

Guidelines on Urolithiasis

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TABLE OF CONTENTS

PAGE

1.	INTRODUCTION	6
1.1	Aims and scope	6
1.2	Panel composition	6
1.3	Available publications	6
1.4	Publication history and summary of changes	6
1.4.1	Publication history	6
1.4.2	Summary of changes	6
2.	METHODS	7
2.1	Data identification	7
2.2	Evidence sources	7
2.3	Peer review	8
2.4	Future plans	8
3.	GUIDELINES	8
3.1	Prevalence, aetiology, risk of recurrence	8
3.1.1	Introduction	8
3.1.2	Stone composition	9
3.1.3	Risk groups for stone formation	9
3.2	Classification of stones	10
3.2.1	Stone size	10
3.2.2	Stone location	10
3.2.3	X-ray characteristics	10
3.3	Diagnostic evaluation	11
3.3.1	Diagnostic imaging	11
3.3.1.1	Evaluation of patients with acute flank pain	11
3.3.1.2	Radiological evaluation of patients for whom further treatment of renal stones is planned	12
3.3.2	Diagnostics - metabolism-related	12
3.3.2.1	Basic laboratory analysis - non-emergency urolithiasis patients	12
3.3.2.2	Analysis of stone composition	13
3.3.3	Diagnosis in special groups and conditions	13
3.3.3.1	Diagnostic imaging during pregnancy	13
3.3.3.2	Children	13
3.3.3.2.1	Diagnostic imaging	14
3.3.3.2.2	Ultrasound	14
3.3.3.2.3	Plain films (KUB radiography)	14
3.3.3.2.4	Intravenous urography (IVU)	14
3.3.3.2.5	Helical computed tomography (CT)	14
3.3.3.2.6	Magnetic resonance urography (MRU)	14
3.4	Disease management	14
3.4.1	Management of patients with renal or ureteral stones	14
3.4.1.1	Renal colic	15
3.4.1.2	Management of sepsis in obstructed kidney	15
3.4.2	Specific stone management in Renal stones	16
3.4.2.1	Types of treatments	16
3.4.2.1.1	Conservative treatment (Observation)	16
3.4.2.1.2	Pharmacological treatment	16
3.4.2.1.2.1	Percutaneous irrigation chemolysis	16
3.4.2.1.2.2	Oral chemolysis	16
3.4.2.1.3	Extracorporeal shock wave lithotripsy (SWL)	17
3.4.2.1.3.1	Contraindications of extracorporeal shock wave lithotripsy	17
3.4.2.1.3.2	Best clinical practice	17
3.4.2.1.3.3	Complications of extracorporeal shock wave lithotripsy	18
3.4.2.1.4	Endourology techniques for renal stone removal	19
3.4.2.1.4.1	Percutaneous nephrolithotomy (PNL)	19

	3.4.2.1.4.1.1	Contraindications	19
	3.4.2.1.4.1.2	Best clinical practice	19
	3.4.2.1.4.1.3	Complications	20
	3.4.2.1.4.2	Ureterorenoscopy for renal stones (RIRS)	21
	3.4.2.1.4.3	Open and laparoscopic surgery for removal of renal stones	21
3.4.2.2		Indication for active stone removal of renal stones	21
3.4.2.3		General recommendations and precautions for renal stone removal	22
	3.4.2.3.1	Antibiotic therapy	22
	3.4.2.3.2	Antithrombotic therapy and stone treatment	22
	3.4.2.3.3	Obesity	23
	3.4.2.3.4	Stone composition	23
	3.4.2.3.5	Steinstrasse	23
3.4.2.3		Selection of procedure for active removal of renal stones	24
	3.4.2.3.1	Stones in renal pelvis or upper/middle calices	24
	3.4.2.3.2	Stones in the lower renal pole	24
	3.4.2.3.3	Recommendations for the selection of procedures for active removal of renal stones	25
3.4.3		Specific stone management of Ureteral stones	26
	3.4.3.1	Types of treatment	26
	3.4.3.1.1	Conservative treatment / observation	26
	3.4.3.1.2	Pharmacological treatment, Medical expulsive therapy (MET)	26
	3.4.3.1.2.1	Factors affecting success of medical expulsive therapy (tamsulosin)	27
	3.4.3.1.2.2	Medical expulsive therapy after extracorporeal shock wave lithotripsy (SWL)	27
	3.4.3.1.2.3	Medical expulsive therapy after ureteroscopy	27
	3.4.3.1.2.4	Medical expulsive therapy and ureteral stents	27
	3.4.3.1.2.5	Duration of medical expulsive therapy treatment	27
	3.4.3.1.2.6	Possible side-effects include retrograde ejaculation and hypotension	27
	3.4.3.1.3	SWL	27
	3.4.3.1.4	Endourology techniques	27
	3.4.3.1.4.1	Ureteroscopy (URS)	27
	3.4.3.1.4.1.1	Contraindications	27
	3.4.3.1.4.1.2	Best clinical practice in ureterorenoscopy (URS)	28
	3.4.3.1.4.1.3	Complications	29
	3.4.3.1.4.2	Percutaneous antegrade ureteroscopy	29
	3.4.3.1.5	Laparoscopic ureteral stone removal	29
3.4.3.2		Indications for active removal of ureteral stones	29
	3.4.3.2.1	General recommendations and precautions	29
	3.4.3.2.1.1	Antibiotic treatment	29
	3.4.3.2.1.2	Obesity	29
	3.4.3.2.1.3	Bleeding disorder	29
3.4.3.3		Selection of procedure for active removal of ureteral stones	29
3.4.4		Management of patients with residual stones	30
	3.4.4.1	Therapy	31
3.4.5		Management of specific patient groups	31
	3.4.5.1	Management of urinary stones and related problems during pregnancy	31
	3.4.5.2	Management of stones in patients with urinary diversion	31
	3.4.5.2.1	Aetiology	31
	3.4.5.2.2	Management	31
	3.4.5.2.3	Prevention	32
3.4.5.3		Management of stones in patients with neurogenic bladder	32
	3.4.5.3.1	Aetiology, clinical presentation and diagnosis	32
	3.4.5.3.2	Management	32
3.4.5.4		Management of stones in transplanted kidneys	33
	3.4.5.4.1	Aetiology	33

3.4.5.4.2	Management	33
3.4.5.4.3	Special problems in stone removal	33
3.4.6	Management of urolithiasis in children	34
3.4.6.1	Stone removal	34
3.4.6.1.1	Medical expulsive therapy (MET) in children	34
3.4.6.1.2	Extracorporeal shock wave lithotripsy	34
3.4.6.1.3	Endourological procedures	35
3.4.6.1.3.1	Percutaneous nephrolithotripsy (PNL)	35
3.4.6.1.3.2	Ureteroscopy	35
3.4.6.1.3.3	Open or laparoscopic surgery	35
3.4.6.1.3.4	Special considerations on recurrence prevention	35
4.	FOLLOW UP METABOLIC EVALUATION AND RECURRENCE PREVENTION	36
4.1	General metabolic considerations for patient work-up	36
4.1.1	Evaluation of patient risk	36
4.1.2	Urine sampling	36
4.1.3	Timing of specific metabolic work-up	37
4.1.4	Reference ranges of laboratory values	37
4.1.5	Risk indices and additional diagnostic tools	37
4.2	General considerations for recurrence prevention	39
4.2.1	Fluid intake	39
4.2.2	Diet	39
4.2.3	Lifestyle	40
4.2.4	Recommendations for recurrence prevention	40
4.3	Stone-specific metabolic evaluation and pharmacological recurrence prevention	40
4.3.1	Introduction	40
4.4	Calcium oxalate stones	42
4.4.1	Diagnosis	42
4.4.2	Interpretation of results and aetiology	42
4.4.3	Specific treatment	43
4.4.4	Recommendations for pharmacological treatment of patients with specific abnormalities in urine composition	43
4.5	Calcium phosphate stones	43
4.5.1	Diagnosis	44
4.5.2	Interpretation of results and aetiology	44
4.5.3	Pharmacological therapy	44
4.5.4	Recommendations for the treatment of calcium phosphate stones	44
4.6	Disorders and diseases related to calcium stones	44
4.6.1	Hyperparathyroidism	44
4.6.2	Granulomatous diseases	45
4.6.3	Primary hyperoxaluria	45
4.6.4	Enteric hyperoxaluria	45
4.6.5	Renal tubular acidosis	45
4.6.6	Nephrocalcinosis	47
4.6.6.1	Diagnosis	47
4.7	Uric acid and ammonium urate stones	47
4.7.1	Diagnosis	47
4.7.2	Interpretation of results	47
4.7.3	Specific treatment	48
4.8	Struvite and infection stones	48
4.8.1	Diagnosis	48
4.8.2	Specific treatment	49
4.8.3	Recommendations for therapeutic measures of infection stones	49
4.9	Cystine stones	50
4.9.1	Diagnosis	50
4.9.2	Specific treatment	51
4.9.2.1	Pharmacological treatment of cystine stones	51
4.9.3	Recommendations for the treatment of cystine stones	52
4.10	2,8-Dihydroxyadenine stones and xanthine stones	52
4.10.1	2,8-Dihydroxyadenine stones	52

4.10.2	Xanthine stones	52
4.10.3	Fluid intake and diet	52
4.11	Drug stones	52
4.12	Matrix Stones	53
4.13	Unknown stone composition	53
5.	REFERENCES	54
6.	CONFLICT OF INTEREST	71

1. INTRODUCTION

1.1 Aims and scope

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 Panel composition

The EAU Urolithiasis Guidelines Panel consists of an international group of clinicians with particular expertise in this area. All experts involved in the production of this document have submitted potential conflict of interest statements.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and in a number of versions for mobile devices. These are abridged versions which may require consultation together with the full text versions. Also a number of translated versions, alongside several scientific publications in European Urology and the Journal of Urology [1-3], are available. All documents can be accessed through the EAU website: <http://www.uroweb.org/guidelines/online-guidelines/>.

1.4 Publication history and summary of changes

1.4.1 Publication history

The EAU published its first guidelines on Urolithiasis in 2000. This 2015 document presents a limited update of the 2014 publication of the EAU Urolithiasis Guidelines.

1.4.2 Summary of changes

Key changes for the 2015 publication:

- The literature for the complete document has been assessed and updated, whenever relevant and 46 new references have been included.
- A new introductory section was added to Section 3.1 (section Prevalence, aetiology, risk of recurrence), as well as a table. Additional data has been added to Table 1.2.
- Diagnostic imaging during pregnancy (section 3.3.3.1).

Recommendation	LE	GR
In pregnant women, ultrasound is the imaging method of choice.	1a	A*
In pregnant women, MRI should be used as a second-line imaging modality.	3	C
In pregnant women, low-dose CT should be considered as a last-line option. The exposure should be less than 0.05 Gy.	3	C

- In Section 3.4.1.2.1.1.1 - Conservative treatment (Observation) – a recommendation on the timing of patient follow-up has been included.

If renal stones are not treated, periodic evaluation is recommended (after 6 months and yearly thereafter).	A*
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- In Section: 3.4.1.3 - Indication for active stone removal of kidney stones - a new recommendation has been added.

Recommendation	LE	GR
Radiolucent stones may be dissolvable (See Section 3.4.1.2.1.1.2.1.3).	2a	B

- In Section 3.4.2.3.3 - Laparoscopic ureteral stone removal – a new recommendation has been included.

For ureterolithotomy, laparoscopy is recommended for large impacted stones when endoscopic lithotripsy or SWL has failed.	2	B
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- In Section 3.4.1.4.1 - Antibiotic treatment – a new recommendation has been included.

Recommendations	LE	GR
UTIs must be excluded or treated prior to endourologic stone removal.	1b	A
In all patients undergoing endourologic treatment, perioperative antibiotic prophylaxis is recommended.	1b	A*

- A new Figure (3.4.2) - Recommended treatment options (if indicated for active stone removal) - has been included.
- In Section 3.4.5 - Management of stones in patients with neurogenic bladder – the recommendation has been expanded.

Recommendation	GR
In myelomeningocele patients, latex allergy is common, thus appropriate measures need to be taken regardless of the treatment. For surgical interventions, general anesthesia remains the only option.	B

- An additional recommendation was included in Table 3.4.6 - Special problems in stone removal.

Horseshoe kidneys	<ul style="list-style-type: none"> • Acceptable stone free rates can be achieved with flexible ureteroscopy [335].
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- Figures 4.2 - Diagnostic and therapeutic algorithm for calcium oxalate stones - and 4.3 - Diagnostic and therapeutic algorithm for calcium phosphate stones - have updated reference values included.
- A new Section on Matrix stones has been added (4.12).
- In Table 4.6 - Pharmacological substances used for stone prevention - characteristics, specifics and dosage - Febuxostat for the treatment of hyperuricosuria and hyperuricaemia has been added.
- Section 4.4.4 - Recommendations for pharmacological treatment of patients with specific abnormalities in urine composition – a recommendation for Febustat has been added.

Hyperuricosuria	Allopurinol	1a	A
	Febuxostat	1b	A

- In Table 4.8 - Pharmacological treatment of renal tubular acidosis – additional alternatives for the treatment of hypercalciuria have been included.

2. METHODS

2.1 Data identification

For this 2015 print of the Urolithiasis guidelines, a scoping search, covering all content, was performed. Time frame of the search was August 2nd 2013 through August 11th 2014. 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 421 unique records.

Selection of the papers was done through a consensus meeting of the Panel held October 25-26th, 2014. Annual scoping searches will be repeated as a standard procedure.

In this 2015 EAU Guidelines compilation, all standard information on levels of evidence (LE) and grading of recommendations (GR) has been taken out of the individual guidelines topics for the sake of brevity. This information is included in the introductory section of this print.

2.2 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 Ovid platform. The searches used the controlled terminology and the use of free text ensured search sensitivity.

2.3 Peer review

This document was subjected to double-blind peer review prior to publication.

2.4 Future plans

The EAU Urolithiasis guidelines panel aim to incorporate the results of a number of ongoing systematic reviews in their 2016 print update.

3. GUIDELINES

3.1 Prevalence, aetiology, risk of recurrence

3.1.1 Introduction

Stone incidence depends on geographical, climatic, ethnic, dietary and genetic factors. The recurrence risk is basically determined by the disease or disorder causing the stone formation. Accordingly, the prevalence rates for urinary stones vary from 1% to 20% [4]. In countries with a high standard of life such as Sweden, Canada or the US, renal stone prevalence is notably high (> 10%). For some areas an increase of more than 37% over the last 20 years is reported [5] (Table 3.1.1).

