Guidelines on Urolithiasis

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1. METHODOLOGY

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

The document covers most aspects of the disease, which is still a cause of significant morbidity despite technological and scientific advances. The Panel is aware of the geographical variations in healthcare provision.

1.2 Data identification
For this 2012 (limited) update of the Urolithiasis guidelines, a scoping search, covering all content, was performed. Time frame of the search was November 2010 to August 10th, 2011. This search was limited to level 1 evidence (systematic reviews [SRs] and meta-analyses of randomised controlled trials [RCTs]) and English language publications in peer-reviewed journals. Animal studies were excluded.

For this limited update 124 unique records were identified of which 28 new references were selected for inclusion in this document. For a number of sections which included recommendations upgraded following panel consensus (High-risk stone formers and familiar risk [2.6], Patient evaluation [3.1.2] and Decompression of obstructed kidney [4.2.1]) additional verification searches were done to assess whether additional evidence has become available over the past year. These searches were not limited to level 1 data. Only in two instances could a higher level of evidence (not influencing the grade of recommendation) be found (3.2.2 Recommendations for repeat analysis of stone composition and 5.7.2.1 Indications for laparoscopic stone surgery). A more detailed summary of changes can be found below.

Annual scoping searches will be repeated as a standard procedure.

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

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

For the 2011 full text update, 4,013 papers were identified and 688 were included in the 2011 print, which also included key publications from other sources were proposed by panel members. Initial assessment and selection were based on citation and abstract only, and when in doubt, full-text papers were consulted. Meta-analysis of the stone-free rates for the section on ureteral calculi was updated. 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 current guidelines by an expert panel. It must be emphasised that clinical guidelines present the best evidence available but following the recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients - also taking personal values and preferences/individual circumstances of patients into account.

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

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

* Modified from Sackett et al. (1).

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

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

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

Table 2: Grade of recommendation (GR)*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nature of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial</td>
</tr>
<tr>
<td>B</td>
<td>Based on well-conducted clinical studies, but without RCTs</td>
</tr>
<tr>
<td>C</td>
<td>Made despite the absence of directly applicable clinical studies of good quality</td>
</tr>
</tbody>
</table>

*Modified from Sackett et al. (1).

1.5 Publication history

The current guidelines present a limited update following a complete update of the 2011 print version. The first EAU Guidelines on Urolithiasis were published in 2000. Subsequent updates were in 2001 (partial), 2005 (comprehensive), 2008 (comprehensive), and 2009 and 2010 (limited). Several summaries have been published in scientific journals; the first in 2001 (5) and subsequently in 2007 (6,7).

A quick reference document presenting the main findings of the urolithiasis guidelines is also available with several scientific publications in the EAU journal European Urology and 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/.

This document was peer-reviewed prior to publication.

1.5.1 Summary of changes

New literature included

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.3</td>
<td>X-ray characteristics</td>
</tr>
<tr>
<td>2.6</td>
<td>Risk groups for stone formation (Table 6)</td>
</tr>
<tr>
<td>5.3.4</td>
<td>Factors affecting success of MET</td>
</tr>
<tr>
<td>5.5.3</td>
<td>Best clinical practice</td>
</tr>
</tbody>
</table>
5.6.1.5.4 Puncture
5.6.1.5.7 Management of complications following PNL (new Table 14)
5.6.2.2.1 Pre-operative work up and preparations
5.6.2.2.6 Stone extraction new data added
5.6.2.2.8 Stenting prior to, and after URS
5.7.2 Laparoscopic surgery
6.4 Selection of procedure for active removal of kidney stones

New literature resulting in a change of LE in the recommendation sections

3.1 Diagnostic imaging: Patient evaluation (3.1.2) for patients in whom treatment of renal stones is planned (NCCT recommended in favour of IVU)
3.2 Recommendations for repeat stone analysis in patients: (LE:2 - old listing LE:3)
5.7.2.1 Indications for laparoscopic stone surgery - recommendations (LE: 3 - old listing LE: 4)

New literature has been including in the following sections resulting in new recommendations or a change in ranking (GR)

5.7.2.1 Indications for laparoscopic stone surgery - New recommendation on large impact stones or when endoscopic lithotripsy or SWL have failed.
6.4.2 Selection of procedure for active removal of kidney stones.

1.6 References
2. CLASSIFICATION OF STONES

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

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

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

2.3 X-ray characteristics
Stones can be classified according to plain X-ray appearance (kidney-ureter-bladder radiography; KUB) (Table 3), which varies according to mineral composition. Non-contrast-enhanced computer tomography (NCCT) can be used to classify stones according to density, inner structure and composition, which can affect treatment decisions (Section 6.3.4) (1,2).

Table 3: X-ray characteristics

<table>
<thead>
<tr>
<th>Radiopaque</th>
<th>Poor radiopacity</th>
<th>Radiolucent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium oxalate dihydrate</td>
<td>Magnesium ammonium phosphate</td>
<td>Uric acid</td>
</tr>
<tr>
<td>Calcium oxalate monohydrate</td>
<td>Apatite</td>
<td>Ammonium urate</td>
</tr>
<tr>
<td>Calcium phosphates</td>
<td>Cystine</td>
<td>Xanthine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2,8-dihydroxyadenine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>'Drug-stones’</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Section 11.11)</td>
</tr>
</tbody>
</table>

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

Table 4: Stones classified by aetiology*

<table>
<thead>
<tr>
<th>Non-infection stones</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>calcium oxalate</td>
<td>calcium phosphate (including brushite and carbonate apatite)</td>
<td>uric acid</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infection stones</th>
<th>Magnesium ammonium phosphate</th>
<th>carbonate apatite</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Genetic causes</th>
<th>cystine</th>
<th>xanthine</th>
</tr>
</thead>
</table>

| Drug stones                | 2,8-dihydroxyadenine           |                             |

*Section 11.4.2

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

<table>
<thead>
<tr>
<th>Chemical composition</th>
<th>Mineral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium oxalate monohydrate</td>
<td>whewellite</td>
</tr>
<tr>
<td>Calcium oxalate dihydrate</td>
<td>wheddellite</td>
</tr>
<tr>
<td>Uric acid dihydrate</td>
<td>uricite</td>
</tr>
<tr>
<td>Ammonium urate</td>
<td></td>
</tr>
<tr>
<td>Magnesium ammonium phosphate</td>
<td>struvite</td>
</tr>
<tr>
<td>Carbonate apatite (phosphate)</td>
<td>dahlite</td>
</tr>
<tr>
<td>Calcium hydrogenphosphate</td>
<td>brushite</td>
</tr>
<tr>
<td>Cystine</td>
<td></td>
</tr>
<tr>
<td>Xanthine</td>
<td></td>
</tr>
<tr>
<td>2,8-dihydroxyadenine</td>
<td></td>
</tr>
<tr>
<td>‘Drug stones’</td>
<td></td>
</tr>
</tbody>
</table>

2.6 Risk groups for stone formation

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

About 50% of recurrent stone formers have just one lifetime recurrence (3,4). Highly recurrent disease is observed in slightly more than 10% of patients. Stone type and disease severity determine low or high risk of recurrence (Table 6) (5-7).

Table 6: High-risk stone formers (7-12)

<table>
<thead>
<tr>
<th>General factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early onset of urolithiasis (especially children and teenagers)</td>
</tr>
<tr>
<td>Familial stone formation</td>
</tr>
<tr>
<td>Brushite-containing stones (calcium hydrogen phosphate; CaHPO₄·2H₂O)</td>
</tr>
<tr>
<td>Uric acid and urate-containing stones</td>
</tr>
<tr>
<td>Infection stones</td>
</tr>
<tr>
<td>Solitary kidney (the solitary kidney itself does not particularly increase risk of stone formation, but prevention of stone recurrence is of more importance)</td>
</tr>
<tr>
<td>Diseases associated with stone formation</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Nephrocalcinosis</td>
</tr>
<tr>
<td>Gastrointestinal diseases (i.e. jejuno-ileal bypass, intestinal resection, Crohn's disease, malabsorptive conditions, enteric hyperoxaluria after urinary diversion)</td>
</tr>
<tr>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Genetically determined stone formation</td>
</tr>
<tr>
<td>Cystinuria (type A, B, AB)</td>
</tr>
<tr>
<td>Primary hyperoxaluria (PH)</td>
</tr>
<tr>
<td>Renal tubular acidosis (RTA) type I</td>
</tr>
<tr>
<td>2,8-dihydroxyadenine</td>
</tr>
<tr>
<td>Xanthinuria</td>
</tr>
<tr>
<td>Lesch-Nyhan syndrome</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Drugs associated with stone formation (Section 11.11)</td>
</tr>
<tr>
<td>Anatomical abnormalities associated with stone formation</td>
</tr>
</tbody>
</table>
Medullary sponge kidney (tubular ectasia)
Ureteropelvic junction (UPJ) obstruction
Calyceal diverticulum, calyceal cyst
Ureteral stricture
Vesico-uretero-renal reflux
Horseshoe kidney
Ureterocele

2.7 References

3. DIAGNOSIS

3.1 Diagnostic imaging
Patients with urinary stones usually present with loin pain, vomiting, and sometimes fever, but may also be asymptomatic. Standard evaluation includes detailed medical history and physical examination. Clinical diagnosis should be supported by appropriate imaging.
If available, ultrasonography should be used as the primary diagnostic imaging tool although pain relief, or any other emergency measures should not be delayed by imaging assessments. It is safe (no risk of radiation), reproducible and inexpensive. It can identify stones located in the calices, pelvis, and pyelo-ureteric and vesicoureteric junctions, as well as upper urinary tract dilatation. For stones > 5 mm, ultrasound has a sensitivity of 96% and specificity of nearly 100% (1). For all stone locations, sensitivity and specificity of ultrasound reduces to 78% and 31%, respectively (1).

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

**Recommendation**

<table>
<thead>
<tr>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>A</td>
</tr>
</tbody>
</table>

*Upgraded following panel consensus.*

3.1.1 **Evaluation of patients with acute flank pain**

Non-contrast-enhanced computer tomography has become the standard for diagnosing acute flank pain, and has replaced intravenous urography (IVU), which was the gold standard for many years. NCCT can determine stone diameter and density. When stones are absent, the cause of abdominal pain should be identified. Compared with IVU, NCCT shows higher sensitivity and specificity for identifying urinary stones (Table 7) (4-8).

**Table 7: Comparison of non-contrast-enhanced computer tomography (NCCT) and intravenous urography (IVU)**

<table>
<thead>
<tr>
<th>Reference</th>
<th>NCCT</th>
<th></th>
<th>IVU</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller (5)</td>
<td>96%</td>
<td>100%</td>
<td>87%</td>
<td>94%</td>
</tr>
<tr>
<td>Niall (7)</td>
<td>100%</td>
<td>92%</td>
<td>64%</td>
<td>92%</td>
</tr>
<tr>
<td>Sourtzis (4)</td>
<td>100%</td>
<td>100%</td>
<td>66%</td>
<td>100%</td>
</tr>
<tr>
<td>Yilmaz (6)</td>
<td>94%</td>
<td>97%</td>
<td>52%</td>
<td>94%</td>
</tr>
<tr>
<td>Wang (8)</td>
<td>99%</td>
<td>100%</td>
<td>51%</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Recommendation**

<table>
<thead>
<tr>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>A</td>
</tr>
</tbody>
</table>

NCCT should be used to confirm stone diagnosis in patients with acute flank pain, because it is superior to IVU (9,10).

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

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

Radiation risk can be reduced by low-dose CT (16). In patients with body mass index (BMI) < 30, low-dose CT was 86% sensitive for detecting ureteric stones < 3 mm and 100% sensitive for detecting calculi > 3 mm (17). A meta-analysis of prospective studies (18) showed that low-dose CT diagnosed urolithiasis with a pooled sensitivity of 96.6% (95% CI: 95.0-97.8) and specificity of 94.9% (92.0-97.0).
Table 8: Radiation exposure of imaging modalities (19-22)

<table>
<thead>
<tr>
<th>Method</th>
<th>Radiation exposure (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KUB</td>
<td>0.5-1</td>
</tr>
<tr>
<td>IVU</td>
<td>1.3-3.5</td>
</tr>
<tr>
<td>Regular-dose NCCT</td>
<td>4.5-5</td>
</tr>
<tr>
<td>Low-dose NCCT</td>
<td>0.97-1.9</td>
</tr>
<tr>
<td>Enhanced CT</td>
<td>25-35</td>
</tr>
</tbody>
</table>

Recommendation

In patients with BMI < 30, low-dose NCCT should be used. 1b A

3.1.2 Evaluation of patients for whom further treatment of renal stones 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 collecting system, as well as measurement of stone density and skin-to-stone distance. IVU may also be used.

Recommendation

A renal contrast study (enhanced CT or IVU) is indicated when planning treatment for renal stones. 3 A*

* Upgraded based on panel consensus.

3.1.3 References

3.2 Diagnostics - metabolism-related

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

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

<table>
<thead>
<tr>
<th>Urine</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary sediment/dipstick test of spot urine sample</td>
<td></td>
</tr>
<tr>
<td>- red cells</td>
<td>A*</td>
</tr>
<tr>
<td>- white cells</td>
<td></td>
</tr>
<tr>
<td>- nitrite</td>
<td></td>
</tr>
<tr>
<td>- approximate urine pH</td>
<td></td>
</tr>
<tr>
<td>Urine culture or microscopy</td>
<td>A</td>
</tr>
<tr>
<td>Blood</td>
<td></td>
</tr>
</tbody>
</table>
3.2.1 Basic analysis - non-emergency stone patients

Biochemical work-up is similar for all stone patients. However, examination of sodium, potassium, CRP, blood coagulation time can be omitted for non-emergency cases.

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

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

3.2.2 Analysis of stone composition

Stone analysis should be performed in all first-time stone formers.
In clinical practice, repeat stone analysis is needed in case of:
• recurrence under pharmacological prevention;
• early recurrence after interventional therapy with complete stone clearance;
• late recurrence after a prolonged stone-free period (6).

