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. Management of bladder stones is not addressed in these guidelines. 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.

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 in a number of versions for mobile devices. These are abridged versions which may require consultation together with the full text versions. Also a number of scientific publications are 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 2017 document presents a limited update of the 2016 publication of the EAU Urolithiasis Guidelines.

1.4.2 Summary of changes

The literature for the entire document has been assessed and updated, whenever relevant (see Methods section below).

Key changes for the 2017 publication:

3.4.1.1 Renal colic

Summary of evidence	**LE**
Administration of daily α-blockers seems to reduce colic episodes, although controversy remains in the published literature.	1b

3.4.2.1.3.2 Best clinical practice

Summary of evidence - Number of shock waves, energy setting and repeat treatment sessions	**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 1.5Hz.	1a

3.4.2.2 Indication for active stone removal of renal stones

Recommendation	**GR**
Offer active treatment for renal stones in case of stone growth, *de novo* obstruction, associated infection, and acute and/or chronic pain.	C

3.4.3.1.2 Pharmacological treatment, Medical expulsive therapy (MET)

Summary of evidence	LE
Medical expulsion therapy (MET) seems to be efficacious treating patients with ureteric stones who are amenable to conservative management. The greatest benefit might be among those with larger (distal) stones.	1a

Recommendations	LE	GR
Select patients for an attempt at spontaneous passage or MET, based on well-controlled pain, no clinical evidence of sepsis, and adequate renal functional reserve.	4	C
Offer α-blockers as MET as one of the treatment options, in particular for (distal) ureteral stones > 5 mm.	1a	A
Counsel patients regarding the controversies in the literature, attendant risks of MET, including associated drug side effects. Inform the patient that α-blockers as MET are administered off-label†**.	1b	A*

† It is not known if tamsulosin harms the human foetus or if it is found in breast milk.

**Upgraded based on panel consensus.*

***MET in children cannot be recommended due to the limited data in this specific population.*

3.4.3.1.4.1.2 Best clinical practice in ureterenoscopy

Summary of evidence	LE
In ureterorenoscopy (URS) (in particular for renal stones), pre-stenting has been shown to improve outcome.	1b

3.4.3.3 Selection of procedure for active removal of ureteral stones

Recommendation	GR
In obese patients ureterorenoscopy is a safe and efficient option to remove renal stones.	2b
Ureterorenoscopy in morbidly obese patients have significantly higher complication rates as compared to normal weight patients.	1a

2. METHODS

2.1 Data identification

For the 2017 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, randomised controlled trials (RCTs), and prospective non-randomised comparative studies only) published in the English language. The search was restricted to articles published between September 1st 2015 and October 12th, 2016. Databases covered by the search included Medline, EMBASE and the Cochrane Libraries. A total of 751 unique records were identified, and screened for relevance. The search strategy is published online: http://uroweb.org/guideline/urolithiasis/?type=appendices-publications.

In addition to the new literature identified through the electronic searches, the authors included one additional, more recent, article as of significant relevance for two sections (3.4.1.1 Renal colic & 3.4.3.1.2 Pharmacological treatment, Medical expulsive therapy (MET) [4].

Two sections of the text have been updated based on two systematic reviews (SRs). These SRs were performed using standard Cochrane SR methodology; http://www.cochranelibrary.com/about/about-cochranesystematic-reviews.html.

Systematic review topics:

- Tract sizes in miniaturized percutaneous nephrolithotomy: A systematic review [5].
- What are the benefits and harms of ureterenoscopy (URS) compared with shock-wave lithotripsy (SWL) in the treatment of upper ureteral stones (UUS): A systematic review [6].
-

Recommendations in this text are assessed according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [7]. Additional methodology information can be found in the general Methodology section of this print, and online at the EAU website: http://uroweb.org/guidelines/.

A list of Associations endorsing the EAU Guidelines can also be viewed on line at the above address.

2.2 Review

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

2.3 Future goals

Further results on ongoing and new SRs will be included in the 2018 update of the Urolithiasis Guidelines.

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 US, 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].

Stones can be classified into those caused by: infection, or non-infectious causes (infection- and non-infection stones); genetic defects [12]; or adverse drug effects (drug stones) (Table 3.1.1).

Table 3.1.1: Stones classified by aetiology*

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

**See Section 4.4.2*

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 3.1.2 lists the clinically most relevant substances and their mineral components.

Table 3.1.2: Stone composition

Chemical name	Mineral name	Chemical formula
Calcium oxalate monohydrate	Whewellite	$CaC_2O_4.H_2O$
Calcium oxalate dihydrate	Wheddelite	$CaC_2O_4.2H_2O$
Basic calcium phosphate	Apatite	$Ca_{10}(PO_4)_6.(OH)_2$
Calcium hydroxyl phosphate	Carbonite apatite	$Ca_5(PO_3)_3(OH)$
b-tricalcium phosphate	Whitlockite	$Ca_3(PO_4)_2$
Carbonate apatite phosphate	Dahllite	$Ca_5(PO_4)_3OH$
Calcium hydrogen phosphate	Brushite	$CaHPO_4.2H_20$
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	Struvite	$MgNH_4PO_4.6H_2O$
Magnesium acid phosphate trihydrate	Newberyite	$MgHPO_4.3H_2O$
Magnesium ammonium phosphate monohydrate	Dittmarite	$MgNH_4(PO_4).1H_2O$
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 • Substances impairing urine composition (Section 4.11)	
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, and is imperative for pharmacological treatment.

About 50% of recurrent stone formers have just one lifetime recurrence [10, 13]. Highly recurrent disease is observed in slightly more than 10% of patients. Stone type and disease severity determine low- or high risk of recurrence (Table 3.1.3) [14, 15].

Table 3.1.3: High-risk stone formers [14-25]

General factors
Early onset of urolithiasis (especially children and teenagers)
Familial stone formation
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) and bariatric surgery [20]
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 factors
Chronic lead exposure

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, 26-28].

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 3.2.1), which varies according to mineral composition [28]. 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 3.4.1.4.4) [27, 28].

Table 3.2.1: X-ray characteristics

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

Stratification of stones according to aetiology, composition and risk of recurrence is addressed in Section 3.1.

3.3 Diagnostic evaluation

*3.3.1 **Diagnostic imaging***

The clinical situation will inform on the most appropriate imaging modality, which will differ for a suspected ureteral stone or a suspected renal stone.

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 [29].

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 calices, pelvis, and pyeloureteric and vesicoureteric junctions (US with filled bladder), as well as in patients with upper urinary tract dilatation. Ultrasound has a sensitivity of 45% and specificity of 94% for ureteric stones and a sensitivity of 45% and specificity of 88% for renal stones [30, 31].

The sensitivity and specificity of KUB (kidney-ureter-bladder radiography) is 44-77% and 80-87%, respectively [32]. Kidney-ureter-bladder radiography should not be performed if NCCT is considered [33]. However, KUB is helpful in differentiating between radiolucent and radiopaque stones and be used for comparison during follow-up.

Recommendation	LE	GR
With fever or solitary kidney, and when diagnosis is doubtful, immediate imaging is indicated.	4	A*

**Upgraded following panel consensus.*

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 computed tomography 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 [34].

Recommendation	LE	GR
Following initial ultrasound assessment, use non-contrast-enhanced computed tomography to confirm stone diagnosis in patients with acute flank pain, as it is superior to intravenous urography.	1a	A

Non-contrast-enhanced computed tomography can detect uric acid and xanthine stones, which are radiolucent on plain films, but not indinavir stones [35]. Non-contrast-enhanced computed tomography can determine stone density, inner structure of the stone and skin-to-stone distance and surrounding anatomy; all of which affect selection of treatment modality [28, 36-38]. 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 [39-42].

Radiation risk can be reduced by low-dose CT, which may, however, be difficult to introduce in standard clinical practice [43, 44]. In patients with a body mass index (BMI) < 30, low-dose CT has been shown to have a sensitivity of 86% for detecting ureteric stones < 3 mm and 100% for calculi > 3 mm [45]. A meta-analysis of prospective studies [46] has shown that low-dose CT diagnosed urolithiasis with a pooled sensitivity of 96.6% (95% CI: 95.0-97.8) and specificity of 94.9% (95% CI: 92.0-97.0).

Dual-energy CT can differentiate uric acid containing stones from calcium-containing stones [47].

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 as well as the level of an obstruction. Non-contrast-enhanced 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 as standard-dose protocols with the exception of detection of very small stones or stones in obese patients [45, 46].

A small randomised study showed that in supine PNL, pre-operative planning using CT compared to IVU, resulted in easier access and shorter operating times [48].

In case stone removal is planned, the renal collecting system needs to be assessed.

Recommendations	LE	GR
Perform a contrast study if stone removal is planned and the anatomy of the renal collecting system needs to be assessed.	3	A*
Use enhanced computed tomography in complex cases because it enables 3D reconstruction of the collecting system, as well as measurement of stone density and skin-to-stone distance. Intravenous urography may also be used.	2a	C

**Upgraded based on panel consensus.*

3.3.2 ***Diagnostics - metabolism-related***

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

Table 3.3.1: Recommendations: basic laboratory analysis - emergency urolithiasis patients [15, 16, 49, 50]

Recommendations	GR
Urine	
Dipstick test of spot urine sample	A*
• red cells • white cells • nitrite • approximate urine pH	A
Urine microscopy and/or culture	
Blood	
Serum blood sample • creatinine • uric acid • (ionised) calcium • sodium • potassium	A*
Blood cell count • C-reactive protein (CRP)	
Perform a coagulation test (partial thromboplastin time [PTT] and international normalised ratio [INR]) if intervention is likely or planned.	A*

**Upgraded based on panel consensus.*

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, and blood coagulation time can be omitted.

Only patients at high risk for stone recurrence should undergo a more specific analytical programme [15]. 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 below (see 3.2.2). 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 [49, 51].

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) [52-54]. Equivalent results can be obtained by polarisation microscopy. Chemical analysis (wet chemistry) is generally deemed to be obsolete [52].

Recommendations	LE	GR
Perform stone analysis in first-time formers using a valid procedure (X-ray diffraction or infrared spectroscopy).	2	A
Repeat stone analysis in patients: • presenting with recurrent stones despite drug therapy; • with early recurrence after complete stone clearance; • with late recurrence after a long stone-free period because stone composition may change.	2	B

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

3.3.3.1 Diagnostic imaging during pregnancy

In pregnant women diagnostic imaging (exposure to ionising radiation) might be associated with teratogenic risks and development of (childhood) malignancies. The risk for the child crucially depends on gestational age and radiation dose delivered. X-ray imaging during the first trimester should be reserved for patients in which alternative imaging methods have failed [55, 56].

Ultrasound (when necessary using change 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 [57].

Magnetic resonance imaging (MRI) can be used, as a second-line procedure, to define the level of urinary tract obstruction, and to visualise stones as a filling defect [58, 59].

Low dose CT protocols reduce the radiation exposure and are currently recommended to be used judicially in pregnant women as a last-line option [60, 61].

Recommendations	LE	GR
Use ultrasound as the preferred method of imaging in pregnant women.	1a	A*
In pregnant women, use magnetic resonance imaging as a second-line imaging modality.	3	C
In pregnant women, use low-dose computed tomography as a last-line option.	3	C

**Upgraded following panel consensus.*

3.3.3.2 Children

Children with urinary stones have a high risk of recurrence; therefore, standard diagnostic procedures for high-risk patients apply (Section 3.1.3 and Chapter 4). The most common non-metabolic disorders facilitating stone formation are vesicoureteral reflux (VUR), UPJ obstruction, neurogenic bladder, and other voiding difficulties [62].

Summary of evidence	LE
In children, the most common non-metabolic disorders facilitating stone formation are vesicoureteral reflux, ureteropelvic junction obstruction, neurogenic bladder, and other voiding difficulties [62].	4

3.3.3.2.1 Diagnostic imaging

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 [63-65]. Again, the principle of ALARA (As Low As Reasonably Achievable) should be observed.

3.3.3.2.2 Ultrasound

Ultrasound is the primary imaging technique [63] 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 [66-70].

Colour Doppler US shows differences in the ureteric jet [67] and resistive index of the arciform arteries of both kidneys, which are indicative of the grade of obstruction [68].

Nevertheless, US fails to identify stones in > 40% of children [69-72] (LE: 4), and provides limited information on renal function.

3.3.3.2.3 Plain films (KUB radiography)

KUB radiography can help to identify stones and their radiopacity, and facilitate follow-up.

3.3.3.2.4 Intravenous urography (IVU)

The radiation dose for IVU is comparable to that for voiding cystourethrography (0.33 mSV) [73]. However, the need for contrast medium injection is a major drawback.

3.3.3.2.5 Helical computed tomography (CT)

Recent low-dose CT protocols have been shown to significantly reduce radiation exposure [42, 74].

In children, only 5% of stones escape detection by NCCT [60, 67, 74]. Sedation or anaesthesia is rarely needed with modern high-speed CT equipment.

3.3.3.2.6 Magnetic resonance urography (MRU)

Magnetic resonance urography 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 [75].

Recommendations	GR
In all children, complete a metabolic evaluation based on stone analysis.	A
Collect stone material for analysis to classify the stone type.	A*
In children, use ultrasound as first-line imaging modality when a stone is suspected; it should include the kidney, fluid-filled bladder and the ureter next to the kidney and the (filled) bladder.	B
If ultrasound will not provide the required information, perform a kidney-ureter-bladder radiography (or low-dose non-contrast-enhanced computed tomography).	B

**Upgraded following panel consensus.*

3.4 Disease management

*3.4.1 **Management of patients with renal or ureteral stones***

Treatment decisions for upper urinary tract calculi are based on several general aspects such as stone composition, stone size, and symptoms.

