-significant 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 [732]. One RCT compared 48 boys < 14 years undergoing transurethral lithotripsy vs. 49 boys undergoing percutaneous lithotripsy with comparable success and complication rates; however, PCCL had a shorter operative time and less need for stone disintegration [755].

6.4.3.4 Extracorporeal shock wave lithotripsy
Extracorporeal SWL is the least invasive therapeutic procedure [742].

6.4.3.4.1 Shock wave lithotripsy in adults
In adults, one RCT compared SWL with transurethral cystolithotripsy in 100 patients with ≤ 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) [742, 756].

Two NRS compared transurethral cystolithotripsy vs. 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. 2.5 cm, p=0.014; and 3.6 vs. 2.6 cm [p value not reported]) [757, 758].

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) [756-758]. No significant differences in major post-operative or intra-operative complications were reported in any study [756-758].

One NRS compared SWL vs. open cystolithotomy in just 43 patients. Stone sizes were not comparable (2.5 vs. 7.4 cm, p < 0.001). Stone-free rates were not significantly different (93.9% vs. 100%, p=0.50). Length of stay favored SWL. There was no significant difference in intra-operative or major post-operative complications [757].

6.4.3.4.2 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 [759].

6.4.3.5 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 [760, 761]. A systematic review found no studies comparing laparoscopic surgery with other procedures [742].

*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 [717]. Only 51% of men had BOO while 10% had detrusor under-activity. Eighteen percent of men had a completely normal urodynamic study and 68% had detrusor over-activity. There was no significant difference between pre- and post-bladder stone removal urodynamic findings [717].

One NRS compared 64 men undergoing transurethral cystolithotripsy with either transurethral resection of the prostate (TURP) or medical management for BPO (α-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 [762]. 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 [739]. 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 [763]. Large prostates 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 [764-766]. 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 [764]. An observational study of 321 men undergoing Holmium laser enucleation of the prostate (HoLEP) found a higher rate of early post-operative incontinence (26.8% vs. 12.5%, p=0.03) in men having concomitant transurethral cystolithotripsy, but no difference in long-term continence rates [766]. Another larger multicenter 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 [767].

6.4.5 ***Special situations***

6.4.5.1 *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 [768-770]. 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 respectively motor-incomplete and motor-complete spinal cord injury patients developing bladder stones over time [722]. 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) [771].

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 [772]. However, another study of 457 spinal cord injury patients for six months found no difference in bladder stones between urethral and suprapubic catheterisation [771]. Spinal cord injury patients with an indwelling urethral catheter are six times more likely to develop bladder stones than patients with normal micturition [770, 772].

The risk of stone recurrence after complete removal in spinal cord injury patients is 16% per year [771]. 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) [773]. However, this study excluded patients who developed autonomic dysreflexia during bladder irrigations. The irrigation volume used was not reported.

6.4.5.2 *Bladder Augmentation*

The incidence of vesical calculus formation after bladder augmentation is 2-44% in adults [774-783], and 4-53% in children [783-797]. Following cystoplasty, stones form after 24-31 months in adults [775, 777, 782], and after 25-68 months in children [788, 791, 792, 796, 798-800]. The reported cumulative incidence of bladder stone formation after ten years is 28-36% and after twenty years is 41% [783, 801].

Risk factors for bladder stone formation after augmentation include excess mucus production, incomplete bladder emptying, non-compliance 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) [441, 775, 778, 780, 781, 788, 792, 795, 801] and voiding by CISC compared with those voiding spontaneously [779]. Gastric segment augmentation confers a lower risk of bladder stones than ileal or colonic segment cystoplasty [784, 788, 792, 795].

In previous stone formers, the rate of recurrence is 15-44% in adults [775-777, 779, 782], and 19-56% in children [441, 783, 784, 788, 790-793, 795, 800]. The risk of recurrence is greatest during the first two years, at about 12% per patient per year, with the risk decreasing with time [800].

Daily, or three-times-weekly bladder irrigations reduce the incidence of bladder stones following bladder augmentation or continent urinary diversion [441, 778]. A randomised study found that daily bladder irrigation with 240 mL 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 [778]. The frequency of bladder irrigations required is unclear.