Table 3.1.1: Prevalence and incidence of urolithiasis from two European countries [6, 7]

	Germany 2000 (%)	Spain 2007 (%)
<i>Prevalence</i>	4.7	5.06
Females	4.0	NA
Males	5.5	NA
<i>Incidence</i>	1.47	0.73
Females	0.63	NA
Males	0.84	NA

Stones can be classified into those caused by: infection, or non-infectious causes (infection and non-infection stones); genetic defects [8]; or adverse drug effects (drug stones) (Table 3.1.2).

Table 3.1.2: Stones classified by aetiology*

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

*See Section 4.4.2

3.1.2 Stone composition

Stone composition is the basis for further diagnostic and management decisions. Stones are often formed from a mixture of substances. Table 3.1.3 lists the clinically most relevant substances and their mineral components.

Table 3.1.3: Stone composition

Chemical name	Mineral name	Chemical formula
Calcium oxalate monohydrate	Whewellite	$\text{CaC}_2\text{O}_4 \cdot \text{H}_2\text{O}$
Calcium oxalate dihydrate	Wheddelite	$\text{CaC}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$
Basic calcium phosphate	Apatite	$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$
Calcium hydroxyl phosphate	Carbonite apatite	$\text{Ca}_5(\text{PO}_3)_3(\text{OH})$
b-tricalcium phosphate	Whitlockite	$\text{Ca}_3(\text{PO}_4)_2$
Carbonate apatite phosphate	Dahllite	$\text{Ca}_5(\text{PO}_4)_3\text{OH}$
Calcium hydrogen phosphate	Brushite	$\text{PO}_4 \cdot 2\text{H}_2\text{O}$
Calcium carbonate	Aragonite	CaCO_3
Octacalcium phosphate		$\text{Ca}_8\text{H}_2(\text{PO}_4)_6 \cdot 5\text{H}_2\text{O}$
Uric acid	Uricite	$\text{C}_5\text{H}_4\text{N}_4\text{O}_3$
Uric acid dihydrate	Uricite	$\text{C}_5\text{H}_4\text{O}_3 \cdot 2\text{H}_2\text{O}$
Ammonium urate		$\text{NH}_4\text{C}_5\text{H}_3\text{N}_4\text{O}_3$
Sodium acid urate monohydrate		$\text{NaC}_5\text{H}_3\text{N}_4\text{O}_3 \cdot \text{H}_2\text{O}$
Magnesium ammonium phosphate	Struvite	$\text{MgNH}_4\text{PO}_4 \cdot 6\text{H}_2\text{O}$
Magnesium acid phosphate trihydrate	Newberyite	$\text{MgHPO}_4 \cdot 3\text{H}_2\text{O}$
Magnesium ammonium phosphate monohydrate	Dittmarite	$\text{MgNH}_4(\text{PO}_4) \cdot \text{H}_2\text{O}$
Cystine		$[\text{SCH}_2\text{CH}(\text{NH}_2)\text{COOH}]_2$
Gypsum	Calcium sulphate dihydrate Zinc phosphate tetrahydrate	$\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$ $\text{Zn}_3(\text{PO}_4)_2 \cdot 4\text{H}_2\text{O}$
Xanthine		
2,8-Dihydroxyadenine		
Proteins		
Cholesterol		
Calcite		
Potassium urate		
Trimagnesium phosphate		
Melamine		
Matrix		
Drug stones	<ul style="list-style-type: none"> • Active compounds crystallising in urine • Substances impairing urine composition (Section 4.11) 	
Foreign body calculi		

3.1.3 Risk groups for stone formation

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

About 50% of recurrent stone formers have just one lifetime recurrence [6, 9]. Highly recurrent disease is observed in slightly more than 10% of patients. Stone type and disease severity determine low or high-risk of recurrence (Table 3.1.4) [10, 11].

Table 3.1.4: High-risk stone formers [10-17]

General factors
Early onset of urolithiasis (especially children and teenagers)
Familial stone formation
Brushite-containing stones (CaHPO ₄ ·2H ₂ O)
Uric acid and urate-containing stones
Infection stones
Solitary kidney (the kidney itself does not particularly increase the risk of stone formation, but prevention of stone recurrence is of more importance)
Diseases associated with stone formation
Hyperparathyroidism
Metabolic syndrome [17]
Nephrocalcinosis
Gastrointestinal diseases (i.e., jejunio-ileal bypass, intestinal resection, Crohn's disease, malabsorptive conditions, enteric hyperoxaluria after urinary diversion) and bariatric surgery [16]
Sarcoidosis
Genetically determined stone formation
Cystinuria (type A, B and AB)
Primary hyperoxaluria (PH)
Renal tubular acidosis (RTA) type I
2,8-Dihydroxyadeninuria
Xanthinuria
Lesch-Nyhan syndrome
Cystic fibrosis
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

3.2 Classification of stones

Urinary stones can be classified according to size, location, X-ray characteristics, aetiology of formation, composition, and risk of recurrence [6, 18-20].

3.2.1 Stone size

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

3.2.2 Stone location

Stones can be classified according to anatomical position: upper, middle or lower calyx; renal pelvis; upper, middle or distal ureter; and urinary bladder. Treatment of bladder stones is not discussed here.

3.2.3 X-ray characteristics

Stones can be classified according to plain X-ray appearance [kidney-ureter-bladder (KUB) radiography] (Table 3.2.1), which varies according to mineral composition [20]. Non-contrast-enhanced computed tomography (NCCT) can be used to classify stones according to density, inner structure and composition, which can affect treatment decisions (Section 3.4.1.4.4) [19, 20].

Table 3.2.1: X-ray characteristics

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

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

3.3 Diagnostic evaluation

3.3.1 Diagnostic imaging

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

Standard evaluation includes a detailed medical history and physical examination. Patients with ureteral stones usually present with loin pain, vomiting, and sometimes fever, but may also be asymptomatic [21].

Ultrasound (US) should be used as the primary diagnostic imaging tool, although pain relief, or any other emergency measures should not be delayed by imaging assessments. 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. US has a sensitivity of 45% and specificity of 94% for ureteric stones and a sensitivity of 45% and specificity of 88% for renal stones [22].

The sensitivity and specificity of KUB radiography is 44-77% and 80-87%, respectively [23]. KUB radiography should not be performed if NCCT is considered [24], 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.

3.3.1.1 Evaluation of patients with acute flank pain

NCCT has become the standard for diagnosing acute flank pain, and has replaced intravenous urography (IVU). NCCT can determine stone diameter and density. When stones are absent, the cause of abdominal pain should be identified. In evaluating patients with suspected acute urolithiasis, NCCT seems to be significantly more accurate than IVP [25].

Recommendation	LE	GR
Following initial US assessment, NCCT should be used to confirm stone diagnosis in patients with acute flank pain, because it is superior to IVU.	1a	A

IVU = intravenous urography; NCCT = non-contrast enhanced computed tomography.

NCCT can detect uric acid and xanthine stones, which are radiolucent on plain films, but not indinavir stones [26]. 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 [20, 27-29]. The advantage of non-contrast imaging must be balanced against loss of information on renal function and urinary collecting system anatomy, as well as higher radiation dose (Table 3.1).

Radiation risk can be reduced by low-dose CT [30]. In patients with body mass index (BMI) < 30, low-dose CT has been shown to have a sensitivity of 86% for detecting ureteric stones < 3 mm and 100% for calculi > 3 mm [31]. A meta-analysis of prospective studies [32] has shown that low-dose CT diagnosed urolithiasis with a pooled sensitivity of 96.6% (95% CI: 95.0-97.8) and specificity of 94.9% (95% CI: 92.0-97.0).

Table 3.3.1: Radiation exposure of imaging modalities [33-36]

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

NCCT = non-contrast enhanced computed tomography.

3.3.1.2 Radiological evaluation of patients for whom further treatment of renal stones is planned

Recommendations	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 in complex cases 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.	4	C

*Upgraded based on panel consensus.

CT – computed tomography; IVU = intravenous urography.

3.3.2 Diagnostics - metabolism-related

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

Table 3.3.2: Recommendations: basic laboratory analysis - emergency urolithiasis patients [11, 12, 37, 38]

Urine	GR
Dipstick test of spot urine sample	A*
<ul style="list-style-type: none"> • red cells • white cells • nitrite • approximate urine pH 	A
Urine microscopy and/or culture	
Blood	
Serum blood sample	A*
<ul style="list-style-type: none"> • creatinine • uric acid • (ionised) calcium • sodium • potassium 	
<ul style="list-style-type: none"> • 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.

3.3.2.1 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 [11]. Stone-specific metabolic evaluation is described in Chapter 4.

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.

3.3.2.2 Analysis of stone composition

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

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

- recurrence under pharmacological prevention;
- early recurrence after interventional therapy with complete stone clearance;
- late recurrence after a prolonged stone-free period [39].

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) [40-42]. Equivalent results can be obtained by polarisation microscopy, but only in centres with expertise. Chemical analysis (wet chemistry) is generally deemed to be obsolete [40].

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: <ul style="list-style-type: none"> • presenting with recurrent stones despite drug therapy; • with early recurrence after complete stone clearance; • with late recurrence after a long stone-free period because stone composition may change [38]. 	2	B

IRS = infrared spectroscopy; XRD = X-ray diffraction.

3.3.3 Diagnosis in special groups and conditions

3.3.3.1 Diagnostic imaging during pregnancy

In pregnant women diagnostic imaging (exposure to ionising radiation) might be associated with teratogenic risks and development of (childhood) malignancies. The risk for the child crucially depends on gestational age and 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 [43, 44].

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 [45].

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

Magnetic resonance imaging (MRI) can be used, as a second-line procedure, to define the level of urinary tract obstruction, and to visualise stones as a filling defect [46, 47].

Low dose CT protocols, or low dose CT scans reduce the radiation exposure and are currently recommended to be used judiciously in pregnant women as a last-line option [48, 49].

Recommendations	LE	GR
In pregnant women, ultrasound is the imaging method of choice.	1a	A*
In pregnant women, MRI should be used as a second-line imaging modality.	3	C
In pregnant women, low-dose CT should be considered as a last-line option. The exposure should be less than 0.05 Gy.	3	C

*Upgraded following panel consensus.

CT = computed tomography; MRI = magnetic resonance imaging.

3.3.3.2 Children

Paediatric patients with urinary stones have a high risk of recurrence, therefore, standard diagnostic procedures for high-risk patients apply (Section 3.1.3 and Chapter 4).

Statement	LE
In paediatric patients, the most common non-metabolic disorders are vesicoureteral reflux, ureteropelvic junction obstruction, neurogenic bladder, and other voiding difficulties [50].	4
Recommendations	GR
In all paediatric patients, efforts should be made to complete a metabolic evaluation based on stone analysis.	A
All efforts should be made to collect stone material that should then be analysed to classify the stone type.	A*

*Upgraded following panel consensus.

3.3.3.2.1 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 [51-53]. Again, the principle of ALARA (As Low As Reasonably Achievable) should be observed.

3.3.3.2.2 Ultrasound

Ultrasound (US) is the primary imaging technique [51] in paediatrics. Its advantages are absence of radiation and no need for anaesthesia.

Colour Doppler US shows differences in the ureteric jet [54] and resistive index of the arciform arteries of both kidneys, which are indicative of the grade of obstruction [55].

Nevertheless, US fails to identify stones in > 40% of paediatric patients [56-59] (LE: 4), and provides no information on 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 [54-57, 60].	2a

3.3.3.2.3 Plain films (KUB radiography)

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

3.3.3.2.4 Intravenous urography (IVU)

The radiation dose for IVU is comparable to that for voiding cystourethrography (0.33 mSV) [61]. However, the need for contrast medium injection is a major drawback.

3.3.3.2.5 Helical computed tomography (CT)

Recent low-dose CT protocols have been shown to significantly reduce radiation exposure [36]. The principle of ALARA (as low as reasonably achievable) should always be observed. In adults it has a sensitivity of 94-100% and specificity of 92-100% [62].

In children, only 5% of stones escape detection by NCCT [54, 62, 63]. Sedation or anaesthesia is rarely needed with modern high-speed CT apparatus.

3.3.3.2.6 Magnetic resonance urography (MRU)

Magnetic resonance urography cannot be used to detect urinary stones. However, it might provide detailed anatomical information about the urinary collecting system, the location of an obstruction or stenosis in the ureter, and renal parenchymal morphology [64].

Recommendations	GR
In children, US is the first-line imaging modality when a stone is suspected.	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.

3.4 Disease management

3.4.1 Management of patients with renal or ureteral stones

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

3.4.1.1 Renal colic

Pain relief

Pain relief is the first therapeutic step in patients with an acute stone episode [65, 66].

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective in patients with acute stone colic [67, 68], 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 [69, 70] (see below). If an opioid is used, it is recommended that it is not pethidine.

Prevention of recurrent renal colic

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

For patients with ureteral stones that are expected to pass spontaneously, NSAID tablets or suppositories (e.g., diclofenac sodium, 100-150 mg/day, 3-10 days) may help reduce inflammation and the risk of recurrent pain [70-72]. Although diclofenac can affect renal function in patients with already reduced function, it has no functional effect in patients with normal kidney function [73] (LE: 1b).

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 [72]. Daily α -blockers reduce recurrent colic (LE: 1a) (Section 3.4.3.1.2).

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

Statement and recommendations for analgesia during renal colic

Statement	LE
For symptomatic ureteral stones, urgent stone removal as first-line treatment is a feasible option.	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. e.g. diclofenac*, indomethacin or ibuprofen**.	A
Second choice: hydromorphone, pentazocine or tramadol.	C
Use α -blockers to reduce recurrent colics.	A

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

**Recommended to counteract recurrent pain after ureteral colic.

3.4.1.2 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.

Decompression

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

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

There is little evidence to support the superiority of percutaneous nephrostomy over retrograde stenting for primary treatment of infected hydronephrosis. There is no good-quality evidence to suggest that ureteric stenting has more complications than percutaneous nephrostomy [74, 75].

Only one RCT [76] 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 [74]. Definitive stone removal should be delayed until the infection is cleared following a complete course of antimicrobial therapy.

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

Recommendations	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

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.

3.4.2 Specific stone management in Renal stones

The natural history of small, non-obstructing asymptomatic calculi is not well defined, and the risk of progression is unclear. There is still no consensus on the follow-up duration, and timing and type of intervention. Treatment options are observation, chemolysis or active stone removal.

3.4.2.1 Types of treatments

3.4.2.1.1 Conservative treatment (Observation)

Observation of renal stones, especially in calices, depends on their natural history (Section 3.4.2.2).