3.4.1.1 Renal colic

Pain relief

Pain relief is the first therapeutic step in patients with an acute stone episode [76].

Non-steroidal anti-inflammatory drugs (NSAIDs) including metamizole (dipyrone), a pyrazolone NSAID, are effective in patients with acute stone colic [77, 78], and have better analgesic efficacy than opioids. The addition of antispasmodics to NSAIDS does not result in better pain control and data on other types of non-opioid, non-NSAID medication is scarce [79]. 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. 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 [80, 81].

Opioids, particularly pethidine, are associated with a high rate of vomiting compared to NSAIDs, and carry a greater likelihood of further analgesia being needed [82] (see below). If an opioid is used, it is recommended that it is not pethidine.

Prevention of recurrent renal colic

Facilitation of passage of ureteral stones is discussed in Section 3.4.3.1.2.

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 [83, 84]. Although diclofenac can affect renal function in patients with already reduced function, it has no functional effect in patients with normal renal function [85] (LE: 1a).

In a double-blind, placebo-controlled trial, recurrent pain episodes of stone colic were significantly fewer in patients treated with NSAIDs (as compared to no NSAIDs) during the first seven days of treatment [86]. Contrary to earlier findings, daily α-blockers did not reduce recurrent pain or analgesia requirements in patients with distal ureteral stones in two recent large high-quality studies [87, 88] (Section 3.4.3.1.2). The most recent SR and meta-analysis by Hollingsworth *et al.* [4] addressed pain reduction as a secondary outcome and concluded that MET seems efficacious in reducing pain episodes of patients with ureteric stones who are amenable to conservative management. Patients benefitting most might be those with larger (distal) stones.

If analgesia cannot be achieved medically, drainage, using stenting or percutaneous nephrostomy or stone removal, should be performed.

Recommendations	**GR**
Provide immediate pain relief in acute stone episodes.	A
Whenever possible, offer a non-steroidal anti-inflammatory as the first drug of choice. e.g. metamizol (dipyrone); alternatively, depending on cardio-vascular risk factors, diclofenac*, indomethacin or ibuprofen**.	A
Offer hydromorphine, pentazocine or tramadol as a second choice.	C

**Affects glomerular filtration rate (GFR) in patients with reduced renal function (LE: 2a).*

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

Summary of evidence	**LE**
Administration of daily α-blockers seems to reduce colic episodes, although controversy remains in the published literature.	1b
For symptomatic ureteral stones, urgent stone removal as first-line treatment is a feasible option in selected cases (see text).	1b

3.4.1.2 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 ureteric stenting has more complications than percutaneous nephrostomy [89, 90].

Only one RCT [91] compared different modalities of decompression of acute infected hydronephrosis. The complications of percutaneous nephrostomy insertion have been reported consistently, but those of ureteric stent insertion are less well described [89]. 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 appropriate antibiotic regimen; however, at the cost of longer hospital stay and higher analgesic requirements [92].

In children, ureteric stents might have some advantage compared to PCN in case of acute anuria [93].

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

Recommendations	LE	GR
Urgently decompress the collecting system in case of sepsis with obstructing stones, using percutaneous drainage or ureteral stenting.	1b	A
Delay definitive treatment of the stone until sepsis is resolved.	1b	A

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 test. Although clinically well accepted, the impact of a second antibiogram test on treatment outcome has not yet been evaluated. Intensive care might become necessary [94].

Recommendations	GR
Collect (again) urine for antibiogram test following decompression.	A*
Start antibiotics immediately (+ intensive care if necessary).	
Re-evaluate antibiotic regimen following antibiogram findings.	

**Upgraded based on panel consensus.*

3.4.1.3 General recommendations and precautions for stone removal

3.4.1.3.1 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, via a stent or percutaneous nephrostomy, before starting stone removal.

Recommendation	GR
Obtain a urine culture or perform urinary microscopy before any treatment is planned.	A*

**Upgraded following panel consensus.*

Perioperative antibiotic prophylaxis

For prevention of infection following ureterenoscopy and percutaneous stone removal, no clear-cut evidence exists [95, 96]. In a review of a large database of patients undergoing percutaneous nephrolithotomy, it was found that in patients with negative baseline urine culture, antibiotic prophylaxis significantly reduced the rate of post-operative fever and other complications [97]. Single dose administration was found to be sufficient [98].

Recommendations	LE	GR
Exclude or treat urinary tract infections prior to stone removal.	1b	A
Offer perioperative antibiotic prophylaxis to all patients undergoing endourological treatment.	1b	A*

3.4.1.3.2 Antithrombotic therapy and stone treatment

Patients with a bleeding diathesis, or receiving antithrombotic therapy, should be referred to an internist for appropriate therapeutic measures before deciding on stone management [99-103]. In patients with an uncorrected bleeding diathesis, the following are at elevated risk of haemorrhage or perinephric haematoma (PNH) (high-risk procedures):

- shock wave lithotripsy (SWL) (hazard ratio of PNH up to 4.2 during anticoagulant/antiplatelet medication [104] [LE: 2]);
- percutaneous nephrolithotripsy;
- percutaneous nephrostomy;
- laparoscopic surgery;
- open surgery [99, 105, 106].

Shock wave lithotripsy is feasible and safe after correction of the underlying coagulopathy [107-111]. In the case of an uncorrected bleeding disorder or continued antithrombotic therapy, ureterorenoscopy (URS), in contrast to SWL and PNL, might offer an alternative approach since it is associated with less morbidity [112-116]. Only data on flexible ureterorenoscopy are available which support the superiority of URS in the treatment of proximal ureteric stones [113, 117].

Table 3.4.1: Risk stratification for bleeding [101-103, 118]

Low-risk bleeding procedures	Cystoscopy Flexible cystoscopy Ureteral catheterisation Extraction of ureteric stentUreterenoscopy
High-risk bleeding procedures	Shock wave lithotripsy Percutaneous nephrostomy Percutaneous nephrolithotripsy

Table 3.4.2: Suggested strategy for antithrombotic therapy in stone removal [101-103]
(In collaboration with cardiologist/internist weigh the risks and benefits of discontinuation of therapy, vs. delaying elective surgical procedures.)

	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 - GPIIb/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 - GPIIb/IIIa inhibitors.

Recommendations	LE	GR
Offer active surveillance to patients at high risk for thrombotic complications in the presence of an asymptomatic calyceal stone.	4	C
Decide on temporary discontinuation, or bridging of antithrombotic therapy in high-risk patients, in consultation with the internist.	3	B
Prefer retrograde (flexible) URS if stone removal is essential and antithrombotic therapy cannot be discontinued, since it is associated with less morbidity.	2a	A*

**Upgraded based on panel consensus.*

3.4.1.3.3 Obesity

Obesity can cause a higher risk due to anesthesiological requirements, and a lower success rate after SWL and PNL.

3.4.1.3.4 Stone composition

Stones composed of brushite, calcium oxalate monohydrate, or cystine are particularly hard as well as stones with high density on NCCT [36]. Percutaneous nephrolithotomy or ureterorenoscopy (RIRS) and URS are alternatives for removal of large SWL-resistant stones.

Recommendations	LE	GR
Consider the 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 computed tomography (CT). Stones with density > 1,000 HU on non-contrast-enhanced CT are less likely to be disintegrated by shock wave lithotripsy.	2-4	B*
Attempt to dissolve radiolucent stones (See Section 3.4.2.1.2.2).	2a	B

**Upgraded in parts based on panel consensus.*

3.4.1.3.5 Steinstrasse

Steinstrasse is an accumulation of stone fragments or stone gravel in the ureter, may interfere with the passage of urine [119]. Steinstrasse occurs in 4-7% cases of SWL [120], and the major factor in in the development of steinstrasse formation is stone size [121].

A major problem of steinstrasse is ureteral obstruction, which may be silent in up to 23% of cases. A meta-analysis including eight RCTs (n = 876) suggests a benefit of stenting before SWL in terms of steinstrasse formation, but does not result in a benefit on stone-free rates (SFRs) or less auxiliary treatments [122-124].

When steinstrasse is asymptomatic, conservative treatment is an initial option. Medical expulsion therapy significantly increases stone expulsion and reduces the need for endoscopic intervention [125, 126].

Summary of evidence	LE
Medical expulsion therapy increases the stone expulsion rate of steinstrasse [125].	1b
When spontaneous passage is unlikely, further treatment of steinstrasse is indicated.	4
Shock wave lithotripsy is indicated in asymptomatic and symptomatic cases, with no evidence of urinary tract infection (UTI), when large stone fragments are present [127].	4
Ureterenoscopy is effective for the treatment of steinstrasse [128].	3
Placement of a percutaneous nephrostomy tube or ureteral stent is indicated for symptomatic ureteric obstruction with/without urinary tract infection.	4

Recommendations	LE	GR
Treat steinstrasse associated with urinary tract infection/fever preferably with percutaneous nephrostomy.	4	C
Treat steinstrasse when large stone fragments are present with shock wave lithotripsy or ureterorenoscopy.	4	C

3.4.2 Specific stone management in 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.

3.4.2.1 Types of treatments

3.4.2.1.1 Conservative treatment (Observation)

Observation of renal stones, especially in calices, depends on their natural history (Section 3.4.2.2). The recommendations provided are not supported by high level literature. 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 stones growing > 5 mm [129].

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

Recommendation	GR
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]).	A*

**Upgraded based on panel consensus.*

3.4.2.1.2 Chemolysis

3.4.2.1.2.1 Percutaneous irrigation chemolysis

Percutaneous chemolysis is rarely used nowadays. Percutaneous irrigation chemolysis may be an option for infection- and uric acid stones [130, 131]. For dissolution of struvite stones, Suby's G solution (10% hemiacidrin; pH 3.5-4) can be used [132].

3.4.2.1.2.2 Oral chemolysis

Stones composed of uric acid, but not sodium or ammonium urate, 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 [131, 133]. 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. Monitoring of radiolucent stones during therapy is the domain of US; however, repeat-NCCT might be necessary.

In the case of uric acid obstruction of the collecting system, oral chemolysis in combination with urinary drainage is indicated [134]. A combination of alkalinisation with tamsulosin can increase the frequency of spontaneous passage of distal ureteral uric acid stones [134].

Recommendations	GR
Inform the patient how to modify the dosage of alkalising medication according to urine pH, which is a direct consequence of such medication.	A
Inform the patient how to monitor urine pH by dipstick three times a day (at regular intervals). Morning urine must be included.	A
Carefully monitor radiolucent stones during/after therapy.	A*
Inform the patient of the significance of compliance.	A

**Upgraded based on panel consensus.*

3.4.2.1.3 Extracorporeal shock wave lithotripsy (SWL)

Success depends on the efficacy of the lithotripter and the following factors:

- size, location (ureteral, pelvic or calyceal), and composition (hardness) of the stones (Section 3.4.3.2);
- patient's habitus (Section 3.4.2.2);
- performance of SWL (best practice, see below).

Each of these factors significantly influence retreatment rate and final outcome of SWL.

3.4.2.1.3.1 Contraindications of extracorporeal shock wave lithotripsy

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

- pregnancy, due to the potential effects on the foetus [135];
- bleeding diatheses, which should be compensated for at least 24 hours before and 48 hours after treatment [136];
- uncontrolled UTIs;

- severe skeletal malformations and severe obesity, which prevent targeting of the stone;
- arterial aneurysm in the vicinity of the stone [137];
- anatomical obstruction distal to the stone.

3.4.2.1.3.2 Best clinical practice

Stenting

Routine use of internal stents before SWL does not improve SFRs, nor lowers the number of auxiliary treatments. It may, however, reduce formation of steinstrasse [122, 124] (LE: 1b).

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 [138].

Shock wave rate

Lowering shock wave frequency from 120 to 60-90 shock waves/min improves SFRs [139-144]. Tissue damage increases with shock wave frequency [145-150].

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.

Starting SWL on a lower energy setting with stepwise power (and SWL sequence) ramping can achieve vasoconstriction during treatment [147], which prevents renal injury [151-153]. Animal studies [154] and a prospective randomised study [155] 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 [156].

There are no conclusive data on the intervals required between repeated SWL sessions. However, clinical experience indicates that repeat sessions are feasible (within 1 day for ureteral stones).

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 1.5Hz.	1a

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 [157]. Ultrasound gel is probably the most widely used agent available for use as a lithotripsy coupling agent [158].

Recommendation	**LE**	**GR**
Ensure correct use of the coupling agent because this is crucial for effective shock wave transportation.	2a	B

Procedural control

Results of treatment are operator dependent, and better results are obtained by experienced clinicians. During the procedure, careful imaging control of localisation contributes to outcome quality [159].

Recommendation	**LE**	**GR**
Maintain careful fluoroscopic and/or ultrasonographic monitoring during shock wave lithotripsy.	3	A*

**Upgraded based on panel consensus.*

Pain control

Careful control of pain during treatment is necessary to limit pain-induced movements and excessive respiratory excursions [160-162].

Recommendation	LE	GR
Use proper analgesia because it improves treatment results by limiting pain-induced movements and excessive respiratory excursions.	4	C

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) [50, 163, 164].

Recommendation	LE	GR
In the case of infected stones or bacteriuria, prescribe antibiotics prior to shock wave lithotripsy.	4	C

Medical therapy after extracorporeal shock wave lithotripsy
In spite of conflicting results, most RCTs and several meta-analyses 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 [165-172].

3.4.2.1.3.3 Complications of extracorporeal shock wave lithotripsy
Compared to PNL and URS, there are fewer overall complications with SWL [173, 174] (Table 3.4.1).

