Guidelines on
Urolithiasis

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**European
Association
of Urology**

TABLE OF CONTENTS   PAGE

A1: Devices for endoscopic disintegration of stones
A2: Approximate stone surface area with known diameters of the stone

1. BACKGROUND

Patients with urolithiasis constitute an important part of everyday urological practice. The optimal clinical management of this disease requires knowledge of the diagnostic procedures, the rational treatment of acute stone colic, stone expulsive treatment and the modern principles of stone removal. It is also essential to have a basic understanding of the aetiological factors of stone formation and how to perform a metabolic risk evaluation in order to provide a sound basis for appropriate measures to prevent stone recurrence.

During the past few decades, the whole field of treatment of patients with urolithiasis has been characterized by changes that are attributable to pronounced technical achievements, an increased understanding of the mechanisms of stone formation and advancements in pharmacological treatment of the various aspects of stone disease.

The guidelines and recommendations given below are based on results published in the modern literature. Some of the therapeutic principles given are based on evidence from randomized or controlled studies, while other statements are based on other kinds of studies or on a substantial clinical experience. According to the principles of the European Association of Urology (EAU) Guidelines Office, the scientific basis for the various recommendations or statements has been classified in terms of level of evidence and grade of recommendation when appropriate.

The criteria for level of evidence (LE) (Table 1) and grades of recommendation (GR) (Table 2) are shown below (1). The abbreviations LE and GR are used in the tables and recommendations given in these guidelines.

Table 1: Level of evidence (LE)

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

Table 2: Grade of recommendation (GR)

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

In several statements presented throughout the text the methods considered have been assigned Preference numbers, 1, 2, 3, etc. Preference numbers are used to indicate which treatment alternative was considered most appropriate or preferred, according to the literature or consensus reached. If two procedures were considered equally useful, they were given the same preference number. The first treatment alternative always has the preference number 1.

For the management of patients with stones in the ureter (Chapter 9), we refer to the 2007 Guideline for the Management of Ureteral Calculi, a document resulting from collaboration between the American Urological Association (AUA) and the EAU (2,3; http://www.auanet.org/guidelines and http://www.uroweb.org/professional-resources/guidelines). At the start of this project, an 'index patient' was defined to describe the typical individual with a ureteral stone whom a urologist treats. The following definition was created:

> *The index patient is a non-pregnant adult with a unilateral noncystine/nonuric acid radiopaque ureteral stone without renal calculi requiring therapy whose contralateral kidney functions normally and whose medical condition, body habitus, and anatomy allow any one of the treatment options to be undertaken.*

Whenever possible, statements are graded where the grading reflects the degree of flexibility in application. The terminology for the three levels used are STANDARD, RECOMMENDATION and OPTION. A 'standard' is the most rigid treatment policy, whereas 'recommendation' has significantly less rigidity and an

'option' allows for the largest amount of flexibility. These terms are defined as follows:

1. **STANDARD**: A guideline statement is a standard if: the health outcomes of the alternative interventions are sufficiently well known to permit meaningful decisions, and there is virtual unanimity about which intervention is preferred.

2. **RECOMMENDATION**: A guideline statement is a recommendation if: the health outcomes of the alternative interventions are sufficiently well known to permit meaningful decisions, and an appreciable, but not unanimous majority agrees on which intervention is preferred.

3. **OPTION**: A guideline statement is an option if: the health outcomes of the interventions are not sufficiently well known to permit meaningful decisions,or preferences are unknown or equivocal.

It is not possible to translate these three levels of grading to the grade of recommendations currently used by the EAU. However, the statements made in Chapter 9 will correspond at least partly to the preference numbers used in the other fields of urolithiasis discussed in this guideline.

For all clinical problems, the various recommendations in this guideline are supported by comments based on the most important relevant publications or by panel opinion when data from the literature are contradictory or lacking. It must be emphasized, however, that no attempt was made to perform a structural analysis of the available literature since such an effort was beyond the possibilities and scope of the work.

When recommendations were made, the main focus was on medical aspects. A discussion of the associated economic issues is beyond the scope of a European guideline document because of the wide geographical diversity of, and variation between, different financial systems in the European healthcare sector.

We are very well aware of the different treatment and technical facilities available geographically. Our intention has been to highlight the alternatives that appear most convenient for the patient in terms of low invasiveness and risk of complications. This does not mean that other methods are not applicable. However, when a certain form of therapy is not recommended, this has been specifically stated.

This edition of Guidelines on Urolithiasis is an update of our previously published documents (4-6).

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2. CLASSIFICATION

2.1 Categories of stone formers

A system for subgrouping stone-forming patients into different categories according to type of stone and severity of the disease is shown in Table 3. These different categories are useful when making decisions regarding the need for metabolic evaluation and medical treatment (1-4).

Table 3: Categories of stone formers

	Definition	Category
NON-CALCIUM STONES	Infection stone: magnesium ammonium phosphate, carbonate apatite or ammonium urate[a]	INF
	Uric acid/ammonium urate[a]/sodium urate stone	UR
	Cystine stone	CY
CALCIUM STONES	First-time stone former **without** residual stone or fragments	S_o
	First-time stone former **with** residual stone or fragments	S_{res}
	Recurrent stone former with **mild** disease and **without** residual stone(s) or fragments	R_{mo}
	Recurrent stone former with **mild** disease and **with** residual stone(s) or fragments	R_{m-res}
	Recurrent stone former with **severe** disease with or without residual stone(s) or fragments or with **specific risk factors** irrespective of otherwise defined category (Table 4)	R_s

[a]   It is of note that ammonium urate stones form when a urease-producing infection occurs in patients with urine that is supersaturated with uric acid/urate.

2.2 Specific risk factors for stone formation

Risk factors for stone formation are listed in Table 4.

Table 4: Risk factors for recurrent stone formation

- Onset of disease early in life, i.e., below 25 years of age

- Stones containing brushite (calcium hydrogen phosphate; $CaHPO_4 \cdot 2H_2O$)

- Strong family history of stone formation

- Only one functioning kidney (although only one kidney does not mean an increased risk of stone formation, these patients should be particularly considered for measures to prevent stone recurrence)

- Diseases associated with stone formation
  - ☐ hyperparathyroidism
  - ☐ renal tubular acidosis (partial/complete)
  - ☐ cystinuria
  - ☐ primary hyperoxaluria
  - ☐ jejunoileal bypass
  - ☐ Crohn's disease
  - ☐ intestinal resection
  - ☐ malabsorptive conditions
  - ☐ sarcoidosis

- Medication associated with stone formation
  - ☐ calcium supplements
  - ☐ vitamin D supplements
  - ☐ acetazolamide
  - ☐ ascorbic acid in megadoses (> 4 g/day)
  - ☐ sulphonamides

| | triamterene |
| | indinavir |

• Anatomical abnormalities associated with stone formation
	tubular ectasia (medullary sponge kidney)
	pelvo-ureteral junction obstruction
	caliceal diverticulum, caliceal cyst
	ureteral stricture
	vesico-ureteral reflux
	horseshoe kidney
	ureterocele

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3. DIAGNOSTIC PROCEDURES

3.1 Diagnostic imaging

Stone disease very often presents as an episode of acute stone colic. Patients with renal stone colic usually have characteristic loin pain, vomiting and mild fever, and they may have a history of stone disease. The clinical diagnosis should be supported by an appropriate imaging procedure. This will immediately help to decide if a conservative approach is justified or if another treatment should be considered.

Imaging is imperative in patients with fever or a solitary kidney, and when the diagnosis of stone is in doubt	LE = 4 GR = C

The diagnostic work-up of all patients with symptoms of urinary tract stones requires a reliable imaging technique (Table 5). In case of an acute stone colic, excretory urography (intravenous pyelography, IVP) has been established as a gold standard. During recent years, unenhanced helical computed tomography (CT) examinations have been introduced as a quick and contrast-free alternative (1-3). In randomized prospective studies, for patients with acute flank pain, the specificity and sensitivity of this method was found to be similar (4,5-9) or superior (10-11) to that obtained with urography.

In selected cases, additional information regarding renal function may be obtained by combining CT with contrast infusion. One great advantage of CT is the demonstration of uric acid and xanthine stones, which are radiolucent on plain films. Another advantage is the ability of CT to detect alternative diagnoses (7,12). However, the advantage of a non-contrast imaging modality has to be balanced against the higher radiation dose given to the patient during CT investigation (3,5,13). It is important to know, however, that CT examination cannot always differentiate between radiolucent and radiopaque stones. Furthermore, CT is less suited for follow-up after treatment of radiopaque stones.

An alternative and commonly applied method for evaluating patients with acute flank pain is a plain film of kidneys, ureters and bladder (KUB) combined with ultrasonography (US). There is a huge bulk of experience to show that these two methods are sufficient in a large proportion of patients for the diagnosis of a ureteral stone.

Special examinations carried out in selected cases include retrograde pyelography, antegrade pyelography and scintigraphy.

Table 5: Imaging modalities in the diagnostic work-up of patients with acute flank pain

Preference number	Examination	LE	GR	References	Comment
1	Non-contrast CT	1	A	1-12	3.1
1	Excretory urography	Standard procedure			3.1
2	KUB + US	2a	B	6	3.1

LE = level of evidence; GR = grade of recommendation; CT = computed tomography; KUB = plain film of kidney, ureters and bladder; US = ultrasonography.

