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. Management of bladder stones are dealt with in a separate guideline authored by the same guideline group.

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 particular expertise in this area. All experts involved in the production of this document have submitted potential conflict of interest statements, 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, both in print and as an app for iOS and Android devices. These are abridged versions, which may require consultation together with the full text versions. A number of scientific publications are also available [1-3]. All documents can be accessed through the EAU website: http://uroweb.org/guideline/urolithiasis/.

1.4 Publication history and summary of changes

1.4.1 Publication history

The EAU Urolithiasis Guidelines were first published in 2000. This 2021 document presents a limited update of the 2020 version.

1.4.2 Summary of changes

The literature for the entire document has been checked and, wherever relevant, updated (see Methods section 2.1).

For 2021, conclusions and recommendations have been rephrased and strength ratings reassessed across several sections. References and supporting text have also been refreshed. Additional information has been added to the chapter on “Prevalence, aetiology, risk of recurrence” including “Table 3.4 Risk factors for chronic kidney disease and end stage kidney disease in stone formers” and “Table 3.5 Risk factors for chronic kidney disease and renal stones”. A consultant nephrologist has now been added to the panel and has reviewed the entire text. Updated recommendation strength ratings include the following:

3.3.2.3 Guidelines for laboratory examinations and stone analysis

Recommendations	Strength rating
Blood	
Serum blood sample: • creatinine; • uric acid; • (ionised) calcium; • sodium; • potassium; • blood cell count; • C-reactive protein.	Strong

4.6.5.1 Guidelines for the management of tubular acidosis

Recommendations	Strength rating
Prescribe alkaline citrates for distal renal tubular acidosis.	Strong

2. METHODS

2.1 Data identification

For the 2020 Urolithiasis Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature.

A broad and comprehensive scoping exercise covering all areas of the guideline was performed. The search was limited to studies representing high levels of evidence only (i.e., systematic reviews with meta-analysis (MA), randomised controlled trials (RCTs), and prospective non-randomised comparative studies) published in the English language. The search was restricted to articles published between 2nd May 2019 and 1st May 2020. Databases covered by the search included Medline, EMBASE, Ovid and the Cochrane Libraries. A total of 887 unique records were identified and screened for relevance. The search strategy is published online: http://uroweb.org/guideline/urolithiasis/?type=appendices-publications.

A total of 27 new references have been added to the Urolithiasis 2021 Guidelines publication.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [4, 5]. Each strength-rating form addresses a number of key elements, namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [6];
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 of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words ‘strong’ or ‘weak’ [7]. 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 nature and variability of patient values and preferences.

Additional information can be found in the general Methodology section of this print, and online at the EAU website: http://www.uroweb.org/guideline/.

A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

The 2015 Urolithiasis Guidelines were subjected to peer-review prior to publication.

2.3 Future goals

For the 2022 text update the Urolithiasis Guidelines Panel aim to provide further guidance on the following topics:

- Chronic kidney disease (CKD) and bone marrow destruction;
- different interventions and best clinical practice;
- expanded and revised section on follow-up.

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% [8]. 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 [9-11]. There is emerging evidence linking nephrolithiasis to the risk of CKD [12].

Stones can be stratified into those caused by: infection, or non-infectious causes, genetic defects [13]; 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
Infection stones		
• Magnesium ammonium phosphate	• Highly-carbonated apatite	• Ammonium urate
Genetic causes		
• Cystine	• Xanthine	• 2,8-Dihydroxyadenine
Drug stones		

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** [33]	**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	$C_5H_4N_4O_3$
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	$MgHPO_4.3H_2O$
Magnesium ammonium phosphate monohydrate	Dittmarite	$MgNH_4(PO_4).H_2O$
Cystine		$[SCH_2CH(NH_2)COOH]_2$
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

The risk status of stone formers is of particular interest because it defines the probability of recurrence or regrowth, the risk of CKD and mineral and bone disorder, and is imperative for pharmacological treatment.

About 50% of recurrent stone formers have just one lifetime recurrence [10, 14]. A recent review of first-time stone formers caculated 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, 17].

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 more importance)
Diseases associated with stone formation
Hyperparathyroidism
Metabolic syndrome
Nephrocalcinosis
Polycystic kidney disease (PKD)
Gastrointestinal diseases (i.e., jejuno-ileal bypass, intestinal resection, Crohn's disease, malabsorptive conditions, enteric hyperoxaluria after 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

A comprehensive evaluation of stone risk in patients should also include the risk of developing CKD, end-stage kidney disease (ESKD), and metabolic stone disease (Tables 3.4, 3.5 and 3.6). 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 [34]. Certain risk factors have been shown to be associated with such a risk in stone formers, as shown below.

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

3.2 Classification of stones

Urinary stones can be classified according to size, location, X-ray characteristics, aetiology of formation, composition, and risk of recurrence [10, 35, 36].

3.2.1 Stone size

Stone size is usually given in one or two dimensions, and stratified into those measuring up to 5, 5-10, 10-20, and > 20 mm in largest diameter.

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. Treatment of bladder stones is not discussed in these guidelines.

3.2.3 X-ray characteristics

Stones can be classified according to plain X-ray appearance [kidney-ureter-bladder (KUB) radiography] (Table 3.6), which varies according to mineral composition [36]. 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) [35, 36].

Table 3.7: X-ray characteristics

Radiopaque	Poor radiopacity	Radiolucent
Calcium oxalate dehydrate	Magnesium ammonium phosphate	Uric acid
Calcium oxalate monohydrate	Apatite	Ammonium urate
Calcium phosphates	Cystine	Xanthine
		2,8-Dihydroxyadenine
		Drug-stones (Section 4.11)

3.3 Diagnostic evaluation

3.3.1 Diagnostic imaging

The most appropriate imaging modality will be determined by the clinical 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 [37]. 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 [38, 39].

The sensitivity and specificity of KUB is 44-77% [40]. Kidney-ureter-bladder radiography should not be performed if NCCT is being considered [41]; however, it is helpful in differentiating between radiolucent and radiopaque stones and should 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 diameter 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 [42].

Non-contrast-enhanced CT can detect uric acid and xanthine stones, which are radiolucent on plain films, but not indinavir stones [43]. Non-contrast-enhanced CT can determine stone density, inner structure of the stone, skin-to-stone distance, and surrounding anatomy; all of which affect selection of treatment modality [36, 44-46]. The advantage of non-contrast imaging must be balanced against loss of information on renal function and urinary collecting system anatomy, as well as higher radiation dose [47-50].

Radiation risk can be reduced by low-dose CT, which may, however, be difficult to introduce in standard clinical practice [51-53]. 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 [54]. A meta-analysis (MA) of prospective studies [53] 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 [55].

3.3.1.2 Radiological evaluation of patients with renal stones

Intravenous urography can provide information about renal function, the anatomy of the collecting system and the level of an obstruction, while CT allows for rapid 3D data acquisition including information on stone size and density, skin-to-stone distance, and surrounding anatomy, but at the cost of increased radiation exposure. Low-dose and ultra-low-dose protocols seem to yield comparable results to standard-dose protocols with the exception of detection of very small stones or stones in obese patients [53, 54, 56, 57].

A small randomised study showed that in supine percutaneous antegrade ureteroscopy, pre-operative planning using CT, compared to IVU, resulted in easier access and shorter operating times [58].

In case stone removal is planned and the renal collecting system needs to be assessed, a contrast study (including retrograde imaging) should be performed [59].

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
Enhanced CT enables 3D reconstruction of the collecting system, as well as measurement of stone density and skin-to-stone distance.	2a

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
Perform a contrast study if stone removal is planned and the anatomy of the renal collecting system needs to be assessed.	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. 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 in 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 [60, 61].

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

The preferred analytical procedures are infrared spectroscopy (IRS) or X-ray diffraction (XRD) [62-64]. Equivalent results can be obtained by polarisation microscopy. Chemical analysis (wet chemistry) is generally deemed to be obsolete [62, 65].

3.3.2.3 Guidelines for laboratory examinations and stone analysis [17, 23, 59, 66]

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 dose and require a threshold dose (< 50 mGy are considered as safe) and depend on the gestation age (minimum risk prior to 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 [67].

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 US [68], X-ray imaging [69, 70], and MRI [71, 72] are used as and when indicated [73-79]. 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 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 [75-77].

Magnetic resonance imaging can be used, as a second-line option [73], to define the level of urinary tract obstruction, and to visualise stones as a filling defect [71]. As 3 Tesla (T) MRI has not been evaluated in pregnancy, the use of 1.5T is currently recommended [74, 79]. The use of gadolinium is not routinely recommended in pregnancy to avoid toxic effects to the embryo [75].

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 [80]. Although low-dose CT protocols reduce the radiation exposure, judicious use is currently recommended in pregnant women as a last-line option [75].

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 non-metabolic disorders facilitating stone formation are vesico-ureteral reflux (VUR), UPJ obstruction, neurogenic bladder, and other voiding difficulties [81].

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 [82-84].

Ultrasound

Ultrasound is the primary imaging technique [85] in children. Its advantages are 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 [86-90]. Colour Doppler US shows differences in the ureteral jet [87] and resistive index of the arciform arteries of both kidneys, which are indicative of the grade of obstruction [88]. Nevertheless, US fails to identify stones in > 40% of children [89-92] and provides limited information on renal function.

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 cysto-urethrography (0.33 mSV) [93]. However, the need for contrast medium injection is a major drawback.

Non-contrast-enhanced computed tomography

Recent low-dose CT protocols have been shown to significantly reduce radiation exposure [50, 57, 94]. In children, only 5% of stones escape detection by NCCT [87, 94, 95]. 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 [96].

3.3.3.2.1 Summary of evidence and guidelines 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

3.4.1 Renal colic

Pain relief

Non-steroidal anti-inflammatory drugs (NSAIDs) (including metamizoledipyrone), and paracetamol are effective in patients with acute stone colic [97-99], and have better analgesic efficacy than opioids [100]. Ibuprofen compared to ketorolac is a more rapid acting drug in controlling pain caused by renal colic with a similar side effect profile [101].

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 manner in which the results have been reported [102]. 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 [99, 100]. Diclofenac is contraindicated in patients with congestive heart failure (New York Heart Association class II-IV), ischaemic heart disease and peripheral arterial- and cerebrovascular disease. 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 [103, 104].

Opioids, particularly pethidine, are associated with a high rate of vomiting compared to NSAIDs and carry a greater likelihood of further analgesia being needed [99, 105] (see below). If an opioid is used, it is recommended that it is not pethidine. Data on other types of non-opioid and non-NSAID medication is increasing. Ketamine in combination with morphine, compared to morphine alone, leads to morphine consumption reduction, less pain, nausea and vomiting [106-108]. Patients receiving ketamine and NSAIDs attained greater reduction in pain scores with less side effects, and better functional state, as well as less further analgesia requirement than those administered pethidine [109]. However, when comparing ketamine vs. NSAID (ketolorac) alone, equal efficacy but higher rates of dizziness, agitation and hypertension with ketamine were observed [110]. Conflicting results have been reported regarding the utility of intravenous lidocaine. Acupuncture seems to be effective in renal colic alone or in combination, but there is limited data [111, 112].

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 [113, 114]. Although diclofenac can affect renal function in patients with already reduced function, it has no functional effect in patients with normal renal function [115].

The systematic review and MA by Hollingsworth *et al*. [116] 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 [117].