Table 3.4.1: Shock wave lithotripsy-related complications [120, 175-188]

Complications			%	Ref.
Related to stone fragments	Steinstrasse		4 - 7	[120, 175, 176]
	Regrowth of residual fragments		21 - 59	[177, 178]
	Renal colic		2 - 4	[179]
Infectious	Bacteriuria in non-infection stones		7.7 - 23	[177, 180]
	Sepsis		1 - 2.7	[177, 180]
Tissue effect	Renal	Haematoma, symptomatic	< 1	[181]
		Haematoma, asymptomatic	4 - 19	[181]
	Cardiovascular	Dysrhythmia	11 - 59	[177, 182]
		Morbid cardiac events	Case reports	[177, 182]
	Gastrointestinal	Bowel perforation	Case reports	[183-185]
		Liver, spleen haematoma	Case reports	[15-188]

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 [189-194].

3.4.2.1.4 Endourology techniques for renal stone removal
3.4.2.1.4.1 Percutaneous nephrolithotomy (PNL)
Percutaneous nephrolithotripsy remains the standard procedure for large renal calculi. Different rigid and flexible endoscopes are available and the selection is mainly based on the surgeon's own preference. Standard access tracts are 24-30 F. Smaller access sheaths, < 18 French, were initially introduced for paediatric use, but are now increasingly popular in adults.

The efficacy of miniaturised systems seems to be high, but longer operation times apply and benefit compared to standard PNL for selected patients has yet to be demonstrated [195]. There is some evidence that smaller tracts cause less bleeding complications, but further studies need to evaluate this issue. Smaller instruments bear the risk of increasing intra-renal pelvic pressure [5, 196-198].

3.4.2.1.4.1.1 Contraindications
Patients receiving anticoagulant therapy must be monitored carefully pre- and post-operatively. Anticoagulant therapy must be discontinued before PNL [112].
Other important contraindications include:
- untreated UTI;

- tumour in the presumptive access tract area;
- potential malignant kidney tumour;
- pregnancy (Section 3.4.3.1).

3.4.2.1.4.1.2 Best clinical practice

Intracorporeal lithotripsy

Several methods for intracorporeal lithotripsy are available (devices are discussed in Section 3.4.1.2.1.1.5). During PNL, ultrasonic and pneumatic systems are most commonly used for rigid nephroscopy. When using miniaturised instruments, laser lithotripsy is associated with lower stone migration than with pneumatic lithotripsy [199]. Flexible endoscopes require laser lithotripsy to maintain tip deflection and the Ho:YAG laser has become the standard [200].

Recommendation	GR
Use ultrasonic, ballistic and holmium: yttrium-aluminium-garnet devices for intracorporeal lithotripsy during percutaneous nephrolithotomy.	A*

**Upgraded based on panel consensus.*

Pre-operative imaging

Pre-procedural evaluations are summarised in Section 3.3.1. In particular, PNL, 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) [201].

Recommendation	GR
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.	A*

**Upgraded based on panel consensus.*

For antibiotic therapy - see General recommendations and precautions for stone removal (Section 3.4.1.4.1).

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 operating room (OR) time. In some series, SFR is lower than for the prone position despite a longer OR time. Prone position offers more options for puncture and is therefore preferred for upper pole or multiple access [202-204]. On the other hand, supine position allows simultaneous retrograde access to the collecting system, using flexible ureteroscope [205]. The Urolithiasis Guidelines Panel aim to set up a SR to assess this topic.

Puncture

Although fluoroscopy is the most common intra-operative imaging method, the (additional) use of US reduces the radiation exposure.

Colon interposition in the access tract of PNL can lead to colon injuries. Pre-operative CT or intra-operative US allows identification of the tissue between the skin and kidney and lowers the incidence of bowel injury. The calyceal puncture may be done under direct visualisation using simultaneous flexible ureterenoscopy [206-209].

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, the difference in outcomes is most likely related to surgeon experience rather than to the technology used [210].

Choice of instruments

The Urolithiasis Panel performed a SR assessing the outcomes of PNL using smaller tract sizes (< 22 Fr, mini-PNL) for removing renal calculi [5]. Stone-free rates were comparable in miniaturised and standard PNL

procedures. Procedures performed with small instruments tended to be associated with significantly lower blood loss, while the duration of procedure tended to be significantly longer. Other complications were not notably different between PNL types. However, the quality of the evidence was poor, drawn mainly from small studies, the majority of which were single-arm case series, and only two of which were RCTs. Furthermore, the tract sizes used, and types of stones treated were heterogeneous. Hence, the risk of bias and confounding were high.

Nephrostomy and stents

The decision on whether or not to place a nephrostomy tube at the end 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 [211, 212]. 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. In uncomplicated cases, the latter procedure results in a shorter hospital stay, with no disadvantages reported [213-215].

Recommendation	LE	GR
In uncomplicated cases, perform a tubeless (without nephrostomy tube) or totally tubeless (without nephrostomy tube and ureteral stent) percutaneous nephrolithotomy procedure as it is a safe alternative.	1b	A

3.4.2.1.4.1.3 Complications

The most common post-operative complications associated with PNL are fever and bleeding, urinary leakage, and problems due to residual stones (Table 3.4.2).

Table 3.4.2: Complications following percutaneous nephrolithotomy [216]

Complications	Trans-fusion	Embolisation	Urinoma	Fever	Sepsis	Thoracic complication	Organ injury	Death	LE
(Range)	(0-20%)	(0-1.5%)	(0-1%)	(0-32.1%)	(0.3-1.1%)	(0-11.6%)	(0-1.7%)	(0-0.3%)	1a
N = 11,929	7%	0.4%	0.2%	10.8%	0.5%	1.5%	0.4%	0.05%	

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 [217, 218]. Intra-operative irrigation pressure < 30 mmHg and unobstructed post-operative urinary drainage may be important factors in preventing post-operative sepsis. Bleeding after PNL may be treated by brief clamping of the nephrostomy tube. Super-selective embolic occlusion of the arterial branch may become necessary in the case of severe bleeding.

3.4.2.1.4.2 Ureterorenoscopy 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 SR addressing renal stones > 2 cm showed a cumulative SFR of 91% with 1.45 procedures/patient; 4.5% of the complications were ≥ Clavien 3 [219-221]. Digital scopes demonstrate shorter operation times due to the improvement in image quality [220, 222, 223]. For best clinical practice see Section 3.4.3.1.4.1.2 - Ureteral stones-URS.

Stones that cannot be extracted directly must be disintegrated. If it is difficult to access stones that need disintegration within the lower renal pole, it may help to displace them into a more accessible calyx [224].

Recommendation	GR
Use flexible ureterorenoscopy in case percutaneous nephrolithotomy or shock wave lithotripsy are not an option (even for stones > 2 cm). However, in that case there is a higher risk that a follow-up procedure and placement of a ureteral stent may be needed. In complex stone cases, use open or laparoscopic approaches as possible alternatives.	B

3.4.2.1.4.3 Open and laparoscopic surgery for removal of renal stones

Advances in SWL and endourological surgery (URS and PNL) have significantly decreased the indications for open or laparoscopic stone surgery [225-231]. 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 a reasonable number of 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 [232-239].

Recommendations	LE	GR
Offer laparoscopic or open surgical stone removal in rare cases in which shock wave lithotripsy, (flexible) ureterorenoscopy and percutaneous nephrolithotomy fail, or are unlikely to be successful.	3	C
When expertise is available, perform surgery laparoscopically before proceeding to open surgery, especially when the stone mass is centrally located.	3	C

3.4.2.2 Indication for active stone removal of renal stones [240]

- stone growth;
- stones in high-risk patients for stone formation;
- obstruction caused by stones;
- infection;
- symptomatic stones (e.g., pain or haematuria);
- 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 of patients with asymptomatic renal stones seems to be ~10-25% per year, with a cumulative five-year event probability of 48.5% [129, 241, 242]. A prospective RCT with > 2 year 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 [243]. Although some have recommended prophylaxis for these stones to prevent renal colic, haematuria, infection, or stone growth, conflicting data have been reported [242, 244, 245]. 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 [178, 246]. 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 [240, 247, 248].

Summary of evidence	LE
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.	3

Recommendations	GR
Offer active treatment for renal stones in case of stone growth, *de novo* obstruction, associated infection, and acute and/or chronic pain.	C
Assess comorbidity and patient preference when making treatment decisions.	C

3.4.2.3 Selection of procedure for active removal of renal stones

For general recommendations and precautions see Section 3.4.1.3.

3.4.2.3.1 Stones in renal pelvis or upper/middle calices

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 [249-252]. Shock wave lithotripsy achieves good SFRs for stones up to 20 mm, except for those at the lower pole [251, 253, 254]. Endourology is considered an alternative because of the reduced need of 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 3.4.1) [173]. 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 [255-257]. However, it may be a first-line option in patients where PNL is not an option or contraindicated.

3.4.2.3.2 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 smaller than 1 cm [173, 249, 250, 252, 253, 257-265].

The following can impair successful stone treatment by SWL [260, 266-269]:

- steep infundibular-pelvic angle;
- long calyx;
- long skin-to-stone distance;
- narrow infundibulum (Table 3.4.4).

Further anatomical parameters cannot yet be established. Supportive measures such as inversion, vibration or hydration may facilitate stone clearance [270].

Table 3.4.4: Unfavourable factors for shock wave lithotripsy success for lower calyceal stones [260, 266, 271]

Factors that make shock wave lithotripsy less likely
Shock wave-resistant stones (calcium oxalate monohydrate, brushite, or cystine).
Steep infundibular-pelvic angle.
Long lower pole calyx (> 10 mm).
Narrow infundibulum (< 5 mm).
Long skin-to-stone distance (> 10 cm).

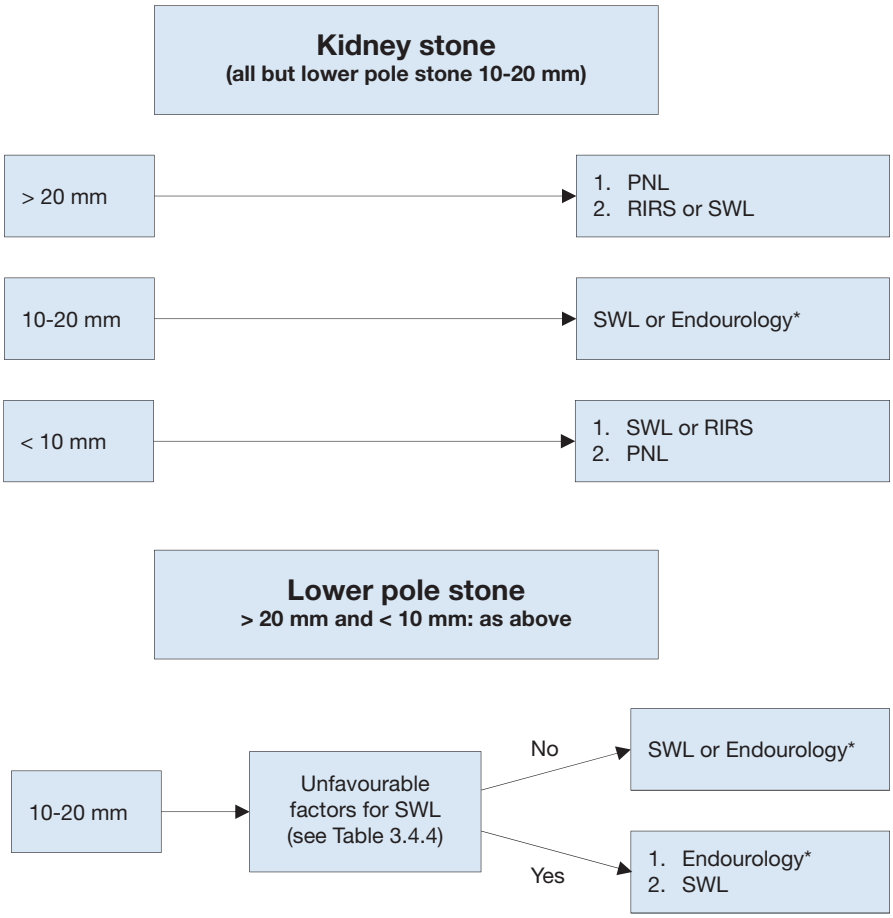
If there are negative predictors for SWL, PNL and RIRS might be reasonable alternatives, even for smaller calculi [258]. Retrograde renal surgery seems to have comparable efficacy to SWL [173, 253]. Recent clinical experience has suggested a higher SFR of RIRS compared to SWL, but at the expense of greater invasiveness. Depending on operator skills, stones up to 3 cm can be treated by RIRS [221, 272-274]. However, staged procedures are frequently required.

In complex stone cases, open or laparoscopic approaches are possible alternatives (see appropriate chapters).

3.4.2.3.3 Recommendations for the selection of procedures for active removal of renal stones

Recommendations	GR
Offer shock wave lithotripsy (SWL) and endourology (percutaneous nephrolithotomy [PNL], retrograde renal surgery [RIRS]) as treatment options for stones < 2 cm within the renal pelvis and upper or middle calices.	B
Perform PNL as first-line treatment of larger stones > 2 cm.	B
In case PNL is not an option, treat larger stones (> 2 cm) with flexible ureterorenoscopy or SWL. However, in such instances there is a higher risk that a follow-up procedure and placement of a ureteral stent may be needed.	B
For the lower pole, perform PNL or RIRS, even for stones > 1 cm, as the efficacy of SWL is limited (depending on favourable and unfavourable factors for SWL).	B

Figure 3.4.1: Treatment algorithm for renal calculi



**The term 'Endourology' encompasses all PNL and URS interventions.*
PNL = percutaneous nephrolithotomy; RIRS = retrograde renal surgery; SWL = shock wave lithotripsy; URS = ureterorenoscopy.

