Guidelines on
Urolithiasis

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European
Association
of Urology

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1. METHODOLOGY

1.1 Introduction

The European Association of Urology (EAU) Urolithiasis Guidelines Panel have prepared these guidelines to help urologists assess evidence-based management of stones/calculi and incorporate recommendations into clinical practice.

The 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.

1.2 Data identification

For this 2012 (limited) update of the Urolithiasis guidelines, a scoping search, covering all content, was performed. Time frame of the search was August 10th, 2011 to October 16th, 2012. This search was limited to level 1 evidence (systematic reviews [SRs] and meta-analyses of randomised controlled trials [RCTs]) and English language publications in peer-reviewed journals. Animal studies were excluded.

The search identified 128 unique records of which 12 references were selected for inclusion in this document, replacing, in some instances, lower level studies, or to underpin new information. Selection of the papers was done through a consensus meeting of the Panel held in December 2012.

A more detailed summary of changes can be found below.

Annual scoping searches will be repeated as a standard procedure.

1.3 Evidence sources

Searches were carried out in the Cochrane Library Database of Systematic Reviews, Cochrane Library of Controlled Clinical Trials, and Medline and Embase on the Dialog-Datastar platform. The searches used the controlled terminology and the use of free text ensured search sensitivity.

Randomised controlled trial strategies were based on Scottish Intercollegiate Guidelines Network (SIGN) and Modified McMaster/Health Information Research Unit (HIRU) filters for RCTs, systematic reviews and practice guidelines on the OVID platform and then translated into Datastar syntax.
There is a need for ongoing re-evaluation of the current guidelines by an expert panel. It must be emphasised that clinical guidelines present the best evidence available but following the recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients - also taking personal values and preferences/individual circumstances of patients into account.

1.4 Level of evidence and grade of recommendation

References in the text have been assessed according to their level of scientific evidence (Table 1), and guideline recommendations have been graded (Table 2) according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (1). Grading aims to provide transparency between the underlying evidence and the recommendation given.

Table 1: Level of evidence (LE)*

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised controlled trials.
1b	Evidence obtained from at least one randomised trial.
2a	Evidence obtained from one well-designed controlled study without randomisation.
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study.
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.

** Modified from Sackett et al. (1).*

When recommendations are graded, the link between the level of evidence and grade of recommendation is not directly linear. Availability of RCTs may not translate into a grade A recommendation when there are methodological limitations or disparity in published results.

Absence of high-level evidence does not necessarily preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. There may be exceptions where corroborating studies cannot be performed, perhaps for ethical or other reasons, and unequivocal recommendations are considered helpful. Whenever this occurs, it is indicated in the text as "upgraded based on panel consensus". The quality of the underlying scientific evidence must be balanced against benefits and burdens, values and preferences and cost when a grade is assigned (2-4).

The EAU Guidelines Office does not perform cost assessments, nor can it address local/national preferences systematically. The expert panels include this information whenever it is available.

Table 2: Grade of recommendation (GR)*

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial.
B	Based on well-conducted clinical studies, but without RCTs.
C	Made despite the absence of directly applicable clinical studies of good quality.

**Modified from Sackett et al. (1).*

1.5 Publication history

The current 2013 print presents an update of the 2012 publication of the EAU Urolithiasis Guidelines, but for Chapter 11 (Metabolic evaluation and recurrence prevention), which has been replaced in its entirety. A more detailed listing is provided in section 1.5.1 "Summary of changes". It has been attempted to limit the discussion and background information, focussing on the presentation of findings resulting in treatment recommendations. The expert panel aim to further progress this strategy in subsequent updates. All flowcharts have been reevaluated, resulting in the adaptation of existing flowcharts and the inclusion of new flowcharts, most notably in the new Chapter 11.

The first EAU Guidelines on Urolithiasis were published in 2000. Subsequent updates were presented in 2001 (partial), 2005 (comprehensive), 2008 (comprehensive), 2009, 2010, 2011 (limited) and 2012 (comprehensive update).

A quick reference document presenting the main findings of the urolithiasis guidelines is also available alongside several scientific publications in European Urology and the Journal of Urology (5-7). All texts can be viewed and downloaded for personal use at the EAU website: http://www.uroweb.org/guidelines/online-guidelines/.

Chapter 11 - Metabolic evaluation and recurrence prevention, was peer-reviewed prior to publication.

1.5.1 Summary of changes

Section	Title	Short description
3.1.2	Evaluation of patients for whom further treatment of renal stones is planned.	Additional recommendation for imaging has been included.
4.1.1	Pain relief.	A statement was added.
4.1.3	Recommendations for analgesia during renal colic.	A recommendation was added.
5.3.1	Choice of medical agents.	The statement has been altered. Nifedipine as a recommended medical treatment has been removed from the recommendations. Additionally, a caution for the use of medical expulsive therapy (MET) in children is provided.
5.6.	Endourology techniques.	This section has been significantly condensed, and technical information was removed.
5.6.2.1.6	Stone extraction.	The recommendations have been amended.
5.6.2.1.8	Stenting before and after URS.	A new recommendation was added on the use of an alpha-blocker to reduce stent-related symptoms.

6.4	Selection of procedure for active removal of kidney stones.	The treatment algorithms for kidney stones and stones in the lower pole have been replaced. For stones > 20 mm laparoscopy is no longer recommended. Treatment options include SWL and RIRS.
7.2	Residual stones. Therapy.	A statement has been added regarding combination therapy.
8.2	Diagnostic imaging for stones in pregnancy.	A statement regarding the limitations of ultrasound as an imaging modality has been included, as well as a statement on ureteroscopy. The recommendation regarding the use of other imaging modalities was removed.
9.1	Management of stone problems in children. Aetiology.	A recommendation for stone analysis was added.
9.1.1	Nuclear imaging.	The recommendations have been expanded.
10.1.2	Stones in urinary diversion and other voiding problems.	Management. A new statement and a recommendation have been added.
10.2.2.	Management of stones in patients with neurogenic bladder.	A caution for latex allergy is included.
10.3.1	Management of stones in transplanted kidney. Aetiology and clinical presentation.	A recommendation has been added for imaging assessment.
11	Metabolic evaluation.	This chapter has been completely replaced. Both the structure as well as the content is entirely new. Diagnostic assessment and considerations have been captured in an algorithm, while treatment options are generally presented in tables.

1.5.2 ***Potential conflict of interest statement***

The expert panel have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guidelines/online-guidelines/.

1.6 References

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2. CLASSIFICATION OF STONES

Urinary stones can be classified according to size, location, X-ray characteristics, aetiology of formation, composition, and risk of recurrence (1-4).

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.

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 here.

2.3 X-ray characteristics

Stones can be classified according to plain X-ray appearance [kidney-ureter-bladder (KUB) radiography] (Table 3), which varies according to mineral composition (3). Non-contrast-enhanced computer tomography (NCCT) can be used to classify stones according to density, inner structure and composition, which can affect treatment decisions (Section 6.3.4) (2,3).

Table 3: 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 11.11)

2.4 Aetiology of stone formation

Stones can be classified into those caused by: infection, or non-infectious causes (infection and non-infection stones); genetic defects; or adverse drug effects (drug stones) (Table 4).

Table 4: Stones classified by aetiology*

Non-infection stones
• Calcium oxalate
• Calcium phosphate (including brushite and carbonate apatite)
• Uric acid
Infection stones
• Magnesium ammonium phosphate
• Carbonate apatite
• Ammonium urate
Genetic causes
• Cystine
• Xanthine
• 2,8-dihydroxyadenine
Drug stones

**Section 11.4.2*

2.5 Stone composition

Metabolic aspects are important in stone formation, and metabolic evaluation is required to rule out any disorders. Analysis in relation to metabolic disorders is the basis for further diagnostic and management decisions. Stones are often formed from a mixture of substances. Table 5 lists the clinically most relevant substances and their mineral components.

Table 5: 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	Hydroxylapatite	$Ca_5(PO_3)3(OH)$
b-tricalcium phosphate	Whitlockite	$Ca_3(PO4)_2$
Carbonate apatite phosphate	Dahllite	$Ca_5(PO4)_3OH$
Calcium hydrogen phosphate	Brushite	$CaHPO_4.2H_2O$
Calcium carbonate	Aragonite	$CaCO_3$
Octacalcium phosphate		$Ca_8H_2(PO_4)_6 . 5H_2O$
Uric acid dihydrate	Uricite	$C_5H_4N_4O_3$
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		$[SCH_2CH(NH_2)COOH]_2$
Gypsum	Calcium sulphate dihydrate Zinc phosphate tetrahydrate	$CaSO_4.2 H_2O$ $Zn_3(PO_4)_2.4H_2O$
Xanthine		
2,8-dihydroxyadenine		
Proteins		
Cholesterol		
Calcite		
Potassium urate		
Trimagnesium phosphate		
Melamine		
Matrix		
Drug stones	• Active compounds crystallising in urine • Substances impairing urine composition (Ch. 11.11)	
Foreign body calculi		

2.6 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 (4,5). 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 6) (6,7).

Table 6: High-risk stone formers (6-12)

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 risk of stone formation, but prevention of stone recurrence is of more importance)
Diseases associated with stone formation
Hyperparathyroidism
Nephrocalcinosis
Gastrointestinal diseases (i.e., jejuno-ileal bypass, intestinal resection, Crohn's disease, malabsorptive conditions, enteric hyperoxaluria after urinary diversion) and bariatric surgery
Sarcoidosis
Genetically determined stone formation
Cystinuria (type A, B and AB)
Primary hyperoxaluria (PH)
Renal tubular acidosis (RTA) type I
2,8-dihydroxyadenine
Xanthinuria
Lesch-Nyhan syndrome
Cystic fibrosis
Drugs associated with stone formation
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

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3. DIAGNOSIS

3.1 Diagnostic imaging

Patients with urinary stones usually present with loin pain, vomiting, and sometimes fever, but may also be asymptomatic. Standard evaluation includes detailed medical history and physical examination. Clinical diagnosis should be supported by appropriate imaging.

If available, ultrasonography (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. US is safe (no risk of radiation), reproducible and inexpensive. It can identify stones located in the calices, pelvis, and pyeloureteric and vesicoureteric junctions, as well as in patients with upper urinary tract dilatation. For stones > 5 mm, US has a sensitivity of 96% and specificity of nearly 100% (1). For all stone locations, sensitivity and specificity of US reduces to 78% and 31%, respectively (1).

The sensitivity and specificity of KUB radiography is 44-77% and 80-87%, respectively (2). KUB radiography should not be performed if NCCT is considered (3), however, it is helpful in differentiating between radiolucent and radiopaque stones and 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.*

3.1.1 Evaluation of patients with acute flank pain

NCCT has become the standard for diagnosing acute flank pain, and has replaced intravenous urography (IVU), which was the gold standard for many years. NCCT can determine stone diameter and density. When stones are absent, the cause of abdominal pain should be identified.

Compared to IVU, NCCT shows higher sensitivity and specificity for identifying urinary stones (Table 7) (4-9).

Table 7: Comparison of NCCT and IVU

Reference	NCCT		IVU	
	Sensitivity	Specificity	Sensitivity	Specificity
Miller (5)	96%	100%	87%	94%
Niall (7)	100%	92%	64%	92%
Sourtzis (4)	100%	100%	66%	100%
Yilmaz (6)	94%	97%	52%	94%
Wang (8)	99%	100%	51%	100%

Recommendation	LE	GR
NCCT should be used to confirm stone diagnosis in patients with acute flank pain, because it is superior to IVU (10).	1a	A

NCCT can detect uric acid and xanthine stones, which are radiolucent on plain films, but not indinavir stones (11).

NCCT can determine stone density, inner structure of the stone and skin-to-stone distance; all of which
affect extracorporeal shock wave lithotripsy (SWL) outcome (12-15). The advantage of non-contrast imaging must be balanced against loss of information about renal function and urinary collecting system anatomy, as well as higher radiation dose (Table 8).

Radiation risk can be reduced by low-dose CT (16). In patients with body mass index (BMI) < 30, low-dose CT has been shown to have sensitivity of 86% for detecting ureteric stones < 3 mm and 100% for calculi > 3 mm (17). A meta-analysis of prospective studies (18) 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% (92.0-97.0).

Table 8: Radiation exposure of imaging modalities (19-22)

Method	Radiation exposure (mSv)
KUB radiography	0.5-1
IVU	1.3-3.5
Regular-dose NCCT	4.5-5
Low-dose NCCT	0.97-1.9
Enhanced CT	25-35

Recommendation	LE	GR
If NCCT is indicated in patients with BMI < 30, use a low-dose technique.	1b	A

3.1.2 Evaluation of patients for whom further treatment of renal stones is planned

Recommendation	LE	GR
A contrast study is recommended if stone removal is planned and the anatomy of the renal collecting system needs to be assessed.	3	A*
Enhanced CT is preferable because it enables 3D reconstruction of the collecting system, as well as measurement of stone density and skin-to-stone distance. IVU may also be used.		

** Upgraded based on panel consensus.*

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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.

Table 9: Recommendations: basic laboratory analysis - emergency urolithiasis patients (1-4)

Urine	**GR**
Urinary sediment/dipstick test of spot urine sample	A*
• red cells • white cells • nitrite • approximate urine pH Urine culture or microscopy	A
Blood	
Serum blood sample • creatinine • uric acid • ionised calcium • sodium • potassium	A*
Blood cell count CRP	A*
If intervention is likely or planned: Coagulation test (PTT and INR)	A*

** Upgraded based on panel consensus.*
CPR = C-reactive protein; INR = international normalised ratio; PTT = partial thromboplastin time.

*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, CRP, and blood coagulation time can be omitted.

Only patients at high risk for stone recurrence should undergo a more specific analytical programme (4). Stone-specific metabolic evaluation is described in Chapter 11.

The easiest means to achieve correct diagnosis is by analysis of a passed stone using a valid method as listed below (see 3.2.2). Once mineral composition is known, the potential metabolic disorders can be identified.

*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 case of:

- recurrence under pharmacological prevention;
- early recurrence after interventional therapy with complete stone clearance;
- late recurrence after a prolonged stone-free period (6).

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) (5,7-10). Equivalent results can be obtained by polarisation microscopy, but only in centres with expertise. Chemical analysis (wet chemistry) is generally deemed to be obsolete (5).

Recommendations	**LE**	**GR**
Always perform stone analysis in first-time formers using a valid procedure (XRD or IRS).	2	A
Repeat stone analysis in patients: • presenting with reccurent 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 (3).	2	B

3.3 References

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4. TREATMENT OF PATIENTS WITH RENAL COLIC

4.1 Renal colic

4.1.1 ***Pain relief***

Pain relief is the first therapeutic step in patients with an acute stone episode (1,2).

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective in patients with acute stone colic (3-6), and have better analgesic efficacy than opioids. Patients receiving NSAIDs are less likely to require further analgesia in the short term.

Opioids, particularly pethidine, are associated with a high rate of vomiting compared to NSAIDs, and carry a greater likelihood of further analgesia being needed (7,8) (Section 4.1.3). If an opioid is used, it is recommended that it is not pethidine.

Statement	LE
For symptomatic ureteral stones, urgent SWL as first-line treatment is a feasible option (9).	1b

Recommendations	GR
In acute stone episodes, pain relief should be initiated immediately.	A
Whenever possible, an NSAID should be the first drug of choice.	A

4.1.2 ***Prevention of recurrent renal colic***

Facilitation of passage of ureteral stones is discussed in Section 5.3.

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 risk of recurrent pain (8,10,11). Although diclofenac can affect renal function in patients with already reduced function, it has no effect in patients with normal kidney function (LE: 1b) (12).