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

The preferred analytical procedures are infrared spectroscopy (IRS) or X-ray diffraction (XRD) (5, 7-10). Equivalent results can be obtained by polarisation microscopy, but only in centres with expertise. Chemical analysis (wet chemistry) is generally deemed to be obsolete (5).

### Table 10: Accuracy of substance identification in stone analysis (5)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Chemical analysis (%)</th>
<th>Infrared spectroscopy</th>
<th>X-ray diffraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric acid</td>
<td>81.0</td>
<td>97.6</td>
<td>97.9</td>
</tr>
<tr>
<td>Ammonium urate</td>
<td>83.1</td>
<td>95.0</td>
<td>96.0</td>
</tr>
<tr>
<td>Cystine</td>
<td>93.5</td>
<td>99.1</td>
<td>98.5</td>
</tr>
<tr>
<td>Xanthine</td>
<td>28.4</td>
<td>96.3</td>
<td>93.2</td>
</tr>
<tr>
<td>2,8-Dihydroxyadenine</td>
<td>6.0</td>
<td>80.0</td>
<td>69.6</td>
</tr>
<tr>
<td>Whewellite</td>
<td>85.6</td>
<td>97.8</td>
<td>98.7</td>
</tr>
<tr>
<td>Struvite</td>
<td>89.5</td>
<td>97.9</td>
<td>98.0</td>
</tr>
<tr>
<td>Brushite</td>
<td>69.6</td>
<td>97.4</td>
<td>100.0</td>
</tr>
<tr>
<td>Apatite</td>
<td>79.4</td>
<td>93.9</td>
<td>100.0</td>
</tr>
<tr>
<td>Calcite</td>
<td>66.0</td>
<td>98.5</td>
<td>98.2</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>38.9</td>
<td>98.6</td>
<td>82.4</td>
</tr>
<tr>
<td>Silicium dioxide</td>
<td>21.6</td>
<td>95.6</td>
<td>98.1</td>
</tr>
<tr>
<td>Gypsum</td>
<td>38.6</td>
<td>96.0</td>
<td>77.1</td>
</tr>
</tbody>
</table>
4. TREATMENT OF PATIENTS WITH RENAL COLIC

4.1 Renal colic

4.1.1 Pain relief

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

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

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

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>In acute stone episodes, pain relief should be initiated immediately.</td>
<td>A</td>
</tr>
<tr>
<td>Whenever possible, an NSAID should be the first drug of choice.</td>
<td>A</td>
</tr>
</tbody>
</table>
4.1.2 **Prevention of recurrent renal colic**

Most ureteral stones pass spontaneously (Section 5.1.1), and facilitation of passage is discussed in Section 5.3.

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

In a double-blind, placebo-controlled trial, recurrent pain episodes of stone colic were significantly fewer in patients treated with NSAIDs (as compared to no NSAIDs) during the first 7 days of treatment (10).

Daily \( \alpha \)-blockers reduce recurrent colic (LE: 1a) (Section 5.3) (12,13).

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

4.1.3 **Recommendations for analgesia during renal colic**

<table>
<thead>
<tr>
<th>LE</th>
<th>GR</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>A</td>
<td>1-4</td>
</tr>
<tr>
<td>4</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

*Recommended to counteract recurrent pain after ureteral colic.*

**Affects glomerular filtration rate (GFR) in patients with reduced but not normal renal function (LE: 2a) (14).**

Although NSAIDs constitute the first choice for medical management of acute renal colic pain, spasmyotics may be given when parenteral administration of a non-narcotic agent is mandatory (third-line treatment) (15,16).

4.1.4 **References**


4.2 Management of sepsis in obstructed kidney

Obstructed, infected kidney is a urological emergency. Urgent decompression is necessary to prevent further complications in infected hydronephrosis secondary to a stone-induced, either unilateral or bilateral renal obstruction.

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

4.2.1 Decompression

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

- placement of an indwelling ureteral catheter under general anaesthesia;
- 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. There is no good-quality evidence to suggest that ureteric stenting under general anaesthesia has more complications than percutaneous nephrostomy. However, the latter has the advantage of avoiding general anaesthesia and instrumentation in the urinary tract (1,4-6).

Only two RCTs (2,5) have assessed decompression of acute infected hydronephrosis. The complications of percutaneous nephrostomy insertion have been reported consistently, but those of ureteric stent insertion are less well described (1).

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

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

Exceptionally, emergency nephrectomy may become necessary for severe sepsis and/or abscess formation.

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>For decompression of the renal collecting system, ureteral stents and percutaneous nephrostomy catheters are equally effective.</td>
<td>1b</td>
</tr>
</tbody>
</table>
4.2.2 Further measures

Following urgent decompression of the obstructed and infected system, urine samples should be sent for culture-antibiogram sensitivity testing, and antibiotics should be initiated immediately thereafter. The regimen should be revisited in the light of the culture-antibiogram test. Intensive care might become necessary.

### Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collect urine for antibiogram test following decompression.</td>
<td>A*</td>
</tr>
<tr>
<td>Start antibiotics immediately thereafter (+ intensive care if necessary).</td>
<td></td>
</tr>
<tr>
<td>Revisit antibiotic treatment regimen following antibiogram findings.</td>
<td></td>
</tr>
</tbody>
</table>

* Upgraded based on panel consensus.

### References

5. STONE RELIEF

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

5.1 Observation of ureteral stones

5.1.1 Stone-passage rates

There are only limited data about spontaneous stone passage according to size (1,2). A meta-analysis of 328 patients harbouring ureteral stones < 10 mm investigated the likelihood of ureteral stone passage (Table 11) (1). These studies had limitations including non-standardisation of stone size measurement, and lack of analysis of stone position, stone-passage history, and time to stone passage.

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

<table>
<thead>
<tr>
<th>Stone size</th>
<th>passage</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 mm (n = 224)</td>
<td>68%</td>
<td>(95% CI 46-85%)</td>
</tr>
<tr>
<td>&gt; 5 mm (n = 104)</td>
<td>47%</td>
<td>(95% CI 36-58%)</td>
</tr>
<tr>
<td>&lt; 2 mm</td>
<td>31 days</td>
<td></td>
</tr>
<tr>
<td>2-4 mm</td>
<td>40 days</td>
<td></td>
</tr>
<tr>
<td>&gt; 4-6 mm</td>
<td>39 days</td>
<td></td>
</tr>
</tbody>
</table>

95% of stones up to 4 mm pass within 40 days (2).

**Recommendations**

In patients with newly diagnosed ureteral stones < 10 mm, and if active removal is not indicated (Chapter 6), observation with periodic evaluation is optional initial treatment.

*see also Section 5.3, Medical expulsive therapy (MET).

5.2 Observation of kidney stones

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

**Statement**

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

**Recommendations**

Kidney stones should be treated in case of growth, formation of de novo obstruction, associated infection, and acute or chronic pain.

Comorbidity and patient preference need to be taken into consideration when making treatment decisions.

If kidney stones are not treated, periodic evaluation is needed.

* Upgraded based on panel consensus.

5.3 Medical expulsive therapy (MET)

Drugs that expel stones might act by relaxing ureteral smooth muscle through inhibition of calcium channel pumps or α-1 receptor blockade (3,4).

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

Meta-analyses have shown that patients with ureteral stones treated with α-blockers or nifedipine are more likely to pass stones with less episodes of colic than those not receiving such therapy (3,5).
There is growing evidence that MET accelerates spontaneous passage of ureteral stones and fragments generated with SWL, and limits pain (3-15).

**5.3.1 Choice of medical agent**

**5.3.1.1 Alpha-blockers**

Tamsulosin is one of the most commonly used alpha-blockers (3,5,16-19). However, one small study has suggested that tamsulosin, terazosin and doxazosin are equally effective, indicating a possible class effect (20). This is also indicated by several trials demonstrating increased stone expulsion using doxazosin (4,20,21) terazosin (20,22) alfuzosin (23-26) and naftopidil (27,28).

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Several trials have demonstrated increased stone expulsion using tamsulosin, doxazosin, terazosin, alfuzosin and naftopidil.</td>
<td>1b</td>
</tr>
</tbody>
</table>

**5.3.1.2 Calcium-channel blockers**

With regard to the class effect of calcium-channel blockers, only nifedipine has been investigated (LE = 1a) (3,8-10, 29,30).

**5.3.1.2.1 Tamsulosin versus nifedipine**

Administration of tamsulosin and nifedipine is safe and effective in patients with distal ureteral stones with renal colic. However, tamsulosin is significantly better than nifedipine in relieving renal colic and facilitating and accelerating ureteral stone expulsion (10,29,30).

**5.3.1.3 Corticosteroids**

Based on studies with a limited number of patients (31,32; LE 1b), no recommendation for the use of corticosteroids in combination with alpha-blockers in MET can be made.

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is no evidence to support the use of corticosteroids as monotherapy for MET. Insufficient data exist to support the use of corticosteroids in combination with alpha-blockers as an accelerating adjunct (3,20,31,32).</td>
<td>1b</td>
</tr>
</tbody>
</table>

**Recommendations for MET**

For MET, alpha-blockers or nifedipine are recommended.

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.†

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.

Patients should be followed once between 1 and 14 days to monitor stone position and to assess for hydronephrosis.

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

* Upgraded based on panel consensus.

**5.3.2 Factors affecting success of medical expulsive therapy (Tamsulosin)**

**5.3.2.1 Stone size**

Due to the high likelihood of spontaneous passage of stones up to ~5 mm, MET is less likely to increase the stone-free rate (4,33-36) (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 have investigated distal ureteral stones (3). One RCT has assessed the effect of tamsulosin on spontaneous passage of proximal ureteral calculi 5-10 mm. The main effect was to encourage stone migration to a more distal part of the ureter (37) (LE: 1b).

**5.3.2.3 Medical expulsive therapy after extracorporeal shock wave lithotripsy (SWL)**

Clinical studies and several meta-analyses have shown that MET after SWL for ureteral or renal stones can

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expedite expulsion and increase stone-free rates and reduce analgesic requirements (6,11,38-46) (LE: 1a).

5.3.2.4 Medical expulsive therapy after ureteroscopy
MET following holmium:YAG laser lithotripsy increases stone-free rates and reduces colic episodes (47) (LE: 1b).

5.3.2.5 Medical expulsive therapy and ureteral stents (section 5.6.2.2.8)

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

5.3.3 Medical expulsive therapy in the paediatric population
A recent study has investigated the expulsion rate and time to expulsion of ureteral stones ≤ 10 mm in children aged 2-14 years receiving doxazosin or ibuprofen, but failed to demonstrate the effectiveness of doxazosin (48) (LE: 2a).

<table>
<thead>
<tr>
<th>Statements</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET has an expulsive effect also on proximal ureteral stones.</td>
<td>1b</td>
</tr>
<tr>
<td>After SWL for ureteral or renal stones, MET seems to expedite and increase stone-free rates, reducing additional analgesic requirements.</td>
<td>1a</td>
</tr>
<tr>
<td>MET in children cannot be recommended due to the limited data in this specific population.</td>
<td>4</td>
</tr>
</tbody>
</table>

5.3.4 References


5.4 Chemolytic dissolution of stones

Oral or percutaneous irrigation chemolysis of stones or their fragments can be useful first-line therapy. It may also be an adjunct to SWL, percutaneous nephrolithotomy (PNL), 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 SWL and chemolysis is a minimal invasive option for patients with partial or complete infection staghorn stones who are not suitable for PNL. Stone fragmentation leads to increased stone surface area and improved efficacy of chemolitholysis.

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

5.4.1 Percutaneous irrigation chemolysis

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>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*.</td>
<td>A</td>
</tr>
<tr>
<td>Pressure- and flow-controlled systems should be used if available.</td>
<td></td>
</tr>
</tbody>
</table>

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

Table 12: Methods of percutaneous irrigation chemolysis

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

5.4.2 Oral chemolysis

Oral chemololitholysis is efficient only for uric acid calculi, and is based on alkalinisation of urine by application of alkaline citrate or sodium bicarbonate (14,16,18,19).
When chemolitholysis is planned, the pH should be adjusted to 7.0-7.2. Addition of allopurinol may support chemolysis and prevention of recurrent stones. No formal recommendation on allopurinol use can be given.

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

**Recommendations**

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

### References

5.5 Extracorporeal shock wave lithotripsy (SWL)

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

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

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

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

5.5.1 Contraindications of extracorporeal shock wave lithotripsy

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

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

5.5.2 Stenting before carrying out extracorporeal shock wave lithotripsy

5.5.2.1 Stenting in kidney stones

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

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

5.5.2.2 Stenting in ureteral stones

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

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine stenting is not recommended as part of SWL treatment of ureteral stones.</td>
<td>1b</td>
<td>A</td>
</tr>
</tbody>
</table>
5.5.3  **Best clinical practice**

5.5.3.1  **Pacemaker**

Patients with a pacemaker can be treated with SWL, provided that appropriate technical precautions are taken; patients with implanted cardioverter defibrillators must be managed with special care (firing mode temporarily reprogrammed during SWL treatment). However, this might not be necessary with new-generation lithotripters (11).

5.5.3.2  **Shock wave rate**

Lowering shock wave frequency from 120 to 60-90 shock waves/min improves stone-free rate (12-16). Tissue damage increases with shock wave frequency (17,18).

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>The optimal shock wave frequency is 1.0-1.5 Hz (16).</td>
<td>1a</td>
<td>A</td>
</tr>
</tbody>
</table>

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

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

Starting SWL on a lower energy setting with stepwise power (and SWL sequence) ramping can achieve vasoconstriction during treatment (19), which prevents renal injury (20). Animal studies (21) and a prospective randomised study (22) have shown better stone-free rate (96% vs. 72%) using stepwise power ramping, but no difference has been found for fragmentation or evidence of complications after SWL, irrespective of whether ramping was used (23).