*3.4.3 **Specific stone management of Ureteral stones***

3.4.3.1 Types of treatment

3.4.3.1.1 Conservative treatment/observation

There are only limited data regarding spontaneous stone passage according to stone size [275]. It is estimated that 95% of stones up to 4 mm pass within 40 days [189].

Observation is feasible in informed patients who develop no complications (infection, refractory pain, deterioration of renal function).

Recommendations	LE	GR
In patients with newly diagnosed small* ureteral stones, if active removal is not indicated (Section 3.4.2.2), observe patient initially with periodic evaluation.	1a	A
Offer patient appropriate medical therapy to facilitate stone passage during observation.		

**See stratification data [189].*

Based on the analysis of available evidence, an exact cut-off size for stones that are likely to pass spontaneously cannot be provided; < 10 mm may be considered a best estimate [189]. Therefore, the Panel decided not to include stone size but rather recommend "small", suggesting < 6 mm. The Panel is aware of the fact that spontaneous stone expulsion decreases with increasing stone size and that there are differences between individual patients.

3.4.3.1.2 Pharmacological treatment, Medical expulsive therapy

Medical expulsive therapy (MET) should only be used in informed patients. Treatment should be discontinued if complications develop (infection, refractory pain, deterioration of renal function). Several substances are in discussion for MET [276-279]. When using α-blockers for MET possible side effects include retrograde ejaculation and hypotension [84].

Meta-analyses have shown that patients with ureteral stones treated with α-blockers or nifedipine are more likely to pass stones with fewer colic episodes than those not receiving such therapy [84, 280]. 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) [87, 88, 281]. A published meta-analysis, including 55 trials with a data search cut-off of July 1st 2015, also including the publications addressed above, assessed stone passage as primary outcome [4]. Based on the well-designed sensitivity analyses of this meta-analysis, α-blockers promote spontaneous stone expulsion of large stones located in any part of the ureter.

The panel concludes that MET seems efficacious in the treatment of patients with ureteric stones who are amenable to conservative management. The greatest benefit might be among those with larger (distal) stones [282].

Summary of evidence	LE
MET seems to be efficacious treating patients with ureteric stones who are amenable to conservative management. The greatest benefit might be among those with larger (distal) stones.	1a

Based on studies with a limited number of patients [279, 283, 284] (LE: 1b), no recommendation for the use of corticosteroids in combination with α-blockers in MET can be made.

Summary of evidence	LE
There is no evidence to support the use of corticosteroids as monotherapy for MET.	1b
Insufficient data exist to support the use of corticosteroids in combination with α-blockers as an accelerating adjunct.	2a

Recommendations	LE	GR
Select patients for an attempt at spontaneous passage or medical expulsive therapy (MET), based on well-controlled pain, no clinical evidence of sepsis, and adequate renal functional reserve.	4	C
Offer α-blockers as MET as one of the treatment options, in particular for (distal) ureteral stones > 5 mm.	1a	A
Counsel patients regarding the controversies in the literature, attendant risks of MET, including associated drug side effects. Inform the patient that α-blockers as MET are administered off-label†**.	1b	A*
Follow-up patients in short intervals to monitor stone position and assess for hydronephrosis.	4	A*

† It is not known if tamsulosin harms the human foetus or if it is found in breast milk.

**Upgraded based on panel consensus.*

***MET in children cannot be recommended due to the limited data in this specific population.*

Medical expulsive therapy in special situations is addressed in the particular chapters

3.4.3.1.2.1 Duration of medical expulsive therapy treatment
Most studies have had a duration of one month. No data are currently available to support other time-intervals.

3.4.3.1.3 Shock wave lithotripsy
For best clinical practice, see Section 3.4.2.1.4.1.2 (Renal stones).

Stenting
The stenting is not recommended as part of SWL, since it does not increase SFRs [189, 285]. When a stent is inserted, patients often suffer from frequency, dysuria, urgency, and suprapubic pain [285].

Recommendation	LE	GR
Do no routinely use a stent as part of shock wave lithotripsy treatment of ureteral stones.	1b	A

3.4.3.1.4 Endourology techniques
3.4.3.1.4.1 Ureterorenoscopy
The current standard for rigid ureterorenoscopes are tip diameters of < 8 F. Rigid URS can be used for the whole ureter [189]. However, technical improvements, as well as the availability of digital scopes also favour the use of flexible ureteroscopes in the ureter [219].

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

3.4.3.1.4.1.2 Best clinical practice in ureterorenoscopy (URS)
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 [286].

Antegrade URS is an option for large, impacted proximal ureteral calculi [287] (Section 3.4.3.1.4.2).

Safety aspects
Fluoroscopic equipment must be available in the OR. We recommend placement of a safety wire, even though some groups have demonstrated that URS can be performed without it [288-290].

Balloon and plastic dilators should be available, if necessary.

Prior rigid ureterenoscopy 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 procedure. Bilateral URS during the same session is feasible resulting in similar SFRs, but slightly higher overall (mostly minor) complication rates [291].

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 upper urinary tract and therefore significantly facilitate URS. The use of ureteral access sheaths improves vision by establishing a continuous outflow, decreasing intra-renal pressure, and potentially reduces operating time [292, 293].

The insertion of ureteral access sheaths may lead to ureteral damage, whereas the risk is lowest in pre-stented systems [294]. No data on long-term side effects are available [294, 295]. 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.

Stones can be extracted by endoscopic forceps or baskets. Only baskets made of nitinol can be used for flexible URS [296].

Recommendation	LE	GR
Do not perform stone extraction using a basket without endoscopic visualisation of the stone (blind basketing).	4	A*

**Upgraded based on panel consensus.*

Intracorporeal lithotripsy

The most effective lithotripsy system is the Ho:YAG laser, which is currently the optimum standard for ureterenoscopy and flexible nephroscopy (Section 3.4.2.1.4.1.2), because it is effective in all stone types [297, 298]. Pneumatic and US systems can be used with high disintegration efficacy in rigid URS [299, 300].

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 [301]. Medical expulsion therapy following Ho:YAG laser lithotripsy increases SFRs and reduces colic episodes [302] (LE: 1b).

Recommendation	LE	GR
Use holmium: yttrium-aluminium-garnet laser lithotripsy for (flexible) ureterorenoscopy.	3	B

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 [303, 304].

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 [305-307]. A ureteric catheter with a shorter indwelling time (one day) may also be used, with similar results [308].

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 1-2 weeks after URS. Alpha-blockers reduce the morbidity of ureteral stents and increase tolerability [309, 310]. A recently published meta-analysis provides evidence for improvement of ureteral stent tolerability with tamsulosin [311].

Medical expulsive therapy after ureterenoscopy

Medical expulsion therapy following Ho:YAG laser lithotripsy accelerates the spontaneous passage of fragments and reduces episodes of colic [302] (LE: 1b).

Summary of evidence	LE
In uncomplicated ureterorenoscopy (URS), a stent need not be inserted.	1a
In URS (in particular for renal stones), pre-stenting has been shown to improve outcome.	1b
An α-blocker can reduce stent-related symptoms and colic episodes.	1b

3.4.3.1.4.1.3 Complications

The overall complication rate after URS is 9-25% [189, 312, 313]. Most are minor and do not require intervention. Ureteral avulsion and strictures are rare (< 1%). Previous perforations are the most important risk factor for complications.

3.4.3.1.4.2 Percutaneous antegrade ureterenoscopy

Percutaneous antegrade removal of ureteral stones is a consideration in selected cases, i.e. large, impacted proximal ureteral calculi with dilated renal collecting system [314], or when the ureter is not amenable to retrograde manipulation [287, 315-318].

Recommendation	GR
Use percutaneous antegrade removal of ureteral stones as an alternative when shock wave lithotripsy is not indicated or has failed, and when the upper urinary tract is not amenable to retrograde ureterorenoscopy.	A

3.4.3.1.5 Laparoscopic ureteral stone removal

Few studies have reported laparoscopic stone removal (Section 3.4.2.1.4.3). 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 [319, 320]. These more invasive procedures have yielded high SFRs and lower auxiliary procedure rates [234].

Recommendation	LE	GR
For ureterolithotomy, perform laparoscopy for large impacted stones when endoscopic lithotripsy or shock wave lithotripsy has failed.	2	B

3.4.3.2 Indications for active removal of ureteral stones [189, 275, 321]

Indications for active removal of ureteral stones are:

- 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).

For general recommendations and precautions see Section 3.4.1.3.

Obesity can cause a lower success rate after SWL and PNL and may influence the choice of treatment.

Summary of evidence	LE
In the case of severe obesity, ureterorenoscopy is a more promising therapeutic option than shock wave lithotripsy.	2b

3.4.3.2.5.1 Bleeding disorder

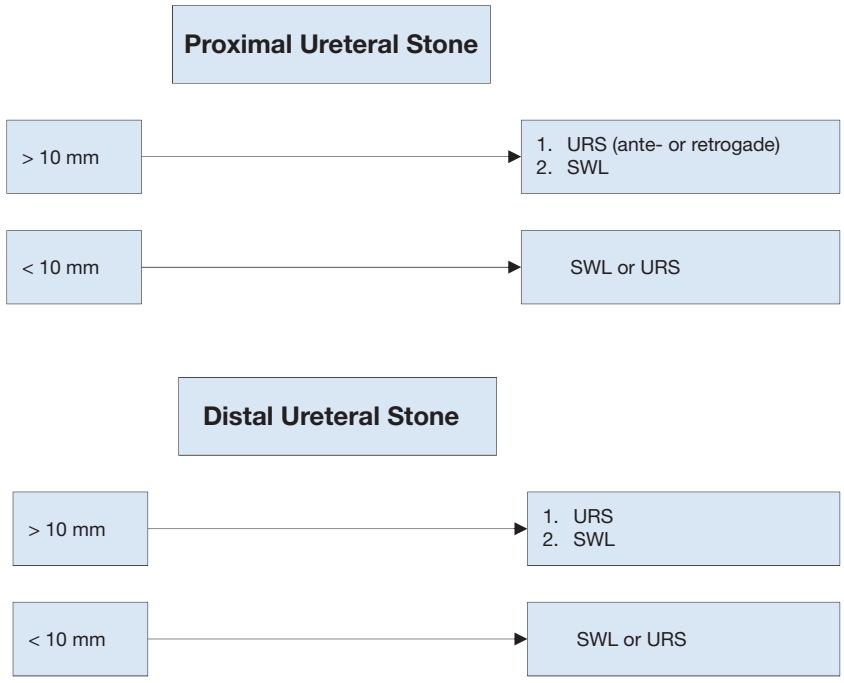
Ureterorenoscopy can be performed in patients with bleeding disorders, with a moderate increase in complications (see also Section 3.4.1.3) [112, 115].

3.4.3.3 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 ureteric calculi, it has greater potential for complications. However, in the current endourological era, the complication rate and morbidity of ureterenoscopy have been significantly reduced [322]. 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 [323].

The Panel performed an SR to assess the benefits and harms of URS compared to SWL [6]. Compared with SWL, URS was associated with a significantly greater SFR up to four weeks, but the difference was not significant at three months in the included studies. Ureterorenoscopy was associated with fewer re-treatments 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 least morbidity. Clavien-Dindo grade complications were, if reported, less frequent in patients treated with SWL.

Figure 3.4.2: Treatment algorithm for ureteral calculi (if indicated for active stone removal) (GR: A*)



**Upgraded following panel consensus.*

SWL = shock wave lithotripsy; URS = ureterenoscopy.

Summary of evidence	LE
In obese patients ureterorenoscopy (URS) is a safe and efficient option to remove renal stones.	2b
Ureterorenoscopy in morbidly obese patients have significantly higher complication rates as compared to normal weight patients.	1a

Recommendations	GR
Inform patients that ureterorenoscopy (URS) has a better chance of achieving stone-free status with a single procedure.	A
Inform patients that URS has higher complication rate when compared to shock wave lithotripsy.	A

3.4.4 Management of patients with residual stones

The clinical problem of residual renal stones is related to the risk of developing:

- new stones from such nidi (heterogeneous nucleation);
- persistent UTI;
- dislocation of fragments with/without obstruction and symptoms [178, 324, 325].

Recommendations	LE	GR
Identify biochemical risk factors and offer appropriate stone prevention to patients with residual fragments or stones [178, 325, 326].	1b	A
Follow-up patients with residual fragments or stones regularly to monitor disease course.	4	C

Recurrence risk in patients with residual fragments after treatment of infection stones is higher than for other stones [326]. 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 [178, 324, 327]. 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 [328].

3.4.4.1 Therapy

The indications for active removal of residual stones and selection of the procedure are based on the same criteria as for primary stone treatment (Section 3.4.2.4) and includes repeat SWL [329].

If intervention is not required, medical therapy according to stone analysis, patient risk group, and metabolic evaluation might help to prevent regrowth of residual fragments [330-332].

Summary of evidence	LE
For well-disintegrated stone material in the lower calix, an inversion therapy with simultaneous mechanical percussion manoeuvre under enforced diuresis may facilitate stone clearance [270].	1b

Recommendation	LE	GR
After shock wave lithotripsy and ureteronoscopy, and in the presence of residual fragments, offer medical expulsive therapy using an α-blocker to improve fragment clearance.	1a	A

Table 3.4.5: Recommendations for the treatment of residual fragments

Residual fragments, stones (largest diameter)	Symptomatic residuals	Asymptomatic residuals	LE	GR
< 4-5 mm	Stone removal	Reasonable follow-up (dependent on risk factors)	4	C
> 5 mm	Stone removal		4	C

3.4.5 Management of specific patient groups

3.4.5.1 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., induction of premature labour), placement of a ureteral stent or a percutaneous nephrostomy tube is necessary [333-335]. Unfortunately, these

temporising therapies are often associated with poor tolerance, and they require multiple exchanges during pregnancy, due to the potential for rapid encrustation. Ureterenoscopy has become a reasonable alternative in these situations [336-338]. Although feasible, retrograde endoscopic and percutaneous removal of renal stones during pregnancy remain an individual decision and should be performed only in experienced centres [339].