3.4.1.1 Summary of evidence and guidelines 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; e.g. metamizol* (dipyrone); alternatively paracetamol or, depending on cardiovascular risk factors, diclofenac**, indomethacin or ibuprofen***.	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

* *Maximum single oral dose recommended 1000 mg, total daily dose up to 5000 mg, not recommended in the last three months of pregnancy [118].*

** *Affects glomerular filtration rate (GFR) in patients with reduced renal function.*

*** *Recommended to counteract recurrent pain after ureteral colic.*

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

Currently, there are two options for urgent decompression of obstructed collecting systems:

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

There is little evidence to support the superiority of percutaneous nephrostomy over retrograde stenting for primary treatment of infected hydronephrosis. There is no good quality evidence to suggest that ureteral stenting has more complications than percutaneous nephrostomy [119, 120].

Only one RCT [121] compared different modalities of decompression of acute infected hydronephrosis. The complications of percutaneous nephrostomy insertion have been reported consistently, but those of ureteral stent insertion are less well described [119]. 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 [122].

Further measures

Following 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 thereafter or continued, if initiated prior to testing. 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. Intensive care might become necessary [123].

3.4.2.1 *Summary of evidence and guidelines 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*

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). Several drug classes are used for MET [124-127]. When using α-blockers for MET, possible side effects include retrograde ejaculation and hypotension [114]. Patients treated with α-blockers, calcium-channel inhibitors (nifedipine) and phosphodiesterase type 5 inhibitors (PDEI-5) (tadalafil) are more likely to pass stones with fewer colic episodes than those not receiving such therapy [114, 128, 129]. Based on studies with a limited number of patients [127, 129-131], no recommendation for the use of PDEI-5 or corticosteroids in combination with α-blockers in MET can be made.

Tamsulosin showed an overall superiority to nifedipine for distal ureteral calculi [132]. A class effect of α-blockers has been demonstrated in MAs [131, 133, 134]. 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 [135-137]. A published MA, including 55 trials with a data search cut-off of July 1st 2015, including the publications addressed above, assessed stone passage as primary outcome [116]. Based on the well-designed sensitivity analyses of this MA, α-blockers promote spontaneous stone expulsion of large stones located in any

part of the ureter. There are small trials of uncertain quality suggesting tadalafil alone or in combination with tamsulosin may be beneficial for ureteric stone passage [129]. A large double-blind, placebo-controlled study of 3,296 patients with distal ureteral stones, across 30 centres, evaluated the efficacy and safety of tamsulosin. Participants were randomly assigned (1:1) to tamsulosin (0.4 mg) or placebo groups for four weeks. Tamsulosin benefits from a higher stone expulsion rate than the placebo (86% vs. 79%; $p < 0.001$) for distal ureteral stones. Subgroup analysis identified a significant benefit of tamsulosin for the treatment of large distal ureteral stones (> 5 mm) but no benefit for smaller stones (≤ 5 mm). Considering the secondary end points, tamsulosin treated patients reported a shorter time to expulsion ($p < 0.001$), required lower use of analgesics compared with placebo ($p < 0.001$), and significantly relieved renal colic ($p < 0.001$). No differences in the incidence of adverse events were identified between the two groups [138].

The primary outcome of most trials assessing MET was stone passage, or follow up, up to four weeks. No data are currently available to support other time-intervals.

The Panel concludes that MET seems efficacious in the treatment of patients with ureteral stones who are amenable to conservative management. The greatest benefit might be among those with > 5 mm distal stones [139].

Medical expulsive therapy in special situations is addressed in the relevant chapters.

3.4.3.1 Summary of evidence and guideline for MET

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

*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 [140-142].

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 chemolitholysis 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. No RCTs are available for this therapy, which has been in use for decades. Rodman, *et al*., [143] reviewed the principles and provided guidance to its clinical use, which was supported by Becker, *et al*., in 2007 [144]. Monitoring of radiolucent stones during therapy is the domain of US; however, repeat-NCCT might be necessary [143, 144].

In the case of uric acid obstruction of the collecting system, oral chemolysis in combination with urinary drainage is indicated [145]. 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 [145].

3.4.4.1 *Summary of evidence and guidelines 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 (ESWL)***

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 final 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 formation of steinstrasse [146-149].

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 [150].

Shock wave rate

Lowering shock wave frequency from 120 to 60-90 shock waves/min improves SFRs [151-159]. Ultraslow frequency 30 shock waves/min may increase SFR [160]. Tissue damage increases with shock wave frequency [161-163].

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 [164]. Starting SWL on a lower energy setting with stepwise power (and SWL sequence) ramping can achieve vasoconstriction during treatment [161], which prevents renal injury [165-167]. Animal studies [168] and a prospective randomised study [169] 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 [170, 171].

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).

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 [172]. Ultrasound gel is probably the most widely-used agent available as a lithotripsy coupling agent [173].

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 [174].

Pain Control
Careful control of pain during treatment is necessary to limit pain-induced movements and excessive respiratory excursions [175-178].

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) [66, 179, 180].

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 adjunct to expedite expulsion and to increase SFRs. Medical expulsion therapy might also reduce analgesic requirements [181-190].

Post-treatment management
Mechanical percussion and diuretic therapy can significantly improve SFRs and accelerate stone passage after SWL [191-193].

Complications of extracorporeal shock wave lithotripsy
Compared to percutaneous nephrolithotomy (PNL) and ureteroscopy (URS), there are fewer overall complications with SWL [194, 195] (Table 3.8).

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 [211-217].

Table 3.8: Shock wave lithotripsy-related complications [196-210]

Complications			**%**	**Reference**
Related to stone fragments	Steinstrasse		4 – 7	[208-210]
	Regrowth of residual fragments		21 – 59	[197, 198]
	Renal colic		2 – 4	[199]
Infectious	Bacteriuria in non-infection stones		7.7 – 23	[197, 200]
	Sepsis		1 – 2.7	[197, 200]
Tissue effect	Renal	Haematoma, symptomatic	< 1	[201]
		Haematoma, asymptomatic	4 – 19	[201]
	Cardiovascular	Dysrhythmia	11 – 59	[197, 202]
		Morbid cardiac events	Case reports	[197, 202]
	Gastrointestinal	Bowel perforation	Case reports	[203-205]
		Liver, spleen haematoma	Case reports	[196, 205-207]

3.4.5.1 Summary of evidence and guidelines for SWL

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 [211]. However, technical improvements, as well as the availability of digital scopes, also favour the use of flexible ureteroscopes in the ureter [218].

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 [219-221], or when the ureter is not amenable to retrograde manipulation [221-225].

Ureteroscopy for renal stones (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 recent 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 [218, 226, 227]. Digital scopes demonstrate shorter operation times due to the improvement in image quality [226].

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 [228].

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. Intravenous sedation is suitable for female patients with distal ureteral stones [229]. Antegrade URS is an option for large, impacted, proximal ureteral calculi [219-221, 230].

Safety aspects

Fluoroscopic equipment must be available in the operating room. The Panel recommend placement of a safety wire, even though some groups have demonstrated that URS can be performed without it [231-233]. 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 [234]. Bilateral URS during the same session is feasible resulting in equivalent-to-lower SFRs, but slightly higher overall complication rates (mostly minor, Clavien 1 and 2) [235, 236].

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 intra-renal pressure, and potentially reduces operating time [237, 238].

The insertion of ureteral access sheaths may lead to ureteral damage, the risk is lowest in presented systems [239]. No data on long-term side effects are available [239, 240]. 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 [241, 242]. Use of ureteral access sheaths depends on the surgeon's preference.

Stone extraction

The aim of URS is complete stone removal. "Dust and go" strategies should be limited to the treatment of large (renal) stones [243]. Stones can be extracted by endoscopic forceps or baskets. Only baskets made of nitinol can be used for flexible URS [244].

Intracorporeal lithotripsy

The most effective lithotripsy system is the holmium:yttrium-aluminium-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 [245, 246]. 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 placement of special anti-migration tools proximal of the stone [249]. Medical expulsion therapy following Ho:YAG laser lithotripsy increases SFRs and reduces colic episodes [250]. New, preliminary studies demonstrate that the Thullium Fiber Laser is a promising alternative laser for lithotripsy, but clinical data is still awaited [251].

Stenting before and after URS

Routine stenting is not necessary before URS. However, pre-stenting facilitates ureteroscopic management of stones, improves the SFR, and reduces intra-operative complications [252, 253].

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 [254-257]. A ureteral catheter with a shorter indwelling time (one day) may also be used, with similar results [258].

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 [259, 260].

Medical expulsive therapy after ureteroscopy

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 9-25% [211, 261, 262]. Most complications are minor and do not require intervention. Ureteral avulsion and strictures are rare (< 1%). Previous perforations are the most important risk factor for complications.

3.4.6.1 Summary of evidence and guidelines 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 (in particular for renal stones), pre-stenting has been shown to improve outcomes.	1b
An α-blocker can reduce stent-related symptoms and colic episodes.	1a
Medical expulsion therapy following Ho:YAG laser lithotripsy accelerates the spontaneous passage of fragments and reduces episodes of colic.	1b
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
Medical expulsion therapy following Ho:YAG laser lithotripsy increases SFRs and reduces colic episodes.	1b
Percutaneous antegrade removal of proximal ureter stones, or laparoscopic ureterolithotomy are feasible alternatives to retrograde ureteroscopy, in selected cases.	1b

Recommendations	**Strength rating**
Use holmium: yttrium-aluminium-garnet (Ho:YAG) 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 in cases where percutaneous nephrolithotomy or SWL are not an option (even for stones > 2 cm). 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 [263].

Contraindications

Patients receiving anti-coagulant therapy must be monitored carefully pre- and post-operatively. Anti-coagulant therapy must be discontinued before PNL [264].

Other important contraindications 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 PNL are available. Ultrasonic and pneumatic systems are most commonly used for rigid nephroscopy, whilst laser is increasingly used for miniaturised instruments [265]. Flexible endoscopes also require laser lithotripsy to maintain tip deflection, with the Ho:YAG laser having become the standard.

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 interpositioned 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, although the supine position confers some advantages, it depends on appropriate equipment being available to position the patient correctly, for example, X-ray devices and an operating table. Most studies cannot demonstrate an advantage of supine PNL in terms of OR time. Prone position offers more options for puncture and is therefore preferred for upper pole or multiple accesses [266, 267]. On the other hand, supine position allows simultaneous retrograde access to the collecting system, using flexible ureteroscope (ECIRS) [268, 269].

Puncture

Although fluoroscopy is the most common intra-operative imaging method, the (additional) use of US reduces radiation exposure [270, 271]. Pre-operative CT or intra-operative US allows identification of the tissue between the skin and kidney and lowers the incidence of visceral injury. The calyceal puncture may be done under direct visualisation using simultaneous flexible URS [269, 271, 272].

Dilatation

Dilatation of the percutaneous access tract can be achieved using a metallic telescope, single (serial) dilators, or a balloon dilatator. 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 [273].

Choice of instruments

The Panel performed a systematic review assessing the outcomes of PNL using smaller tract sizes (< 22 F, mini-PNL) for removing renal calculi [263]. Stone-free rates were comparable in miniaturised and standard PNL procedures. Procedures performed with small instruments tend to be associated with significantly lower blood loss, but the duration of procedure tends to be significantly longer. There were no significant differences in any other complications. However, the quality of the evidence was poor with only two RCTs and the majority of the remaining studies were single-arm case series only. Furthermore, the tract sizes used, and types of stones treated, were heterogeneous; therefore, the risk of bias and confounding were high.

