Guidelines on Urolithiasis

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1. METHODOLOGY

1.1 Introduction

The European Association of Urology (EAU) Urolithiasis Guideline Panel have prepared these guidelines to help urologists assess the evidence-based management of stones/calculi and to incorporate guideline recommendations into their clinical practice. The EAU Guidelines Panel consists of an international group of experts in this field.

The document is comprehensive and covers most aspects of the disease. Notwithstanding technological and scientific advances, stone disease is still a cause of significant morbidity in our society.
The Panel is aware of the geographical variations in the availability of healthcare provision.

1.2 Data identification

Literature searches were carried out for all sections of the Urolithiasis guideline, covering a minimum time frame of 2007 until November 2010. For some sections no time limits were applied.

Focus of the searches was identification of all level 1 scientific papers (systematic reviews and meta-analyses of randomised controlled trials) in accordance with EAU methodology. In case sufficient data was identified to answer the clinical question, the search was not expanded to include lower level literature. The search was limited to English language publications, animal studies were excluded.

1.3 Evidence sources

Searches were carried out in the Cochrane Library database of Systematic Reviews, the Cochrane Library of Controlled Clinical Trials, and Medline and Embase on the Dialog-Datastar platform. The searches used the controlled terminology of the respective databases. Both MesH and EMTREE were analysed for relevant terms. In many cases the use of free text ensured the sensitivity of the searches.

Randomised controlled trial (RCT) strategies used were based on Scottish Intercollegiate Guidelines Network (SIGN) and Modified McMaster/Health Information Research Unit (HIRU) filters for RCTs, systematic reviews and practice guidelines on the OVID platform and then translated into Datastar syntax.

For all searches a total of 4,013 papers were identified, of which 688 were included in the final document. Additionally, key publications from other sources were proposed by panel members. Initial assessment and selection of papers was based on citation and abstract only, when in doubt full text papers were consulted. The stone free rates meta-analysis for the section on Ureteral calculi was updated. Finally, an overall scoping search was conducted to ensure that the individual searches met the minimum requirement of identification of all level 1 evidence.

There is a need for ongoing re-evaluation of the information presented in the current guideline by an expert panel. It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account.

1.4 Level of evidence and grade of recommendation

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

Table 1: Level of evidence (LE)*

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

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

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

Alternatively, absence of high level evidence does not necessarily preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. In addition, there may be exceptional situations where corroborating studies cannot be performed, perhaps for ethical or other reasons and in this case unequivocal recommendations are considered helpful for the reader. Whenever this occurs, it has been clearly indicated in the text with an asterix, as “upgraded based on panel consensus”. The quality of the underlying scientific evidence - although a very important factor - has to be balanced against benefits and burdens, values and preferences and cost when a grade is assigned (2-4).

The EAU Guidelines Office, do not perform cost assessments, nor can they address local/national preferences in a systematic fashion. But whenever this data is available, the expert panels will include the information.

Table 2: Grade of recommendation (GR)*

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

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

1.5 Publication history

The current guidelines present a complete update of the 2010 print version. The EAU published a first guideline on Urolithiasis in 2000. Subsequent updates were made of the text in 2001 (partial), 2005 (comprehensive update), 2008 (comprehensive update), and limited updates published in 2009 and 2010.
A number of summaries have been published in scientific journals, the first paper dating back to 2001 (5), with subsequent publications in 2007 (6,7).

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

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2. CLASSIFICATION OF STONES

Urinary stones can be classified according to the following aspects: stone size, stone location, X-ray characteristics of stone, aetiology of stone formation, stone composition (mineralogy), and risk group for recurrent stone formation.

2.1 Stone size

The size of a stone is usually given in millimetres, using one- or two-dimensional measures. Stones can also be stratified further into those measuring up to 5 mm, > 5-10 mm, > 10-20 mm, and > 20 mm.

2.2 Stone location

A stone can be classified according to its anatomical position in the urinary collecting system at diagnosis: upper calyx, middle calyx or lower calyx, renal pelvis, upper ureter, middle ureter or distal ureter, and urinary bladder. However, treatment of stones found in the urinary bladder is not discussed in these guidelines.

2.3 X-ray characteristics

A stone can be classified according to its appearance on plain X-ray (KUB: kidney-ureter-bladder) (Table 3), which varies according to its mineral composition. If non-enhanced computer tomography is used, Hounsfield Units (HU) might be given for stratification since it provides information on stone density and stone composition (hardness of the stone). This information will directly impact treatment decisions (*see* Section 6.3.4).

Table 3: X-ray characteristics

Radiopaque	Poor radiopaque	Radiolucent
Calcium oxalate dihydrate	Magnesium ammonium phosphate	Uric acid
Calcium oxalate monohydrate	Apatite	Ammonium urate
Calcium phosphates	Cystine	Xanthine
		2,8-dihydroxyadenine
		'Drug-stones' (*see Section* 11.11)

2.4 Aetiology of stone formation

Stones can be classified into those caused by infection and those not caused by infection (i.e. infection-stones and non-infection stones), stones arising from genetic defects, and stones formed as a side-effect of medication (i.e. 'drug stones') (Table 4).

Table 4: Stones classified according to their aetiology*

Non-infection stones Calcium oxalates Calcium phosphates Uric acid
Infection stones Magnesium-ammonium-phosphate Apatite Ammonium urate
Genetic causes Cystine Xanthine 2,8-dihydroxyadenine
'Drug stones'

**See section 11.4.2*

2.5 Stone composition (mineralogy)

Metabolic aspects play an important role in stone formation and a metabolic evaluation is required to rule out any disorders. Additionally, a correct stone analysis in relation to any metabolic disorders will be the basis for further diagnostic and management decisions.

Stones are often made from a mix of different substances. The substance comprising the largest part(s) of the stone is considered to be the most important.

The clinically most relevant substances and their mineral component are listed in Table 5.

Table 5: Stone composition

Chemical composition	Mineral
Calcium oxalate monohydrate	whewellite
Calcium-oxalate-dihydrate	wheddelite
Uric acid dihydrate	uricite
Ammonium urate	
Magnesium ammonium phosphate	struvite
Carbonate apatite (phosphate)	dahllite
Calcium hydrogenphosphate	brushite
Cystine	
Xanthine	
2,8-dihydroxyadenine	
'Drug stones'	

2.6 Risk groups for stone formation

The risk status of a stone former is of particular interest as it defines both probability of recurrence or (re)growth of stones and imperative for pharmacological treatment.

About 50% of all recurrent stone formers have just one recurrence during lifetime (1,2). Highly recurrent disease is observed in slightly more than 10% of all stone formers. Stone type and severity of disease are the determinants which define the patient to be at low risk or at high risk for stone recurrences (Table 6) (3-5).

Table 6: High risk stone formers (5-7)

General factors
Early onset of urolithiasis in life (especially children and teenagers)
Familial stone formation
Brushite containing stones (calcium hydrogen phosphate; $CaHPO_4 . 2H_2O$)
Uric acid and urate containing stones
Infection stones
Solitary kidney (The solitary kidney itself does not have a particular increased risk of stone formation, but the prevention of a potential stone recurrence is of more importance)
Diseases associated with stone formation
Hyperparathyroidism
Nephrocalcinosis
Gastrointestinal diseases or disorders (i.e. jejuno-ileal bypass, intestinal resection, Crohn's disease, malabsorptive conditions)
Sarcoidosis
Genetically determined stone formation
Cystinuria (type A, B, AB)
Primary hyperoxaluria (PH)
Renal tubular acidosis (RTA) type I
2,8-dihydroxyadenine
Xanthinuria
Lesh-Nyhan-Syndrome
Cystic fibrosis
Drugs associated with stone formation (see metabolic evaluation section 11.11)
Anatomical and urodynamic 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
Urinary diversion (via enteric hyperoxaluria)
Neurogenic bladder dysfunction

2.7 References

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3. DIAGNOSIS

3.1 Diagnostic imaging

Patients with renal stone disease usually present with characteristic loin pain, vomiting, and sometimes fever. Patients may also be asymptomatic. The standard evaluation of a patient includes taking a detailed medical history and physical examination. The clinical diagnosis should be supported by an appropriate imaging procedure.

Ultrasonography should be used as the primary procedure. It is a safe (no risk of radiation), reproducible and inexpensive method of urinary stone detection.

Ultrasonography can identify stones located in the calices, pelvis, pyelo-ureteric junction and vesico-ureteric junction, as well as dilatation of the upper urinary tract. For renal stones > 5mm, ultrasound has a sensitivity of 96% and a specificity of nearly 100% (1). For all stone locations, the sensitivity and specificity of ultrasound reduces to 78% and 31% respectively (1,2).

The sensitivity and specificity of KUB (kidney-ureter-bladder radiograph) ranges from 44% to 77% and from 80% to 87%, respectively (3). A KUB should not be performed if a non-contrast enhanced computed tomography (NCCT) is being considered (4,5). However, a KUB can be helpful in differentiating between radiolucent and radiopaque stones and for comparison during follow up.

Recommendation

	LE	GR
In patients with fever or a solitary kidney, and when the diagnosis of stone is in doubt, immediate imaging is indicated.	4	A

3.1.1 Evaluation of patients with acute flank pain

Non-contrast enhanced CT has become the standard method for diagnosing acute flank pain. It has replaced intravenous urography (IVU), which was previously the gold standard for many years. It can also identify the presence of the stone, its diameter, and density. When the stone is not presented, the cause of abdominal pain should be identified. Compared with IVU, NCCT showed higher sensitivity and specificity in identifying urinary stones (Table 7) (5-9).

Table 7: Comparison of NCCT and IVU

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

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

Recommendation

	LE	GR
NCCT should be used to confirm a stone diagnosis in patients presenting with acute flank pain because it is superior to IVU (10,11).	1a	A

Uric acid and xanthine stones are radiolucent on plain films and can be detected by NCCT. However, indinavir stones cannot be detected on NNCT (12).

In addition, NCCT can determine mean stone density and the skin-to-stone distance, both of which affect ESWL outcome (13,14). However, the advantage of a non-contrast imaging modality must be balanced against the loss of information on renal function and the anatomy of the urinary collecting system, as well as the higher radiation dose of NCCT (Table 8).

Radiation risk can be reduced using low-dose CT (15). Poletti showed that in patients with a BMI < 30, low-dose CT was 86% sensitive for detecting ureteric stones < 3 mm and 100% sensitive for detecting calculi > 3 mm (16). In a meta-analysis of prospective studies by Nieman (17), low-dose CT diagnosed urolithiasis with a pooled sensitivity of 0.966% (95% CI: 0.950-0.978) and specificity of 0.949% (95% CI: 0.920-0.97).

Table 8: Radiation exposure of different imaging modalities (18-21)

Method	Radiation exposure (mSv)
KUB	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

CT = computed tomography ; IVU = intravenous urography ; KUB = kidney-ureter-bladder radiograph; NCCT = non-contrast enhanced computed tomography.

Recommendation

	LE	GR
In patients with a BMI < 30, low-dose protocols should be used in NCCT.	1b	A

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

A contrast study is recommended if stone removal is planned and the renal collecting system anatomy is not known. Enhanced CT is preferable because it enables 3D-reconstruction of the renal collecting system, as well as measurement of stone density and of skin-to-stone distance. Intravenous urography may also be used.

Recommendation

	LE	GR
A renal contrast study (enhanced CT or IVU) is indicated when planning treatment for a renal stone.	3	A*

** Upgraded based on panel consensus.*

3.1.3 References

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3.2 Diagnostics - metabolism-related

Each emergency patient with urolithiasis needs a succinct biochemical work-up of urine and blood besides the imaging studies. At that point no difference is made between high and low risk patients.

Table 9: Recommendations: Basic analysis - emergency stone patient (1-4)

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

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

*3.2.1 **Basic analysis - non emergency stone patient***

Biochemical work-up is almost the same for all stone patients. However, examination of sodium, potassium, CRP, blood, and coagulation time can be omitted in the non-emergency stone patient.

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

The easiest access to the correct diagnostic pathway is an analysis of a passed stone using a valid analytical method (*see* section 2.5). Once mineral composition is known, the potential metabolic disorders can be identified. Valid analytical methods are *infrared spectroscopy* and *X-ray diffraction* (5).

*3.2.2 **Analysis of stone composition***

Stone analysis should be performed in all first-time stone formers.
In clinical practice repeat stone analysis is needed in case of:

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

The patient should be instructed to filter the urine to retrieve a concrement for analysis. Passage of the stone and restoration of normal renal function should be confirmed using appropriate methods.

The preferred analytical procedures are (5,7-9):

- X-ray diffraction;
- infrared spectroscopy.

Polarisation microscopy is equivalent, but solely in centres with expertise.
Wet chemistry generally deems as obsolete (4,5).

Table 10: Accuracy of stone analysis methods in identification of substance (5,8)

Accuracy of identification of substance (%)	Chemical analysis	Infrared spectroscopy	X-ray diffraction
Uric acid	81,0	97,6	97,9
Ammonium urate	83,1	95,0	96,0
Cystine	93,5	99,1	98,5
Xanthine	28,4	96,3	93,2
2,8-Dihydroxyadenine	6,0	80,0	69,6
Whewellite	85,6	97,8	98,7
Struvite	89,5	97,9	98,0
Brushite	69,6	97,4	100,0
Apatite	79,4	93,9	100,0
Calcite	66,0	98,5	98,2
Cholesterol	38.9	98.6	82.4
Silicium dioxide	21.6	95.6	98.1
Gypsum	38.6	96.0	77.1

Recommendations

	LE	GR
Always perform a stone analysis in first time stone formers using a valid analytical procedure (X-ray diffraction or infrared spectroscopy).	2	A
Repeat stone analysis in patients: • presenting with recurring stones in spite of pharmacological prevention therapy; • early recurrence after complete stone clearance; • late recurrence after a long stone free period since stone composition may change (3).	3	B

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4. TREATMENT OF PATIENT WITH RENAL COLIC

4.1 Renal colic

4.1.1 ***Pain relief***

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

Clinical trials have clearly shown that non-steroidal anti-inflammatory drugs (NSAIDs) (e.g. diclofenac) provide effective relief in patients who have acute stone colic (3-6). These agents have a better efficacy than opioids in relieving the pain of acute renal colic and patients receiving NSAIDs achieve greater reduction in pain scores and are less likely to require further analgesia in the short term.

However, if an opioid is used, it is recommended that it is not pethidine. This is because opioids, particularly pethidine, are associated with a high rate of vomiting compared with NSAIDs, and carry a greater likelihood of further analgesia being needed (7,8) (*see* Section 4.1.3).

Recommendations

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

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

Most ureteral stones will pass spontaneously (*see* Section 5.1.1 Stone passage rates), and the facilitation of ureteral stone passage is discussed further in Section 5.3, Medical Expulsive Therapy (MET).

For patients with ureteral stones that are expected to pass spontaneously, NSAID tablets or suppositories (i.e. diclofenac sodium, 100-150 mg/day, over 3-10 days) may help to reduce inflammation and the risk of recurrent pain (8-10). Although diclofenac can affect renal function in patients with an already reduced renal function, it has no effect on renal function in normally functioning kidneys (LE: 1b) (11).

In a double-blind, placebo-controlled trial, recurrent pain episodes of stone colic were significantly fewer in patients treated with NSAIDs during the first 7 days of treatment (10).

Alpha-blocking agents, given on a daily basis, also reduce recurrent colic (LE: 1a) (*see* Section 5.3, MET) (12,13).

If pain relief cannot be achieved by medical means, drainage, using stenting or percutaneous nephrostomy, or stone removal, should be carried out.

4.1.3 *Recommendations for pain relief during renal colic*

	LE	GR	refs.
1st choice: treatment should be started with an NSAID Diclophenac sodium*, Indomethacin, Ibuprofen	1b	A	1-4
2nd choice: Hydromorphine Pentazocine Tramadol	4	C	
Diclofenac sodium* is recommended to counteract recurrent pain after an episode of ureteral colic	1b	A	7

NSAID = non-steroidal anti-inflammatory drug.
* Diclofenac sodium affects glomerular filtration rate (GFR) in patients with reduced renal function, but not in patients with normal renal function (LE: 2a) (14).

Although NSAIDs constitute the first choice in the medical management of acute renal colic pain; spasmolytics (metamizole sodium etc.) are alternatives which may be given in circumstances in which parenteral administration of a non-narcotic agent is mandatory (third-line treatment) (15,16).

4.1.4 *References*

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4.2 Management of sepsis in the obstructed kidney

The obstructed, infected kidney is a urological emergency. Urgent decompression of the system is necessary to prevent further complications in infected hydronephrosis secondary to a stone, single kidneys with obstruction, and bilateral renal obstruction.

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

*4.2.1 **Decompression***

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

- placement of an indwelling ureteral catheter under general anaesthesia for a period of time;
- percutaneous placement of a nephrostomy catheter.

There is little evidence to support the superiority of percutaneous nephrostomy over retrograde stenting as primary treatment of infected hydronephrosis. Certainly, there is no good-quality evidence to suggest that ureteric stenting under general anaesthesia may have higher complication rates than percutaneous nephrostomy. However, percutaneous nephrostomy has the advantages of avoiding general anaesthesia and instrumentation of the urinary tract (1,4-6).

Only two randomised controlled trials (2,5) have assessed the best method of decompressing infected hydronephrosis in an acute situation, though the patient numbers were small and the two trials had different outcome measures. The complications of percutaneous nephrostomy insertion were well reported and relatively consistent, but the complications of ureteric stent insertion were less well described (1).

Adopting the 'stent first where possible' approach may reduce the requirement for out-of-hours nephrostomy placement in patients with infected hydronephrosis, although clearly it will not eliminate the demand for nephrostomy (1-8).

Definitive treatment of the stone should be delayed until sepsis has resolved and the infection is cleared following a complete course of appropriate antimicrobial therapy (9).

In exceptional cases, with severe sepsis and/or the formation of abscesses, an emergency nephrectomy may become necessary.

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

Recommendation

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

** Upgraded based on panel consensus.*

*4.2.2 **Further measures***

Following urgent decompression of the obstructed and infected system; a urine sample from drainage should be sent for culture -antibiogram sensitivity test and an antibiotic treatment should immediately be initiated thereafter. The treatment regimen should be revisited in the light of the culture-antibiogram test. Intensive care might become necessary.