Statement	LE
It is still debatable whether renal 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
If renal stones are not treated, periodic evaluation is recommended (after 6 months and yearly follow-up of symptoms and stone status [US, KUB or CT]).	A*

*Upgraded based on panel consensus.

3.4.2.1.2 Pharmacological treatment

3.4.2.1.2.1 Percutaneous irrigation chemolysis

Today, percutaneous chemolysis is rarely used. Percutaneous irrigation chemolysis may be an option for infection- and uric acid stones [77, 78]. For dissolution of struvite stones, Suby's G solution (10% hemiacidrin; pH 3.5-4) can be used [79].

3.4.2.1.2.2 Oral chemolysis

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

Oral chemolitholysis is based on alkalinisation of urine by application of alkaline citrate or sodium bicarbonate [78, 80]. The pH should be adjusted to 7.0-7.2. Within this range, chemolysis is more effective at a higher pH, which might lead to calcium phosphate stone formation.

Monitoring of radiolucent stones during therapy is the domain of US, however, repeat NCCT might be necessary.

In the case of uric acid obstruction of the collecting system, oral chemolysis in combination with urinary drainage is indicated [81]. A combination of alkalinisation with tamsulosin seems to achieve the highest SFRs for distal ureteral stones [81].

Recommendations	GR
The dosage of alkalisating 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 three times a day (at regular intervals). Morning urine must be included.	A

Careful monitoring of radiolucent stones during/after therapy is imperative.	A*
The physician should clearly inform the patient of the significance of compliance.	A

*Upgraded based on panel consensus.

3.4.2.1.3 Extracorporeal shock wave lithotripsy (SWL)

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

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

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

3.4.2.1.3.1 Contraindications of extracorporeal shock wave lithotripsy

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

- pregnancy, due to the potential effects on the foetus [82];
- bleeding diatheses, which should be compensated for at least 24 h before and 48 h after treatment [83];
- uncontrolled UTIs;
- severe skeletal malformations and severe obesity, which prevent targeting of the stone;
- arterial aneurysm in the vicinity of the stone [84];
- anatomical obstruction distal to the stone.

3.4.2.1.3.2 Best clinical practice

Stenting

Routine use of internal stents before SWL does not improve SFR [85] (LE: 1b). A JJ stent reduces the risk of renal colic and obstruction, but does not reduce formation of steinstrasse or infective complications [86].

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 [87].

Shock wave rate

Lowering shock wave frequency from 120 to 60-90 shock waves/min improves SFR [88-93]. Tissue damage increases with shock wave frequency [94-97].

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

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 [98], which prevents renal injury [99, 100]. Animal studies [101] and a prospective randomised study [102] 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 [103].

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

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 [104]. US gel is probably the most widely used agent available for use as a lithotripsy coupling agent [105].

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

Procedural control

Results of treatment are operator dependent, and better results are obtained by experienced clinicians. During the procedure, careful imaging control of localisation contributes to outcome quality [106].

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

**Upgraded based on panel consensus.*

Pain control

Careful control of pain during treatment is necessary to limit pain-induced movements and excessive respiratory excursions [107-109].

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

Antibiotic prophylaxis

No standard antibiotic prophylaxis before SWL is recommended. However, prophylaxis is recommended in the case of internal stent placement ahead of anticipated treatments and in the presence of increased bacterial burden (e.g., indwelling catheter, nephrostomy tube, or infectious stones) [110-112].

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

Medical therapy after extracorporeal shock wave lithotripsy

MET after SWL for ureteral or renal stones can expedite expulsion and increase SFRs, as well as reduce additional analgesic requirements [113-121] (Section 3.4.2.1.2.1.2).

3.4.2.1.3.3 Complications of extracorporeal shock wave lithotripsy

Compared to PNL and URS, there are fewer overall complications with SWL [122, 123] (Table 3.4.1).

Table 3.4.1: SWL-related complications [124-138]

Complications			%	Ref.
Related to stone fragments	Steinstrasse		4 - 7	[124-126]
	Regrowth of residual fragments		21 - 59	[127, 128]
	Renal colic		2 - 4	[129]
Infectious	Bacteriuria in non-infection stones		7.7 - 23	[127, 130]
	Sepsis		1 - 2.7	[127, 130]
Tissue effect	Renal	Haematoma, symptomatic	< 1	[131]
		Haematoma, asymptomatic	4 - 19	[131]
	Cardiovascular	Dysrhythmia	11 - 59	[127, 132]
		Morbid cardiac events	Case reports	[127, 132]
	Gastrointestinal	Bowel perforation	Case reports	[133-135]
		Liver, spleen haematoma	Case reports	[135-138]

The relationship between SWL and hypertension or diabetes is unclear. Published data are contradictory and no conclusion can be reached [3, 139-141].

3.4.2.1.4 Endourology techniques for renal stone removal

3.4.2.1.4.1 Percutaneous nephrolithotomy (PNL)

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

The efficacy of miniaturized systems seems to be high, but longer OR times apply and benefit compared to standard PNL for selected patients has yet to be demonstrated [142]. There is some evidence that smaller tracts cause less bleeding complications, but further studies need to evaluate this issue [143-146].

3.4.2.1.4.1.1 Contraindications

Patients receiving anticoagulant therapy must be monitored carefully pre- and postoperatively. Anticoagulant therapy must be discontinued before PNL [147].

Other important contraindications include:

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

3.4.2.1.4.1.2 Best clinical practice

Intracorporeal lithotripsy

Several methods for intracorporeal lithotripsy are available (the devices are discussed in Section 3.4.1.2.1.1.5). During PNL, ultrasonic and pneumatic systems are most commonly used for rigid nephroscopy. When using miniaturized instruments, laser lithotripsy is associated with lower stone migration than with pneumatic lithotripsy [148]. Flexible endoscopes require laser lithotripsy to maintain tip deflection and the Ho:YAG laser has become the standard, as for ureteroscopy [149]. Electrohydraulic lithotripsy (EHL) is highly effective, but is no longer considered as a first-line technique, due to possible collateral damage [150].

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.

Preoperative imaging

Preprocedural evaluations are summarised in Section 3.3.1. In particular, PNL, US or CT of the kidney and the surrounding structures can provide information regarding interpositioned organs within the planned percutaneous path (e.g., spleen, liver, large bowel, pleura, and lung) [151].

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 renal stone.	A*

*Upgraded based on panel consensus.

Antibiotic therapy – see General recommendations and precautions for stone removal (See Section 3.4.1.4.1).

Positioning of the patient

Both prone and supine positions are equally safe.

Although the supine position confers some advantages, it depends on appropriate equipment being available to position the patient correctly, for example, X-ray devices and an operating table. Most studies cannot demonstrate an advantage of supine PNL in terms of OR time. In some series, stone-free rate is lower than for the prone position despite a longer OR time. Prone position offers more options for puncture and is therefore preferred for upper pole or multiple access [152-154]. The Urolithiasis Guidelines Panel will be setting up a systematic review to assess this topic.

Puncture

Colon interposition in the access tract of PNL can lead to colon injuries. Preoperative CT or intraoperative US allows identification of the tissue between the skin and kidney and lowers the incidence of bowel injury [155, 156].

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 [155].

Nephrostomy and stents

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

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

Small bore nephrostomies seem to have advantages in terms of postoperative pain [157, 158].

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 [159-161].

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

3.4.2.1.4.1.3 Complications

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

Table 3.4.2: Complications following PNL [162]

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%	0.05%	

Perioperative fever can occur, even with a sterile preoperative urinary culture and perioperative antibiotic prophylaxis, because the renal stones themselves may be a source of infection. Intraoperative renal stone culture may therefore help to select postoperative antibiotics [163, 164]. Intraoperative irrigation pressure < 30 mm Hg and unobstructed postoperative urinary drainage may be important factors in preventing postoperative sepsis. Bleeding after PNL may be treated by brief clamping of the nephrostomy tube. Super-selective embolic occlusion of the arterial branch may become necessary in the case of severe bleeding.

3.4.2.1.4.2 Ureterorenoscopy for renal stones (RIRS)

Technical improvements including endoscope miniaturisation, improved deflection mechanism, enhanced optical quality and tools, and introduction of disposables have led to an increased use of URS for both, renal and ureteral stones. Major technological progress has been achieved for retrograde intrarenal surgery (RIRS), [165-167]. Initial experience with digital scopes demonstrated shorter operation times due to the improvement in image quality [166-168]. For best clinical practice see Section 3.4.3.1.4.1.2 (Ureteral stones-URS).

Stones that cannot be extracted directly must be disintegrated. If it is difficult to access stones that need disintegration within the lower renal pole, it may help to displace them into a more accessible calyx [169].

Recommendation	GR
In case PNL is not an option, larger stones, even larger than 2 cm, may be treated with flexible URS. However, in that case there is a higher risk that a follow-up procedure and placement of a ureteral stent may be needed. In complex stone cases, open or laparoscopic approaches are possible alternatives.	B

GR = grade of recommendation; PNL = percutaneous nephrolithotomy; URS = ureterorenoscopy.

3.4.2.1.4.3 Open and laparoscopic surgery for removal of renal stones

Advances in SWL and endourological surgery (URS and PNL) have significantly decreased the indications for open or laparoscopic stone surgery [170-176]. There is a consensus that most complex stones, including partial and complete staghorn stones, should be approached primarily with PNL. Additionally, a combined approach with PNL and retrograde flexible uretero-rensoscopy (RIRS) may also be an appropriate alternative. However, if a reasonable number of percutaneous approaches are not likely to be successful, or if multiple, endourological approaches have been performed unsuccessfully, open or laparoscopic surgery may be a valid treatment option [177-180].

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, especially when the stone mass is centrally located.	3	C

3.4.2.2 Indication for active stone removal of renal stones [181]

- 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.

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 [181-183].	3

The risk of a symptomatic episode or need for intervention seems to be ~10-25% per year, with a cumulative 5-year event probability of 48.5% [184-187]. A prospective RCT with > 2 years clinical follow-up 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 [188]. Although some have recommended prophylaxis for these stones to prevent renal colic, haematuria, infection, or stone growth, conflicting data have been reported [184, 186, 189]. In a follow-up period of almost 5 years after SWL, two series have demonstrated that up to 25% of patients with small residual fragments needed treatment [128, 190].

Recommendations	GR
Renal stones should be treated in the 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

*Upgraded based on panel consensus.

3.4.2.3 General recommendations and precautions for renal stone removal

3.4.2.3.1 Antibiotic therapy

Urinary tract infections should always be treated if stone removal is planned. In patients with clinically significant infection and obstruction, drainage should be performed for several days, via a stent or percutaneous nephrostomy, before starting stone removal.

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

*Upgraded following panel consensus.

Perioperative antibiotic prophylaxis

For risk of infection following ureteroscopy and percutaneous stone removal, no clear-cut evidence exists [191]. In a review of a large database of patients undergoing percutaneous nephrolithotomy, it was found that in patients with negative baseline urine culture, antibiotic prophylaxis significantly reduced the rate of postoperative fever and other complications [192]. Single dose administration was found to be sufficient [193, 194].

Recommendations	LE	GR
UTIs must be excluded or treated prior to endourologic stone removal.	1b	A
In all patients, perioperative antibiotic prophylaxis is recommended.	1b	A*

UTI = urinary tract infection.

3.4.2.3.2 Antithrombotic therapy and stone treatment

Patients with a bleeding diathesis, or receiving antithrombotic therapy, should be referred to an internist for appropriate therapeutic measures before deciding on and during stone removal [195-199]. In patients with an uncorrected bleeding diathesis, the following are at elevated risk of haemorrhage or perinephritic haematoma (PNH) (high-risk procedures):

- SWL (hazard ratio of PNH up to 4.2 during anticoagulant/antiplatelet medication [200] [LE: 2];
- PNL;
- percutaneous nephrostomy;
- laparoscopic surgery;
- open surgery [195, 201, 202].

SWL is feasible and safe after correction of the underlying coagulopathy [203-205]. In the case of an uncorrected bleeding disorder or continued antithrombotic therapy, URS, in contrast to SWL and PNL, might offer an alternative approach since it is associated with less morbidity [147, 206-209]. Only data on flexible ureteroscopy is available which support the superiority of URS in the treatment of proximal ureteric stones [206, 210].

Recommendations	LE	GR
In patients at high-risk for complications (due to antithrombotic therapy) in the presence of an asymptomatic caliceal stone, active surveillance should be offered.		C
Temporary discontinuation, or bridging of antithrombotic therapy in high-risk patients, should be decided in consultation with the internist.	3	B
Antithrombotic therapy should be stopped before stone removal after weighing the thrombotic risk.	3	B
If stone removal is essential and antithrombotic therapy cannot be discontinued, retrograde (flexible) ureterorenoscopy is the preferred approach since it is associated with less morbidity.	2a	A*

*Upgraded based on panel consensus.

3.4.2.3.3 Obesity

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

3.4.2.3.4 Stone composition

Stones composed of brushite, calcium oxalate monohydrate, or cystine are particularly hard [27]. Percutaneous 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 patient 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) [27].		
Radiolucent stones may be dissolvable (See Section 3.4.2.1.2.2).	2a	B

CT = computed tomography; HU = Hounsfield unit; NCCT = non-contrast enhanced computed tomography; SWL = shockwave lithotripsy.

3.4.2.3.5 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 [211]. Steinstrasse occurs in 4-7% cases of SWL [126], and the major factor in steinstrasse formation is stone size [212].

Insertion of a ureteral stent before SWL prevents formation of steinstrasse in stones > 15 mm in diameter [213]. A major problem of steinstrasse is ureter obstruction, which can be silent in 23% of cases [125, 214].

When steinstrasse is asymptomatic, conservative treatment is an initial option. Medical expulsion therapy significantly increases stone expulsion and reduces the need for endoscopic intervention [215, 216].

Table 3.4.3: Treatment of steinstrasse

Asymptomatic	LE	Symptomatic	LE	Symptomatic + fever	LE
1. MET	1	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 indicate first, second and third choice (Panel consensus).