Nephrostomy and stents

The decision on whether, or not, to place a nephrostomy tube at the conclusion of the PNL procedure depends on several factors, including:

- presence of residual stones;
- likelihood of a second-look procedure;
- significant intra-operative blood loss;
- 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 [263, 274, 275]. Tubeless PNL is performed without a nephrostomy tube. When neither a nephrostomy tube nor a ureteral stent is introduced, the procedure is known as totally tubeless PNL [276]. In uncomplicated cases, the latter procedure results in a shorter hospital stay, with no disadvantages reported [277].

Complications of percutaneous nephrolithotomy

A systematic review of almost 12,000 patients shows the incidence of complications associated with PNL; 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% [278].

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. Intra-operative renal stone culture may therefore help to select post-operative antibiotics [279]. Intra-operative irrigation pressure < 30 mmHg and unobstructed post-operative urinary drainage may be important factors in preventing post-operative sepsis [280]. Bleeding after PNL 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.

3.4.7.1 Summary of evidence and guidelines 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).	1a
Both prone and supine positions are equally safe, but neither has a proven advantage in operating time or 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 PNL results in a shorter hospital stay, with no increase in complication rate.	1a

Recommendations	**Strength rating**
Perform pre-procedural imaging, including contrast medium where possible 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 procedure, in uncomplicated cases.	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 [281].

Peri-operative antibiotic prophylaxis

For prevention of infection following URS and percutaneous stone removal, no clear-cut evidence exists [282]. In a review of a large database of patients undergoing PNL, it was found that in patients with negative baseline urine culture, antibiotic prophylaxis significantly reduced the rate of post-operative fever and other complications [283]. Single dose administration was found to be sufficient [284].

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 [285-289]. 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 [290-292]);
- PNL;
- percutaneous nephrostomy;
- laparoscopic surgery;
- open surgery [285].

Shock wave lithotripsy is feasible and safe after correction of the underlying coagulopathy [293-297]. In the case of an uncorrected bleeding disorder or continued antithrombotic therapy, URS, in contrast to SWL and PNL, might offer an alternative approach since it is associated with less morbidity [298-300]. Despite appropriate cessation of anti-platelet agents, following standardised protocols, prolonged haematuria in tube drainage after PNL has been reported [301]. Only data on flexible URS are available which support the superiority of URS in the treatment of proximal ureteral stones [302, 303]. Although URS is safe in patients with bleeding disorders or anticoagulation, an individualised patient-approach is necessary [300].

Table 3.9: Risk stratification for bleeding [287-289, 304]

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 3.10: Suggested strategy for antithrombotic therapy in stone removal [287-289]
(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 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 guidelines 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 PNL and may influence the choice of treatment [305].

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 [44, 306]. 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 [307];
- bleeding disorders, which should be compensated for at least 24 hours before and 48 hours after treatment [308];
- uncontrolled UTIs;
- severe skeletal malformations and severe obesity, which prevent targeting of the stone;
- arterial aneurysm in the vicinity of the stone [309];
- 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 PNL

Patients receiving anti-coagulant therapy must be monitored carefully pre- and post-operatively. Anti-coagulant therapy must be discontinued before PNL [300]. Other important contraindications include:

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

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 [310]. It is estimated that 95% of stones up to 4 mm pass within 40 days [211].

Based on an analysis of available evidence, an exact cut-off size for stones that are likely to pass spontaneously cannot be provided [211].

Spontaneous stone passage was reported for 49% of upper ureteral stones, 58% of mid ureteral stones and 68% 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) [311]. The Panel is aware of the fact that spontaneous stone expulsion decreases with increasing stone size and that there are differences between individual patients.

Sexual intercourse has been reported to be beneficial in facilitating stone expulsion in men with ureteral stones, in one MA consisting of three RCTs [312].

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 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 active removal of ureteral stones

Indications for active removal of ureteral stones are [211, 310, 313]:

- 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 active removal of ureteral stones

Overall, SFRs after URS or SWL for ureteral stones are comparable. However, larger stones achieve earlier stone-free status with URS. Although URS is effective for ureteral calculi, it has greater potential for complications. However, in the current endourological era, the complication rate and morbidity of URS has been significantly reduced [314]. It has been demonstrated that URS is a safe option in obese patients (BMI > 30 kg/m^2) with comparable SFRs and complication rates. However, in morbidly obese patients (BMI > 35 kg/m^2) the overall complication rates double [315].

The Panel performed a systematic review to assess the benefits and harms of URS compared to SWL [316]. 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 need for secondary procedures, but with a higher need for adjunctive procedures, greater complication rates and longer hospital stay. Counterbalancing for URS's higher SFRs, SWL is associated with lower morbidity. Clavien-Dindo grade complications were, if reported, less frequent in patients treated with SWL.

Bleeding disorder

Ureteroscopy can be performed in patients with bleeding disorders, with a moderate increase in complications (see also Section 3.4.8.2) [300].

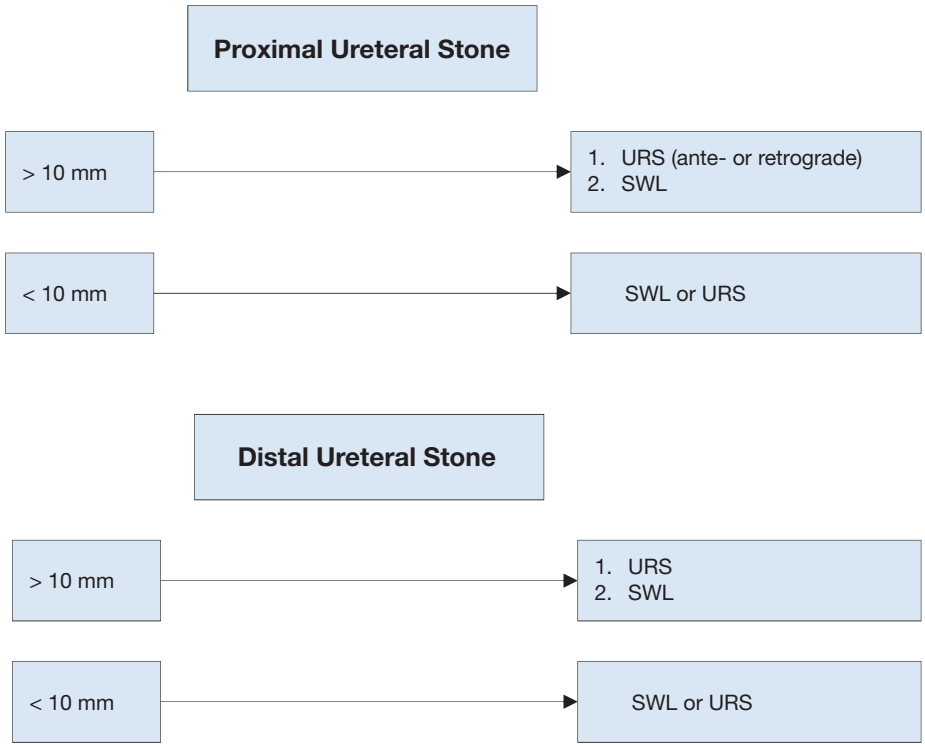
3.4.9.4.1 Summary of evidence and guidelines for selection of procedure for active removal of ureteral stones

Summary of evidence	**LE**
Observation is feasible in informed patients who develop no complications (infection, refractory pain, deterioration of renal function).	1a
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 [211].*

Figure 3.1: Treatment algorithm for ureteral stones (if active 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. Treatment options are chemolysis or active stone removal.

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 [317]. 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. Intervention is advised for growing stones > 5 mm [318].
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% [317].

3.4.10.2 Pharmacological treatment of renal stones

Dissolution of stones through pharmacological treatment is an option for uric acid stones only, but information on the composition of the stone will need to guide the type of treatment selected. See sections 3.4.4. and 3.4.8.4.

3.4.10.3 Indications for active 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) [319];
- stones > 15 mm;
- stones < 15 mm if observation is not the option of choice;
- patient preference;
- comorbidity;
- social situation of the patient (e.g., profession or travelling);
- choice of treatment.

The risk of a symptomatic episode or need for intervention in patients with asymptomatic renal stones seems to be ~10-25% per year, with a cumulative five-year event probability of 48.5% [318, 320, 321]. A prospective RCT with more than two years clinical follow-up reported no significant difference between SWL and observation when comparing asymptomatic calyceal stones < 15 mm in terms of SFR, symptoms, requirement for additional treatment, quality of life (QoL), renal function, or hospital admission [322]. Although some have recommended prophylaxis for these stones to prevent renal colic, haematuria, infection, or stone growth, conflicting data have been reported [321, 323, 324]. In a follow-up period of almost five years after SWL, two series have demonstrated that up to 25% of patients with small residual fragments needed treatment [198, 325]. Although the question of whether 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 [319, 326, 327].

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 renal pelvis or upper/middle calyces

Shock wave lithotripsy, PNL and RIRS are available treatment modalities for renal calculi. While PNL efficacy is hardly affected by stone size, the SFRs after SWL or URS are inversely proportional to stone size [328-331]. Shock wave lithotripsy achieves good SFRs for stones up to 20 mm, except for those at the lower pole [330, 332, 333]. Endourology is considered an alternative because of the reduced need for repeated procedures and consequently a shorter time until stone-free status is achieved. Stones > 20 mm should be treated primarily by PNL, 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) [194]. 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 [334-336]. However, it may be a first-line option in patients where PNL is not an option or contraindicated.

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 [194, 328, 329, 331, 332, 336-347].

The following can impair successful stone treatment by SWL [339, 348-353]:

- 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 ESWL) [192, 354].

If there are negative predictors for SWL, PNL and RIRS might be reasonable alternatives, even for smaller calculi [337]. Retrograde renal surgery seems to have comparable efficacy to SWL [194, 329, 332, 355]. Recent 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 [227, 356-358]. However, staged procedures are frequently required.

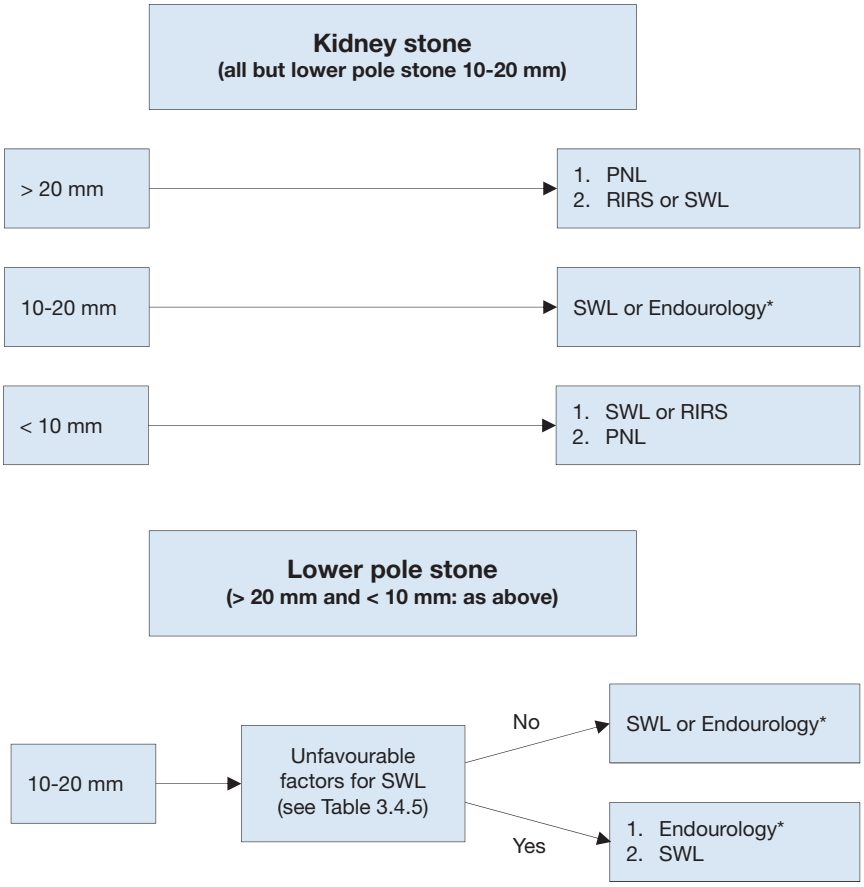
In complex stone cases, open or laparoscopic approaches are possible alternatives although they are infrequently used.