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 7 days of treatment (11).

Daily α-blockers reduce recurrent colic (LE: 1a) (Section 5.3) (13,14).

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

4.1.3 ***Recommendations for analgesia during renal colic***

	LE	GR
First choice: start with an NSAID, e.g. diclofenac*, indomethacin or ibuprofen**.	1b	A
Second choice: hydromorphine, pentazocine or tramadol.	4	C
Use α-blockers to reduce recurrent colics.	1a	A

**Affects glomerular filtration rate (GFR) in patients with reduced renal function (15) (LE: 2a).*
***Recommended to counteract recurrent pain after ureteral colic.*

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4.2 Management of sepsis in obstructed kidney

The obstructed kidney with all signs of urinary tract infection (UTI) 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.

The optimal method of decompression has yet to be established (1-3). However, it is known that compromised delivery of antibiotics into the obstructed kidney means that the collecting system must be drained to encourage resolution of infection.

*4.2.1 **Decompression***

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

- placement of an indwelling ureteral catheter;
- percutaneous placement of a nephrostomy catheter.

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 (1,4,5).

Only two RCTs (2,5) have assessed 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 (1).

Definitive stone removal should be delayed until the infection is cleared following a complete course of antimicrobial therapy (6,7).

Emergency nephrectomy may become necessary in highly complicated cases to eliminate further complications.

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

Recommendation	**LE**	**GR**
For sepsis with obstructing stones, the collecting system should be urgently decompressed, using percutaneous drainage or ureteral stenting.	1b	A
Definitive treatment of the stone should be delayed until sepsis is resolved.	1b	A

*4.2.2 **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. The regimen should be re-evaluated in the light of the culture-antibiogram test. Intensive care might become necessary.

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

** Upgraded based on panel consensus.*

*4.2.3 **References***

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5. STONE RELIEF

When deciding between active stone removal and conservative treatment with medical expulsive therapy (MET), it is important to consider all the patients' circumstances that may affect treatment decisions (1).

5.1 Observation of ureteral stones

5.1.1 Stone-passage rates

There are only limited data about spontaneous stone passage according to size (2,3). A meta-analysis of 328 patients harbouring ureteral stones < 10 mm investigated the likelihood of ureteral stone passage (Table 10) (2). These studies had limitations including non-standardisation of stone size measurement, and lack of analysis of stone position, stone-passage history, and time to stone passage.

Table 10: Likelihood of ureteral stone passage of ureteral stones (2)

Stone size	Average time to pass	Percentage of passages (95% CI)
< 5 mm (n = 224)		68% (46-85%)
> 5 mm (n = 104)		47% (36-58%)
< 2 mm	31 days	
2-4 mm	40 days	
4-6 mm	39 days	

95% of stones up to 4 mm pass within 40 days (3).

Recommendations	LE	GR
In patients with newly diagnosed ureteral stones < 10 mm, and if active removal is not indicated (Chapter 6), observation with periodic evaluation is an optional initial treatment.	1a	A
Such patients may be offered appropriate medical therapy to facilitate stone passage during observation.*		

**see Section 5.3, Medical expusive therapy (MET).*

5.2 Observation of kidney stones

Observation of kidney stones, especially in calices, depends on their natural history (Section 6.2.1).

Statement	LE
It is still debatable whether kidney stones should be treated, or whether annual follow-up is sufficient for asymptomatic caliceal stones that have remained stable for 6 months.	4

Recommendations	GR
Kidney stones should be treated in case of growth, formation of de novo obstruction, associated infection, and acute or chronic pain.	A
Comorbidity and patient preference need to be taken into consideration when making treatment Decisions.	C
If kidney stones are not treated, periodic evaluation is needed.	A

** Upgraded based on panel consensus.*

5.3 Medical expulsive therapy (MET)

Drugs that expel stones might act by relaxing ureteral smooth muscle through inhibition of calcium channel pumps or α-1 receptor blockade (4,5).

MET should only be used in patients who are comfortable with this approach and when there is no obvious
advantage from immediate active stone removal.

Meta-analyses have shown that patients with ureteral stones treated with α-blockers or nifedipine are more likely to pass stones with fewer episodes of colic than those not receiving such therapy (4,5).

Statement	LE
There is good evidence that MET accelerates spontaneous passage of ureteral stones and fragments generated with SWL, and limits pain (4-16).	1a

5.3.1 Medical agents

Tamsulosin is one of the most commonly used α-blockers (4,6,17-20). However, one small study has suggested that tamsulosin, terazosin and doxazosin are equally effective, indicating a possible class effect (21). This is also indicated by several trials demonstrating increased stone expulsion using doxazosin (4,21,22), terazosin (21,23), alfuzosin (24-27) naftopidil (28,29), and silodosin (30,31).

Statement	LE
Several trials have demonstrated an α-blocker class effect on stone expulsion rates.	1b

With regard to the class effect of calcium-channel blockers, only nifedipine has been investigated (LE = 1a) (4,9-11,32,33).

Administration of tamsulosin and nifedipine is safe and effective in patients with distal ureteral stones with renal colic. However, tamsulosin is significantly better than nifedipine in relieving renal colic and facilitating and accelerating ureteral stone expulsion (11,32,33).

Based on studies with a limited number of patients (34,35) (LE 1b), no recommendation for the use of corticosteroids in combination with α-blockers in MET can be made.

Statement	LE
There is no evidence to support the use of corticosteroids as monotherapy for MET. Insufficient data exist to support the use of corticosteroids in combination with α-blockers as an accelerating adjunct (3,21,34,35).	1b

Recommendations for MET	LE	GR
For MET, α-blockers are recommended.	1a	A
Patients should be counseled about the attendant risks of MET, including associated drug side effects, and should be informed that it is administered off-label†**.		A*
Patients, who elect for an attempt at spontaneous passage or MET, should have well-controlled pain, no clinical evidence of sepsis, and adequate renal functional reserve.		A
Patients should be followed once between 1 and 14 days to monitor stone position and be assessed 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.*

5.3.2 Factors affecting success of medical expulsive therapy (tamsulosin)

5.3.2.1 Stone size

Due to the high likelihood of spontaneous passage of stones up to ~5 mm, MET is less likely to increase the stone-free rate (SFR) (5,36-39) (LE: 1b). However, MET does reduce the need for analgesics (4,6) (LE: 1a).

5.3.2.2 Stone location

The vast majority of trials have investigated distal ureteral stones (4). One RCT has assessed the effect of tamsulosin on spontaneous passage of proximal ureteral calculi 5-10 mm. The main effect was to encourage stone migration to a more distal part of the ureter (40) (LE: 1b).

5.3.2.3 Medical expulsive therapy after extracorporeal shock wave lithotripsy (SWL)
Clinical studies and several meta-analyses have shown that MET after SWL for ureteral or renal stones can expedite expulsion and increase SFRs and reduce analgesic requirements (7,12,41-49) (LE: 1a).

5.3.2.4 Medical expulsive therapy after ureteroscopy
MET following holmium:YAG laser lithotripsy increases SFRs and reduces colic episodes (50) (LE: 1b).

5.3.2.5 Medical expulsive therapy and ureteral stents (Section 5.6.2.1.8)

5.3.2.6 Duration of medical expulsive therapy treatment
Most studies have had a duration of 1 month or 30 days. No data are currently available to support other time-intervals.

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5.4 Chemolytic dissolution of stones

Oral or percutaneous irrigation chemolysis of stones or their fragments can be useful first-line therapy. It may also be an adjunct to SWL, percutaneous nephrolithotomy (PNL), ureterorenoscopy (URS) or open surgery to support elimination of small residual fragments, considering that its use as first-line therapy may take several weeks to be effective.

Combined treatment with SWL and chemolysis is a minimally invasive option for patients with partial or complete infection staghorn stones who are not eligible for PNL. Stone fragmentation leads to increased stone surface area and improved efficacy of chemolitholysis.

Chemolysis is possible only for the stone compositions listed below, therefore, knowledge of stone composition is mandatory before treatment.

*5.4.1 **Percutaneous irrigation chemolysis***

Percutaneous irrigation chemolysis may be an option for infection- and uric acid stones (1,2).

Recommendations	GR
In percutaneous chemolysis, at least two nephrostomy catheters should be used to allow irrigation of the renal collecting system, while preventing chemolytic fluid draining into the bladder and reducing the risk of increased intrarenal pressure*.	A
Pressure- and flow-controlled systems should be used if available.	

** Alternatively, one nephrostomy catheter with a JJ stent and bladder catheter can serve as a through-flow system preventing high pressure.*

Table 11: Methods of percutaneous irrigation chemolysis

Stone composition	Refs.	Irrigation solution	Comments
Struvite Carbon apatite	1-6	10% hemiacidrin, pH 3.5-4, Suby's G	Combination with SWL for staghorn stones.
			Risk of cardiac arrest due to hypermagnesaemia.
Brushite	7	Hemiacidrin Suby's G	Can be considered for residual fragments.
Cystine	8-13	Trihydroxymethyl aminomethane (THAM; 0.3 or 0.6 mol/L), pH 8.5-9.0, N-acetylcysteine (200 mg/L)	Takes significantly longer time than for uric acid stones.
			Used for elimination of residual fragments.
Uric acid	10,14-18	THAM (0.3 or 0.6 mol/L), pH 8.5-9.0	Oral chemolysis is the preferred option.

Irrigation chemolysis appears to the panel to be used rarely, probably because of the complexity of the technique and the possible side effects.

*5.4.2 **Oral chemolysis***

Oral chemolitholysis is efficient only for uric acid calculi, and is based on alkalinisation of urine by application of alkaline citrate or sodium bicarbonate (3-6).

When chemolitholysis is planned, the pH should be adjusted to 6.5-7.2. Within this range chemolysis is more effective at a higher pH, which, however, might lead to calcium phosphate stone formation.

In case of uric acid obstruction of the collecting system, oral chemolysis in combination with urinary drainage is indicated (7). A combination of alkalinisation with tamsulosin seems to achieve the highest SFRs for distal ureteral stones (8).

Recommendations	GR
The dosage of alkalising medication must be modified by the patient according to urine pH, which is a direct consequence of such medication.	A
Dipstick monitoring of urine pH by the patient is required at regular intervals during the day. Morning urine must be included.	A
The physician should clearly inform the patient of the significance of compliance.	A

5.4.3 ***References***

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5.5 Extracorporeal shock wave lithotripsy (SWL)

Introduction of SWL in the early 1980s dramatically changed the management of urinary tract stones. The development of new lithotripters, modified indications, and treatment principles has also completely changed urolithiasis treatment. Modern lithotripters are smaller and usually included in uroradiological tables. They ensure application of SWL and other associated diagnostic and ancillary procedures.

More than 90% of stones in adults might be suitable for SWL treatment (1-3). However, success depends on the efficacy of the lithotripter and the following factors:

- size, location (ureteral, pelvic or calyceal), and composition (hardness) of the stones (Chapter 6);
- patient's habitus (Chapter 6);
- performance of SWL (best practice, see below).

Each of these factors has an important influence on retreatment rate and final outcome of SWL.

5.5.1 ***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 (4);
- bleeding diatheses, which should be compensated for at least 24 h before and 48 h after treatment (5);
- uncontrolled UTIs;
- severe skeletal malformations and severe obesity, which prevent targeting of the stone;
- arterial aneurysm in the vicinity of the stone (6);
- anatomical obstruction distal to the stone.

5.5.2 ***Stenting before carrying out extracorporeal shock wave lithotripsy***

5.5.2.1 Stenting in kidney stones

Routine use of internal stents before SWL does not improve SFR (LE: 1b) (7). A JJ stent reduces the risk of renal colic and obstruction, but does not reduce formation of steinstrasse or infective complications (8).

However, stone particles may pass along stents while urine flows in and around the stent. This usually prevents obstruction and loss of ureteral contractions. Occasionally, stents do not efficiently drain purulent or mucoid material, increasing the risk of obstructive pyelonephritis. If fever occurs and lasts for a few days despite proven correct stent position, the stent must be removed and replaced by a new JJ stent or a percutaneous nephrostomy tube, even when US does not reveal any dilatation. (panel consensus)

5.5.2.2 Stenting in ureteral stones

The 2007 AUA/EAU Guidelines on the management of ureteral calculi state that routine stenting is not recommended as part of SWL (9). When the stent is inserted, patients often suffer from frequency, dysuria, urgency, and suprapubic pain (10).

Recommendation	LE	GR
Routine stenting is not recommended as part of SWL treatment of ureteral stones.	1b	A

5.5.3 ***Best clinical practice***

5.5.3.1 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 (11).

5.5.3.2 Shock wave rate

Lowering shock wave frequency from 120 to 60-90 shock waves/min improves SFR (12-16). Tissue damage increases with shock wave frequency (17-19).

Recommendation	LE	GR
The optimal shock wave frequency is 1.0-1.5 Hz (16).	1a	A

5.5.3.3 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 (20), which prevents renal injury (21). Animal studies (22) and a prospective randomised study (23) 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 (24,25).

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).

Statement	LE
Clinical experience has shown that repeat sessions are feasible (within 1 day for ureteral stones).	4

5.5.3.4 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 reflect 99% of shock waves. A defect of only 2% in the gel layer covering the cushion reduces stone fragmentation by 20-40% (26). US gel is probably the optimum agent available for use as a lithotripsy coupling agent (27). To reduce air pockets, the gel should be applied to the water cushion straight from the container, rather than by hand (28).

Recommendation	LE	GR
Ensure correct use of the coupling gel because this is crucial for effective shock wave transportation (26).	2a	B

5.5.3.5 Procedural control

Results of treatment are operator dependent, and better results are obtained by experienced urologists. During the procedure, careful imaging control of localisation contributes to outcome quality (29).

Recommendation	LE	GR
Maintain careful fluoroscopic and/or ultrasonographic monitoring during the procedure.	4	A*

** Upgraded based on panel consensus.*

5.5.3.6 Pain control

Careful control of pain during treatment is necessary to limit pain-induced movements and excessive respiratory excursions (30-32).

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

5.5.3.7 Antibiotic prophylaxis

No standard antibiotic prophylaxis before SWL is recommended. However, prophylaxis is recommended in 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) (33,34).

Recommendation	LE	GR
In case of infected stones or bacteriuria, antibiotics should be given prior to SWL.	4	C

5.5.3.8 Medical expulsive therapy after extracorporal shock wave lithotripsy

MET after SWL for ureteral or renal stones can expedite expulsion and increase SFRs, as well as reduce additional analgesic requirements (35-45) (Section 5.3.2.3).

*5.5.4 **Complications of extracorporeal shock wave lithotripsy***

Compared to PNL and ureteroscopy, there are fewer overall complications with SWL (46,47) (Table 12).

Table 12: SWL-related complications (1,4,46-48)

Complications			%	Refs.
Related to stone fragments		Steinstrasse	4 - 7	49-51
		Regrowth of residual fragments	21 - 59	52
		Renal colic	2 - 4	48
Infectious		Bacteriuria in non-infection stones	7.7 - 23	52,53
		Sepsis	1 - 2.7	52,53
Tissue effect	Renal	Haematoma, symptomatic	< 1	1,54
		Haematoma, asymptomatic	4 - 19	1,54
	Cardiovascular	Dysrhythmia	11 - 59	52,55
		Morbid cardiac events	Case reports	52,55
	Gastrointestinal	Bowel perforation	Case reports	56-58
		Liver, spleen haematoma	Case reports	58-60

The relationship between SWL and hypertension or diabetes is unclear. Published data are contradictory and no conclusion can be reached (9,61-63).