Statements	LE
Medical expulsion therapy increases the stone expulsion rate of steinstrasse [215].	1b
When spontaneous passage is unlikely, further treatment of steinstrasse is indicated.	4
SWL is indicated in asymptomatic and symptomatic cases, with no evidence of UTI, when large stone fragments are present [217].	4
Ureteroscopy is effective for the treatment of steinstrasse [218].	3
Placement of a percutaneous nephrostomy tube or ureteral stent is indicated for symptomatic ureteric obstruction with/without UTI.	4

Recommendations	LE	GR
Percutaneous nephrostomy is indicated for steinstrasse associated with urinary tract infection/fever.	4	C
Shockwave lithotripsy or ureterorenoscopy are indicated for steinstrasse when large stone fragments are present.	4	C

3.4.2.3 Selection of procedure for active removal of renal stones

3.4.2.3.1 Stones in renal pelvis or upper/middle calices

Shockwave lithotripsy, PNL and RIRS are available treatment modalities for renal calculi. While PNL efficacy is hardly affected by stone size, the SFRs after SWL or URS are inversely proportional to stone size [219-222]. Shockwave lithotripsy achieves good SFRs for stones up to 20 mm, except for those at the lower pole [221, 223]. Endourology is considered an alternative because of the reduced need of repeated procedures and consequently a shorter time until stone-free status is achieved. Stones > 20 mm should be treated primarily by PNL, because SWL often requires multiple treatments, and has the risk of ureteral obstruction (colic or steinstrasse) with the need for adjunctive procedures (Figure 3.4.1) [122]. Retrograde renal surgery cannot be recommended as first-line treatment for stones > 20 mm in uncomplicated cases as SFR is decreasing, and staged procedures have become necessary. However, it may be a first-line option in patients where PNL is not an option or contraindicated.

3.4.2.3.2 Stones in the lower renal pole

The stone clearance rate after SWL seems to be lower for stones in the inferior calyx than for other 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 [122, 219-223].

The following can impair successful stone treatment by SWL:

- steep infundibular-pelvic angle;
- long calyx;
- narrow infundibulum (Table 3.4.4) [98, 224].

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

Table 3.4.4: Unfavourable factors for SWL success [98, 224-226]

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 [122, 223]. Recent clinical experience has suggested an advantage of URS over SWL, but at the expense of greater invasiveness. Depending on operator skills, stones up to 3 cm can be treated efficiently by RIRS [224, 227-229]. However, staged procedures are frequently required.

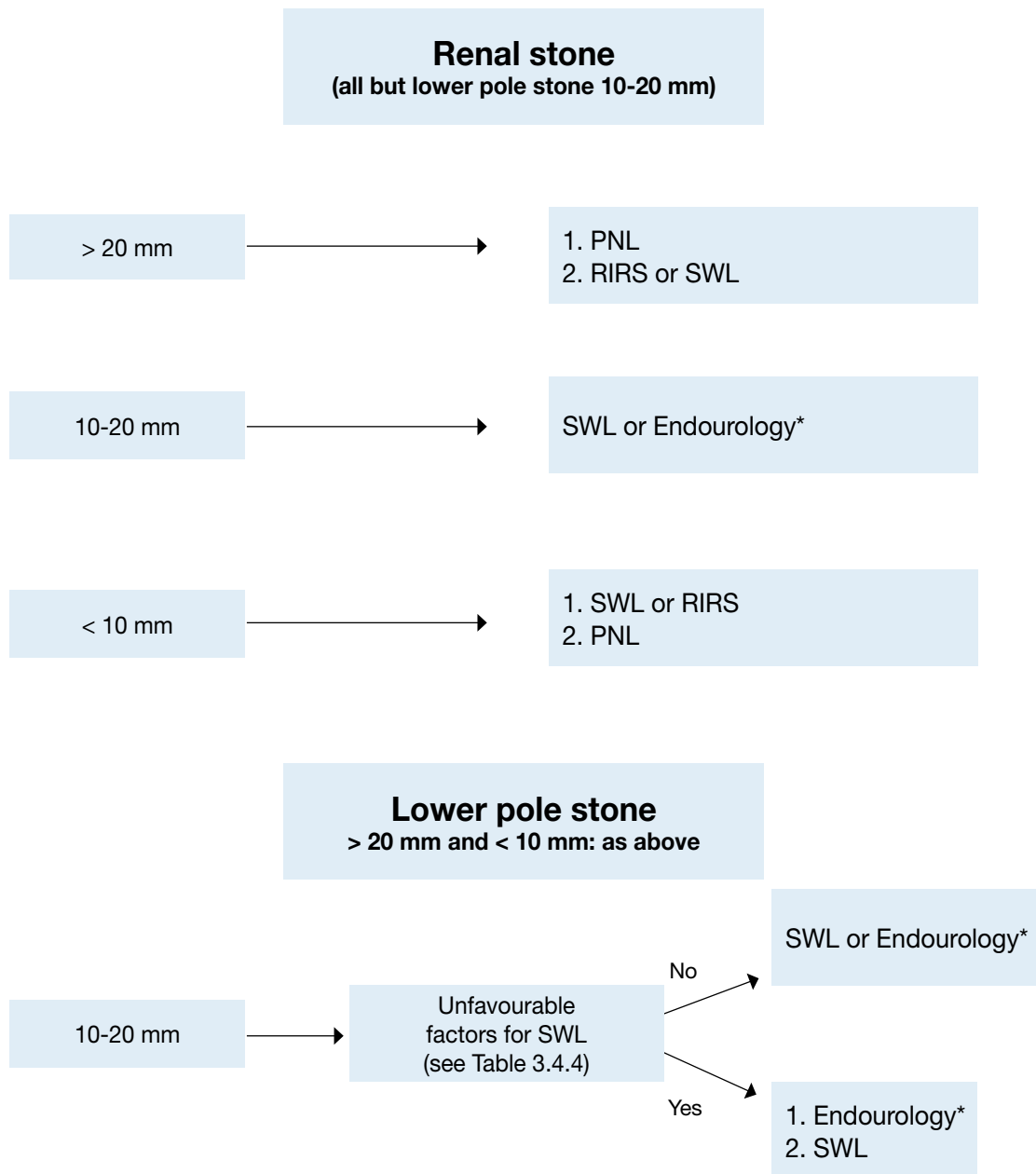
In complex stone cases, open or laparoscopic approaches are possible alternatives (see appropriate chapters).

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

Recommendations	GR
SWL and endourology (PNL, RIRS) are treatment options for stones < 2 cm within the renal pelvis and upper or middle calices.	B
PNL should be used as first-line treatment of larger stones > 2 cm.	B
In case PNL is not an option, larger stones (> 2 cm) may be treated with flexible URS. However, in that case there is a higher risk that a follow-up procedure and placement of a ureteral stent may be needed.	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

PNL = percutaneous nephrolithotomy; RIRS = retrograde renal surgery; SWL = shock wave lithotripsy; URS = ureterorenoscopy.

Figure 3.4.1: Treatment algorithm for renal calculi



*The term 'Endourology' encompasses all PNL and URS interventions.

SWL = shockwave lithotripsy; PNL = percutaneous nephrolithotomy; URS = ureterorenoscopy; SFR = stone-free rate; RIRS = retrograde renal surgery

3.4.3 **Specific stone management of Ureteral stones**

3.4.3.1 *Types of treatment*

3.4.3.1.1 Conservative treatment / observation

There are only limited data regarding spontaneous stone passage according to stone size [230]. It is estimated that 95% of stones up to 4 mm pass within 40 days [3].

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

Recommendations	LE	GR
In patients with newly diagnosed small* ureteral stones, if active removal is not indicated (Section 3.4.2.2), observation with periodic evaluation is an optional initial treatment.	1a	A
Appropriate medical therapy should be offered to these patients to facilitate stone passage during observation.		

*See stratification data [3].

Based on the analysis of available evidence, an exact cut-off size for stones that are likely to pass spontaneously cannot be provided; ≤ 10 mm may be considered a best estimate [3]. Therefore, the Panel decided not to include stone size in this recommendation and would rather limit “small”, suggesting ≤ 6 mm. The Panel is aware of the fact that spontaneous stone expulsion decreases with increasing stone size and that there are differences between individual patients.

3.4.3.1.2 Pharmacological treatment, Medical expulsive therapy (MET)

MET should only be used in informed patients. Treatment should be discontinued in case complications develop (infection, refractory pain, deterioration of renal function).

Meta-analyses have shown that patients with ureteral stones treated with α -blockers or nifedipine are more likely to pass stones with fewer colic episodes than those not receiving such therapy [72, 231].

Statement	LE
There is good evidence that MET accelerates spontaneous passage of ureteral stones and fragments generated with SWL, and limits pain [72, 216, 231-237].	1a

Medical agents

Tamsulosin is one of the most commonly used α -blockers [72, 232, 233]. However, one small study has suggested that tamsulosin, terazosin and doxazosin are equally effective, indicating a possible class effect [238]. This is also indicated by several trials demonstrating increased stone expulsion using doxazosin [72, 238, 239], terazosin [238, 240], alfuzosin [241-244] naftopidil [245, 246], and silodosin [247-249].

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 [72, 234-236, 250, 251] (LE = 1a).

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 [236, 250, 251].

Based on studies with a limited number of patients [252, 253] (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 [238, 252, 253].	1b

Recommendations for MET	LE	GR
For MET, α -blockers are recommended.	1a	A
Patients should be counseled regarding 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 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.

MET = medical expulsion therapy.

3.4.3.1.2.1 Factors affecting success of medical expulsive therapy (tamsulosin)

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) [72, 233] (LE: 1b). However, MET does reduce the need for analgesics [72, 232] (LE: 1a).

Stone location

The vast majority of trials have investigated distal ureteral stones [72]. Two RCT assessed the effect of tamsulosin on spontaneous passage of proximal ureteral calculi <10 mm demonstrating stone migration to a more distal part of the ureter [254] and a significantly higher stone expulsion rate and shorter expulsion time for stones < 6 mm [255].

3.4.3.1.2.2 Medical expulsive therapy after extracorporeal shock wave lithotripsy (SWL)

One RCT and a meta-analysis have shown that MET after SWL for ureteral or renal stones can expedite expulsion and increase SFRs and reduce analgesic requirements [119, 237] (LE: 1a).

3.4.3.1.2.3 Medical expulsive therapy after ureteroscopy

MET following holmium:YAG laser lithotripsy increases SFRs and reduces colic episodes [256] (LE: 1b).

3.4.3.1.2.4 Medical expulsive therapy and ureteral stents (Section below)

3.4.3.1.2.5 Duration of medical expulsive therapy treatment

Most studies have had a duration of 1 month. No data are currently available to support other time-intervals.

3.4.3.1.2.6 Possible side-effects include retrograde ejaculation and hypotension [72]

3.4.3.1.3 SWL

Best clinical practice see Section 3.4.2.1.4.1.2 (renal stones).

Stenting

The 2007 AUA/EAU Guidelines on the management of ureteral calculi state that routine stenting is not recommended as part of SWL [3]. When the stent is inserted, patients often suffer from frequency, dysuria, urgency, and suprapubic pain [257].

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

SWL = shock wave lithotripsy.

3.4.3.1.4 Endourology techniques

3.4.3.1.4.1 Ureteroscopy (URS)

The current standard for rigid ureterorenoscopes are tip diameters of < 8 F. Rigid URS can be used for the whole ureter [3]. However, technical improvements, enhanced quality and tools as well as the availability of digital scopes also favour the use of flexible ureteroscopes in the ureter [165].

3.4.3.1.4.1.1 Contraindications

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

3.4.3.1.4.1.2 Best clinical practice in ureterorenoscopy (URS)

Access to the upper urinary tract

Most interventions are performed under general anaesthesia, although local or spinal anaesthesia is possible. Intravenous sedation is suitable for female patients with distal ureteral stones [258].

Antegrade URS is an option for large, impacted proximal ureteral calculi [259] (Section 3.4.2.6).

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 [260, 261].

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.*

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 reduces operating time [262, 263].

The insertion of ureteral access sheaths may lead to ureteral damage, whereas the risk was lowest in pre-stented systems [264]. No data on long-term consequences are available [264, 265]. Use of ureteral access sheaths depends on the surgeon's preference.

Stone extraction

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

Stones can be extracted by endoscopic forceps or baskets. Only baskets made of nitinol can be used for flexible URS [266].

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.*

Intracorporeal lithotripsy

The most effective lithotripsy system is the Ho:YAG laser, which has become the gold standard for ureteroscopy and flexible nephroscopy (Section 3.4.2.1.4.1.2), because it is effective for all stone types [267, 268]. Pneumatic and US systems can be used with high disintegration efficacy in rigid URS [269, 270].

However, stone migration into the kidney is a common problem, which can be prevented by placement of special antimigration tools proximal of the stone [271].

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

Ho:YAG = holmium:yttrium-aluminium-garnet (laser); US = ultrasound.

Stenting before and after URS

Routine stenting is not necessary before URS. However, pre-stenting facilitates ureteroscopic management of stones, improves the SFR, and reduces complications [272].

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 [273-275]. A ureteric catheter with a shorter indwelling time (1 day) may also be used, with similar results [276].

Stents should be inserted in patients who are at increased risk of complications (e.g., ureteral trauma, residual fragments, bleeding, perforation, UTIs, or pregnancy), and in all doubtful cases, to avoid stressful emergencies. The ideal duration of stenting is not known. Most urologists favour 1-2 weeks after URS.

Alpha-blockers reduce the morbidity of ureteral stents and increase tolerability [277, 278]. A recently published

meta-analysis provides evidence for improvement of ureteral stent tolerability with tamsulosin [279].

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

3.4.3.1.4.1.3 Complications

The overall complication rate after URS is 9-25% [3, 280, 281]. Most are minor and do not require intervention. Ureteral avulsion and strictures are rare (< 1%). Previous perforations are the most important risk factor for complications.

3.4.3.1.4.2 Percutaneous antegrade ureteroscopy

Percutaneous antegrade removal of ureteral stones is a consideration in selected cases, i. e. large, impacted proximal ureteral calculi with dilated renal collecting system [284], or when the ureter is not amenable to retrograde manipulation [259, 285-288].

Recommendation	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

SWL = shock wave lithotripsy; URS ureterorenoscopy

3.4.3.1.5 Laparoscopic ureteral stone removal

Few studies have reported laparoscopic stone removal (Section 3.4.2.1.4.3). These procedures are usually reserved for special cases, 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.

For ureterolithotomy, laparoscopy is recommended for large impacted stones when endoscopic lithotripsy or SWL has failed.	2	B
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SWL = shock wave lithotripsy.

3.4.3.2 Indications for active removal of ureteral stones [3, 230, 282]

Indications for active removal of ureteral stones are:

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

3.4.3.2.1 General recommendations and precautions

3.4.3.2.1.1 Antibiotic treatment

The same considerations apply as in renal stone removal (Section 3.4.1.4.2).

Single dose administration was found to be sufficient as perioperative antibiotic prophylaxis [193, 194].

Recommendations	LE	GR
UTIs must be excluded or treated prior to endourologic stone removal.	1b	A
In all patients undergoing endourologic treatment, perioperative antibiotic prophylaxis is recommended.	1b	A*

UTI = urinary tract infection.