Although the intravascular administration of contrast medium is usually a concern for the radiologist, contrast medium is occasionally used as an auxiliary procedure for stone localization during shock-wave lithotripsy. Many urologists also take responsibility for the diagnostic radiological work-up of patients with stone problems. It is therefore essential to have a basic understanding of the risks associated with the use of contrast medium and the necessary precautions (Table 6).

3.1.1 Allergy to contrast medium
The following precautions should be taken when contrast medium needs to be adminstered to patients who have either reported allergic reactions or who may be at such a risk (14,15):
* Always use low-molecular non-ionic contrast medium.
* Give a corticosteroid (e.g. prednisolone 30 mg) between 12 and 2 hours before the contrast medium is injected.
* Corticosteroid can be combined with an intramuscular injection of an antihistamine agent (e.g. clemastine 2 mg), given 1 hour before administration of contrast medium.

3.1.2 Metformin
The administration of metformin (a drug used to treat diabetes type II) may give rise to lactic acidosis in case of contrast-induced anuria (16-18). This is an unusual complication caused by retention of dimethylbiguanide.

Unfortunately, lactic acidosis is associated with high mortality and great care needs to be taken when using contrast medium in patients taking metformin, particularly in the presence of reduced renal function (i.e. serum creatinine level > 130 µmol/L or > 1.50 mg/100 mL).

According to the recommendations given by the European Society of Urogenital Radiology (14,15), the serum creatinine level should be measured in every patient with diabetes being treated with metformin. In addition, the following should be considered:
* In metformin-treated patients with a normal serum creatinine, contrast medium can be administered, but the intake of metformin should be stopped from the time of the radiological examination until 48 hours have passed and the serum creatinine remains normal.
* In patients with reduced renal function, medication with metformin should be stopped and administration of contrast medium delayed until 48 hours have passed after the last intake of metformin. Treatment with metformin may resume 48 hours after the examination provided that serum creatinine remains at the pre-examination level.
* In a situation where no information on renal function is available, alternative imaging techniques should be used.
* In a situation where contrast medium has been given to a patient on metformin treatment, without information on the renal function, or with a reduced renal function, the metformin should be stopped immediately and the patient should be hydrated so that diuresis is $\geq$ 100 ml/h during 24 hours. Serum creatinine, lactic acid and blood pH should be monitored. Symptoms of lactic acidosis are vomiting, somnolence, epigastric pain, anorexia, hyperpnoea, lethargy, diarrhoea and thirst. The investigative findings are a blood pH < 7.25 and serum lactic acid concentration > 5 mmol/L (16,17).

3.1.3 Reduced renal function
Intravenous administration of contrast medium may result in a reduced renal perfusion and toxic effect on tubular cells. The vasoconstriction of glomerular afferent arterioles causes a reduced glomerular filtration rate (GFR) and increased renal vascular resistance. Nephrotoxicity caused by contrast medium is diagnosed by the demonstration of an increase of 25%, or at least 44 µmol/L, in the level of serum creatinine during the 3 days that follow intravascular administration of the agent when there is no alternative explanation.

Risk factors for the development of reduced renal function

The following risk factors should be noted before intravenous contrast medium is used:

- Increased serum creatinine
- Dehydration
- Age over 70
- Diabetes
- Congestive heart failure
- Concurrent treatment with nephrotoxic drugs, such as non-steroidal anti-inflammatory agents (NSAIDs) and aminoglycosides (the latter should be stopped for at least 24 hours).

Patients with multiple myeloma should either be examined with an alternative method or after adequate hydration.

Avoid repeated injections of contrast medium at intervals less than 48 hours (see Section 3.1.2.) to 72 hours.

Dosage of iodine

Reduced renal function means that the serum creatinine $\geq$ 140 µmol/L or that the GFR is $\leq$ 70 mL/min.

For a patient with a GFR of 80-120 mL/min, the administered dose of iodine should not exceed 80-90 g. When the GFR is reduced to a level at 50-80 mL/min, the dose of iodine should not exceed the same amount as the GFR expressed in mL/min/1.73m² body surface area (12,13). Table 7 lists useful formulae for calculating GFR and body surface area (19). For further advice regarding the appropriate dose of contrast medium, the reader is referred to guidelines presented by the Radiological Society.

In patients with a serum/plasma-creatinine level exceeding 140 µmol/L (1.6 mg/100 mL), hydration, before and after use of contrast medium, may be beneficial in order to prevent nephropathy. The administration of N-acetylcysteine 600 mg twice on the day before contrast injection has been recommended to prevent renal failure caused by contrast medium (20).

3.1.4   Untreated hyperthyroidism

For patients in whom hyperthyroidism is suspected, the level of thyroid stimulating hormone should be assessed before use of contrast medium. Contrast medium should not be given unless these patients are appropriately treated.

Table 6: General considerations regarding the use of contrast medium

Contrast medium should <u>not</u> be given to, or avoided, in the following circumstances	LE/GR	GR	Selected references	Comment
• Patients with an allergy to contrast media	–	–	14,15	3.1.1
• When the serum or plasma creatinine level is > 150 µmol/L	4	C	15	3.1.1
• To patients on medication with metformin	3	B	15-18	3.1.2
• Untreated hyperthyroidism	3	B	–	3.1.4
• To patients with myelomatosis	3	B	15	3.1.3

Table 7: Formulae for calculating glomerular filtration rate (GFR) and body surface area (19)

Men	GFR = (140 – age) x kg/(0.82 x serum creatinine)
Women	GFR = (0.85 x (140 – age) x kg/(0.82 x serum creatinine)
For patients < 20 years, the following formula should be used:	Body surface area = $kg^{0.425}$ x $height(cm)^{0.725}$ x 0.007184
	GFR = creatinine clearance x 1.73m²
	Creatinine clearance= (42.5 x height(cm)/serum creatinine) x $(kg/70)^{0.07}$

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3.2   Analysis of stone composition

Stones that pass spontaneously, are removed surgically, or excreted as fragments following disintegration, should be subjected to stone analysis to determine their composition (1-5). The preferred analytical procedures are X-ray crystallography and infrared spectroscopy. All patients should have at least one stone analysed. Repeated analysis is indicated when any changes in urine composition, due to medical treatment, dietary habits, environment or diseases, can be expected to have influenced the stone composition.

When stone(s) or stone material have not been retrieved, conclusions on stone composition may be based on the following observations:
•   Qualitative cystine tests, e.g. sodium nitroprusside test, Brand's test (6), or any other cystine test.
•   Bacteriuria/urine culture (in the case of a positive culture, ask for urease-producing micro-organisms).
•   Demonstration of crystals of struvite or cystine upon microscopic examination of the urinary sediment.
•   Serum urate (in cases where a uric acid or urate stone is a possible alternative).
•   Urine pH (low in patients with uric acid stones, high in patients with infection stones).
•   Radiographic characteristics of the stone.

An appropriate quantitative or semi-quantitative analysis of the stone material should enable conclusions to be drawn regarding the main constituent or constituents.

The following calcium stones, which are not associated with infection, are referred to as radiopaque stones:
•   Calcium oxalate
    ○   calcium oxalate monohydrate
    ○   calcium oxalate dihydrate
•   Calcium phosphate
    ○   hydroxyapatite
    ○   carbonate apatite
    ○   octacalcium phosphate
    ○   brushite
    ○   whitlockite.

The following stones, which are not associated with infection, are referred to as uric acid/urate stones:
•   Uric acid
•   Sodium urate.

Infection stones have the following typical constituents:
•   Magnesium ammonium phosphate
•   Carbonate apatite.

Less common stone constituents include 2,8-dihydroxyadenine, xanthine and various drug metabolites (e.g. sulphonamide, indinavir). Calcium stones, uric acid/urate stones and cystine stones associated with infection are referred to as 'stones with infection'.

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3.3 Biochemical investigations

3.3.1 *Analytical work-up in the acute phase (Table 8)*

Table 8: Biochemical analyses recommended for patients with an acute stone episode

For all patients	Urinary sediment/dipstick test for demonstration of red cells
	White cells. Test for bacteriuria (nitrite) and urine culture in case of a positve reaction
	Serum creatinine should be analysed as a measure of the renal function
For patients with fever	C-reactive protein and blood cell count
For patients who vomit	Serum/plasma sodium
	Serum/plasma potassium
Optional useful information	Approximate pH level[a]
	Serum/plasma calcium[b]
	All other examinations that might be necessary in case of intervention

[a] Knowledge of pH might reflect the type of stone that the patient has formed.

[b] This might be the only occasion on which patients with hypercalcaemia are identified.

3.3.2 *Analysis of urine in search for risk factors of stone formation*

For an identification of metabolic risk factors of stone formation, an analytical programme for the different categories of stone formers is shown in Table 9.

Table 9: Analytical programme for patients with stone disease

Category of stone former*	Blood analysis (serum/plasma)	Urine analysis follow-up	Prevention
INF	Creatinine	Culture, pH	Yes
UR	Creatinine, urate	Urate, pH	Yes
CY	Creatinine[a]	Cystine, pH	Yes
S_o	Yes (see Table 11a)	Limited urine analysis (only fasting spot urine)	No
S_{res}	Yes (see Table 11b)	Yes (see Table 11)	Yes
R_{mo}	Yes (see Table 11a)	Limited urine analysis (only fasting spot urine)	No
R_{m-res}	Yes (see Table 11b)	Yes (see Table 11)	Yes
R_s	Yes (see Table 11b)	Yes (see Table 11)	Yes

*See Table 3 in Chapter 2 for an explanation of the categories of stone formers.