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

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical experience has shown that repeat sessions are feasible (within 1 day for ureteral stones).</td>
<td>4</td>
</tr>
</tbody>
</table>

5.5.3.4  **Improvement of acoustic coupling**

Proper acoustic coupling between the cushion of the treatment head and the patient’s skin is important. Defects (air pockets) in the coupling gel reflect 99% of shock waves. Only a 2% defect in the gel layer covering the cushion reduces 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 applied to the water cushion straight from the container, rather than by hand (26).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure correct use of the coupling gel because this is crucial for effective shock wave transportation (24).</td>
<td>2a</td>
<td>B</td>
</tr>
</tbody>
</table>

5.5.3.5  **Procedural control**

Results of treatment are operator dependent, and better results are obtained by urologists who treat larger numbers of patients. During the procedure, careful imaging control of localisation contributes to outcome quality (27).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintain careful fluoroscopic and/or ultrasonographic monitoring during the procedure.</td>
<td>4</td>
<td>A*</td>
</tr>
</tbody>
</table>

* 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).
5.5.3.7 Antibiotic prophylaxis
No standard prophylaxis before SWL is recommended. However, prophylaxis is recommended in case of internal stent placement ahead of anticipated treatments and in the presence of increased bacterial burden (e.g. indwelling catheter, nephrostomy tube, infectious stones) (31,32).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use proper analgesia because it improves treatment results by limiting induced movements and excessive respiratory excursions.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.5.3.8 Medical expulsive therapy after extracorporeal shock wave lithotripsy
MET after SWL for ureteral or renal stones can expedite expulsion and increase stone-free rates, as well as reduce additional analgesic requirements (33-43) (Section 5.3.2.3).

5.5.4 Complications of extracorporeal shock wave lithotripsy
Compared to PNL and ureteroscopy, there are fewer overall complications with SWL (44,45) (Table 13).

Table 13: SWL-related complications (1,4,44-46)

<table>
<thead>
<tr>
<th>Complications</th>
<th>%</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related to stone fragments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steinstrasse</td>
<td>4-7</td>
<td>47-49</td>
</tr>
<tr>
<td>Regrowth of residual fragments</td>
<td>21-59</td>
<td>50</td>
</tr>
<tr>
<td>Renal colic</td>
<td>2-4</td>
<td>46</td>
</tr>
<tr>
<td>Infectious</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteriuria in non-infection stones</td>
<td>7.7-23</td>
<td>50,51</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1-2.7</td>
<td>50,51</td>
</tr>
<tr>
<td>Tissue effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Haematoma, symptomatic</td>
<td>&lt; 1</td>
<td>1,52</td>
</tr>
<tr>
<td>Renal Haematoma, asymptomatic</td>
<td>4-19</td>
<td>1,52</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysrhythmia</td>
<td>11-59</td>
<td>50,53</td>
</tr>
<tr>
<td>Morbid cardiac events</td>
<td>Case reports</td>
<td>50,53</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowel perforation</td>
<td>Case reports</td>
<td>54-56</td>
</tr>
<tr>
<td>Liver, spleen haematoma</td>
<td>Case reports</td>
<td>56-58</td>
</tr>
</tbody>
</table>

The relationship between SWL and hypertension or diabetes is unclear. Published data are contradictory and no conclusion can be reached (9,59-61).

5.5.5 References


5.6 Endourology techniques

5.6.1 Percutaneous nephrolithotomy (PNL)

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 endourological procedures. Currently, percutaneous nephrolithotomy (PNL) is a minimally invasive surgical procedure for removal of kidney stones (1,2). Rigid and flexible nephroscopes of different sizes have been developed.

5.6.1.1 Rigid nephroscopes

Rigid nephroscopes are available in diameters up to 28 Ch [Charrière (French) gauge], allowing maximal working and irrigation channels. Thinner nephroscopes are available for Mini-PNL (also known as Mini-perc), which uses nephroscopes of diameter 11-18 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 results in smaller working channels.

Mini-PNL is associated with less morbidity than standard PNL. However, the benefit of using a smaller-calibre nephroscope to preserve 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) (Section 9.2.3).

5.6.1.2 Flexible nephroscopes

In complex cases, such as multiple or staghorn stones, or difficult anatomy, such as horseshoe kidneys, the use of rigid nephroscopes may require multiple access procedures. However, the use of flexible nephroscopes, or combination 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 to improve visibility and handling. Complete stone clearance is viewed endoscopically and by X-ray.

5.6.1.3 Intracorporeal lithotripsy

Intracorporeal lithotripsy can be performed in several different ways (devices are discussed in Section 5.6.2.2.7). During PNL procedures, ultrasonic or pneumatic lithotripters are most commonly used. Electrohydraulic intracorporeal lithotripsy is effective even for hard kidney stones; however, due to potential damage to surrounding tissue, it should only be used in carefully selected cases, such as hard cystine stones.

With the increase in the use of flexible nephroscopes, the holmium:ytrrium-aluminium-garnet (Ho:YAG) laser is becoming more important in ureteroscopy and PNL. It can be used for lithotripsy 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).

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasonic, ballistic and Ho:YAG devices are recommended for intracorporeal lithotripsy using rigid nephroscopes.</td>
<td>A*</td>
</tr>
<tr>
<td>When using flexible instruments, the Ho:YAG laser is currently the most effective device.</td>
<td></td>
</tr>
</tbody>
</table>

*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 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 calices.
5.6.1.5 Best clinical practice

5.6.1.5.1 Contraindications

All contraindications for general anaesthesia apply. Patients receiving anticoagulant therapy must be monitored carefully pre- and postoperatively. Anticoagulant therapy must be discontinued before PNL (6).

Other important contraindications include:
- untreated UTI;
- atypical bowel interposition;
- tumour in the presumptive access tract area;
- potential malignant kidney tumour;
- pregnancy (see Section 8.2).

5.6.1.5.2 Preoperative 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).

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

* Upgraded based on panel consensus.

5.6.1.5.3 Positioning of the patient

Traditionally, the patient is positioned prone for PNL. Supine position is also possible, with or without flank upholstering. Both positions are equally safe. The advantages of the supine position for PNL are (9,10):
- shorter operating time;
- possibility of simultaneous retrograde transurethral manipulation;
- more convenient position for the operator;
- easier anaesthesia.

Although the supine position confers some advantages (9,10), it depends on appropriate equipment being available to position the patient correctly, e.g. X-ray devices and operating table. The supine position can limit the manoeuvrability of instruments (11).

5.6.1.5.4 Puncture

After the insertion of a ureteric catheter, balloon or otherwise, 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 are more likely when operating on the left kidney. The colon is not reliably detectable with ultrasound, so preprocedural imaging is recommended. In particular, preoperative CT provides further information (13,14). However, ultrasound-guided puncture will allow identification of the tissue between the skin and kidney and lower the incidence of bowel injury (15).

5.6.1.5.5 Dilatation

Dilatation of the percutaneous access tract can be achieved using a metallic telescope, single (serial) dilators, or a ureteral balloon dilator. Use of balloon dilatation can reduce blood transfusion rates (16). One-stage dilatation has been shown to be safe and effective, even in patients with a history of open surgery on the same kidney (17,18).

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;
• solitary kidney;
• bleeding diathesis;
• planned percutaneous chemolitholysis.

Ureteral stenting at the end of the procedure is common procedure using antegrade placement of a JJ stent. 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 JJ stent (19).

Tubeless PNL is performed without a nephrostomy tube. When neither a nephrostomy tube nor a ureteral stent is introduced, the procedure is known as totally tubeless PNL. In uncomplicated cases, the latter procedure results in a shorter hospital stay, with no disadvantages reported (20-24).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>In uncomplicated cases, tubeless (without nephrostomy tube) or totally tubeless (without nephrostomy tube and without ureteral stent) PNL procedures provide a safe alternative.</td>
<td>1b</td>
<td>A</td>
</tr>
</tbody>
</table>

5.6.1.5.7 Management of complications

The most common postoperative complications associated with PNL are fever and bleeding, urinary leakage and problems due to residual stones. A recent review on complications following PNL used the validated Dindo-modified Clavien system and showed a normal (uncomplicated) postoperative course in 76.7% of patients (Clavien 0) (25) (Table 14). See also the EAU Guidelines on Reporting and Grading of Complications after Surgical Procedures (26).

Table 14: Complications following PNL

<table>
<thead>
<tr>
<th>Complications</th>
<th>Transfusion</th>
<th>Embolisation</th>
<th>Urinoma</th>
<th>Fever</th>
<th>Sepsis</th>
<th>Thoracic complication</th>
<th>Organ injury</th>
<th>Death</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Range)</td>
<td>(0-20%)</td>
<td>(0-1.5%)</td>
<td>(0-1%)</td>
<td>(0-32.1%)</td>
<td>(0.3-1.1%)</td>
<td>(0-11.6%)</td>
<td>(0-1.7%)</td>
<td>(0-0.3%)</td>
<td>1a</td>
</tr>
<tr>
<td>N = 11,929</td>
<td>7%</td>
<td>0.4%</td>
<td>0.2%</td>
<td>10.8%</td>
<td>0.5%</td>
<td>1.5%</td>
<td>0.4%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Perioperative fever can occur, even with a sterile preoperative urinary culture and perioperative antibiotic prophylaxis, because the kidney stones themselves may be a source of infection. Intraoperative kidney stone culture may therefore help to select postoperative antibiotics (27,28). Intraoperative irrigation pressure < 30 mm Hg and unobstructed postoperative urinary drainage may be important factors in preventing postoperative sepsis. Well-positioned or specially designed access sheaths can prevent high intrapelvic irrigation pressure (29-31).

Bleeding after PNL may be due to intraparenchymal haemorrhage or acquired intrarenal aneurysm. With the former, brief clamping of the nephrostomy may stem bleeding. The latter may be marked by intense bleeding, and it can be treated by super-selective embolic occlusion of the artery supplying the aneurysm (32).

5.6.1.6 References


5.6.2 **Ureterorenoscopy (URS) (including retrograde access to renal collecting system)**
During the past 20 years, ureterorenoscopy (URS) has dramatically changed the management of ureteral calculi. Major technical improvements include endoscope miniaturization, enhanced optical quality and tools, and introduction of disposables. URS has had a great impact on active stone removal and is performed increasingly worldwide.

5.6.2.1 *Instruments*
5.6.2.1.1 Rigid scopes
Semi-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 proximal and distal ureteral calculi, but an increasing number of urologists prefer flexible endoscopes for proximal calculi. However, rigid URS is safe even for proximal ureteral calculi (1-11).

5.6.2.1.2 Flexible endoscopes
Technological advances have been responsible for the evolution of flexible URS (12), especially for improved deflection mechanisms, which have reached almost 300° in the latest generation, facilitating intrarenal manoeuvrability (13,14). The latest endoscopes have also made it possible to visualise the lower pole in almost all kidneys. 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 by stiffer shaft construction (17,18).

As with rigid scopes, the tip diameters of flexible scopes usually do not exceed 8.7 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, the optical quality and durability.

Digital URS eliminates the need for fragile low-resolution fibreoptics. The tips of digital ureteroscopes contain digital camera chips (complementary metal-oxide semiconductors 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 marked improvement in image quality, with efficacy comparable to that achieved with analogue URS (23,24). To prevent damage to the camera chip, ballistic lithotripsy can no longer be used.

5.6.2.2 Best clinical practice in ureterorenoscopy (URS)
5.6.2.2.1 Preoperative work-up and preparations
Before the procedure, the following information should be sought and actions taken (LE: 4):

- patient history;
- physical examination because anatomical and congenital abnormalities may complicate or prevent retrograde stone manipulation;
- thrombocyte aggregation inhibitors/anticoagulation (anti-platelet drugs) should be discontinued if possible, however URS can be performed in patients with bleeding disorders, with a moderate increase in complications (25,26);
- imaging.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term antibiotic prophylaxis should be administered (27).</td>
<td>4</td>
<td>A*</td>
</tr>
</tbody>
</table>

* Upgraded based on panel consensus.

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 such as ureteral strictures may prevent successful retrograde stone management.

5.6.2.2.3 Access to the upper urinary tract
Most interventions are performed under general anaesthesia, although local anaesthesia or spinal anaesthesia are possible. Instrument miniaturisation means that intravenous sedation can be used to achieve the same outcome (28,29).

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

Antegrade URS is an option for large, impacted proximal ureteral calculi (5,30) (see Section 6.5.3).

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

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

Balloon and plastic dilators are available if necessary. If insertion of a flexible URS is difficult, prior rigid ureteroscopy can be helpful for optical dilatation. If ureteral access is not possible, insertion of a JJ stent followed by URS after 7-14 days offers an alternative procedure.
Recommendation
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 (usual inner diameter of 9 or 12/13 Ch), can be inserted via a guide wire, with the tip placed in the proximal ureter.

Ureteral access sheaths allow easy multiple access to the upper urinary tract and therefore significantly facilitate URS. The use of ureteral access sheaths improves vision by establishing a continuous outflow, decrease intrarenal pressure and potentially reduce operating time (19,33-36).

Ureteral access sheaths allow continuous outflow of irrigation fluid, which improves visual quality and maintains a low-pressure system (36,37).

Ureteral access sheaths are widely accepted and used regularly, despite ongoing debate about potential hazards, including increased ureteral stricture, which has not yet been demonstrated (33).

5.6.2.2.6 Stone extraction
The aim of endourological intervention is complete stone removal (especially in ureteric stones). “Smash and go” strategies might have a higher risk of stone regrowth and postoperative complications (38).

Stones can be extracted by endoscopic forceps or baskets. Forceps allow safe release of stone fragments if they become stuck within the ureter, but extraction takes longer than when using baskets. Only baskets made of nitinol (nickel-titanium alloy) can be used for flexible URS (39-42).

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

A*  Upgraded based on panel consensus.

Stones that cannot be extracted directly must be disintegrated. If it is difficult to access stones that need disintegration within the lower renal pole, it may help to displace them into a more accessible calyx (see Section 6.4.2) (43).