3.4.3.2.1.2 Obesity

Obesity can cause a lower success rate after SWL and PNL.

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

3.4.3.2.1.3 Bleeding disorder

URS can be performed in patients with bleeding disorders, with a moderate increase in complications [147, 208]. Discontinuation of anticoagulant therapy should be weighed against the risk, in each individual patient.

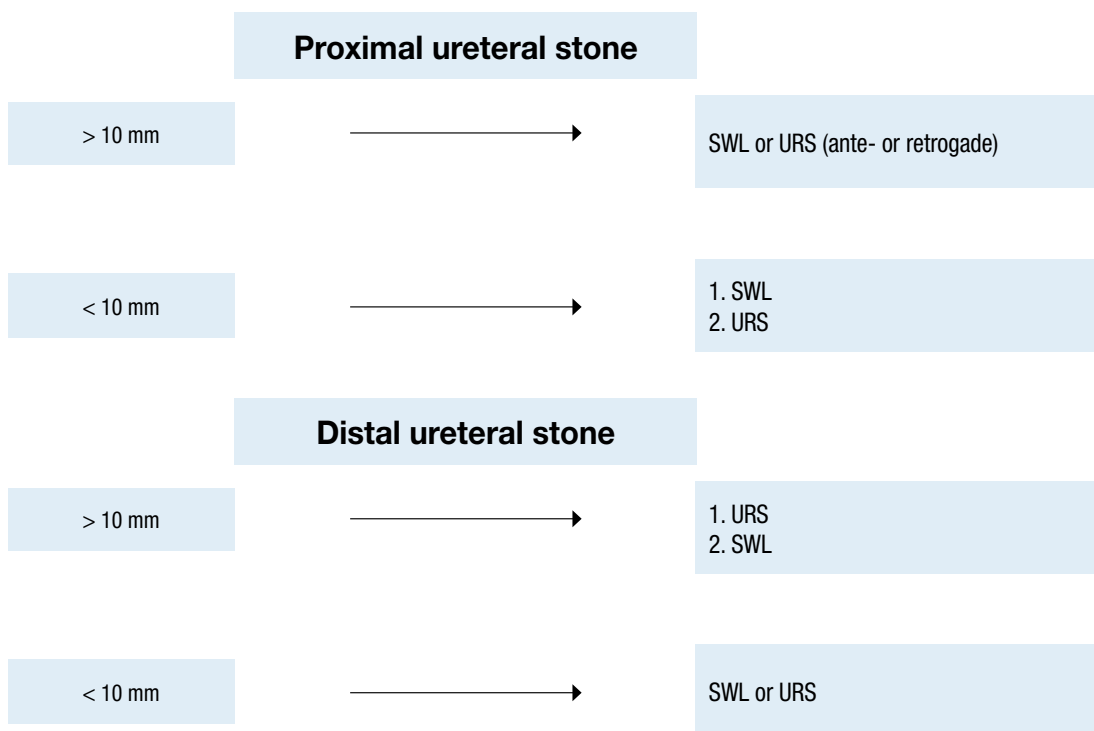
3.4.3.3 Selection of procedure for active removal of ureteral stones

Overall stone-free rates after URS or ESWL for ureteral stones are comparable. However, larger stones achieve

earlier stone-free status with URS. Although URS is effective for ureteric calculi, it has greater potential for complications. However, in the current endourological era, the complication rate and morbidity of ureteroscopy have been significantly reduced [283].

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 3.4.2.1.3.3 (Complications of SWL) and 3.4.3.1.4.1.3 (Complications of URS)].

Figure 3.4.2: Recommended treatment options (if indicated for active stone removal) (GR: A*)



*Upgraded following panel consensus.

SWL = shockwave lithotripsy; URS = ureterorenoscopy.

3.4.4 Management of patients with residual stones

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

- new stones from such nidi (heterogeneous nucleation);
- persistent UTI;
- dislocation of fragments with/without obstruction and symptoms [128, 289, 290].

Recommendations	LE	GR
Identification of biochemical risk factors and appropriate stone prevention is particularly indicated in patients with residual fragments or stones [128, 290, 291].	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 [291]. 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 [128, 289, 292].

Table 3.4.5: Recommendations for the treatment of residual fragments

Residual fragments, stones (largest diameter)	Symptomatic residuals	Asymptomatic residuals	LE	GR
< 4-5 mm	Stone removal	Reasonable follow-up (dependent on risk factors)	4	C
> 6-7 mm	Stone removal			

3.4.4.1 Therapy

The indications for active removal of residual stones and selection of the procedure are based on the same criteria as for primary stone treatment (Section 3.4.2.4) and includes repeat SWL [293].

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 [294-296].

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 [297].	1b

Recommendations	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 = ureteroscopy; MET = medical expulsive therapy

3.4.5 Management of specific patient groups

3.4.5.1 Management of urinary stones and related problems during pregnancy

Clinical management of a pregnant urolithiasis patient is complex and demands close collaboration between patient, radiologist, obstetrician and urologist. For diagnostic imaging see Section 3.3.1).

If spontaneous passage does not occur, or if complications develop (e.g., induction of premature labour), placement of a ureteral stent or a percutaneous nephrostomy tube is necessary [298-300]. Unfortunately, these temporising therapies are often associated with poor tolerance, and they require multiple exchanges during pregnancy, due to the potential for rapid encrustation. Ureteroscopy has become a reasonable alternative in these situations [301, 302]. Although feasible, retrograde endoscopic and percutaneous removal of renal stones during pregnancy remain an individual decision and should be performed only in experienced centres [303]. 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.	1a
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

3.4.5.2 Management of stones in patients with urinary diversion

3.4.5.2.1 Aetiology

Patients with urinary diversion are at high risk for stone formation in the renal collecting system and ureter or in the conduit or continent reservoir [304-306]. Metabolic factors (hypercalciuria, hyperoxaluria and hypocitraturia), infection with urease-producing bacteria, foreign bodies, mucus secretion, and urinary stasis are responsible for stone formation [307] (Section 3.1.3). One study has shown that the risk for recurrent upper-tract stones in patients with urinary diversion subjected to PNL was 63% at 5 years [308].

3.4.5.2.2 Management

Smaller upper-tract stones can be treated effectively with SWL [286, 309]. In the majority, endourological techniques are necessary to achieve stone-free status [285]. In individuals with long, tortuous conduits or with

invisible ureter orifices a retrograde endoscopic approach might be difficult or impossible.

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. Trans-stomal manipulations in continent urinary diversion must be performed carefully to avoid disturbance of the continence mechanism [310].

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

3.4.5.2.3 Prevention

Recurrence risk is high in these patients [308]. Metabolic evaluation and close follow-up of the patients 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 [312].

3.4.5.3 Management of stones in patients with neurogenic bladder

3.4.5.3.1 Aetiology, clinical presentation and diagnosis

Patients with neurogenic bladder develop urinary calculi because of additional risk factors such as bacteriuria, pelvicicectasis, vesicoureteral reflux, renal scarring, lower urinary tract reconstruction, and thoracic spinal defect [313]. The main issues are urinary stasis and infection (Section 3.1.3). Indwelling catheters and surgical interposition of bowel segments for treatment of bladder dysfunction both facilitate UTI. Although calculi can form at any level of the urinary tract, they occur more frequently in the bladder; especially if bladder augmentation has been performed [314, 315].

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

3.4.5.3.2 Management

Management of calculi in patients with neurogenic bladder is similar to that described in Section 3.3.3. In MMC (myelomeningocele) patients, latex allergy is common, therefore, appropriate measures need to be taken regardless of the treatment [316]. 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 [317]. The risk of stone formation after augmentation cystoplasty in immobile patients with sensory impairment can be significantly reduced by irrigation protocols [312].

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, thus appropriate measures need to be taken regardless of the treatment. For surgical interventions, general anesthesia remains the only option.	B

3.4.5.4 Management of stones in transplanted kidneys

3.4.5.4.1 Aetiology

Transplant patients depend on their solitary kidney for renal function. Impairment causing urinary stasis/obstruction therefore requires immediate intervention or drainage of the transplanted kidney. Risk factors in these patients are multifold:

- Immunosuppression increases the infection risk, resulting in recurrent UTIs.
- Hyperfiltration, excessively alkaline urine, renal tubular acidosis, and increased serum calcium caused by persistent tertiary hyperparathyroidism [318] are biochemical risk factors.

Stones in kidney allografts have an incidence of 0.2-1.7% [319-321].

Recommendation	LE	GR
In patients with transplanted kidneys, unexplained fever, or unexplained failure to thrive (particularly in children), US or NCCT should be performed to rule out calculi [322].	4	B

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

3.4.5.4.2 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 [323-326], additional factors such as transplant function, coagulative status, and anatomical obstacles due to the iliacal position of the organ, directly influence the surgical strategy.

For large or ureteral stones, careful percutaneous access and subsequent antegrade endoscopy are more favourable. The introduction of small flexible ureteroscopes and the holmium laser has made ureteroscopy a valid treatment option for transplant calculi. However, one must be aware of potential injury to adjacent organs [327-329]. Retrograde access to transplanted kidneys is difficult due to the anterior location of the ureteral anastomosis, and ureteral tortuosity [330-332].

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 [333, 334].	4

Recommendation	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.

3.4.5.4.3 Special problems in stone removal

Table 3.4.6: Special problems in stone removal

Caliceal diverticulum stones	<ul style="list-style-type: none"> • SWL, PNL (if possible) or RIRS. • Can also be removed using laparoscopic retroperitoneal surgery [335-339] • 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	<ul style="list-style-type: none"> • Can be treated in line with the options described above [340] • Passage of fragments after SWL might be poor • Acceptable stone free rates can be achieved with flexible ureteroscopy [341]
Stones in pelvic kidneys	<ul style="list-style-type: none"> • SWL, RIRS, PNL or laparoscopic surgery • For obese patients, the options are RIRS, PNL or open surgery
Stones formed in a continent reservoir	<ul style="list-style-type: none"> • Section 3.4.4 • Each stone must be considered and treated individually

Patients with obstruction of the ureteropelvic junction	<ul style="list-style-type: none"> • 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 pelvi-ureteral incision [342-345].
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SWL = shockwave lithotripsy; PNL = percutaneous nephrolithotomy; URS = ureterorenoscopy; RIRS = retrograde renal surgery

3.4.6 Management of urolithiasis in children

Rates of urolithiasis have increased in developed countries, and there has been a shift in the age group experiencing a first stone episode [6, 346, 347]. 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 [348-351].

For diagnostic procedures see Section 3.3.3.2.

3.4.6.1 Stone removal

Several factors must be considered when selecting treatment procedures for children. Compared to adults, children pass fragments more rapidly after SWL [40]. 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 in adults [50].	4

3.4.6.1.1 Medical expulsive therapy (MET) in children

Medical expulsive therapy has already been discussed in Section 3.4.3.1.2 but not addressing children. Although the use of α -blockers is very common in adults, there are few data to demonstrate their safety and efficacy in children, however Tamsulosin seems to support stone passage [352, 353].

3.4.6.1.2 Extracorporeal shock wave lithotripsy

Extracorporeal shock wave lithotripsy remains the least-invasive procedure for stone management in children [354-358].

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 [356, 359]. As in adults the slow delivery rate of shock waves may improve the stone clearance rates [359]. 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% [356, 358].

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 [356, 358]. With modern lithotripters, intravenous sedation or patient-controlled analgesia have been used in selected cooperative older children [360] (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 [361-364].

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 [354-356].

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

3.4.6.1.3 Endourological procedures

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

3.4.6.1.3.1 Percutaneous nephrolithotripsy (PNL)

Preoperative evaluation and indications for PNL in children are similar to those in adults. Provided appropriate size instruments and US guidance are used, age is not a limiting factor, and PNL can be performed safely by experienced operators, with less radiation exposure, even for large and complex stones [365-368]. SFRs are between 68% and 100% after a single session, and increase with adjunctive measures, such as second-look PNL, SWL and URS [365].

As for adults, tubeless PNL is safe in children, in well-selected cases [369].

Statements	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).	C

PNL = percutaneous nephrolithotomy.

3.4.6.1.3.2 Ureteroscopy

Although SWL is still the first-line treatment for most ureteral stones, it is unlikely to be successful for stones > 10 mm in diameter, or for impacted, calcium oxalate monohydrate or cystine stones, or stones in children with unfavourable anatomy and in whom localisation is difficult [370, 371].

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 [370-373].

Different lithotripsy techniques, including ultrasonic, pneumatic and laser lithotripsy, are all safe and effective (Section 3.4.3.1.4.1.2) [374, 375].

Recommendation	LE	GR
For intracorporeal lithotripsy, the same devices as in adults can be used (Ho:Yag laser, pneumatic- and US lithotripters).	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 [376-378].

3.4.6.1.3.3 Open or laparoscopic surgery

Most stones in children can be managed by SWL and endoscopic techniques. Therefore, the rate of open procedure has dropped significantly [379-381]. 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 [354, 355, 366]. Open surgery can be replaced by laparoscopic procedures in experienced hands [380, 381].

3.4.6.1.3.4 Special considerations on recurrence prevention

All paediatric stone formers need metabolic evaluation and recurrence prevention with respect to the detected stone type. In radiolucent stones oral chemolysis could be considered as an alternative to SWL [382]. In the case of obstructive pathology in association with the established metabolic abnormalities, treatment should not be delayed. Children are in the high-risk group for stone recurrence [383] (Chapter 4).