Recommendations

	GR
Collect urine following decompression for antibiogram.	A*
Start antibiotic treatment immediatedly thereafter (+ intensive care if necessary).	
Revisit antibiotic treatment regimen following antibiogram findings.	

** Upgraded based on panel consensus.*

*4.2.3 **References***

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5. STONE RELIEF

When deciding between active stone removal and conservative treatment with MET, it is important to carefully consider all the individual circumstances of a patient that may affect treatment decisions.

5.1 Observation of ureteral stones

*5.1.1 **Stone-passage rates***

Only limited data are available on the topic of spontaneous passage by stone size (1,2). A meta-analysis of five patient groups including 328 patients harbouring ureteral stones < 10 mm investigated the likelihood of ureteral stone passage (Table 11) (1). The Panel recognised that these studies had certain limitations including non-standardisation of the stone size measurement methods and lack of analysis of stone position, stone-passage history, and time to stone passage in some.

Table 11: Likelihood of passage of ureteral stones (1)

Stone size	**passage**	**CI**
< 5 mm (n=224)	68%	(95% CI 46-85%)
> 5 mm (n=104)	47%	(95% CI 36-58%)
95% of stones passed within (2):		
< 2 mm	31 days	
2-4 mm	40 days	
> 4-6 mm	39 days	

Recommendation

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

**see also Section 5.3, MET.*

5.2 Observation of kidney stones

Observation of kidney stones, especially when located in calices, depend on their natural history, which is discussed in Section 6.2.1.

Statements	**LE**
It is still debatable whether kidney stones should be treated, or whether annual follow-up is sufficient in an asymptomatic caliceal stone which has remained stable for 6 months.	**4**

Recommendations

	GR*
Kidney stones should be treated in case of stone growth, formation of de novo obstruction, associated infection, and acute and/or chronic pain.	A
Patient's comorbidities and preferences (social situation) need to be taken into consideration when making a treatment decision.	C
If kidney stones are not treated, periodic evaluation is needed.	A

** Upgraded based on panel consensus.*

5.3 Medical expulsive therapy (MET)

Drugs used to expel stones are thought to act by relaxing ureteral smooth muscle through either the inhibition of calcium channel pumps or alpha-1 receptor blockade (3,4).

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

Hollingsworth, et al. (4) and Seitz, et al. (3) recently performed a meta-analysis of studies involving alpha-blockers or nifedipine in patients with ureteral stones. Patients receiving either one of these agents were more likely to pass stones with less episodes of colic than those not receiving such therapy.

Statement	LE
There is growing evidence that MET accelerates the spontaneous passage of ureteral stones and of stone fragments generated with ESWL as well as limits pain (3,5-15).	1a

*5.3.1 **Choice of medical agent***

5.3.1.1 Alpha-blockers

Tamsulosin, 0.4 mg (0.2 mg in Asian populations), has been the most commonly used alpha blocker in these studies (5,3,16-19). However, one small study suggested that tamsulosin, terazosin, and doxazosin are equally effective, indicating a possible class effect (20). A class effect is also supported by several trials demonstrating increased stone expulsion rates using doxazosin (4,20,21) terazosin (20,22) alfuzosin (23-25) and naftopidil (26) (LE: 1b).

Statement	LE
Several trials have demonstrated increased stone expulsion rates using tamsulosin, doxazosin, terazosin, alfuzosin and naftopidil.	1b

5.3.1.2 Calcium-channel blockers

As far as the class effect of calcium-channel blockers is concerned, only nifedipine has been investigated (LE: 1a). (3,8-10).

5.3.1.3 Corticosteroids

Corticosteroids in combination with alpha-blockers may expedite stone expulsion compared to alpha-blockers alone (27) (LE: 1b).

Statement	LE
There is no evidence to support the use of corticosteroids as monotherapy for MET (3,20,27,28).	1b

Recommendations for MET	LE	GR
For MET, alpha-blockers or nifedipine are recommended.		A
Patients should be counselled about the attendant risks of MET, including associated drug side effects, and should be informed that it is administered as ‘off-label’ use.		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 to monitor stone position and to assess for hydronephrosis.	4	A*

** Upgraded based on panel consensus.*

*5.3.2 **Factors affecting success of MET (Tamsulosin)***

5.3.2.1 Stone size

Due to the high likelihood of spontaneous passage for stones up to approximately 5 mm, MET is less likely to increase the stone-free rate because of the high spontaneous expulsion rate (4,29,30) (LE: 1b). However, MET does reduce the need for analgesics (3,5) (LE: 1a).

5.3.2.2 Stone location

The vast majority of trials investigated distal ureteral stones (3). One randomised controlled trial assessed the efficacy of tamsulosin, an alpha-receptor antagonist, on the spontaneous passage of proximal ureteral calculi ≤ 10 mm. The main effect of tamsulosin on the 5-10 mm stones was to encourage stone migration to a more distal part of the ureter (31).

5.3.2.3 MET after ESWL

Clinical studies and several meta-analyses have shown that MET after ESWL for ureteral or renal stones can expedite expulsion and increase stone-free rates and reduces analgesic requirements (6,11,32-36).

5.3.2.4 MET after ureteroscopy

MET following holmium:YAG laser lithotripsy increased stone-free rates and reduced colic episodes (37).

5.3.2.5 Duration of MET treatment

Most studies included a duration of MET of 1 month or 30 days.

5.3.2.6 MET in the paediatric population

A recent study investigated the expulsion rate and time-to-stone expulsion of ureteral stones ≤ 10 mm in 19 children, aged 2-14 years, receiving doxazosin 0.03 mg/kg/day, versus 20 controls receiving ibuprofen. The effectiveness of doxazosin could not be demonstrated (38).

Statements	**LE**
MET has an expulsive effect also on proximal ureteral stones.	1b
After ESWL for ureteral or renal stones, MET seems to expedite and increase stone-free rates, reducing additional analgesic requirements.	1a
MET in children cannot be recommended due to the limited data in this specific population (small study).	4

5.3.3 ***References***

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5.4 Chemolytic dissolution of stones

Oral or percutaneous irrigation chemolysis of stones or stone fragments can be a useful first-line therapy (oral). It may also be an adjunct to ESWL, PNL, URS or open surgery to support elimination of small residual fragments. However, because its use as first-line therapy may take weeks to be effective, it is mainly used as an adjunct to endourological therapy.

Combined treatment with ESWL and chemolysis is a minimal invasive option for patients who have partial or complete infection staghorn stones and are not suitable for PNL. Stone fragmentation leads to an increased stone surface area and therefore an improved efficacy of chemolitholysis.

Chemolysis is possible only for the stone compositions listed below. Knowledge of stone composition is therefore mandatory prior to chemolysis.

*5.4.1 **Percutaneous irrigation chemolysis***

Recommendations

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

Table 12: Methods of percutaneous irrigation chemolysis

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

*5.4.2 **Oral Chemolysis***

Oral chemolitholysis is efficient only for uric acid calculi. The treatment is based on alkalinisation of the urine by application of alkaline citrate or sodium bicarbonate (14,16,18,19).

When chemolitholysis is planned, the pH should be adjusted to between 7.0 and 7.2. Additional application of allopurinol may support the chemolysis and prevention of recurrent stones. No formal recommendation on the use of allopurinol can be given.

In case of uric acid obstruction of the collecting system, oral chemolysis in combination with urinary drainage is indicated (6).

Recommendations

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

*5.4.3 **References***

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5.5 ESWL (extracorporeal shock wave lithotripsy)

The introduction of extracorporeal shockwave lithotripsy (ESWL) in the early 1980s was a dramatic change in the management of urinary tract stones. The development of new lithotripters, modified indications and treatment principles has completely changed the treatment of kidney stones. Modern lithotripters are smaller and usually included in uroradiological tables. They ensure application of not only ESWL, but other diagnostic and ancillary procedures associated with ESWL.

Extracorporeal shockwave lithotripsy can remove > 90% of stones in adults (1-3). However, the success rate for ESWL depends on the efficacy of the lithotripter and upon the following factors:

- size, location of stone mass (ureteral, pelvic or calyceal), and composition (hardness) of the stones;
- patient's habitus (*see* Section 10.1.2);
- performance of ESWL (best practice, *see below*).

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

*5.5.1 **Contraindications of ESWL***

There are several contraindications to the use of ESWL, including:

- pregnancy, due to the potential effects of the shock wave energy on the foetus (4);
- bleeding diatheses, which should be compensated at least 24 hours before and 48 hour after treatment (5);
- uncontrolled urinary tract infections;
- severe skeletal malformations and severe obesity, which will not allow targeting of the stone;

- arterial aneurysm in the vicinity of the stone treated (6);
- anatomical obstruction distal of the stone.

*5.5.2 **Stenting before carrying out ESWL***

5.5.2.1 Stenting in kidney stones

A recent randomised study reported that the routine use of internal stents before ESWL does not improve outcome in terms of stone-free rate (LE: 1b; GR: A) (7). A double-J stent reduces the complications (evidence of renal colic), but does not reduce formation of steinstrasse or evidence of infective complications (8).

However, stone particles may pass along stents while urine flows in and around the stent. This usually prevents obstruction and loss of ureteral contraction. Occasionally, stents do not efficiently drain purulent or mucoid material, increasing the risk of obstructive pyelonephritis. If fever lasts for a few days in spite of a correct positioned stent, a percutaneous nephrostomy tube is needed, even when ultrasound does not reveal any dilatation.

5.5.2.2 Stenting in Ureteric stones

In ESWL treatment of ureteric stones, the 2007 AUA/EAU *Guideline on the management of ureteral calculi*, stated that routine stenting is not recommended as part of shockwave lithotripsy (ESWL) (9). When the stent is inserted, patients often suffer from frequency, dysuria, urgency, and suprapubic pain (10).

Recommendation

	LE	GR
Routine stenting is not recommended as part of ESWL treatment of ureteric stones.	1b	A

*5.5.3 **Best clinical practice***

5.5.3.1 Pacemaker

Patients with a pacemaker can be treated with ESWL provided the patient's cardiologist is consulted before ESWL is undertaken. Patients with implanted cardioverter defibrillators must be managed with special care, as some devices need to be de-activated during ESWL; however, this might not be necessary with new-generation lithotripters (11).

5.5.3.2 Shock wave rate

Prospective randomised trials have shown that lowering wave frequency from 120 to 60-90 shock waves per minute improves the stone-free rate (12-15), especially in stones greater than 100 mm^2 (13). A meta-analysis noted that treatment results were also improved in smaller stones (16).

Recommendation

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

5.5.3.3 Number of shock waves, energy setting and repeat treatment sessions

The number of shock waves that can be delivered at each session depends on the type of lithotripter and shock-wave power. There is no consensus on the maximum number of shock waves.

However, as the shock-wave frequency increases, tissue damage increases (17,18). Starting ESWL on a lower energy setting with stepwise power ramping can achieve vasoconstriction during ESWL treatment (19), which prevents renal injury (20). Animal studies (21) and some prospective randomised studies (22) showed a better stone fragmentation and stone-free rate (96% vs 72%; $p < 0.05$), but no difference has been found in fragmentation or in the evidence of complications after ESWL, irrespective of whether ramping was used or not (23).

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

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

5.5.3.4 Improvement of acoustic coupling

Proper acoustic coupling between the cushion of the treatment head and the patient's skin is important. Defect (air pocket) presented in the coupling gel reflects 99% of shock waves. Only 2% defect in the gel layer covering of the cushion, reduce stone fragmentation by 20%-40% (24). Ultrasonography gel is probably the optimum agent available for use as a lithotripsy coupling agent (25). To reduce air pockets, ultrasonography gel should be put on the water cushion straight from the container, instead of applying gel by hand (26) (LE: 2a).

Recommendation

	GR
Ensure correct use of the coupling gel, as this is crucial for an effective shockwave transportation (24).	B

5.5.3.5 Procedural control

The results of treatment are operator dependent; the better results are obtained by the urologist who treated the greatest number of patients. During the procedure, careful imaging control of localisation will contribute to the quality of outcome (27) (LE :4).

Recommendation

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

** Upgraded based on panel consensus.*

5.5.3.6 Pain control

Careful control of pain during treatment is necessary to limit pain-induced movements and excessive respiratory excursions (28-30) (LE: 4).

Recommendation

	GR
Use proper analgesia since it will improve treatment results by limiting induced movements and excessive respiratory excursions.	C

5.5.3.7 Antibiotic prophylaxis

No standard prophylaxis prior to ESWL is recommended. However, prophylaxis is recommended in cases of internal stent and treatment, due to the increased bacterial burden (e.g. indwelling catheter, nephrostomy tube, infectious stones) (31,32) (LE: 4).

Recommendation

	GR
In case of infected stones or bacteriuria, antibiotics should be given before ESWL and continued for at least 4 days after treatment.	C

5.5.3.8 Medical expulsive therapy (MET) after ESWL

Clinical studies and several meta-analyses have shown that MET after ESWL for ureteral or renal stones can expedite expulsion and increase stone-free rates, as well as result in a reduction in additional analgesic requirements (33-40) (see also Section 5.3.2.3).

5.5.4 ***Complications of ESWL***

When compared with PNL and ureteroscopy, the data on ESWL support the finding that less complications occur with ESWL than with the other two procedures (41,42) (Table 13).

The most frequent complication after ESWL treatment are pain due to renal colic, occurring in 2-4% of cases, and urinary tract infection or sepsis, occurring in 1- 2% of cases (43). The risk of ESWL-induced renal haematomas is less than 1% in symptomatic cases and 4% in asymptomatic cases (1). Steinstrasse, an accumulation of stone fragments or gravel in the ureter, occurs in 4-7% cases of ESWL (44-46).

Table 13: ESWL-related complications

Complications			**%**	**Refs.**
Related to stone fragments		Steinstrasse	4-7	44-46
		Re-growth of residual fragments	21-59	47
		Renal colic	2-4	43
Infectious		Bacteriuria in non-infection stones	7.7-23	47,48
		Sepsis	1-2.7	47,48
Tissue effect	Renal	Haematoma, symptomatic	< 1	1,49
		Haematoma, asymptomatic	4	1,49
	Cardiovascular	Dysrhythmia	11-59	47,50
		Morbid cardiac events	Case reports	47,50
	Gastrointestinal	Bowel perforation	Case reports	51-53
		Liver, spleen haematoma	Case reports	53-55

The relationship between ESWL and hypertension or diabetes is unclear. Published data are contradictory and no conclusion can be reached (9,56-58).

5.5.5 ***References***

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5.6 Endourology techniques

5.6.1 ***Percutaneous nephrolitholapaxy***

Since Goodwin, et al. first punctured the kidney in 1955, and Harris, et al. used a bronchoscope for nephroscopy in 1975, rapid technological advances have revolutionised endourology procedures. Today, percutaneous nephrolitholapaxy (PNL) is a minimally invasive surgical procedure for the removal of renal (kidney) stones (1,2). There has also been the development of rigid and flexible nephroscopes of different sizes.

5.6.1.1 Rigid nephroscopes

Rigid nephroscopes are available in diameters up to 28 Ch (Charrière [French] gauge), allowing maximal size of working and irrigation channels. Thinner nephroscopes are available for Mini-PNL (also known as Mini-perc), which uses nephroscopes ranging in diameter from 11 Ch to 18 Ch. The term Mini-PNL (Mini-perc), although not precisely defined, indicates the use of smaller diameter nephroscopes compared with standard PNL. The smaller diameter gives rise to smaller working channels for stone extractions.

Mini-PNL appears to be associated with less morbidity than standard PNL. However, the benefit of using a smaller calibre nephroscope with the sole aim of preserving renal parenchyma has not been confirmed (3-5). The use of Mini-PNL in adult patients is controversial, but Mini-PNL is the standard procedure for percutaneous

stone removal in children (3,4) (see Section 9.2.3).

5.6.1.2 Flexible nephroscopes

In some complex cases, such as multiple or staghorn stones, or difficult anatomy, e.g. horseshoe kidneys, the use of rigid nephroscopes may require multiple access procedures. However, the use of flexible nephroscopes, or the combined use of retrograde flexible ureteroscopy with standard nephroscopy, reduces the need for multiple access procedures. New 'chip-on-the-tip' endoscopes are equipped with a camera on the tip of the instrument and a light-emitting diode (LED) to improve visibility and handling. Complete stone clearance is viewed endoscopically and by X-ray.

The use of rigid and flexible nephroscopes for antegrade ureteroscopy is discussed in Sections 5.6.1.1 and 5.6.1.2.

5.6.1.3 Intracorporeal lithotripsy

Intracorporeal stone disintegration can be performed in several different ways: devices are also discussed in Section 5.6.2.2.7. During PNL procedures, ultrasonic or pneumatic lithotripters are most commonly used.

Electrohydraulic intracorporeal lithotripsy is very effective even for hard kidney stones; however, due to its potential to damage surrounding tissue, it should only be used in very carefully selected cases, such as hard cystine stones.

With the increase in the use of flexible nephroscopes, the Ho:YAG laser (holmium:yttrium-aluminium-garnet laser) is becoming more important, not only in ureteroscopy, but also in PNL. It can be used for stone disintegration in parts of the calyceal system that are only accessible with flexible nephroscopes. Where flexible devices are used for PNL, the Ho:YAG laser has become the preferred intracorporeal lithotripter (5).

Recommendation

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

** Upgraded based on panel consensus.*

5.6.1.4 Extraction tools

Stones or stone fragments are extracted from the kidney through the access sheath of the nephroscope using either forceps or baskets, washing out with irrigation fluid, or using a suction device. New baskets made of nitinol (nickel-titanium alloy) provide additional advantages compared with steel wire baskets. Tipless versions of nitinol baskets are also available for use in calicies.

5.6.1.5 Best clinical practice

5.6.1.5.1 Contraindications

All contraindications for general anaesthesia apply, including bleeding disorders. Anticoagulant therapy must be discontinued prior to the PNL procedure. Patients receiving anticoagulant therapy must be monitored carefully both pre- and post-operatively (6).

Other important contraindications include:

- untreated urinary infection;
- atypical bowel interposition;
- tumour in the presumptive access tract area;
- potential malignant tumour of the kidney;
- Pregnancy (during pregnancy, conservative stone treatment should be preferred where possible (see Section 8.2) (GR: A).

5.6.1.5.2 Pre-operative imaging

Preprocedural evaluations are summarised in Chapter 3. In particular for PNL, ultrasonography or CT of the kidney and the surrounding structures can provide information about interpositioned organs within the planned percutaneous path (e.g. spleen, liver, large bowel, pleura, lung) (7,8).