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5.6 Endourology techniques

*5.6.1 **Percutaneous nephrolithotomy (PNL)***

Since the 1980s PNL has been developed as 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. So called "Mini-PNL" was introduced initially for paediatric use, but has also become popular in adults. Usually, the term Mini-PNL is used for access sheaths < 18 F, however, the terminology has not been standardised. The benefits of such miniaturised instruments remain controversial (1,2).

5.6.1.2 Intracorporeal lithotripsy

Several methods for intracorporal lithotripsy are available (the devices are discussed in Section 5.6.2.2.7). During PNL, ultrasonic and pneumatic systems are most commonly used for rigid nephroscopy. Flexible endoscopes require laser lithotripsy to maintain tip deflection and the Ho:YAG laser has become the standard, as for ureteroscopy (3) . Electrohydraulic lithotripsy (EHL) is highly effective but is no longer considered as a first-line technique, due to frequent collateral damage (4).

Recommendations	GR
Ultrasonic, ballistic and Ho:YAG devices are recommended for intracorporeal lithotripsy during PNL.	A*
When using flexible instruments, the Ho:YAG laser is currently the most effective device.	

** Upgraded based on panel consensus.*

5.6.1.3 Extraction tools

Stones or stone fragments are extracted from the kidney through the access sheath of the nephroscope using forceps or baskets. Nitinol (nickel-titanium alloy) baskets provide additional advantages compared with steel wire baskets, such as increased flexibility. Tipless versions of nitinol baskets are also available for use in calices.

5.6.1.4 Best clinical practice

5.6.1.4.1 Contraindications

All contraindications for general anaesthesia apply. Patients receiving anticoagulant therapy must be monitored carefully pre- and postoperatively. Anticoagulant therapy must be discontinued before PNL (5).

Other important contraindications include:

- untreated UTI;
- atypical bowel interposition;
- tumour in the presumptive access tract area;
- potential malignant kidney tumour;
- pregnancy (Section 8.2).

5.6.1.4.2 Preoperative imaging

Preprocedural evaluations are summarised in Chapter 3. In particular for PNL, US or CT of the kidney and the surrounding structures can provide information about interpositioned organs within the planned percutaneous path (e.g., spleen, liver, large bowel, pleura, and lung) (6).

Recommendation	GR
Preprocedural imaging, including contrast medium where possible or retrograde study when starting the procedure, is mandatory to assess stone comprehensiveness, view the anatomy of the collecting system, and ensure safe access to the kidney stone.	A*

** Upgraded based on panel consensus.*

5.6.1.4.3 Positioning of the patient

Traditionally, the patient is positioned prone for PNL. The supine position is also possible, with or without flank upholstering. Both positions are equally safe. The advantages of the supine position for PNL are (7,8):

- shorter operating time;
- possibility of simultaneous retrograde transurethral manipulation;
- more convenient position for the operator;
- easier anaesthesia.

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 operating table.

5.6.1.4.4 Puncture

Colon interposition in the access tract of PNL can lead to colon injuries. Although rare, such injuries are more likely when operating on the left kidney. Preoperative CT or intraoperative US allows identification of the tissue between the skin and kidney and lowers the incidence of bowel injury (9-11).

5.6.1.4.5 Dilatation

Dilatation of the percutaneous access tract can be achieved using a metallic telescope, single (serial) dilators, or a balloon dilatator. The difference in outcomes is less related to the technology used than to the experience of the surgeon (12).

5.6.1.4.6 Nephrostomy and stents

The decision about 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 intraoperative blood loss;
- urine extravasation;
- ureteral obstruction;
- potential persistent bacteriuria due to infected stones;
- solitary kidney;
- bleeding diathesis;
- planned percutaneous chemolitholysis.

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 (13-16).

Recommendation	LE	GR
In uncomplicated cases, tubeless (without nephrostomy tube) or totally tubeless (without nephrostomy tube and ureteral stent) PNL procedures provide a safe alternative.	1b	A

5.6.1.6 Management of complications

The most common postoperative complications associated with PNL are fever and bleeding, urinary leakage, and problems due to residual stones. A recent review on complications following PNL used the validated Dindo-modified Clavien System and showed a normal (uncomplicated) postoperative course in 76.7% of patients (Clavien 0) (25) (Table 13). See also the EAU Guidelines on Reporting and Grading of Complications after Surgical Procedures (17).

Table 13: Complications following PNL

Complications	Transfusion	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%		

Urinary leakage and stone clearance can be viewed endoscopically and by X-ray anlaysis. In doubtful cases, complications can be minimised by performing standard rather than totally tubeless PNL.

Perioperative fever can occur, even with a sterile preoperative urinary culture and perioperative antibiotic prophylaxis, because the kidney stones themselves may be a source of infection. Intraoperative kidney stone culture may therefore help to select postoperative antibiotics (18,19). Intraoperative irrigation pressure < 30 mm Hg and unobstructed postoperative urinary drainage may be important factors in preventing postoperative sepsis. Well-positioned or specially designed access sheaths can prevent high intrapelvic irrigation pressure (20).

Bleeding after PNL may be treated by brief clamping of the nephrostomy tube. Super-selective embolic occlusion of the artery may become necessary in case of severe bleeding.

*5.6.2 **Ureterorenoscopy (URS) (including retrograde access to renal collecting system)***

URS has dramatically changed the management of ureteral calculi. Major technical improvements include endoscope miniaturisation, enhanced optical quality and tools, and introduction of disposables. The current standard for rigid ureterorenoscopes are tip diameters of < 8 F. Rigid URS can be used for the whole ureter (21). Major technological progress has been achieved for retrograde intrarenal surgery [RIRS (flexible URS)], with improved deflection mechanisms, better durability, and recently, digital optical systems (22-24). Initial experience with digital scopes has demonstrated shorter operation times due to the improvement in image quality (25-27). In Europe, RIRS is mainly used for the renal collecting system and - in cases with difficult anatomy - the upper ureter.

5.6.2.1 Best clinical practice in ureterorenoscopy (URS)

5.6.2.1.1 Preoperative work-up and preparations

Before the procedure, the following information should be sought and actions taken (LE: 4):

- patient history;
- physical examination, because anatomical and congenital abnormalities may complicate or prevent retrograde stone manipulation;
- thrombocyte aggregation inhibitors/anticoagulants (antiplatelet drugs) should be discontinued if possible, however URS can be performed in patients with bleeding disorders, with a moderate increase in complications (5,28);
- imaging.

Recommendation	LE	GR
Short-term antibiotic prophylaxis should be administered (27).	4	A*

** Upgraded based on panel consensus.*

5.6.2.1.2 Contraindications

Apart from general problems, for example, with general anaesthesia or untreated UTIs, URS can be performed in all patients without any specific contraindications. Specific problems such as ureteral strictures may prevent successful retrograde stone management.

5.6.2.1.3 Access to the upper urinary tract

Most interventions are performed under general anaesthesia, although local or spinal anaesthesia is possible. Instrument miniaturisation means that intravenous sedation can be used to achieve the same outcome (29).

Intravenous sedation with miniaturised instruments is especially suitable for female patients with distal ureteral stones. However, kidney movement is more pronounced with local or intravenous anaesthesia, which may hinder RIRS.

Antegrade URS is an option for large, impacted proximal ureteral calculi (30) (Section 6.5.3).

5.6.2.1.4 Safety aspects

Fluoroscopic equipment must be available in the operating room. We recommend placement of a safety wire, even though some groups have demonstrated that URS can be performed without it (31,32). A safety wire prevents false passage in case of perforation, and ensures that a JJ stent can be inserted in difficult situations, thus avoiding more significant complications.

Retrograde access to the upper urinary tract is usually obtained under endoscopic guidance.

Balloon and plastic dilators are available if necessary. If insertion of a flexible URS is difficult, prior rigid ureteroscopy can be helpful for optical dilatation. If ureteral access is not possible, insertion of a JJ stent followed by URS after 7-14 days offers an alternative procedure.

Recommendation	GR
Placement of a safety wire is recommended.	A*

** Upgraded based on panel consensus.*

5.6.2.1.5 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 intrarenal pressure, and potentially reducing operating time (33,34).

Ureteral access sheaths allow continuous outflow of irrigation fluid, which improves visual quality and maintains a low-pressure system (35,36). The insertion of ureteral access sheaths may lead to ureteral damage, however, no data on long-term consequences are available (37). Use of ureteral access sheaths depends on the surgeon's preference.

5.6.2.1.6 Stone extraction

The aim of URS is complete stone removal (especially ureteric stones). "Smash and go" strategies should be limited to the treatment of large renal stones.

Stones can be extracted by endoscopic forceps or baskets. Forceps allow safe release of stone fragments if they become stuck within the ureter, but extraction takes longer than when using baskets. Only baskets made of nitinol can be used for RIRS (38).

Statements
Nitinol baskets preserve the tip deflection of flexible ureterorenoscopes, and the tipless design reduces the risk of mucosal injury.
Nitinol baskets are the only baskets suitable for use in RIRS.

Recommendation	LE	GR
Stone extraction using a basket without endoscopic visualisation of the stone (blind basketing) should not be performed.	4	A*

** Upgraded based on panel consensus.*

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 (Section 6.4.2) (43).

5.6.2.1.7 Intracorporeal lithotripsy

The most effective lithotripsy system is the Ho:YAG laser, which has become the gold standard for ureteroscopy and flexible nephroscopy (Section 5.6.1.2), because it is effective for all stone types (3,39-41). Pneumatic and US systems can be used with high disintegration efficacy in rigid URS (42-44). However, stone migration into the kidney is a common problem, which can be prevented by placement of special tools proximal of the stone (45).

Recommendation	LE	GR
Ho:YAG laser lithotripsy is the preferred method for (flexible) URS.	3	B

5.6.2.1.8 Stenting before and after URS

Routine stenting is no longer necessary before URS. However, pre-stenting facilitates ureteroscopic management of stones, improves the SFR, and reduces complications (46).

Most urologists routinely insert a JJ stent following URS, although several randomised prospective trials have found that routine stenting after uncomplicated URS (complete stone removal) is not necessary; stenting might be associated with higher postoperative morbidity (47-49). A ureteric catheter with a shorter indwelling time (1 day) may be used as well, with similar results (50).

Stents should be inserted in patients who are at increased risk of complications (e.g., 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. Patients should be followed up with a plain abdominal film (KUB), CT or US.

α-Blockers reduce the morbidity of ureteral stents and increase tolerability (51). A recently published meta-analysis provides evidence for improvement of ureteral stent tolerability with tamsulosin (52).

Statement	LE
In uncomplicated URS, a stent need not be inserted.	1a
An α-blocker can reduce stent-related symptoms.	1a

5.6.2.2 Complications

The overall complication rate after URS is 9-25% (21,53) (Table 14). Most are minor and do not require intervention. Ureteral avulsion and strictures used to be greatly feared, but nowadays are rare in experienced hands (< 1%). Previous perforations are the most important risk factor for complications.

Table 14: Complications of URS*

	Rate (%)
Intraoperative complications	3.6
Mucosal injury	1.5
Ureteral perforation	1.7
Significant bleeding	0.1
Ureteral avulsion	0.1
Early complications	6.0
Fever or urosepsis	1.1
Persistent haematuria	2.0
Renal colic	2.2
Late complications	0.2
Ureteral stricture	0.1
Persistent vesicoureteral reflux	0.1

**From Geavlete, et al.(53).*

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5.7 Open and laparoscopic surgery for removal of renal stones

*5.7.1 **Open surgery***

Advances in SWL and endourological surgery (URS and PNL) have significantly decreased the indications for open stone surgery, which is now often a second- or third-line treatment option needed in only 1.0-5.4% of cases (1-5). The incidence of open stone surgery is ~1.5% of all stone removal interventions in developed countries, and in developing countries, it has dropped from 26% to 3.5% in recent years (3,5).

However, open surgery is still needed for the most difficult stones, which supports the importance of maintaining proficiency, skills and expertise in open renal and ureteral surgical techniques such as extended pyelolithotomy, pyelonephrolithotomy, anatrophic nephrolithotomy, multiple radial nephrotomy, partial nephrectomy, and renal surgery under hypothermia (6-10) (Table 15).

Recently, intraoperative B-mode scanning and Doppler sonography (11,12) have been used to identify avascular areas in the renal parenchyma that are close to the stone or dilated calices. This allows removal of large staghorn stones by multiple small radial nephrotomy, without loss of kidney function.
The efficacy of open surgery compared to less-invasive therapy in terms of SFRs, is based on historical data, but no comparative studies are available (13-16).

5.7.1.1 Indications for open surgery

There is a consensus that most complex stones, including partial and complete staghorn stones, should be approached primarily with PNL or combined PNL and SWL. If a reasonable number of percutaneous approaches are not likely to be successful, or if multiple, endourological approaches have been performed unsuccessfully, open surgery may be a valid treatment option.

Table 15: Indications for open surgery

Complex stone burden.
Failure of SWL, PNL, or ureteroscopic procedure.
Intrarenal anatomical abnormalities: infundibular stenosis; stone in the calyceal diverticulum (particularly in an anterior calyx); obstruction of the ureteropelvic junction; and stricture if endourologic procedures have failed or are not promising.
Morbid obesity.
Skeletal deformity, contractures and fixed deformities of hips and legs.
Comorbidity.
Concomitant open surgery.
Non-functioning lower pole (partial nephrectomy), non-functioning kidney (nephrectomy).
Patient choice following failed minimally invasive procedures; the patient may prefer a single procedure and avoid the risk of needing more than one PNL procedure.
Stone in an ectopic kidney where percutaneous access and SWL may be difficult or impossible.
For the paediatric population, the same considerations apply as for adults.

*5.7.2 **Laparoscopic surgery***

Laparoscopic urological surgery is increasingly replacing open surgery. Today laparoscopic surgery is used to remove renal and ureteric stones in certain situations, including complex stone burden, failed previous SWL and/or endourological procedures, anatomical abnormalities or morbid obesity, and planned nephrectomy of a stone-containing non-functioning kidney. Although surgical pyelolithotomy is rarely indicated (Table 16), laparoscopic removal of solitary large renal pelvic (17) as well as anterior caliceal diverticular stones is possible in selected cases (18). Stone-free rates are reported to be equal to PNL, but complications are more frequent, using laparoscopic retroperitoneal pyelolithotomy (17). Additionally, as a less-invasive option, laparoscopic anatrophic nephrolithotomy has been found to be effective for the removal of complex staghorn stones; however, PNL is still the method of choice and laparoscopic stone removal should be reserved for selected cases (19,20).

Laparoscopic ureterolithotomy is relatively easy, with SFRs up to 100% provided expertise is available (21-24). It can replace open surgery in most situations (15,16). Retroperitoneal and transperitoneal laparoscopic access to all portions of the ureter has been reported (24-30), although laparoscopic ureterolithotomy in the distal ureter is less successful than in the middle and proximal ureter, but the size of the stone does not appear to influence outcome. Although highly effective, laparoscopic ureterolithotomy is not first-line therapy in most cases because of its invasiveness, longer recovery time, and greater risk of associated complications compared to SWL and URS (21-24) (Table 16).

5.7.2.1 Table 16: Indications for laparoscopic stone surgery

Indications for laparoscopic kidney-stone surgery include: • Complex stone burden • Failed previous SWL and/or endourological procedures • Anatomical abnormalities • Morbid obesity • Nephrectomy in case of non-functioning kidney.
Indications for laparoscopic ureteral stone surgery include: • Large impacted ureteral stones • In cases of concurrent conditions requiring surgery • When other non-invasive or low-invasive procedures have failed • For upper ureteral calculi, laparoscopic urolithomy has the highest stone-free rate compared to URS and SWL (31) (LE: 1b).