5.6.2.2.7 Intracorporeal lithotripsy
Intracorporeal lithotripsy is usually necessary before stone extraction.

5.6.2.2.7.1 Electrohydraulic systems
Flexible electrohydraulic lithotripsy probes are available for semi-rigid and flexible ureterorenoscopes. If lasers are unavailable, electrohydraulic lithotripsy can disintegrate all types of stones (even cystine or hard stones, such as calcium oxalate monohydrate), even though there is an increased risk of surrounding tissue damage (44-46).

5.6.2.2.7.2 Pneumatic systems
Pneumatic or ballistic lithotripters are often used with 2.4 Ch probes for safe rigid URS and can achieve > 90% disintegration (47–49). Proximal stone migration is a common occurrence (50,51), but can be avoided by using a basket or special tools (6,52-56).

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 but not in flexible endoscopes (57,58).
5.6.2.2.7.4 Laser systems

The most efficient laser system for treatment of all types of stones in all locations is the Ho:YAG system (59-70) (LE: 3), which is the gold standard for rigid and flexible URS (65). Compared with the Nd-YAG laser, its rapid absorption in water (3 mm) and minimal tissue penetration (0.4 mm) reduces thermal damage and improves safety (69). Contact with the surface of the stone is required. Other laser systems are being evaluated, but have yet to prove superior in efficacy or safety.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ho:YAG laser lithotripsy is the preferred method for (flexible) URS.</td>
<td>3</td>
<td>B</td>
</tr>
</tbody>
</table>

5.6.2.2.8 Stenting before and after URS

Routine stenting is no longer necessary before URS. However, pre-stenting facilitates ureteroscopic management of stones, improves the stone-free rate, and reduces complications (71-73).

Most urologists routinely insert a JJ stent following URS, although several randomised prospective trials have found that routine stenting after uncomplicated URS (complete stone removal) is no longer necessary (71,74-85). Ureteric stenting can be associated with lower urinary tract symptoms and pain reducing quality of life (86).

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

The ideal duration of stenting is not known. Most urologists favour 1-2 weeks after URS (71,74). Patients should be followed up with a plain abdominal film (kidney-ureter-bladder), CT or ultrasound.

Alpha-blockers reduce the morbidity of ureteral stents and increase tolerability (87-90). A recently published meta-analysis provides evidence for improvement of ureteral stent tolerability with tamsulosin (91).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenting is optional after uncomplicated URS.</td>
<td>1a</td>
<td>A</td>
</tr>
</tbody>
</table>

5.6.2.2.9 Complications

The overall complication rate after URS is 9-25% (1,9,33,35,66,92) (Table 15). Most are minor and do not require intervention. Ureteral avulsion and strictures used to be greatly feared, but nowadays are rare in experienced hands (< 1%). Previous perforations are the most important risk factor for complications.

Table 15: Complications of URS*

<table>
<thead>
<tr>
<th></th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intraoperative complications</strong></td>
<td></td>
</tr>
<tr>
<td>Mucosal injury</td>
<td>1.5</td>
</tr>
<tr>
<td>Ureteral perforation</td>
<td>1.7</td>
</tr>
<tr>
<td>Significant bleeding</td>
<td>0.1</td>
</tr>
<tr>
<td>Ureteral avulsion</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Early complications</strong></td>
<td></td>
</tr>
<tr>
<td>Fever or urosepsis</td>
<td>1.1</td>
</tr>
<tr>
<td>Persistent haematuria</td>
<td>2.0</td>
</tr>
<tr>
<td>Renal colic</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>Late complications</strong></td>
<td></td>
</tr>
<tr>
<td>Ureteral stricture</td>
<td>0.2</td>
</tr>
<tr>
<td>Persistent vesicoureteral reflux</td>
<td>0.1</td>
</tr>
</tbody>
</table>

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


5.7 Open and laparoscopic surgery for removal of renal stones

5.7.1 Open surgery

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

However, open surgery is still needed for the most difficult stones, which supports the importance of maintaining proficiency, skills and expertise in open renal and ureteral surgical techniques such as extended pyelolithotomy, pyelonephrolithotomy, anatrophic nephrolithotomy, multiple radial nephrotomy, partial nephrectomy and renal surgery under hypothermia (6-10) (Table 16).

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

The efficacy of open surgery and 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 combined PNL and SWL. If a reasonable number of percutaneous approaches are not likely to be successful, or if multiple, endourological approaches have been performed unsuccessfully, open surgery may be a valid treatment option.

Table 16: Indications for open surgery

<table>
<thead>
<tr>
<th>Complex stone burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure of SWL and/or PNL, or failed ureteroscopic procedure</td>
</tr>
<tr>
<td>Intrarenal anatomical abnormalities: infundibular stenosis, stone in the calyceal diverticulum (particularly in an anterior calyx), obstruction of the ureteropelvic junction, stricture if endourologic procedures have failed or are not promising</td>
</tr>
<tr>
<td>Morbid obesity</td>
</tr>
<tr>
<td>Skeletal deformity, contractures and fixed deformities of hips and legs</td>
</tr>
<tr>
<td>Comorbidity</td>
</tr>
<tr>
<td>Concomitant open surgery</td>
</tr>
<tr>
<td>Non-functioning lower pole (partial nephrectomy), non-functioning kidney (nephrectomy)</td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>Stone in an ectopic kidney where percutaneous access and SWL may be difficult or impossible</td>
</tr>
<tr>
<td>For the paediatric population, the same considerations apply as for adults</td>
</tr>
</tbody>
</table>

5.7.2 Laparoscopic surgery

Laparoscopic urological surgery is increasingly replacing open surgery as a result of accumulated surgical experience. Laparoscopy is associated with lower postoperative morbidity, shorter hospital stay and time to convalescence, and better cosmetic results with comparably good functional results (17-24).

Laparoscopic surgery is now used to remove renal and ureteric stones in certain situations, including complex stone burden, failed previous SWL and/or endourological procedures, anatomical abnormalities or morbid obesity, and planned nephrectomy of a stone-containing non-functioning kidney.

Surgical pyelolithotomy is rarely indicated (see Table 16) and feasible laparoscopically, e.g. stone removal from an anterior caliceal diverticulum (34).

Laparoscopic ureterolithotomy is relatively easy, with stone-free rates up to 100% provided expertise is available (25-28). It can replace open surgery in most situations (15,16). Retroperitoneal and transperitoneal laparoscopic access to all portions of the ureter have been reported (28-33,35) although laparoscopic ureterolithotomy in the distal ureter is less successful than in the middle and proximal ureter, but the size of the...
stone does not appear to influence outcome. Although highly effective, laparoscopic ureterolithotomy is not first-line therapy in most cases because of its invasiveness, longer recovery time, and greater risk of associated complications compared to SWL and URS (25-28) (Table 17).

5.7.2.1 Indications for laparoscopic stone surgery (Table 17)

<table>
<thead>
<tr>
<th>Indications for laparoscopic kidney-stone surgery include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Complex stone burden</td>
</tr>
<tr>
<td>• Failed previous SWL and/or endourological procedures</td>
</tr>
<tr>
<td>• Anatomical abnormalities</td>
</tr>
<tr>
<td>• Morbid obesity</td>
</tr>
<tr>
<td>• Nephrectomy in case of non-functioning kidney</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indications for laparoscopic ureteral stone surgery include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Large impacted stones</td>
</tr>
<tr>
<td>• Multiple ureteral stones</td>
</tr>
<tr>
<td>• In cases of concurrent conditions requiring surgery</td>
</tr>
<tr>
<td>• When other non-invasive or low-invasive procedures have failed</td>
</tr>
<tr>
<td>• If indicated, for upper ureteral calculi, laparoscopic urolithotomy has the highest stone free rate compared to URS and SWL (LE: 1a)</td>
</tr>
</tbody>
</table>

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

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

5.7.3 References

6. **INDICATION FOR ACTIVE STONE REMOVAL AND SELECTION OF PROCEDURE**

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

### 6.1 Indication for active removal of ureteral stones (1,2)
- Stones with low likelihood of spontaneous passage;
- persistent pain despite adequate pain medication;
- persistent obstruction;
- renal insufficiency (renal failure, bilateral obstruction, single kidney).

### 6.2 Indication for active 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;
- comorbidity;
- social situation of the patient (e.g., profession, travelling);
- > 2-3 years stone persistence.

The suspected stone composition might influence the choice of treatment.

### 6.2.1 Natural history of caliceal stones
Natural history of small, non-obstructing asymptomatic lower pole calculi is not well defined, and the risk of progression is unclear. There is still no consensus on the follow-up duration, timing and type of intervention.
Although the question of whether caliceal stones should be treated is still unanswered, stone growth, de novo obstruction, associated infection, and acute and/or chronic pain are indications for treatment (1-3).

Glowacki et al. have reported that the risk of a symptomatic episode or need for intervention was ~10% per year, with a cumulative 5-year event probability of 48.5% (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 increased 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). Inci et al. have investigated lower pole caliceal stones, and 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 increased stone size, but only three (11%) required intervention (7).

However, in a prospective RCT with 2.2 years clinical follow-up, Keeley et al. have reported no significant difference between SWL and observation when they compared asymptomatic caliceal stones < 15 mm in terms of stone-free rate, symptoms, requirement for additional treatment, quality of life, renal function, or hospital admission (10). Although some have recommended prophylaxis for these stones to prevent renal colic, haematuria, infection or stone growth conflicting data have been reported (4,6,11).

SWL has been increasingly used for treatment of caliceal stones to reduce the risk of complications and the need for invasive procedures.

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

<table>
<thead>
<tr>
<th>References</th>
</tr>
</thead>
</table>
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 stone removal.

Recommendation

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine culture or urinary microscopy is mandatory before any treatment is planned.</td>
<td>A*</td>
</tr>
</tbody>
</table>

*Upgraded following panel consensus.

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

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

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

Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation therapy including salicylates should be stopped before stone removal, in particular if SWL is planned.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>If intervention for stone removal is essential and salicylate therapy should not be interrupted, retrograde URS is the preferred treatment of choice.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Statement

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In case of severe obesity, URS is a more promising therapeutic option than SWL.</td>
<td>2b</td>
</tr>
</tbody>
</table>
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 respond well or poorly to SWL (10). PNL or retrograde intrarenal surgery (RIRS) are alternatives for removal of large SWL-resistant stones.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider the stone composition before deciding on the method of removal (former stone analysis of the patient, HU in unenhanced CT). Stones with medium density &gt; 1,000 HU on NCCT are less likely to be disintegrated by SWL.</td>
<td>2a</td>
<td>B</td>
</tr>
</tbody>
</table>

6.3.5 **Radiolucent stones**

Uric acid concrements can be localised using US or intravenous or retrograde administration of contrast medium. Stones composed of uric acid, but not sodium or ammonium urate, can be dissolved by oral chemolysis. Differentiation is done by urinary pH measurement (see Section 5.4.2). Postoperative monitoring of radiolucent stones during chemolysis or after SWL is the domain of ultrasound, however repeat NCCT might be necessary.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Careful monitoring of radiolucent stones during/after therapy is imperative.</td>
<td>A*</td>
</tr>
</tbody>
</table>

* Upgraded based on panel consensus.

6.3.6 **Steinstrasse**

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

Insertion of a ureteral stent before SWL prevents formation of steinstrasse only in stones > 15 mm in diameter (16). Symptoms include flank pain, fever, nausea and vomiting, bladder irritation, or it may asymptomatic. A major problem of steinstrasse is ureter obstruction, 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 asymptomatic, conservative treatment is an initial option, depending on patient preference and willingness to comply with close surveillance. Medical expulsion therapy significantly increases stone expulsion and reduces the need for endoscopic intervention (18,19).

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical expulsion therapy increases stone expulsion rate of steinstrasse (16).</td>
<td>1b</td>
</tr>
</tbody>
</table>

When spontaneous passage is unlikely, further treatment of steinstrasse is indicated.

SWL is indicated in asymptomatic and symptomatic cases, with no evidence of UTI, when large stone fragments are present (19). There is an 80% chance of clearance of the steinstrasse (13).

Ureteroscopy is equally effective as SWL for treatment of steinstrasse (13,20,21). Placement of a percutaneous nephrostomy tube is indicated for symptomatic ureteric obstruction with/without UTI, and it is effective in 83% of cases (13).
Table 18: Treatment of steinstrasse

<table>
<thead>
<tr>
<th>Asymptomatic LE</th>
<th>Symptomatic LE</th>
<th>Symptomatic + fever LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. MET 1b</td>
<td>1. URS 3</td>
<td>1. PCN 1a</td>
</tr>
<tr>
<td>2. SWL 3</td>
<td>1. PCN 3</td>
<td>2. Stent</td>
</tr>
<tr>
<td>3. URS 3</td>
<td>1. SWL 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Stent 3</td>
<td></td>
</tr>
</tbody>
</table>

Numbers 1, 2, and 3 indicate first, second and third choice.

Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCN is indicated for steinstrasse associated with UTI/fever.</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>SWL is indicated for steinstrasse when large stone fragments are present.</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>Ureteroscopy is indicated for symptomatic steinstrasse and treatment failure.</td>
<td>4</td>
<td>C</td>
</tr>
</tbody>
</table>

6.3.7 References


6.4 Selection of procedure for active removal of kidney stones

6.4.1 Stones in renal pelvis or upper/middle calices

SWL, PNL or flexible URS are available treatment modalities for renal calculi. Although PNL efficacy is hardly affected by stone size, the stone-free rates (SFRs) after SWL or URS are inversely proportional to stone size (1-4). SWL achieves excellent SFRs for stones up to 20 mm, except for those at the lower pole (3,5). Therefore, SWL remains the first method of choice for such stones. Larger stones > 20 mm should be treated by PNL primarily, because SWL often requires multiple treatments, and has the risk of ureteral obstruction (colic, steinstrasse) with the need for adjunctive procedures (Figure 1) (6). 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 SWL seems to be lower for stones in the inferior calyx than for other intrarenal locations. Although the disintegration efficacy of SWL is not limited compared to other locations, the fragments often remain in the calyx and cause recurrent stone formation. The reported SFR of SWL for lower pole calculi is 25-85%. The preferential use of endoscopic procedures is under discussion (1-6).