[a] The type of medical treatment in these patient will determine which other blood variables need to be included in the follow-up analysis.

Two urine collections for each set of analyses are recommended. The urine collections are repeated when necessary (1-3). A number of alternative collection options are feasible, with a few examples listed in Table 10.

Table 10: Alternatives for urine collection

Alternative	Timing of collection	Description of collection
1	Two 24-hour collections	Sample 1 collected in a bottle containing 30 mL of 6 mol/L hydrochloric acid
		Sample 2 collected in a bottle containing 30 mL of 0.3 mol/L sodium azide
2	One 24-hour collection	Sample collected in a bottle containing 30 mL of 6 mol/L hydrochloric acid
3	One 16-hour urine collection and one 8-hour urine collection	Sample 1 collected between 06.00 and 22.00 hours in a bottle containing 20 mL of 6 mol/L hydrochloric acid
		Sample 2 collected between 22.00 and 06.00 hours in a bottle containing 10 mL of 0.3 mol/L sodium azide
4	Spot urine sample	The excretion of each urine variable is related to the creatinine level

The presence of hydrochloric acid (HCl) prevents the precipitation of calcium oxalate and calcium phosphate in the container during storage. In addition, HCl counteracts the oxidation of ascorbate to oxalate. In acidified samples, uric acid precipitates and has to be dissolved by alkalinization if urate excretion is of interest. Urate can be analysed in samples collected with sodium azide as preservative.

A collection of urine without HCl is necessary for pH measurement. In this respect, a sample collected with sodium azide is useful. A night-time urine sample in which pH is measured soon after the urine has been collected is useful because the pH may alter during urine storage.

A patient with uncomplicated stone disease is one who is either stone-free after the first stone episode or who has a history of mild recurrent disease with long intervals between stone episodes (categories S_o, R_{mo}; Table 3). The stone, blood (serum or plasma) and urine analyses recommended for such patients are shown in Table 11a.

Although the ideal situation would be to analyse a fasting morning urine sample, this is not always easy to accomplish in the clinical routine work, for which reason a spot urine sample might serve as a rough guide to the need of further analyses.

A patient with complicated stone disease has a history of frequent recurrences, with or without residual fragments or stones in the kidney, or the patient presents specific risk factors. First-time stone formers with residual fragments may also be considered in this category (categories: R_s, S_{res}, R_{m-res}; Table 3). The stone, blood and urine analyses recommended for these patients are shown in Table 11b (4-12). Urine collection should be postponed until at least 4 weeks have passed after stone removal or after an episode of obstruction and should never be carried out in the presence of infection or haematuria. Special tests that may be required are shown in Table 12 (13-18).

Table 11a: Analyses in patients with complicated stone disease: blood and spot urine samples

Stone analysis	Blood analysis	Urine analysis
In every patient **one** stone should be analysed	Calcium	*Fasting morning spot urine or spot urine sample:*
	Albumin[1]	
	Creatinine	pH
	Urate[2]	Leucocytes/bacteria
		Cystine test

[1]. Either analysis of calcium + albumin to correct for differences in calcium concentration attributable to albumin binding, or direct analysis of ionized (free) calcium.

[2]. Optional analysis.

Table 11b: Analyses in patients with complicated stone disease: urine collection

Urine collection during a defined period of time[1]

Preference	Urine varables
1	Calcium
1	Oxalate
1	Citrate
1	Creatinine
1	Volume
2	Urate[2]
2	Magnesium[3]
2	Phosphate[3,4]
2	Urea[3,4]
3	Sodium[2,4]
3	Potassium[2,4]

[1.] 24-hour urine, 16-hour + 8-hour urine or any other collection period can be chosen provided normal excretion data are available (4-7). A spot urine sample can be used with creatinine-related variables (7).

[2.] As uric acid precipitates in acid solutions, urate has to be analysed in a sample that has not been acidified or following alkalinization to dissolve uric acid. When a 16-hour urine sample has been collected in a bottle with an acid preservative, the remaining 8 hours of the 24-hour period can be used to collect urine in a bottle with sodium azide for urate analysis.

[3.] Analysis of magnesium and phosphate is necessary to calculate approximate estimates of supersaturation with calcium oxalate (CaOx) and calcium phosphate (CaP), such as AP(CaOx) index and AP(CaP) index (8-12). Formulaes are given below.

[4.] Urea, phosphate, sodium and potassium measurements are useful for to assessing the dietary habits of the patient.

3.3.3 Comments on the analytical work-up

The purpose of analysing serum or plasma calcium is to identify patients with hyperparathyroidism or other conditions associated with hypercalcaemia. In the case of a high calcium concentration (> 2.60 mmol/L), the diagnosis of hyperparathyroidism should be established or excluded by repeated calcium analyses and assessment of the parathyroid hormone level (19-24).

In those patients in whom a stone analysis has not been carried out, a high serum urate level together with a radiolucent stone support the suspicion of a uric acid stone. In this regard, it needs to be emphasized that whereas a uric acid stone is usually invisible on a plain film (KUB), it is clearly demonstrated with a CT examination.

A spot morning urine sample should be used to measure pH (25). A pH above 5.8 in *fasting morning urine* raises the suspicion of incomplete or complete renal tubular acidosis (26). In the same fasting morning or spot urine sample, bacteriuria and cystinuria can be excluded or confirmed by an appropriate test (27).

The aim of adding serum potassium to the analytical programme is to obtain further support for a diagnosis of suspected RTA. Hypokalaemic hypocitraturia may be one reason for therapeutic failures in patients treated with thiazides.

The recommendation to collect two urine samples is based on observations that such an approach will increase the likelihood of detecting urine abnormalities. Various collection periods, such as for 24 hours, 16 hours, 17 hours, 12 hours, 4 hours, or even spot urine samples, are useful for this purpose, provided a set of normal values is available for the collection period (4-7).

It must be emphasized that the urine sample used for analysis of calcium, oxalate, citrate and phosphate has to be acidified, preferably with HCl. The reasons for this acidification are:
- To maintain calcium, oxalate and phosphate in solution, during and after the collection period.
- To prevent bacterial growth and the associated alteration of urine composition.
- To prevent the in-vitro oxidation of ascorbate to oxalate (28,29).

The following urine variables can be analysed in the acidified sample: calcium, oxalate, citrate, magnesium, phosphate, urea, sodium, chloride and potassium.

Although the creatinine concentration might be slightly affected, it has to be assessed in the same sample when creatinine-related variables are used and also for conclusions on the completeness of the collection. Urate forms uric acid in the acidified urine and has to be analysed either following complete dissolution with alkali or in a urine sample that has not been acidified.

The optional analysis of urea, phosphate and sodium helps to assess dietary factors of therapeutic

significance. The protein intake can be derived from the urea excretion (Uurea, mmol/L) and urine volume in litres (V) as follows (30):

Intake of protein (gram) during the 24h period = (U$_{urea}$ (mmol/24h) x 0.18) + 13

An estimate of the ion-activity products of calcium oxalate (AP[CaOx] index) and calcium phosphate, known as the AP[CaP] index, can be calculated as follows (31-37):

AP[CaOx] index = 1.9 x Ca$^{0.84}$ x Ox x Cit$^{-0.22}$ x Mg$^{-0.12}$ x V$^{-1.03}$

In this formula, the urine volume (V) is expressed in litres (L). The urine variables Ca (calcium), Ox (oxalate), Cit (citrate), and Mg (magnesium) are expressed in millimoles (mmol) excreted during the collection period. The factor 1.9 is specific for the 24-hour period; for a 16-hour urine sample, this factor is 2.3. For other collection periods, the reader should consult reference 5.

The AP[CaOx] index approximately corresponds to 10^8 x AP$_{CaOx}$ (where AP$_{CaOx}$ is the ion-activity product of calcium oxalate).

The AP[CaP] index for a 24-hour urine sample is calculated in the following way:

AP[CaP] index = 2.7 x 10^{-3} x Ca$^{1.07}$ x P$^{0.70}$ x (pH - 4.5)$^{6.8}$ x Cit$^{-0.20}$ x V$^{-1.31}$

The AP[CaP] index approximately corresponds to 10^{15} x AP$_{CaP}$ (where AP$_{CaP}$ is the ion-activity product of calcium phosphate). Factors for other collection periods can be found in reference 5. P is used for phosphate. A relationship between abnormalities in urine composition and severity of calcium stone formation has been demonstrated (38-44). It should be noted that although individual abnormal urine variables might indicate a risk of stone formation, it is the concerted action of the various urine constituents that produces supersaturation and crystallization of the stone.

Occasionally, it may be necessary to measure pH variation during the day or to make an acid loading for identification of disturbances in urine acidification. The principles for such a work-up are summarized in Table 12.

Analytical findings in patients with incomplete and complete renal tubular acidosis are summarized in Table 13.