Recommendation

	GR
Pre-procedural imaging, which includes a contrast media study, is mandatory to assess stone comprehensiveness, view the anatomy of the collecting system, and ensure safe access to the kidney stone.	A*

** Upgraded based on panel consensus.*

5.6.1.5.3 Positioning of the patient: prone or supine?
Traditionally, the patient is positioned prone for PNL. Use of the supine position is also possible and has been described, with or without flank upholstering. The supine position is as safe as the prone position. Compared with the prone position, the advantages of the supine position for PNL are:

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

Where it can be done, the supine position confers some advantages (9,10). However, use of the supine position depends on the appropriate equipment being available to position the patient correctly, e.g. X-ray devices and operating table. In addition, the supine position can limit the manoeuverability of instruments (11).

5.6.1.5.4 Puncture
After placement of a balloon catheter, the appropriate calyx is punctured, using fluoroscopy or ultrasonography guidance. Ultrasonography guidance is associated with decreased radiation hazards (12).

Colon interposition in the access tract of PNL can lead to colon injuries. Although rare, such injuries seem to be more likely when operating on the left kidney. The colon is not reliably detectable with ultrasound, so pre-procedural imaging is recommended. In particular, a pre-operative CT scan can provide further information (13,14).

5.6.1.5.5 Dilatation
Dilatation of the percutaneous access tract can be achieved using a metallic telescope, single dilators, or a ureteral balloon dilatator. Use of balloon dilatation can reduce blood transfusion rates (15). One-stage dilatation has been shown to be safe and effective, even in patients with a history of open surgery on the same kidney (16,17).

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

- presence of residual stones;
- likelihood of a second-look procedure;
- significant intraoperative blood loss;
- urine extravasation;
- ureteral obstruction;
- potential persistent bacteriuria due to infected stones.

Double-J stents are the most commonly used ureteral stents for PNL. They are usually placed using the antegrade approach at the end of the procedure. The most important criteria for ureteral stenting are residual stone fragments, inadequate transureteral drainage, or alterations to the pyeloureteral junction. An external ureteral catheter can be used instead of a double-J stent (18).

Tubeless PNL is percutaneous nephrolithotomy carried out without the introduction of 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, clinical studies show that totally tubeless PNL procedures result in a shorter hospital stay, with no disadvantages reported (19-23).

Recommendation

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

5.6.1.5.7 Management of complications

The most common post-operative complications associated with PNL are urinary leakage, problems due to residual stones, fever and bleeding. Urinary leakage and stone clearance can be viewed endoscopically and by X-ray at the end of the procedure. In doubtful cases, complications can be minimised by performing the standard PNL procedure instead of opting for a totally tubeless PNL procedure.

Peri-operative fever can occur, even in the presence of a sterile pre-operative urinary culture and peri-operative antibiotic prophylaxis, as the kidney stones themselves may be a source of infection. An intra-operative kidney stone culture may therefore help in selecting the post-operative antibiotic (24,25). An intra-operative irrigation pressure below 30 mm Hg and unobstructed post-operative urinary drainage may be important factors in preventing post-operative sepsis. Well-positioned or specially designed access sheaths can prevent high intrapelvic irrigation pressure (26-28).

Bleeding after PNL may be due to intraparenchymal haemorrhage or an acquired intrarenal aneurysm. With intraparenchymal haemorrhage, brief clamping of the nephrostomy may stem bleeding. An acquired intrarenal aneurysm may be marked by intense bleeding. It can be treated by super-selective embolic occlusion of the artery supplying the aneurysm (29).

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

During the past 20 years, ureterorenoscopy (URS) has dramatically changed the management of ureteral calculi. There have been tremendous technical improvements, including miniaturization of endoscopes, and enhancement of optical quality and tools and the introduction of disposables. As a result, URS has had a great impact on active stone removal and is being performed throughout the world with increasing frequency.

5.6.2.1 Instruments

5.6.2.1.1 Rigid scopes

Rigid ureteroscopy for urinary stone removal became a standard procedure in the 1990s. Today, small endoscopes with tip diameters < 8 Ch are mainly used. In Europe, rigid URS is used for both proximal and distal ureteral calculi, while urologists in the USA prefer to use flexible scopes for proximal calculi. However, the available literature show that rigid URS is safe even for proximal ureteral calculi (1-11).

5.6.2.1.2 Flexible scopes

Technological advances have been responsible for the evolution of flexible URS (12). This is especially true of improvements in deflection mechanisms, which have reached almost 300° in the latest generation scopes, making it much easier to manoeuvre intrarenally (13,14). The latest endoscopes have also made it possible to visualise the lower pole in almost all kidney anatomies. Although a secondary active deflection mechanism has been introduced, it has not yet demonstrated its superiority over conventional flexible URS (15,16).

The durability of the latest generation of flexible scopes has been improved as a result of stiffer shaft construction (17,18).

As with rigid scopes, the tip diameters of flexible scopes usually do not exceed 8 Ch.

5.6.2.1.3 Digital scopes

The miniaturisation of flexible scopes has significantly improved their effectiveness (19-21), but it has also reduced the number of fibreoptics and therefore both the optical quality and durability of the scopes.

The development of digital URS has eliminated the need for fragile low-resolution fibreoptics. The tips of digital ureteroscopes contain digital camera chips (either complementary metal-oxide semi-conductors or charge-coupled devices), which produce superior image resolution. The tips also have light-emitting diode-driven light carriers, which provide a substitute for an external light source (22).

Initial experience with digital scopes has demonstrated a remarkable improvement in image quality, with efficacy comparable to that achieved with analogue URS (23,24). To prevent damage to the camera chip, ballistic lithotripsy systems can no longer be used, meaning that intra-corporal lithotripsy must be performed exclusively with lasers.

5.6.2.2 Best clinical practice in URS

5.6.2.2.1 Pre-operative work-up and preparations

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

- patient's history;
- physical examination because anatomical and congenital abnormalities may complicate or prevent retrograde stone manipulation;
- thrombocyte aggregation inhibitors/anticoagulation treatment should be discontinued. However, this is not compulsory because URS can be performed in patients with bleeding disorders, with only a moderate increase in complications (25,26);
- imaging.

Recommendation

	GR
Short-term antibiotic prophylaxis (< 24 hours) should be administered.	A

5.6.2.2.2 Contraindications

Apart from general problems, e.g. with general anaesthesia or untreated urinary infections, URS can be performed in all patients without any specific contraindications. Specific problems as ureteral strictures may occur and prevent successful retrograde stone management.

5.6.2.2.3 Access to the upper urinary tract
Most interventions are performed under general anaesthesia, although it is possible to use local anaesthesia. Because instruments are miniaturised, intravenous sedation can be used to achieve the same outcome (27,28).

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

Antegrade URS is an option in cases with large, impacted proximal ureteral calculi (5,29) (see also Section 6.5.3).

5.6.2.2.4 Safety aspects
Fluoroscopic equipment must be available in the operating room. We strongly recommend placement of a safety wire, even though some groups have demonstrated that URS can be performed without it (30,31). A safety wire prevents false passage in case of perforation, and ensures that it is possible to insert a double-J stent in difficult situations, helping to avoid more significant complications.

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

If dilatation is necessary, balloon and plastic dilators are available. If insertion of a flexible URS is difficult, prior rigid ureteroscopy can be helpful for optical dilatation. If ureteral access is not possible, the insertion of a double-J stent followed by URS after a delay of 7-14 days offers an appropriate alternative to dilatation.

Recommendation

	GR
Placement of a safety wire is recommended.	A*

** Upgraded based on panel consensus.*

5.6.2.2.5 Ureteral access sheaths
Hydrophilic-coated ureteral access sheaths, which are available in different calibres (usually with an inner diameter of 9 Ch or 12/13 Ch), can be inserted via a guide wire, with the tip placed in the proximal ureter.

The sheaths allow easy multiple accesses to the proximal ureter and the kidney, and significantly facilitate URS, particularly in patients with a large stone mass requiring multiple ureteral passes. This leads to improved stone-free rates and reduced time in the operating theatre (19,32-34).

Ureteral access sheaths also allow the continuous outflow of irrigation fluid, which helps to improve visual quality and to maintain a low-pressure system (35,36).

Ureteral access sheaths have gained wide acceptance and are used on a regular basis. This is despite an ongoing debate about their potential hazards, including an alleged increase in ureteral strictures, which has not yet been demonstrated (32).

5.6.2.2.6 Stone extraction
The aim of endourological intervention is to achieve complete stone removal, as ‘smash and go’ strategies leave patients with a higher risk of stone regrowth and post-operative complications (37).

Stones can be extracted by endoscopic forceps or baskets. Forceps allow the safe releasing of stone fragments if they should get stuck within the ureter, but extraction takes longer compared than when using baskets. Only baskets made of nitinol (nickel-titanium alloy) can be used for flexible URS (38-41).

Recommendations

	LE	GR
Stone extraction using a basket without endoscopic visualisation of the stone (blind basketing) should not be performed.	4	A*
Nitinol baskets preserve the tip deflection of flexible ureterorenoscopes, and the tipless design reduces the risk of mucosa injury.	3	B
Nitinol baskets are most suitable for use in flexible URS.		

** Upgraded based on panel consensus.*

Stones that cannot be extracted directly must first be disintegrated (*see* Section 6.4.2). If it is difficult to access stones in need of disintegration within the lower renal pole, it may help to displace the calculi into a more accessible calyx (42).

5.6.2.2.7 Intracorporal lithotripsy
Intracorporal lithotripsy is usually necessary prior to extraction of larger fragments. Various systems with different physical principles are available.

5.6.2.2.7.1 Electrohydraulic systems
Flexible electrohydraulic lithotripsy probes are available in different sizes for semi-rigid and flexible ureterorenoscopes. In general, if lasers are unavailable, electrohydraulic lithotripsy can be used to disintegrate all stones (even cystine or hard stones, such as calcium oxalate monohydrate), even though there is an increased risk of damage to the surrounding tissues (43-45).

5.6.2.2.7.2 Pneumatic systems
Pneumatic or ballistic lithotripters are often used with 2.4 Ch probes for safe rigid ureterorenoscopy and have achieved rates of disintegration > 90% (46-48). Proximal stone migration is a common occurrence (49,50), but can be avoided with the use of a basket or special tools (6,51-55).

5.6.2.2.7.3 Ultrasound
Ultrasound can be used alone or in combination with pneumatic lithotripsy. However, ultrasound can only be used in larger scopes (56,57) and not in flexible scopes.

5.6.2.2.7.4 Laser systems
The most efficient laser system for the treatment of stones in all locations and of all mineral compositions is the Ho:YAG system (58-69) (LE: 3), which has become the gold standard for both rigid and flexible URS (64). Compared with the neodymium: yttrium-aluminium-garnet laser, its rapid absorption in water (3 mm) and minimal tissue penetration (0.4 mm) reduces thermal damage and improves the safety profile (68). It is necessary to achieve contact with the surface of the stone. Other laser systems are currently being evaluated, but have yet to prove superior in efficacy or safety.

Recommendation

	GR
Ho:YAG laser lithotripsy is the preferred method when carrying out URS.	B

5.6.2.2.8 Stenting prior to and after URS
Routine stenting is no longer necessary prior to URS. However, pre-stenting facilitates the ureteroscopic management of stones, improves the stone-free rate, and reduces the complication rate (70-72).

Most urologists routinely insert a double-J stent following URS (73), although several randomised prospective trials have found that routine stenting after uncomplicated URS (complete stone removal) is no longer necessary (70,74-84). It should be noted that ureteric stenting is associated with lower urinary tract symptoms, as well as pain, which even if only transitory in nature can reduce the quality of life (85).

Stents should be inserted in patients who are at increased risk of complications (e.g. residual fragments, bleeding, perforation, urinary tract infections or pregnancy). A stent should also be inserted in all doubtful cases in order to avoid stressful emergency situations.

There is no evidence in the literature on the ideal duration of a stent. In practice, most urologists seem to favour 1-2 weeks after URS (70,73). Patients should be followed up with a plain abdominal film (kidney-ureter-bladder), CT or ultrasound.

Recent evidence suggests that alpha-blockers, such as tamsulosin, reduce the morbidity of ureteral stents and therefore increase tolerability (86-89).

Recommendation

	LE	GR
Stenting is optional after uncomplicated URS.	1a	A

5.6.2.2.9 Complications

The literature shows that the overall rate of complications after URS is 9-25% (1,9,32,34,65,90) (Table 14). Most complications are minor and do not require intervention. Ureteral strictures used to be greatly feared, but nowadays are rare (< 1%). Similarly, ureteral avulsion, which is the most significant complication of URS, has also become rare (0.11%) (9). Previous perforations are the most important risk factor for complications.

Table 14: Complications of URS*

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

**From Geavlete,* et al. *(9).*

5.6.2.2.10 References

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5.7 Open and laparoscopic surgery for removal of renal stones

*5.7.1 **Open surgery***

Advances in ESWL and endourological surgery (i.e. URS and PNL) have resulted in a significant decrease in the indications for open stone surgery. Often, open stone surgery has become a second- or third-line treatment option. Centres with the equipment, expertise and experience in surgical treatment of renal tract stones report that open surgery is needed in 1.0-5.4% of cases (1-5). The incidence of open stone surgery has been reported to be around 1.5% of all stone removal interventions in developed countries, however in developing countries this has dropped from as high as 26% to 3.5 % in recent years (3,5).

Today, an open surgical approach is needed in most cases of difficult stone situations, which supports the importance of maintaining proficiency, skills and expertise in open renal and ureteral surgical techniques for all urologists (6-10) (Table 15).

Because many hospitals now have only limited experience with open stone surgery it may be advisable to send patients to a centre experienced in the use of special open surgical techniques, which are rarely performed today, such as extended pyelolithotomy, pyelonephrolithotomy, anatrophic nephrolithotomy, multiple radial nephrotomy, partial nephrectomy and renal surgery under hypothermia (10).

Recently, intra-operative B-mode scanning and Doppler sonography (11,12) have been used to identify avascular areas in the renal parenchyma that are close to the stone or dilated calices. This allows the removal of large staghorn stones by multiple small radial nephrotomies, without the loss of kidney function.

The efficacy of open surgery over less invasive therapy, in terms of stone-free rates, is based on historical data, but no comparative studies are available (13-16).

5.7.1.1 Indications for open surgery

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

Table 15: Indications for open surgery

Indications
• Complex stone burden
• Treatment failure of ESWL and/or PNL, or failed ureteroscopic procedure
• Intrarenal anatomical abnormalities: infundibular stenosis, stone in the calyceal diverticulum (particularly in an anterior calyx), obstruction of the ureteropelvic junction, stricture
• Morbid obesity
• Skeletal deformity, contractures and fixed deformities of hips and legs
• Co-morbid medical disease
• Concomitant open surgery
• Non-functioning lower pole (partial nephrectomy), non-functioning kidney (nephrectomy)
• Patient choice following failed minimally invasive procedures; the patient may prefer a single procedure and avoid the risk of needing more than one PNL procedure
• Stone in an ectopic kidney where percutaneous access and ESWL may be difficult or impossible
• For the paediatric population, the same considerations apply as for adults

*5.7.2 **Laparoscopic surgery***

The indications for open surgery for renal stones have decreased significantly over the past 20 years. Laparoscopic urological surgery has increasingly begun to replace open surgery as a result of accumulated surgical experience.

Laparoscopic surgery is now being used to remove both renal and ureteric stones in certain situations, including complex stone burden, failed previous ESWL and/or endourological procedures, anatomical abnormalities or morbid obesity and in case of planned nephrectomy of a stone-containing non-functioning kidney. In other words, laparoscopy is a method that reproduces the steps of open surgery and may be indicated as an alternative in cases of therapeutic failure using less invasive methods.

Laparoscopy is associated with lower post-operative morbidity, shorter hospital stay and time to convalescence, and better cosmetic results with comparably good functional results (17-24).

Moreover, laparoscopic surgery is effective for complex renal stones and allows adjunctive procedures, such as dismembered or non-dismembered pyeloplasty, ablation of calyceal diverticula, partial nephrectomy, heminephrectomy and nephrectomy. It can also be an alternative to PNL in the absence of availability (developing countries) or PNL failure and as an adjunct to PNL, especially when access proves difficult (ectopic kidneys).

Regarding the management of ureteral calculi, ESWL, URS, and percutaneous antegrade URS is successful in the vast majority of stone cases. In particular situations, or in cases of simultaneous open surgery for another purpose, open surgical ureterolithotomy might rarely be considered. For most cases with very large, impacted, and/or multiple ureteral stones in which ESWL and URS have either failed or are unlikely to succeed, laparoscopic ureterolithotomy is a better alternative than open surgery. However, this is relatively easy, with stone-free rates up to 100% provided expertise is available in laparoscopic techniques (25-28). Both retroperitoneal and transperitoneal laparoscopic access to all portions of the ureter have been reported.

Laparoscopic ureterolithotomy in the distal ureter is somewhat less successful than in the middle and proximal ureter, but the size of the stone does not appear to influence outcome. Although highly effective, laparoscopic ureterolithotomy is not a first-line therapy in most cases because of its invasiveness, longer recovery time, and the greater risk of associated complications compared to ESWL and URS (25-28). However, it may provide an alternative procedure for primary or salvage treatment in very difficult situations, e.g. very large, impacted stones and/or multiple ureteral stones, or in cases of concurrent conditions requiring surgery. Laparoscopic ureterolithotomy is a less invasive alternative to open surgery in this setting.

Comparative series indicate that open surgical ureterolithotomy can be replaced by laparoscopic ureterolithotomy in most situations (15,16). Patients with impacted ureteric stones have been treated successfully using laparoscopic ureterolithotomy, with less than 2% being converted to open surgery.

Laparosopic ureterolitothomy can be carried out using either retroperitoneal or transperitoneal access. Laparoscopic ureterolithotomy should be considered when other non-invasive or low-invasive procedures have failed (28-32) (Table 16).