Recommendations	LE	GR
Laparoscopic or open surgical stone removal may be considered in rare cases in which SWL, URS, and percutaneous URS fail or are unlikely to be successful.	3	C
When expertise is available, laparoscopic surgery should be the preferred option before proceeding to open surgery. An exception is complex renal stone burden and/or stone location.	3	C
For ureterolithotomy, laparoscopy is recommended for large impact stones or when endoscopic lithotripsy or SWL has failed.	2	B

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6. INDICATION FOR ACTIVE STONE REMOVAL AND SELECTION OF PROCEDURE

Although kidney stones might be asymptomatic, ureteral stones cause acute renal colic in most cases. Treatment decisions for upper urinary tract calculi are based on several general aspects such as stone composition, stone size, and symptoms.

6.1 Indications for active removal of ureteral stones (1-3)

- Stones with low likelihood of spontaneous passage.
- Persistent pain despite adequate analgesic medication.
- Persistent obstruction.
- Renal insufficiency (renal failure, bilateral obstruction, or single kidney).

6.2 Indications for active removal of kidney stones (4)

- 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.

6.2.1 Natural history of caliceal stones

Natural history of small, non-obstructing asymptomatic lower pole calculi is not well defined, and the risk of progression is unclear. There is still no consensus on the follow-up duration, and timing and type of intervention.

Statement	LE
Although the question of whether caliceal stones should be treated is still unanswered, stone growth, de novo obstruction, associated infection, and acute and/or chronic pain are indications for treatment (4-6).	3

Glowacki et al. have reported that the risk of a symptomatic episode or need for intervention was ~10% per year, with a cumulative 5-year event probability of 48.5% (7). In a recent retrospective study, 77% of asymptomatic patients with renal stones of all sizes experienced disease progression, with 26% requiring surgical intervention (8).

In a retrospective study, Hubner and Porpaczy have assumed that 83% of caliceal calculi require intervention within the first 5 years of diagnosis (9). Inci et al. have investigated lower pole caliceal stones, and observed that within a follow-up period of 52.3 months, nine (33.3%) patients had increased stone size, and three (11%) required intervention (10).

However, in a prospective RCT with 2.2 years clinical follow-up, Keeley et al. have reported no significant difference between SWL and observation when they compared asymptomatic caliceal stones < 15 mm in terms of SFR, symptoms, requirement for additional treatment, quality of life, renal function, or hospital admission (11). Although some have recommended prophylaxis for these stones to prevent renal colic, haematuria, infection, or stone growth, conflicting data have been reported (7,9,12).

In a follow-up period of almost 5 years after SWL, Osman et al. have demonstrated that 21.4% of patients with small residual fragments needed treatment. A similar figure is given by Rebuck et al. Although these studies are based on residuals after SWL and URS respectively, they may serve as information about natural history of renal stones (13,14).

Excellent SFRs and pain relief have been reported after removal of small caliceal stones by SWL, PNL or URS, which indicates the need for removal of symptomatic caliceal stones (12-14).

Recommendations	GR
For asymptomatic caliceal stones in general, active surveillance with annual follow-up of symptoms and stone status (KUB radiography, US, or NCCT) is an option for 2-3 years, whereas intervention should be considered after this period provided patients are adequately informed.	C
Observation might be associated with a greater risk of necessitating more invasive procedures.	

6.2.2 *References*

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6.3 General recommendations and precautions for stone removal

6.3.1 *Infections*

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
Urine culture or urinary microscopy is mandatory before any treatment is planned.	A*

**Upgraded following panel consensus.*

6.3.2 *Anticoagulation and stone treatment*

Patients with a bleeding diathesis, or receiving anticoagulation, should be referred to an internist for appropriate therapeutic measures before and during stone removal (1-3). In patients with an uncorrected bleeding diathesis, the following are contraindicated:

- SWL;
- PNL;
- percutaneous nephrostomy;
- laparoscopic surgery;
- open surgery (4-6).

Although SWL is feasible and safe after correction of underlying coagulopathy (7-9), URS might offer an alternative approach and is associated with less morbidity. In contrast to ESWL and PNL, in URS the problem of coagulation disorders is less pronounced.

Recommendations	LE	GR
Anticoagulation therapy including salicylates should be stopped before stone removal.	3	B
If intervention for stone removal is essential and salicylate therapy should not be interrupted, retrograde ureterorenoscopy is the preferred treatment of choice.		

6.3.3 *Obesity*

Obesity can cause a higher risk due to anaesthesiological measurements, and a lower success rate after SWL and PNL (Section 5.5).

Statement	LE
In case of severe obesity, URS is a more promising therapeutic option than SWL.	2b

6.3.4 *Hard stones*

Stones composed of brushite, calcium oxalate monohydrate, or cystine are particularly hard (10). Percutaneos nephrolithotomy or RIRS are alternatives for removal of large SWL-resistant stones.

Recommendation	LE	GR
Consider the stone composition before deciding on the method of removal (based on patients history, former stone analysis of the patient or HU in unenhanced CT. Stones with medium density > 1,000 HU on NCCT are less likely to be disintegrated by SWL) (10).	2a	B

6.3.5 *Radiolucent stones*

Stones composed of uric acid, but not sodium or ammonium urate, can be dissolved by oral chemolysis. Differentiation is done by urinary pH measurement (Section 5.4.2). Postoperative monitoring of radiolucent stones during therapy is the domain of US, however repeat NCCT might be necessary.

Recommendation	GR
Careful monitoring of radiolucent stones during/after therapy is imperative.	A*

** Upgraded based on panel consensus.*

6.3.6 *Steinstrasse*

Steinstrasse is an accumulation of stone fragments or stone gravel in the ureter, which does not pass within a reasonable period of time, and interferes with the passage of urine (11,12). Steinstrasse occurs in 4-7% cases of SWL (13), and the major factor in steinstrasse formation is stone size (14).

Insertion of a ureteral stent before SWL prevents formation of steinstrasse only in stones > 15 mm in diameter (15). Symptoms of steinstrasse include flank pain, fever, nausea and vomiting, bladder irritation, or it may be asymptomatic. A major problem of steinstrasse is ureter obstruction, which can be silent in 23% of cases (16) and lead to kidney failure (17). Anuria occurs in 5% of cases of steinstrasse in treatment of solitary kidneys (16).

When steinstrasse is asymptomatic, conservative treatment is an initial option, depending on patient preference and willingness to comply with close surveillance. Medical expulsion therapy significantly increases stone expulsion and reduces the need for endoscopic intervention (18,19).

Table 17: Treatment of steinstrasse

Asymptomatic	LE	Symptomatic	LE	Symptomatic + fever	LE
1. MET	1b	1. URS	3	1. PCN	1
2. SWL	3	1. PCN	3	2. Stent	2
3. URS	3	1. SWL	3		
		2. Stent	3		

Numbers 1, 2 and 3 in Asymptomatic column indicate first, second and third choice. See note; LE in Table 17 would then have to be priority.

Statements	LE
Medical expulsion therapy increases the stone expulsion rate of steinstrasse (15).	1b
When spontaneous passage is unlikely, further treatment of steinstrasse is indicated.	
SWL is indicated in asymptomatic and symptomatic cases, with no evidence of UTI, when large stone fragments are present (19).	
Ureteroscopy is equally effective as SWL for treatment of steinstrasse (20,21).	
Placement of a percutaneous nephrostomy tube or ureteral stent is indicated for symptomatic ureteric obstruction with/without UTI.	

Recommendations	LE	GR
Percutaneous nephrostomy is indicated for steinstrasse associated with urinary tract infection/ fever.	4	C
Shockwave lithotripsy is indicated for steinstrasse when large stone fragments are present.	4	C
Ureteroscopy is indicated for symptomatic steinstrasse and treatment failure.	4	C

6.3.7 References

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6.4 Selection of procedure for active removal of kidney stones

6.4.1 ***Stones in renal pelvis or upper/middle calices***

Shockwave lithotripsy, PNL and RIRS are available treatment modalities for renal calculi. Although PNL efficacy is hardly affected by stone size, the SFRs after SWL or URS are inversely proportional to stone size (1-4). Shockwave lithotripsy achieves excellent SFRs for stones up to 20 mm, except for those at the lower pole (3,5). Therefore, SWL remains the first method of choice for such stones. Larger stones > 20 mm should be treated primarily by PNL, because SWL often requires multiple treatments, and has the risk of ureteral obstruction (colic or steinstrasse) with the need for adjunctive procedures (Figure 1) (6). Retrograde renal surgery cannot be recommended as first-line treatment for stones > 20 mm, for which SFR is decreasing, and staged procedures have become necessary (7,8). However, RIRS can be successful in experienced hands in high-volume centres (4,9).

6.4.2 ***Stones in the lower renal pole***

The stone clearance rate after SWL seems to be lower for stones in the inferior calyx than for other intrarenal locations. Although the disintegration efficacy of SWL is not limited compared to other locations, the fragments often remain in the calyx and cause recurrent stone formation. The reported SFR of SWL for lower pole calculi is 25-85%. The preferential use of endoscopic procedures is under discussion (1-6).

The following can impair successful stone treatment by SWL:

- steep infundibular-pelvic angle;
- long calyx;
- narrow infundibulum (Table 18) (7,8,10-14).

Further anatomical parameters cannot yet be established. The value of supportive measures such as inversion, vibration or hydration remains under discussion (7,8).

Table 18: Unfavourable factors for SWL success (10-16)

Factors that make SWL less likely
Shockwave-resistant stones (calcium oxalate monohydrate, brushite, or cystine).
Steep infundibular-pelvic angle.
Long lower pole calyx (> 10 mm).
Narrow infundibulum (< 5 mm).

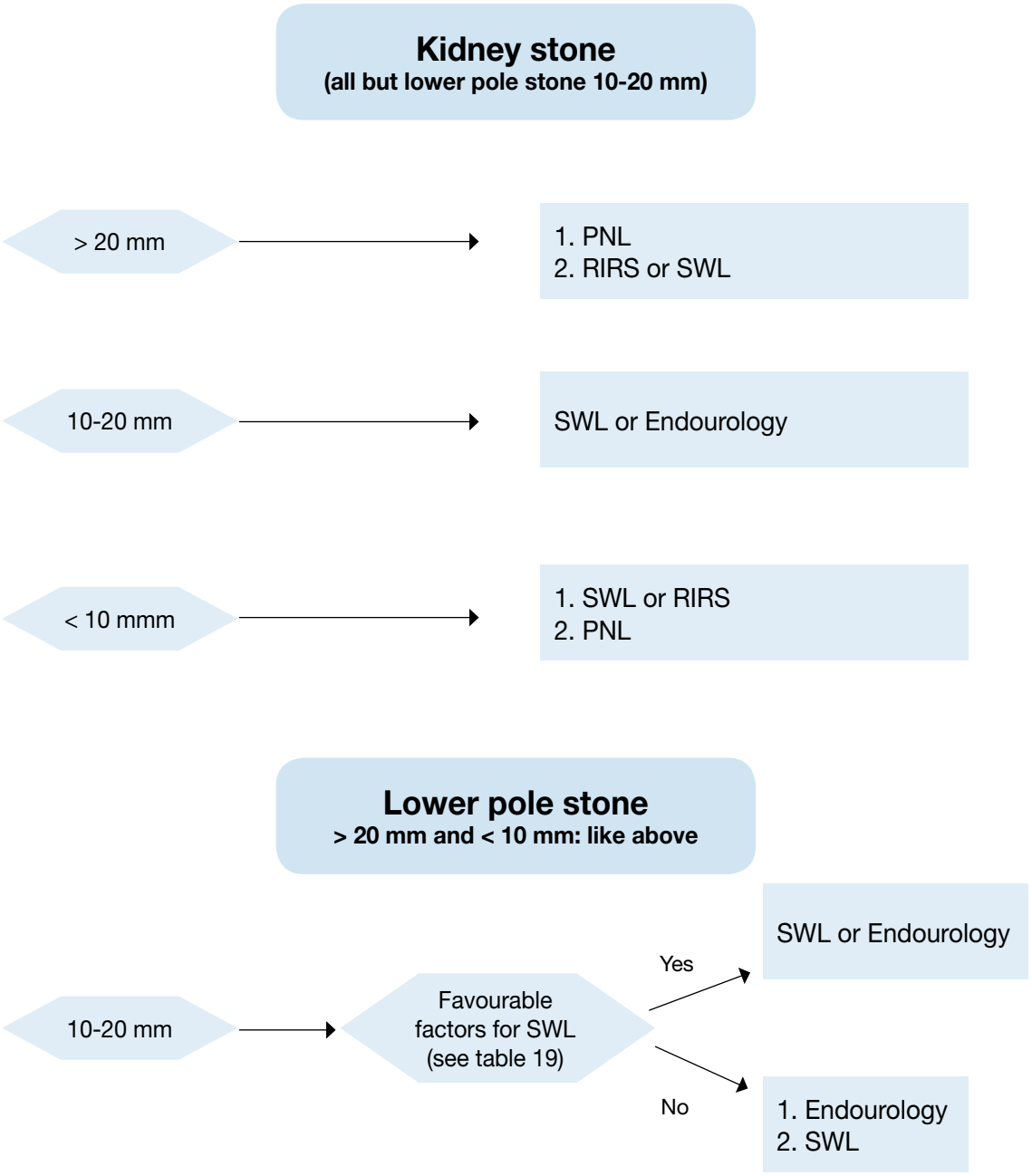
Shockwave lithotripsy for the lower pole is often disappointing, therefore, endourological procedures (PNL and RIRS) are recommended for stones > 15 mm. If there are negative predictors for SWL, PNL and RIRS might be a reasonable alternative, even for smaller calculi.

Retrograde renal surgery seems to have comparable efficacy to SWL (5,6). Recent clinical experience with last-generation ureterorenoscopes has suggested an advantage of URS over SWL, but at the expense of greater invasiveness (17,18). Depending on operator skills, stones up to 3 cm can be treated efficiently by RIRS (9,17,19-22). In complex stone cases, a combined antegrade and retrograde approach may be indicated (23-25). However, staged procedures are frequently required.

Recommendations	GR
SWL remains the method of first choice for stones < 2 cm within the renal pelvis and upper or middle calices. Larger stones should be treated by PNL.	B*
Flexible URS cannot be recommended as first-line treatment, especially for stones > 1.5 cm in the renal pelvis and upper or middle calices, for which SFR after RIRS is decreasing, and staged procedures become necessary.	B*
For the lower pole, PNL or RIRS is recommended, even for stones > 1.5 cm, because the efficacy of SWL is limited (depending on favourable and unfavourable factors for SWL).	B*

**Upgraded following panel consensus*
SWL = shockwave lithotripsy; PNL = percutaneous nephrolithotomy; URS = ureterorenoscopy; SFR = stone free rate; RIRS = retrograde renal surgery

Figure 1: Treatment algorithm for renal calculi



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

6.4.3 ***References***

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6.5 Selection of procedure for active removal of ureteral stones

*6.5.1 **Methodology***

Stone free rates were analysed for SWL and URS. If the study reported the SFR after all primary procedures, that rate was used for analysis. If not, and the study reported the SFR after the first procedure, then that rate was used. The Panel aimed to present an estimate of the number of primary procedures and the associated SFRs. There is a lack of uniformity in reporting the time to stone-free status, thereby limiting the ability to comment on the timing of this parameter.

*6.5.2 **Extracorporeal shock wave lithotripsy and ureteroscopy***

For proximal stones, no difference in overall SFRs between SWL and URS was detected. However, after stratifying for stone size, in proximal ureteral stones < 10 mm (n = 1,285), SWL had a higher SFR than URS had. For stones > 10 mm (n = 819), URS had superior SFRs. This can be attributed to the fact that proximal ureteral stones treated with URS did not vary significantly with size, whereas the SFR following SWL negatively correlated with stone size.