Table 12: Additional analytical work-up in patients with calcium stone disease

pH profile (13)
Repeated measurements of pH during the 24-hour period
• Frequent samples should be collected for immediate measurement of pH with pH paper or a glass electrode
• Sampling every second hour or otherwise as appropriate
Acid loading (14-18)
This test is carried out together with blood sampling to show whether or not the patient has a complete or an incomplete acidification defect:
• Breakfast + ammonium chloride tablets (0.1 g/kg body weight), drink 150 mL
• 09.00 Collect urine and measure pH, drink 150 mL
• 10.00 Collect urine and measure pH, drink 150 mL
• 11.00 Collect urine and measure pH, drink 150 mL
• 12.00 Collect urine and measure pH, drink 150 mL
• 13.00 Collect urine and measure pH, lunch

Interpretation
pH of 5.4 or lower indicates no renal tubular acidosis

Table 13: Analytical findings in patients with complete and incomplete distal renal tubular acidosis (13)

Test	Incomplete RTA	Complete RTA
• Blood (pH)	Low	Normal
• Plasma bicarbonate	Low	Normal
• Plasma/serum potassium	Low	Normal
• Plasma/serum chloride	High	Normal
• Urinary calcium	High	High
• Urinary phosphate	High	High
• Urinary citrate	Low	Low
RTA = renal tubular acidosis.		

3.3.3.4   A simplified overview of the principles of analytical work-up in patients
A correct categorization of the patients requires both information on the stone composition and an actual imaging procedure. The principles shown below in Figure 1 can be applied to all patients provided a reasonable assumption of the category can be made. If this is not possible an alternative analytical approach has to be chosen until more data have been collected.

Figure 1. Recommendations regarding analysis of stones, blood and urine in different categories of stone forming patients

CATEGORY	STONE	BLOOD	URINE
INF	YES	Creatinine	Culture Urease? pH
UR	YES	Urate Creatinine	Urate pH Volume
CY	YES	Creatinine	Cystine pH Volume
Calcium stone So Rmo	YES	Calcium Albumin Creatinine (Urate)	Bacteria pH
Calcium stone Sres Rmres / Calcium stone Rs	YES	Calcium Albumin Creatinine (Urate)	Bacteria pH ········· Calcium Oxalate Citrate Creatinine Volume (Magnesium) (Phosphate) (Urea) (Urate)

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4.   STONE BURDEN

The size of a concrement (stone burden) can be expressed in different ways. A notation of the largest diameter is the most common way of expressing size in the literature, i.e. the length of the stone as measured on the plain film. With knowledge of the length (l) and the width (w), an appropriate estimate of the stone surface area (SA) can be obtained for most stones (1):

$$SA = l \times w \times \pi \times 0.25$$

For a quick estimate of the stone surface area, please refer to Table A1 (Appendix 2).

The surface area can also be measured using computerized systems and from CT scans, but these are not always easy procedures and the software is not always available. With knowledge of the surface area, the stone volume can be calculated by the formula below (2):

Volume = 0.6 x SA$^{1.27}$

In this guideline document, we have based our statements on the stone surface area as well as on the largest stone diameter.

With the more common use of CT examinations, it is possible to obtain an even better estimate of the stone volume (SV) by combining measures of lengh (l), width (w) and depth (d):

SV = l x w x d x π x 0.52

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5.   TREATMENT OF PATIENTS WITH RENAL COLIC

5.1   Pain relief

The relief of pain is usually the most urgent therapeutic step in patients with an acute stone episode (Table 14). Pain relief involves the administration of the following agents by various routes:

Table 14: Pain relief for patients with acute stone colic

Preference	Pharmacological agent	LE	GR	References	Comment
1	Diclophenac sodium	1b	A	1-4	5.1
1	Indomethacin Ibuprophen				
2	Hydromorphine hydrochloride+ atropine Methamizol Pentazocine Tramadol	4	C		

5.1.1   Treatment with non-steroidal anti-inflammatory drugs (NSAIDs)

The usefulness of NSAID agents was first shown with indomethacin in 1978 (1). A double-blind study comparing diclofenac and spasmofen (a narcotic analgesic) demonstrated a better effect with diclofenac and fewer side effects (2). In another double-blind, placebo-controlled study, the efficacy of diclofenac was clearly demonstrated (3). When diclofenac was compared with ketoprofen and ketorolac in randomized, double-blind, comparative studies, no differences were recorded between the two substances (4,5). Moreover, the resistant index was reduced in patients with renal colic when NSAID treatment was given (6).

The recommendation is to start with diclofenac whenever possible (Table 15) and change to an alternative drug if the pain persists. Because of the increased risk of vomiting, avoid giving hydromorphone and other opiates without simultaneous administration of atropine.

5.1.2   Prevention of recurrent episodes of renal colic

In a double-blind, placebo-controlled trial, it was shown that recurrent pain episodes of stone colic were significantly fewer in patients treated with 50 mg of diclofenac three times daily during the first 7 days. The effect was most pronounced in the first four treatment days (7). For patients with ureteral stones that are expected to pass spontaneously, suppositories or tablets of diclofenac sodium, 50 mg administered twice daily over 3-10 days, might therefore be useful in reducing the inflammatory process and the risk of recurrent pain.

Facilitation of stone passage might be accomplished by administration of alpha-blocking agents or possibly niphedipine. This therapeutic approach is further discussed in detail in Chapter 9.

The patient should be instructed to sieve the urine in order to retrieve a concrement for analysis. Passage of the stone and normalization of renal function should be confirmed using appropriate methods.

When pain relief cannot be obtained by medical means, drainage by stenting or percutaneous nephrostomy or by stone removal should be carried out.

5.1.3   Effects of diclofenac on renal function
Although the renal function can be affected in patients with an already reduced function, **this is not the case for normally functioning kidneys** (LE = 1b; GR = A) (8).

Table 15: Recommendations and considerations regarding treatment of the patient with renal colic

Recommendations	LE	GR	Selected references	Comment
Treatment should be started with an NSAID	1b	A	1-4	5.1.1
Diclofenac sodium affects GFR in patients with reduced renal function, but not in patients with normal renal function	2a	2a	8	5.1.3
Diclofenac sodium is recommended as a method to counteract recurrent pain after an episode of ureteral colic	1b	A	7	5.1.2
GFR = glomerular filtration rate; NSAID = non-steroidal anti-inflammatory drug.				

5.2   Spontaneous passage of stones
Most ureteral stones pass spontaneously. For further details, please see Chapter 6 and Chapter 9 (9,10).

5.3   Medical expulsive treatment (MET)
Methods are available for facilitation of ureteral stone passage. This problem is thoroughly discussed in Chapter 9 (9,10).

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6.   INDICATIONS FOR ACTIVE STONE REMOVAL

The size, site and shape of the stone at the initial presentation are factors that influence the decision to remove the stone (Table 16). The likelihood of spontaneous passage must also be evaluated. Spontaneous stone passage can be expected in up to 80% in patients with stones $\leq$ 4 mm in diameter. For stones with a diameter $\geq$ 7 mm, the chance of spontaneous passage is very low (1-4).
The overall passage rate of ureteral stones is:
•   Proximal ureteral stones: 25%.
•   Mid-ureteral stones: 45%.
•   Distal ureteral stones: 70%.
        Stone removal is accordingly indicated for stones with a diameter exceeding 6-7 mm. Studies have shown that asymptomatic stones in the kidney sooner or later give rise to clinical problems (5).
        It should also be observed that small stones (< 6-7 mm) residing in a calyx can cause considerable pain or discomfort (6-12). Such stones should be removed with a technique that is as minimally invasive as possible. A narrow caliceal neck may require dilatation.

Table 16: Indications for active stone removal

Indications for considering active stone removal	LE	GR	Selected references
• When stone diameter is $\geq$ 7 mm because of a low rate of spontaneous passage	2a	B	1-5
• When adequate pain relief cannot be achieved	4	B	
• When stone obstruction is associated with infection*	4	B	
• When there is a risk of pyonephrosis or urosepsis*	4	B	
• In single kidneys with obstruction*	4	B	
• Bilateral obstruction*	4	B	

* Diversion of urine with a percutaneous nephrostomy catheter or bypassing the stone with a stent are minimal requirements in these patients.
LE = level of evidence; GR = grade of recommendation.

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7.   ACTIVE REMOVAL OF STONES IN THE KIDNEY

7.1   Extracorporeal shock-wave lithotripsy (ESWL) for removal of stones in the kidney

There is no doubt that the clinical introduction of ESWL during the early 1980s dramatically changed the management of patients with urinary tract stones. During the more than 20 years since the worldwide dissemination of this technology, the development of new lithotripters, modified indications and principles for treatment, have changed completely the way in which patients with renal stones are treated. Modern lithotripters are smaller and, in the vast majority of cases, part of uroradiological tables allowing the application of not only ESWL, but also of all other diagnostic and ancillary procedures associated with the ESWL treatment. Recent developments have given us a tool with an efficacy that is the same as, or superior to, that of the first lithotripters on the market, but at a much lower cost and with greater versatility.

Currently, there are few contraindications to ESWL treatment. The most obvious are pregnancy, severe skeletal malformations, severe obesity and aortic and/or renal artery aneurysms, uncontrolled blood coagulation or uncontrolled urinary tract infections (1,2). It is generally considered that ESWL can be used successfully for stone removal of more than 90% of stones seen in adults (3-5).