4. FOLLOW UP METABOLIC EVALUATION AND RECURRENCE PREVENTION

4.1 General metabolic considerations for patient work-up

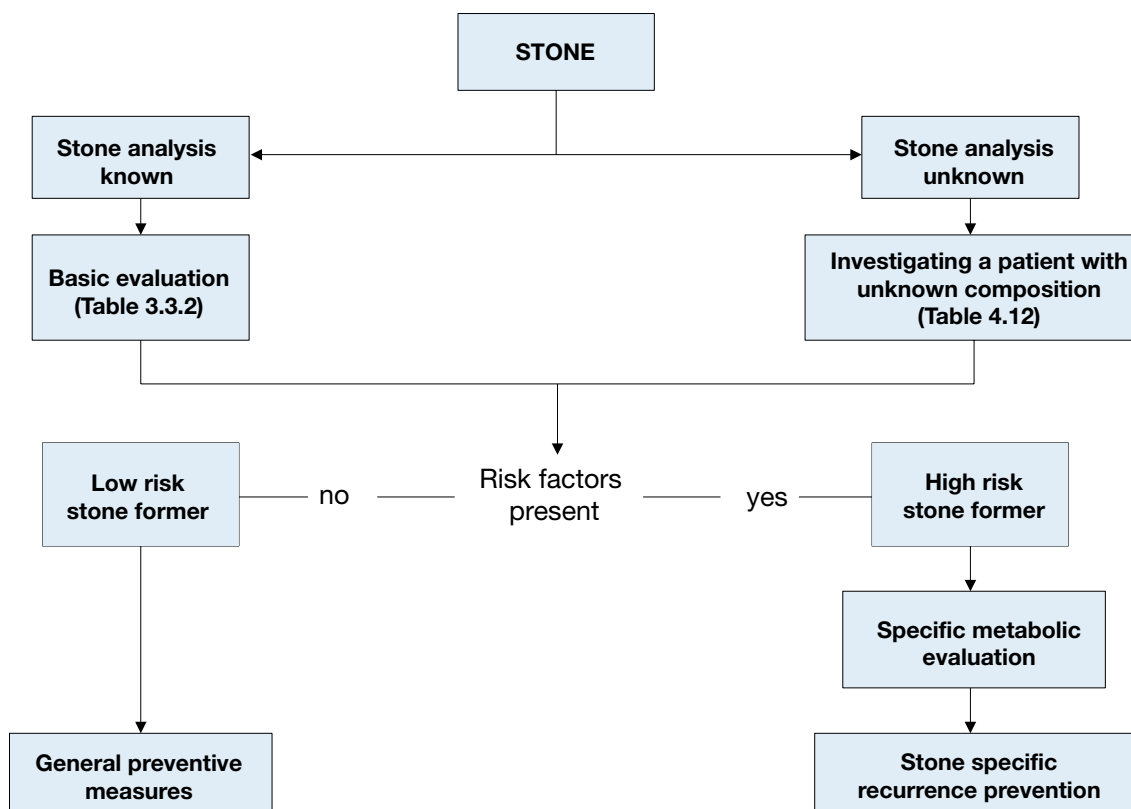
4.1.1 Evaluation of patient risk

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

For correct classification, two items are mandatory:

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

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



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

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

4.1.2 Urine sampling

Specific metabolic evaluation requires collection of two consecutive 24-h urine samples [384, 385]. The collecting bottles should be prepared with 5% thymol in isopropanol or stored at $\leq 8^{\circ}\text{C}$ during collection with the risk of spontaneous crystallisation in the urine [386, 387]. 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 [386, 388] using sensitive pH-dipsticks or a pH-meter.

Spot urine samples are an alternative method of sampling, particularly when 24-h urine collection is difficult, for example, in non-toilet trained children [389]. Spot urine studies normally link the excretion rates to creatinine [389], but these are of limited use because the results may vary with collection time and patients' sex, body weight and age.

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

For the initial specific metabolic work-up, the patient should stay on a self-determined diet under normal daily conditions and should ideally be stone free for at least 20 days [390].

Follow-up studies are necessary in patients taking medication for recurrence prevention [391]. The first follow-up 24-h urine measurement is suggested 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. The Urolithiasis Guidelines Panel aim to set up a systematic review on the ideal timing of the 24-hour urine collection.

4.1.4 **Reference ranges of laboratory values**

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

Table 4.1: Normal laboratory values for blood parameters in adults [388]

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).

4.1.5 **Risk indices and additional diagnostic tools**

Several risk indices have been developed to describe the crystallisation risk for calcium oxalate or calcium phosphate in urine [392-395]. However, clinical validation of these risk indices for recurrence prediction or therapy improvement is ongoing.

Table 4.2: Normal laboratory values for urinary parameters in adults

Urinary Parameters	Reference ranges and limits for medical attention
pH	Constantly > 5.8 (suspicious of RTA)
	Constantly > 7.0 (suspicious of infection)
	Constantly ≤ 5.8 (suspicious of acidic arrest)
Specific weight	> 1.010
Creatinine	7-13 mmol/day females
	13-18 mmol/day males
Calcium	> 5.0 mmol/day (see Fig. 4.2)
	≥ 8.0 mmol/day (see Fig. 4.2)
Oxalate	> 0.5 mmol/day (suspicious of enteric hyperoxaluria)
	≥ 1.0 mmol/day (suspicious of primary hyperoxaluria)
Uric acid	> 4.0 mmol/day (women), 5 mmol/day (men)
Citrate	< 2.5 mmol/day
Magnesium	< 3.0 mmol/day
Inorganic phosphate	> 35 mmol/day
Ammonium	> 50 mmol/day
Cystine	> 0.8 mmol/day

Table 4.3: Normal values for spot urine samples: creatinine ratios (solute/creatinine) in adults [396]

Parameter/Patient age	Ratio of solute to creatinine	units
Calcium	mol/mol	mg/mg
< 12 months	< 2.0	0.81
1-3 years	< 1.5	0.53
1-5 years	< 1.1	0.39
5-7 years	< 0.8	0.28
> 7 years	< 0.6	0.21
Oxalate	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 μmol/L) per GFR (ratio x plasma creatinine)	
> 2 years		

Table 4.4: Solute excretion in 24-h urine samples [396]**

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

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

4.2 General considerations for recurrence prevention

All stone formers, independent of their individual risk, should follow the preventive measures in Table 4.5. The main focus 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 4.5: General preventive measures

Fluid intake (drinking advice)	Fluid amount: 2.5-3.0 L/day Circadian drinking Neutral pH beverages Diuresis: 2.0-2.5 L/day Specific weight of urine: < 1010
Nutritional advice for a balanced diet	Balanced diet* Rich in vegetables and fibre Normal calcium content: 1-1.2 g/day Limited NaCl content: 4-5 g/day Limited animal protein content: 0.8-1.0 g/kg/day
Lifestyle advice to normalise general risk factors	BMI: retain a normal BMI level Adequate physical activity Balancing of excessive fluid loss

Caution: The protein need is age-group dependent, therefore protein restriction in childhood should be handled carefully.

* Avoid excessive consumption of vitamin supplements.

4.2.1 Fluid intake

An inverse relationship between high fluid intake and stone formation has been repeatedly demonstrated [397-399]. The effect of fruit juices is mainly determined by the presence of citrate or bicarbonate [400]. If hydrogen ions are present, the net result is neutralisation. However, if potassium is present, both pH and citrate are increased [401, 402]. One large fair-quality RCT randomly assigned men with more than one past renal stone of any type and softdrink consumption greater than 160 mL/day to reduced softdrink intake or no treatment. Although the intervention significantly reduced the risk for symptomatic recurrent stones (RR, 0.83 [CI: 0.71-0.98]), the level of evidence for this outcome was low because results were from only 1 trial.” [399, 403].

4.2.2 Diet

A common sense approach to diet should be taken, that is, a mixed balanced diet with contributions from all food groups, but without any excesses [399, 404, 405].

Fruits, vegetables and fibres: fruit and vegetable intake should be encouraged because of the beneficial effects of fibre, although the role of the latter in preventing stone recurrences is debatable [406-409]. 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 [400], 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 [410]. However, it seems wise to advise calcium oxalate stone formers to avoid excessive intake.

Animal protein: should not be taken in excess [411, 412] and limited to 0.8-1.0 g/kg body weight. Excessive consumption of animal protein has several effects that favour stone formation, including hypocitraturia, low urine pH, hyperoxaluria and hyperuricosuria.

Calcium intake: should not be restricted unless there are strong reasons due to the inverse relationship between dietary calcium and stone formation [407, 413]. The daily requirement for calcium is 1000 to 1200 mg [12]. Calcium supplements are not recommended except in enteric hyperoxaluria, when additional calcium should be taken with meals to bind intestinal oxalate [399, 412, 414].

Sodium: the daily sodium (NaCl) intake should not exceed 3-5 g [12]. 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 [411, 412]. A positive correlation between sodium consumption and risk of first-time stone formation has been confirmed only in women [413, 415]. There have been no prospective clinical trials on the role of sodium restriction as an independent variable in reducing the risk of stone formation.

Urate: intake of purine-rich food should be restricted in patients with hyperuricosuric calcium oxalate [416, 417] and uric acid stones. Intake should not exceed 500 mg/day [12].

4.2.3 **Lifestyle**

Lifestyle factors may influence the risk of stone formation, for example, obesity [418] and arterial hypertension [419, 420].

4.2.4 **Recommendations for recurrence prevention**

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

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

4.3.1 **Introduction**

Pharmacological treatment is necessary in patients at high-risk for recurrent stone formation. The ideal drug should halt stone formation, have no side effects, and be easy to administer. Each of these aspects is important to achieve good compliance. Table 4.6 highlights the most important characteristics of commonly used medication.

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

Agent	Rationale	Dose	Specifics and side effects	Stone type	Ref
Alkaline citrates	Alkalinisation Hypocitraturia Inhibition of calcium oxalate crystallisation	5-12 g/d (14-36 mmol/d) Children: 0.1-0.15 g/kg/d	Daily dose for alkalinisation depends on urine pH	Calcium oxalate Uric acid Cystine	[38, 399, 421-427]
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	[428-432]
Calcium	Enteric hyperoxaluria	1000 mg/d	Intake 30 min before meals	Calcium oxalate	[412-414]
Captopril	Cystinuria Active decrease of urinary cystine levels	75-150 mg	Second-line option due to significant side effects	Cystine	[433, 434]
Febuxostat	Hyperuricosuria Hyperuricaemia	80-120 mg/d	Acute gout contraindicated, pregnancy, xanthine stone formation	Calcium oxalate Uric acid	[435, 436]
L-Methionine	Acidification	600-1500 mg/d	Hypercalciuria, bone demineralisation, systemic acidosis. No long-term therapy.	Infection stones Ammonium urate Calcium phosphate	[38, 437, 438]
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	[439, 440] low evidence
Sodium bicarbonate	Alkalinisation Hypocitraturia	4.5 g/d		Calcium oxalate Uric acid, Cystine	[441]
Pyridoxine	Primary hyperoxaluria	Initial dose 5 mg/kg/d Max. 20 mg/kg/d	Polyneuropathia	Calcium oxalate	[442]

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	[38, 439, 443-451]
Tiopronin	Cystinuria Active decrease of urinary cystine levels	Initial dose 250 mg/d Max. 2000 mg/d	Risk for tachyphylaxis and proteinuria.	Cystine	[452-455]

4.4 Calcium oxalate stones

The criteria for identification of calcium oxalate stone formers with high recurrence risk are listed in Section 3.1.2.

4.4.1 *Diagnosis*

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

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

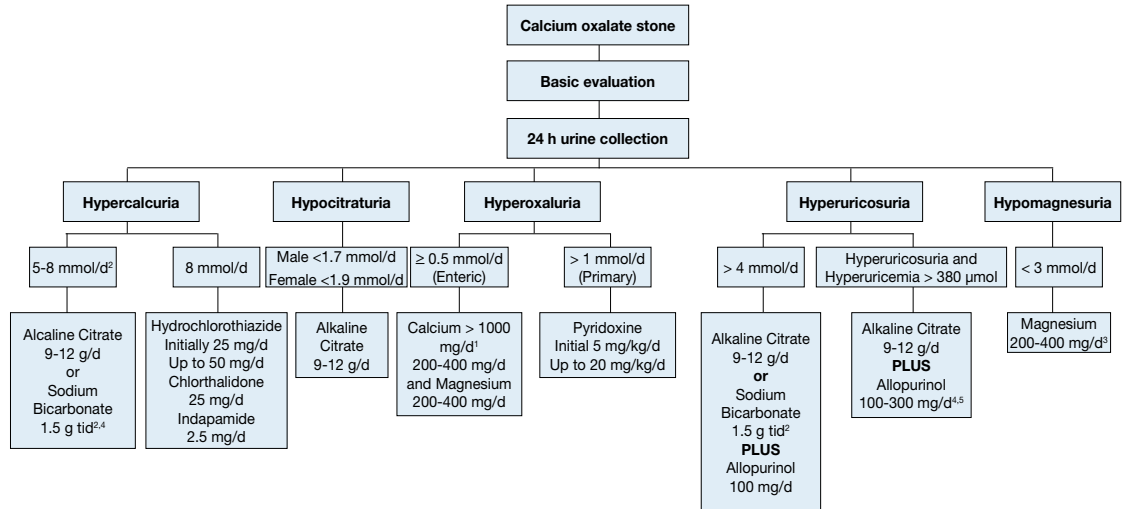
4.4.2 *Interpretation of results and aetiology*

The diagnostic and therapeutic algorithm for calcium oxalate stones is shown in Figure 4.2 [38, 399, 422-424, 428-430, 435, 439-441, 443-450, 456-460].

The most common metabolic abnormalities associated with calcium stone formation are hypercalciuria, which affects 30-60% of adult stone formers, and hyperoxaluria (26-67%), followed by hyperuricosuria (15-46%), hypomagnesuria (7-23%), and hypocitraturia (5-29%). However, ranges tend to differ based on ethnicity [456].

- 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 4.6.5).
- Hypercalciuria may be associated with normocalcemia (idiopathic hypercalciuria, or granulomatous diseases) or hypercalcaemia (hyperparathyroidism, granulomatous diseases, vitamin D excess, or malignancy).
- Hypocitraturia (male <1.7 mmol/d, female < 1.9 mmol/d) may be idiopathic or secondary to metabolic acidosis or hypokalaemia.
- Oxalate excretion > 0.5 mmol/day in adults (> 0.37 mmol/1.73 m²/day in children) confirms hyperoxaluria.
 - o primary hyperoxaluria (oxalate excretion mostly ≥ 1 mmol/day), appears in three genetically determined forms;
 - o secondary hyperoxaluria (oxalate excretion ≥ 0.5 mmol/day, usually < 1 mmol/day), occurs due to intestinal hyperabsorption of oxalate or extreme dietary oxalate intake;
 - o mild hyperoxaluria (oxalate excretion 0.45-0.85 mmol/day), commonly found in idiopathic calcium oxalate stone formers.
- Hypomagnesuria (< 3.0 mmol/day) may be related to poor dietary intake or to reduced intestinal absorption (chronic diarrhoea).

Figure 4.2: Diagnostic and therapeutic algorithm for calcium oxalate stones



¹ Be aware of excess calcium excretion.

² tid = three times/day (24h).

³ No magnesium therapy for patients with renal insufficiency.

⁴ There is no evidence that combination therapy (thiazide + citrate) (thiazide + allopurinol) is superior to thiazide therapy alone [443, 450].

⁵ Febuxostat 80 mg/d.