5.7.2.1 Indications for laparoscopic stone surgery (table 16)

Indications for laparoscopic kidney-stone surgery include: • Complex stone burden • Failed previous ESWL and/or endourological procedures • Anatomical abnormalities • Morbid obesity • Nephrectomy in case of non-functioning kidney
Indications for laparoscopic ureteral stone surgery include: • Large, impacted stones • Multiple ureteral stones • In cases of concurrent conditions requiring surgery • When other non-invasive or low-invasive procedures have failed

Recommendations

	LE	GR
Laparoscopic or open surgical stone removal may be considered in rare cases where ESWL, URS, and percutaneous URS fail or are unlikely to be successful.	4	C
When expertise is available, laparoscopic surgery should be the preferred option before proceeding to open surgery. An exception will be complex renal stone burden and/or stone location.	4	C

Skolarikos, et al. have tried to identify the level of the evidence and grade of recommendation, according to the evidence-based medicine criteria, in studies supporting the laparoscopic approach to stone extraction. The highest level of evidence (2a) was found for laparoscopic ureterolithotomy.

With its technically feasible and minimally invasive nature, with lower postoperative morbidity, this approach is superior to open ureterolithotomy in selected cases. It is mostly recommended (GR: B) for large impacted stones or when endoscopic ureterolithotripsy or shock wave stone disintegration have failed.

Laparoscopic pyelolithotomy has been found to be feasible but rarely indicated in the present era (LE: 3; GR: B). Laparoscopic nephrolithotomy has been indicated to remove a stone from an anterior diverticulum or when PNL or flexible ureteroscopy have failed (LE: 3) (33).

Based on the published data so far, laparoscopy, another minimally invasive treatment, is gaining place in the treatment of urinary stones, mainly replacing open surgery. The laparoscopic approach is associated with a lower post-operative morbidity, shorter hospital stay and time to convalescence, and better cosmetic results with comparably good functional results.

5.7.3 ***References***

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6. INDICATION FOR ACTIVE STONE REMOVAL AND SELECTION OF PROCEDURE

Although kidney stones might be asymptomatic, ureteral stones cause acute renal colic in most cases. The decision upon active treatment of upper urinary tract calculi is based on general aspects such as stone composition, stone size, and symptoms.

6.1 Indication for active stone removal of ureteral stones (1,2)

Stones with low likelihood of spontaneous passage
- persistent pain in spite of adequate pain medication;
- persistent obstruction;
- renal insufficiency (renal failure, bilateral obstruction, single kidney).

6.2 Indication for active stone removal of kidney stones (2)

- stone growth;
- stones in high-risk patients for stone formation;
- obstruction caused by stones;
- infection;
- symptomatic stones (e.g. pain, haematuria);
- stones > 15 mm;
- stones < 15 mm if observation is not the option of choice;
- patient preference (medical and social situation);
- > 2-3 years persistent stones;

The suspected stone composition might influence the choice of treatment modality.

6.2.1 Natural history of caliceal stones

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

Statement	LE
Although the question of whether these stones should be treated is still unanswered, stone growth, formation of *de novo* obstruction, associated infection and acute and/or chronic pain are indications for treatment of such stones (1-3).	3

Glowacki, *et al*. have reported that the risk of a symptomatic episode or need for intervention was approximately 10% per year, with a cumulative 5-year event probability of 48.5% (4). In a recent retrospective study, 77% of asymptomatic patients with renal stones experienced disease progression, with 26% requiring surgical intervention (5).

In a retrospective study, Hubner and Porpaczy have reported that infection developed in 68% of patients with asymptomatic caliceal stones, and 45% had an increase in stone size after 7.4 years follow-up. They have suggested that 83% of caliceal calculi require intervention within the first 5 years of diagnosis (6). Finally, in their original study, Inci, *et al*. have included specifically lower pole caliceal stones, and they have observed that no patient required intervention during 24 months follow-up. In addition, an increase in stone size without any need for intervention was observed in eight of 27 renal units (29.6%). When the follow-up period was increased to 52.3 months, nine (33.3%) patients had an increase in stone size, but, only three (11%) patients required intervention (7).

However, in a prospective randomised controlled trial with 2.2 years clinical follow-up, Keeley, *et al.* have reported no significant difference between ESWL and observation when they compared asymptomatic caliceal stones < 15 mm in terms of stone-free rate, symptoms, requirement for additional treatment, quality of life, renal function, or hospital admission rate (10). Thus, although some authors have recommended prophylactic treatment for these stones to prevent renal colic, haematuria, infection or stone growth, conflicting data have been reported in the literature on this subject (4,6,11).

Statement	LE
ESWL has been increasingly used for the treatment of caliceal stones to reduce the risk of complications and the need for invasive procedures.	4

Excellent stone-free rates as well as pain relief have been reported after the removal of small caliceal stones by ESWL, percutaneous nephrolithotomy (PNL), or URS, which indicates the need for removal of a symptomatic caliceal stone (12-14).

Recommendation

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

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6.3 General recommendations and precautions for stone removal

*6.3.1 **Infections***

Urinary 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 active intervention for stone removal.

Recommendation

	GR
Urine culture is mandatory before any treatment is planned.	A*

**Upgraded following panel consensus.*

*6.3.2 **Anticoagulation and stone treatment***

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

- ESWL;
- PNL;
- Percutaneous nephrostomy;
- Open surgery (4-6).

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

Recommendations

	LE	GR
Salicylates should be stopped before planned stone removal.	3	B
If intervention for stone removal is essential and salicylate therapy should not be interrupted, retrograde URS is the preferred treatment of choice.		

6.3.3 *Obesity*

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

Statement	LE
In case of severe obesity, URS is the more promising therapeutic option compared to ESWL.	2b

6.3.4 *Hard stones*

Stones composed of brushite or calcium oxalate monohydrate are particularly hard. Percutaneous removal of these stones might be appropriate, particularly if they are large. Chemolytic treatment of brushite stone fragments is possible.

Cystine stones either respond well to ESWL or respond poorly (10). PNL or retrograde intrarenal surgery (RIRS) are the alternatives for efficient removal of large ESWL-resistant stones.

Recommendation

	LE	GR
Consider the stone composition before deciding on the type of stone removal therapy (former stone analysis of the patient, HU in unenhanced CT). Stones with medium density > 1,000 HU on NCCT are less likely to be disintegrated by ESWL.	2a	B

6.3.5 *Radiolucent stones*

Uric acid concrements can be localised using either US or intravenous or retrograde administration of contrast medium. Only uric acid stones, but not sodium urate or ammonium urate stones, can be dissolved by oral chemolysis. Differentiation is done by urinary pH (see Oral chemolysis, section 5.4.2).

Postoperative monitoring of radiolucent stones during chemolysis or after ESWL is the domain of ultrasound, however repeat NCCT might be necessary.

Recommendation

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

** Upgraded based on panel consensus.*

6.3.6 *Steinstrasse*

Steinstrasse is an accumulation of stone fragments or stone gravel in the ureter, which does not pass within a reasonable period of time, and interferes with the passage of urine (11,12). Steinstrasse occurs in 4-7% cases of ESWL (13-15), and the major factor of formation of steinstrasse is stone size (14).

Insertion of a ureteral stent before ESWL prevents formation of steinstrasse (16).

Steinstrasse can cause no symptoms or patients present with flank pain, fever, nausea and vomiting or bladder irritation. A major problem of steinstrasse is obstruction of the ureter, which can be silent in 23% of cases (14) and lead to kidney failure (17). Anuria occurs in 5% of cases of steinstrasse in treatment of solitary kidneys (14). When steinstrasse is not symptomatic, conservative treatment is an initial option, depending on patient preference and willingness to comply with a close surveillance schedule. Medical expulsion therapy significantly increases stone expulsion rate and reduces the need for endoscopic intervention (18,19).

Statement	LE
Medical expulsion therapy increases stone expulsion rate of steinstrasse (16).	1b

In case spontaneous passage is unlikely, further treatment of steinstrasse is indicated.

Amongst the options, ESWL treatment is indicated in asymptomatic or symptomatic cases, with no evidence of urinary tract infection (UTI), when large stone fragments are present (19). There is an 80% chance of clearance of the steinstrasse (13).

Ureteroscopy is equally effective as ESWL for treatment of steinstrasse (13,20,21).

Placement of a percutaneous nephrostomy tube is indicated in cases of symptomatic ureteric obstruction with/without UTI, and it is effective in 83% of cases (13).

Table 17: Treatment of steinstrasse

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

Numbers 1,2, and 3 indicate first, second and third choice.
ESWL = extracopereal shock wave lithotripsy; MET = medical expulsion therapy; PCN = percutaneous nephrostomy; URS = ureteronoscopy.

Recommendation

	LE	GR
PCN is indicated in the presence of a confirmed UTI/fever associated with steinstrasse.	4	C
Performance of ESWL is indicated for treatment of steinstrasse when larger stone fragments are present.	4	C
Performance of ureteroscopy is indicated for treatment of symptomatic steinstrasse and for treatment failure.	4	C

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6.4 Selection of procedure for active removal of kidney stones

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

ESWL, PNL or flexible URS are available treatment modalities for renal calculi. Although the efficacy of PNL is hardly affected by stone size, the stone-free rates (SFRs) after ESWL or URS are negative proportional to the stone size (1-4). ESWL achieves excellent SFRs for stones up to 20 mm at all intrarenal locations, except for the lower pole (see below) (3,5). Therefore ESWL remains the first method of choice for such stones. Larger stones > 20 mm should be treated by PNL primarily, because ESWL often requires multiple treatments, and has the risk of ureteral obstruction (colic, steinstrasse) with the need for adjunctive procedures (Figure 1) (6). Based on the available literature, flexible URS cannot be recommended as first-line treatment, especially for stones > 15 mm, for which SFR is decreasing, and staged procedures have become necessary (7,8).

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

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

The following factors are supposed to impair successful stone treatment by ESWL: steep infundibular-pelvic angle, long calyx, and a narrow infundibulum (Table 18) (7-13). Further anatomical parameters cannot yet be established. The value of supportive measures as inversion, vibration or hydration remains under discussion (7,8).

Table 18: Unfavourable factors for ESWL success (9-15)

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

As the results of ESWL for the lower pole are often disappointing, PNL is recommended for stone sizes > 15 mm. If negative predictors for ESWL success are present, PNL might be a reasonable alternative even for smaller calculi.

Based on the available literature, flexible URS seems to have comparable efficacy as ESWL (5,6). However, clinical experience with last generation ureterorenoscopes suggests an advantage of URS over ESWL, by paying the price of higher invasiveness.

Recommendations

	GR
ESWL remains the method of first choice for stones < 2 cm within the renal pelvis and upper or middle calices. Larger stones should be treated by PNL.	
Flexible URS cannot be recommended as first-line treatment, especially for stones > 1.5 cm for which SFR is decreasing and staged procedures become necessary.	
For the lower pole, PNL is recommended even for stones > 1.5 cm as the efficacy of ESWL is limited.	

Figure 1: Treatment algorithm for renal calculi within the renal pelvis or upper and middle calices

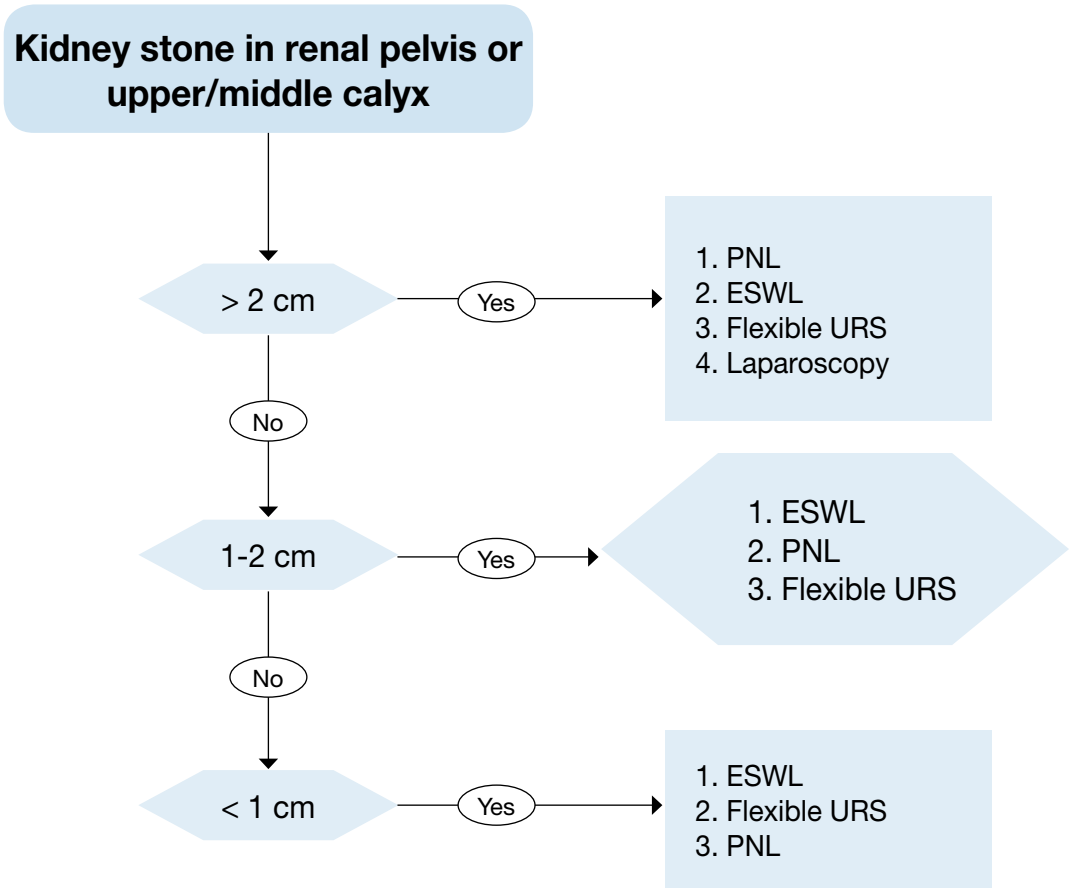
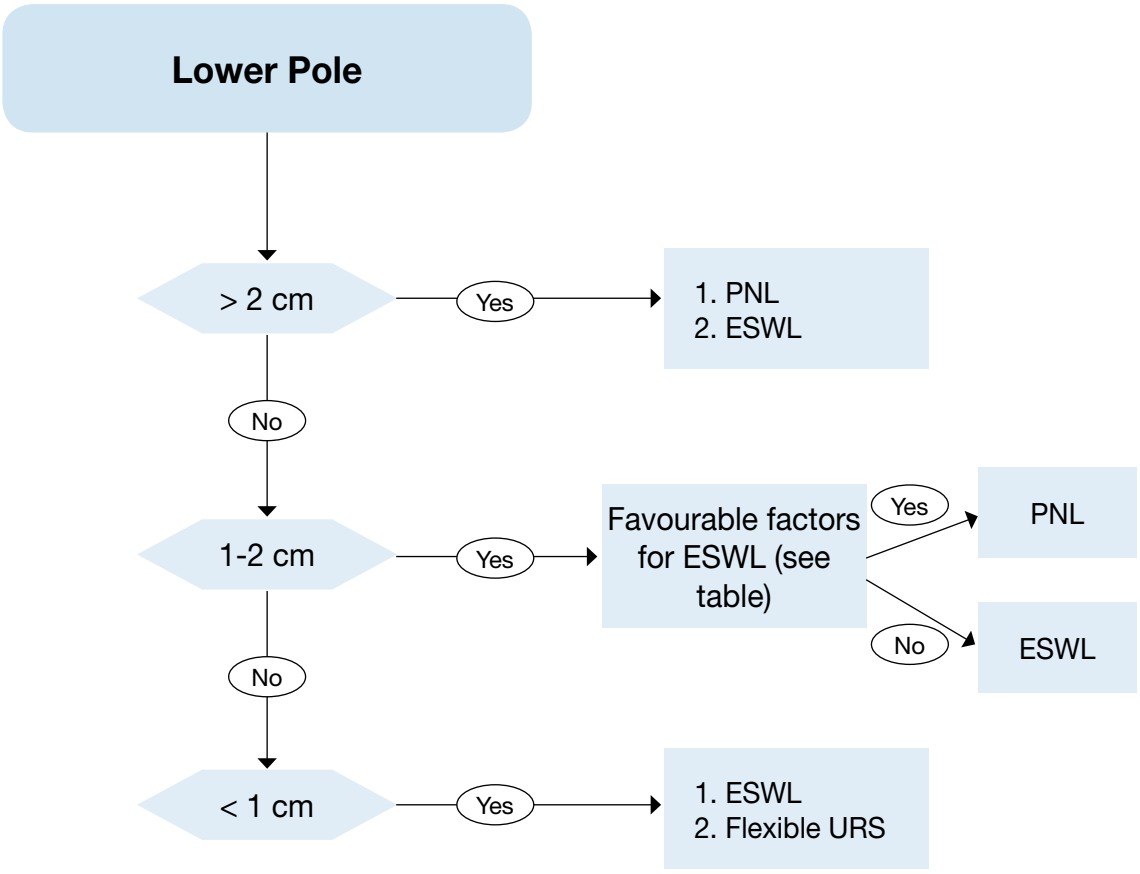


Figure 2: Treatment algorithm for lower pole calculi



6.4.3 ***References***

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6.5 Selection of procedure for active stone removal of ureteral stones

*6.5.1 **Methodology***

Stone free rates were analysed for a number of variant methods of performing ESWL and URS. If the study reported the SFR after all primary procedures, that number was used. If not, and the study reported the SFR after the first procedure, then that number was used. The intention of the Panel was to provide an estimate of the number of primary procedures and the SFR after those procedures. There is a lack of uniformity in the literature in reporting the time to stone-free status, thereby limiting the ability to comment on the timing of this parameter.

*6.5.2 **ESWL and ureteroscopy***

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

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

6.5.2.1 Stone free rates (SFRs)

The results of the meta-analysis of SFRs are presented for the overall group in Table 19. The results are presented as medians of the posterior distribution (best central estimate) with 95% Bayesian Credible Intervals (CIs). This represents an update of the EAU/AUA collaborative guidelines project (1). Outcomes show no significant changes.