Accumulated experience has clearly shown that, in addition to the efficacy of the lithotripter, the success rate of ESWL depends on the size (volume), number, location and hardness of the concrements as well as on the habitus of the patient and the ambition and experience of the operator (6). All these factors have an important effect on the retreatment rate and final outcome, which has led to the conclusion that large and hard stones are better treated with alternative techniques, usually by a percutaneous approach (*see below*). This issue has been addressed by many authors in recent years (3-5,7-17).

Generally, the disintegrating power of ESWL is very good and the concerns about ESWL treatment of

large stones are mainly related to the common occurrence of residual fragments and the need for repeated treatment sessions. The latter factor has probably become more important with later generations of lithotripters, because of their smaller focal volumes compared to, for example, the Dornier HM$_3$-lithotripter, which is considered to be the 'gold standard'. When repeated treatments are necessary, it is recommended that the number of shock waves and the power used should be restricted in order to avoid damage to the renal tissue and bleeding complications (*see below*).

It is recommended that the number of ESWL sessions should not exceed three to five (dependent on the lithotripter used); otherwise, a percutaneous method might be considered to be a more rational option.

In the case of infected stones or bacteriuria, antibiotic therapy should be given before ESWL treatment and continued for at least 4 days after the treatment	**LE = 4** **GR = C**

There are no clearly established rules on how often ESWL sessions can be repeated. It is reasonable to assume, however, that the interval between two successive sessions must be longer for electrohydraulic and electromagnetic lithotripsy than for treatments with piezoelectric equipment. Moreover, the risk of damage to the renal tissue is most pronounced with treatments directed towards stones in the kidney.

Shorter intervals between treatment sessions are usually acceptable for stones in the ureter. Clinical experience supports this view	**LE = 4** **GR = C**

It stands to reason, however, that the interval between two treatments should be determined by the energy level used and the number of shock waves given. In view of the numerous types of lithotripters presently in use, it is not possible to give a general recommendation in this regard. It might, however, be helpful to note that the time required for resolution of contusions in the renal tissue is in the range of about 2 weeks (18) and it might accordingly be wise to allow 10-14 days to pass between two successive ESWL sessions for stones located in the kidney.

There is no consensus on the maximum number of shock waves that can be delivered at each session. This number depends on the type of lithotripter and the shock-wave power being used. It is also important to consider the fact that tissue damage seems to increase with increased frequency of shock-wave delivery during treatment (19) and that stone disintegration becomes better at lower frequencies.

It has been concluded, however, that a frequency of 1-1.5 Hz is acceptable and optimal (20)	**LE = 3** **GR = C**

One factor that might affect the result of ESWL treatment is the presence of anatomical abnormalities. Malformations of the renal collecting system can be the reason for stone formation due to an altered mechanism of urine elimination and thus to impaired stone fragment passage. The need for auxiliary procedures is high in these patients. One study showed that only 50% of the patients were stone-free at 3 months' follow-up (21). In horseshoe kidneys, the incidence of stones is around 20%. The success rate depends mainly on the lithotripter used and varies between 53% and 60%. In one treatment series, the incidence of auxiliary procedures was reported to be 24% and the re-treatment rate 27% (22). Some authors claim that percutaneous surgery is the treatment of choice for these patients (23,24), but in view of the greater morbidity and complication rate of this technique percutaneous lithotripsy should be reserved for those patients in whom ESWL treatment has failed.

There are some reports indicating that ESWL is also useful in patients with medullary sponge kidneys (tubular ectasia) and nephrocalcinosis (25,26). In ectopic kidneys, the efficacy of ESWL is strictly related to the position of the kidney. In transplanted kidneys, the efficacy of ESWL is similar to that in normal kidneys and well tolerated, without any particular side effects (27).

Table 17 summarizes the stone-free rates of ESWL treatment of non-staghorn stones located in the kidney as reported in the literature.

Table 17: Stone-free rates following ESWL of non-staghorn stones

	n	Stone-free rate %	References
Dornier HM$_3$ lithotripter	10,623	45-90	29
Second and third generation lithotripters	20,141	51-100	28
Recently reported results		41-99	29-39

In a series of 35,100 patients treated for kidney stones with ESWL, satisfactory disintegration was recorded in 32,255 cases, which is 92%. The stone-free rate in these patients was 70% with re-treatments in

10.5% (40-70). When results reported during the past 7 years were considered separately, the stone-free rates between 41% and 90% corresponded very well to those reported for the Dornier HM$_3$-lithotripter and for subsequently developed second- and third-generation lithotripters.

Patient selection, stone location, frequency of repeated treatment sessions, use of auxiliary procedures and the experience of the operator might explain the viable outcome. When the treatment result was compared between the Dornier HM$_3$ and the Lithostar Plus lithotripters in a prospective randomized trial, the stone free rates were 89% and 87%, respectively (32). Although there might be considerable differences in the disintegrating capacity between various devices, it seems that late-generation lithotripters are efficient enough for treating stones in the kidney.

7.1.2 Factors of importance for the outcome of ESWL

Recent results of ESWL for removal of stones with diameters below and above 20 mm and located in the kidney showed stone-free rates from 66-99% for smaller stones and 45-60% for larger stones (29-31). Similar results were found with the Dornier HM$_3$ lithotripter, with stone-free rates that varied from 75-89% for stones up to a diameter of 20 mm compared to 39-63% for stones larger than this (28).

ESWL for the treatment of large renal stones often causes problems. Frequent complications are pain, hydronephrosis, fever and occasional urosepsis, due to difficulties in the passage of stone particles, especially in cases of insufficient disintegration (71-76).

The use of a double-J stent reduces the obstructive and infective complications after ESWL associated with large renal stones.

Insertion of an internal stent before ESWL is recommended for stones with a diameter ≥ 20 mm (~300 mm²) (77)	**LE = 3** **GR = B**

In a recent randomized comparison of patients with and without an internal stent, stone-free rates were found to be similar, with no benefits shown for stented patients. The author inserted stents for stones larger than 1 cm. The study concluded that the routine use of internal stents does not improve the outcome (LE = 1b, GR = A) (78).

Stone particles may pass easily along stents while urine flows in and around the stent. This usually prevents obstruction and loss of ureteral contraction. Sometimes, stents are not efficient in draining purulent ormucoid material, leading to a risk of obstructive pyelonephritis. In case of fever lasting for a few days, a percutaneous nephrostomy tube is necessary, even when US does not reveal any dilatation.

The following factors are crucial with respect to treatment success:
• Location of stone mass (pelvic or caliceal)
• Total stone burden
• State of contralateral kidney: nephrectomy or functionless kidney on the other side
• Composition and hardness of the stone.

7.1.2.1 Location of the stone mass

Lower caliceal stones are considered to have a lower successful clearance rate than stones located elsewhere in the kidney. A faster clearance of upper pole stones has been observed. Almost since the introduction of ESWL, there has been a continuous debate on the best way to treat stones in the lower calix. This is an important issue because a large number of kidney stones are located in this part of the kidney. Moreover, it is well recognized that most residual fragments are lodged in the lower caliceal system. Such fragments either emerge from stones originally found in this part of the kidney or from stones at other locations. It is still unknown why stones preferentially develop in the lower pole calices, although the accumulation of fragments in this position is most probably due to the effect of gravity.

It has been observed that the lower calices are insufficiently cleared of disintegrated stone material in up to 35% of ESWL-treated patients. Attempts have been made to explain the insufficient clearance of fragments and to predict the outcome of ESWL treatments from geometrical observations of the anatomy of the lower calix.

By taking measurements of the infundibulopelvic angle, as well as the infundibulum length and width, several authors have concluded that an acute infundibulum angle (79-83), a long infundibulum (79,83) and/or a narrow infundibulum (79-81,83) have a negative influence on fragment clearance. Alternatively, the distance between the calix bottom and the lower pelvic lip in combination with the angle between the calix and a vertical line is considered to play a role (84). In other studies, however, no such relationship has been demonstrated (85-90). In one report, the authors even noted that the clearance of fragments was better with an infundibulopelvic angle below, rather than above, 70° (89). In the absence of a geometrical explanation, the size of the stones has been found to be the most important determining factor (85,87-89). This conclusion has been based both on observations in a randomized prospective study comparing ESWL and percutaneous

nephrolithotomy (PNL) (87) and in a multivariate analysis (85). Although the geometry of the lower calix system is certainly important in the clearance of fragments, the discriminating power is not sufficiently strong to predict the outcome of ESWL and to use it for selecting alternative methods for stone removal (35). The results are contradictory. Another factor that most certainly is of great importance is the less well-understood caliceal physiology (83,90).

Several authors have shown that a better stone-free rate can be obtained with PNL, particularly when the stones become larger. The invariance and morbidity of PNL undoubtedly needs to be taken into account. At least for stones with a largest diameter of 20 mm (surface area ~ 300 mm^2), ESWL is the recommended treatment, despite the lower clearance rate of fragments. It might be relevant to note that a previous percutaneous procedure in one study (90) was considered as a negative determinant of fragment clearance. Morover, a multicentre randomized comparison between ESWL and ureteroscopic removal of stones from the lower calix system failed to show a significantly better result with uretoscopy (91) (LE = 1b; GR = A).

7.1.2.2 Stone burden
Although the problems associated with removal of stones from the kidney increases with the volume of the stone, there is no clear cut-off for a critical stone size. Today, most authors consider a largest stone diameter of 20 mm as a practical upper limit for ESWL, but larger stones are also successfully treated with ESWL in some centres and other limits for ESWL have been suggested (36,92).