The following can impair successful stone treatment by SWL:
- steep infundibular-pelvic angle;
- long calyx;
- narrow infundibulum (Table 19) (7-13).

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

Table 19: Unfavourable factors for SWL success (9-15)

<table>
<thead>
<tr>
<th>Factors that make SWL less likely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shockwave-resistant stones (calcium oxalate monohydrate, brushite, cystine)</td>
</tr>
<tr>
<td>Steep infundibular-pelvic angle</td>
</tr>
<tr>
<td>Long lower pole calyx (&gt; 10 mm)</td>
</tr>
<tr>
<td>Narrow infundibulum (&lt; 5 mm)</td>
</tr>
</tbody>
</table>
SWL for the lower pole is often disappointing, therefore, endourological procedures (PNL, flexible URS) are recommended for stones > 15 mm. If there are negative predictors for SWL, PNL and flexible URS might be a reasonable alternative even for smaller calculi.

Flexible URS seems to have comparable efficacy to SWL (5,6). Recent clinical experience with last-generation ureterorenoscopes suggests an advantage of URS over SWL, by paying the price of greater invasiveness (16,17). Depending on operator skills, stones up to 3 cm can be treated efficiently by flexible URS (16,18-20). However, staged procedures are frequently required.

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

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

Kidney stone in renal pelvis or upper/middle calyx

> 2 cm
1. Endourology (PNL, flex. URS*)
2. SWL
3. Laparoscopy

1-2 cm
SWL or Endourology*, **

< 1 cm
1. SWL
2. Flex. URS
3. PNL
6.4.3 References

*Flexible URS is used less as first-line therapy for renal stones > 1.5 cm, although some expert centers have reported such for renal stones > 1.5 cm.

The high number of staged procedures of URS underline the superiority of PNL. A combined approach (PNL+flexible URS) might be an option in specialised centres.

** The ranking of the recommendations reflects a panel majority vote.

*** see Table 19 on page 55.


6.5 Selection of procedure for active removal of ureteral stones

6.5.1 Methodology

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

6.5.2 Extracorporeal shock wave lithotripsy and ureteroscopy

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

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

6.5.2.1 Stone free rates (SFRs)

Table 20 shows the results of a meta-analysis of SFRs. 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>
<thead>
<tr>
<th>Stone Free Rates (SFRs)</th>
<th>SWL</th>
<th>URS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal ureter</td>
<td>Number of patients</td>
<td>SFR/95% CI</td>
</tr>
<tr>
<td>&lt; 10 mm</td>
<td>7217</td>
<td>74% (73-75)</td>
</tr>
<tr>
<td>&gt; 10 mm</td>
<td>1684</td>
<td>86% (80-91)</td>
</tr>
<tr>
<td>Mid ureter</td>
<td>Number of patients</td>
<td>SFR/95% CI</td>
</tr>
<tr>
<td>&lt; 10 mm</td>
<td>966</td>
<td>74% (57-87)</td>
</tr>
<tr>
<td>&gt; 10 mm</td>
<td>1697</td>
<td>73% (71-75)</td>
</tr>
<tr>
<td>Proximal ureter</td>
<td>Number of patients</td>
<td>SFR/95% CI</td>
</tr>
<tr>
<td>&lt; 10 mm</td>
<td>44</td>
<td>84% (65-95)</td>
</tr>
<tr>
<td>&gt; 10 mm</td>
<td>15</td>
<td>76% (36-97)</td>
</tr>
</tbody>
</table>

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

Although there are not sufficient data to compare 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 technical improvement of flexible URS continue.

6.5.2.2 Complications

Although URS is effective for ureteric calculi, it has greater potential for complications. In the current endourological era, with access to newer, smaller rigid and flexible instruments and use of small-calibre intracorporeal lithotripsy devices, the complication rate and morbidity of ureteroscopy have been significantly reduced (6).
Patients should be informed that URS has a better chance of achieving stone-free status with a single procedure, but has higher complication rates [Sections 5.5.4 (Complications of SWL) and 5.6.2.2.9 (Complications of URS)].

6.5.3 **Percutaneous antegrade ureteroscopy**

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

### Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percutaneous antegrade removal of ureteral stones is an alternative when SWL is not indicated or has failed, and when the upper urinary tract is not amenable to retrograde URS (13-15).</td>
<td>A</td>
</tr>
<tr>
<td>A patient must be informed about the existing active treatment modalities, including the relative benefits and risks associated with each modality.</td>
<td>A</td>
</tr>
</tbody>
</table>

### Table 21: Recommended treatment options (if indicated for active stone removal) (GR A*)

<table>
<thead>
<tr>
<th>Stone Location</th>
<th>First choice</th>
<th>Second choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal ureter &lt; 10 mm</td>
<td>SWL</td>
<td>URS</td>
</tr>
<tr>
<td>Proximal ureter &gt; 10 mm</td>
<td>URS (retrograde or antegrade) or SWL</td>
<td>SWL</td>
</tr>
<tr>
<td>Distal ureter &lt; 10 mm</td>
<td>URS or SWL</td>
<td>SWL</td>
</tr>
<tr>
<td>Distal ureter &gt; 10 mm</td>
<td>URS</td>
<td>SWL</td>
</tr>
</tbody>
</table>

*Upgraded following panel consensus.

### Recommendation

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment choices should be based on stone size and location and available equipment for stone removal.</td>
<td>A</td>
</tr>
</tbody>
</table>

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 could not be used to compare procedures with each other or with SWL or URS. These more invasive procedures have yielded high SFRs.

6.5.5 **References**


7. RESIDUAL STONES

7.1 Clinical evidence
Residual fragments are commonly seen after SWL and sometimes after intracorporeal lithotripsy, and mostly in the lower calix.

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

The clinical problem of residual kidney stones is related to the risk of developing:
• new stones from such nidi (heterogeneous nucleation);
• persistent UTI;
• dislocation of fragments with/without obstruction and symptoms (1-5).

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification of biochemical risk factors and appropriate stone prevention is particularly indicated in patients with residual fragments or stones (3-5).</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Patients with residual fragments or stones should be followed up regularly to monitor disease course.</td>
<td>4</td>
<td>C</td>
</tr>
</tbody>
</table>

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

Table 22: Recommendations for the treatment of residual fragments

<table>
<thead>
<tr>
<th>Residual fragments, stones (largest diameter)</th>
<th>Symptomatic residuals</th>
<th>Asymptomatic residuals</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4-5 mm</td>
<td>Stone removal</td>
<td>Reasonable follow-up (dependent on risk factors)</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>&gt; 6-7 mm</td>
<td>Stone removal</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>After SWL and URS, MET is recommended using an alpha-blocker to improve fragment clearance and reduce probability of residual stones (Chapter 7).</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>For well-disintegrated stone material in the lower calix, inversion therapy during high diuresis and mechanical percussion facilitate clearance (8).</td>
<td>1a</td>
<td>B</td>
</tr>
</tbody>
</table>

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

If intervention is not required, medical therapy according to stone analysis, patient risk group, and metabolic evaluation might help to prevent regrowth of residual fragments (10-13).

7.3 References


8. MANAGEMENT OF URINARY STONES AND RELATED PROBLEMS DURING PREGNANCY

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

8.1 Diagnostic options
Diagnostic options are limited in pregnant women due to the possible teratogenic, carcinogenic, and mutagenic risk of foetal radiation exposure. The risk depends crucially on gestational age and amount of radiation delivered. Clinicians must consider carefully the risk-benefit ratio of an examination that involves radiation during the first trimester (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. NCCT results in an even higher dose of radiation exposure. However, US is limited by poor sound transmission through gas and bone and its operator-dependent nature. Similarly, it can be difficult to differentiate physiological dilation of pregnancy from ureteral obstruction, and US is therefore of limited value in acute obstruction (7,8).

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

Among other modalities, magnetic resonance urography (MRU) can be used to evaluate the urinary tract, thus avoiding ionising radiation and iodinated contrast medium, which is important in pregnancy. Magnetic resonance imaging can define the level of obstruction, and stones can be seen as a filling defect. However, these findings are non-specific. There is little experience with using this imaging modality during pregnancy (9-11).

<table>
<thead>
<tr>
<th>Statements</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>US is the method of choice for practical and safe evaluation of pregnant women.</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>In symptomatic patients with suspicion of ureteral stones during pregnancy, limited IVU, MRU, or isotope renography is a possible diagnostic method.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8.2 Management
Management of pregnant urolithiasis patients poses significant multiple challenges to the patient, obstetrician and urologist, but many symptomatic stones (70-80%) pass spontaneously. Conservative management with analgesia can result in spontaneous passage.

If spontaneous passage does not occur, or if complications develop (e.g. induction of premature labour),
placement of an internal stent or percutaneous nephrostomy tube, or ureteroscopy is an alternative treatment (12-19). However, the temporising therapies (e.g. ureteral stenting or percutaneous nephrostomy) are often associated with poor tolerance, and they require multiple exchanges of stents or nephrostomy tubes during 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 over emphasise the necessity for care during URS, which should be performed only in centres with sufficient experience (20,22-24). When intracorporeal lithotripsy is necessary during URS 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 few studies (21), SWL is still experimental, and pregnancy remains an absolute contraindication.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Following correct diagnosis, conservative management should be the first-line treatment for all non-complicated cases of urolithiasis in pregnancy (except those that have clinical indications for intervention).</td>
<td>A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Statements</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>If intervention becomes necessary, placement of a internal stent, percutaneous nephrostomy, or ureteroscopy are options.</td>
<td>3</td>
</tr>
<tr>
<td>Regular follow-up until final stone removal is necessary due to higher encrustation tendency of stents during pregnancy.</td>
<td></td>
</tr>
</tbody>
</table>

8.3 References
9. MANAGEMENT OF STONE PROBLEMS IN CHILDREN

Rates of urolithiasis have increased in developed countries, and there has been a shift in the age group experiencing a first stone episode (1-3). More than 1% of all urinary stones are seen in patients aged < 18 years. As a result of malnutrition and racial factors, paediatric urolithiasis remains an endemic disease in some areas (e.g. Turkey and Far East); elsewhere, the rates are similar to those observed in developed countries (4-11).
9.1 Investigations
Paediatric patients with urinary stones have a high risk of recurrence, therefore, standard diagnostic procedures for high-risk patients apply (see Chapters 2.6 and 11).

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In paediatric patients, the most common non-metabolic disorders are vesicoureteral reflux, ureteropelvic junction obstruction, neurogenic bladder, or other voiding difficulties (11,12).</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>In all paediatric patients, complete metabolic stone evaluation based on stone analysis (if available) is necessary.</td>
<td>A</td>
</tr>
</tbody>
</table>

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). In paediatrics, its advantages are absence of irradiation and 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 of the urinary collecting system. It also indicates signs of abnormalities that facilitate stone formation.

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

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound evaluation is the first choice for imaging in children and should include the kidney, filled bladder, and adjoining portions of the ureter (14,20).</td>
<td>2a</td>
</tr>
</tbody>
</table>

9.1.1.2 Plain films (KUB)
KUB can help to identify stones and their radio-opacity, and facilitate follow-up.

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

9.1.1.4 Helical computed tomography (CT)
Recent CT protocols have been shown to reduce radiation exposure significantly (22). The principle of ALARA (As Low As Reasonable Achievable) should always be observed. Like in adults it has a sensitivity of 94-100% and specificity of 92-100% (23).

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

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

9.1.1.6 Nuclear imaging
$^{99m}$Tc-dimercaptosuccinyl acid scanning provides information about cortical abnormalities such as scarring, but does not aid primary diagnosis of urolithiasis. Diuretic renography with injection of a radiotracer (MAG3 or DPTA) 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 treatment procedures for children. Compared to adults, children pass fragments more rapidly after SWL, and all stones should be evaluated for further metaphylactic measures (26). For endourological procedures, the smaller organs in children must be considered when selecting instruments for PNL or URS. To eliminate radiation exposure, US can be used for localisation during SWL or endourological procedures. Anticipation of the expected stone composition helps with selection of the appropriate procedure for removal (cystine stones are more resistant to SWL).

<table>
<thead>
<tr>
<th>Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous passage of a stone is more likely in children than adults (6,11,12).</td>
<td>4</td>
</tr>
</tbody>
</table>

9.2.1 Medical expulsive therapy (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 are insufficient data to demonstrate their safety and efficacy in children (27).

9.2.2 Extracorporeal shock wave lithotripsy
Despite increasing application of PNL, and development of smaller-diameter flexible ureteroscopes and ancillary instruments, SWL is still the least-invasive procedure for stone management 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, compared with adults, SWL can achieve more effective disintegration of large stones, together with swifter and uncomplicated discharge of large fragments (32-34). Stones located in calices, as well as abnormal kidneys, and large stones, are more difficult to disintegrate and clear. The likelihood of urinary obstruction is higher in such cases, and children should be followed closely for the prolonged risk of urinary tract obstruction. The retreatment rate is 13.9-53.9%, and the need for ancillary procedures and/or additional interventions is 7-33% (32-34,36).

The need for general anaesthesia during SWL depends on patient age and the lithotripter used. General or dissociative anaesthesia is administered in most children aged < 10 years, to avoid patient and stone motion and the need for repositioning (32,36). With modern lithotriptors, intravenous sedation or patient-controlled analgesia has been used in selected cooperative older children (37) (LE: 2b). There are concerns regarding the safety and potential biological effects of SWL on immature kidneys and surrounding organs in children. However, during short- and long-term follow-up, no irreversible functional or morphological side effects of high-energy shock waves have been demonstrated. In addition, when the potential deterioration of renal function is taken into account (although transient), restricting the number of shock waves and the energy used during each treatment session helps protect the kidneys (38-41).