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

	ESWL		URS	
	Number of patients	**SFR/95% CI**	**Number of patients**	**SFR/95% CI**
Distal ureter	7217	74% (73-75)	10372	93% (93-94)
< 10 mm	1684	86% (80-91)	2013	97% (96-98)
> 10 mm	966	74% (57-87)	668	93% (91-95)
Mid ureter	1697	73% (71-75)	1140	87% (85-89)
< 10 mm	44	84% (65-95)	116	93% (88-98)
> 10 mm	15	76% (36-97)	110	79% (71-87)
Proximal ureter	6682	82% (81-83)	2448	82% (81-84)
< 10 mm	967	89% (87-91)	318	84% (80-88)
> 10 mm	481	70% (66-74)	338	81% (77-85)

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

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

6.5.2.2 Complications

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

Patients should be informed that URS is associated with a better chance of achieving stone-free status with a single procedure, but has higher complication rates. See section 5.5.4 (Complications of ESWL), and section 5.6.2.2.9 (Complications of URS).

6.5.3 Percutaneous antegrade Ureteroscopy

Percutaneous antegrade removal of ureteral stones is a consideration in selected cases, for example, for the treatment of very large (> 15 mm diameter) impacted stones in the proximal ureter between the ureteropelvic junction and the lower border of the fourth lumbar vertebra (7-10). In these cases with SFRs between 85% and 100%, its superiority to standard techniques has been evaluated in three prospective randomised (10-12) and two prospective studies (7,13). The complication rate was low, acceptable, and not specifically different from any other percutaneous procedure. However, percutaneous antegrade removal of ureteral stones was associated with longer operative times, longer hospital stay, and a longer interval to return to normal activities (10).

Recommendation

	GR
Percutaneous antegrade removal of ureteral stones is an alternative when **ESWL** is not indicated or has failed, and when the upper urinary tract is not amenable to retrograde URS (13-15).	A
A patient must be informed about the existing active treatment modalities, including the relative benefits and risks associated with each modality.	A

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

	First choice	Second choice
Proximal ureter < 10 mm	ESWL	URS
Proximal ureter > 10 mm	URS (retrograde or antegrade) or ESWL	
Distal ureter < 10 mm	URS or ESWL	
Distal ureter > 10 mm	URS	ESWL

**Upgraded following panel consensus.*

Recommendation

	GR
Treatment choices should be based on the size and location of the stone and available equipment for stone removal.	A

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

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

*6.5.5 **References***

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7. RESIDUAL STONES

7.1 Clinical Evidence

Residual fragments are commonly seen after both, ESWL and sometimes after intracorporeal lithotripsy, and most frequently are present in the lower calix.
Reports on residual fragments vary between institutions, depending on which imaging method has been used. However, the clinical value of being able to detect very small concretions remains debatable.

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

- new stones from such nidi (heterogeneous nucleation);
- persistent UTI;
- dislocation of fragments with/without obstruction and symptoms (1-5).

Recommendation

	LE	GR
Identification of biochemical risk factors and appropriate stone prevention is particularly indicated in patients with residual fragments or stones (35).	1b	A
Patients with residual fragments or stones should be followed up regularly to monitor the course of their disease.	4	C

The risk of recurrence in patients with residual fragments after treatment of infection stones is higher than for other stone compositions. In a 2.2-year follow-up of 53 patients, 78% with stone fragments at 3 months after treatment experienced stone progression. The SFR was 20%, and the remaining 2% had stable disease (6). Out of all stone compositions, 21-59% of patients with residual stones require treatment within 5 years. Fragments > 5 mm have greater probability for necessary intervention than smaller ones (2,3,5,7).

Table 21: Recommendations for the treatment of residual fragments (LE: 4; GR: C)

Residual fragments, stones (largest diameter)	Symptomatic residuals	Asymptomatic residuals
< 4-5 mm	Stone removal	Reasonable follow-up
> 6-7 mm	Stone removal	

7.2 Therapy

To avoid residual fragments or facilitate further clearance, medical and physical adjunctive therapy can be suggested.

Recommendations

	LE	GR
After ESWL and URS, adjunctive treatment with tamsulosin could improve fragment clearance and reduce the probability of residual stones (see Chapter 7).	1a	A
For well-disintegrated stone material residing in the lower calix, inversion therapy during high diuresis and mechanical percussion facilitate stone clearance (8).	1a	B

The indication for active stone removal and selection of the procedure is based on the same criteria as for primary stone treatment (see Chapter 6) and also includes repeat ESWL (9).

If there is no necessity for intervention, medical therapy according stone analysis, risk group of the patient, and metabolic evaluation might be helpful to prevent regrowth of residual fragments (10-12).

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8. MANAGEMENT OF URINARY STONES AND RELATED PROBLEMS DURING PREGNANCY

Although it is not a common pathology, urolithiasis during pregnancy, is a challenging condition from a diagnostic as well as therapeutic point of view. In most cases, the disease becomes symptomatic in the second or third trimester (1-4).

8.1 Diagnostic options

Diagnostic options are limited in pregnant women due to the risk of foetal radiation exposure for possible teratogenesis, carcinogenesis, and mutagenesis. The risk depends crucially on the gestational age and the amount of radiation delivered. Thus, clinicians must weigh carefully the risk-benefit ratio of an examination that involves radiation during the first trimester of pregnancy (1,2,5,6).

Currently, when evaluating pregnant patients suspected of renal colic, US (using change in resistive index and transvaginal ultrasound when necessary) has become the primary radiological diagnostic tool, with a limited excretory urogram only necessary in complicated cases. However, poor sound transmission through gas and bone limiting the quality of the examination and the operator-dependent nature of the modality are limitations of this technique in pregnant and non-pregnant patients. Similarly, it can be difficult to differentiate the physiological dilation of pregnancy from ureteral obstruction, and US is therefore of limited value in cases of acute obstruction (7,8).

Transvaginal/endoluminal US might be particularly important in the evaluation of possible stones at the vesicoureteral junction. An endoluminal ultrasound probe can help to elucidate the level of obstruction and can also be useful to facilitate subsequent endoscopic ureteral stent placement.

In complicated cases, a limited excretory urogram may become necessary. A typical regimen includes a preliminary plain radiograph (KUB) and two films, 15 and 60 min after contrast administration. NCCT results in an even higher dose of radiation exposure.

Among the other modalities used, magnetic resonance urography (MRU) can be used to evaluate the urinary tract, thus avoiding ionising radiation and administration of iodinated contrast medium, which has important considerations for pregnant patients. Magnetic resonance imaging can define the level of obstruction, and a stone can be seen as a filling defect. However, these findings are non-specific. In addition, there is a paucity of experience with using this imaging modality during pregnancy (9-11).

Statements	LE	GR
Ultrasonography is the method of choice in the practical and safe evaluation of a pregnant women.	1a	A
In symptomatic patients with suspicion of ureteral stones during pregnancy, limited IVU, MRU, or isotope renography is a useful diagnostic method.		

8.2 Management

Management of these patients can pose significant multiple challenges to the patient, obstetrician and urologist, but fortunately, many symptomatic stones (70-80%) pass spontaneously. Conservative management with appropriate analgesia can result in spontaneous passage of most stones in the majority of these cases.

If spontaneous passage does not occur, or if complications develop (commonly the induction of premature labour), among the other established treatment options, placement of an internal stent or percutaneous nephrostomy tube, or ureteroscopy is an alternative for treatment (12-19). However, the temporising therapies (e.g. ureteral stenting or percutaneous nephrostomy), are often associated with poor patient tolerance. Additionally, the temporising approach typically requires multiple exchanges of stents or nephrostomy tubes during the rest period of pregnancy, due to the potential for rapid encrustation of these devices (20-23).

Improvements in diagnostic technology, as well as experience in endoscopic instrumentation have made the endoscopic approach feasible and safe for diagnosis and treatment of ureteral stones. Nevertheless, one cannot overemphasise the necessity for the greatest possible care during URS, which should be performed only in centres with sufficient experience (20,22-25). When intracorporeal lithotripsy is necessary during ureteroscopic treatment of calculi in pregnant patients, the holmium laser has the advantage of minimal tissue penetration, thereby theoretically limiting risk of foetal injury.

Although percutaneous stone removal in the early stages of pregnancy has been reported in a limited number of studies (21), ESWL is still experimental, and pregnancy remains an absolute contraindication.

In conclusion, urolithiasis in pregnancy remains a diagnostic and therapeutic challenge. Although sonography is the method of choice for the practical and safe evaluation of pregnant women, in case of failure to reveal a calculus in a symptomatic patient with hydronephrosis, then limited IVU, isotope renography or MRU is useful in delineating the level and grade of obstruction. If these modalities are not available, insertion of a stent or nephrostomy tube is justified, because it relieves symptoms immediately.

Depending on the stage of pregnancy, conservative management with bed rest, hydration, and analgesia results in spontaneous passage of the stone in the majority of patients. If conservative treatment fails, temporary urinary diversion with percutaneous nephrostomy or an internal stent might be appropriate. Among the indications for a more aggressive approach in pregnant patients, failure of expectant therapy, urosepsis, obstruction of a solitary kidney, and renal failure can be listed.

With careful regard for the mother and foetus, the use of well-established endourological techniques maximises the possibility of an excellent, stone-free outcome.

Statements	**LE**
If intervention becomes necessary, placement of a internal stent, percutaneous nephrostomy, or ureteroscopy are treatment options.	**3**
Regular follow-up until final stone removal is necessary due to higher incrustation tendency of stents during pregnancy.	

Recommendation

	GR
Following the establishment of the correct diagnosis, conservative management should be the first-line treatment for all non-complicated cases of urolithiasis in pregnancy (except those who have clinical indications for intervention).	A

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9. MANAGEMENT OF STONE PROBLEMS IN CHILDREN

In addition to the global increase in the rates of urolithiasis in developed countries, there has been a shift in the age group experiencing a first stone episode (1-3). More than 1% of all urinary stones have been registered 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 Far East); in other regions the rates are similar to those observed in developed countries (4-11).

9.1 Investigations

Paediatric patients with urinary stones are considered high-risk patients for developing recurrent stones and therefore standard diagnostic procedures for high-risk patients apply (see section 2.6 and Chapter 11).

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

Recommendation

	GR
In all paediatric patients, a complete metabolic stone evaluation based on stone analysis (if possible) is necessary.	A

*9.1.1 **Imaging***

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

9.1.1.1 Ultrasound

Ultrasound is the most popular and practical imaging technique (13). For paediatric patients, its advantages are absence of irradiation and that there is no need for anaesthesia. US can be used to obtain information about the presence, size and location of a stone, and the grade of dilatation and obstruction. It also indicates signs of abnormalities that facilitate the formation of stones.

Colour Doppler US shows differences in the ureteric jet (14) and in the resistive index of the arciform arteries of both kidneys, which are indicative of the grade of obstruction (15). Nevertheless, US fails to identify stones in > 40% of paediatric patients (16-19) (LE: 4), and provides no information about renal function. Ultrasound is part of the metaphylactic work-up in these cases.

Statement

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

9.1.1.2 Plain films (KUB)

KUB can help to identify stones and their radio-opacity, as well as facilitate follow-up.

9.1.1.3 IVU

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

9.1.1.4 Helical CT

Recently developed CT protocols might further reduce exposure to radiation (22). However, the radiation dose and the extent of information about renal function must be considered when using non-enhanced helical CT. Non-enhanced helical CT is a well-established procedure for diagnosing urolithiasis in adults with a sensitivity of 94-100% and a specificity of 92-100% (23).

In paediatric patients, only 5% of stones escape detection by non-enhanced helical CT (14,23,24). Sedation or anaesthesia is rarely needed when modern high-speed CT apparatus is used (11).

9.1.1.5 MRU

Magnetic resonance urography cannot be used to detect urinary stones. However, it might provide detailed information about the anatomy of the urinary collecting system, the location of an obstruction or stenosis in the ureter, and the morphology of renal parenchyma (25).

9.1.1.6 Nuclear imaging

99mTc-dimercaptosuccinyl acid scanning provides information about cortical abnormalities such as scarring, but does not help in the primary diagnosis of urolithiasis. A diuretic renogram with injection of a radiotracer (MAG3 or DPTA) (Mercapto acetyltriglycine or Diethylene triamine pentaacetic acid) and furosemide can be used to demonstrate renal function, identify obstruction in the kidney after injection of furosemide, and indicate the anatomical level of the obstruction (11,14).

9.2 Stone removal

Several factors must be considered when selecting the procedure to be used in children. Compared to adults, children pass fragments more rapidly after ESWL and all stones obtained should be evaluated for further metaphylactic measures (26). For endourological procedures, the smaller organ size in children must be considered when selecting instruments for PNL or URS. To eliminate radiation exposure, US can be used for localisation during ESWL or endourologic procedures. Anticipation of the expected stone composition wherever possible is helpful for selection of the appropriate procedure for stone removal (cystine stones are more resistant to ESWL).

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

*9.2.1 **MET in children***

MET in children has already been discussed in section 5.3.2.6. Although the use of nifedipine or α-blockers is very common in adults, there is insufficient data to demonstrate their safety and efficacy in paediatric patients (27).

*9.2.2 **Interventional stone removal in children***

In paediatric patients, ESWL and endourologic procedures are effective for stone removal.

*9.2.3 **ESWL***

Despite the increasing application of PNL, and the development of smaller-diameter flexible ureteroscopes and ancillary instruments, ESWL is still the least invasive procedure for the management of most stones in children (28-36).

Stone free rates of 67-93% in short-term and 57- 92% in long-term follow-up studies have been reported. In children, as compared to adults, more effective disintegration of even larger stones, together with swifter and uncomplicated discharge of larger fragments, can be achieved with ESWL (32-34). Stones located in calices, as well as in abnormal kidneys, and larger stones, are more difficult to disintegrate and clear. Additionally, the likelihood of urinary obstruction is higher in such cases, and children should be followed closely for the prolonged risk of urinary tract obstruction. Depending on the stone-related factors, the retreatment rate ranges from 13.9% to 53.9%, and the need for ancillary procedures and/or additional interventions ranges from 7% to 33% (32-34,36).

The need for general anaesthesia during ESWL depends on the patient's age and the lithotripter used. General or dissociative anaesthesia is administered in the majority of smaller children (< 10 years of age), to avoid patient and stone motion and the need for repeated repositioning (32,36). However, with the use of modern lithotriptors, intravenous sedation or patient-controlled analgesia has been successfully employed in select cooperative older children (37) (LE: 2b). Additionally, theoretical concerns have been raised regarding the safety and bioeffects that ESWL might have in children on the immature, growing kidney and surrounding organs. However, during short- and long-term follow-up, no irreversible functional or morphological side effects of high-energy shockwaves have been demonstrated. In addition, when the potential deterioration of renal function is taken into account (although it is transient), restriction of the number of shockwaves and the energy used during each treatment session will help to protect the kidneys (38-41).

Compared to adults, children pass stone fragments easily, and the need for a stent is rare. If the stone burden is large enough to require a ureteral stent, alternative procedures should be considered. Although internal stents are seldom needed following ESWL of upper tract stones, ureteral pre-stenting appeared to have decreased the SFR after initial treatment (28,30-32).

Statements	LE
For paediatric patients, the indications for ESWL are similar to those in adults, however they pass fragments more easily.	3
Children with renal stones with a diameter up to 20 mm (~300 mm^2) are ideal for this form of stone removal.	1b

*9.2.4 **Endourological procedures***

The improvement of intracorporeal lithotripsy devices and the development of smaller instruments facilitate PNL and URS in children.

9.2.4.1 Percutaneous nephrolithotripsy (PNL)

Preoperative evaluation and indications for PNL in children are similar to those in adults. Although this approach is performed as monotherapy in the majority of cases, it can also be used as an adjunctive procedure. With the availability of appropriate-size instruments and the use of ultrasound guidance, age is not a limiting factor for when the procedure can now be performed safely in experienced hands, with less radiation exposure even for larger and complex stones (42-46). The SFRs are reported to be between 68% and 100% after a single session. These rates increase with adjunctive measures, such as second-look PNL, ESWL and URS (42,43).

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

Recommendation

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

9.2.4.2 Ureteroscopy

Although acceptable success rates have made ESWL a favourable first-line treatment for most proximal ureteral stones; currently, ESWL is unlikely to be successful for the treatment of stones with a diameter > 10 mm, or for impacted stones, calcium oxalate monohydrate and cystine stones, or stones in children with unfavourable anatomy and in whom localisation difficulties exist. Intervention is required for large, as well as for impacted stones. The success rate of ESWL decreases as the stone passes to the more distal parts of the ureter. Overall SFRs have ranged from 80% to 97% in different series, and the success rates for proximal and distal ureteral stones from 75% to 100%, respectively (47-50). At present, ureteroscopy can be used for diagnostic and/or therapeutic purposes, and with the clinical introduction of fine, smaller calibre instruments, this modality has become the treatment of choice in middle and distal ureteric stones in children (48-50).

Different lithotripsy techniques, including ultrasonic, pneumatic and laser lithotripsy, have all been shown to be safe and effective. As a result of the smaller size of the probes, laser energy is easier to use in smaller instruments and is more useful for paediatric cases (53,54) (See section 5.6.2.2.7 Intracorporeal lithotripsy).

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

Last but not least, as an evolving procedure in this specific population, flexible ureteroscopy has proved itself to be an efficacious modality in the treatment of paediatric upper urinary tract stones. Flexible ureteroscopy might be particularly effective for treatment of proximal ureteral calculi, especially those (< 1.5 cm) in the lower pole calices where, as the primary choice of treatment, ESWL fails to disintegrate the stones (56-58).

9.2.5 ***Open or laparoscopic surgery***

Most stones in children can be managed by ESWL and endoscopic techniques (59). Yet, in some situations, open surgery is inevitable. Good candidates for open stone surgery include very young children with large stones and/or a congenitally obstructed system that also requires surgical correction. Open surgery is also a necessity for such children.

Due to the highly successful management of the majority of stones by ESWL and endoscopic techniques; as with the adult population, the rate of open procedures has dropped significantly in children (60-64). Indications for surgery include failure of primary therapy for stone removal, very young children with complex stones, congenitally obstructed system that requires simultaneous surgical correction, severe orthopaedic deformities that limit positioning for endoscopic procedures, and abnormal position of the kidney (29,31,44,45). However, open surgery, if required, can be replaced by laparoscopic procedures in experienced hands (62-64).

9.3 Special considerations on methaphylaxis

It should be kept in mind that, in addition to stone removal procedures, treatment of paediatric urolithiasis requires a thorough metabolic and environmental evaluation of all patients on an individual basis. Obstructive pathologies along with the established metabolic abnormalities should be treated on time. Children are in the high-risk group for stone recurrence (See Chapter 11).