3.4.10.5 Summary of evidence and guidelines 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
Follow-up periodically in cases where renal stones are not treated (initially after six months then yearly, evaluating symptoms and stone status, either by ultrasound, kidney-ureter bladder radiography or computed tomography (CT)).	Strong
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. Stones with density > 1,000 HU (and with high homogeneity) on non-contrast-enhanced CT are less likely to be disintegrated by shock wave lithotripsy.	Strong
Perform percutaneous nephrolithotomy (PNL) 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 PNL 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 PNL 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 PNL and URS interventions.*
PNL = 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 PNL) have significantly decreased the indications for open or laparoscopic stone surgery [359-364]. There is a consensus that most complex stones, including partial and complete staghorn stones, should be approached primarily with PNL. Additionally, a combined approach with PNL 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 [365-371].

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 [372, 373]. These more invasive procedures have yielded high SFRs and lower auxiliary procedure rates [220, 230, 374]. A recent systematic review showed no difference in the post-operative phase for stented or unstented laparoscopic ureterolithotomy [374].

A few studies with limited numbers of patients have reported using robotic surgery in the treatment of urinary stones [375]. Open surgery should be considered as the last treatment option, after all other possibilities have been explored.

3.4.11.1 Summary of evidence and guideline 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 [376]. Steinstrasse occurs in 4-7% cases of SWL [208], and the major factor in the development of steinstrasse formation is stone size [377].

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 [147]. When steinstrasse is asymptomatic, conservative treatment is an initial option. Medical expulsion therapy increases stone expulsion and reduces the need for endoscopic intervention [378, 379]. Ureteroscopy and SWL are effective in treatment of steinstrasse [210, 380]. In the event of UTI or fever, the urinary system should be decompressed, preferably by percutaneous nephrostomy [120, 122].

3.4.12.1 Summary of evidence and guidelines 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 PNL, residual fragments may remain and require additional intervention [325, 381, 382]. Most of the 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 [383-385]. 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 [386, 387]. However, more than half of the patients with a residual fragment on NCCT images may not experience a stone-related event [388].

It is clear that NCCT has the highest sensitivity to detect residual fragments; however, this must be balanced against the increased detection of clinically insignificant fragments and the exposure to ionising radiation when compared with KUB and US. In the absence of high-level supporting evidence, the timing of follow-up imaging studies and need for secondary intervention is left to the discretion of the treating physician. Recurrence risk in patients with residual fragments after treatment of infection stones is higher than for other stones [389]. For all stone compositions, 21-59% of patients with residual stones required treatment within five years. Fragments

> 5 mm are more likely than smaller ones to require intervention [198, 390, 391]. There is evidence that fragments > 2 mm are more likely to grow, although this is not associated with increased re-intervention rates at one year follow up [381].

3.4.13.1 Summary of evidence and guideline for management of patients with residual stones

Summary of evidence	LE
To detect residual fragments after SWL, URS or PNL, deferred imaging is more appropriate than immediate imaging post intervention.	3

Recommendation	Strength rating
Perform imaging after shock wave lithotripsy, ureteroscopy or percutaneous antegrade ureteroscopy to determine presence of residual fragments.	Strong

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 urolithiasis patient is complex and demands close collaboration between patient, radiologist, obstetrician, and urologist. For diagnostic imaging see Section 3.3.1.

If spontaneous passage does not occur, or if complications develop (e.g., intractable symptoms, severe hydronephrosis 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 [392, 393].

Unfortunately, these temporising therapies are often associated with poor tolerance, and they require multiple exchanges during pregnancy, due to the potential for rapid encrustation [394].

Ureteroscopy has become a reasonable alternative in these situations [385, 395]. 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 [396].

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 [75].

Although feasible, percutaneous removal of renal stones during pregnancy remains an individual decision and should be performed only in experienced centres [397]. Pregnancy remains an absolute contraindication for SWL.

3.4.14.1.1 Summary of evidence and guideline 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 [398, 399]. Metabolic factors (hypercalciuria, hyperoxaluria and hypocitraturia), infection with urease-producing bacteria, foreign bodies, mucus secretion, and urinary stasis are responsible for stone formation [400] (section 3.1.3). One study has shown that the risk for recurrent upper tract stones in patients with urinary diversion subjected to PNL was 63% at five years [401].

Management

Smaller upper-tract stones can be treated effectively with SWL [225, 402]. In the majority of cases, endourological techniques are necessary to achieve stone-free status [222]. In individuals with long, tortuous conduits or with invisible ureter orifices, a retrograde endoscopic approach might be difficult or impossible [403].

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 [404].

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 [405], and if present, an open surgical approach should be considered.

Prevention

Recurrence risk is high in these patients [401]. 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 hyperdiuresis or regular irrigation of continent reservoirs [406].

3.4.14.2.1 Summary of evidence and guideline 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 [407]. 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 [408, 409].

Diagnosis of stones may be difficult and delayed in the absence of clinical symptoms due to sensory impairment and vesico-urethral 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 3.3.3. In myelomeningocele patients, latex allergy is common; therefore, appropriate measures need to be taken regardless of the treatment [410]. 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 [411]. The risk of stone formation after augmentation cystoplasty in immobile patients with sensory impairment can be significantly reduced by irrigation protocols [406].

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 guideline 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
In myelomeningocele patients, latex allergy is common.	2

Recommendation	Strength rating
Take appropriate measures regardless of the treatment provided since in myelomeningocele patients latex allergy is common.	Strong

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 [412].

Aetiology

Transplant patients depend on their solitary kidney 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 1% [413]. 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 [414] are biochemical risk factors.

Management

Selecting the appropriate technique for stone removal in a transplanted kidney is difficult, although management principles are similar to those applied in other single renal units [415-417]. Additional factors such as transplant function, coagulative status, and anatomical obstacles due to the iliacal 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 [417-419]. Retrograde access to transplanted kidneys is difficult due to the anterior location of the ureteral anastomosis, and ureteral tortuosity [420-422].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 SFR of 60-100% with an overall complication rate of 12.9% for post-transplant URS; most complications were Clavien 1 [423].

3.4.14.4.1 Summary of evidence and guideline 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 and SFRs are poor.	4

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

3.4.14.5 Special problems in stone removal

Table 3.11: Special problems in stone removal

Calyceal diverticulum stones	• SWL, PNL [424] (if possible) or RIRS [424, 425]. • Can also be removed using laparoscopic retroperitoneal surgery [426, 427]. • 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 [428]. • 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 [429, 430].
Stones in pelvic kidneys	• SWL, RIRS, PNL or laparoscopic surgery [431].
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 PNL together with percutaneous endopyelotomy or open/laparoscopic reconstructive surgery. • URS together with endopyelotomy with Ho:YAG laser. • Incision with an Acucise® balloon catheter might be considered, provided the stones can be prevented from falling into the pelvic-ureteral incision [432-435]. • Open surgery with correction of the UPJ obstruction (pyeloplasty) and stone removal is a feasible option [436].

*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 nation-wide epidemiological studies, studies performed in different counties worldwide [437] and large-scale databases [438, 439] indicate that the incidence and prevalence of paediatric urinary stone disease has increased over the last few decades. Although boys are most commonly affected in the first decade of life [440] the greatest increase in incidence has been seen in older female adolescences [437].

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 [441-443]. Hypocitraturia, low urine volume and hypercalciuria predominate [84, 441-443]. 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 [443]. 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 [441, 444]. 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 [445-447].

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 [448] while in older children flank pain, micro or gross haematuria and recurrent UTIs are more common [449].

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 [450, 451] or residual fragments remained after SWL, RIRS or PNL [452]. 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 [450]. Intervention may be needed for stones located elsewhere independently of their size [450-452].

3.4.15.3 Medical expulsive therapy in children

There are limited studies on MET as off-label expulsive therapy for children with stones which show conflicting outcomes. A recent MA of five trials showed that adrenergic α-antagonists (tamsulosin 0.2-0.4 mg/day and doxazosin 0.03 mg/kg/day) are effective for MET increasing SFR compared to control (OR = 2.7, p = 0.001) without significantly increasing the treatment-emergent adverse events (OR = 2.01, p = 0.17) [453]. Similarly, an updated systematic review of six placebo-controlled studies showed that α-blockers might increase SFR of distal ureteric stones (RR: 1.34, 95% CI: 1.16 - 1.54) [454]. Due to study limitations and very serious imprecision, no conclusion could be drawn regarding the effect of MET on hospital stay, pain episodes or secondary procedures for residual fragments after definitive stone treatment [454].

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 [455].

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 [456-460]. 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 [455]. For best clinical practice see Section 3.4.5. A recent 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 [454]. 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 [461].

Based on the results of a recent MA 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 [454]. 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) [462].

3.4.15.5 Endourological procedures

Rigid/semi-rigid ureteroscopy

In recent years ureteroscopy is increasingly used in children with ureteral stones [463]. Ureteroscopy proved to be effective with SFR of 81-98% [464-466], retreatment rates of 6.3%-10% [467] and complication rates of 1.9-23% [464-466, 468]. Similar to adults, routine stenting is not necessary before URS. Pre-stenting may facilitate URS, increase SFR and decrease complication rates [469, 470].

Flexible ureteroscopy/retrograde intrarenal surgery

Retrograde intra-renal surgery with flexible ureteroscopes (FURS) has become an efficacious treatment modality for paediatric renal stones. Recent studies report SFRs of 76-100%, retreatment rates of 0-19% and complication rates of 0-28% [471-474]. Younger age, cystine composition [475], large stone diameter [474] and lack of pre-stenting predispose to FURS failure in children [469].

Although high-level evidence is lacking to support a strong recommendation [454], FURS may be a particularly effective treatment option for lower calceal stones in the presence of unfavourable factors for SWL [466, 472, 476].

For large and complex kidney stones RIRS has a significantly lower SFR compared to PNL (71% vs. 95%), but is associated with less radiation exposure, lower complication rates and a shorter hospital stay [477]. Similarly, retrospectively data indicate that RIRS may achieve lower SFRs compared to minor micropercutaneous surgery in favour of shorter operative time, shorter fluoroscopy time, and less hospitalisation time [478, 479]. A recently published MA confirmed these results [480].

Percutaneous nephrolithotomy

Indications for PNL in children are similar to those in adults, and include renal stones > 2 cm, or smaller stones resistant to SWL and ureteroscopic treatment. Reported SFRs with paediatric PNL are 71.4-95% after a single session [477-479, 481, 482] with an overall complication rate of 20% [483]. High degree of hydronephrosis,

increased number of tracts and operative time [484] and large tract size [482, 485-487] are associated with increased blood loss. Child age [486] and stone burden [482] predispose to the use of larger instruments during PNL in children. Miniaturisation of equipment increases the opportunity to perform tubeless PNL in appropriately selected children, which can reduce the length of hospital stay and post-operative pain [488, 489].