6.4.5.3 *Urinary diversion*

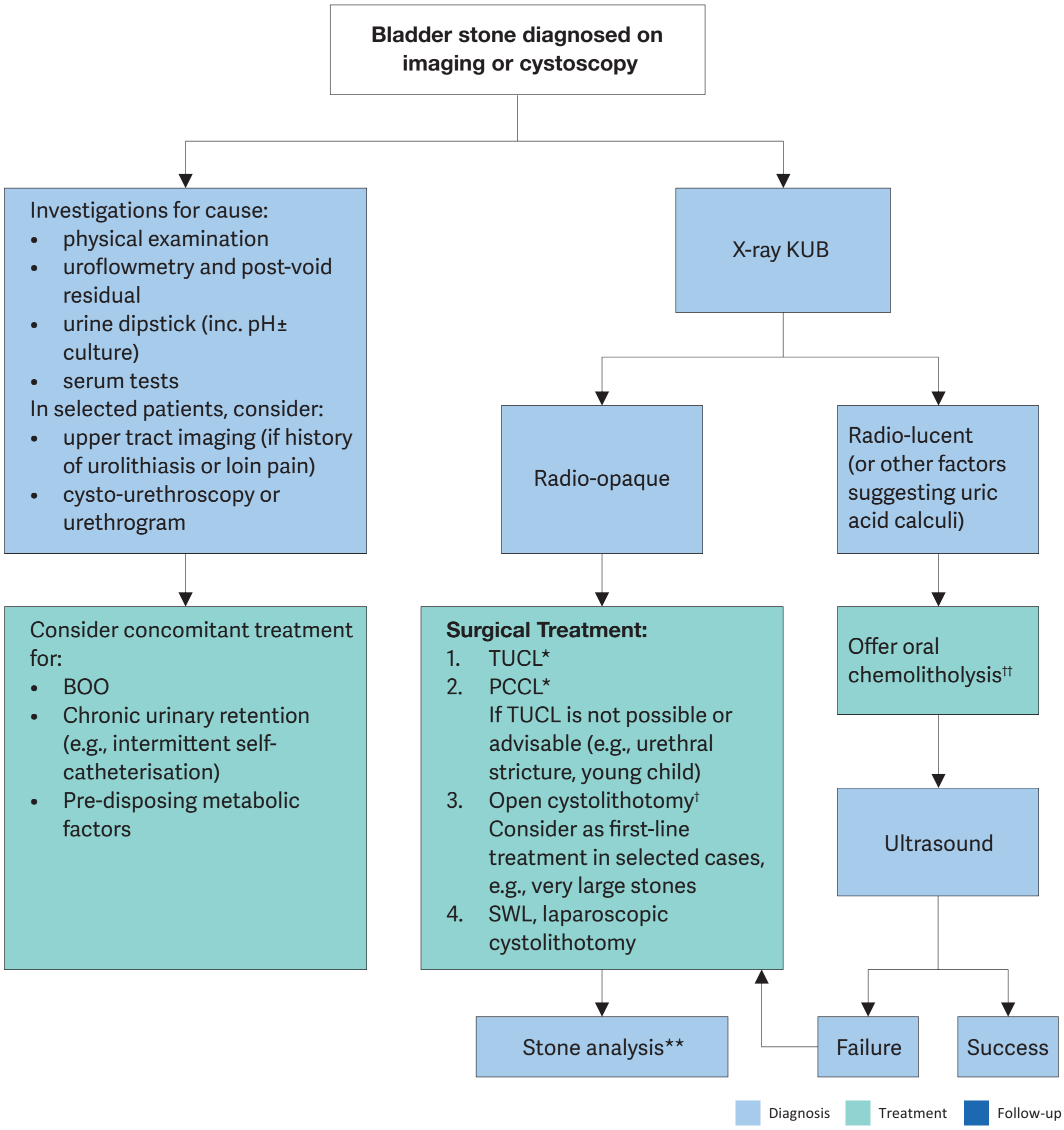
The incidence of stone formation after urinary diversion with an ileal or colon conduit is 0-3% [802, 803]. The incidence of stone formation is 0-34% in orthotopic ileal neobladders (Hautmann, hemi-Kock, Studer, T-pouch or w-neobladder) [439, 779, 803-811], and 4-6% in orthotopic sigmoid neobladders (Reddy) [808, 812]. 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) [431, 779, 802, 803, 811, 813]. The average interval from construction of the urinary diversion to stone detection is 71-99 months [807, 814]. In children, the incidence of neobladder stone formation is 30% after Mainz II diversion (rectosigmoid reservoir) [785], and 27% after Kock ileal reservoir construction [797].

6.4.5.4 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 [790]. However, often access cannot be obtained through a continent vesico-entero-cystostomy without damaging the continence apparatus; hence a percutaneous or open approach is typically preferred [790].

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 [815, 816] 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% [815, 816], but appears to be unrelated to the modality used for stone removal [782, 788, 792, 793, 795, 800].

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 guideline).*
†† 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 = Trans-urethral 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 Diagnosing the cause of bladder stones).

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 Guideline on Urolithiasis, based on evidence from upper tract stones, constitute the best available recommendations, especially for migratory bladder stones (see Section 4 Metabolic Evaluation and Recurrence Prevention 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, or 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 Special Situations) [773, 778, 803].

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 cows' milk after one year of age are recommended to prevent a recurrence [729].

Finally, there are contradictory reports on a possible association between bladder calculi and the future development of bladder cancer [817-819]. 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 pre-disposing 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 (trans-urethral 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 post-operative complications when compared to BOO treatment alone in adults. However, concomitant bladder stone treatment does increase the rates of short-term post-operative 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: • uroflowmetry and post-void residual; • urine dipstick, pH, ± culture; • metabolic assessment and stone analysis (see sections 3.3.2.3 and 4.1 of the Urolithiasis guidelines for further details). In selected patients, consider: • upper tract imaging (in patients with a history of urolithiasis or loin pain); • cysto-urethroscopy or urethrogram.	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	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: • whether the underlying functional predisposition to stone formation can be treated (e.g., TURP); • metabolic risk.	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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All members of the Urolithiasis Guidelines Panel 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 publicly accessible through the European Association of Urology website: http://www.uroweb.org/guidelines/. 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 assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

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