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10. STONES IN URINARY DIVERSIONS AND OTHER VOIDING PROBLEMS

10.1 Management of stones in patients with urinary diversion

10.1.1 Etiology and preventive measures

Patients undergoing urinary diversion due to various pathologies are at risk for stone formation in the renal collecting systems, ureters, and conduit or continent reservoir (1-3). Metabolic factors such as hypercalciuria and hypocitraturia, infection with urease-producing organisms, foreign bodies, mucus secretion, and urinary stasis could play a certain role in stone formation in these cases (4).

These patients are also at high risk for stone recurrence, which warrants a very close follow-up for effective

prevention. Preventive measures might include medical management of documented metabolic abnormalities, appropriate therapy of urinary infections, and regular irrigation of continent reservoirs (5). Cohen and associates have reported that the risk for recurrent upper-tract stones in patients with urinary diversion subjected to PNL is 63% at 5 years (6).

10.1.2 ***Management***

With regard to management, although patients with smaller upper-tract stones can be treated effectively with ESWL (7,8) depending on the size of the calculi, outcome of ESWL, body habitus of the patient, anatomy of the reno-ureteral collecting system, other well-established endourological management techniques might be necessary to achieve a stone-free status.

Some patients with small- or large-bowel conduits can be treated with URS under fluoroscopic guidance. Although the identification of the targeted ureteral orifice is generally difficult, successful localisation can be accomplished using a flexible cystoscope and/or by administration of intravenous indigo carmine to facilitate identification. After the introduction of a hydrophilic guidewire, a flexible ureteroscope is passed over one of the guidewires, and the endoscope is directed up to the level of the stone under fluoroscopic guidance. Stone removal and fragmentation are then undertaken using standard techniques. However, this approach might be difficult or impossible in those individuals with long, tortuous conduits.

Percutaneous nephrolithotomy is the preferred treatment alternative for the effective removal of large renal stones in these cases, as well as ureteral stones that cannot be accessed via a retrograde approach or are not amenable to ESWL (9). Standard PNL techniques are utilised by accessing the collecting system under fluoroscopic or ultrasound guidance. Finally, CT-guided renal puncture might be necessary for safe entry into the renal collecting system in some of these patients.

Stones can also form in the conduits after urinary diversion procedures, and this event typically is associated with a foreign body. A trans-stomal approach can be successful to remove all stone material (along with the foreign body encountered, e.g., staple or suture) by using standard techniques, including intracorporeal lithotripsy if necessary. However, with regard to management of calculi in continent urinary diversion, although a trans-stomal approach might be successful in some patients, there is some risk of disturbing the continence mechanism with this approach. If the stones are readily accessible and of a size that can be fragmented and removed easily, this technique is a good option in this situation. Stein and associates (10) have reported an 89% success rate with a trans-stomal approach for management of patients with stones in Kock reservoirs with afferent nipples. Patients with relatively larger stones, however, are the best candidates for percutaneous removal.

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 (11). If overlying bowel is present, an open surgical approach should be considered. In patients with no overlying viscera, ultrasound- or CT-guided access is recommended to facilitate safe placement of a sheath into the reservoir. Standard PNL techniques can then be utilised for stone removal. Jarrett and colleagues have described an approach in which a 12-mm laparoscopic trocar is placed in the continent reservoir, through which a specimen retrieval bag is inserted. Trans-stomal flexible endoscopy is used to facilitate manipulation of the stones into the entrapment bag. The stones are then fragmented in the bag using a rigid nephroscope and standard intracorporeal lithotripsy techniques. This technique allows total removal of the stone without dispersal of stone fragments in a capacious reservoir (12). At the end of the procedure, a large-calibre catheter is placed in the reservoir through the trocar or sheath, and left in place for at least 2-3 weeks to allow tract maturation.

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10.2 Management of stones in patients with neurogenic bladder

10.2.1 ***Etiology and clinical presentation***

Patients with neurogenic bladder disorder of varying aetiology can develop calculi in the urinary tract because of the presence of various risk factors, such as urinary stasis and infection. In addition, the use of indwelling catheters and surgical interposition of bowel segments for treatment of bladder dysfunction favours the introduction of foreign bodies and infection. 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 (1,2). Rare cases have been reported of vaginal calculi secondary to urinary stasis (3) or vesicovaginal fistulas (4). Bacteriuria, pelvicalicectasis, vesicoureteral reflux, renal scarring, lower urinary tract reconstruction, and a thoracic level spinal defect have been reported as risk factors for renal stone formation in these patients (5).

Kondo has found that bladder lithiasis is 10 times more prevalent in patients with myelomeningocele (MMC) operated on with enterocystoplasy (2). The risk of stone formation after augmentation cystoplasty in immobile patients with sensory impairment can be significantly reduced by the use of irrigation protocols (6). Diagnosis is more difficult because of the absence of clinical expression and difficult visualisation by imaging techniques. As a result of their sensory impairment and vesicourethral dysfunction, these patients generally do not report troublesome symptoms until their calculi reach large sizes (7). A complaint of difficulty in self-catheterisation should lead to suspicion of possible bladder calculi.

10.2.2 ***Management***

The management of calculi that develop in patients with neurogenic bladder is similar to the management principles mentioned above (see section 10.1). However, it should be kept in mind that, whatever the type of treatment used, latex allergy is common in patients with MMC and appropriate measures need to be taken (8). Additionally, any surgical treatment in these patients must be performed under general anaesthesia because of the impossibility of using spinal anaesthesia. Bone deformities often complicate patient positioning on the operating table and the venous accesses that might be required. These deformities can even prevent the use of general anaesthesia (9), which makes early diagnosis of any lithiasis essential.

Statements	LE
Patients undergoing urinary diversion and/or suffering from neurogenic bladder dysfunction are at risk for recurrent stone formation.	3
Careful patient follow-up, utilisation of the appropriate stone-removing approach, and implementation of effective preventive strategies are the cornerstones for the successful management of this population.	3

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10.3 Management of stones in transplanted kidneys

10.3.1 ***Etiology and clinical presentation***

Transplant patients depend on their solitary kidney for renal function, therefore, any impairment causing urinary stasis requires immediate intervention. Although immunosuppression renders these cases more vulnerable to infection, they also have conditions that predispose them to developing urolithiasis, for example, hyperfiltration, excessively alkaline urine, renal tubular acidosis, recurrent UTIs, and increased serum calcium caused by persistent tertiary hyperparathyroidism (1). Stones in kidney allografts are an uncommon clinical problem, with published incidence rates of 0.2-1.7% (2-4).

Allograft kidneys are single renal units and calculi should be treated aggressively to minimise the possibility of obstruction and loss of graft function. Unexplained fever, graft rejection, or unexplained failure to thrive requires US or NCCT to rule out calculi (5).

10.3.2 ***Management***

Treatment of renal calculi in the transplant patient is a difficult clinical problem, however, management principles are similar to the concepts applied in other single renal units (6-9).

Only for very small asymptomatic stones can a conservative regimen under close surveillance be an option. Although ESWL for small calyceal stones is appealing because of minimal complications, localisation of the calculus can be difficult and SFRs are poor (10,11). However, for large or ureteral stones, percutaneous and antegrade endoscopic techniques seem to be more favourable, because primary complete stone removal with immediately restored renal function can be achieved. In many cases, the best modality to treat stones in transplanted kidneys/ureters is with a percutaneous approach but concerns exist about potential injury to adjacent organs using this technique (12-14).

The introduction of small flexible ureteroscopes and the holmium laser has made ureteroscopy an attractive first-line treatment for transplant calculi. Retrograde access to a transplanted kidney is typically difficult owing to the anterior location of the ureteral anastamosis, tortuosity of the ureter and, as such, ureteroscopy is not an easy option for stone management (15-17).

Recommendations

	GR
Use of PNL is recommended, as it is a safe and effective modality with excellent SFRs. However, attempts at observation and stone passage, ESWL, or (flexible) ureteroscopy can also be valuable alternatives in selected cases.	B
Metabolic evaluations should be completed once the stones have been removed.	A

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10.4 Special problems in stone removal

Table 22: Special problems in stone removal

Caliceal diverticulum stones	• ESWL, PNL (if possible) or RIRS • Can also be removed using video-endoscopic retroperitoneal surgery (1-5) • If there is only a narrow communication between the diverticulum and the renal collecting system, well-disintegrated stone material will remain in the original position • Patients may become asymptomatic due to stone disintegration only
Horseshoe kidneys	• Can be treated in line with the stone treatment options described above (6) • Passage of fragments after ESWL might be poor
Stones in pelvic kidneys	• ESWL, RIRS or video-endoscopic laparoscopic surgery • For obese patients, the options are ESWL, PNL, RIRS or open surgery
Stones formed in a continent reservoir	• Present a varied and often difficult problem. See also 10.1. • Each stone problem must be considered and treated individually
Patients with obstruction of the ureteropelvic junction	• When the outflow abnormality has to be corrected, stones can be removed with either percutaneous endopyelotomy (15-35) or open reconstructive surgery • Transureteral endopyelotomy with Ho:YAG laser endopyelotomy can also be used to correct this abnormality • Incision with an Acucise balloon catheter might also be considered, provided the stones can be prevented from falling into the pelvo-ureteral incision (7-10)

10.5 References

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11. METABOLIC EVALUATION-METAPHYLAXIS

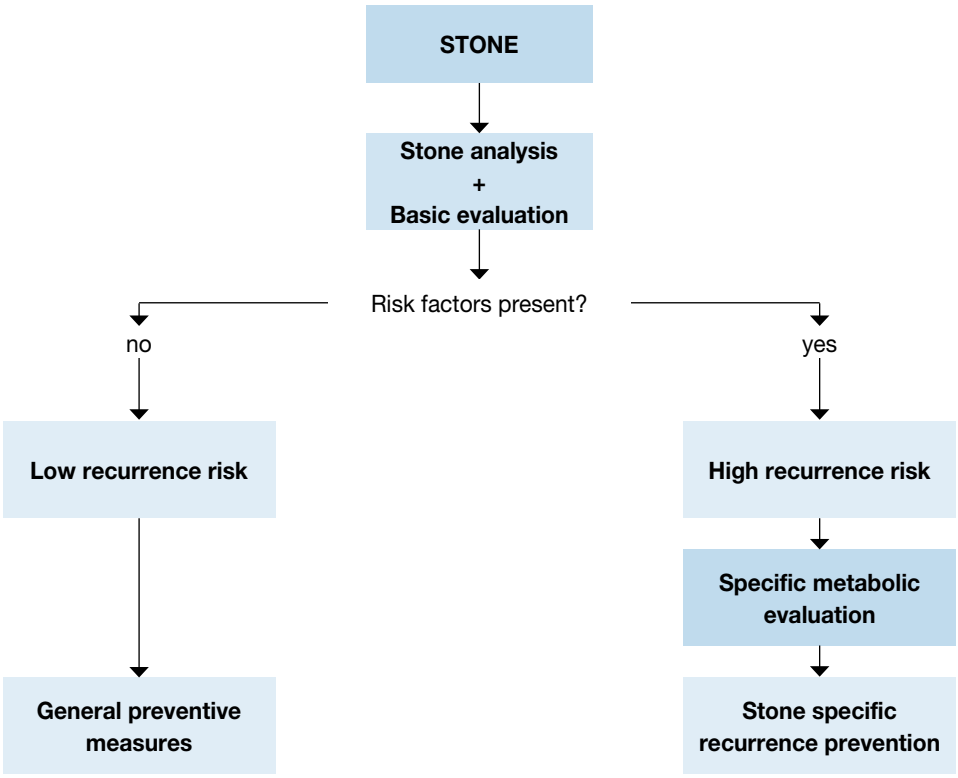
11.1 General metabolic considerations for patient work-up

*11.1.1 **Evaluation of patients' risk***

After stone passage, every patient should be assigned to either a low-risk or high-risk group of stone formers (Figure 3). For correct classification, two items are mandatory:

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

Figure 3: Assignment of patients to low-risk or high-risk groups of stone formers



As shown in Figure 3, only high-risk stone formers are obliged to undergo a specific metabolic evaluation. The type of stone is the deciding factor in selecting further diagnostic tests. The different types of stone include:

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

*11.1.2 **Urine sampling***

Specific metabolic evaluation generally requires the collection of two consecutive 24-hour urine samples (1-3). The collecting bottles should be either prepared with 5% thymol in isopropanol (10 mL for a 2-L bottle) or stored at a cool temperature (< 8°C or less) during the collection period (4). Pre-analytical errors can be minimised by carrying out urinalysis immediately after urine collection has finished. Urine pH should be assessed during the collection of freshly voided urine four times daily (5).

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

Spot urine samples can be an alternative method of urine sampling, particularly when it may be difficult to carry out 24-hour collections, e.g. in younger children (7,8). Spot urine studies normally index the excretion rates to creatinine (8,9). Spot urine studies are limited by the fact that results may vary with collection time and the patient's gender, body weight and age.

*11.1.3 **Timing of the specific metabolic work-up***

For the initial specific metabolic work-up, the patient should be stone free. A minimum of 20 days is recommended between stone expulsion or removal and 24-hour urine collection (4).

Follow-up studies are necessary in patients receiving treatment to prevent recurrent stones (1). The first follow-up 24-hour urine measurement should be performed at 8 to 12 weeks after a patient has started pharmacological treatment to prevent stone recurrence. This enables dosage of the medication to be adjusted if urinary risk factors have not normalised, with further, repeated, 24-hour urine measurements if necessary. Once normalisation in urinary parameters have been achieved, it will be sufficient to perform a 24-hour urine evaluation every 12 months.

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

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

Tables 23-25 provide the internationally accepted reference ranges for the different laboratory values in serum and urine.

Table 23: Normal laboratory values for blood parameters in adults

Blood parameter	Reference range	
Creatinine	20-100 µmol/L	
Sodium	135-145 mmol/L	
Potassium	3.5-5.5 mmol/L	
Calcium	2.0-2.5 mmol/L (total calcium) 1.12-1.32 mmol/L (ionized 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

HCO3 = bicarbonate, pCO_2 pressure of carbon dioxide, PO_2 = pressure of oxygen; BE = base excess (the loss of buffer base to neutralise acid); pH = acidity-alkalinity.

*11.1.5 **Risk indices and additional diagnostic tools***

Several risk indices have been developed to describe the crystallisation risk for calcium oxalate or calcium phosphate in the urine:

- AP_{CaOx}index (10,11);
- EQUIL (12-14);
- Bonn Risk Index (15-17).

Another approach to risk assessment is the Joint Expert Speciation System (JESS), which is based on an extensive database of physiochemical constants and is most like the EQUIL (18).

However, the clinical validation of these risk indices in terms of recurrence prediction or therapy improvement is still ongoing and the benefit remains controversial.

Table 24: Normal laboratory values for urinary parameters in adults

Urinary arameters	**Reference ranges and limits for medical attention**
pH	Constantly > 5.8 Constantly > 7.0 Constantly ≤ 5.8
Specific weight	> 1010
Creatinine	7-13 mmol/day females 13-18 mmol/day males
Calcium	> 5.0 mmol/day ≥8.0 mmol/day
Oxalate	> 0.5 mmol/day 0.45-0.85 mmol/day ≥1.0 mmol/l
Uric acid	> 4.0 mmol/day
Citrate	< 2.5 mmol/day
Magnesium	< 3.0 mmol/day
Inorganic phosphate	> 35 mmol/day
Ammonium	> 50 mmol/day
Cystine	> 0.8 mmol/day

Table 25: Reference urinary values in paediatric patients (9)

Soluble:creatinine ratio (spot urine samples)

Calcium:creatinine ratio			Citrate:creatinine ratio			Cystine:creatinine ratio			Oxalate:creatinine ratio			Urate:creatinine ratio		
	mol/mol	g/g		mol/mol	g/g		mmol/mol	mg/g		mmol/mol	mg/g		mol/mol	g/g
< 12 mos	< 2.2	< 0.8				< 1 month	< 85	< 180	0-6 mos	< 325-360	< 260-88	< 12 mos	< 1.5	< 2.2
1-3 y	< 1.5	< 0.53	0-5 y	> 0.12-0.25	> 0.2-0.42				7-24 mos	< 132-174	< 110-39	1-3 y	< 1.3	< 1.9
3-5 y	< 1.1	< 0.4				1-6 mos	< 53	< 112	2-5 y	< 98-101	< 80-81	3-5 y	< 1.0	< 1.5
5-7 y	< 0.8	< 0.3							5-14 y	< 70-82	< 60-65	5-10 y	< 0.6	< 0.9
> 7 y	< 0.6	< 0.21	> 5 y	> 0.08-0.15	> 0.14-0.25	> 6 mos	< 18	< 38	> 14 y	< 40	< 32	> 10 y	< 0.4	< 0.6

Urinary excretion of soluble excretion in 24-hour urine samples

Calcium excretion		Citrate excretion			Cystine excretion	Oxalate excretion		Urate excretion	
			Boys > 1.9 mmol/1.73 m²/24 h > 365 mg/1.73 m²/24 h	< 10 y	< 55 µmol/1.73 m²/24 h < 13 mg/1.73 m²/24 h			< 1 year	< 70 µmol/kg/24 h < 1.3 mg/kg/24 h
All age groups	< 0.1 mmol/kg/24 h < 4 mg/kg/24 h	All age groups	Girls > 1.6 mmol/1.73 m²/24 h > 310 mg/1.73 m²/24 h	> 10 y	< 200 µmol/1.73 m²/24 h < 48 mg/1.73 m²/24 h	All age groups	< 0.5 mmol/1.73 m²/24 h < 45 mg /1.73 m²/24 h	1-5 y	< 65 µmol/kg/24 h < 1.1 mg/kg/24 h
								> 5 y	< 55 µmol/kg/24 h < 0.9 mg/kg/24 h

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11.2 General considerations for recurrence prevention

All stone formers, independent of their individual risk, should follow the general preventive measures described in Table 26. The main focus of these general preventive measures is 'normalisation' of the patient's dietary habits and lifestyle risks. Stone formers at high risk also need specific preventive treatment for recurrence,

which is usually pharmacological treatment and based on stone analysis.