4.4.3 Specific treatment

General preventive measures are recommended for fluid intake and diet. Hyperoxaluric stone formers should consume foods with low oxalate content, whereas hyperuricosuric stone formers benefit from daily dietary reduction of purine. Figure 4.2 summarises the diagnostic algorithm and the pharmacological treatment of calcium oxalate stones [38, 399, 422-424, 428-430, 435, 439-441, 443-450, 456-460]. There is only low level evidence on the efficacy of preventing stone recurrence through pre-treatment stone composition and biochemistry measures, or on-treatment biochemistry measures [399].

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

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

4.5 Calcium phosphate stones

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

Calcium phosphate mainly appears in two completely different minerals: carbonate apatite and brushite. Carbonate apatite crystallisation occurs at a pH ≥ 6.8 and may be associated with infection.

Brushite crystallises at an optimum pH of 6.5-6.8, at high urinary concentrations of calcium (> 8 mmol/day) and phosphate (> 35 mmol/day). Its occurrence is not related to UTI.

Possible causes of calcium phosphate stones include HPT, RTA and UTI; each of which requires different therapy.

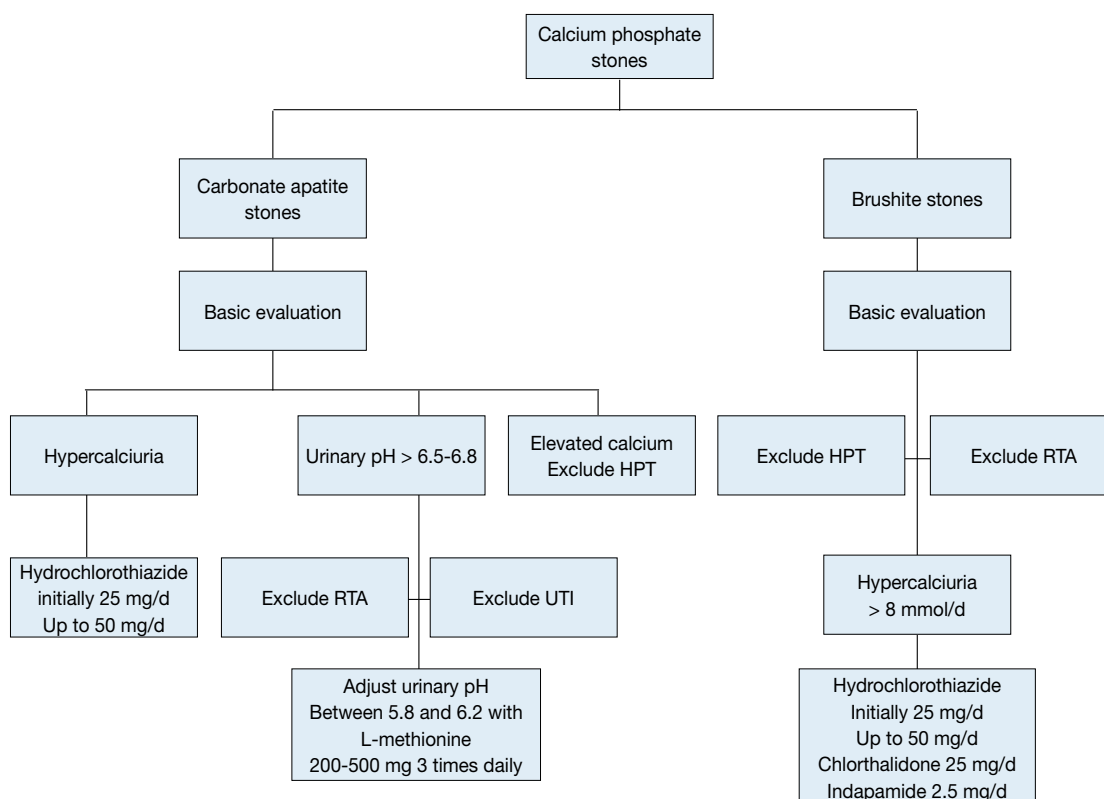
4.5.1 **Diagnosis**

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

4.5.2 **Interpretation of results and aetiology**

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

Figure 4.3: Diagnostic and therapeutic algorithm for calcium phosphate stones



4.5.3 **Pharmacological therapy [38, 399, 443, 444, 448, 460]**

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 it is not commonly used and needs monitoring for systemic acidosis development. For infection-associated calcium phosphate stones, it is important to consider the guidance given for infection stones.

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

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

4.6 **Disorders and diseases related to calcium stones**

4.6.1 **Hyperparathyroidism [461-464]**

Primary HPT is responsible for an estimated 5% of all calcium stone formation. Renal stones occur in approximately 20% of patients with primary HPT. Elevated levels of PTH significantly increase calcium turnover,

leading to hypercalcaemia and hypercalciuria. Serum calcium may be mildly elevated and serum PTH 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.

4.6.2 **Granulomatous diseases [465]**

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

4.6.3 **Primary hyperoxaluria [442]**

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/m² body surface area) and following a circadian drinking regimen.

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

Treatment regimens are:

- Pyridoxine in PH type I: 5-20 mg/kg/day according to urinary oxalate excretion and patient tolerance;
- Alkaline citrate: 9-12 g/day in adults, 0.1-0.15 meq/kg/day in children;
- Magnesium: 200-400 mg/day (no magnesium in the case of renal insufficiency).

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

4.6.4 **Enteric hyperoxaluria [414, 466]**

Enteric hyperoxaluria is a particularly problematic condition in patients with intestinal malabsorption of fat. This abnormality is associated with a high risk of stone formation, and is seen after intestinal resection and malabsorptive bariatric surgery and in Crohn's disease and pancreas insufficiency. In addition to hyperoxaluria, these patients usually present with hypocitraturia due to loss of alkali. Urine pH is usually low, as are urinary calcium and urine volume. All these abnormalities contribute to high levels of supersaturation with calcium oxalate, crystalluria, and stone formation.

Specific preventive measures are:

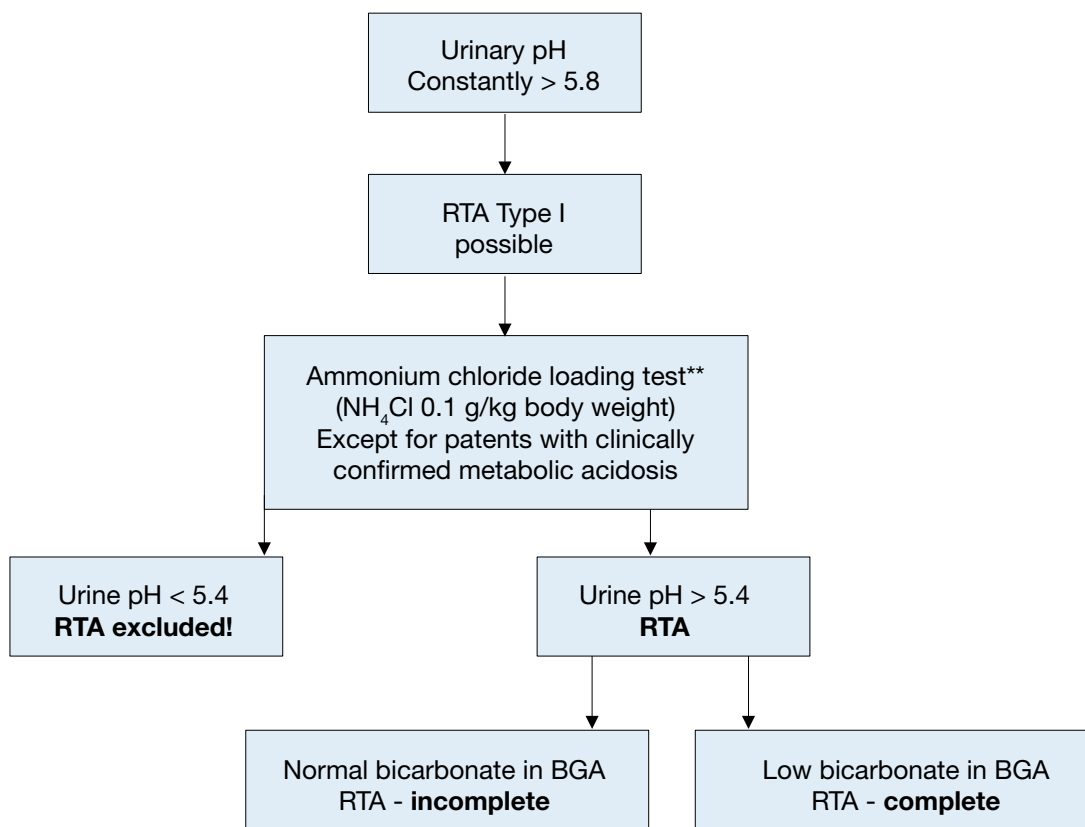
- Restricted intake of oxalate-rich foods;
- Restricted fat intake;
- Calcium supplementation at meal times to enable calcium oxalate complex formation in the intestine [414, 466];
- Sufficient fluid intake to balance intestinal loss of water caused by diarrhoea;
- Alkaline citrates to raise urinary pH and citrate.

Urinary risk factor	Suggested treatment	LE	GR
Enteric hyperoxaluria	Potassium citrate	3-4	C
	Calcium supplement	2	B
	Diet reduced in fat and oxalate	3	B
Small urine volume	Increased fluid intake	1b	A

4.6.5 **Renal tubular acidosis [467, 468]**

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

Figure 4.4: Diagnosis of renal tubular acidosis



** An alternative Ammonium Chloride loading test using NH_4Cl load with 0.05 g/kg body weight over 3 days might provide similar results and may be better tolerated by the patient. A second alternative in these cases could be the furosemide acidification test.

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

Table 4.7: Inherited causes of renal tubular acidosis

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

The main therapeutic aim is restoring a normal acid-base equilibrium. Despite the alkaline pH of urine in RTA, alkalinisation using alkaline citrates or sodium bicarbonate is key to normalising the metabolic changes (intracellular acidosis) responsible for stone formation (Table 4.8). The alkali load reduces tubular reabsorption of citrate, which in turn normalises citrate excretion and simultaneously reduces calcium turnover. Therapeutic success can be monitored by venous blood gas analysis (base excess: ± 2.0 mmol/L) in complete RTA. If excessive calcium excretion (> 8 mmol/day) persists after re-establishing acid-base equilibrium, thiazides may lower urinary calcium excretion.

Table 4.8: Pharmacological treatment of renal tubular acidosis

Biochemical risk factor	Rationale for pharmacological therapy	Medication
Hypercalciuria	Calcium excretion > 8 mmol/day	Hydrochlorothiazide, - in adults: 25 mg/day initially, up to 50 mg/day - in children: 0.5-1 mg/kg/day Alternatives in adults: Chlorthalidone 25 mg/d Indapamide 2.5 mg/d
Inadequate urine pH	Intracellular acidosis in nephron	Alkaline citrate, 9-12 g/day divided in 3 doses 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

4.6.6 Nephrocalcinosis [396]

Nephrocalcinosis (NC) refers to increased crystal deposition within the renal cortex or medulla, and occurs alone or in combination with renal stones. There are various metabolic causes. The main risk factors are: HPT, PH, RTA, vitamin D metabolic disorders, idiopathic hypercalciuria and hypocitraturia, and genetic disorders, including Dent’s disease, Bartter’s syndrome and Medullary sponge kidney. The many causes of NC means there is no single standard therapy. Therapeutic attention must focus on the underlying metabolic or genetic disease, while minimising the biochemical risk factors.

4.6.6.1 Diagnosis

Diagnosis requires the following blood analysis: PTH (in the case of increased calcium levels), vitamin D and metabolites, vitamin A, sodium, potassium, magnesium, chloride, and blood gas analysis. Urinalysis should investigate: urine pH profile (minimum 4 times daily), daily urine volume, specific weight of urine, and levels of calcium, oxalate, phosphate, uric acid, magnesium and citrate.

4.7 Uric acid and ammonium urate stones

All uric acid and ammonium urate stone formers are considered to be at high risk of recurrence [12]. Uric acid nephrolithiasis is responsible for approximately 10% of renal stones [469]. 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 [470]. Low urinary pH may be caused by decreased urinary ammonium excretion (insulin resistance or gout), increased endogenous acid production (insulin resistance, metabolic syndrome, or exercise-induced lactic acidosis), increased acid intake (high animal protein intake), or increased base loss (diarrhoea) [470].

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 3 and 4 evidence.

4.7.1 Diagnosis

Figure 4.5 shows the diagnostic and therapeutic algorithm for uric acid and ammonium urate stones. Blood analysis requires measurement of creatinine, potassium and uric acid levels. Urinalysis requires measurement of urine volume, urine pH profile, specific weight of urine, and uric acid level. Urine culture is needed in the case of ammonium urate stones.

4.7.2 Interpretation of results

Uric acid and ammonium urate stones form under completely different biochemical conditions. Acidic arrest (urine pH constantly < 5.8) promotes uric acid crystallisation.