Pregnancy remains an absolute contraindication for SWL.

Summary of evidence	LE
If intervention becomes necessary, placement of a ureteral stent or a percutaneous nephrostomy tube is a readily available primary option.	3
Ureterenoscopy is a reasonable alternative to avoid long-term stenting/drainage.	1a
Regular follow-up until final stone removal is necessary due to the higher encrustation tendency of stents during pregnancy.	

Recommendation	GR
Treat all uncomplicated cases of urolithiasis in pregnancy conservatively (except those that have clinical indications for intervention).	A

3.4.5.2 Management of stones in patients with urinary diversion

3.4.5.2.1 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 [340-342]. Metabolic factors (hypercalciuria, hyperoxaluria and hypocitraturia), infection with urease-producing bacteria, foreign bodies, mucus secretion, and urinary stasis are responsible for stone formation [343] (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 [344].

3.4.5.2.2 Management

Smaller upper-tract stones can be treated effectively with SWL [316, 345]. In the majority, endourological techniques are necessary to achieve stone-free status [315]. In individuals with long, tortuous conduits or with invisible ureter orifices, a retrograde endoscopic approach might be difficult or impossible.

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 ureterorenoscopy is the alternative.	4

Recommendation	GR
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.	A*

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 [346].

Before considering any percutaneous approach in these cases, CT should be undertaken to assess the presence of an overlying bowel, which could make this approach unsafe [347], and if present, an open surgical approach should be considered.

3.4.5.2.3 Prevention

Recurrence risk is high in these patients [344]. 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 [348].

3.4.5.3 Management of stones in patients with neurogenic bladder

3.4.5.3.1 Aetiology, clinical presentation and diagnosis

Patients with neurogenic bladder develop urinary calculi because of additional risk factors such as bacteriuria, pelvicaliectasis, VUR, renal scarring, lower urinary tract reconstruction, and thoracic spinal defect [349]. 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 [350, 351].

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

3.4.5.3.2 Management

Management of calculi in patients with neurogenic bladder is similar to that described in Section 3.3.3. In MMC (myelomeningocele) patients, latex allergy is common, therefore, appropriate measures need to be taken regardless of the treatment [352]. 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 [353]. The risk of stone formation after augmentation cystoplasty in immobile patients with sensory impairment can be significantly reduced by irrigation protocols [348].

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.

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

Recommendation	GR
Take appropriate measures regardless of the treatment provided since in myelomeningocele patients latex allergy is common.	B

3.4.5.4 Management of stones in transplanted kidneys

3.4.5.4.1 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. Risk factors in these patients are multifold:

- immunosuppression increases the infection risk, resulting in recurrent UTIs;
- hyper filtration, excessively alkaline urine, renal tubular acidosis, and increased serum calcium caused by persistent tertiary hyperparathyroidism [354] are biochemical risk factors.

Stones in kidney allografts have an incidence of 0.2-1.7% [355-357].

Recommendation	LE	GR
Perform ultrasound or non-contrast-enhanced computed tomography to rule out calculi in patients with transplanted kidneys, unexplained fever, or unexplained failure to thrive (particularly in children) [358].	4	B

3.4.5.4.2 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 [359-362]. 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 ureterenoscopy a valid treatment option for transplant calculi. However, one must be aware of potential injury to adjacent organs [363-365]. Retrograde access to transplanted kidneys is difficult due to the anterior location of the ureteral anastomosis, and ureteral tortuosity [366-368].

Summary of evidence	LE
Conservative treatment for small asymptomatic stones is only possible under close surveillance and in absolutely compliant patients.	
Shock wave lithotripsy for small calyceal stones is an option with minimal complication risk, but localisation of the stone can be challenging and stone-free rates are poor [369, 370].	4

Recommendations	GR
Offer patients with transplanted kidneys, any of the contemporary management options, including shock wave therapy, flexible ureterenoscopy and percutaneous nephrolithotomy.	B
Complete metabolic evaluation after stone removal.	A*

**Upgraded following panel consensus.*

3.4.5.4.3 Special problems in stone removal

Table 3.4.6: Special problems in stone removal

Calyceal diverticulum stones	• Shock wave lithotripsy (SWL), percutaneous nephrolithotomy (PNL) (if possible) or retrograde renal surgery (RIRS). • Can also be removed using laparoscopic retroperitoneal surgery [371-375]. • 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 [376]. • Passage of fragments after SWL might be poor. • Acceptable SFRs can be achieved with flexible ureteroscopy [377].
Stones in pelvic kidneys	• SWL, RIRS, PNL or laparoscopic surgery. • In obese patients, the options are RIRS, PNL or open surgery.
Stones formed in a continent reservoir	• See Section 3.4.4. • Each stone must be considered and treated individually.
Patients with obstruction of the ureteropelvic junction	• When outflow abnormality requires correction, stones can be removed by PNL together with percutaneous endopyelotomy or open/laparoscopic reconstructive surgery. • Ureterorenoscopy together with endopyelotomy with holmium: yttrium-aluminium-garnet laser. • Incision with an Acucise® balloon catheter might be considered, provided the stones can be prevented from falling into the pelvi-ureteral incision [378-381]. • Open surgery with correction of the UPJ obstruction (pyeloplasty) and stone removal is a feasible option [382].

3.4.6 Management of urolithiasis in children

Rates of urolithiasis have increased in developed countries, and there has been a shift in the age group experiencing a first stone episode [10, 383, 384]. More than 1% of all urinary stones are seen in patients aged < 18 years. As a result of malnutrition and racial factors, paediatric urolithiasis remains an endemic disease in some areas (e.g., Turkey and the Far East); elsewhere, the rates are similar to those observed in developed countries [385-388].

For diagnostic procedures see Section 3.3.3.2, for acute decompression see Section 3.4.1.2.

3.4.6.1 Stone removal

Several factors must be considered when selecting treatment procedures for children. Compared to adults, children pass fragments more rapidly after SWL [52]. For endourological procedures, the smaller organs in children must be considered when selecting instruments for PNL or URS. Stone composition should be taken into account when selecting the appropriate procedure for stone removal (cystine stones are more resistant to SWL).

Summary of evidence	LE
Spontaneous passage of a stone is more likely in children than in adults [62].	4

3.4.6.1.1 Medical expulsive therapy in children

Medical expulsive therapy has already been discussed in Section 3.4.3.1.2 but not addressing children. Although the use of α-blockers is very common in adults, there are limited data to demonstrate their safety and efficacy in children; however, tamsulosin seems to support stone passage [65, 389-393].

3.4.6.1.2 Extracorporeal shock wave lithotripsy

Extracorporeal shock wave lithotripsy remains the least-invasive procedure for stone management in children [394-399].

Stone-free-rates of 67-93% in short-term and 57-92% in long-term follow-up studies have been reported. In children, compared with adults, SWL can achieve more effective disintegration of large stones, together with swifter and uncomplicated discharge of large fragments [396, 400]. As in adults, the slow delivery rate of shock waves may improve the stone clearance rates [400]. Stones located in calices, as well as in abnormal kidneys, and large stones, are more difficult to disintegrate and clear. The likelihood of urinary obstruction is higher in such cases, and children should be followed closely for the prolonged risk of urinary tract obstruction. The retreatment rate is 13.9-53.9%, and the need for ancillary procedures and/or additional interventions is 7-33% [396, 398].

The need for general anaesthesia during SWL depends on patient age and the lithotripter used. General or dissociative anaesthesia is administered in most children aged < 10 years, to prevent patient and stone motion and the need for repositioning [396, 398]. With modern lithotripters, intravenous sedation or patient-controlled analgesia have been used in selected co-operative older children [401] (LE: 2b). There are concerns regarding the safety and potential biological effects of SWL on immature kidneys and surrounding organs in children. However, during short- and long-term follow-up, no irreversible functional or morphological side effects of high-energy shock waves have been demonstrated. In addition, when the potential deterioration of renal function is taken into account (although transient), restricting the number of shock waves and the energy used during each treatment session helps protect the kidneys [402-405].

If the stone burden requires a ureteral stent, alternative procedures should be considered. Ureteral stents are seldom needed following SWL of upper tract stones, ureteral pre-stenting decreases the SFR after initial treatment [394-396].

Summary of evidence	LE
In children, the indications for shock wave lithotripsy are similar to those in adults; however, children pass fragments more easily.	3
Children with renal stones of a diameter up to 20 mm (~300 mm^2) are ideal candidates for shock wave lithotripsy.	1b

3.4.6.1.3 Endourological procedures

Improvement in intracorporeal lithotripsy devices and development of smaller instruments facilitate PNL and URS in children.

3.4.6.1.3.1 Percutaneous nephrolithotomy

Pre-operative evaluation and indications for PNL in children are similar to those in adults. Provided appropriate size instruments and US guidance are used, age is not a limiting factor, and PNL can be performed safely by experienced operators, with less radiation exposure, even for large and complex stones [406-410]. Stone-free rates are between 68% and 100% after a single session, and increase with adjunctive measures, such as second-look PNL, SWL and URS [406].

As for adults, tubeless PNL is safe in children, in well-selected cases [411, 412].

Summary of evidence	LE
In children, the indications for percutaneous nephrolithotomy are similar to those in adults.	1a

Recommendation	GR
In children, perform percutaneous nephrolithotomy for the treatment of renal pelvic or calyceal stones with a diameter > 20 mm (~300 mm^2). For ureteral stones, ureterorenoscopy may be an alternative, in case shockwave lithotripsy does not look promising.	

3.4.6.1.3.2 Ureterenoscopy

Although SWL is still the first-line treatment for most ureteral stones, it is unlikely to be successful for stones > 10 mm in diameter, or for impacted stones, calcium oxalate monohydrate or cystine stones, or stones in children with unfavourable anatomy and in whom localisation is difficult [413, 414].

If SWL is not promising, ureterenoscopy can be used. With the clinical introduction of smaller-calibre instruments, this modality has become the treatment of choice for medium and larger distal ureteric stones in children [413-417].

Different lithotripsy techniques, including ultrasonic, pneumatic and laser lithotripsy, are all safe and effective (Section 3.4.3.1.4.1.2) [418, 419].

Recommendation	LE	GR
For intracorporeal lithotripsy, use the same devices as in adults (holmium: yttrium-aluminium-garnet laser, pneumatic- and ultrasound lithotripters).	3	C

Flexible URS

Despite concerns about the potential risks and complications related to endoscopic surgery of children's delicate ureter and collecting system, with the development of smaller size endoscopes, flexible ureterenoscopy (RIRS) has become an efficacious treatment modality for renal and ureteral stones [413, 419-421] and might be a particularly effective treatment option for lower calyx stones in the presence of unfavourable factors for SWL.

Similar to adults, routine stenting is not necessary before URS. However, leaving a ureteral stent for the subsequent session must be considered in case of failure of ureterenoscopy. Pre-stenting facilitates URS, increases SFR and decreases complication rates [422].

For large and complex kidney stones PNL has a higher SFR compared to RIRS, but RIRS is associated with less radiation exposure, lower complication rates and a shorter hospital stay [423]. The experience of the surgical team is of the utmost importance for the success of both endourological techniques.

3.4.6.1.3.3 Open or laparoscopic surgery

Most stones in children can be managed by SWL and endoscopic techniques. Therefore, the rate of open procedures has dropped significantly [424-426]. Indications for surgery include: failure of primary therapy for stone removal; very young children with complex stones; congenital obstruction that requires simultaneous surgical correction; severe orthopaedic deformities that limit positioning for endoscopic procedures; and abnormal kidney position [394, 395, 407]. Open surgery can be replaced by laparoscopic procedures in experienced hands [425, 426].

3.4.6.1.3.4 Special considerations on recurrence prevention

All paediatric stone formers need metabolic evaluation and recurrence prevention with respect to the detected stone type. In radiolucent stones oral chemolysis may be considered as an alternative to SWL [427]. In the case of obstructive pathology in association with the established metabolic abnormalities, treatment should not be delayed. Children are in the high-risk group for stone recurrence [65, 428] (Chapter 4).