Concerns have been raised regarding possible adverse effects of PNL on the renal parenchyma of the developing child. However, focal damage is only reported in 5% of cases [490]. Using pre- and post-PNL dimercaptosuccinic acid (DMSA) scans, Cicekbilek *et al.* demonstrated that PNL tracts between 12-24 Charrière in size did not cause significant harm to paediatric kidneys [481].

3.4.15.6 Open and laparoscopic/robot-assisted stone surgery

With the advances in ESWL, PNL 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 [491]. 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 ≥1cm single stone located in an extra-renal pelvis [492], or when laparoscopic ureterolithotomy was applied to impacted ureteric stones ≥ 1.5 cm, or to ureteric stones that were refractory to SWL or URS [493]. There are extremely limited data available on efficacy and complications of robot-assisted laparoscopic management of paediatric urolithiasis [494].

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 guidelines for the management of stones in children

Summary of evidence	**LE**
In children, the indications for SWL, URS and PNL 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 PNL are similar to those in adults.	1a

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

4. FOLLOW UP: METABOLIC EVALUATION AND RECURRENCE PREVENTION

4.1 General metabolic considerations for patient work-up

*4.1.1 **Evaluation of patient risk***

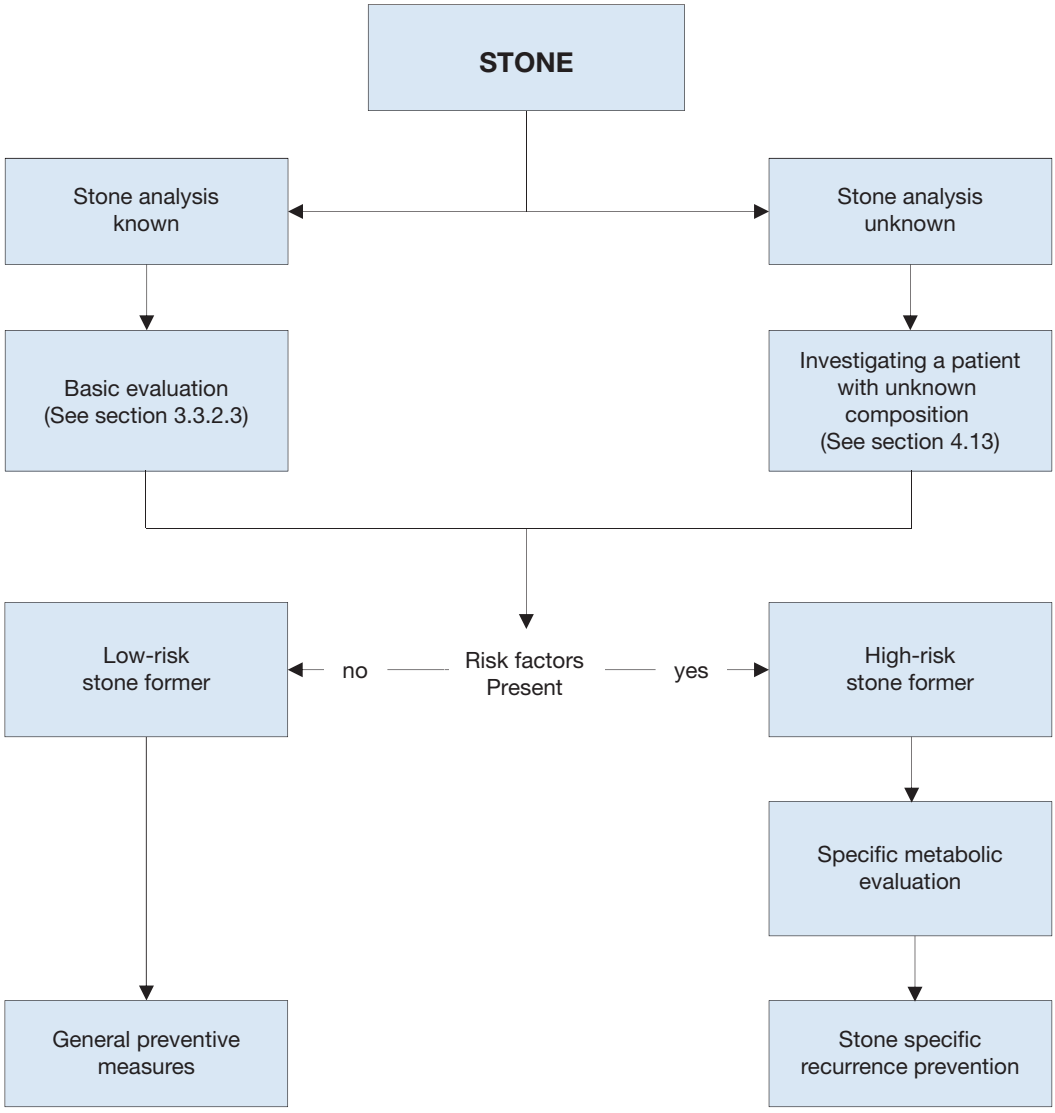
After stone passage, every patient should be assigned to a low- or high-risk group for stone formation (Figure 4.1). For correct classification, two items are mandatory:

- reliable stone analysis by infrared spectroscopy or X-ray diffraction;
- basic analysis (Section 3.3.2).

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 collection of two consecutive 24-hour urine samples [495, 496]. The collecting bottles should be prepared with 5% thymol in isopropanol or stored at < 8°C during collection to prevent the risk of spontaneous crystallisation in the urine. 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. The collecting method should be chosen in close cooperation with the laboratory. Urine pH should be assessed during collection of freshly voided urine at different times throughout the day using sensitive pH-dipsticks or a pH-meter [23, 497].

Spot urine samples are an alternative method of sampling, particularly when 24-hour's urine collection is difficult, for example, in non-toilet trained children [498]. Spot urine studies normally link the excretion rates to creatinine [499], 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 [500]. Follow-up studies are necessary in patients taking medication for recurrence prevention [501]. The first follow-up 24-hour urine measurement is suggested eight to twelve weeks after starting pharmacological prevention of stone recurrence. This enables 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 24-hour urine evaluation every twelve months. On this issue the Panel realise 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 [501, 502]

Blood parameter	Reference range	
Creatinine	20-100 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 urine [503-506]. However, clinical validation of these risk indices for recurrence prediction or therapy improvement is ongoing.

Table 4.2: Normal laboratory values for urinary parameters in adults

Urinary Parameters	Reference ranges and limits for medical attention
pH	Constantly > 5.8 (suspicious of renal tubular acidosis)
	Constantly > 7.0 (suspicious of infection)
	Constantly < 5.8 (suspicious of acidic arrest)
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	< 2.5 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 [507]

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 [508, 509]*

Calcium/24 hour	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 m^2/24 h	> 1.6 mmol/1.73 m^2/24 h	< 55 µmol/1.73 m^2/24 h	< 200 µmol/1.73 m^2/24 h	< 0.5 mmol/1.73 m^2/24 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 m^2/24 h	> 310 mg/1.73 m^2/24 h	< 13 mg/1.73 m^2/24 h	< 48 mg/1.73 m^2/24 h	< 45 mg /1.73 m^2/24 h	< 13 mg/kg/24 h	< 11 mg/kg/24 h	< 9.3 mg/kg/24 h

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 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.

Table 4.5: General preventive measures

Fluid intake (drinking advice)	Fluid amount: 2.5-3.0 L/day
	Circadian drinking
	Neutral pH beverages
	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 advice to normalise general risk factors	BMI: Retain a normal BMI level
	Adequate physical activity
	Balancing of excessive fluid loss

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 [508-511]. The effect of fruit juices is mainly determined by the presence of citrate or bicarbonate [512]. If hydrogen ions are present, the net result is neutralisation. However, if potassium is present, both pH and citrate are increased [513, 514]. 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 results were from only one trial [515]. An analysis on the 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 [516].

*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 [517-519].

Fruit, vegetables and fibre: Fruit and vegetable intake should be encouraged because of the beneficial effects of fibre, although the role of the latter in preventing stone recurrences is debatable [520-523]. The alkaline content of a vegetarian diet also increases urinary pH.

Oxalate: Excessive intake of oxalate-rich products should be limited or avoided to prevent high oxalate load [524], 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 [525]. However, it seems wise to advise calcium oxalate stone formers to avoid excessive intake.

Animal protein: Animal protein should not be consumed in excess [509, 526] 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 [521, 527]. 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 [509, 517, 524, 528]. 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 [529].

Sodium: Daily sodium (NaCl) intake should not exceed 3-5 g [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 [509, 526]. A positive correlation between sodium consumption and risk of first-time stone formation has been confirmed only in women [527]. 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 [530, 531] 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, obesity [532] and arterial hypertension [533, 534].

*4.2.4 **Summary of evidence and guideline for recurrence prevention***

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

Recommendation	Strength rating
Advise patients that a generous fluid intake 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. 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	5-12 g/d (14-36 mmol/d) Children: 0.1-0.15 g/kg/d	Daily dose for alkalinisation depends on urine pH.	Calcium oxalate Uric acid Cystine	[535-540]
Allopurinol	Hyperuricosuria Hyperuricaemia	100-300 mg/d Children: 1-3 mg/kg/d	100 mg in isolated hyperuricosuria. Renal insufficiency demands dose correction. Allergies from trivial to very severe forms, xanthine stone formation.	Calcium oxalate Uric acid Ammonium urate 2,8-Dihydroxyadenine	[517, 541-544]
Calcium	Enteric hyperoxaluria	Up to 2,000 mg/d depending on oxalate excretion	Intake 30 min before meals.	Calcium oxalate	[509, 527, 528]
Captopril	Cystinuria Active decrease of urinary cystine levels	75-150 mg	Second-line option due to significant side effects of tiopronin.	Cystine	[545, 546]
Febuxostat	Hyperuricosuria Hyperuricaemia	80-120 mg/d	Acute gout contraindicated, pregnancy, xanthine stone formation.	Calcium oxalate Uric acid	[547, 548]
L-Methionine	Acidification	600-1,500 mg/d	Hypercalciuria, bone demineralisation, systemic acidosis. No long-term therapy.	Infection stones Ammonium urate Calcium phosphate	[535, 549]
Magnesium	Isolated hypomagnesiuria Enteric hyperoxaluria	200-400 mg/d Children: 6 mg/kg/d	Renal insufficiency demands dose correction. Diarrhoea, chronic alkali losses, hypocitraturia.	Calcium oxalate	[550, 551] (Low level of evidence)
Sodium bicarbonate	Alkalinisation Hypocitraturia	4.5 g/d	N/A	Calcium oxalate Uric acid, Cystine	[552]
Pyridoxine	Primary hyperoxaluria	Initial dose 5 mg/kg/d Max. 20 mg/kg/d	Polyneuropathia	Calcium oxalate	[553]
Thiazide (Hydrochlorothiazide*)	Hypercalciuria	25-50 mg/d Children: 0.5-1 mg/kg/d	Risk for hypotonic blood pressure, diabetes, hyperuricaemia, hypokalaemia, followed by intracellular acidosis and hypocitraturia.	Calcium oxalate Calcium phosphate	[535, 530, 534-561]
Tiopronin	Cystinuria Active decrease of urinary cystine levels	Initial dose 800 mg/d Avg. 1,000 mg/d**	Risk for tachyphylaxis and proteinuria.	Cystine	[562-565]

** Patients on hydrochlorothiazides 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). In patients with history of NMSC the indication for the intake of hydrochlorothiazides should be thoroughly reviewed [566, 567].*

*** Recommended initial dosage in paediatric patients 20 kg and greater is 15 mg/kg/day. Avoid dosages*

> 50 mg/kg per day in paediatric patients. No information is available on maximum dose and patients may be initiated on a very low dose if they have had previously had reactions to tiopronin or penicillamine. For all patients, dosage should be titrated according to 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 high recurrence risk are listed in section 3.1.2.