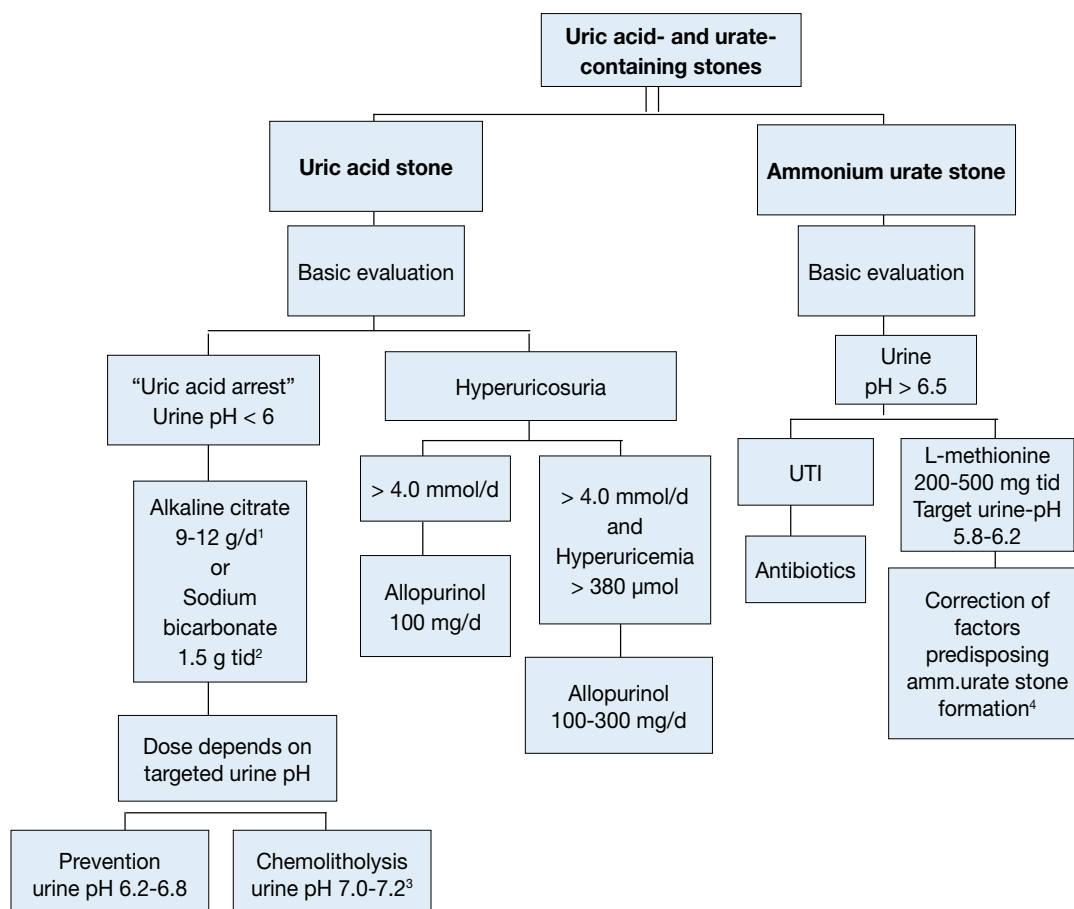
Hyperuricosuria is defined as uric acid excretion ≥ 4 mmol/day in adults or > 0.12 mmol/kg/day in children. Hyperuricaemia may be present, but there is only weak evidence for its association with stone formation.

Hyperuricosuric calcium oxalate stone formation can be distinguished from uric acid stone formation by: urinary pH, which is usually > 5.5 in calcium oxalate stone formation and < 5.5 in uric acid stone formation and occasional absence of hyperuricosuria in patients with pure uric acid stones [471, 472]. Ammonium urate crystals form in urine at pH > 6.5 , at high uric acid concentration and ammonium being present to serve as a cation [473-475].

4.7.3 Specific treatment

General preventive measures are recommended for fluid intake and diet. Hyperuricosuric stone formers benefit from purine reduction in their daily diet. Figure 4.5 describes pharmacological treatment [12, 389, 469-481]. For uric acid stones, allopurinol may change the stone composition distribution in patients with gout to a pattern similar to that in stone formers without gout [482].

Figure 4.5: Diagnostic and therapeutic algorithm for uric acid- and ammonium urate stones



¹ d: day.

² tid three times a day.

³ A higher pH may lead to calcium phosphate stone formation.

⁴ In patients with high uric acid excretion, Allopurinol may be helpful.

4.8 Struvite and infection stones

All infection-stone formers are deemed at high risk of recurrence.

Struvite stones represent 2-15% of the stones sent for analysis. Stones that contain struvite may originate de novo or grow on pre-existing stones, which are infected with urea-splitting bacteria [483]. There are several factors predisposing patients to struvite stone formation (Table 4.9) [484].

4.8.1 Diagnosis

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

Interpretation

Infection stones contain the following minerals: struvite and/or carbonate apatite and/or ammonium urate.

Urine culture typically provides evidence for urease-producing bacteria, which increase ammonia ions and develop alkaline urine (Table 4.10). Carbonate apatite starts to crystallise at a urine pH level of 6.8. Struvite only precipitates at pH > 7.2 [485, 486]. *Proteus mirabilis* accounts for more than half of all urease-positive UTIs [487, 488].

4.8.2 Specific treatment

General preventive measures are recommended for fluid intake and diet. Specific measures include complete surgical stone removal [484] short- or long-term antibiotic treatment [489], urinary acidification using methionine [437] or ammonium chloride [490], and urease inhibition [491, 492]. For severe infections, acetohydroxamic acid may be an option [491, 492] (Figure 4.6), however, it is not licensed/available in all European countries.

4.8.3 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.

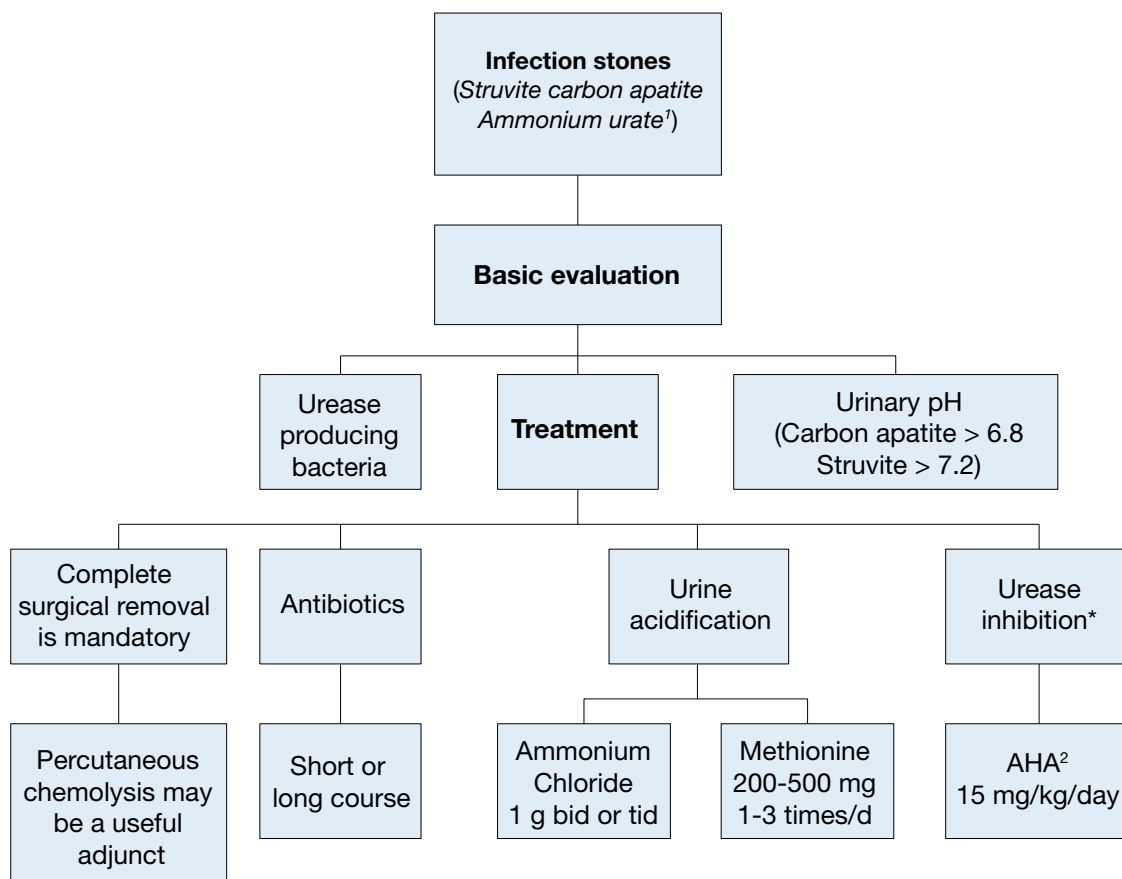
Table 4.9: Factors predisposing to struvite stone formation

Neurogenic bladder Spinal cord injury/paralysis Continent urinary diversion Ileal conduit Foreign body Stone disease Indwelling urinary catheter Urethral stricture Benign prostatic hyperplasia Bladder diverticulum Cystocele Caliceal diverticulum Ureteropelvic junction obstruction
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Table 4.10: Most important species of urease-producing bacteria

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

Figure 4.6: Diagnostic and therapeutic algorithm for infection stones



¹ Discussed with uric acid stones,

² Acetohydroxamic acid

* When nationally available.

bid = twice a day; tid = three times a day.

4.9 Cystine stones

Cystine stones account for 1-2% of all urinary stones in adults and 6-8% of the stones reported in paediatric studies [18, 493]. All cystine stone formers are deemed at high risk of recurrence.

4.9.1 Diagnosis

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

Interpretation

- Cystine is poorly soluble in urine and crystallises spontaneously within the physiological urinary pH range.
- Cystine solubility depends strongly on urine pH: at pH 6.0, the limit of solubility is 1.33 mmol/L.
- Routine analysis of cystine is not suitable for therapeutic monitoring.
- Regardless of phenotype or genotype of the cystinuric patient, the clinical manifestations are the same [494].
- There is no role for genotyping patients in the routine management of cystinuria [495, 496].
- Reductive therapy targets the disulphide binding in the cysteine molecule. For therapy monitoring, it is essential to differentiate between cystine, cysteine and drug-cysteine complexes. Only high-performance liquid chromatography (HPLC)-based analysis differentiates between the different complexes formed by therapy.
- Diagnosis is established by stone analysis. The typical hexagonal crystals are detectable in only 20-25% of urine specimens from patients with cystinuria [497].
- 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 [498, 499].
- Quantitative 24-h urinary cystine excretion confirms the diagnosis in the absence of stone analysis. Levels above 30 mg/day are considered abnormal [500, 501].

4.9.2 Specific treatment

General preventative measures for fluid intake and diet are recommended. A diet low in methionine may theoretically reduce urinary excretion of cystine; however, patients are unlikely to comply sufficiently with such a diet. A restricted intake of sodium is more easily achieved and is more effective in reducing urinary cystine. Patients are usually advised to avoid sodium consumption > 2 g/day [502].

A high level of diuresis is of fundamental importance, aiming for a 24-h urine volume of ≥ 3 L [503]. A considerable fluid intake evenly distributed throughout the day is necessary.

4.9.2.1 Pharmacological treatment of cystine stones

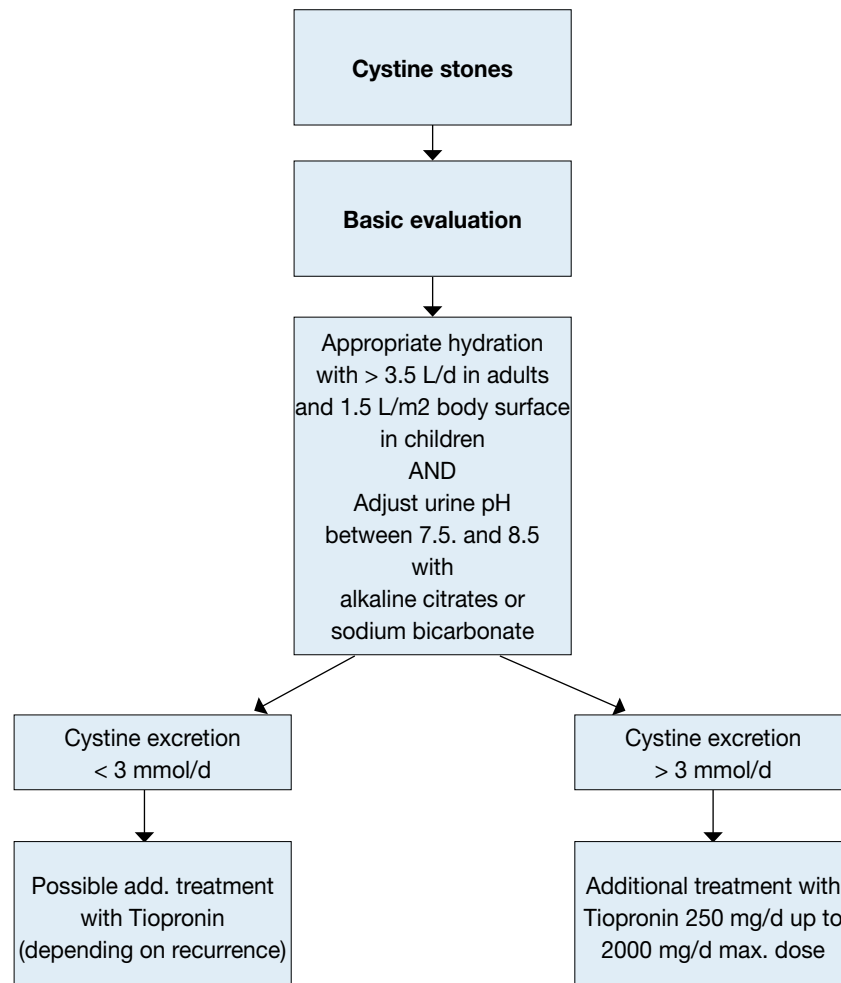
The main therapeutic option for avoiding cystine crystallisation is to maintain urine pH > 7.5, to improve cystine solubility and ensure appropriate hydration with a minimum of 3.5 L/day in adults, or 1.5 L/m² body surface area in children.

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

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

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

Figure 4.7: Metabolic management of cystine stones



4.9.3 Recommendations for the treatment of cystine stones

Therapeutic measures	LE	GR
Urine dilution 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.	3	B

4.10 2,8-Dihydroxyadenine stones and xanthine stones [12]

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 acid stones.

4.10.1 2,8-Dihydroxyadenine stones

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

4.10.2 Xanthine stones

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

4.10.3 Fluid intake and diet

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

4.11 Drug stones [38]

Drug stones are induced by pharmacological treatment [504] (Table 4.11). Two types exist:

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

Table 4.11: Compounds that cause drug stones

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

4.12 Matrix Stones

Pure matrix stones are extremely rare with less than 70 cases described in the literature. They are more prevalent in females. The main risk factors are recurrent urinary tract infections, especially due to *Proteus mirabilis* or *Escherichia coli*, previous surgery for stone disease, chronic renal failure and haemodialysis. Complete endourological removal, frequently via the percutaneous approach, is critical. Given the rarity of matrix calculi a specific prophylactic regimen to minimize recurrence cannot be recommended. Eliminating infections and prophylactic use of antibiotics are most commonly proposed [505].

4.13 Unknown stone composition [11]

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

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

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

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 [498, 499].

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

Table 4.12: Investigating patients with stones of unknown composition

Investigation	Rationale for investigation
Medical history	<ul style="list-style-type: none"> Stone history (former stone events, family history) Dietary habits Medication chart
Diagnostic imaging	<ul style="list-style-type: none"> Ultrasound in the case of a suspected stone Unenhanced helical CT (Determination of Hounsfield units provides information about the possible stone composition)
Blood analysis	<ul style="list-style-type: none"> Creatinine Calcium (ionised calcium or total calcium + albumin) Uric acid
Urinalysis	<ul style="list-style-type: none"> 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.

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6. CONFLICT OF INTEREST

All members of the Urolithiasis Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: <http://www.uroweb.org/guidelines/online-guidelines/>. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.