Table 26: General preventive measures

Fluid intake (drinking advice)	Fluid amount: 2.5-3.0 L/day Circadian drinking Neutral pH beverages Diuresis: 2.0-2.5 L/day Specific weight of urine: < 1010
Nutritional advice for a balanced diet	Balanced diet* Rich in vegetable and fibre Normal calcium content: 1000-1200 mg/day** Limited sodium chloride content: 4-5 g/day Limited animal protein content: 0.8-1.0 g/kg/day
Lifestyle advice to normalise general risk factors	Body mass index: 18-25 kg/m^2 (target adult value, not applicable to children) Stress limitation measures Adequate physical activity Balancing of excessive fluid loss

Caution: *The protein need is age-group dependent, therefore protein restriction in the childhood should be handled carefully.*
** Avoid excessive consume of vitamin supplements.*
*** Exception: Patients with absorptive hypercalciuria, calcium excretion ≥ 8 mmol/d.*

11.2.1 ***Fluid intake***

An inverse relationship between high fluid intake and stone formation has been repeatedly demonstrated (1,2). The general recommendation for calcium stone formers is therefore to maintain a high urine flow with a generous intake of fluids. Most beverages can be drunk to increase fluid intake and so help to prevent stone formation. The effect of fruit juices is mainly determined by the presence of citrate or bicarbonate (3). If hydrogen ions are present, the net result is neutralisation. However, if potassium is present, both pH and citrate are increased (4,5).

Recommendation

	LE	GR
The aim should be to obtain a 24-hour urine volume of at least 2 L.	1b	A

11.2.2 ***Diet***

A commonsense approach to diet should be taken, i.e. a mixed balanced diet with contributions from all food groups, but without excesses of any kind (6).

Fruits, vegetables and fibres: fruit and vegetable intake should be encouraged because of the beneficial effects of fibre (7). The alkaline content of a vegetarian diet also results in a desirable increase in urinary pH.

Oxalate: excessive intake of oxalate-rich products should be limited or avoided to prevent an oxalate load (3), particularly in patients who have a high oxalate excretion.

Vitamin C: although vitamin C is a precursor of oxalate, its role as a risk factor in calcium oxalate stone formation remains controversial (8-11). However, it seems wise to advise calcium oxalate stone formers to avoid excessive intake of vitamin C.

Animal protein should not be taken in excessive amounts (12-14), and intake should be limited to 0.8-1.0 g/kg body weight. Excessive consumption of animal protein gives rise to several effects that favour stone formation, including hypocitraturia, low urine pH, hyperoxaluria and hyperuricosuria.

Calcium intake should not be restricted unless there are very strong reasons because of the inverse relationship between dietary calcium and calcium stone formation (15). The minimum daily requirement for calcium is 800 mg and the general recommendation is 1000 mg/day (16). Calcium supplements are not recommended except

in cases of enteric hyperoxaluria, when additional calcium should be taken with meals to bind intestinal oxalate (14,17-19).

Sodium: the daily sodium intake should not exceed 3-5 g. A high sodium intake has an unfavourable influence on urine composition:

- calcium excretion is increased by reduced tubular reabsorption;
- urinary citrate is reduced due to the loss of bicarbonate;
- increased risk of sodium urate crystal formation.

Studies have shown that calcium stone formation can be reduced by restricting both sodium and animal protein (13,14). A positive correlation between sodium consumption and the risk of first-time stone formation has been confirmed only in women, and not in men (15,20). In addition, there have been no prospective clinical trials of the role of sodium restriction as an independent variable in reducing the risk of stone formation.

Urate: The intake of food particularly rich in urate should be restricted in patients with hyperuricosuric calcium oxalate stone disease (21-24), as well as in patients with uric acid stone disease (16). The intake of urate should not exceed 500 mg/day.

11.2.3 ***Lifestyle***

Some studies have suggested lifestyle factors may influence the risk of stone formation, e.g. being overweight and obesity (25-27). Another risk factor is arterial hypertension (28,29).

11.2.4 ***References***

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11.3 Stone-specific metabolic work-up and pharmacological recurrence prevention

11.3.1 ***Introduction***

Pharmacological treatment is necessary in patients at high risk for recurrent stone formation. Normally, medication is used together with general preventive measures. The ideal pharmacological agent should halt the formation of stones, be free of side effects and be easy to administer. Each of these aspects are of utmost importance in order to achieve reasonably good compliance overall. The following descriptions highlight the most important characteristics of commonly used medication in preventing recurrent stones.

11.3.1.1 Thiazides and thiazide-like agents

Hydrochlorothiazide, bendroflumethiazide, trichlorothiazide and the non-thiazide indapamide have been used for recurrence prevention in patients with calcium stone disease. The purpose of thiazide treatment is to reduce the excretion of calcium in hypercalciuric patients, but calcium reduction has also been reported in patients with normocalciuria (1,2). The hypocalciuric action of thiazides is thought to be mediated by increased re-absorption of calcium in the proximal and distal parts of the nephron (3).

More than 35 years of clinical experience and good evidence from RCTs has proven that thiazides are effective in the prevention of calcium stone recurrences (Table 27) (4).

Table 27: Randomised, controlled 'thiazide' trials for prevention of recurrent stone formation (LE: 1b)

Author	Treatment	Selection	Duration of Study (yrs)	No. pts.	Stones/ pt/yr	Remission rate (%)	p-value
Borghi, et al (5)	Indapamide No tx	Hypercalciuria	3	19 21	0.06 0.28	84.2 57.1	< 0.05
Brocks, et al (6)	BFMZ Placebo	Non-selective	4	33 29	0.09 0.11	84.8 82.8	NS
Ettinger, et al (7)	Chlorthalidone Placebo	Non-selective	4	23 31	0.05 0.22	87.0 54.8	< 0.05
Mortensen, et al (8)	BFMZ Placebo	Non-selective	2	12 10	- -	100.0 60.0	< 0.1
Laerum and Larsen (9)	HCTZ Placebo	Non-selective	3	23 25	0.07 0.18	78.3 52.0	< 0.05
Ohkawa, et al (10)	Triclorme-thiazide No Tx	Hypercalciuria	2	82 93	0.13 0.31	86.5 55.9	< 0.05
Robertson, et al (11)	BFMZ No Tx	Non-selective	3	13 9	0.22 0.58	- -	"sig"
Scholz, et al (12)	HCTZ Placebo	Non-selective	1	25 26	0.20 0.20	76.0 76.9	NS
Wilson, et al (13)	HCTZ No Rx	Non-selective	3	23 21	0.15 0.31	- -	< 0.05

BFMZ = bendroflumethiazide.

However, thiazide treatment has a major drawback in the side effects caused by taking thiazides. The unmasking of normocalcaemic hyperparathyroidism, development of diabetes and gout, as well as erectile dysfunction, all contribute to a limited tolerance and a high drop-out rate, resulting in an overall 50-70% compliance rate.

In addition, the use of thiazide induces potassium loss. This can be compensated for by giving potassium citrate (3.5-7.0 mmol twice daily). Potassium citrate is preferable to potassium chloride as it results in better potassium substitution (14).

11.3.1.2 Alkaline citrate

Commonly used alkalinising agents are: sodium potassium citrate, potassium citrate, sodium citrate, potassium magnesium citrate, potassium bicarbonate and sodium bicarbonate. Tubular cell alkalinisation is responsible for increased levels of urinary citrate, though only a small fraction of the administered citrate is directly excreted. Alkaline citrates are used for:

- correction of hypocitraturia;
- urine alkalinisation;
- inhibition of growth and aggregation of calcium oxalate;
- inhibition of agglomeration of calcium phosphate (15).

There is evidence from RCTs that alkaline citrates are effective in preventing calcium stone recurrences (4) (Table 28).

Table 28: RCTs evaluating alkali citrate therapy in preventing stone recurrence (LE: 1b)

Author	Treatment	Selection	Duration of Study (yrs)	N	Stones/ pt/yr	Remission (%)	p-value
Barcelo, et al (16)	K-cit	Hypocitraturia	3	18	0.01	73.23	< 0.05
	Placebo			20	1.1	20	
Hofbauer, et al (17)	Na-K-cit	Non-selective	3	16	0.9	31.3	NS
	No Rx			22	0.7	27.3	
Ettinger, et al (18)	K-Mag-C	Non-selective	3	16	-	87.1	rr=0.06
	Placebo			25	-	36.4	

Two studies of potassium citrate (16,19), sodium potassium in one study (70) and potassium magnesium citrate in another study (4). reported a significantly reduced recurrence rate. Another study reported a favourable effect with potassium magnesium citrate (18), but not with sodium potassium citrate. Although potassium magnesium citrate appears efficient in preventing recurrent stone formation, this compound is not yet generally available. Further studies are necessary to show whether it is superior to potassium citrate.

Because alkaline citrate treatment has a fairly high occurrence of side effects, the overall compliance rates are not higher than about 50%.

11.3.1.3 Magnesium
Magnesium oxide, magnesium hydroxide, potassium magnesium citrate and magnesium aspartate have been used to increase urinary magnesium excretion. Biochemically increased urinary magnesium levels reduce the ion-activity product of calcium oxalate and inhibit the growth of calcium phosphate crystals. Magnesium is also considered important for the transformation between various calcium phosphate crystal phases. A high urinary concentration of magnesium is therefore thought to decrease the risk of brushite formation.

However, there is still not enough evidence to recommend magnesium as monotherapy in calcium stone prevention. There are two RCTs on the clinical effects of magnesium, one in which treatment with magnesium hydroxide was compared with a placebo control group (7) and one with magnesium oxide and untreated controls (13). None of them showed a statistically significant effect on stone formation, despite follow-up periods of 4 and 3 years, respectively. The positive effects of magnesium administration reported previously (20,21) have not been confirmed by recent controlled studies (22).

11.3.1.4 Calcium supplements
See Section 11.2.2, Calcium intake.

11.3.1.5 Allopurinol
Allopurinol is an inhibitor of xanthine oxidase. It has been used for the recurrence prevention of calcium oxalate stones ever since a relationship was found between hyperuricosuria and calcium oxalate stone formation (23). Although allopurinol tolerance is normally good, severe side effects have been reported with high doses. There is no information on compliance.

The potential benefits of allopurinol on calcium oxalate stone formation risk are:
- reduced salting-out effect;
- decreased risk of uric acid or urate crystals as promoters of calcium oxalate precipitation;
- complex formation between colloidal urate and macromolecular inhibitors, *and/or*
- reduced excretion of oxalate.

A placebo-controlled, randomised study of allopurinol-treated, hyperuricosuric, calcium-oxalate stone formers reported that 75% of patients given allopurinol became free of recurrent stone formation compared with 45% in the placebo group (statistically significant) (24). The effectiveness of allopurinol (daily dosage 300 mg) has been tested in four RCTs that compared calcium oxalate stone formers treated with those who were placebo-treated or untreated (13,24,25). Only one of the four trials demonstrated a significant benefit of allopurinol therapy in preventing stone recurrence (25). However, this trial solely enrolled patients with hyperuricosuria, while the other three trials enrolled patients without regard to metabolic background.

11.3.1.6 Pyridoxine

Theoretically, administration of pyridoxine (vitamin B6) might favourably influence the endogenous production of oxalate, probably due to an increased transamination of glyoxylate resulting from the action of the co-enzyme pyridoxal phosphate.

Due to the rarity (and severity) of primary hyperoxaluria, there are no randomised studies on pyridoxine efficacy. However, several reports have confirmed that a few patients with type 1 hyperoxaluria responded favourably to large doses of pyridoxine (26-28).

Because of the lack of other effective forms of treatment, it is definitely worth trying pyridoxine therapeutically, with the aim of reducing oxalate excretion in patients with primary hyperoxaluria type I.

There are no controlled studies to support the use of pyridoxine in patients with idiopathic calcium oxalate stone disease.

11.3.1.7 L-Methionine

Acidification of urine can be achieved using a daily dose of 600-1500 mg of the sulfur-containing amino acid, L-methionine. Methionine acidifies urine pH by donating protons (hydrogen ions). Stable acidification is difficult to achieve. Long-term acidification in children is not justified (4).

11.3.1.8 Tiopronin-α-mercaptopropionyglycine

Tiopronin - which has a thiol-containing biomolecule - is able to form drug-cysteine complexes by splitting the disulphide binding of cystine. As a consequence cystine saturation of urine decreases, while solubility increases significantly. This effect was demonstrated in vitro and clinically (29-31). Although no RCTs have been reported, tiopronin appears to lower cystine stone formation, when stone formation rates pre and post-treatment are compared (32-35). Due to the significant level of side effects the use of tiopronin (and other cysteine binding drugs) should be reserved for patients who are unable to control stone formation with high fluid intake, dietary modification and urine alkalinisation. The side effects appear to be dose related. Reported side effects include: nausea, rash, fatigue, fever, and proteinuria.

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

Urinary risk factor	**Suggested treatment**	**LE**	**GR**
Hypercalciuria	Thiazide + potassium citrate	1a	A
Hyperoxaluria	Oxalate restriction	2b	A
Hypocitraturia	Potassium citrate	1b	A
Enteric hyperoxaluria	Potassium citrate Calcium supplement Oxalate absorption	3-4 2 3	C B 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
Distal renal tubular acidosis	Potassium citrate	2b	B
Primary hyperoxaluria	Pyridoxine	3	B
No abnormality identified	High fluid intake	2b	B

11.3.3 ***References***

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11.4 Calcium oxalate stones

Criteria for the identification of calcium oxalate stone formers at high recurrence risk will be found in section 2.6.

11.4.1 ***Diagnosis***

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

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

- Elevated levels of ionized calcium in serum (or total calcium and albumin) demand the assessment of intact parathyroid hormone (PTH) to confirm or exclude suspected hyperparathyroidism (HPT).
- 'Acidic arrest' (urine pH constantly < 6) may promote the co-crystallisation of uric acid and calcium oxalate. In the same way, increased uric acid excretion (> 4 mmol/day in adults or > 0.12 mmol/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 has been excluded. An ammonium chloride loading test will confirm RTA and identify the RTA subtype (*see* Section 11.6.4).
- Oxalate excretion rates above 0.5 mmol/day in adults (> 0.37 mmol/1.73 m^2/day in children) confirm hyperoxaluria:
  - primary hyperoxaluria (oxalate excretion mostly ≥ 1 mmol/day), appears in three genetically determined forms;
  - secondary hyperoxaluria (oxalate excretion ≥ 0.5 mmol/day, usually < 1 mmol/day), occurs due to intestinal hyperabsorption of oxalate or extreme dietary oxalate intake;
  - mild hyperoxaluria (oxalate excretion 0.45-0.85 mmol/day), commonly found in idiopathic calcium oxalate stone formers.

11.4.3 ***Specific treatment***

General preventive measures are recommended for fluid intake and diet. In addition, hyperoxaluric stone formers should consume foods with low oxalate content, while hyperuricosuric stone formers benefit from purine reduction in their daily diet. Table 29 summarises the pharmacological treatment of calcium oxalate stones.

Table 29: Pharmacological treatment of calcium oxalate stones

Biochemical risk factor	Rationale for pharmacological therapy	Medication
Hypercalciuria	Calcium excretion 5-8 mmol/day	Alkaline citrate, 9-12 g/day, **OR** Sodium bicarbonate, 1.5 g 3 times daily
	Calcium excretion > 8 mmol/day	Hydrochlorothiazide, 25 mg/day initially, up to 50 mg/day
hypocitraturia	Citrate excretion < 2.5 mmol/day	Alkaline citrate, 9-12 g/day
Hyperoxaluria (enteric)	Oxalate excretion > 0.5 mmol/day	Calcium, ≥ 500 mg/day with meals **NB: BE AWARE OF EXCESS CALCIUM EXCRETION** Magnesium, 200-400 mg/day **NB: NO MAGNESIUM THERAPY IN PATIENTS WITH RENAL INSUFFICIENCY**
Hyperuricosuria	Uric acid excretion > 4.0 mmol/day	Alkaline citrate, 9-12 g/day **OR** Sodium bicarbonate, 1.5 g 3 times daily **PLUS** Allopurinol,100 mg/day
	Hyperuricosuria and hyperuricemia > 380 µmol	Alkaline citrate, 9-12 g/day **PLUS** Allopurionol, 100-300 mg/day, depending on kidney function
Hypomagnesiuria	Magnesium excretion < 3.0 mmol/day	Magnesium, 200-400 mg/day **NB: NO MAGNESIUM THERAPY IN CASE OF RENAL INSUFFICIENCY**

11.5 Calcium phosphate stones

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

Calcium phosphate mainly appears in two completely different minerals: carbonate apatite and brushite:

- Carbonate apatite crystallisation occurs at pH levels ≥6.8 and may be associated with infection.
- Brushite crystallises in a narrow pH range (optimum pH 6.5-6.8) at high urinary concentrations of calcium (> 8 mmol/day) and phosphate (> 35 mmol/day). Its occurrence is not related to urinary tract infection.

Possible causes of calcium phosphate stones include HPT, RTA and urinary tract infection. Each of them requires a different therapy.

11.5.1 ***Diagnosis***

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

11.5.2 ***Specific treatment***

General preventive measures are recommended for fluid intake and diet.

11.5.3 ***Pharmacological therapy*** *(Table 30)*

Hyperparathyroidism and RTA are common causes of calcium phosphate stone formation. Although most patients with primary HPT require surgical therapy, it is possible to correct RTA pharmacologically. If a diagnosis of primary HPT and RTA has been excluded, pharmacotherapy for calcium phosphate calculi depends on effective reduction of urinary calcium levels using thiazides. Additionally, if urine pH remains constantly > 6.2, urinary acidification therapy with L-methionine may be helpful. In case of infection-associated calcium phosphate stones, it is also important to consider the guidance given for 'infection stones'.

Table 30: Pharmacological treatment of calcium phosphate stones

Biochemical risk factor	Rationale for pharmacological therapy	Medication
Hypercalciuria	Calcium excretion > 8 mmol/day	Hydrochlorothiazide, initially 25 mg/day, increasing up to 50 mg/day
Inadequate urine pH	pH constantly > 6.2	L-Methionine, 200-500 mg 3 times daily, with the aim of reducing urine pH to 5.8-6.2
Urinary tract infection	Eradication of urea-splitting bacteria	Antibiotics

11.6 Disorders and diseases related to calcium stones

11.6.1 ***Hyperparathyroidism*** *(1-6)*

The clinical appearance of HPT typically comprises bone loss, gastric ulcer and urolithiasis. Elevated levels of PTH significantly increase the calcium turnover, subsequently leading to hypercalcaemia and hypercalciuria. If HPT is suspected, a neck exploration should be carried out to confirm the diagnosis. Primary HPT can only be cured by surgery. All pharmacological interventions provide only symptomatic relief.