For all mid-ureteral stones, URS appears superior to SWL, but after stratification for stone size, the small number of patients limits the significance. For all distal stones, URS yields better SFRs overall, compared to other methods for active stone removal, independent of stone size.

*6.5.2.1 **Stone free rates (SFRs)***

Table 19 shows the results of a meta-analysis of SFRs. The results are presented as medians of the posterior distribution (best central estimate) with 95% confidence intervals (CIs). This represents an update of the EAU/AUA Collaborative Guidelines Project (1). Outcomes show no significant changes.

Table 19: SFRs after primary treatment with SWL and URS in the overall population (1-5)

Stone location and size	SWL		URS	
	No. of patients	SFR/95% CI	No. of patients	SFR/95% CI
Distal ureter	7217	74% (73-75)	10,372	93% (93-94)
< 10 mm	1684	86% (80-91)	2,013	97% (96-98)
> 10 mm	966	74% (57-87)	668	93% (91-95)
Mid ureter	1697	73% (71-75)	1,140	87% (85-89)
< 10 mm	44	84% (65-95)	116	93% (88-98)
> 10 mm	15	76% (36-97)	110	79% (71-87)
Proximal ureter	6682	82% (81-83)	2,448	82% (81-84)
< 10 mm	967	89% (87-91)	318	84% (80-88)
> 10 mm	481	70% (66-74)	338	81% (77-85)

Unfortunately, RCTs comparing these treatments have been lacking. However, the posterior distributions from the meta-analysis can be subtracted, which yields a distribution for the difference between the treatments. If the CI does not include zero, then the result can be considered to be significantly different. This operation is mathematically justifiable but operationally risky: if the patients receive different treatments or the outcome measures are different, the results might be meaningless. Nonetheless, the SFRs for URS remained significantly better than those for SWL for distal ureteral stones < 10 mm and > 10 mm and for proximal ureteral stones > 10 mm. The SFRs for mid-ureteral stones did not differ significantly between URS and SWL.

Although there are not sufficient data to compare flexible and rigid URS statistically for proximal ureteral stones, favourable SFRs have been reported using RIRS (87%) or rigid or semi-rigid URS (77%) (1). SFRs have probably continued to improve with the distribution and technical improvement of RIRS.

6.5.2.2 Complications

Although URS is effective for ureteric calculi, it has greater potential for complications. In the current endourological era, with access to newer and smaller rigid and flexible instruments, and use of small-calibre intracorporeal lithotripsy devices, the complication rate and morbidity of ureteroscopy have been significantly reduced (6).

Patients should be informed that URS has a better chance of achieving stone-free status with a single procedure, but has higher complication rates [Sections 5.5.4 (Complications of SWL) and 5.6.2.2.9 (Complications of URS)].

*6.5.3 **Percutaneous antegrade ureteroscopy***

Percutaneous antegrade removal of ureteral stones is a consideration in selected cases. For example, for very large (> 15 mm diameter) impacted stones in the proximal ureter between the ureteropelvic junction and the lower border of the fourth lumbar vertebra (7-10), or when the ureter is not amenable to retrograde manipulation (11-13). With SFRs of 85-100%, its superiority to standard techniques has been evaluated (7,10,11,14,15). The complication rate is low, and no different than for any other percutaneous procedure. However, percutaneous antegrade removal of ureteral stones is associated with longer operative times, hospital stay, and time to return to normal activities (10). (11-13).

Recommendations	GR
Percutaneous antegrade removal of ureteral stones is an alternative when SWL is not indicated or has failed, and when the upper urinary tract is not amenable to retrograde URS.	A

Table 20: Recommended treatment options (if indicated for active stone removal) (GR A*)

Stone location and size	First choice	Second choice
Proximal ureter < 10 mm	SWL	URS
Proximal ureter > 10 mm	URS (retrograde or antegrade) or SWL	
Distal ureter < 10 mm	URS or SWL	
Distal ureter > 10 mm	URS	SWL

**Upgraded following panel consensus.*

Recommendation	GR
Treatment choices should be based on stone size and location, available equipment, and patient preference for stone removal.	A

*6.5.4 **Other methods for ureteral stone removal***

Few studies have reported laparoscopic stone removal (Section 5.7.2), and open surgery (Section 5.7.1). These procedures are usually reserved for special cases, therefore, the reported data could not be used to compare procedures with each other or with SWL or URS. These more invasive procedures have yielded high SFRs.

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7. RESIDUAL STONES

7.1 Clinical evidence

Residual fragments are commonly seen in the kidney (mostly in the lower calix) after SWL and sometimes after intracorporeal lithotripsy.

Reports on residual fragments vary between institutions, according to imaging method. However, the clinical value of detecting very small concretions remains debatable.

The clinical problem of residual kidney 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 (1-6).

Recommendations	LE	GR
Identification of biochemical risk factors and appropriate stone prevention is particularly indicated in patients with residual fragments or stones (3-5).	1b	A
Patients with residual fragments or stones should be followed up 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. In a 2.2-year follow-up of 53 patients, 78% with stone fragments at 3 months after treatment experienced stone progression. The SFR was 20%, and the remaining 2% had stable disease (7). For all stone compositions, 21-59% of patients with residual stones required treatment within 5 years. Fragments > 5 mm are more likely than smaller ones to require intervention (2,3,5,8).

Table 21: 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
> 6-7 mm	Stone removal			

7.2 Therapy

Residual fragments after PNL can be avoided by a second look using the existing percutaneous tract 1-3 days after the first procedure (9). To facilitate further clearance, medical and physical adjunctive therapy can be suggested.

The indications for active stone removal and selection of the procedure are based on the same criteria as for primary stone treatment (Chapter 6) and includes repeat SWL (10).

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 (11-14).

Statement	LE
For well-disintegrated stone material in the lower calix, an inversion therapy with simultaneous mechanical percussion maneuver under enforced diuresis may facilitate stone clearance (14).	1b

Recommendation	LE	GR
After SWL and URS, and in the presence of residual fragments, MET is recommended using an α-blocker to improve fragment clearance.	1a	A

SWL = shockwave lithotripsy; URS = ureteronoscopy; MET = medical expulsive therapy

7.3 References

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8. MANAGEMENT OF URINARY STONES AND RELATED PROBLEMS DURING PREGNANCY

Urolithiasis during pregnancy is a diagnostic and therapeutic challenge. In most cases, it becomes symptomatic in the second or third trimester (1-4).

8.1 Diagnostic imaging

Diagnostic options in pregnant women are limited due to the possible teratogenic, carcinogenic, and mutagenic risk of foetal radiation exposure. The risk for the child crucially depends on gestational age and amount of radiation delivered. X-ray imaging during the first trimester should be reserved for diagnostic and therapeutic situations in which alternative imaging methods have failed (1,2,5,6).

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 (7,8).

Statement	LE
Normal physiological changes in pregnancy can mimic ureteral obstruction, therefore, US may not help to differentiate dilatation properly and has a limited role in acute obstruction.	3

X-ray imaging options in pregnancy are: limited excretory urography and NCCT (considering the higher dose of radiation exposure).

Magnetic resonance urography (MRU) can be used to define the level of urinary tract obstruction, and to visualize stones as a filling defect. MRU studies avoid ionising radiation and iodinated contrast medium.

However, findings are non-specific and there is little experience using this imaging modality during pregnancy (9-11).

Recommendation	LE	GR
Ultrasound is the method of choice for practical and safe evaluation of pregnant women.	1a	A

8.2 Management

Clinical management of a pregnant urolithiasis patient is complex and demands close collaboration between patient, obstetrician and urologist.

Approximately 70-80% of the symptomatic stones pass spontaneously. 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. Unfortunately, these temporising therapies are often associated with poor tolerance, and they require multiple exchanges during pregnancy, due to the potential for rapid encrustation (20-23). Ureteroscopy has become a reasonable alternative in these situations (12-19). Although feasible, retrograde endoscopic and percutaneous stone removal procedures during pregnancy remain an individual decision and should be performed only in experienced centres (20-24).

Pregnancy remains an absolute contraindication for SWL.

Statements	LE
If intervention becomes necessary, placement of a ureteral stent or a percutaneous nephrostomy tube are readily available primary options.	3
Ureteroscopy is a reasonable alternative to avoid long-term stenting/drainage.	2a
Regular follow-up until final stone removal is necessary due to the higher encrustation tendency of stents during pregnancy.	

Recommendation	GR
Conservative management should be the first-line treatment for all non-complicated cases of urolithiasis in pregnancy (except those that have clinical indications for intervention).	A

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9. MANAGEMENT OF STONE PROBLEMS 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 (1-3). 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 (4-11).

9.1 Aetiology

Paediatric patients forming urinary stones have a high risk of recurrence, therefore, standard diagnostic procedures for high-risk patients apply (Chapters 2.6 and 11).

Statement	LE
In paediatric patients, the most common non-metabolic disorders are vesicoureteral reflux, ureteropelvic junction obstruction, neurogenic bladder, and other voiding difficulties (11,12).	4

Recommendations	GR
In all paediatric patients, complete metabolic evaluation based on stone analysis (if available) is necessary.	A
All efforts should be made to collect stone material that then should be analysed to classify the stone type.	A*

**Upgrade following panel consensus.*

9.2 Diagnostic imaging

When selecting diagnostic procedures to identify urolithiasis in paediatric patients, it should be remembered that these patients might be uncooperative, require anaesthesia, or be sensitive to ionising radiation (13).

*9.2.1 **Ultrasound***

Ultrasound (US) is the primary imaging technique (13) in paediatrics. Its advantages are absence of radiation and no need for anaesthesia. Ultrasound (US) provides information about the presence, size and location of a stone, and the grade of dilatation/obstruction of the urinary collecting system and the severity of nephrocalcinosis. It also indicates anatomical abnormalities.

Colour Doppler US shows differences in the ureteric jet (14) and resistive index of the arciform arteries of both kidneys, which are indicative of the grade of obstruction (15).

Nevertheless, US fails to identify stones in > 40% of paediatric patients (16-19) (LE: 4), and provides no information about renal function.

Statement	LE
US is the first choice for imaging in children and should include the kidney, filled bladder, and adjoining portions of the ureter (14,20).	2a

*9.2.2 **Plain films (KUB radiography)***

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

*9.2.3 **Intravenous urography (IVU)***

Intravenous urography is an important diagnostic tool. However, the need for contrast medium injection is a major drawback. The radiation dose for IVU is comparable to that for voiding cystourethrography (0.33 mSV) (21).

*9.2.4 **Helical computed tomography (CT)***

Recent CT protocols have been shown to reduce radiation exposure significantly (22). The principle of ALARA (as low as reasonable achievable) should always be observed. In adults it has a sensitivity of 94-100% and specificity of 92-100% (23).

In children, only 5% of stones escape detection by NCCT (14,23,24). Sedation or anaesthesia is rarely needed with modern high-speed CT apparatus (11).

*9.2.5 **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 (25).

*9.2.6 **Nuclear imaging***

99mTc-dimercaptosuccinyl acid scanning provides information about cortical abnormalities such as scarring, but does not aid primary diagnosis of urolithiasis. Diuretic renography with injection of a radiotracer (MAG3 [Mercaptoacetyltriglycin] or DPTA [Diethylentriaminpentaacetat]) and furosemide can be used to demonstrate renal function, identify obstruction in the kidney after injection of furosemide, and indicate the anatomical level of the obstruction (11,14).

Recommendations	GR
In children, US is the first-line imaging modality when suspecting a stone.	B
If US does not provide the required information, KUB radiography (or NCCT) should be performed.	B

US = ultrasound; KUB = kidney, ureter, bladder; NCCT = non-contrast enhanced computed tomography.

9.3 Stone removal

Several factors must be considered when selecting treatment procedures for children. Compared to adults, children pass fragments more rapidly after SWL (26). For endourological procedures, the smaller organs in children must be considered when selecting instruments for PNL or URS. Anticipation of the expected stone composition should be taken into account when selecting the appropriate procedure for stone removal (cystine stones are more resistant to SWL).

Statement	LE
Spontaneous passage of a stone is more likely in children than adults (6,11,12).	4

*9.3.1 **Medical expulsive therapy (MET) in children***

Medical expulsive therapy in children has already been discussed in Section 5.3.2.6. Although the use of α-blockers is very common in adults, there are insufficient data to demonstrate their safety and efficacy in children (27).

*9.3.2 **Extracorporeal shock wave lithotripsy***

Extracorporeal shock wave lithotripsy remains least-invasive procedure for stone management in children (28-36).

SFRs 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 (32-34). Stones located in calices, as well as 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% (32-34,36).

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 avoid patient and stone motion and the need for repositioning (32,36). With modern lithotriptors, intravenous sedation or patient-controlled analgesia have been used in selected cooperative older children (37) (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 (38-41).

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 (28,30-32).

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

*9.3.3 **Endourological procedures***

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

9.3.3.1 Percutaneous nephrolithotripsy (PNL)

Preoperative evaluation and indications for PNL in children are similar to those in adults. Although PNL is performed as monotherapy in most cases, it can be used as an adjunctive procedure. Availability of appropriate-size instruments and US guidance mean that age is not a limiting factor, and PNL can now be performed safely by experienced operators, with less radiation exposure, even for large and complex stones (42-46). SFRs are between 68% and 100% after a single session, and increase with adjunctive measures, such as second-look PNL, SWL and URS (42,43).

Statement	LE
For paediatric patients, the indications for PNL are similar to those in adults.	1a

Recommendation	GR
In children, PNL is recommended for treatment of renal pelvic or caliceal stones with a diameter > 20 mm (~300 mm^2).	A

9.3.3.2 Ureteroscopy

Although SWL still is the first-line treatment for most ureteral stones, it is unlikely to be successful for stones > 10 mm in diameter, or for impacted, calcium oxalate monohydrate or cystine stones, or stones in children with unfavourable anatomy and in whom localisation is difficult (47-50).

If SWL is not promising, ureteroscopy 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 (48-50).

Different lithotripsy techniques, including ultrasonic, pneumatic and laser lithotripsy, are all safe and effective (Section 5.6.2.2.7).

Recommendation	LE	GR
For intracorporeal lithotripsy, the same devices as in adults can be used (Ho:Yag laser, pneumatic and US lithotriptors).	3	C

Flexible ureteroscopy has become an efficacious treatment for paediatric upper urinary tract stones. It might be particularly effective for treatment of proximal ureteral calculi and for stones < 1.5 cm in the lower pole calices (56-58).

*9.3.4 **Open or laparoscopic surgery***

Most stones in children can be managed by SWL and endoscopic techniques (59). Therefore, the rate of open procedure has dropped significantly (60-64). In some situations, open surgery is inevitable. 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 (29,31,44,45). Open surgery can be replaced by laparoscopic procedures in experienced hands (62-64).

9.4 Special considerations on recurrence prevention

All paediatric stone formers need metabolic evaluation and recurrence prevention with respect to the detected stone type. In 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 (Chapter 11).

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10. STONES IN URINARY DIVERSION AND OTHER VOIDING PROBLEMS

10.1 Management of stones in patients with urinary diversion

*10.1.1 **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 (1-3). Metabolic factors (hypercalciuria, hyperoxaluria and hypocitraturia), infection with urease-producing bacteria, foreign bodies, mucus secretion, and urinary stasis are responsible for stone formation (4) (Chapter 2.6). One study has shown that the risk for recurrent upper-tract stones in patients with urinary diversion subjected to PNL was 63% at 5 years (5).

*10.1.2 **Management***

Some patients with smaller upper-tract stones can be treated effectively with SWL (6,7). However, in the majority, well-established endourological techniques are necessary to achieve stone-free status (8).