4. FOLLOW UP: METABOLIC EVALUATION AND RECURRENCE PREVENTION

4.1 General metabolic considerations for patient work-up

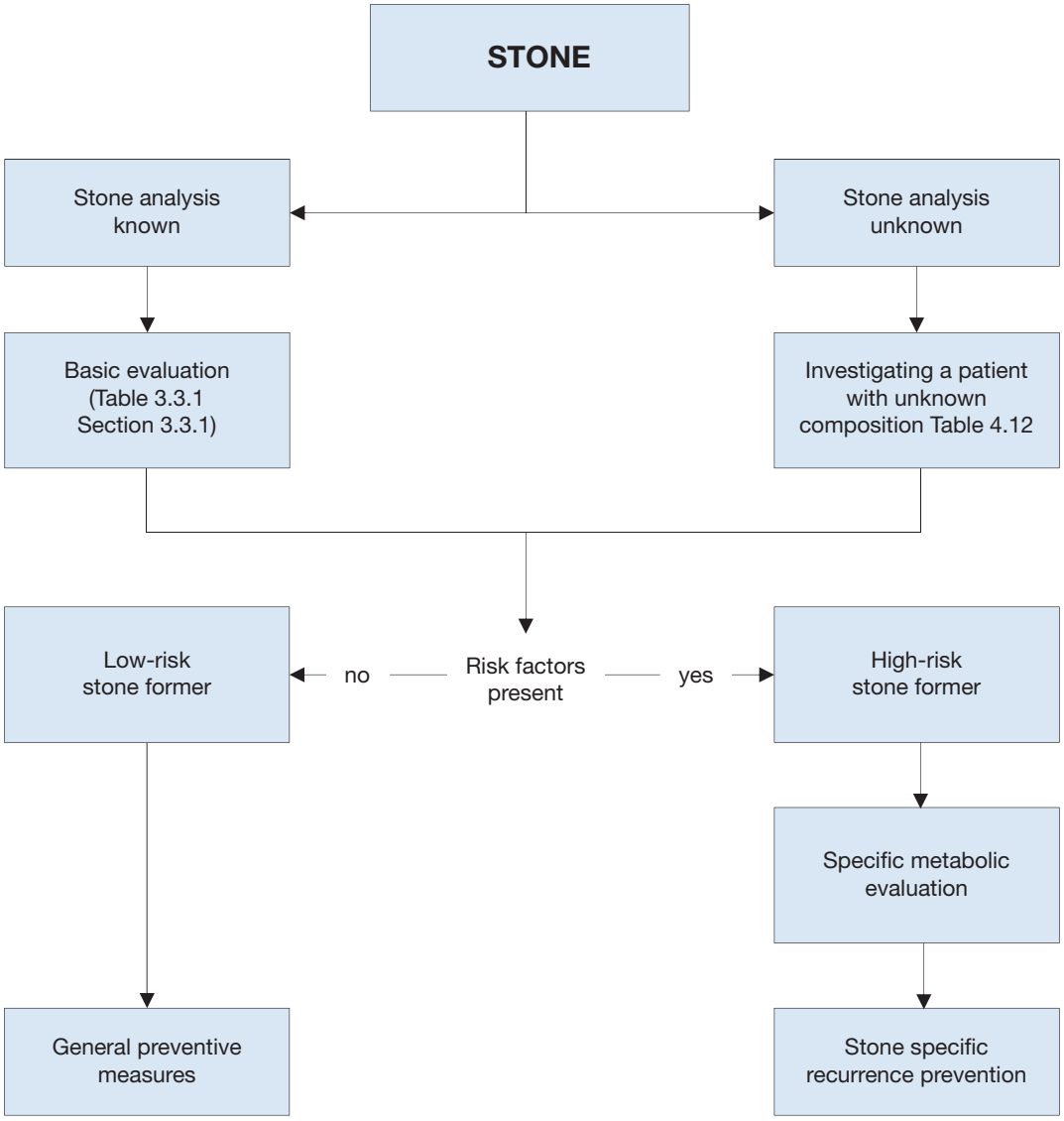
4.1.1 Evaluation of patient risk

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).

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



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.

*4.1.2 **Urine sampling***

Specific metabolic evaluation requires collection of two consecutive 24-hour urine samples [429, 430]. 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 [431, 432]. 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 particular laboratory. Urine pH should be assessed during collection of freshly voided urine four times daily [16, 431] using sensitive pH-dipsticks or a pH-meter.

Spot urine samples are an alternative method of sampling, particularly when 24-hours urine collection is difficult, for example, in non-toilet trained children [433]. Spot urine studies normally link the excretion rates to creatinine [433], 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 [434].

Follow-up studies are necessary in patients taking medication for recurrence prevention [435]. The first follow-up 24-hour urine measurement is suggested eight-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. The panel realise that on this issue there is only very limited published evidence. The Urolithiasis Guidelines Panel aim to set up a SR on the ideal timing of the 24-hour urine collection.

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 [436]

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	± 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 [437-440]. 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	> 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 (women), 5 mmol/day (men)
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 adults [441]

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/g**
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	< 0.56 mg/dl (33 imol/L) per GFR (ratio x plasma creatinine)	
> 2 years		

Table 4.4: Solute excretion in 24-hour urine samples in children [441]**

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 < 4 mg/kg/24 h	> 1.9 mmol/ 1.73 m^2/24 h > 365 mg/ 1.73 m^2/24 h	> 1.6 mmol/ 1.73 m^2/24 h > 310 mg/ 1.73 m^2/24 h	< 55 µmol/ 1.73 m^2/24 h < 13 mg/ 1.73 m^2/24 h	< 200 µmol/ 1.73 m^2/24 h < 48 mg/ 1.73 m^2/24 h	< 0.5 mmol/ 1.73 m^2/24 h < 45 mg / 1.73 m^2/24 h	< 70 µmol/ kg/24 h < 13 mg/ kg/24 h	< 65 mµmol/ kg/24 h < 11 mg/ kg/24 h	< 55 µmol/ kg/24 h < 9.3 mg/ kg/24 h

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

4.2 General considerations for recurrence prevention

All stone formers, independent of their individual risk, should follow the preventive measures in Table 4.5. The main focus of these 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: < 1010
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: The protein need is 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 [442-444]. The effect of fruit juices is mainly determined by the presence of citrate or bicarbonate [445]. If hydrogen ions are present, the net result is neutralisation. However, if potassium is present, both pH and citrate are increased [446, 447]. One large fair-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 was low because results were from only one trial [444, 448].

*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 [444, 449, 450].

Fruits, vegetables and fibres: 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 [451-454]. 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 [445], 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 [455]. However, it seems wise to advise calcium oxalate stone formers to avoid excessive intake.

Animal protein: should not be taken in excess [456, 457] 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: should not be restricted unless there are strong reasons due to the inverse relationship between dietary calcium and stone formation [452, 458]. The daily requirement for calcium is 1,000 to 1,200 mg [16]. Calcium supplements are not recommended except in enteric hyperoxaluria, when additional calcium should be taken with meals to bind intestinal oxalate [444, 457, 459]. 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 [460].

Sodium: the daily sodium (NaCl) intake should not exceed 3-5 g [16]. High intake adversely affects urine composition:

- calcium excretion is increased by reduced tubular reabsorption;
- 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 [456, 457]. A positive correlation between sodium consumption and risk of first-time stone formation has been confirmed only in women [458, 461]. 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 [462, 463] and uric acid stones. Intake should not exceed 500 mg/day [16].

4.2.3 ***Lifestyle***

Lifestyle factors may influence the risk of stone formation, for example, obesity [464] and arterial hypertension [465, 466].

4.2.4 ***Recommendations for recurrence prevention***

Recommendations	LE	GR
Advise patients that a generous fluid intake is to be maintained, allowing for a 24-hour urine volume > 2.5 L.	1b	A
Advise patients with a small urine volume to increase their fluid intake.	1b	a

4.3 Stone-specific metabolic evaluation and pharmacological recurrence prevention

4.3.1 ***Introduction***

Pharmacological treatment is necessary in patients at high risk for recurrent 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	[49, 444, 467-474]
Allopurinol	Hyperuricosuria Hyperuricaemia	100-300 mg/d Children: 1-3 mg/kg/d	100 mg in isolated hyperuricosuria Renal insufficiency demands dose correction	Calcium oxalate Uric acid Ammonium urate 2,8-Dihydroxyadenine	[475-479]
Calcium	Enteric hyperoxaluria	1000 mg/d	Intake 30 min before meals	Calcium oxalate	[457-459]
Captopril	Cystinuria Active decrease of urinary cystine levels	75-150 mg	Second-line option due to significant side effects	Cystine	[480, 481]
Febuxostat	Hyperuricosuria Hyperuricaemia	80-120 mg/d	Acute gout contraindicated, pregnancy, xanthine stone formation	Calcium oxalate Uric acid	[482, 483]
L-Methionine	Acidification	600-1500 mg/d	Hypercalciuria, bone demineralisation, systemic acidosis. No long-term therapy.	Infection stones Ammonium urate Calcium phosphate	[49, 484, 485]
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	[486, 487] low evidence
Sodium bicarbonate	Alkalinisation Hypocitraturia	4.5 g/d		Calcium oxalate Uric acid, Cystine	[488]
Pyridoxine	Primary hyperoxaluria	Initial dose 5 mg/kg/d Max. 20 mg/kg/d	Polyneuropathia	Calcium oxalate	[489]
Thiazide (Hydrochlorothiazide)	Hypercalciuria	25-50 mg/d Children: 0.5-1 mg/kg/d	Risk for agent-induced hypotonic blood pressure, diabetes, hyperuricaemia, hypokalaemia, followed by intracellular acidosis and hypocitraturia.	Calcium oxalate Calcium phosphate	[49, 486, 490-498]
Tiopronin	Cystinuria Active decrease of urinary cystine levels	Initial dose 250 mg/d Max. 2000 mg/d	Risk for tachyphylaxis and proteinuria.	Cystine	[499-502]

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), uric acid, and parathyroid hormone (PTH) (and vitamin D) in the case of increased calcium levels. Urinalysis requires measurement of urine volume, urine pH profile, specific weight, calcium, oxalate, uric acid, citrate, sodium and magnesium.

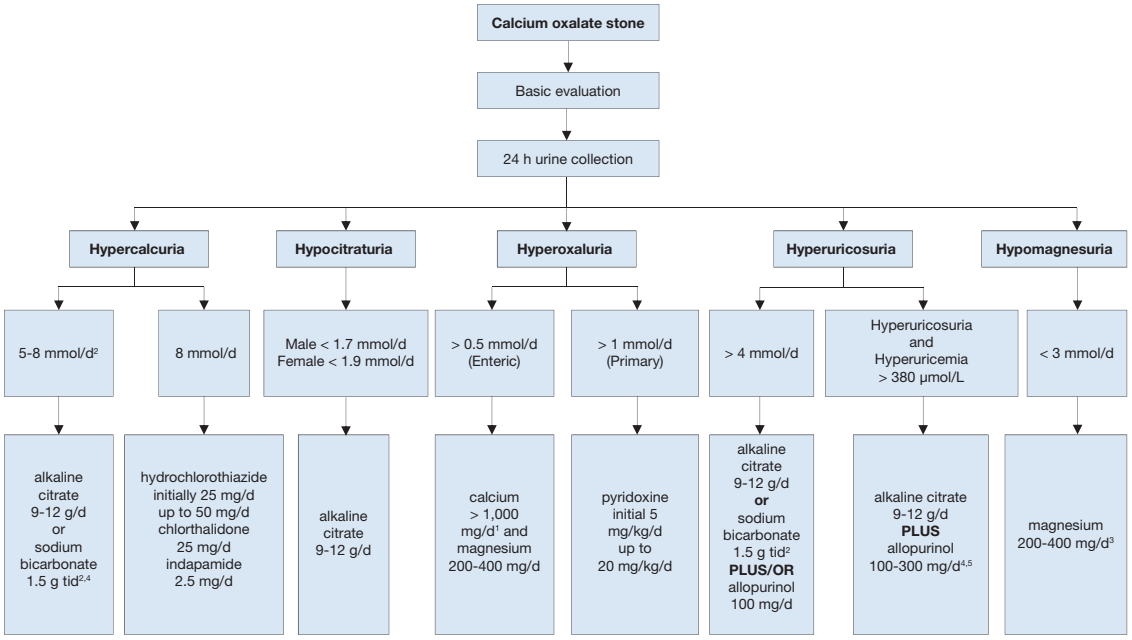
*4.4.2 **Interpretation of results and aetiology***

The diagnostic and therapeutic algorithm for calcium oxalate stones is shown in Figure 4.2 [49, 444, 468-470, 475-477, 482, 486-488, 490-497, 503-507].

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 [503].

- 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” (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 indicate renal tubular acidosis (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.
- Hypomagnesuria (< 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) (thiazide + allopurinol) is superior to thiazide therapy alone [490, 497].
[5] Febuxostat 80 mg/d.

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 [49, 444, 468-470, 475-477, 482, 486-488, 490-497, 503-507]. There is only low level evidence on the efficacy of preventing stone recurrence through pre-treatment stone composition and biochemistry measures, or on-treatment biochemistry measures [444].

4.4.4 Recommendations for pharmacological treatment of patients with specific abnormalities in urine composition (based on 24-hour urine samples)

Urinary risk factor	Suggested treatment	LE	GR
Hypercalciuria	Thiazide + potassium citrate	1a	A
Hyperoxaluria	Oxalate restriction	2b	A
Enteric hyperoxaluria	Potassium citrate	3-4	C
	Calcium supplement	2	B
	Diet reduced in fat and oxalate	3	B
Hypocitraturia	Potassium citrate	1b	A
Hypocitraturia	Sodium bicarbonate if intolerant to potassium citrate	1b	A
Hyperuricosuria	Allopurinol	1a	A
	Febuxostat	1b	A
High sodium excretion	Restricted intake of salt	1b	A
Small urine volume	Increased fluid intake	1b	A
Urea level indicating a high intake of animal protein	Avoid excessive intake of animal protein	1b	A
No abnormality identified	High fluid intake	2b	B

4.5 Calcium phosphate stones

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.