*4.4.1 **Diagnosis***

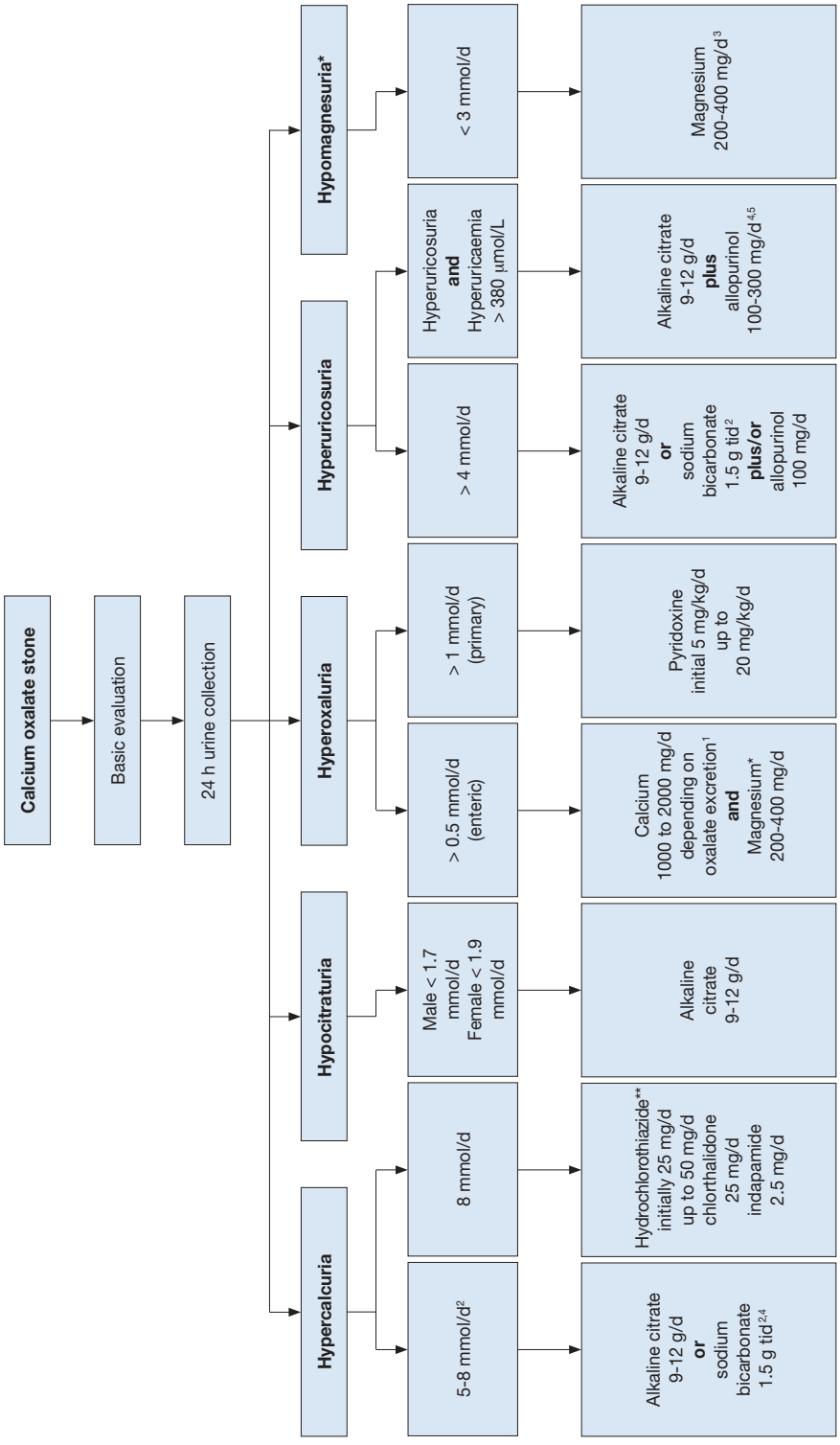
Blood analysis requires measurement of creatinine, sodium, potassium, chloride, ionised calcium (or total calcium + albumin), phosphate, uric acid; and, in the case of increased calcium levels, parathyroid hormone (PTH) and vitamin D. Urinalysis requires measurement of urine volume, urine pH profile,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

*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%), hypomagnesiuria (7-23%), and hypocitraturia (5-29%). However, ranges tend to differ based on ethnicity [568].

- Elevated levels of ionised calcium in serum (or total calcium and albumin) require assessment of intact PTH to confirm or exclude suspected hyperparathyroidism (HPT).
- “Acidic arrest” (circadian urine pH constantly < 5.8) 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.
- Urine pH levels constantly > 5.8 in the day profile may indicate RTA, provided UTI has been excluded. An ammonium chloride loading test confirms RTA and identifies RTA subtype (Section 4.6.5).
- Hypercalciuria may be associated with normocalcemia (idiopathic hypercalciuria, or granulomatous diseases) or hypercalcaemia (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 (> 0.37 mmol/1.73 m^2/day in children) confirms hyperoxaluria.
    - o primary hyperoxaluria (oxalate excretion mostly > 1 mmol/day), appears in three genetically determined forms;
    - o secondary hyperoxaluria (oxalate excretion > 0.5 mmol/day, usually < 1 mmol/day), occurs due to intestinal hyperabsorption of oxalate or extreme dietary oxalate intake;
    - o mild hyperoxaluria (oxalate excretion 0.45-0.85 mmol/day), commonly found in idiopathic calcium oxalate stone formers.
- Hypomagnesiuria (< 3.0 mmol/day) may be related to poor dietary intake or to reduced intestinal absorption (chronic diarrhoea).

Figure 4.2: Diagnostic and 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 [516, 550].*

[5] *Febuxostat 80 mg/d.*

** low evidence (see text)*

***Patients on hydrochlorothiazides should be advised to get their skin checked on a regular basis as they have a higher risk for developing non-melanoma skin cancer (NMSC). In patients with history of NMSC the indication for the intake of hydrochlorothiazides should be thoroughly reviewed.*

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 4.2 summarises the diagnostic algorithm and the pharmacological treatment of calcium oxalate stones [514, 517, 535-538, 541, 542, 544, 547, 550-552, 554-561, 568, 570-572]. 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 [517].

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

Summary of evidence	LE
Thiazide or alkaline citrates or both can reduce stone formation.	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 hypercalcuria*.	Strong
Advise oxalate restriction if hyperoxaluria is present.	Weak
Offer alkaline citrates in enteric hyperoxaluria.	Weak
Offer calcium supplement in enteric hyperoxaluria.	Weak
Advise reduced dietary fat and oxalate in enteric hyperoxaluria.	Weak
Prescribe alkaline citrates and sodium bicarbonate in case of hypocitraturia.	Strong
Prescribe allopurinol in case of hyperuricosuria.	Strong
Offer febuxostat as second-line treatment of hypericosuria.	Strong
Avoid excessive intake of animal protein in hypericosuria.	Strong
Advise restricted intake of salt if there is high urinary sodium excretion.	Strong

** Patients on hydrochlorothiazides 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). In patients with history of NMSC the indication for the intake of hydrochlorothiazides should be thoroughly reviewed [566, 567].*

4.5 Calcium phosphate stones [517, 535, 544, 554, 555, 559, 573]

Some calcium phosphate stone formers are at high risk of recurrence. Further information on identifying high-risk patients is provided in Section 3.1.2.

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.

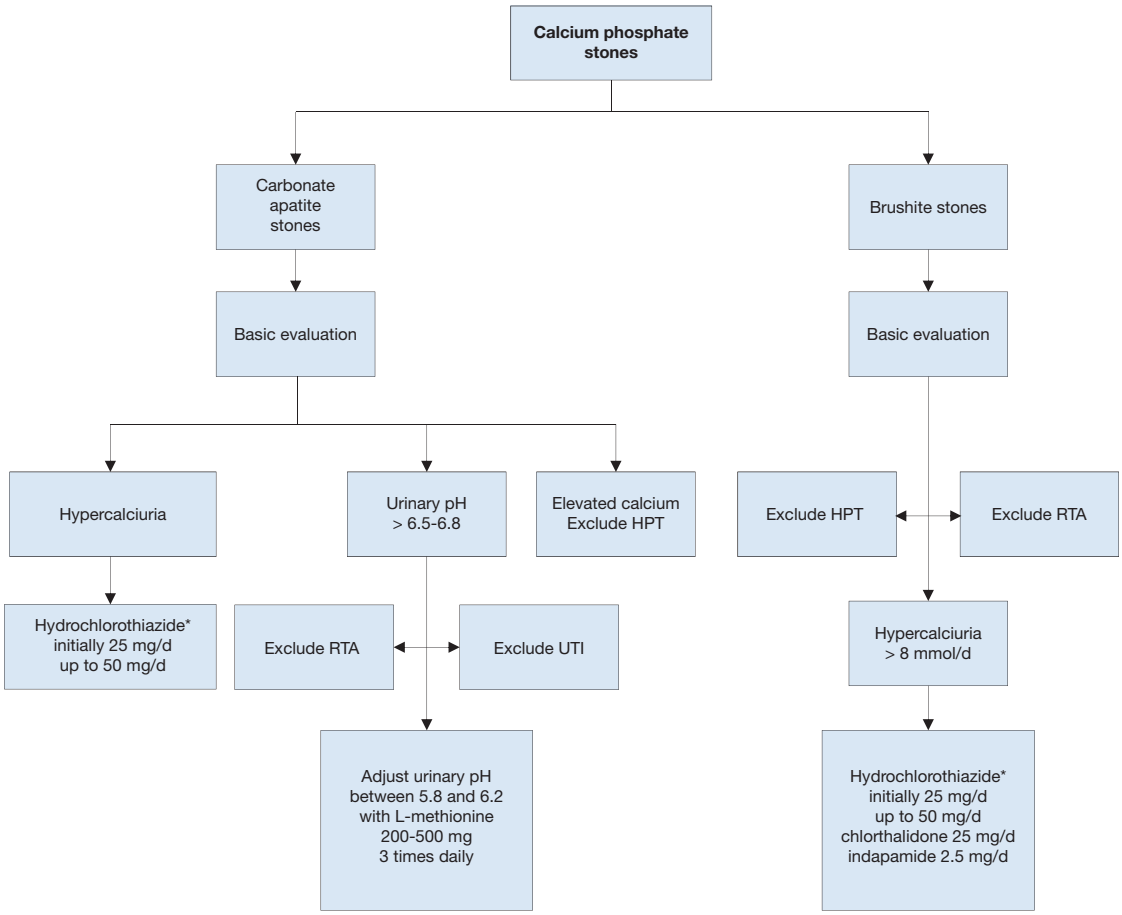
4.5.1 *Diagnosis*

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 profile, specific weight, calcium, phosphate and citrate.

4.5.2 *Interpretation of results and aetiology*

General preventative measures are recommended for fluid intake and diet. The diagnostic and therapeutic algorithm for calcium phosphate stones is shown in Figure 4.3.

Figure 4.3: Diagnostic and therapeutic algorithm for calcium phosphate stones



HPT = hyperparathyroidism; RTA = renal tubular acidosis; UTI = urinary tract infection.