Compared to adults, children pass stone fragments easily, and stenting is rarely needed. If the stone burden requires a ureteral stent, alternative procedures should be considered. Although internal stents are seldom needed following SWL of upper tract stones, ureteral pre-stenting decreases the SFR after initial treatment (28,30-32).

<table>
<thead>
<tr>
<th>Statements</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In children, the indications for SWL are similar to those in adults, however they pass fragments more easily.</td>
<td>3</td>
</tr>
<tr>
<td>Children with renal stones of a diameter up to 20 mm (~300 mm²) are ideal for SWL.</td>
<td>1b</td>
</tr>
</tbody>
</table>

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

9.2.3.1 Percutaneous nephrolithotripsy (PNL)
Preoperative evaluation and indications for PNL in children are similar to those in adults. Although PNL is performed as monotherapy in most cases, it can be used as an adjunctive procedure. Availability of appropriate-size instruments and ultrasound guidance mean that age is not a limiting factor, and PNL can now be performed safely by experienced operators, with less radiation exposure even for large and complex stones (42-46). SFRs are between 68% and 100% after a single session, and increase with adjunctive measures, such as second-look PNL, SWL and URS (42,43).
9.2.3.2 Ureteroscopy
While SWL still is the first-line treatment for most ureteral stones it is unlikely to be successful for stones > 10 mm in diameter, or for impacted, calcium oxalate monohydrate or cystine stones, or stones in children with unfavourable anatomy and in whom localisation is difficult. The success rate of SWL decreases for stones in the more distal parts of the ureter. Overall SFRs after SWL range from 75 to 100% (47-50).
If SWL is not promising ureteroscopy can be used. With the clinical introduction of smaller-calibre instruments, this modality has become the treatment of choice in middle and larger distal ureteric stones in children (48-50).

Different lithotripsy techniques, including ultrasonic, pneumatic and laser lithotripsy, are all 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).

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

9.2.4 Open or laparoscopic surgery
Most stones in children can be managed by SWL and endoscopic techniques (59). Therefore the rate of open procedure has dropped significantly (60-64). In some situations, open surgery is inevitable. Indications for surgery include failure of primary therapy for stone removal, very young children with complex stones, congenital obstruction that requires simultaneous surgical correction, severe orthopaedic deformities that limit positioning for endoscopic procedures, and abnormal kidney position (29,31,44,45). Open surgery can be replaced by laparoscopic procedures in experienced hands (62-64).

9.3 Special considerations on recurrence prevention
It should be kept in mind that, in addition to stone removal procedures, treatment of paediatric urolithiasis requires a thorough metabolic and environmental evaluation on an individual basis. In case of obstructive pathologies along with the established metabolic abnormalities treatment should not be delayed. Children are in the high-risk group for stone recurrence (see Chapter 11).

9.4 References


10. STONES IN URINARY DIVERSION AND OTHER VOIDING PROBLEMS

10.1 Management of stones in patients with urinary diversion

10.1.1 Aetiology and preventive measures

Patients with urinary diversion are at risk for stone formation in the renal collecting system, 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 be involved in stone formation in these cases (4).

These patients are also at high risk for stone recurrence, which warrants close follow-up for effective prevention. Preventive measures include medical management of metabolic abnormalities, appropriate therapy of urinary infections, and regular irrigation of continent reservoirs (5). One study showed that the risk for recurrent upper-tract stones in patients with urinary diversion subjected to PNL was 63% at 5 years (6).

10.1.2 Management

Although patients with smaller upper-tract stones can be treated effectively with SWL (7,8) other well-established endourological techniques might be necessary to achieve stone-free status.

Some patients with small- or large-bowel conduits can be treated with URS under fluoroscopic guidance. Although identification of the targeted ureteral orifice is difficult, it can be localised by flexible cystoscopy and/or administration of intravenous indigo carmine and a hydrophilic guidewire can be placed followed by regular flexible ureteroscopy. Stone removal and fragmentation are then undertaken using standard techniques. This approach might be difficult or impossible in individuals with long, tortuous conduits; percutaneous placement of an antegrade guidewire may facilitate stone removal procedures.

PNL is the preferred treatment alternative for removal of large renal stones in patients with urinary diversion, as well as ureteral stones that cannot be accessed via a retrograde approach or are not amenable to SWL (9).

Stones can form in the conduits after urinary diversion procedures, which is typically associated with a foreign body. A trans-stomal approach can be used to remove all stone material (along with the foreign body) using standard techniques, including intracorporeal lithotripsy. However, for calculi in continent urinary diversion, although a trans-stomal approach might be successful in some patients, there is a risk of disturbing the continence mechanism. A success rate of 89% has been reported for trans-stomal management of patients with stones in Kock reservoirs with afferent nipples (10). Patients with relatively larger stones 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), and if present, an open surgical approach should be considered. In patients with no overlying visceral, ultrasound- or CT-guided access is recommended to facilitate safe placement of a sheath into the reservoir followed by standard PNL. 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 (12). Trans-stomal flexible endoscopy facilitates manipulation of the stones into the entrapment bag. The stones are then fragmented in the bag using a rigid nephroscope and standard intracorporeal lithotripsy. This technique allows total stone removal without dispersal of fragments in a capacious reservoir. 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.

10.1.3 References


10.2 Management of stones in patients with neurogenic bladder

10.2.1 Aetiology and clinical presentation

Patients with neurogenic bladder can develop urinary calculi because of additional risk factors such as urinary stasis and infection. Indwelling catheters and surgical interposition of bowel segments for treatment of bladder dysfunction can facilitate 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). Recent cases have been reported of vaginal calculi secondary to urinary stasis (3) or vesicovaginal fistulae (4). Bacteriuria, pelvicaliectasis, vesicoureteral reflux, renal scarring, lower urinary tract reconstruction, and thoracic spinal defect are risk factors for renal stone formation in patients with neurogenic bladder (5).

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

Management of calculi in patients with neurogenic bladder is similar to that described above (see Section 10.1). Regardless of the treatment used, latex allergy is common in patients with MMC and appropriate measures need to be taken (8). Any surgery in these patients must be performed under general anaesthesia because of the impossibility of using spinal anaesthesia. Bone deformities often complicate positioning on the operating table and the necessary venous access. These deformities can even prevent general anaesthesia (9), which makes early diagnosis of lithiasis essential.

<table>
<thead>
<tr>
<th>Statements</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients undergoing urinary diversion and/or suffering from neurogenic bladder dysfunction are at risk for recurrent stone formation.</td>
<td>3</td>
</tr>
<tr>
<td>Careful patient follow-up, utilisation of the appropriate stone-removal approach, and implementation of effective preventive strategies are the cornerstones of successful management.</td>
<td>3</td>
</tr>
</tbody>
</table>

10.2.3 References


10.3 Management of stones in transplanted kidneys

10.3.1 Aetiology and clinical presentation

Transplant patients depend on their solitary kidney for renal function, therefore, any impairment causing urinary stasis requires immediate intervention. Although immunosuppression renders these patients more vulnerable to infection, they also have conditions that predispose them to 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 have a incidence of 0.2-1.7% (2-4). 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 difficult, however, management principles are similar to those applied in other single renal units (6-9).

Conservative treatment under close surveillance is only possible for small asymptomatic stones. Although SWL for small calyceal stones is appealing because of minimal complications, localisation can be difficult and SFRs are poor (10,11). However, for large or ureteral stones, percutaneous and antegrade endoscopic techniques are more favourable, but concerns exist about significant injury to adjacent organs (12-14).
The introduction of small flexible ureteroscopes and holmium laser has made ureteroscopy another treatment option for transplant calculi. Retrograde access to transplanted kidneys is difficult owing to the anterior location of the ureteral anastomosis and ureteral tortuosity (15-17).

**Recommendations**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All contemporary endoscopic treatment modalities, including SWL, (flexible)</td>
<td>B</td>
</tr>
<tr>
<td>ureteroscopy and percutaneous nephrolithotomy are management options in patients</td>
<td></td>
</tr>
<tr>
<td>with transplanted kidneys.</td>
<td></td>
</tr>
<tr>
<td>Metabolic evaluation should be completed after stone removal.</td>
<td>A*</td>
</tr>
</tbody>
</table>

*Upgraded following panel consensus.

10.3.3 **References**


10.4 Special problems in stone removal

Table 23: Special problems in stone removal

<table>
<thead>
<tr>
<th>Type of Stone</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caliceal diverticulum stones</td>
<td>- SWL, PNL (if possible) or RIRS&lt;br&gt; - Can also be removed using laparoscopic retroperitoneal surgery (1-5)&lt;br&gt; - Patients may become asymptomatic due to stone disintegration (SWL) whilst well-disintegrated stone material remains in the original position due to narrow caliceal neck</td>
</tr>
<tr>
<td>Horseshoe kidneys</td>
<td>- Can be treated in line with the options described above (6)&lt;br&gt; - Passage of fragments after SWL might be poor</td>
</tr>
<tr>
<td>Stones in pelvic kidneys</td>
<td>- SWL, RIRS or laparoscopic surgery&lt;br&gt; - For obese patients, the options are SWL, PNL, RIRS or open surgery</td>
</tr>
<tr>
<td>Stones formed in a continent reservoir</td>
<td>- See 10.1&lt;br&gt; - Each stone problem must be considered and treated individually</td>
</tr>
<tr>
<td>Patients with obstruction of the ureteropelvic junction</td>
<td>- When outflow abnormality requires correction, stones can be removed by PNL together with percutaneous endopyelotomy (15-35) or open/ laparoscopic reconstructive surgery&lt;br&gt; - URS together with endopyelotomy with Ho:YAG&lt;br&gt; - Incision with an Acucise balloon catheter might be considered, provided the stones can be prevented from falling into the pelvi-ureteral incision (7-10)</td>
</tr>
</tbody>
</table>

10.5 References
11. METABOLIC EVALUATION AND RECURRENCE PREVENTION

11.1 General metabolic considerations for patient work-up

11.1.1 Evaluation of patient risk

After stone passage, every patient should be assigned to a low- or high-risk group 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).

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

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

11.1.2 Urine sampling

Specific metabolic evaluation requires collection of two consecutive 24-h urine samples (1-3). The collecting bottles should be prepared with 5% thymol in isopropanol or stored at ≤ 8°C during collection (4). Preanalytical errors can be minimised by carrying out urinalysis immediately after collection. Urine pH should be assessed during collection of freshly voided urine four times daily (5).

HCl can be used as a preservative in special situations to prevent precipitation of calcium oxalate and calcium phosphate. However, in samples preserved with HCl, pH measurement is impossible and uric acid precipitates immediately. Alkalisation is needed to dissolve urate crystals if urate excretion is of interest (6).
Spot urine samples are an alternative method of sampling, particularly when 24-h urine collection is difficult, e.g. in younger children (7,8). Spot urine studies normally link the excretion rates to creatinine (8,9). Spot urine studies are limited because the results may vary with collection time and patients’ sex, body weight and age.

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

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

Follow-up studies are necessary in patients receiving recurrent stone prophylaxis (1). The first follow-up 24-h urine measurement should be at 8-12 weeks after starting pharmacological prevention of stone recurrence. This enables drug dosage to be adjusted if urinary risk factors have not normalised, with further 24-h urine measurements if necessary. Once urinary parameters have been normalised, it is sufficient to perform 24-h urine evaluation every 12 months.

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

11.1.4 **Reference ranges of laboratory values**

Tables 24-26 provide the internationally accepted reference ranges for the different laboratory values in serum and urine.

**Table 24: Normal laboratory values for blood parameters in adults**

<table>
<thead>
<tr>
<th>Blood parameter</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>20-100 µmol/L</td>
</tr>
<tr>
<td>Sodium</td>
<td>135-145 mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.5-5.5 mmol/L</td>
</tr>
<tr>
<td>Calcium</td>
<td>2.0-2.5 mmol/L (total calcium)</td>
</tr>
<tr>
<td></td>
<td>1.12-1.32 mmol/L (ionised calcium)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>119-380 µmol/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>98-112 mmol/L</td>
</tr>
<tr>
<td>Phosphate</td>
<td>0.81-1.29 mmol/L</td>
</tr>
<tr>
<td>Blood gas analysis</td>
<td>pH 7.35-7.45</td>
</tr>
<tr>
<td></td>
<td>pO2 80-90 mmHg</td>
</tr>
<tr>
<td></td>
<td>pCO2 35-45 mmHg</td>
</tr>
<tr>
<td></td>
<td>HCO3 22-26 mmol/L</td>
</tr>
<tr>
<td></td>
<td>BE ± 2</td>
</tr>
</tbody>
</table>

*BE = base excess (loss of buffer base to neutralise acid).*

11.1.5 **Risk indices and additional diagnostic tools**

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

- 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, clinical validation of these risk indices for recurrence prediction or therapy improvement is ongoing and the benefit remains controversial.
Table 25: Normal laboratory values for urinary parameters in adults

<table>
<thead>
<tr>
<th>Urinary Parameters</th>
<th>Reference ranges and limits for medical attention</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>Constantly &gt; 5.8</td>
</tr>
<tr>
<td></td>
<td>Constantly &gt; 7.0</td>
</tr>
<tr>
<td></td>
<td>Constantly ≤ 5.8</td>
</tr>
<tr>
<td>Specific weight</td>
<td>&gt; 1010</td>
</tr>
<tr>
<td>Creatinine</td>
<td>&gt; 7-13 mmol/day females</td>
</tr>
<tr>
<td></td>
<td>13-18 mmol/day males</td>
</tr>
<tr>
<td>Calcium</td>
<td>&gt; 5.0 mmol/day</td>
</tr>
<tr>
<td></td>
<td>≥ 8.0 mmol/day</td>
</tr>
<tr>
<td>Oxalate</td>
<td>&gt; 0.5 mmol/day</td>
</tr>
<tr>
<td></td>
<td>0.45-0.85 mmol/day</td>
</tr>
<tr>
<td></td>
<td>≥ 1.0 mmol/day</td>
</tr>
<tr>
<td>Uric acid</td>
<td>&gt; 4.0 mmol/day</td>
</tr>
<tr>
<td>Citrate</td>
<td>&lt; 2.5 mmol/day</td>
</tr>
<tr>
<td>Magnesium</td>
<td>&lt; 3.0 mmol/day</td>
</tr>
<tr>
<td>Inorganic phosphate</td>
<td>&gt; 35 mmol/day</td>
</tr>
<tr>
<td>Ammonium</td>
<td>&gt; 50 mmol/day</td>
</tr>
<tr>
<td>Cystine</td>
<td>&gt; 0.8 mmol/day</td>
</tr>
</tbody>
</table>
### Table 26: Reference urinary values in paediatric patients (19)