Since residual fragments are found in patients with stones smaller than 20 mm (300 mm^2) and since very large stones can be successfully disintegrated with only one ESWL session, it is difficult to formulate specific guidelines on how to remove stones from the kidney. The recommended upper size limit for ESWL in this document is set at 20 mm (300 mm^2). Below this size, ESWL should be considered to be the first choice for treatment. For larger stones, the problem might be more rationally solved using PNL. However, ESWL can still be considered a treatment option, provided the pros and cons are clear.

In the treatment of stones with an area larger than 40 x 30 mm (940 mm^2), the combination of PNL and ESWL (sandwich approach) has emerged as a solution, with success rates of 71-96% and acceptable morbidity and complications. ESWL after PNL seems to be more effective than PNL after ESWL. The indication for open stone surgery has become extremely rare because of the invasiveness of this approach (73,74). It is of note, however, that the risk of complications for either combined treatment or PNL alone is higher than for ESWL monotherapy. In the case of a solitary kidney, it might be feasible to try ESWL monotherapy first, even if the stone has an area larger than 40 x 30 mm (75).

7.1.2.3 Composition and hardness of the stone
ESWL monotherapy of large calcium- or struvite-containing stones provides reasonable results in terms of stone removal and complications (76). About 1% of all patients treated for urinary tract stones by ESWL have cystine stones. A total of 76% of cystine stones have a maximum diameter larger than 25 mm (while only 29% of all stone patients have stones of this size). Patients with large cystine stones need up to 66% more ESWL sessions and shock waves to reach satisfactory results compared to other stone patients (93). ESWL monotherapy provided satisfactory results only in patients with pelvic stones smaller than 1 cm.

Instead of multiple ESWL sessions, PNL, possibly combined with ESWL, is an effective treatment for all other patients with cystine stones (93,94). It is important to note that there are two types of cystine stone morphology: smooth and rough. The latter is much more susceptible to shock waves than the first one (95).

Stone composition can be an important factor in the disintegration and subsequent elimination of fragments.

Stones composed of uric acid and calcium oxalate dihydrate have a better coefficient of fragmentation than those composed of calcium oxalate monohydrate and cystine. Success rates for these two groups of stones were shown to be 38-81% and 60-63%, respectively (12). For cystine stones with a diameter less than 15 mm, a stone-free rate of about 71% was reported, a figure that dropped to 40% when the diameter exceeded 20 mm (13). Thus, for cystine stones with a diameter greater than 15 mm, ESWL as monotherapy is currently not recommended.

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7.2 Percutaneous removal of renal stones

The majority of renal stones can be removed by percutaneous surgery. However, if ESWL is available, the indications for PNL should be limited to those cases likely to have a less favourable outcome after ESWL. Although PNL is minimally invasive, it is still a surgical procedure and thus it is necessary to carefully consider the patient's anatomy in order to avoid complications.

Pre-procedural KUB and intravenous urography or CT scan should be used to plan access. These images and anamnestic data will also give some hints about whether the stones will respond poorly to ESWL (such as stones composed of cystine, calcium oxalate monohydrate, brushite) or if fragments are unlikely to pass (large stones, stones in caliceal diverticulae or horseshoe kidneys). Pre-procedural sonography and fluoroscopy of the kidney and the surrounding structures are recommended to determine the optimal access site and the position of the stone in the kidney (ventral or dorsal), and to ensure that organs adjacent to the kidney (such as the spleen, liver, large bowel, pleura and lungs) are not within the planned percutaneous path (1,2).

The percutaneous puncture may be facilitated by the preliminary placement of a balloon ureteral catheter to dilate and opacify the collecting system. Furthermore, such a catheter will prevent fragments from falling into the ureter. The puncture can be performed under combined US and X-ray control or under biplanar fluoroscopy. The use of US allows easy identification of neighbouring organs and therefore decreases the risk of injuries to adjacent organs (3). In rare cases with anatomical anomalies, CT-guided renal access may be an option (4).

The access site used most often is the dorsal calix of the lower pole. In the least traumatic access, the puncture site on the skin lies in the extension of the long axis of the target calix and the puncture passes through the papilla. There are no major vessels in this region and there is only minimal bleeding. It is also the safest point of access because it uses the infundibulum as a conduit to the pelvis.

Dilatation of the tract is possible with the Amplatz system, balloon dilators or metallic dilators. The choice is a matter of experience, availability and costs. Although standard nephroscopes have shaft calibres of 24-30 F, so-called 'mini-perc' instruments have smaller dimensions with 12-20 F. These small-calibre instruments possibly have a lower rate of tract dilation-related complications, such as bleeding or renal trauma. However, treatment time increases with stone size, which is why this method is recommended only for stones with a diameter < 20 mm (5). While the value of mini-perc in adults has not been determined, it is the method of choice for percutaneous stone removal in children (6-8).

In lower pole stones, ESWL, PNL and flexible uretero-nephroscopy are competing procedures with different success and complication rates and patient acceptance (9-10) (LE = 1b; GR = A).

Stones can be extracted straightaway, or following disintegration by US-, electrohydraulic-, laser- or hydro-pneumatic probes. To reduce the number of residual fragments, continuous removal of small fragments by suction or extraction is preferred. After completion of the procedure, a self-retaining balloon nephrostomy tube tamponading the tract and maintaining access to the collecting system is preferred in complicated procedures or when a second intervention is necessary. Tubeless percutaneous nephrolithotomy, with or without tract fulguration, application of a sealant or double-J stenting, is a safe alternative in uncomplicated cases (8,11) (LE = 1b; GR = A).

7.2.1   Complications
Major but rare complications are lesions to adjacent organs. This can be avoided by puncture under US guidance. Bleeding is generally avoided by an anatomically oriented access, as described above. Sepsis and 'transurethral resection syndrome' indicate a poor technique resulting in high pressure within the collecting system during manipulation. These problems can be avoided by using continuous flow instruments or an Amplatz sheath (1,8). Major bleeding during the procedure requires termination of the operation, placement of a nephrostomy tube and secondary intervention at a later date. Venous bleeding stops in most cases when the nephrostomy tube is clamped for some hours. Persistent or late secondary bleeding is caused by an arterial injury and can be managed by angiographic super-selective embolization.

As with open surgery, percutaneous procedures have different degrees of difficulty. A difficult procedure is to be expected when anatomical conditions offer only limited space for the initial puncture, dilatation and instrumentation, such as stones in diverticulae or stones completely filling the target calix, as well as a large stone burden caused by complete or partial staghorn stones. The procedure should only be carried out by experienced surgeons in these cases.

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7.3   Retrograde removal of ureteral and renal stones (retrograde intrarenal surgery [RIRS])

During the past 20 years, ureterorenoscopy (URS) has dramatically changed the management of ureteral calculi and URS is now extensively used in many urological centres all over the world. However, it is a more invasive technique compared to ESWL, and the treatment of choice for ureteral stones has therefore become controversial. For renal calculi, ESWL and PNL are the recommended primary treatment options. Following the wider availability and improvement of flexible URS, its value for renal calculi has to be determined.

7.3.1   Standard endoscopic technique
The basic endoscopic technique has been well standardized (1-3).

Antibiotic prophylaxis should be administered before the procedure to ensure sterile urine (4,5)	**LE = 4** **GR = C**

Pre-operative imaging of the urinary tract is obtained to confirm the location of the stone and to identify anatomic abnormalities. The operating room must have fluoroscopic equipment.

Under general anaesthesia, spinal anaesthesia or intravenous sedation, the patient is placed in the lithotomy position. The procedure starts with rigid or flexible cystoscopy. A safety wire (usually an 0.035-inch, non-hydrophylic, floppy tip) is introduced under endoscopic and fluoroscopic control and secured to the drapes. The safety guide wire prevents the risk of false passage in case of perforation. Intramural ureteral dilatation is not indicated routinely, but depends on the size of the ureteroscope and the width of the ureter. Retrograde access to the upper urinary tract is usually obtained under video guidance with a rigid ureteroscope alongside the safety wire. Flexible ureteroscopes are most easily introduced via an additional guidewire or through an ureteral access sheath, although last-generation scopes allow bare passage in experienced hands.

Endoscopic lithotripsy is based on the use of different devices in order to break the stone into dust or

fragments small enough for extraction. The stone may be fragmented by ultrasonic lithotripsy, electrohydraulic lithotripsy (EHL), laser lithotripsy or ballistic (= pneumatic) lithotripsy. Lithotripsy devices are described in detail in Appendix 1. Small stones and fragments are best retrieved with a basket or a forceps (6-9).

Stone extraction with a basket without endoscopic visualization of the stone (blind basketing) should not be performed (Chapter 9)	LE = 4 GR = C

Irrigation, which can be facilitated with a piston syringe, is needed to ensure good direct vision. However, caution should be undertaken to avoid high-pressure irrigation that is potentially associated with an increased complication rate. Stent placement at the end of the procedure is optional and a matter of debate (10-16). However, most urologists leave the stent for about 1 week, although there is no evidence on the best interval. Patients should be followed up after 2-12 weeks by plain abdominal film, intravenous urography, computer tomography or ultrasonography.