** Patients on hydrochlorothiazides should be advised to get their skin checked on a regular basis as they have a higher risk for developing non-melanoma skin cancer (NMSC). In patients with history of NMSC the indication for the intake of hydrochlorothiazides should be thoroughly reviewed.*

*4.5.3 **Pharmacological therapy** [517, 535, 544, 554, 555, 559, 573]*

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 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 guidelines for the management of calcium phosphate stones***

Summary of evidence	LE
Thiazide is beneficial in case of hypercalciuria.	1a

Recommendation	Strength rating
Prescribe thiazide in case of hypercalciuria.	Strong

4.6 Disorders and diseases related to calcium stones

*4.6.1 **Hyperparathyroidism** [574-576]*

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 hypercalcaemia and hypercalciuria and bone disease. Serum calcium may be mildly elevated and serum PTH may be within the upper normal limits and, 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. Primary HPT can only be cured by surgery.

*4.6.2 **Granulomatous diseases** [577]*

Granulomatous diseases, such as sarcoidosis, may be complicated by hypercalcaemia 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** [553]*

Patients with primary hyperoxaluria (PH) should be referred to specialised centres, 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/m^2 body surface area) and following a circadian drinking regimen.

Therapeutic options for preventing calcium oxalate crystallisation include hyperdiuresis, alkaline citrates and magnesium. However, in end-stage renal failure, PH requires simultaneous liver-kidney transplantation.

Treatment regimens are:

- pyridoxine in PH type I: 5-20 mg/kg/day according to urinary oxalate excretion and patient tolerance;
- alkaline citrate: 9-12 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).

4.6.3.1 Summary of evidence and guideline for the management of primary hyperoxaluria

Summary of evidence	**LE**
Pyridoxine can reduce the urinary oxalate excretion in primary hyperoxaluria.	3

Recommendation	**Strength rating**
Prescribe pyridoxine for primary hyperoxaluria.	Strong

*4.6.4 **Enteric hyperoxaluria** [524, 528, 578-580]*

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 [524];
- restricted fat intake [524];
- calcium supplementation at meal times to enable calcium oxalate complex formation in the intestine [528, 578-580];
- sufficient fluid intake to balance intestinal loss of water caused by diarrhoea;
- alkaline citrates to raise urinary pH and citrate.

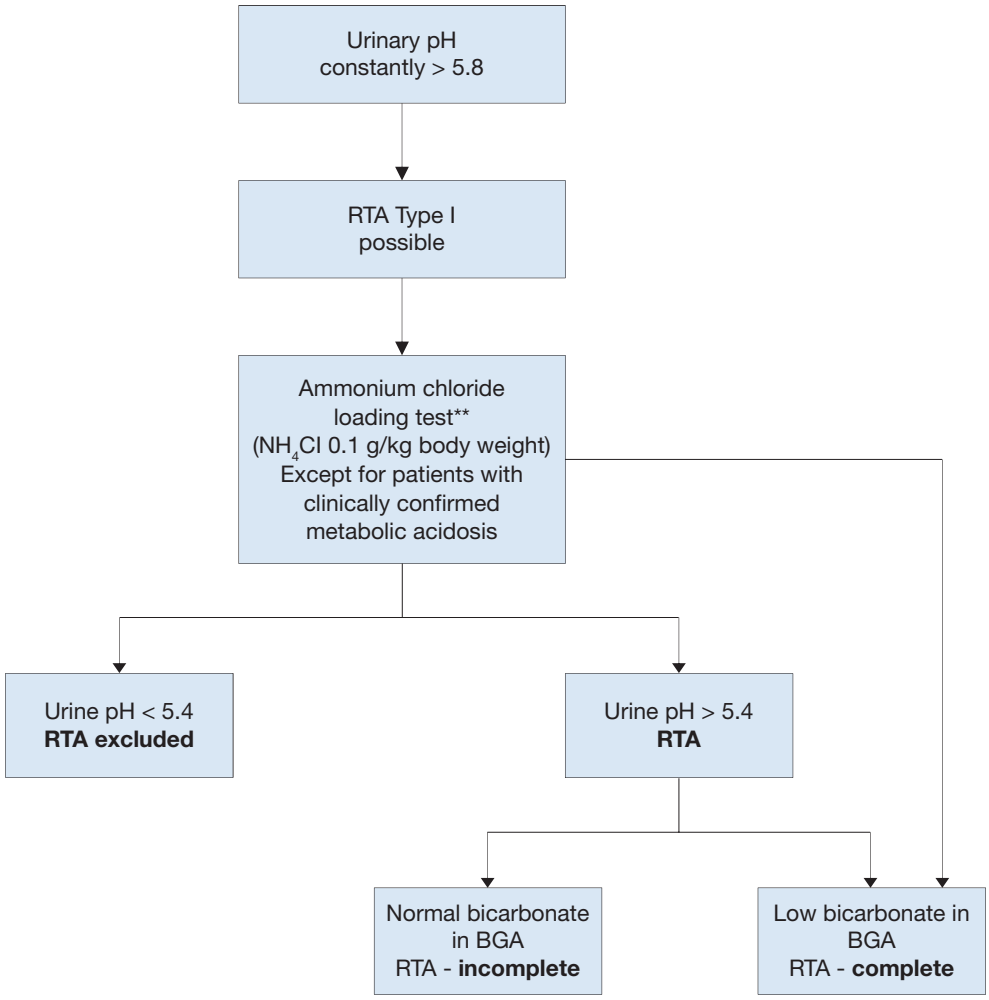
Summary of evidence	LE
Alkaline citrates can be beneficial to replace citrate loss and raise urine pH.	3
Calcium supplements with meals enable calcium oxalate complex formation in the intestine.	2
Reduction in dietary fat and oxalate can be beneficial in intestinal malabsorption.	3

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

*4.6.5 **Renal tubular acidosis** [517, 544, 581, 582]*

Renal tubular acidosis is caused by severe impairment of proton or bicarbonate handling along the nephron. Kidney stone formation most probably occurs in patients with distal RTA type I. Figure 4.4 outlines the diagnosis of RTA. Table 4.7 shows acquired and inherited causes of RTA.

Figure 4.4: Diagnosis of renal tubular acidosis



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

*** An alternative ammonium chloride loading test using NH_4Cl load with 0.05 g/kg body weight over three days might provide similar results and may be better tolerated by the patient. A second alternative in these cases could be the furosemide/fludrocortisone acidification test [583].*

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).

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

More 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 < 320 mg/d	Alkaline citrate, 9-12 g/day divided in three doses ***OR*** Sodium bicarbonate, 1.5 g, three times daily

** Patients on hydrochlorothiazides should be advised to get their skin checked on a regular basis as they have a higher risk of developing non-melanoma skin cancer (NMSC). In patients with history of NMSC the indication for the intake of hydrochlorothiazides should be thoroughly reviewed [566, 567].*

4.6.5.1 Summary of evidence and guidelines for the management of tubular acidosis

Summary of evidence	LE
Alkaline citrates can be beneficial in distal renal tubular acidosis to correct the intracellular acidosis.	2b
Thiazide and alkaline citrates are beneficial for hypercalciuria.	1a

Recommendations	Strength rating
Prescribe alkaline citrates for distal renal tubular acidosis.	Strong
Prescribe thiazide and alkaline citrates for hypercalciuria.	Strong

4.6.6 ***Nephrocalcinosis*** *[584]*

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, 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 [585], daily urine volume, specific weight of urine, and levels of calcium, oxalate, phosphate, uric acid, magnesium, and citrate.

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 [586] and 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 [587]. Low urinary pH may be caused by decreased urinary ammonium excretion (insulin resistance or gout), 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) [587].

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

*4.7.1 **Diagnosis***

Figure 4.5 shows the diagnostic and therapeutic algorithm for uric acid and ammonium urate stones. Blood analysis requires measurement of creatinine, potassium, and uric acid levels. Urinalysis requires measurement of urine volume, urine pH profile, 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. Acidic arrest (circadian urine pH constantly < 5.8) promotes uric acid crystallisation.

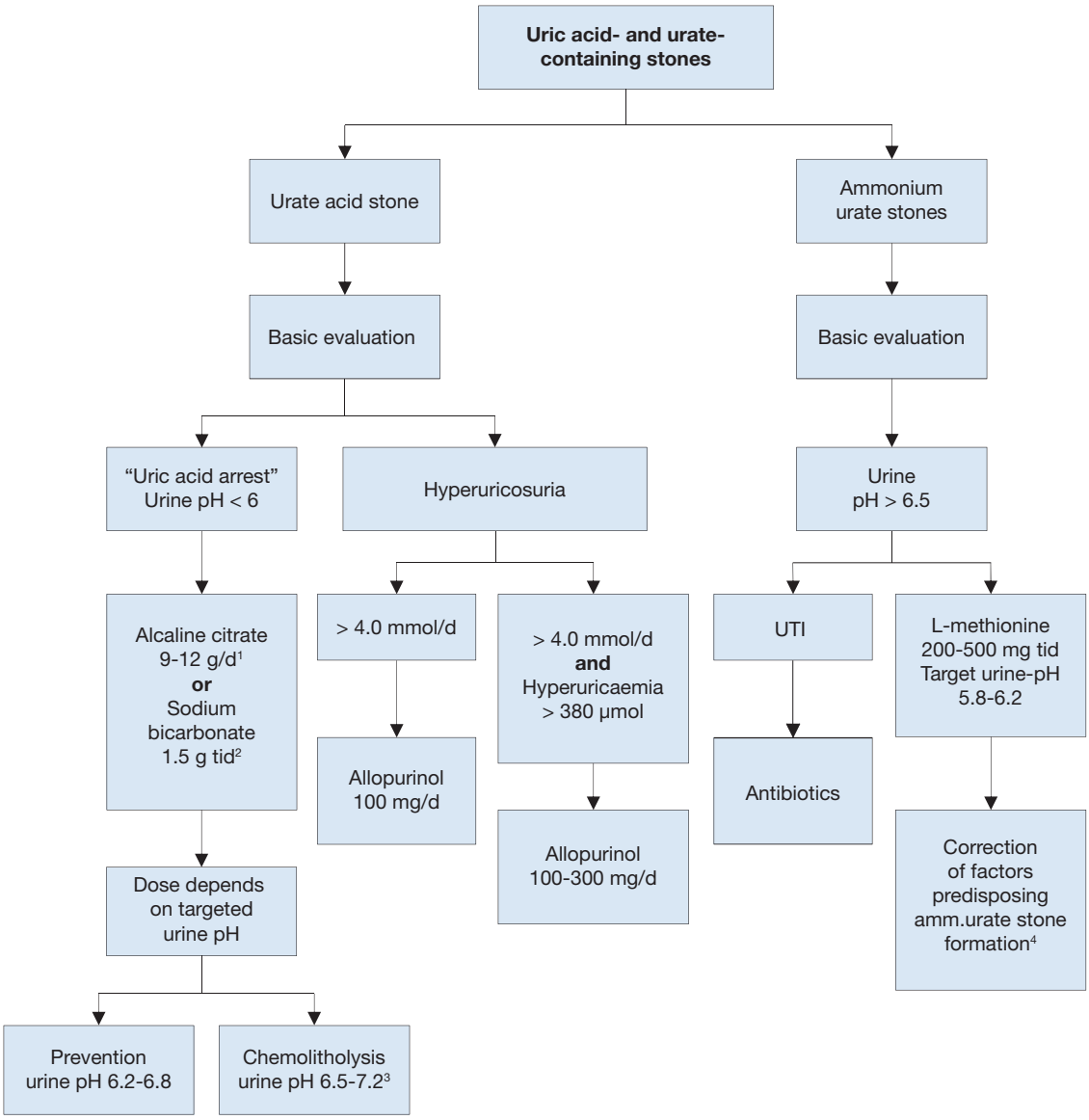
Hyperuricosuria is defined as uric acid excretion > 4 mmol/day in adults or > 0.12 mmol/kg/day in children. Hyperuricaemia may be present, but there is only weak evidence for its association with stone formation [588].