An endoscopic approach might be difficult or impossible in individuals with long, tortuous conduits or with invisible ureter orifices.

Statement	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 URS is the alternative.	4

Recommendation	GR
PNL is the preferred treatment for removal of 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 SWL.	A*

PNL = percutaneous nephrolithotomy; SWL = shockwave lithotripsy.

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. The same applies for continent urinary diversion where trans-stomal manipulations must be performed carefully to avoid disturbance of the continence mechanism (9).

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 (10), and if present, an open surgical approach should be considered.

10.1.3 ***Prevention***

Recurrence risk is high in these patients (5). Close follow-up and metabolic evaluation 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 (11).

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10.2 Management of stones in patients with neurogenic bladder

10.2.1 ***Aetiology, clinical presentation and diagnosis***

Patients with neurogenic bladder develop urinary calculi because of additional risk factors such as bacteriuria, pelvicalicectasis, vesicoureteral reflux, renal scarring, lower urinary tract reconstruction, and thoracic spinal defect (1). The main issues are urinary stasis and infection (Chapter 2.6). 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 (2,3).

Diagnosis of stones may be difficult and late in the absence of clinical symptoms due to sensory impairment and vesicourethral dysfunction (4). Difficulties in self-catheterisation should lead to suspicion of bladder calculi.

Imaging studies are needed (US, CT) to confirm clinical diagnosis prior to surgical intervention.

*10.2.2 **Management***

Management of calculi in patients with neurogenic bladder is similar to that described in Section 10.1.

In MMC (myelomeningocele-) patients, latex allergy is common, therefore, appropriate measures need to be taken regardless of the treatment (5). 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.

The risk of stone formation after augmentation cystoplasty in immobile patients with sensory impairment can be significantly reduced by irrigation protocols (6).

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.

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

Recommendation	GR
In myelomeningocele patients, latex allergy is common so that appropriate measures need to be taken regardless of the treatment.	B

*10.2.3 **References***

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10.3 Management of stones in transplanted kidneys

*10.3.1 **Aetiology and clinical presentation***

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.
- Hyperfiltration, excessively alkaline urine, renal tubular acidosis, and increased serum calcium caused by persistent tertiary hyperparathyroidism (1) are biochemical risk factors.

Stones in kidney allografts have a incidence of 0.2-1.7% (2-4).

Recommendation	LE	GR
In patients with transplanted kidneys, unexplained fever, or unexplained failure to thrive, US or NCCT should be performed to rule out calculi (5).	4	B

US = ultrasound; NCCT = non-contrast enhanced computed tomograpy.

10.3.2 ***Management***

Treatment decisions for selecting the appropriate technique for stone removal from a transplanted kidney are difficult. Although management principles are similar to those applied in other single renal units (6-9), 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 holmium laser has made ureteroscopy a valid treatment option for transplant calculi. However, one must be aware of potential injury to adjacent organs (12-14). Retrograde access to transplanted kidneys is difficult due to the anterior location of the ureteral anastomosis, and ureteral tortuosity (15-17).

Statements	**LE**
Conservative treatment for small asymptomatic stones is only possible under close surveillance and in absolutely compliant patients.	
SWL for small calyceal stones is an option with minimal complication risk, but localisation of the stone can be challenging and SFRs are poor (10,11).	4

Recommendations	**GR**
In patients with transplanted kidneys, all contemporary treatment modalities, including shockwave therapy, (flexible) ureteroscopy, and percutaneous nephrolithotomy are management options.	B
Metabolic evaluation should be completed after stone removal.	A*

**Upgraded following panel consensus.*

10.3.3 ***References***

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10.4 Special problems in stone removal

Table 22: Special problems in stone removal

Caliceal diverticulum stones	• SWL, PNL (if possible) or RIRS. • Can also be removed using laparoscopic retroperitoneal surgery (1-5). • Patients may become asymptomatic due to stone disintegration (SWL) whilst well-disintegrated stone material remains in the original position due to narrow caliceal neck.
Horseshoe kidneys	• Can be treated in line with the options described above (6.) • Passage of fragments after SWL might be poor.
Stones in pelvic kidneys	• SWL, RIRS or laparoscopic surgery. • For obese patients, the options are SWL, PNL, RIRS or open surgery.
Stones formed in a continent reservoir	• Section 10.1. • Each stone problem 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. • URS together with endopyelotomy with Ho:YAG. • Incision with an Acucise balloon catheter might be considered, provided the stones can be prevented from falling into the pelviureteral incision (7-10).

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11. METABOLIC EVALUATION AND RECURRENCE PREVENTION

11.1 General metabolic considerations for patient work-up

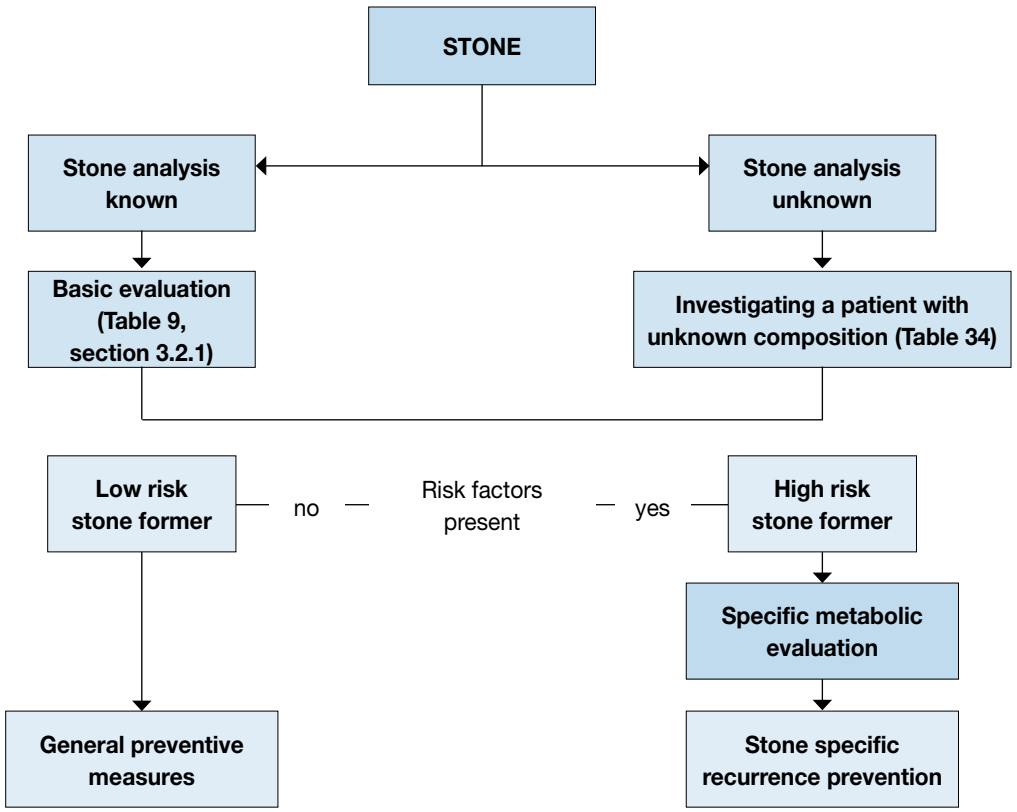
*11.1.1 **Evaluation of patient risk***

After stone passage, every patient should be assigned to a low- or high-risk group for stone formation (Figure 2).

For correct classification, two items are mandatory:

- reliable stone analysis by infrared spectroscopy or X-ray diffraction;
- basic analysis (Section 3.2).

Figure 2: 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;
- unknown composition.

*11.1.2 **Urine sampling***

Specific metabolic evaluation requires collection of two consecutive 24-h urine samples (1-3). The collecting bottles should be prepared with 5% thymol in isopropanol or stored at ≤ 8°C during collection with the risk of spontaneous crystallisation in the urine (4). Preanalytical 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 (5) using sensitive pH-dipsticks or ph-meter.

HCl can be used as a preservative in special situations to prevent precipitation of calcium oxalate and calcium phosphate. However, in samples preserved with HCl, pH measurement is impossible and uric acid precipitates immediately. Alkalinisation is needed to dissolve urate crystals if urate excretion is of interest (6).

Spot urine samples are an alternative method of sampling, particularly when 24-h urine collection is difficult, for example, in non-toilet trained children (7,8). Spot urine studies normally link the excretion rates to creatinine (8,9), but these are limited because the results may vary with collection time and patients' sex, body weight and age.

*11.1.3 **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. A minimum of 20 days is recommended (3 months suggested) between stone expulsion or removal and 24-h urine collection (4,10).

Follow-up studies are necessary in patients receiving recurrent stone prophylaxis (1). The first follow-up 24-h urine measurement should be at 8-12 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-h urine measurements if necessary. Once urinary parameters have been normalised, it is sufficient to perform 24-h urine evaluation every 12 months.

The panel realise that on this issue there is only very limited published evidence.

*11.1.4 **Reference ranges of laboratory values***

Tables 23-26 provide the internationally accepted reference ranges for the different laboratory values in serum and urine.

Table 23: Normal laboratory values for blood parameters in adults

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).

*11.1.5 **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:

- APCaOxindex (11,12);
- EQUIL, a computer program to calculate relative supersaturations (13-15);
- Bonn Risk Index (16-18).

Another approach to risk assessment is the Joint Expert Speciation System (JESS), which is based on an extensive database of physiochemical constants and is similar to the EQUIL (19). However, clinical validation of these risk indices for recurrence prediction or therapy improvement is ongoing and the benefit remains controversial.

Table 24: Normal laboratory values for urinary parameters in adults

Urinary Parameters	Reference ranges and limits for medical attention
pH	Constantly > 5.8
	Constantly > 7.0
	Constantly ≤ 5.8
Specific weight	> 1.010
Creatinine	7-13 mmol/day females
	13-18 mmol/day males
Calcium	> 5.0 mmol/day
	≥ 8.0 mmol/day
Oxalate	> 0.5 mmol/day
	0.45-0.85 mmol/day
	≥ 1.0 mmol/day
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 25: Normal values for spot urine samples: creatinine ratios (solute/creatinine) (20)

Parameter/Patient age	**Ratio of solute to creatinine**	
Calcium	**mol/mol**	**mg/mg**
< 12 months	< 2	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	**mmol/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 ìmol/l) per GFR (ratio x plasma creatinine	
> 2 years		

Table 26: Urinary excretion of soluble excretion in 24-h urine samples**

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

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

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11.2 General considerations for recurrence prevention

All stone formers, independent of their individual risk, should follow the preventive measures in Table 27. 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 and based on stone analysis.

Table 27: 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 vegetable 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: 18-25 kg/m2 (target adult value, not applicable to children) Stress limitation measures Adequate physical activity Balancing of excessive fluid loss

Caution: The protein need is age-group dependent, therefore protein restriction in childhood should be handled carefully.
** Avoid excessive consumption of vitamin supplements.*

11.2.1 ***Fluid intake***

An inverse relationship between high fluid intake and stone formation has been repeatedly demonstrated (1,2). The effect of fruit juices is mainly determined by the presence of citrate or bicarbonate (3). If hydrogen ions are present, the net result is neutralisation. However, if potassium is present, both pH and citrate are increased (4,5).

11.2.2 ***Diet***

A common sense approach to diet should be taken, that is, a mixed balanced diet with contributions from all food groups, but without any excesses (6).

Fruits, vegetables and fibres: fruit and vegetable intake should be encouraged because of the beneficial effects of fibre (7). 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 (3), 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 (8-10). However, it seems wise to advise calcium oxalate stone formers to avoid excessive intake.

Animal protein should not be taken in excess (11,12) 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 because of the inverse relationship between dietary calcium and stone formation (13). The daily requirement for calcium is 1000 to 1200 mg/day (14). Calcium supplements are not recommended except in enteric hyperoxaluria, when additional calcium should be taken with meals to bind intestinal oxalate (12,15-17).

Sodium: the daily sodium (NaCl) intake should not exceed 3-5 g. 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 (11,12). A positive correlation between sodium consumption and risk of first-time stone formation has been confirmed only in women (13,18). 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 urate-rich food should be restricted in patients with hyperuricosuric calcium oxalate (19-21) and uric acid (16) stones. Intake should not exceed 500 mg/day.

11.2.3 ***Lifestyle***

Lifestyle factors may influence the risk of stone formation, for example, overweight and obesity (22-24). Another risk factor is arterial hypertension (25,26).

Recommendations		**LE**	**GR**
The aim should be to obtain a 24-h urine volume ≥ 2.5 L.		1b	A
Hyperoxaluria	Oxalate restriction	2b	B
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

11.2.4 ***References***

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11.3 Stone-specific metabolic evaluation and pharmacological recurrence prevention

11.3.1 ***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 28 highlights the most important characteristics of commonly used medication.

Table 28: 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	1 -6
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	7-9
Calcium	Enteric hyperoxaluria	500 mg/d	Intake 30 min before the meals	Calcium oxalate	10-13
Captopril	Cystinuria Active decrease of urinary cystine levels	75-150 mg	Second-line option due to significant side effects	Cystine	14,15
l-Methionine	Acidification	600-1500 mg/d	Hypercalciuria, bone demineralization, systemic acidosis. No long-term therapy.	Infection stones Ammonium urate Calcium phosphate	1,16, 17
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	18-21 low evidence
Sodium bicarbonate	Alkalinisation Hypocitraturia	4.5 g/d		Calcium oxalate Uric acid Cystine	
Pyridoxine	Primary hyperoxaluria	Initial dose 5 mg/kg/d Max. 20 mg/kg/d	Polyneuropathia	Calcium oxalate	22-24
Thiazide (Hydrochloro-thiazide)	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	1,18,25-36
Tiopronin	Cystinuria Active decrease of urinary cystine levels	Initial dose 250 mg/d Max. 2000 mg/d	Risk for tachyphylaxis and proteinuria.	Cystine	37-42

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11.4 Calcium oxalate stones

The criteria for identification of calcium oxalate stone formers with high recurrence risk are listed in Section 2.6.