11.6.2 ***Primary hyperoxaluria*** *(7-13)*

Patients with primary hyperoxaluria (PH) should be referred to specialised centres, as successful management requires an interdisciplinary team and a lot of experience. The main target of therapy is to reduce endogenous oxalate production, which is dramatically increased in patients with PH. In approximately one-third of patients with PH type I, pyridoxine therapy (an AGT co-factor) leads to normalisation or significant reduction of urinary oxalate excretion. The goal of adequate urine dilution is achieved by adjusting daily fluid intake to between 3.5 and 4.0 L in adults (children 1.5 L/m^2 body surface area) and following a circadian drinking regime.

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

Treatment dosage regimens are as follows:

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

11.6.3 ***Enteric hyperoxaluria*** *(14-19)*

Enteric hyperoxaluria is a particularly problematic condition in patients with intestinal malabsorption of fat. This abnormality, which is associated with a high risk of stone formation, is seen after intestinal resection, following jejunoileal bypass for treatment of obesity, in Crohn's disease, and in pancreas insufficiency. The intestinal loss of fatty acids is combined with a loss of calcium. The normal complex formation between oxalate and calcium is therefore disturbed and oxalate absorption is dramatically increased. In addition to the ensuing hyperoxaluria, these patients usually present with hypocitraturia because of loss of alkali. Urine pH is usually low and so are urinary calcium and the urine volume. All these abnormalities contribute to particularly high levels of supersaturation with calcium oxalate, crystalluria and stone formation.

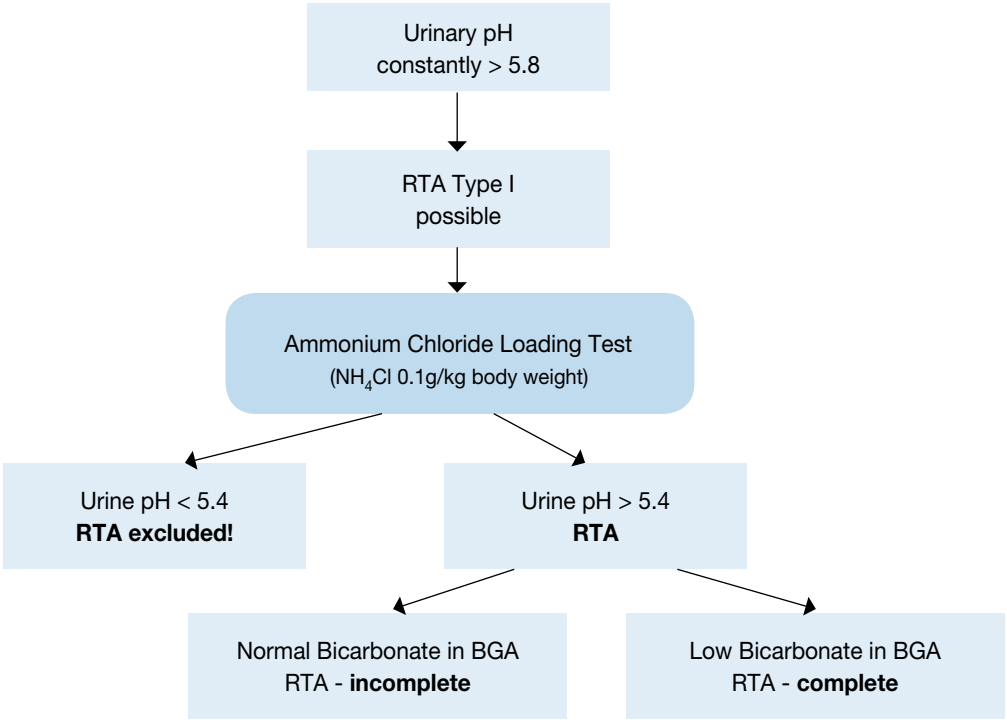
Specific preventive measures are:

- Restricted intake of oxalate-rich foods;
- Restricted fat intake;
- Calcium supplementation at meal times to enable calcium oxalate complex formation in the intestine (20,21);
- Sufficient fluid intake to balance the intestinal loss of water caused by the diarrhoea;
- Alkaline citrates to raise urinary pH and citrate (22).

11.6.4 ***Renal tubular acidosis*** *(23,24)*

Renal tubular acidosis (RTA) is caused by a severe impairment of proton or bicarbonate handling along the nephron. Kidney stone formation is most likely to occur in patients with distal RTA type I. Figure 4 outlines the diagnosis of RTA.

Figure 4: Diagnosis of RTA



The main therapeutic aim is restoring a normal acid-base equilibrium. Despite the alkaline pH of urine in RTA patients, alkalinisation therapy using alkaline citrates or sodium bicarbonate is the key to normalising the metabolic changes (intracellular acidosis) responsible for stone formation (Table 31). The alkali load reduces tubular re-absorption 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 levels ± 2.0) in case of complete RTA. If excessive calcium excretion (> 8 mmol/day) persists after re-establishing the acid-base equilibrium, the addition of thiazides may lower urinary calcium excretion.

Table 31: Pharmacological treatment of renal tubular acidosis

Biochemical risk factor	Rationale for pharmacological therapy	Medication
Hypercalciuria	Calcium excretion > 8 mmol/day	Hydrochlorothiazide, - in adults, 25 mg/day initially, up to 50 mg/day - in children, 0.5-1 mg/kg/day
Inadequate urine pH	Intracellular acidosis in nephron	Alkaline citrate, 9-12 g/day **OR** Sodium bicarbonate, 1.5 g 3 times daily

11.6.5 ***Nephrocalcinosis*** *(25,26)*

The term nephrocalcinosis (NC) refers to an increased crystal deposition within the cortex or medulla of the kidney. Nephrocalcinosis occurs either alone or in combination with kidney stone formation. There are various metabolic causes for NC. The main risk factors are: HPT, PH, RTA, vitamin D metabolic disorders, idiopathic hypercalcuria and hypocitraturia, and genetic disorders, including Dent's disease and Bartter's syndrome. 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 for NC as much as possible.

11.6.5.1 Diagnosis

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

11.6.6 ***References***

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11.7 Uric acid and ammonium urate stones

All uric acid and ammonium urate stone formers are considered to be at high risk of recurrence (1). Hyperuricosuria may be a result of dietary excess, endogenous overproduction (enzyme defects), myeloproliferative disorders, tumour lysis syndrome, drugs (e.g. probenicid), gout or catabolic metabolism (2). Ammonium urate crystals are associated with urinary tract infection, malabsorption syndromes and malnutrition.

11.7.1 ***Diagnosis***

Blood analysis requires measurement of creatinine and uric acid levels. Urinalysis requires measurement of urine volume, urine pH profile, specific weight of urine, and uric acid level.

Interpretation of results

Uric acid and ammonium urate stones form under completely different biochemical conditions.
'Acidic arrest' (urine pH constantly < 6) 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. Ammonium urate crystals form in urines with pH levels > 6.5, at high uric acid concentration, and in the presence of a cation.

*11.7.2 **Specific treatment***

General preventive measures are recommended for fluid intake and diet. Hyperuricosuric stone formers benefit from purine reduction of their daily diet. Table 32 describes pharmacological measures for treatment.

Table 32: Pharmacological treatment of uric acid and ammonium urate stones

Biochemical risk factor	**Rationale for pharmacological therapy**	**Medication**
Inadequate urine pH	Urine pH constantly ≤ 6.0; 'acidic arrest' in **uric acid stones**	Alkaline citrate, 9-12 g/day **OR** Sodium bicarbonate, 1.5 g 3 times daily **NB: DOSE DEPENDS ON TARGETED URINE PH** Prevention: targeted urine pH **6.2-6.8** Chemolitholysis: targeted urine pH **7.0-7.2**
	Urine pH constantly > 6.5 in **ammonium urate stones**	Adequate antibiotics in case of urinary tract infection with urea-degrading bacteria L-Methionine, 200-500 mg 3 times daily; targeted urine pH **5.8-6.2**
Hyperuricosuria	Uric acid excretion > 4.0 mmol/day	Allopurinol, 100 mg/day
	Hyperuricosuria and hyperuricemia > 380 µmol	Allopurinol, 100-300 mg/day, depending on kidney function

Recommendations for uric acid and ammonium urate stones

Objective	**Therapeutic measures**	**Ref**	**LE**	**GR**
Prevention	**Urine dilution**	1,3-5	3	B
	A high fluid intake; 24-hour urine volume exceeding 2-2.5 L			
	Alkalinisation	6-9	2b	B
	Potassium citrate 3-7 mmol x 2-3			
	In patients with a high serum or urine level of urate	10	3	B
	allopurinol 300 mg x 1			
Medical dissolution of uric acid stones	**Urine dilution**			
	A high fluid intake; 24-hour urine volume exceeding 2-2.5L		4	C
	Alkalinisation	1,11	1b	A
	Potassium citrate 6-10 mmol x 2-3			
	always reduce urate excretion		4	C
	allopurinol 300 mg x 1			

*11.7.3 **References***

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11.8 Struvite and infection stones

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

11.8.1 ***Diagnosis***

Blood analysis requires measurement of creatinine, while urinalysis requires urine pH profile and urine culture.

Interpretation

- Infection stones contain struvite and/or carbonate apatite and/or ammonium urate.
- Urine culture typically provides evidence for urease-producing bacteria (Table 33).

Table 33: Most important species of urease-producing bacteria

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

11.8.2 ***Specific treatment***

General preventive measures are recommended for fluid intake and diet. Specific therapeutic measures include the surgical removal of stone(s) as completely as possible (1); short- or long-term antibiotic treatment (2), urinary acidification using methionine (3) or ammonium chloride (4), and urease inhibition (5,6). In very selected cases with severe infections, treatment with acetohydroxamic acid (Lithostat) may be an option.

Recommendations for therapeutic measures

Therapeutic measure recommendations	Refs.	LE	GR
Surgical removal of the stone material as completely as possible	1		
Short-term antibiotic course	2	3	B
Long-term antibiotic course	2	3	B
Urinary acidification: ammonium chloride, 1 g x 2-3 daily	4	3	B
Urinary acidification: methionine, 200-500 mg, 1 to 3 times daily	3	3	B
Urease inhibition	5,6	1b	A

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11.9 Cystine stones

All cystine stone formers are deemed at high risk of stone recurrence.

11.9.1 ***Diagnosis***

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

Interpretation

- Cystine crystallises spontaneously in urine because of its poor solubility.
- 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.
- Reductive therapy targets the splitting of cystine's disulfide binding; it is essential to differentiate between cystine, cysteine and drug cysteine-complexes. Only HPLC-based analytic methods can differentiate between the different complexes formed by therapy.

11.9.2 ***Specific treatment***

General preventative measures for fluid intake and diet are recommended. Although theoretically a diet low in methionine may help to reduce urinary excretion of cystine, patients are unlikely to comply sufficiently with such a diet and it is therefore not usually recommended. However, a restricted intake of sodium is more easily achieved by the patient and will therefore be more effective in reducing urinary cystine. Patients are usually advised to avoid a daily consumption of sodium above 2 g (1).

A high diuresis is of fundamental importance, with the aim being a 24-hour urine volume of at least 3 L (2,3). To reach this goal, a considerable fluid intake evenly distributed during the day is necessary.

11.9.2.1 Pharmacological treatment of cystine stones

The main therapeutic option for avoiding cystine crystallisation is to maintain urine pH above 7.5 to improve cystine solubility (Table 34) and to ensure appropriate hydration with a minimum of 3.5 L/day in adults, or 1.5 L/m^2 body surface area in children.

In addition, the free cystine concentration can be decreased by giving reductive substances, which act by splitting the disulfide binding of the cystine molecule .

Tiopronin: Currently, tiopronin (α-mercapto-propionyl glycine) is the best choice for cystine reduction. However, the side effects associated with tiopronin often lead to either the patient stopping treatment, e.g. when nephritic syndrome develops, or being poorly compliant, 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 the patient's recurrence risk, tiopronin is recommended at cystine levels ≥3.0 mmol/day or in the case of troublesome disease.

Ascorbic acid is used when cystine excretion < 3.0 mmol/day. However, it has limited reductive power and is estimated to lower urinary cystine levels by about 20% (4). The effectiveness and use of ascorbic acid as a standard therapeutic regimen are controversial (5).

Captopril: results for the angiotensin-converting enzyme (ACE) inhibitor, captopril, are controversial (6). Captopril remains a second-line option, for use when tiopronin therapy is unfeasible or unsuccessful.

Table 34: Pharmacological treatment of cystine stones

Biochemical risk factor	Rationale for pharmacological therapy	Medication
Cystinuria	Cystine excretion > 3.0-3.5 mmol/day	Tiopronin, 250 mg/day initially, up to a maximum dose of 2 g/day **NB: TACHYPHYLAXIS IS POSSIBLE**
Inadequate urine pH	Improvement of cystine solubility Urine pH optimum 7.5-8.5	*Alkaline Citrate* dose: according to urine pH alternative *Sodium Bicarbonate* Dosage is according to urine pH

Recommendations for treatment of cystine stones

Therapeutic measures	Refs.	LE	GR
Urine dilution A high fluid intake is recommended so that the 24-hour urine volume exceeds 3 L. To achieve this goal, the intake should be at least 150 mL/hour	1-3,5	3	B
Alkalinisation For patients with a cystine excretion below 3 mmol/24 hour: Potassium citrate 3-10 mmol 2-3 times daily should be given to achieve a pH > 7.5	1-3,5	3	B
Complex formation with cystine For patients with a cystine excretion above 3 mmol/24 hour, or when other measures are insufficient: Tiopronin (α-mercapto-propionyl glycine), 250-2000 mg/day **or** Captopril, 75-150 mg	1-6	3	B

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

All 2,8-dihydroxyadenine and xanthine stone formers are considered to be at high risk of recurrence. Both stone types are rare. In principle, diagnosis and specific prevention is similar to that of uric acid stones.

11.10.1 ***2,8-dihydroxyadenine stones***

A genetically determined defect of adenine phosphoribosyl transferase (APRT) causes a high urinary excretion of poorly soluble 2,8-dihydroxyadenine. High-dose allopurinol is a therapeutic option, but should only be tried with regular laboratory monitoring.

11.10.2 ***Xanthine stones***

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

11.10.3 ***Fluid intake and diet***

Recommendations for general preventive measures apply. As pharmacological intervention is difficult, a high fluid intake ensures optimal specific weight levels of urine under 1.010. In addition, a purine-reduced diet will reduce the risk of spontaneous crystallisation in urine.

11.11 Drug stones (2)

Drug stones are stones induced by pharmacological treatment (3,4) (Table 35). Two types of drug stone exist:

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

Table 35: Compounds that cause drug stones

Active compounds crystallizing in urine
• Allopurinol / oxypurinol
• Amoxicillin / ampicillin
• Ceftriaxone
• Ciprofloxacin
• Ephedrine
• Indinavir
• Magnesium trisilicate
• Sulfonamide
• Triamterene
Substances impairing urine composition
• Acetazolamide
• Allopurinol
• Aluminium magnesium hydroxide
• Ascorbic acid
• Calcium
• Furosemide
• Laxatives
• Methoxyflurane
• Vitamin D

11.12 Unknown stone composition (5)

The taking of an accurate medical history is the first step towards identifying a patient's risk factors (Table 36).

Diagnostic imaging begins with an ultrasound examination of both kidneys to find out whether or not the patient is stone-free. The detection of stones by ultrasound should be followed by an unenhanced multislice CT in adult patients to differentiate between calcium-containing and non-calcium stones based on Houndsfield Unit determination.

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

Urinalysis will be performed routinely with a dipstick test as described above. In the presence of infection signs, urine culture is required.

Constant urine pH values higher than pH 6 in the daily profile indicate an 'acidic arrest', which may promote the crystallisation of uric acid. A persistent urine pH > 5.8 in the daily profile is an indication of RTA, provided urinary tract infection has been excluded.

Microscopy of the urinary sediment can help to discover rare stone types, as crystals of 2,8-dihydroxyadenine, cystine and xanthine are pathognomonic for the corresponding disease.

Following this programme, the most probable stone type can be assumed and a specific evaluation of the patient can follow.

However, if any expulsed stone material of the patient is available it should be analysed by the means of diagnosis confirmation or - in the adverse case - diagnosis correction.

Table 36: Investigating a patient with stones of unknown composition

Investigation	Rationale for investigation
Medical history	Stone history (former stone events, family history) Dietary habits Medication chart
Diagnostic imaging	Ultrasound in case of a suspected stone NCCT (Determination of the Houndsfield unit provides information about the possible stone composition)
Blood analysis	Creatinine Calcium (ionized calcium or total calcium + albumin) Uric acid
Urinalysis	Urine pH profile (measurement after each voiding, minimum 4 times a day) Dipstick test: leucocytes, erythrocytes, nitrite, protein, urine pH, specific weight Urine culture Microscopy of urinary sediment (morning urine)

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12. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

APRT	adenine phosphoribosyl transferase
CI	credible intervals
CT	Computed tomography
EAU	European Association of Urology
ESWL	extracorporeal shock wave lithotripsy
GR	grade of recommendation
HCl	hydrochloric acid
HIRU	Health Information Research Unit
Ho:YAG	holmium:yttrium-aluminium-garnet [laser]
HPT	hyperparathyroidism
HU	Hounsfield Units
INR	international normalised ratio
IVU	intravenous urography
JESS	joint expert speciation system
KUB	Kidney ureter bladder
LE	level of evidence
LED	light-emitting diode
MET	medical expulsive therapy
MMC	myelomeningocele
MRU	magnetic resonance urography
NC	nephrocalcinosis
NCCT	Non-contrast enhanced computed tomography
NSAIDs	non-steroidal anti-inflammatory drugs
PCN	percutaneous nephrostomy
PH	Primary Hyperoxaluria
PNL	percutaneous nephrolithotomy
PTT	partial thrombolastin time
RCT	Randomised controlled trial
RTA	Renal tubular acidosis
SFR	stone free rates
SIGN	Scottish Intercollegiate Guidelines Network
SWL	shockwave lithotripsy
THAM	tris-hydroxymethyl-aminomethane
UPJ	Ureteropelvic junction
URS	ureterorenoscopy
US	ultrasonography

Conflict of interest

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