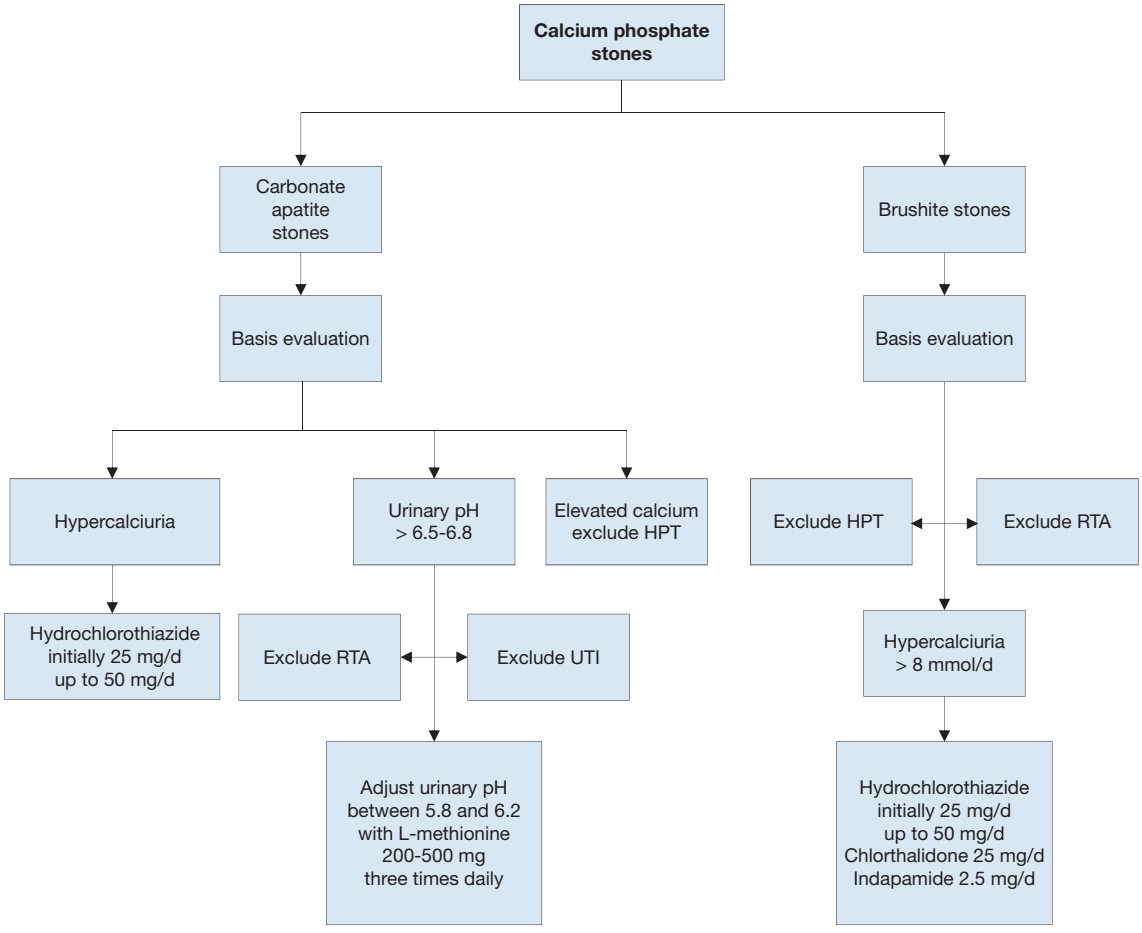
*4.5.1 **Diagnosis***

Diagnosis requires blood analysis for: creatinine, sodium, potassium, chloride, ionised calcium (or total calcium + albumin), 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 preventive 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.

*4.5.3 **Pharmacological therapy** [49, 444, 490, 491, 495, 507]*

Hyperparathyroidism and RTA are common causes of calcium phosphate stone formation. Although most patients with primary HPT require surgery, RTA can be corrected pharmacologically. If primary HPT and RTA have been excluded, pharmacotherapy for calcium phosphate calculi depends on effective reduction of urinary calcium levels using thiazides. If urine pH remains constantly > 6.2, urinary acidification with L-methionine may be beneficial; however, it is not commonly used and needs monitoring for systemic acidosis development. For

infection-associated calcium phosphate stones, it is important to consider the guidance given for infection stones.

*4.5.4 **Recommendations for the treatment of calcium phosphate stones***

Urinary risk factor and suggested treatment	LE	GR
Prescribe thiazide in case of hypercalciuria.	1a	A
Advise patients to acidify their urine in case of inadequate urine pH.	3-4	C
Prescribe antibiotics in case of a urinary tract infection.	3-4	C

4.6 Disorders and diseases related to calcium stones

*4.6.1 **Hyperparathyroidism** [508-511]*

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. Serum calcium may be mildly elevated and serum PTH may be within the upper normal limits, therefore, repeated measurements may be needed; preferably with the patient fasting. Stones of HPT patients may contain both calcium oxalate and calcium phosphate.

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** [511]*

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 focusses on the activity of the granulomatous diseases and may require steroids, hydroxychloroquine or ketoconazole. Treatment should be reserved for the specialist.

*4.6.3 **Primary hyperoxaluria** [489]*

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 meq/kg/day in children;
- magnesium: 200-400 mg/day (no magnesium in the case of renal insufficiency).

Urinary risk factor and suggested management of primary hyperoxaluria	LE	GR
Refer patients diagnosed with primary hyperoxaluria to a specialised centre where multidisciplinary care can be provided.		
Prescribe pyridoxine for primary hyperoxaluria.	3	B

*4.6.4 **Enteric hyperoxaluria** [459, 512]*

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 and 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, and stone formation.

Specific preventive measures are:

- restricted intake of oxalate-rich foods;

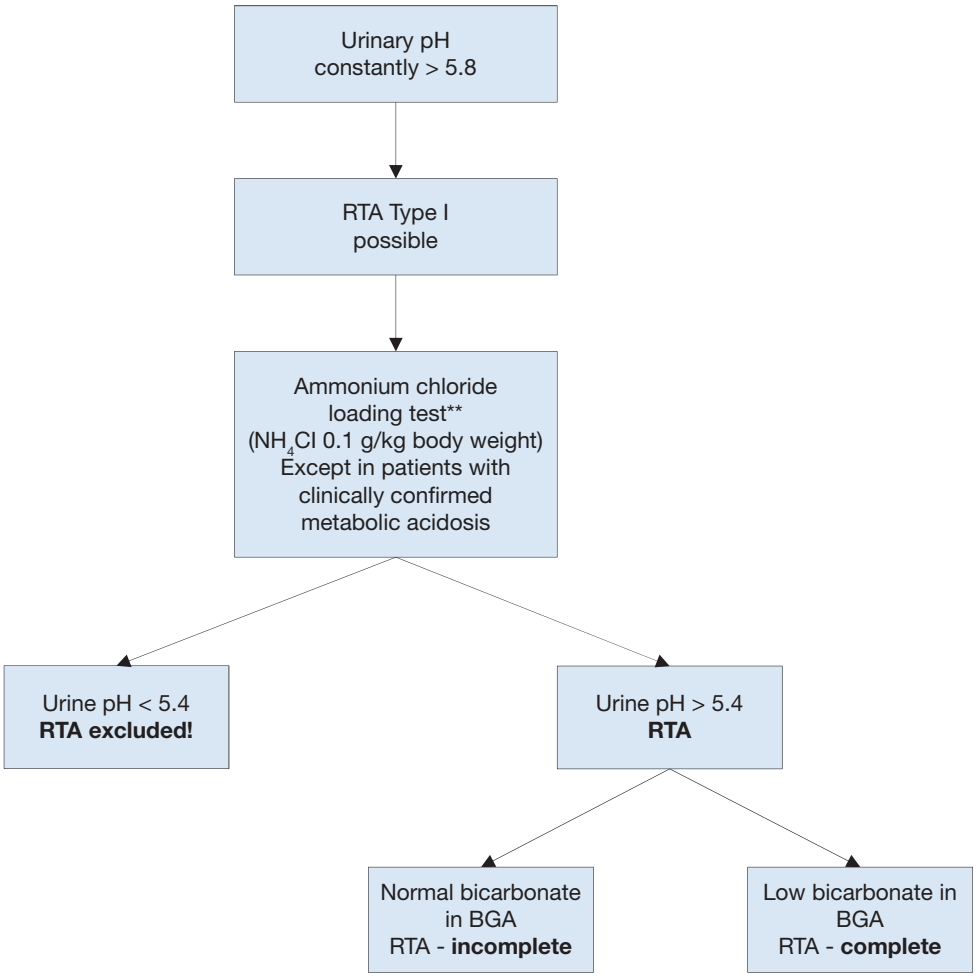
- restricted fat intake;
- calcium supplementation at meal times to enable calcium oxalate complex formation in the intestine [459, 512];
- sufficient fluid intake to balance intestinal loss of water caused by diarrhoea;
- alkaline citrates to raise urinary pH and citrate.

Urinary risk factor and suggested management of enteric hyperoxaluria	LE	GR
Prescribe potassium citrate.	4	C
Advise patients to take a calcium supplement.	2	B
Advise patients to follow a diet with a low fat and oxalate content.	3	B

*4.6.5 **Renal tubular acidosis** [513, 514]*

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



*** 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 acidification test.*

Renal tubular acidosis can be acquired or inherited. Reasons for acquired RTA can be obstructive uropathy, recurrent pyelonephritis, acute tubular necrosis, renal transplantation, analgesic nephropathy, sarcoidosis, idiopathic hypercalciuria, and primary parathyroidism; it may also be drug-induced (e.g. zonisamide). Table 4.7 shows the inherited causes of RTA.

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, osteomalacia
Autosomal recessive with hearing loss	ATP6V1B1/B1 subunit of vacuolar H-ATPase/proton secretion	Hypercalciuria, hypokalaemia, rickets
Autosomal recessive	ATP6V0A4/A4 subunit of vacuolar H-ATPase/proton secretion	Hypercalciuria, hypokalaemia, rickets

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 key to normalising the metabolic changes (intracellular acidosis) responsible for stone formation (Table 4.8). The alkali load reduces tubular reabsorption of citrate, which in turn normalises citrate excretion and simultaneously reduces calcium turnover. 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	Rationale 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	Intracellular acidosis in nephron	Alkaline citrate, 9-12 g/day divided in three doses OR Sodium bicarbonate, 1.5 g, three times daily

Urinary risk factor and suggested management of renal tubular acidosis	LE	GR
Prescribe potassium citrate for distal renal tubular acidosis.	2b	B
Prescribe thiazide + potassium citrate for hypercalciuria.	1a	A

*4.6.6 **Nephrocalcinosis** [441]*

Nephrocalcinosis (NC) refers to increased crystal deposition within the renal cortex or medulla, and occurs alone or in combination with renal stones. There are various metabolic causes. The main risk factors are: HPT, PH, RTA, vitamin D metabolic disorders, idiopathic hypercalciuria and hypocitraturia, and genetic disorders, including Dent's disease, Bartter's syndrome and Medullary sponge kidney. The many causes of NC means there is no single standard therapy. Therapeutic attention must focus on the underlying metabolic or genetic disease, 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 blood gas analysis. Urinalysis should investigate: urine pH profile (minimum four times daily), 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 [16]. Uric acid nephrolithiasis is responsible for approximately 10% of renal stones [515]. They are associated with hyperuricosuria or low urinary pH. Hyperuricosuria may be a result of dietary excess, endogenous

overproduction (enzyme defects), myeloproliferative disorders, tumour lysis syndrome, drugs, gout or catabolism [516]. 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) [516].

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), potassium deficiency, hypokalaemia and malnutrition.

Suggestions on uric acid and ammonium urate nephrolithiasis are based on level 3 and 4 evidence.

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 (urine pH constantly < 5.8) promotes uric acid crystallisation.

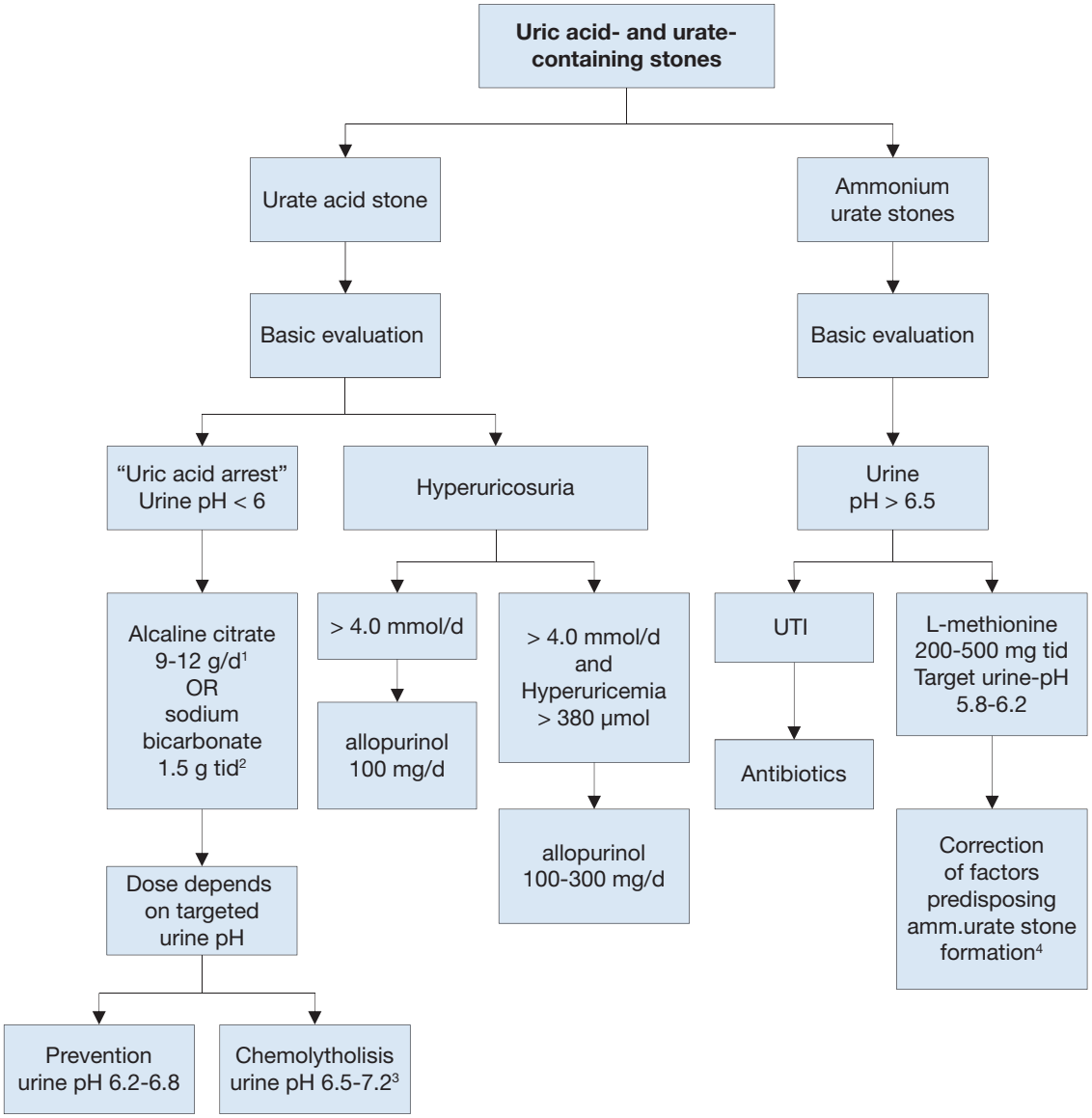
Hyperuricosuria is defined as uric acid excretion > 4 mmol/day in adults or > 0.12 mmol/kg/day in children. Hyperuricaemia may be present, but there is only weak evidence for its association with stone formation.