11.4.1 ***Diagnosis***

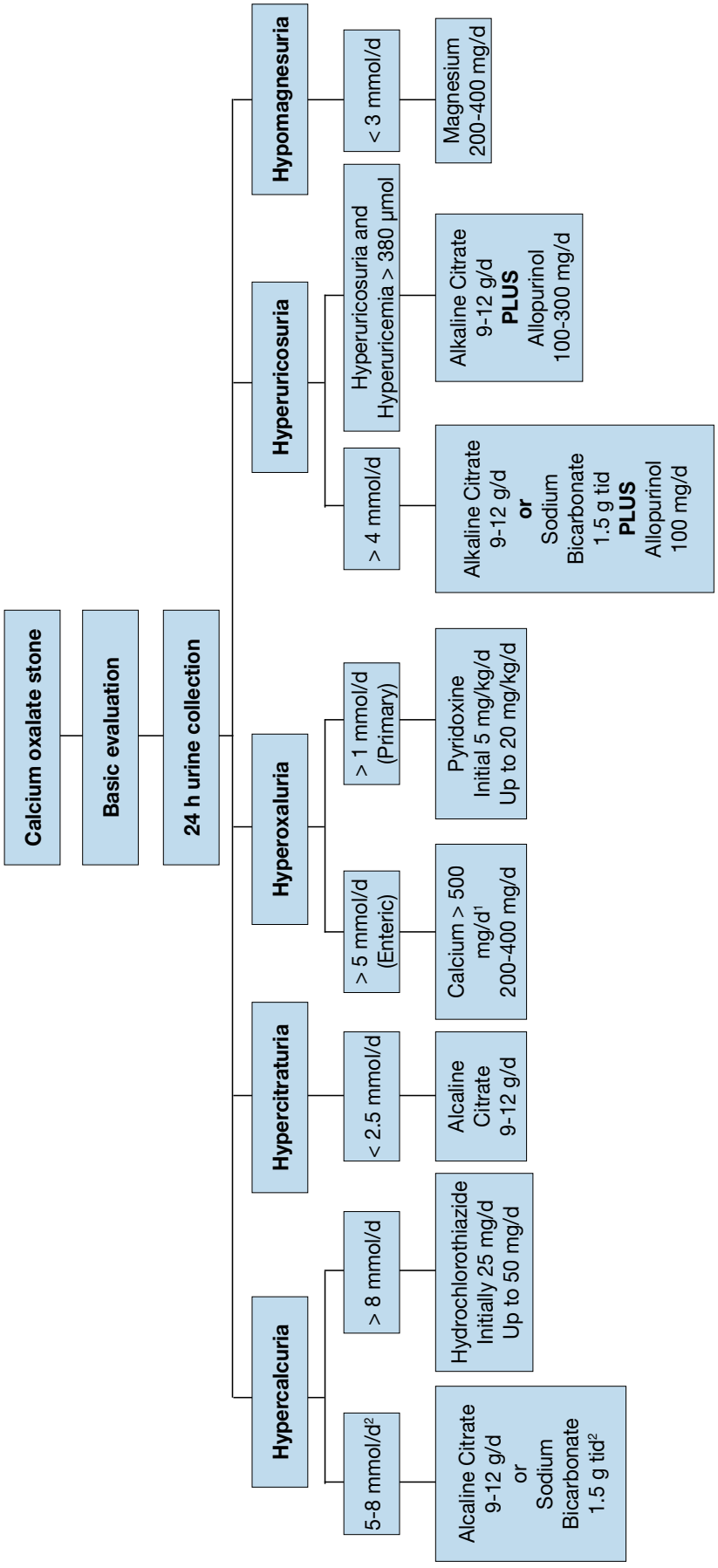
Blood analysis requires measurement of creatinine, sodium, potassium, chloride, ionised calcium (or total calcium + albumin), uric acid, and parathyroid hormone (PTH) (and vitamin D) in case of increased calcium levels.

Urinalysis requires measurement of urine volume, urine pH profile, specific weight, calcium, oxalate, uric acid, citrate, sodium and magnesium.

11.4.2 ***Interpretation of results and aetiology***

The diagnostic and therapeutic algorithm for calcium oxalate stones is shown in Figure 3 (1-26).

Figure 3: Diagnostic and therapeutic algorithm for calcium oxalate stones



[1] Be aware of excess calcium excretion [2] d: day(24h) [3] No magnesium therapy for patients with renal insufficiency

The most common metabolic abnormality associated with calcium stone formation are hypercalciuria, which affects 30-60% of adult stone formers, and hyperoxaluria (26-67%), followed by hyperuricosuria (15-46%), hypomagesuria (7-23%), and hypocitraturia (5-29%). However, ranges tend to differ for different ethnic groups (1).

- 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 < 6) 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 urinary tract infection (UTI) has been excluded. An ammonium chloride loading test confirms RTA and identifies RTA subtype (Section 11.6.4).
- Hypercalciuria may be associated with normocalcemia (idiopathic hypercalciuria, or granulomatous diseases) or hypercalcaemia (hyperparathyroidism, granulomatous diseases, vitamin D excess, or malignancy).
- Hypocitraturia (< 2.5 mmol/day) 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.
    - primary hyperoxaluria (oxalate excretion mostly ≥ 1 mmol/day), appears in three genetically determined forms;
    - secondary hyperoxaluria (oxalate excretion ≥ 0.5 mmol/day, usually < 1 mmol/day), occurs due to intestinal hyperabsorption of oxalate or extreme dietary oxalate intake;
    - mild hyperoxaluria (oxalate excretion 0.45-0.85 mmol/day), commonly found in idiopathic calcium oxalate stone formers.
- Hypomagnesuria (< 3.0 mmol/day) may be related to poor dietary intake or to reduced intestinal absorption (chronic diarrhoea)

*11.4.3 **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 3 summarises the diagnostic algorithm and the pharmacological treatment of calcium oxalate stones (2-26).

*11.4.4 **Recommendations for pharmacological treatment of patients with specific abnormalities in urine composition***

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
	Oxalate absorption	3	B
Hypocitraturia	Potassium citrate	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

*11.4.5 **References***

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11.5 Calcium phosphate stones

Some calcium phosphate stone formers are at high risk of recurrence. Further information on identifying high-risk patients is given in Section 2.6.

Calcium phosphate mainly appears in two completely different minerals: carbonate apatite and brushite: Carbonate apatite crystallisation occurs at 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.

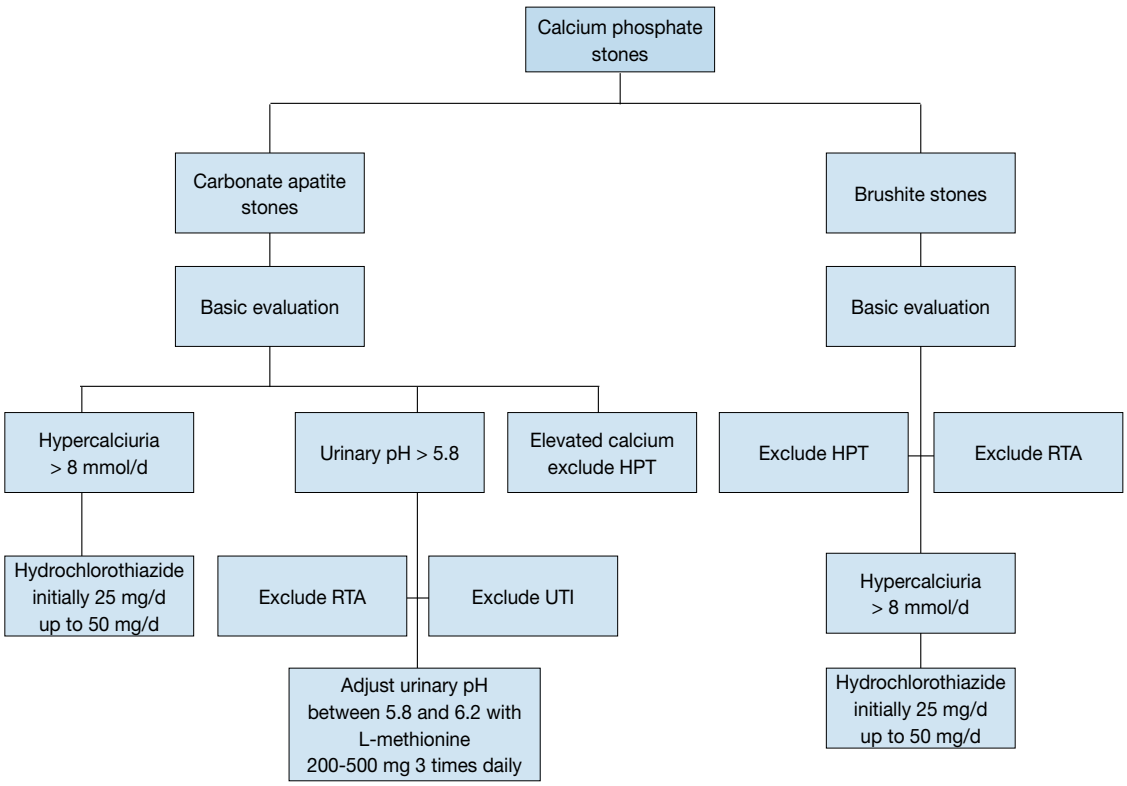
11.5.1 ***Diagnosis***

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

11.5.2 ***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.

Figure 4: Diagnostic and therapeutic algorithm for calcium phosphate stones



11.5.3 ***Pharmacological therapy*** *(1-9)*

HPT 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 helpful however 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.

Recommendations for the treatment of calcium phosphate stones

Urinary risk factor	Suggested treatment	LE	GR
Hypercalciuria	Thiazide	1a	A
Inadequate urine pH	Acidification	3-4	C
UTI	Antibiotics	3-4	C

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11.6 Disorders and diseases related to calcium stones

11.6.1 ***Hyperparathyroidism*** *(1-10)*

Primary HPT is responsible for an estimated 5% of all calcium stone formation. Kidney stones occur in approximately 20% of patients with primary HPT. The clinical appearance of HPT typically comprises bone loss, gastric ulcers and urolithiasis. Elevated levels of PTH significantly increase calcium turnover, leading to hypercalcaemia and hypercalciuria. Serum calcium may be mildly elevated and serum PTH within the upper normal limits, therefore, repeated measurements may be needed; preferably with the patient fasting.
Stones of PTH 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.

11.6.2 ***Granulomatous diseases*** *(11,12)*

Granulomatous diseases, such as sarcoidosis, may be complicated by hypercalcaemia and hypercalciuria secondary to increased calcitriol production. The later 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. It should be reserved to the specialist.

11.6.3 ***Primary hyperoxaluria*** *(13-19)*

Patients with primary hyperoxaluria (PH) should be referred to specialised centres, because 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, primary 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 case of renal insufficiency).

Urinary risk factor	Suggested treatment	LE	GR
Primary hyperoxaluria	Pyridoxine	3	B

11.6.4 ***Enteric hyperoxaluria*** *(20-28)*

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. Intestinal loss of fatty acids is combined with loss of calcium. The normal complex formation between oxalate and calcium is therefore disturbed and oxalate absorption is increased. In addition to hyperoxaluria, these patients usually present with hypocitraturia because of 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:

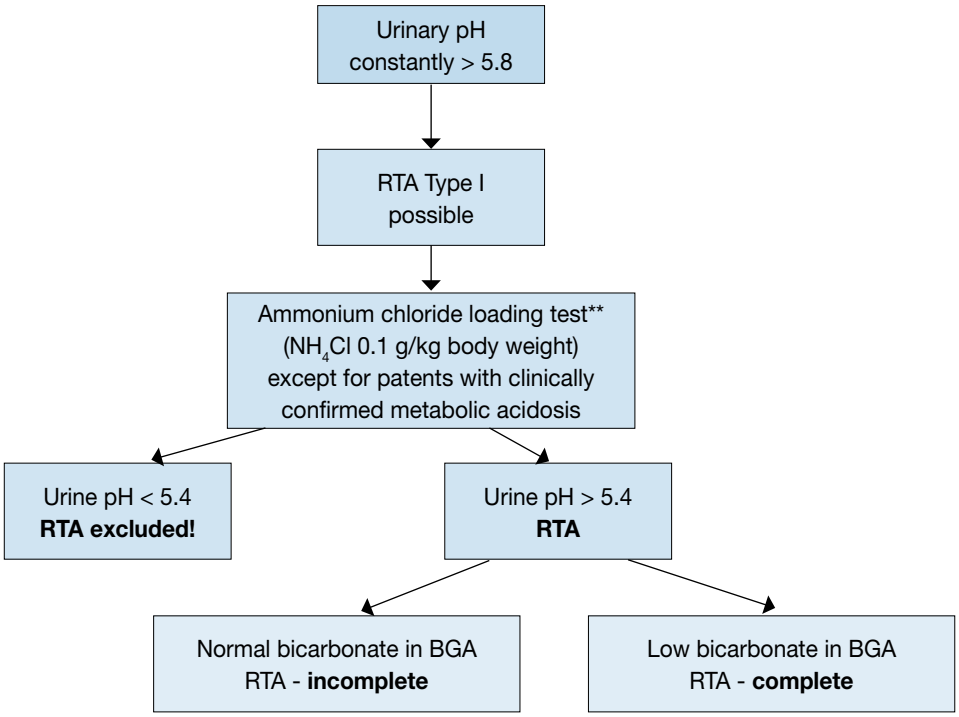
- restricted intake of oxalate-rich foods;
- restricted fat intake;
- calcium supplementation at meal times to enable calcium oxalate complex formation in the intestine (20,21);
- sufficient fluid intake to balance intestinal loss of water caused by diarrhoea;
- alkaline citrates to raise urinary pH and citrate.

Urinary risk factor	Suggested treatment	LE	GR
Enteric hyperoxaluria	Potassium citrate	3-4	C
	Calcium supplement	2	B
	Oxalate absorption	3	B
Small urine volume	Increased fluid intake	1b	A

11.6.5 ***Renal tubular acidosis*** *(29-31)*

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 5 outlines the diagnosis of RTA. Table 29 shows acquired and inherited causes of RTA.

Figure 5: Diagnosis of renal tubular acidosis



*** An alternative Ammonium Chloride loading test using NH4Cl load with 0.05 g/kg body weight over 3 days might provide similar results and may be better tolerated by the patient (31).*

RTA 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, and drug-induced (e.g. zonisamide). Table 29 shows the inherited causes of RTA.

Table 29: 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 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 30). 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 30: 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
Inadequate urine pH	Intracellular acidosis in nephron	Alkaline citrate, 9-12 g/day devided in 3 dosages OR Sodium bicarbonate, 1.5 g, 3 times daily

Urinary risk factor	Suggested treatment	LE	GR
Distal RTA	Potassium citrate	2b	B
Hypercalciuria	Thiazide + potassium citrate	1a	A

11.6.6 ***Nephrocalcinosis*** *(32,33)*

Nephrocalcinosis (NC) refers to increased crystal deposition within the renal cortex or medulla, and occurs alone or in combination with kidney 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.

11.6.6.1 Diagnosis

Diagnosis requires the following blood analysis: PTH (in 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 4 times daily), daily urine volume, specific weight of urine, and levels of calcium, oxalate, phosphate, uric acid, magnesium and citrate.

11.6.7 ***References***

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11.7 Uric acid and ammonium urate stones

All uric acid and ammonium urate stone formers are considered to be at high risk of recurrence (1). Uric acid nephrolithiasis is responsible for approximately 10% of kidney stones (2). 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 (3). Low urinary pH may be caused by decreased urinary ammonium excretion (insulin resistance or gout), increased endogenous acid production (insulin resistance, metabolic syndrome, or exersice-induced lactic acidosis), increased acid intake (high animal protein intake), or increased base loss (diarrhoea) (3).

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, hypokalemia and malnutrition.

Suggestions on uric acid and ammonium urate nephrolithiasis are based on level III and IV evidence.

11.7.1 ***Diagnosis***

Figure 6 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 case of ammonium urate stones.

11.7.2 ***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.