7.3.2 Anaesthesia
The improvement of ureteroscopes and stone retrieval instruments allows ureteroscopic procedures for ureteral calculi to be carried out under sedation analgesia with a similar success rate (88-97%) to general anaesthesia (17-19). This is a technique that is particularly useful for removal of distal ureteral stones in women (20). For treatment of renal calculi with flexible URS, general anaesthesia might be advantageous by minimizing movements of the kidney.

7.3.3 Assessment of different devices
7.3.3.1 Ureteroscopes
Rigid and flexible ureteroscopes are available. Miniaturization (and regular pre-stenting of the ureter) avoid the need to dilate the intramural ureter (with associated complications) in most cases (21-23). The small tip diameters (5.0-7.5 F) allow easier and safer progression of rigid ureteroscopes up to the proximal ureter.

The use of flexible ureteroscopes (5-7.5 F) has been evaluated (3,24-27). They are suitable for access to the upper part of the ureter and renal collecting system, without dilatation of the intramural ureter in most cases. In the lower ureter, a flexible ureteroscope is less suitable because of its tendency to fall back into the bladder. Current scopes provide higher tip deflections and are more durable than the older generation (28-30).

7.3.3.2 Disintegration devices
Disintegrations devices are discussed in detail in Appendix 1. In brief, holmium:yttrium aluminium garnet (Ho:YAG) laser lithotripsy is a reliable method for the treatment of urinary calculi, regardless of the hardness of the stone (31-34). It is the preferred method when performing flexible URS (3,34-36) (LE = 3; GR = B/C). A 365 µm laser fibre is the best choice for ureteral stones, while the 200 µm fibre preserves tip deflection of flexible ureterorenoscopes and allows fragmentation of intracaliceal calculi (38). If manipulated with care, laser lithotripsy is safe, while significant side effects may be more common with EHL (39-43). Ho:YAG lithotripsy seems to give better stone-free results at 3 months than EHL (97% versus 87%) for distal ureteral stones (39).

Ballistic lithotriptors (pneumatic or electropneumatic) using a 2.4 F probe in a semi-rigid ureteroscope provide excellent fragmentation rates (90-96%). Low costs with simple and safe handling are major advantages of this type of device (44-46). Nevertheless, migration of stones towards the renal pelvis from the mid- or proximal ureter might be a limiting factor of ballistic lithotripsy (47,48).

7.3.3.3 Baskets and forceps
Ureteroscopic removal of small ureteral stones with a basket or forceps is a relatively quick procedure with a lower morbidity rate than lithotripsy (8,9). Several new designs of endoscopic stone retrieval baskets are available.

Nitinol baskets preserve tip deflection of flexible ureterorenoscopes and the tipless design reduces the risk of mucosa injury (38). **They are therefore most suitable for use in flexible URS**	LE = 2b/3 GR = B

However, nitinol baskets are more vulnerable than a stainless steel basket and laser or EHL might break the wires of the basket (49,50).

7.3.3.4 Dilatation, ureteral access sheaths and stenting

Attempts to modify the standard technique of dilatation and stenting have been conducted during recent years. Reduced dilatation (0-40%), operating time and post-operative ureteral stenting have resulted from the use of thin ureteroscopes.

Ureteral access sheaths are today widely used to facilitate retrograde manipulation in the proximal ureter and the kidney. Available access sheaths (9-16 F) have a hydrophilic surface and are introduced via a guide wire with the tip placed in the proximal ureter. Operating room time might be reduced for higher stone burdens where multiple ureter passages are necessary (51-53). A further advantage is the maintenance of a low-pressure irrigation system by continuous outflow through the sheath (54-55). First follow-up series indicate a low rate of ureteral strictures, comparable to sheathless URS (56).

Stenting following uncomplicated URS is optional (see also Chapter 9)	**LE = 1a** **GR = A**

Several randomized prospective trials have demonstrated that routine stenting after uncomplicated URS may not be necessary (10-16,57-60). It is well documented that ureteric stenting is associated with bothersome lower urinary tract symptoms and pain that can, even if it is only temporary, alter quality of life (58-64). In addition, there are complications associated with ureteral stenting, including stent migration, urinary tract infection, breakage, encrustation and obstruction. Moreover, ureteral stents add some expense to the overall ureteroscopic procedure and unless a pull-string is attached to the distal end of the stent, secondary cystoscopy is required for stent removal (13). There are clear indications for stenting after the completion of URS. These include ureteral injury, stricture, solitary kidney, renal insufficiency, or a large residual stone burden.

7.3.4 Clinical results
7.3.4.1 Renal calculi

Current guideline recommendations suggest ESWL, as the therapy of first choice for all intrarenal calculi with sizes < 20 mm, while larger stones should be treated by PNL (69,70). However, as the results for lower pole stones are poor, primary PNL might be justified for smaller calculi starting from $\geq$ 15 mm in this location (69-73). To date, flexible URS has not been mentioned by most guidelines. It may offer an alternative to ESWL or PNL. Unfortunately, only little comparative data is available on the use of flexible URS for renal calculi. Last-generation ureterenoscopes allow access to almost all calices and, together with laser lithotripsy, ureteral access sheaths and nitional retrieval tools, the removal of most calculi. Reported stone-free rates for calculi $\leq$1.5 cm are from 50-80% (51,74-78), while larger stones can also be treated successfully.

Flexible URS has been demonstrated to be an effective treatment for ESWL-refractory calculi (79-80)

So far, flexible URS has not been recommended as a first-line treatment for renal calculi and there is a lack of valid data to indicate such a recommendation. However, because of the poor results of ESWL for lower pole stones, it is possible that flexible URS could become a reliable first-line treatment for lower pole stones $\leq$ 1.5 cm.

Some authors reported the combination of flexible URS with ESWL or PNL to improve stone-free rates (81-82). The simultaneous use of flexible URS and PNL may offer an attractive approach to achieve complete stone-free states after one procedure and to avoid multiple percutaneous tracts. However, such an approach requires significant experience and equipment and is therefore not routinely used.

7.3.5. Complications

An evaluation of the most relevant complications of sepsis, Steinstrasse, stricture, ureteral injury and urinary tract infection (UTI) by a meta-analysis of the EAU-AUA Guidelines panel has demonstrated that URS for ureteral calculi has minimal side effects (65-66). Serious complications, including death and loss of kidney, were sufficiently rare that data were not available to estimate their rates of occurrence. The complication rates for the overall population by treatment, size, and location are shown in Table 5, Chapter 9 .

Significant acute complication rates of 11% and 9% have been reported for the proximal and distal ureters, respectively (65,66). Ureteral strictures were the only long-term complication reported, with the estimated rate being 1%. There is a pronounced relationship between the complication rate and the equipment used and/or the expertise of the urologist (83). The overall complication rates reported in the recent literature are 5–9%, with a 1% rate of significant complications (7,44,46,83-86). The major acute complication remains ureteral avulsion (44,87). Autologous transplantation or uretero-ileoplasty are the methods of choice such cases. Ureteral perforation at the site of the stone is the primary risk factor for stricture. Most perforations seen during the procedure are successfully treated with approximately 2 weeks of stenting (46,83,85).

Ureteroscopy can also be applied when ESWL might be contraindicated or ill-advised	**LE = 4** **GR = C**

Ureteroscopy can be performed safely in select patients in whom cessation of anticoagulants is considered unsafe (42). In addition, URS has been shown to be effective, regardless of patient body habitus. Several studies have shown that morbidly obese patients can be treated with success rates and complication rates comparable to the general population (88,89). Several authors have demonstrated that URS is safe even during pregnancy (90-91). However, such an approach should be limited to carefully selected cases. Finally, URS can be used safely to treat simultaneously bilateral ureteral stones in select cases (92,93).

7.3.6 Conclusion

Improvements in the design of ureteroscopes, accessories and the URS technique have led to a significant increase in the success rate for the removal of ureteral stones and decreased morbidity (65,66). In experienced hands, this means that the new generation of ureteroscopes can be used for the treatment of proximal as well as distal ureteric stones. Flexible URS has been demonstrated as being an efficient treatment for ESWL-refractory renal calculi.

Further studies are needed to determine whether flexible URS has a place as a first-line treatment for renal calculi where, depending on size and location, ESWL or PNL remain recommended procedures of first choice. For ureteric calculi, both ESWL and URS can be considered acceptable treatment alternatives. While ESWL is less invasive and has the lowest complication rates, a stone-free state can be achieved faster with URS. Stone-free rates might be advantageous for larger calculi with URS.

Randomized and prospective studies are needed to compare all forms of stone removal for renal and ureteric calculi.

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7.4   Open surgery for removal of renal stones

With the advances in ESWL and endourological surgery, i.e. ureteroscopy (URS) and PNL, during the past 20 years, the indications for open stone surgery have markedly diminished. Centres with the equipment, expertize and experience in the surgical treatment of renal tract stones report a need for open surgery in 1-5.4% of cases (1-5). It is now accepted that, in some circumstances, there is a place for open surgical removal of calculi.

Since most of these cases will usually involve difficult stone situations, it is important that urologists maintain proficiency, skills and expertize in open renal and ureteral surgical techniques. However, with the various treatment modalities now available for the surgical management of stones, there will inevitably be some controversy as to when open operation is, or is not, appropriate in a particular case. Thus, it is only possible to propose general principles for open surgery based on a consensus of opinion based on experience and the technical limitations of the less invasive alternative approaches.