#### Soluble:creatinine ratio (spot urine samples)

<table>
<thead>
<tr>
<th>Calcium:creatinine ratio</th>
<th>Citrate:creatinine ratio</th>
<th>Cystine:creatinine ratio</th>
<th>Oxalate:creatinine ratio</th>
<th>Urate:creatinine ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>mol/mol</td>
<td>g/g</td>
<td>mol/mol</td>
<td>mg/g</td>
<td>mmol/mol</td>
</tr>
<tr>
<td>g/g</td>
<td></td>
<td>g/g</td>
<td>mg/g</td>
<td>g/g</td>
</tr>
<tr>
<td>&lt; 12 mos</td>
<td>&lt; 2.2</td>
<td>&lt; 0.8</td>
<td>&lt; 0.12-0.25</td>
<td>&gt; 0.8-0.42</td>
</tr>
<tr>
<td>0-5 y</td>
<td>&gt; 0.12-0.25</td>
<td>&lt; 0.2-0.42</td>
<td>&lt; 1 month</td>
<td>&lt; 180</td>
</tr>
<tr>
<td>0-6 mos</td>
<td>&lt; 1 month</td>
<td>&lt; 85</td>
<td>0-6 mos</td>
<td>&lt; 325-360</td>
</tr>
<tr>
<td>1-3 y</td>
<td>&gt; 0.12-0.25</td>
<td>&lt; 0.2-0.42</td>
<td>7-24 mos</td>
<td>&lt; 132-174</td>
</tr>
<tr>
<td>1-6 mos</td>
<td>&lt; 1 month</td>
<td>&lt; 85</td>
<td>2-5 y</td>
<td>&lt; 98-101</td>
</tr>
<tr>
<td>2-5 y</td>
<td>&gt; 0.12-0.25</td>
<td>&lt; 0.2-0.42</td>
<td>5-14 y</td>
<td>&lt; 70-82</td>
</tr>
<tr>
<td>5-7 y</td>
<td>&gt; 0.12-0.25</td>
<td>&lt; 0.2-0.42</td>
<td>1-3 y</td>
<td>&lt; 13 mmol/1.73 m²/24 h</td>
</tr>
<tr>
<td>&gt; 7 y</td>
<td>&gt; 0.12-0.25</td>
<td>&lt; 0.2-0.42</td>
<td>&gt; 10 y</td>
<td>&lt; 40</td>
</tr>
</tbody>
</table>

#### Urinary excretion of soluble excretion in 24-hour urine samples

<table>
<thead>
<tr>
<th>Calcium excretion</th>
<th>Citrate excretion</th>
<th>Cystine excretion</th>
<th>Oxalate excretion</th>
<th>Urate excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/kg/24 h</td>
<td>mmol/1.73 m²/24 h</td>
<td>&lt; 0.5 mmol/1.73 m²/24 h</td>
<td>&lt; 0.5 mmol/1.73 m²/24 h</td>
<td>&lt; 0.5 mmol/1.73 m²/24 h</td>
</tr>
<tr>
<td>mg/kg/24 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>&lt; 1 mmol/1.73 m²/24 h</td>
<td>&lt; 1 mmol/1.73 m²/24 h</td>
<td>&lt; 1 mmol/1.73 m²/24 h</td>
<td>&lt; 1 mmol/1.73 m²/24 h</td>
</tr>
<tr>
<td>&lt; 0.5 mmol/1.73 m²/24 h</td>
<td>&lt; 0.5 mmol/1.73 m²/24 h</td>
<td>&lt; 0.5 mmol/1.73 m²/24 h</td>
<td>&lt; 0.5 mmol/1.73 m²/24 h</td>
<td>&lt; 0.5 mmol/1.73 m²/24 h</td>
</tr>
<tr>
<td>1-5 y</td>
<td>&lt; 1 mmol/1.73 m²/24 h</td>
<td>&lt; 1 mmol/1.73 m²/24 h</td>
<td>&lt; 1 mmol/1.73 m²/24 h</td>
<td>&lt; 1 mmol/1.73 m²/24 h</td>
</tr>
<tr>
<td>&gt; 5 y</td>
<td>&lt; 1 mmol/1.73 m²/24 h</td>
<td>&lt; 1 mmol/1.73 m²/24 h</td>
<td>&lt; 1 mmol/1.73 m²/24 h</td>
<td>&lt; 1 mmol/1.73 m²/24 h</td>
</tr>
</tbody>
</table>
11.1.6 References


11.2 General considerations for recurrence prevention
All stone formers, independent of their individual risk, should follow the preventive measures in Table 27. The main focus of these is normalisation of dietary habits and lifestyle risks. Stone formers at high risk need specific prophylaxis for recurrence, which is usually pharmacological treatment and based on stone analysis.

Table 27: General preventive measures

| Fluid intake (drinking advice) | Fluid amount: 2.5-3.0 L/day  
| Circadian drinking  
| Neutral pH beverages  
| Diuresis: 2.0-2.5 L/day  
| Specific weight of urine: < 1010 |
| Nutritional advice for a balanced diet | Balanced diet*  
| Rich in vegetable and fibre  
| Normal calcium content: 1-1.2 g/day**  
| Limited NaCl content: 4-5 g/day  
| Limited animal protein content: 0.8-1.0 g/kg/day |
| Lifestyle advice to normalise general risk factors | BMI: 18-25 kg/m² (target adult value, not applicable to children)  
| Stress limitation measures  
| Adequate physical activity  
| Balancing of excessive fluid loss |

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

* Avoid excessive consumption of vitamin supplements.

** Exception: Patients with absorptive hypercalciuria, calcium excretion ≥ 8 mmol/day.

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

Recommendation LE GR
The aim should be to obtain a 24-h urine volume ≥ 2 L. 1b A

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

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

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

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

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

Calcium intake should not be restricted unless there are strong reasons because of the inverse relationship between dietary calcium and stone formation (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 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. High intake adversely affects urine composition:
• calcium excretion is increased by reduced tubular reabsorption;
• urinary citrate is reduced due to loss of bicarbonate;
• increased risk of sodium urate crystal formation.

Calcium stone formation can be reduced by restricting sodium and animal protein (13,14). A positive correlation between sodium consumption and risk of first-time stone formation has been confirmed only in women (15,20). There have been no prospective clinical trials on the role of sodium restriction as an independent variable in reducing the risk of stone formation.

Urate: Intake of urate-rich food should be restricted in patients with hyperuricosuric calcium oxalate stones (21-24) and uric acid stones (16). Intake should not exceed 500 mg/day.

11.2.3 Lifestyle
Lifestyle factors may influence the risk of stone formation, e.g. overweight and obesity (25-27). Another risk factor is arterial hypertension (28,29).

11.2.4 References
    http://www.icud.info/publications.html


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, which is normally used with general preventive measures. The ideal drug should halt stone formation, have no side effects, and be easy to administer. Each of these aspects is important to achieve good compliance. The following descriptions highlight the most important characteristics of commonly used medication.

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 stones. Thiazide treatment aims to reduce excretion
of calcium in hypercalciuria, but calcium reduction is also found in patients with normocalciuria (1,2). The hypocalciuric action of thiazides is thought to be mediated by increased reabsorption of calcium in the proximal and distal nephron (3).

Good evidence from RCTs has proven that thiazides are effective in preventing calcium stone recurrence (Table 28) (4).

Table 28: RCTs of thiazides for the prevention of recurrent stone formation (LE: 1b)

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

BFMZ = bendroflumethiazide; HCTZ = hydrochlorothiazide; Tx = treatment.

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

The use of thiazide induces potassium loss. This can be compensated for by giving potassium citrate (3.5-7.0 mmol twice daily), which is preferable to KCl because 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, although 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 recurrence (4) (Table 29).
Table 29: RCTs evaluating alkali citrate therapy in preventing stone recurrence (LE: 1b)

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

Potassium citrate (16,19), sodium citrate and potassium magnesium citrate (4) significantly reduce recurrence rate. A favourable effect has been reported with potassium magnesium citrate (18), but not sodium potassium citrate. Although potassium magnesium citrate appears to prevent stone recurrence, it is not yet generally available. Further studies are necessary to show whether it is superior to potassium citrate.

Alkaline citrate has a high occurrence of side effects, therefore, overall compliance rates do not exceed ~50%.

11.3.1.3 Magnesium

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

There is still not enough evidence to recommend magnesium as monotherapy in calcium stone prevention. In two RCTs, magnesium hydroxide was compared with placebo (7) and magnesium oxide with untreated controls (13). Neither showed a significant effect on stone formation, despite follow-up of 4 and 3 years, respectively. The previously reported positive effects of magnesium (20,21) have not been confirmed by recent studies (22).

11.3.1.4 Calcium supplements

See Section 11.2.2.

11.3.1.5 Allopurinol

Allopurinol is an inhibitor of xanthine oxidase. It has been used to prevent recurrence of calcium oxalate stones ever since a relationship was found between hyperuricosuria and calcium oxalate stone formation (23).

Although allopurinol tolerance is normally good, there are severe side effects with high doses. The potential benefits of allopurinol on calcium oxalate stone formation 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;
- reduced excretion of oxalate.

In a placebo-controlled, randomised study of hyperuricosuric calcium-oxalate stone formers, 75% of those treated with allopurinol were free of recurrent stone formation compared with 45% in the placebo group (significant difference) (24). The effectiveness of allopurinol (300 mg/day) has been tested in RCTs in calcium oxalate stone formers (13,24,25). Only one trial demonstrated a significant benefit of allopurinol in preventing stone recurrence (25). However, this trial solely enrolled patients with hyperuricosuria, while the other three enrolled patients regardless of metabolic background.

11.3.1.6 Pyridoxine

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

Due to the rarity (and severity) of primary hyperoxaluria, there are no randomised studies on pyridoxine efficacy. However, it has been confirmed that a few patients with type 1 hyperoxaluria respond favourably to large doses of pyridoxine (26-28).
Due to the lack of other effective treatments, it is worth trying pyridoxine, 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 stones.

11.3.1.7 L-Methionine
Acidification of urine can be achieved with 600-1500 mg/day L-methionine. Methionine acidifies urine pH by donating protons. Stable acidification is difficult to achieve. Long-term acidification in children is not justified (4).

11.3.1.8 Tiopronin - α-mercaptopropionylglycine
Tiopronin - which has a thiol-containing biomolecule - is able to form drug-cysteine complexes by splitting the disulphide binding of cystine. Consequently, cystine saturation of urine decreases, while solubility increases significantly (29-31). Although no RCTs have been reported, tiopronin lowers cystine stone formation, when rates before and after treatment are compared (32-35). Due to the significant level of side effects, 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, including: nausea, rash, fatigue, fever, and proteinuria.

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

<table>
<thead>
<tr>
<th>Urinary risk factor</th>
<th>Suggested treatment</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalciuria</td>
<td>Thiazide + potassium citrate</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Hyperoxaluria</td>
<td>Oxalate restriction</td>
<td>2b</td>
<td>A</td>
</tr>
<tr>
<td>Hypocitraturia</td>
<td>Potassium citrate</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Enteric hyperoxaluria</td>
<td>Potassium citrate</td>
<td>3-4</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Calcium supplement</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Oxalate absorption</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>High sodium excretion</td>
<td>Restricted intake of salt</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Small urine volume</td>
<td>Increased fluid intake</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Urea level indicating a high intake of animal protein</td>
<td>Avoid excessive intake of animal protein</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Distal renal tubular acidosis</td>
<td>Potassium citrate</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Primary hyperoxaluria</td>
<td>Pyridoxine</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>No abnormality identified</td>
<td>High fluid intake</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>

11.3.3 References
   http://www.icud.info/publications.html


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

11.4.1 Diagnosis
Blood analysis requires measurement of creatinine, sodium, potassium, chloride, ionized calcium (or total calcium + albumin), uric acid, and parathyroid hormone (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 ionised calcium in serum (or total calcium and albumin) require assessment of intact PTH to confirm or exclude suspected hyperparathyroidism (HPT).
- “Acidic arrest” (urine pH constantly < 6) may promote co-crystallisation of uric acid and calcium oxalate. Similarly, increased uric acid excretion (> 4 mmol/day in adults or > 12 mg/kg/day in children) can act as a promoter.
- Urine pH levels constantly > 5.8 in the day profile indicate renal tubular acidosis (RTA), provided UTI has been excluded. An ammonium chloride loading test confirms RTA and identifies RTA subtype (see Section 11.6.4).
- Oxalate excretion > 0.5 mmol/day in adults (> 0.37 mmol/1.73 m²/day in children) confirms hyperoxaluria:
  - primary hyperoxaluria (oxalate excretion mostly ≥ 1 mmol/day), appears in three genetically determined forms;
  - secondary hyperoxaluria (oxalate excretion > 0.5 mmol/day, usually < 1 mmol/day), occurs due to intestinal hyperabsorption of oxalate or extreme dietary oxalate intake;
  - mild hyperoxaluria (oxalate excretion 0.45-0.85 mmol/day), commonly found in idiopathic calcium oxalate stone formers.