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 [517, 518]. Ammonium urate crystals form in urine at pH > 6.5, at high uric acid concentration when ammonium is present to serve as a cation [519-521].

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 [16, 433, 515-527]. 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 [528].

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.*

4.8 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 [529]. There are several factors predisposing patients to struvite stone formation (Table 4.9) [530].

*4.8.1 **Diagnosis***

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

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 [531, 532]. *Proteus mirabilis* accounts for more than half of all urease-positive UTIs [533, 534].

4.8.2 *Specific treatment*

General preventive measures are recommended for fluid intake and diet. Specific measures include complete surgical stone removal [530], short- or long-term antibiotic treatment [535], urinary acidification using methionine [484] or ammonium chloride [536], and advice to restrict intake of urease [537, 538]. For severe infections, acetohydroxamic acid may be an option [537, 538] (Figure 4.6); however, it is not licensed/available in all European countries.

4.8.3 *Recommendations for therapeutic measures of infection stones*

Recommendations	LE	GR
Surgically remove the stone material as completely as possible.	3-4	A*
Prescribe a short-term antibiotic course.	3	B
Prescribe a long-term antibiotic course in case of recurrent infections.	3	B
Prescribe ammonium chloride, 1 g, two or three times daily to ensure urinary acidification.	3	B
Prescribe methionine, 200-500 mg, one-three times daily, as an alternative, to ensure urinary acidification.	3	B
Consider prescription of urease inhibitors in case of severe infection (if licensed).	1b	A

**Upgraded following panel consensus.*

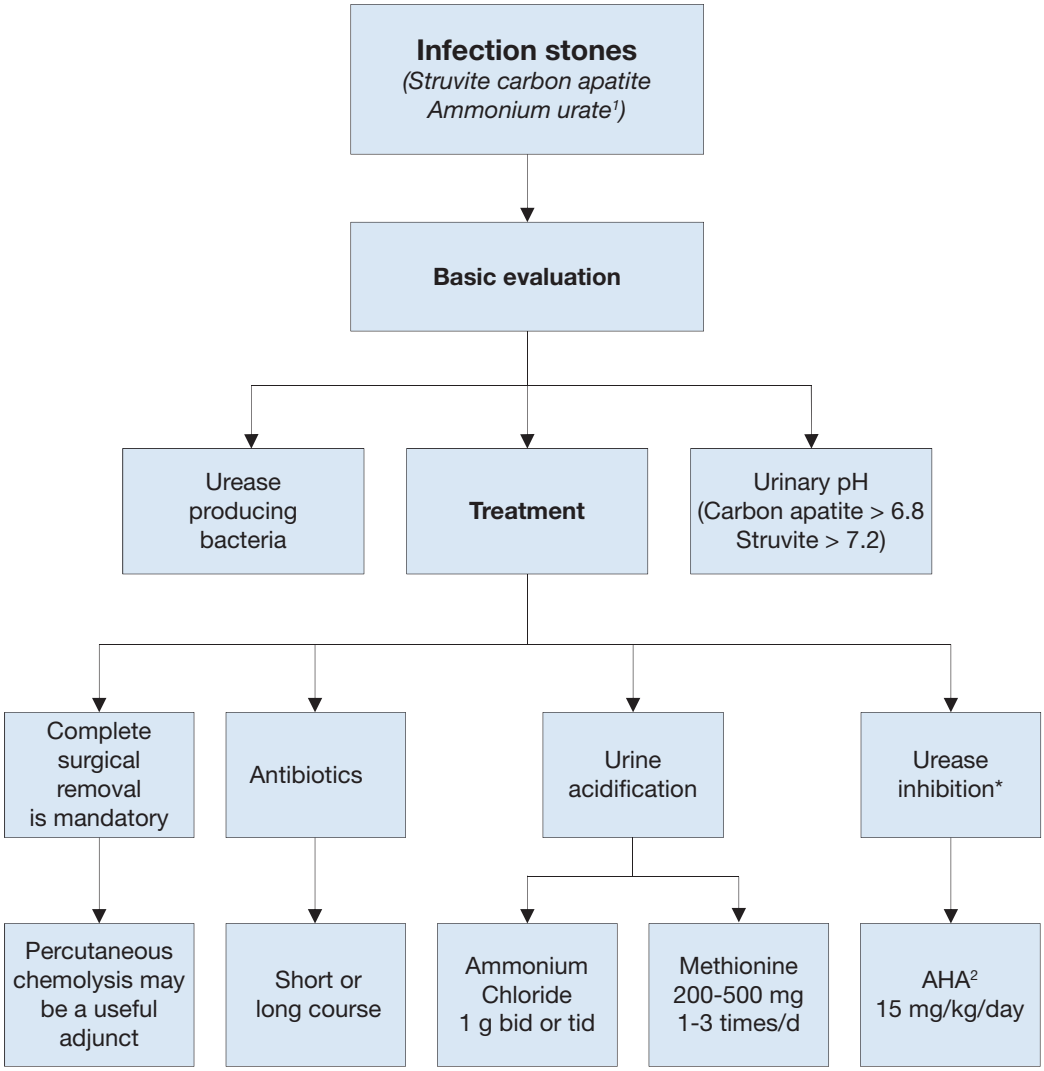
Table 4.9: Factors predisposing to struvite stone formation

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.

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 [26, 539]. All cystine stone formers are deemed at high risk of recurrence.

*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 [540].
- There is no role for genotyping patients in the routine management of cystinuria [541, 542].
- Reductive therapy targets the disulphide binding in the cysteine molecule. For therapy monitoring, it is essential to differentiate between cystine, cysteine and drug-cysteine complexes. Only high-performance liquid chromatography (HPLC)-based analysis differentiates between the different complexes formed 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 [543].

- 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
- Quantitative 24-hour urinary cystine excretion confirms the diagnosis in the absence of stone analysis.
- Levels above 30 mg/day are considered abnormal [544, 545].

*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 [546].

A high level of diuresis is of fundamental importance, aiming for a 24-hour urine volume of > 3 L [547].

A considerable fluid intake evenly distributed throughout the day is necessary.

4.9.2.1 Pharmacological treatment of cystine stones

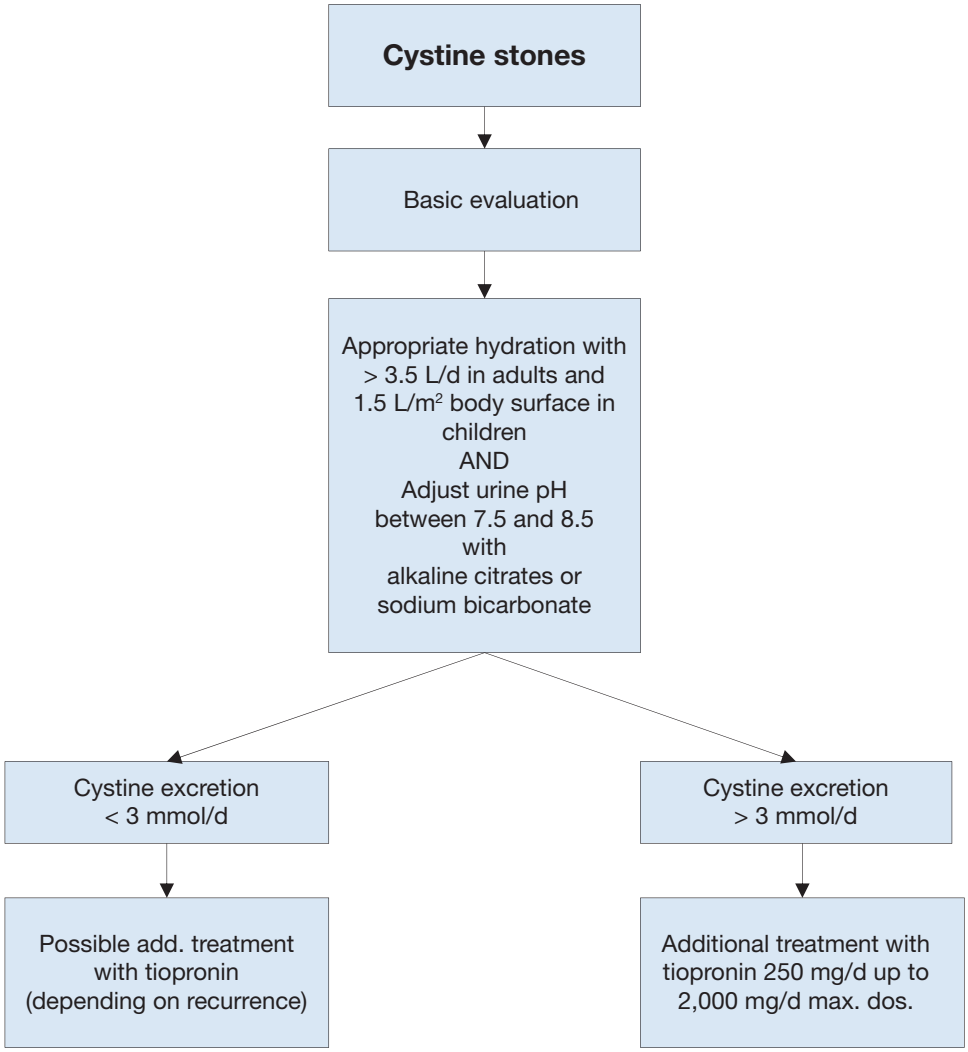
The main therapeutic option for avoiding cystine crystallisation is to maintain urine pH > 7.5, to improve cystine solubility and ensure appropriate hydration with a minimum of 3.5 L/day in adults, or 1.5 L/m^2 body surface area in children.

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

Tiopronin is currently the best choice for cystine reduction. However, side effects often lead to treatment termination, for example, when nephrotic syndrome develops, or poor compliance, especially with long-term use.

After carefully considering the risk of early tachyphylaxis, putting into place a dose-escape phenomenon for long-term use, and recurrence risk, tiopronin is recommended at cystine levels > 3.0 mmol/day or in the case of recurring stone formation, notwithstanding other preventive measures.

Figure 4.7: Metabolic management of cystine stones



4.9.3 Recommendations for the treatment of cystine stones

Therapeutic measures	LE	GR
Urine dilution Advise patients to increase their fluid intake so that 24-hour urine volume exceeds 3 L. Intake should be > 150 mL/h.	3	B
Alkalinisation For patients with cystine excretion < 3 mmol/day, prescribe potassium citrate 3-10 mmol two or three times daily, to achieve pH > 7.5.	3	B
Complex formation with cystine For patients with cystine excretion, > 3 mmol/day, or when other measures are insufficient: prescribe in addition to other measures tiopronin, 250-2,000 mg/day.	3	B

4.10 2,8-Dihydroxyandenine stones and xanthine stones [16]

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.

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. High-dose allopurinol or febuxostat are important options, but should be given with regular monitoring.

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. A purine-reduced diet decreases the risk of spontaneous crystallisation in urine.

4.11 Drug stones [49]

Drug stones are induced by pharmacological treatment [548] (Table 4.11). 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
Allopurinol/oxypurinol
Amoxicillin/ampicillin
Ceftriaxone
Quinolones
Ephedrine
Indinavir
Magnesium trisilicate
Sulphonamides
Triamterene
Zonisamide
Substances impairing urine composition
Acetazolamide
Allopurinol
Aluminium magnesium hydroxide
Ascorbic acid
Calcium
Furosemide
Laxatives
Methoxyflurane
Vitamin D
Topiramate

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 *Proteous mirabilis* or *Escherichia 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 [233].

4.13 Unknown stone composition [15]

An accurate medical history is the first step towards identifying risk factors (Table 4.12).

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 is additionally 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 indicates acidic arrest, which may promote uric acid

crystallisation. Persistent urine pH > 5.8 in the daily profile indicates RTA, if UTI is excluded.

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 [549, 550].

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.

Table 4.12: Recommendations for the assessment of patients with stones of unknown composition

Investigation	Rationale for investigation
Take a medical history	• Stone history (former stone events, family history) • Dietary habits • Medication chart
Perform diagnostic imaging	• Ultrasound in the case of a suspected stone • Unenhanced helical computed tomography • Determination of Hounsfield units provides information about the possible stone composition
Perform a blood analysis	• Creatinine • Calcium (ionised calcium or total calcium + albumin) • Uric acid
Perform a urinalysis	• Urine pH profile (measurement after each voiding, minimum four times daily) • Dipstick test: leukocytes, erythrocytes, nitrite, 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.

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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/online-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.