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 [589, 590]. Ammonium urate crystals form in urine at pH > 6.5, high uric acid concentration when ammonium is present [591, 592].

*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 4.5 describes pharmacological treatment [23, 499, 586, 587, 589-598]. 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 [599].

Figure 4.5: Diagnostic and 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 guidelines 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 [600]. There are several factors predisposing patients to struvite stone formation (Table 4.9) [601].

*4.8.1 **Diagnosis***

Blood analysis requires measurement of creatinine, and urinalysis requires repeat urine pH measurements and urine culture.

*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 [602, 603]. *Proteus mirabilis* accounts for more than half of all urease-positive UTIs [604, 605].

*4.8.3 **Specific treatment***

General preventive measures are recommended for fluid intake and diet. Specific measures include complete surgical stone removal [601], short- or long-term antibiotic treatment [606], urinary acidification using methionine [549] or ammonium chloride [607], and advice to restrict intake of urease [608, 609]. For severe infections, acetohydroxamic acid may be an option [608, 609] (Figure 4.6); 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
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

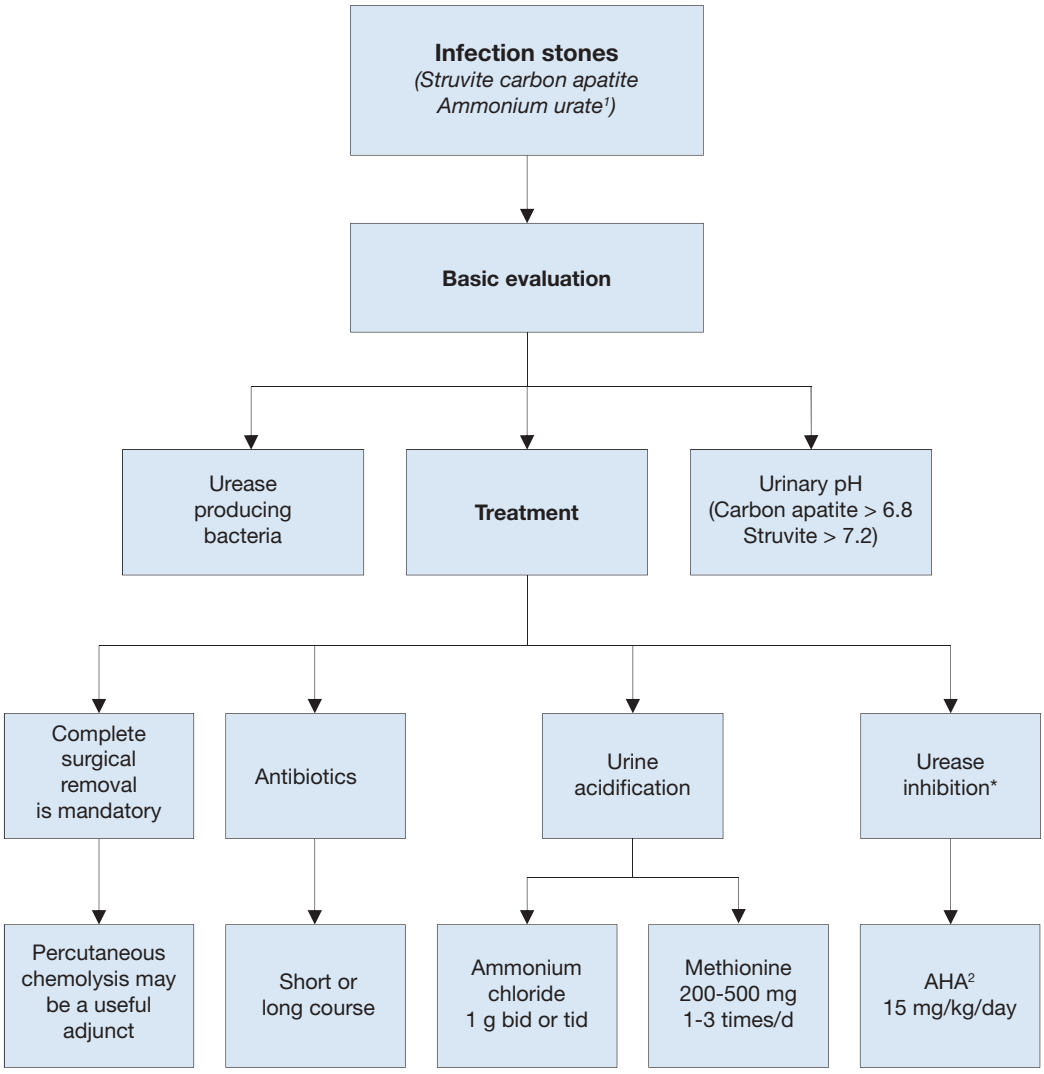
Table 4.9: Factors predisposing to struvite stone formation

• 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 4.6: 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 [35, 610]. All cystine stone formers are deemed at high risk of recurrence and CKD [611, 612].

4.9.1 ***Diagnosis***

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

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 phenotype or genotype of the cystinuric patient, the clinical manifestations are the same [613].
- There is no role for genotyping patients in the routine management of cystinuria [614, 615].
- Reductive therapy targets the disulphide binding in the cystine molecule. For therapy monitoring, it is essential to differentiate between cystine, cysteine and drug-cysteine complexes. Only high-performance liquid chromatography (HPLC)-based analysis differentiates between the different complexes formed by therapy.
- Diagnosis is established by stone analysis. The typical hexagonal crystals are detectable in only 20-25% of urine specimens from patients with cystinuria [616].
- The cyanide nitroprusside colorimetric qualitative test detects the presence of cystine at a threshold concentration of 75 mg/L, with a sensitivity of 72% and specificity of 95%. False-positive results in patients with Fanconi's syndrome, homocystinuria, or those taking various drugs, including infection stones [617].
- 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 [618, 619].

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) [620]. A high level of diuresis is of fundamental importance, aiming for a 24-hour urine volume of > 3 L [613, 616, 620, 621]. A considerable fluid intake evenly distributed throughout the day is necessary.

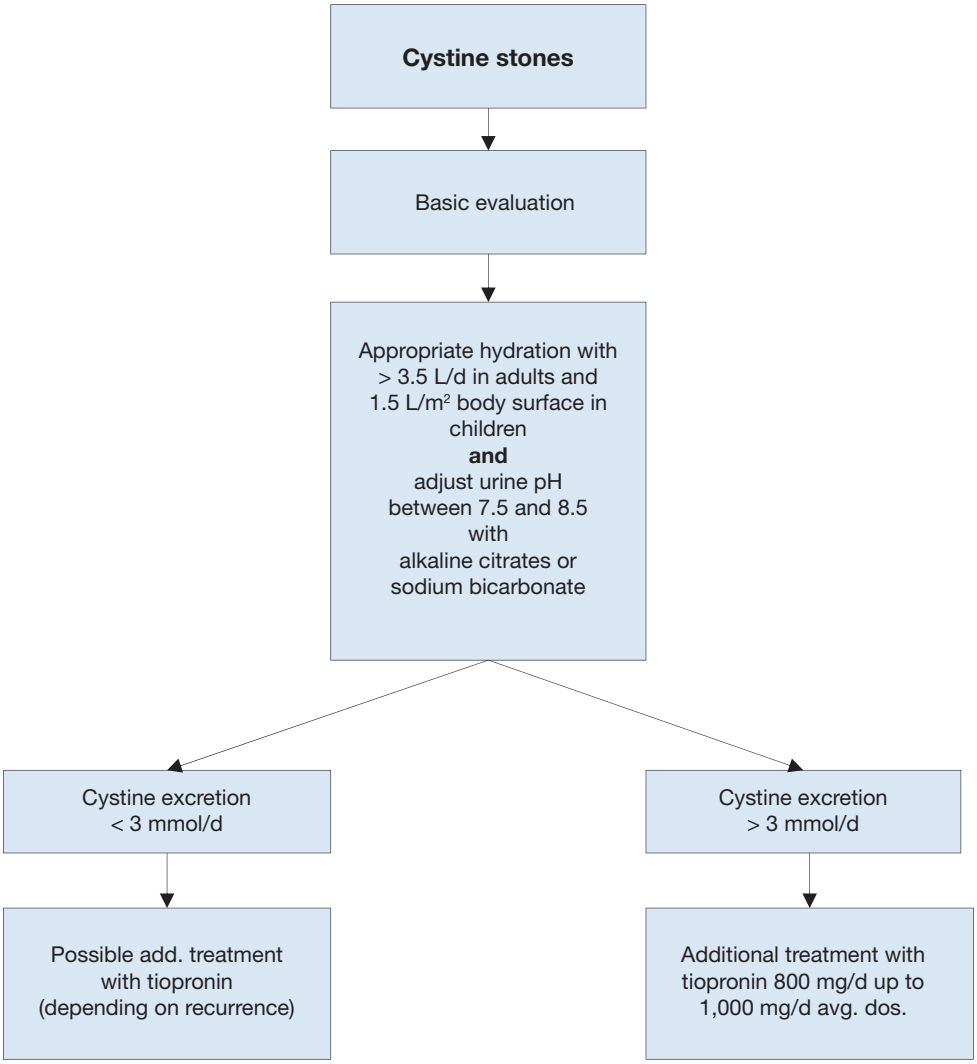
4.9.2.1 Pharmacological treatment of cystine stones

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 3.5 L/day in adults, or 1.5 L/m^2 body surface area in children [613, 616, 620, 621].

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, put 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 [613, 616, 620, 621].

Figure 4.7: Metabolic management of cystine stones



4.9.3 Summary of evidence and guidelines 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, 800-1,000 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 for patients with cystine excretion < 3 mmol/day.	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, 800-1,000 mg/day.	Strong

4.10 2,8-Dihydroxyandenine stones and xanthine stones

All 2,8-Dihydroxyadenine and xanthine stone formers are considered to be 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 [622]. High-dose allopurinol or febuxostat are important options, but should be given with regular monitoring [623].

*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 [535, 624] (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 • Allopurinol • Aluminium magnesium hydroxide • Ascorbic acid • Calcium • Furosemide • 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 [625].

4.13 Unknown stone composition [16]

An accurate medical history is the first step towards identifying risk factors as summarised below (see Chapter 4.13.1).

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

Blood analysis demonstrates severe metabolic and organic disorders, such as renal insufficiency, HPT or other hypercalcaemic states and hyperuricaemia. In children, hyperoxalaemia should additionally be screened for.

Urinalysis is performed routinely with a dipstick test as described above. Urine culture is required if there are signs of infection. Constant urine pH < 5.8 in the daily profile may indicate acidic arrest, which could promote uric acid crystallisation. Persistent urine pH > 5.8 in the daily profile may indicate RTA, if UTI is excluded [581, 582].

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 [617, 626].

Following this programme, the most probable stone type can be assumed, and specific patient evaluation can follow. However, if any expulsed stone material is available, it should be analysed by diagnostic confirmation or correction.

4.13.1 ***Recommendations for investigations for the assessment of patients with stones of unknown composition*** [17, 23, 66, 535]

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	• Urine pH profile (measurement after each voiding, minimum four times daily) • Dipstick test: leukocytes, erythrocytes, nitrites, protein, urine pH, 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

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6. CONFLICT OF INTEREST

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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