11.4.3 Specific treatment
General preventive measures are recommended for fluid intake and diet. Hyperoxaluric stone formers should consume foods with low oxalate content, while hyperuricosuric stone formers benefit from daily dietary reduction of purine. Table 30 summarises pharmacological treatment of calcium oxalate stones.
Table 30: Pharmacological treatment of calcium oxalate stones

<table>
<thead>
<tr>
<th>Biochemical risk factor</th>
<th>Rationale for pharmacological therapy</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalciuria</td>
<td>Calcium excretion 5-8 mmol/day</td>
<td>Alkaline citrate, 9-12 g/day, OR Sodium bicarbonate, 1.5 g 3 times daily</td>
</tr>
<tr>
<td></td>
<td>Calcium excretion &gt; 8 mmol/day</td>
<td>Hydrochlorothiazide, 25 mg/day initially, up to 50 mg/day</td>
</tr>
<tr>
<td>Hypocitraturia</td>
<td>Citrate excretion &lt; 2.5 mmol/day</td>
<td>Alkaline citrate, 9-12 g/day</td>
</tr>
<tr>
<td>Hyperoxaluria (enteric)</td>
<td>Oxalate excretion &gt; 0.5 mmol/day</td>
<td>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</td>
</tr>
<tr>
<td>Hyperuricosuria</td>
<td>Uric acid excretion &gt; 4.0 mmol/day</td>
<td>Alkaline citrate, 9-12 g/day OR Sodium bicarbonate, 1.5 g, 3 times daily PLUS Allopurinol, 100 mg/day</td>
</tr>
<tr>
<td></td>
<td>Hyperuricosuria and hyperuricemia &gt; 380 μmol</td>
<td>Alkaline citrate, 9-12 g/day PLUS Allopurinol, 100-300 mg/day, depending on kidney function</td>
</tr>
<tr>
<td>Hypomagnesiuria</td>
<td>Magnesium excretion &lt; 3.0 mmol/day</td>
<td>Magnesium, 200-400 mg/day NB: NO MAGNESIUM THERAPY IN CASE OF RENAL INSUFFICIENCY</td>
</tr>
</tbody>
</table>

11.5 Calcium phosphate stones

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

Calcium phosphate mainly appears in two completely different minerals: carbonate apatite and brushite:
- Carbonate apatite crystallisation occurs at pH > 6.8 and may be associated with infection.
- Brushite crystallises at an optimum pH of 6.5-6.8, at high urinary concentrations of calcium (> 8 mmol/day) and phosphate (> 35 mmol/day). Its occurrence is not related to UTI.

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

11.5.1 Diagnosis

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

11.5.2 Specific treatment

General preventive measures are recommended for fluid intake and diet.

11.5.3 Pharmacological therapy (Table 31)

HPT and RTA are common causes of calcium phosphate stone formation. Although most patients with primary HPT require surgery, RTA can be corrected pharmacologically. If primary HPT and RTA have been excluded, pharmacotherapy for calcium phosphate calculi depends on effective reduction of urinary calcium levels using thiazides. If urine pH remains constantly > 6.2, urinary acidification with L-methionine may be helpful. For
infection-associated calcium phosphate stones, it is important to consider the guidance given for infection stones.

**Table 31: Pharmacological treatment of calcium phosphate stones**

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

**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 ulcers and urolithiasis. Elevated levels of PTH significantly increase calcium turnover, leading to hypercalcaemia and hypercalciuria. If HPT is suspected, neck exploration should be performed to confirm the diagnosis (7). Primary HPT can only be cured by surgery.

**11.6.2 Primary hyperoxaluria (PH) (8-14)**
Patients with primary hyperoxaluria (PH) should be referred to specialised centres, because successful management requires an experienced interdisciplinary team. The main therapeutic aim is to reduce endogenous oxalate production, which is increased in patients with PH. In approximately one-third of patients with PH type I, pyridoxine therapy normalises or significantly reduces urinary oxalate excretion. The goal of adequate urine dilution is achieved by adjusting fluid intake to 3.5-4.0 L/day in adults (children 1.5 L/m² body surface area) and following a circadian drinking regimen.

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

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

**11.6.3 Enteric hyperoxaluria (15-20)**
Enteric hyperoxaluria is a particularly problematic condition in patients with intestinal malabsorption of fat. This abnormality is associated with a high risk of stone formation, and is seen after intestinal resection, jejunoileal bypass for treatment of obesity, and in Crohn’s disease and pancreas insufficiency. Intestinal loss of fatty acids is combined with loss of calcium. The normal complex formation between oxalate and calcium is therefore disturbed and oxalate absorption is increased. In addition to hyperoxaluria, these patients usually present with hypocitraturia because of loss of alkali. Urine pH is usually low, as are urinary calcium and urine volume. All these abnormalities contribute to high levels of supersaturation with calcium oxalate, crystalluria and stone formation.

Specific preventive measures are:

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

**11.6.4 Renal tubular acidosis (RTA) (24,25)**
Renal tubular acidosis is caused by severe impairment of proton or bicarbonate handling along the nephron. Kidney stone formation most probably occurs in patients with distal RTA type I. Figure 4 outlines the diagnosis of RTA.
The main therapeutic aim is restoring a normal acid-base equilibrium. Despite the alkaline pH of urine in RTA, alkalinisation using alkaline citrates or sodium bicarbonate is key to normalising the metabolic changes (intracellular acidosis) responsible for stone formation (Table 32). The alkali load reduces tubular reabsorption of citrate, which in turn normalises citrate excretion and simultaneously reduces calcium turnover. Therapeutic success can be monitored by venous blood gas analysis (base excess: ± 2.0) in complete RTA. If excessive calcium excretion (> 8 mmol/day) persists after re-establishing acid-base equilibrium, thiazides may lower urinary calcium excretion.

### Table 32: Pharmacological treatment of renal tubular acidosis

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

11.6.5 **Nephrocalcinosis (26,27)**

Nephrocalcinosis (NC) refers to increased crystal deposition within the renal cortex or medulla, and occurs alone or in combination with kidney stones. There are various metabolic causes. The main risk factors are: HPT, PH, RTA, vitamin D metabolic disorders, idiopathic hypercalciuria and hypocitraturia, and genetic disorders, including Dent’s disease 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.

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

11.6.6 References


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, gout or catabolism (2). Ammonium urate crystals are associated with UTI, malabsorption 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 urine at pH > 6.5, at high uric acid concentration, and in the presence of cations.

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 33 describes pharmacological treatment.
Table 33: Pharmacological treatment of uric acid and ammonium urate stones

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

11.7.3 References

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, and 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 34).

Table 34: Most important species of urease-producing bacteria

<table>
<thead>
<tr>
<th>Obligate urease-producing bacteria (&gt; 98 %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Proteus spp.</td>
</tr>
<tr>
<td>- Providencia rettgeri</td>
</tr>
<tr>
<td>- Morganella morganii</td>
</tr>
<tr>
<td>- Corynebacterium urealyticum</td>
</tr>
<tr>
<td>- Ureaplasma urealyticum</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Facultative urease-producing bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Enterobacter gergoviae</td>
</tr>
<tr>
<td>- Klebsiella spp.</td>
</tr>
<tr>
<td>- Providencia stuartii</td>
</tr>
<tr>
<td>- Serratia marcescens</td>
</tr>
<tr>
<td>- Staphylococcus spp.</td>
</tr>
</tbody>
</table>

CAUTION:
About 0-5% of strains of Escherichia coli, Enterococcus and Pseudomonas aeruginosa may produce urease.

11.8.2 Specific treatment
General preventive measures are recommended for fluid intake and diet. Specific measures include complete surgical stone removal (1), short- or long-term antibiotic treatment (2), urinary acidification using methionine (3) or ammonium chloride (4), and urease inhibition (5,6). For severe infections, acetohydroxamic acid (Lithostat) may be an option.

Recommendations for therapeutic measures

<table>
<thead>
<tr>
<th>Recommendations for therapeutic measures</th>
<th>Refs.</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical removal of the stone material as completely as possible</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-term antibiotic course</td>
<td>2</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Long-term antibiotic course</td>
<td>2</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Urinary acidification: ammonium chloride, 1 g x 2-3 daily</td>
<td>4</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Urinary acidification: methionine, 200-500 mg, 1-3 times daily</td>
<td>3</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Urease inhibition</td>
<td>5,6</td>
<td>1b</td>
<td>A</td>
</tr>
</tbody>
</table>

11.8.3 References


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

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

*Interpretation*
- Cystine is poorly soluble in urine and crystallizes spontaneously within the physiological range of urine pH.
- 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 disulphide bond splitting in cystine; it is essential to differentiate between cystine, cysteine and drug-cysteine complexes. Only HPLC-based analysis differentiates 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 reduce urinary excretion of cystine, patients are unlikely to comply sufficiently with such a diet. However, a restricted intake of sodium is more easily achieved and is more effective in reducing urinary cystine. Patients are usually advised to avoid sodium consumption > 2 g/day (1).

A high diuresis is of fundamental importance, aiming for 24-h urine volume of ≥ 3 L (2,3). 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 35) and to ensure appropriate hydration with a minimum of 3.5 L/day in adults, or 1.5 L/m² body surface area in children.

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

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

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

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

Results for the angiotensin-converting enzyme inhibitor, captopril, are controversial (6-10). Captopril remains a second-line option, for use when tiopronin is not feasible or unsuccessful.
Table 35: Pharmacological treatment of cystine stones

<table>
<thead>
<tr>
<th>Biochemical risk factor</th>
<th>Rationale for pharmacological therapy</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystinuria</td>
<td>Cystine excretion &gt; 3.0-3.5 mmol/day</td>
<td>Tiopronin, 250 mg/day initially, up to a maximum dose of 2 g/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>NB: TACHYPHYLAXIS IS POSSIBLE</strong></td>
</tr>
<tr>
<td>Inadequate urine pH</td>
<td>Improvement of cystine solubility. Urine pH optimum 7.5-8.5</td>
<td><strong>Alkaline Citrate</strong> dose according to urine pH alternative <strong>Sodium Bicarbonate</strong> dose according to urine pH</td>
</tr>
</tbody>
</table>

Recommendations for the treatment of cystine stones

<table>
<thead>
<tr>
<th>Therapeutic measures</th>
<th>Refs.</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine dilution</td>
<td>1-3,5</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>High fluid intake recommended so that 24-h urine volume exceeds 3 L. Intake should be ≥ 150 mL/h.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkalisation</td>
<td>1-3,5</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>For cystine excretion &lt; 3 mmol/day:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>potassium citrate 3-10 mmol 2 or 3 times daily, to achieve pH &gt; 7.5.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex formation with cystine</td>
<td>1-10</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>For patients with cystine excretion &gt; 3 mmol/day, or when other measures are insufficient: tiopronin, 250-2000 mg/day; captopril, 75-150 mg remains a second-line option in case tiopronin is unfeasible or unsuccessful.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

11.9.3 References


11. 2,8-dihydroxyadenine stones and xanthine stones (1)

All 2,8-dihydroxyadenine and xanthine stone formers are considered to be at high risk of recurrence. Both stone types are rare. Diagnosis and specific prevention are similar to those for uric acid stones.

11.10 2,8-dihydroxyadenine stones

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

11.10.1 Xanthine stones

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

11.10.2 Fluid intake and diet

Recommendations for general preventive measures apply. Pharmacological intervention is difficult, therefore, high fluid intake ensures optimal specific weight levels of urine < 1.01. A purine-reduced diet decreases risk of spontaneous crystallisation in urine.

11.11 Drug stones (2)

Drug stones are induced by pharmacological treatment (3,4) (Table 36). Two types exist:
- stones formed by crystallised compounds of the drug;
- stones formed due to unfavourable changes in urine composition under drug therapy.

Table 36: Compounds that cause drug stones

<table>
<thead>
<tr>
<th>Active compounds crystallizing in urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Allopurinol/oxypurinol</td>
</tr>
<tr>
<td>• Amoxicillin/ampicillin</td>
</tr>
<tr>
<td>• Ceftriaxone</td>
</tr>
<tr>
<td>• Ciprofloxacin</td>
</tr>
<tr>
<td>• Ephedrine</td>
</tr>
<tr>
<td>• Indinavir</td>
</tr>
<tr>
<td>• Magnesium trisilicate</td>
</tr>
<tr>
<td>• Sulfonamide</td>
</tr>
<tr>
<td>• Triamterene</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substances impairing urine composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Acetazolamide</td>
</tr>
<tr>
<td>• Allopurinol</td>
</tr>
<tr>
<td>• Aluminium magnesium hydroxide</td>
</tr>
<tr>
<td>• Ascorbic acid</td>
</tr>
<tr>
<td>• Calcium</td>
</tr>
<tr>
<td>• Furosemide</td>
</tr>
<tr>
<td>• Laxatives</td>
</tr>
<tr>
<td>• Methoxyflurane</td>
</tr>
<tr>
<td>• Vitamin D</td>
</tr>
</tbody>
</table>

11.12 Unknown stone composition (5)

An accurate medical history is the first step towards identifying risk factors (Table 37).

Diagnostic imaging begins with ultrasound examination of both kidneys to establish whether the patient is stone-free. Stone detection by ultrasound should be followed by KUB and unenhanced multislice CT in adults to differentiate between calcium-containing and non-calcium stones.
Blood analysis demonstrates severe metabolic and organic disorders, such as renal insufficiency, HPT or other hypercalcaemic states and hyperuricaemia. In children, hyperoxalaemia is additionally screened.

Urinalysis is performed routinely with a dipstick test as described above. Urine culture is required if there are signs of infection.

Constant urine pH > 6 in the daily profile indicates acidic arrest, which may promote uric acid crystallisation. Persistent urine pH > 5.8 in the daily profile indicates RTA, if UTI is excluded.

Microscopy of urinary sediment can help to discover rare stone types, 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 specific patient evaluation can follow.

However, if any expelled stone material is available, it should be analysed by diagnostic confirmation or correction.

Table 37: Investigating patients with stones of unknown composition

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

11.13 References


## 12. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

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

All members of the Urolithiasis Guidelines working group have provided disclosure statements on all relationships that they have and that might be perceived to be a potential source of conflict of interest. This information is kept on file in the European Association of Urology Central Office database. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.