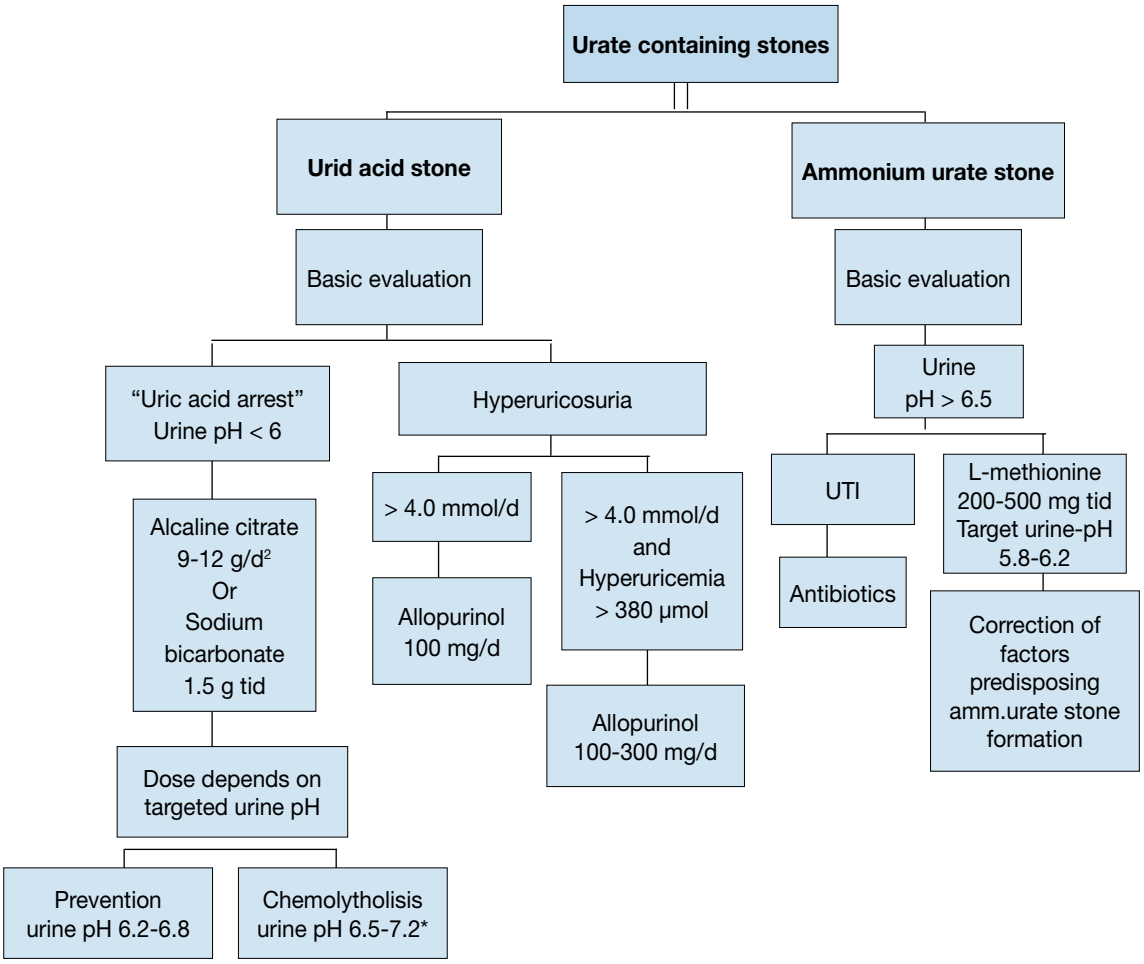
Hyperuricosuric calcium oxalate stone formation can be distinguished from uric acid stone formation by: urinary pH, which is usually > 5.5 in calcium oxalate stone formation and < 5.5 in uric acid stone formation and occasional absence of hyperuricosuria in patients with pure uric acid stones (7,8).

Ammonium urate crystals form in urine at pH > 6.5, at high uric acid concentration and ammonium being present to serve as cation (4-6).

11.7.3 ***Specific treatment***

General preventive measures are recommended for fluid intake and diet. Hyperuricosuric stone formers benefit from purine reduction of their daily diet. Figure 6 describes pharmacological treatment (1-15).

Figure 6: Diagnostic and therapeutic algorithm for uric acid and ammonium urate stones



1 d: day (24h)

** A higher pH may lead to calcium phosphate stone formation.*

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11.8 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 (1,2). There are several factors predisposing patients to struvite stone formation (Table 31) (3,4).

*11.8.1 **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 32). Carbonate apatite starts to crystallise at a urine pH level of 6.8. Struvite only precipitates at pH > 7.2 (4,6,7). Proteus mirabilis accounts for more than half of all urease-positive UTIs (8,9).

*11.8.2 **Specific treatment***

General preventive measures are recommended for fluid intake and diet. Specific measures include complete surgical stone removal (10), short- or long-term antibiotic treatment (11), urinary acidification using methionine (12) or ammonium chloride (13), and urease inhibition (14,15). For severe infections, acetohydroxamic acid may be an option (14,15) (Figure 1), however it is not licensed/available in all European countries.

*11.8.3 **Recommendations for therapeutic measures of infection stones***

Recommendations for therapeutic measures	LE	GR
Surgical removal of the stone material as completely as possible	3,4	A*
Short-term antibiotic course	3	B
Long-term antibiotic course	3	B
Urinary acidification: ammonium chloride, 1 g 2 or 3 times daily	3	B
Urinary acidification: methionine, 200-500 mg, 1-3 times daily	3	B
Urease inhibition	1b	A

** upgraded following panel consensus.*

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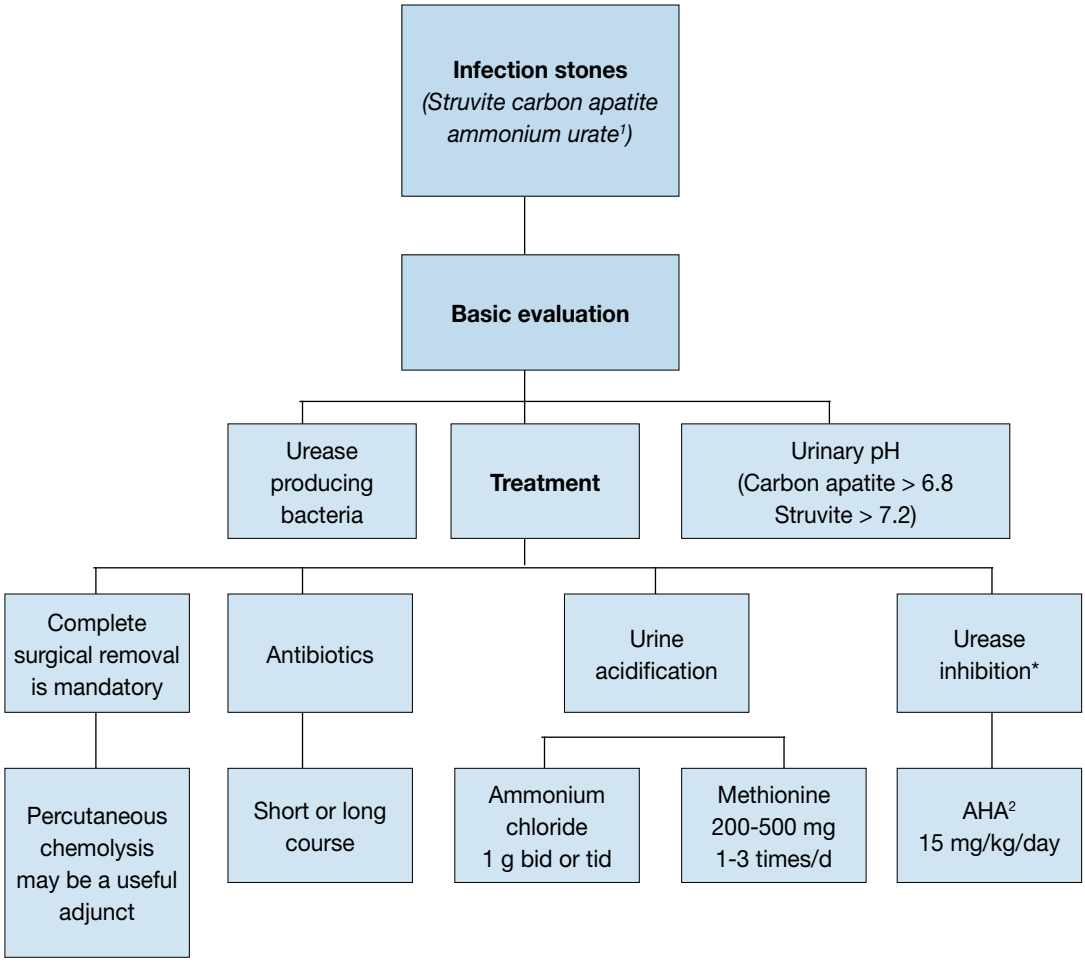
Table 31: Factors predisposing to struvite stone formation

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

Table 32: 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 strains of *Escherichia coli, Entercoccus spp*. and *Pseudomonas aeruginosa* may produce urease.

Figure 7: Diagnostic and therapeutic algorithm for infection stones



[1] *Discussed with uric acid stones, 4 acetohydroxamic acid*
* *When nationally available.*

11.9 Cystine stones

Cystine stones account for 1-2% of all urinary stones in adults and 6-8% of the stones reported in paediatric studies (1,2). All cystine stone formers are deemed at high risk of recurrence.

11.9.1 ***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 (3).
- There is no role for genotyping patients in the routine management of cystinuria (4-6).
- 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 chromatoghraphy (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 (7).
- 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 ampicillin or sulfa-containing medication (8,9).

- Quantitative 24-h urinary cystine excretion confirms the diagnosis in the absence of stone analysis. Levels above 30 mg/day are considered abnormal (10-13).

11.9.2 ***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 (14).

A high level of diuresis is of fundamental importance, aiming for a 24-h urine volume of ≥ 3 L (15,16). A considerable fluid intake evenly distributed throughout the day is necessary.

11.9.2.1 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.

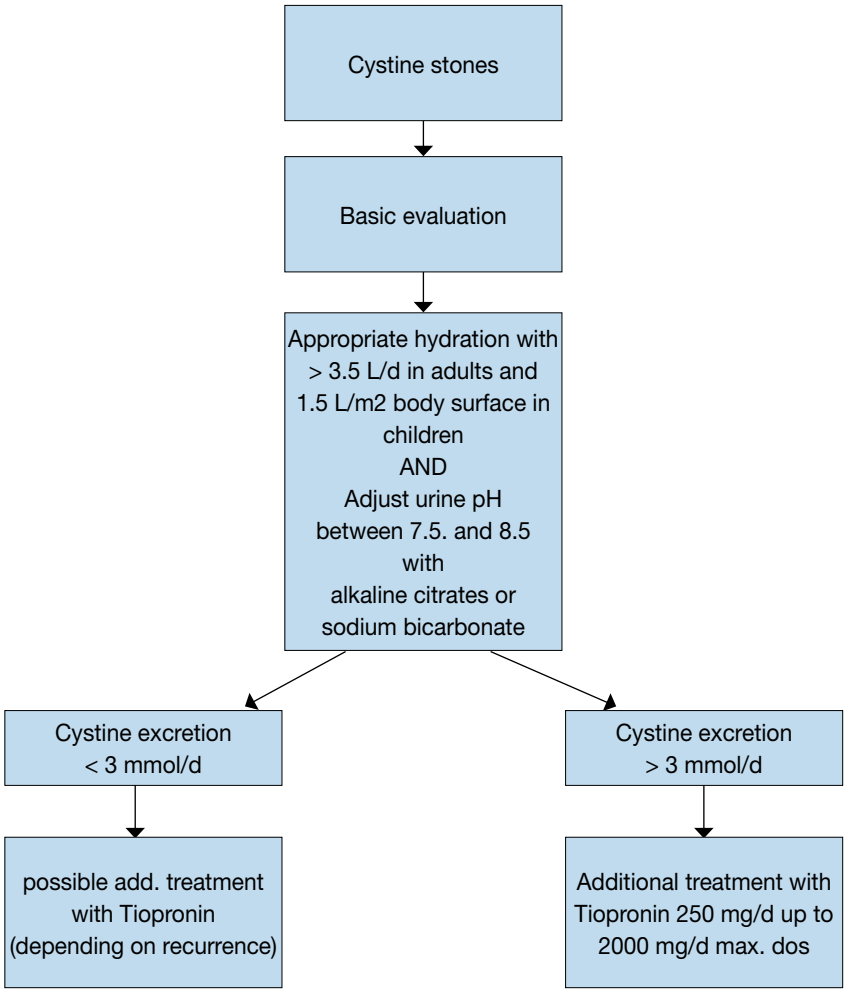
Tiopronin is currently the best choice for cystine reduction. However, side effects often lead to treatment termination, for example, when nephritic syndrome develops, or poor compliance, especially with long-term use.

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 reccuring stone formation, notwithstanding other preventive measures.

Ascorbic acid (as effervescent tablets) can be used when cystine excretion is < 3.0 mmol/day. However, it has uncertain, limited reductive power and is estimated to lower urinary cystine levels by ~20% (17). The effectiveness and use of ascorbic acid as a standard therapeutic regimen are controversial (18).

Results for the angiotensin-converting enzyme inhibitor, captopril, are controversial, and hypotonus and hyperkalaemia are possible side effects (19-23). Captopril remains a second-line option, for use when tiopronin is not feasible or unsuccessful.

Figure 8: Metabolic management of cystine stones



Recommendations for the treatment of cystine stones

Therapeutic measures	LE	GR
Urine dilution High fluid intake recommended so that 24-h urine volume exceeds 3 L. Intake should be ≥ 150 mL/h.	3	B
Alkalinisation For cystine excretion < 3 mmol/day: potassium citrate 3-10 mmol 2 or 3 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: tiopronin, 250-2000 mg/day. Captopril, 75-150 mg/d, remains a second-line option if tiopronin is not feasible or unsuccessful.	3	B

*11.9.3 **References***

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11.10 2,8-dihydroyadenine stones and xanthine stones (1)

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.

11.10.1 ***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.

11.10.2 ***Xanthine stones***

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

11.10.3 ***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.

11.11 Drug stones (2)

Drug stones are induced by pharmacological treatment (3,4) (Table 33). Two types exist:

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

Table 33: 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

11.12 Unknown stone composition (5)

An accurate medical history is the first step towards identifying risk factors (Table 34).

Diagnostic imaging begins with ultrasound examination of both kidneys to establish whether the patient is stone free. Stone detection by ultrasound 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.

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 (6,7).

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 34: Investigating patients with stones of unknown composition

Investigation	Rationale for investigation
Medical history	• Stone history (former stone events, family history) • Dietary habits • Medication chart
Diagnostic imaging	• Ultrasound in case of a suspected stone • Unenhanced helical CT • (Determination of Hounsfield units provides information about the possible stone composition)
Blood analysis	• Creatinine • Calcium (ionised calcium or total calcium + albumin) • Uric acid
Urinalysis	• Urine pH profile (measurement after each voiding, minimum 4 times daily) • Dipstick test: leukocytes, erythrocytes, nitrite, protein, urine pH, specific weight • Urine culture • Microscopy of urinary sediment (morning urine) • Cyanide nitroprusside test (cystine exclusion)

Further examinations depend on the results of the investigations listed above

11.13 References

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12. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

BFMZ	bendroflumethiazide
BMI	body mass index
CI	credible intervals
CT	computed tomography
DPTA	diethylene triamine pertaacetic acid (radiotracer)
EAU	European Association of Urology
GR	grade of recommendation
HCTZ	hydrochlorothiazide
HIRU	Health Information Research Unit
Ho:YAG	holmium:yttrium-aluminium-garnet [laser]
HPT	hyperparathyroidism
INR	international normalised ratio
IRS	infrared spectroscopy
IVU	intravenous urography
JESS	joint expert speciation system
KUB	Kidney ureter bladder
LE	level of evidence
MAG 3	mercapto acetyltriglycine (radiotracer)
MET	medical expulsive therapy
MMC	myelomeningocele
MRU	magnetic resonance urography
NC	nephrocalcinosis
NCCT	non-contrast enhanced computed tomography
NSAIDs	non-steroidal anti-inflammatory drugs
PCN	percutaneous nephrostomy
PH	primary Hyperoxaluria
PNL	percutaneous nephrolithotomy
PTH	parathyroid hormone
PTT	partial thrombolastin time
RCT	randomised controlled trial
RIRS	retrograde renal surgery
RTA	renal tubular acidosis
SFR	stone free rate
SIGN	Scottish Intercollegiate Guidelines Network
SWL	(extracorporeal) shock wave lithotripsy
THAM	tris-hydroxymethyl-aminomethane
UPJ	ureteropelvic junction
URS	ureterorenoscopy
US	ultrasound
UTI	urinary tract infection
XRD	X-ray diffraction

Conflict of interest

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