An open surgical procedure may be preferred whenever the major stone volume is located peripherally in the calices, especially if these calices are obstructed so that either several percutaneous accesses and several, probably unsuccessful, shock-wave sessions will be necessary for complete stone removal. However, with today's limited experience with open stone surgery in many hospitals, it may be advisable to send patients to a centre where the urologists still know how to perform properly the techniques of extended pyelocalicotomy (6), anatrophic nephrolithotomy (7-10), multiple radial nephrotomy (11,12) and renal surgery under hypothermia.

The latest progress in this area has been the introduction of intra-operative B-mode scanning and Doppler sonography (13,14) to identify avascular areas in the renal parenchyma close to the stone or dilated calices to enable removal of large staghorn stones by multiple small radial nephrotomies without loss of kidney function.

7.4.1   *Indications for open and laparoscopic surgery*
Indications for open surgery for stone removal include:
•   Complex stone burden
•   Treatment failure with ESWL and/or PNL or failed ureteroscopic procedure
•   Intrarenal anatomical abnormalities: infundibular stenosis, stone in the caliceal diverticulum (particularly in an anterior calyx), obstruction of the ureteropelvic junction, stricture
•   Morbid obesity
•   Skeletal deformity, contractures and fixed deformities of hips and legs
•   Co-morbid medical disease
•   Concomitant open surgery
•   Non-functioning lower pole (partial nephrectomy), non-functioning kidney (nephrectomy)
•   Patient choice following failed minimally invasive procedures, i.e. single procedure in preference to possibly more than one PNL procedure
•   Stone in an ectopic kidney where percutaneous access and ESWL may be difficult or impossible.
•   Cystolithotomy for giant bladder calculus

- A large stone burden in children because of easy surgical access and the need for only one anaesthetic procedure.

7.4.2 Operative procedures
Operative procedures that can be carried out include:
- Simple and extended pyelolithotomy
- Pyelonephrolithotomy
- Anatrophic nephrolithotomy
- Ureterolithotomy
- Radial nephrolithotomy
- Pyeloplasty
- Partial nephrectomy and nephrectomy
- Removal of calculus with re-implantation of the ureter, i.e. ureteroneocystotomy.

The superiority of open surgery over less invasive therapy in terms of stone-free rates is based on considerable historical experience, but (as yet) there are no comparative studies available (LE 4).

In one recent report, the reasons given for performing open surgery were (5):
- A complex stone burden in 55% of cases
- Failed low invasive surgery in 29%
- Anatomical abnormalities in 24%
- Morbid obesity in 10%
- Co-morbid medical diseases in 7%.

Another report mentions 25 open surgical procedures in 799 treatments for renal stones, while a retrospective study lists the reasons for open surgery as a large stone burden in association with abnormal anatomy limiting endoscopic access in 31% of the cases, concurrent surgical procedures in 24% and previously failed endourologic procedures as the reason for open surgery in another 17% of cases is listed in a retrospective study (15). A 2% need for open surgery was recorded in 2,651 stone procedures carried out in Singapore (16).

Open surgery for renal tract stones has become almost obsolete, with laparoscopic surgery increasingly used in situations for which open surgery would previously have been used, including complex stone burden, failed previous ESWL and /or endourological procedures, anatomical abnormalities, morbid obesity, etc. Laparoscopic surgery was initially used for ablative surgery in renal cancer and correction of pelvi-ureteric junction obstruction, but is now being used to remove both renal and ureteric stones. Although, there are anecdotal reports of successful anatrophic nephrolithotomy (17), it is in the removal of ureteric stones that laparoscopy appears to have found its place.

Large numbers of patients with impacted ureteric stones have now been successfully treated by laparoscopic ureterolithotomy, with less than 2% of cases needing conversion to open surgery. Laparosopic ureterolitothomy can be carried out by both a retroperitoneal and transperitoneal access with comparable results and success (17-22). It is definitely an option to consider when other non-invasive or low-invasive procedures have failed to solve the problem (23-39). Laparoscopic (video-endoscopic) surgery may be useful, particularly for removal of stones located in a ventral caliceal diverticulum (33).

Clearly, laparoscopic surgery is a highly specialized skill and should only be carried out by surgeons trained in the technique, in well-equipped, dedicated centres. The advantages are low post-operative morbidity, reduced hospital stay and minimal blood loss. However, the procedure takes considerably longer than conventional surgery.

Where the expertise is available, the laparoscopic approach should be an alternative before proceeding to open surgery (40)	**LE = 4** **GR = C**

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7.5   Chemolytic possibilities by percutaneous irrigation.

Chemolytic dissolution of stones or stone fragments is a useful adjunct to ESWL, PNL, URS or open surgery for a more complete elimination of small residing stones or residual fragments. The combined treatment of ESWL and chemolysis is a particularly low-invasive option for selected patients with partial or complete infection staghorn stones. Oral chemolytic treatment is also a very attractive therapeutic alternative for the removal of uric acid stones. This section provides a summary of chemolytic treatment options.

For percutaneous chemolysis, the patient should have at least two nephrostomy catheters. This enables irrigation of the renal collecting system while preventing chemolytic fluid from draining into the bladder and reducing the risk of increased intrarenal pressure. In the case of a large stone burden, the ureter should be protected by a double-J stent during the procedure (1,2).

7.5.1   Infection stones

Stones composed of magnesium ammonium phosphate and carbonate apatite can be dissolved with a 10% solution of hemiacidrin (Renacidin), which is an acid solution with a pH between 3.5 and 4. Another useful agent is Suby's solution. During appropriate antibiotic treatment, the chemolytic solution is allowed to flow in through one nephrostomy catheter and out through another. The contact surface area between the stone or the stone remnants and the chemolytic agent is increased by ESWL.

The time required for dissolution depends on the stone burden and chemical composition of the stone, but several weeks will be necessary to dissolve a complete staghorn stone using chemolysis combined with ESWL. The major advantage of this therapeutic approach is that it can be carried out without anaesthesia and might thus be an option for high-risk patients or for any other patients in whom anaesthesia or other surgical procedures must be avoided (3-13).

It should be noted that Hemiacidirin and Suby G solutions carry a potential risk of mortality (cardiac arrest) from hypermagnesemia if there is leakage and magnesium absorption occurs. This form of treatment must only be used when there is good evidence that the renal tract has healed following surgery and should never be infused in the immediate post-operative stage.

7.5.2   Brushite stones

Brushite is also soluble in the acid solutions mentioned above in Section 7.5.1. This option should be considered in patients with residual brushite fragments after other stone-removing procedures. This is a particularly interesting treatment approach in view of the very high recurrence rate of brushite stones.

7.5.3   Cystine stones

Cystine is soluble in an alkaline environment. For this purpose, 0.3 or 0.6 mol/L trihydroxymethyl aminomethan (THAM) solution can be used. The pH of these solutions is in the range 8.5-9.0. Another option is N-acetylcysteine. These two solutions can be used to improve elimination of fragments and stone residuals from

the collecting system. Percutaneous chemolysis is a useful method for complete stone clearance in combination with other stone-removing techniques (14-18).

7.5.4 Uric acid stones
A high concentration of urate and a low (acidic) pH are the determinants of uric acid stone formation.

Percutaneous dissolution can be accomplished with THAM solutions. Oral chemolysis is, however, the most attractive alternative. This method involves lowering urate concentration using allopurinol and a high fluid intake, and increasing the pH to alkali (19-21).

Uric acid stones can also be removed by oral chemolysis using an alkali and allopurinol.

Further details of this regimen are given in Section 17.2.

7.5.5 Calcium oxalate and ammonium urate stones
There is currently no physiologically useful chemolytic agents for dissolving stones composed of calcium oxalate or ammonium urate (22). The presence of calcium oxalate in an infection stone markedly reduces the solubility in Hemiacidrin (6).

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7.6   Recommendations for removal of renal stones

Recommendations on the most appropriate method for removal of stones from the kidney are based on several important considerations. The available options are ESWL, PNL, retrograde intrarenal surgery (RIRS) with a flexible ureteroscope, as well as video-endoscopic laparoscopic and open surgery. All these methods are applicable. However, for any given stone situation, it is logical to select a method with low invasiveness and low morbidity.

More than 20 years of experience with low invasive methods have clearly shown that open surgery is necessary only in exceptional cases and mainly for those patients in whom anatomical reconstruction is necessary. Video-endoscopic retroperitoneal or laparoscopic surgery has no place as a standard procedure for removal of stones from the kidney. However, this technique should be considered as an alternative before proceeding to open surgery, and it is advantageous in some types of reconstructive surgery.

For small stones (up to a maximum diameter of 20 mm or a surface area of approximately 300 mm^2), ESWL has been established as the standard procedure because it is non-invasive, has a low rate of complications and there is (at least for adults) no need for regional or general anaesthesia.

There continues to be a debate about whether large renal stones are best treated with ESWL or with PNL. Although larger stones can also be treated successfully with ESWL, the drawbacks of ESWL are a frequent need for repeated treatments and the relatively common occurrence of residual fragments. Although PNL might be preferable to ESWL for faster debulking of the stone, it must be emphasized that considerable expertize and experience is required for complete clearance of stones from the caliceal system. Unless percutaneous surgery is carried out with a meticulous technique, residual fragments of the stone may also be left behind following PNL.

Residual fragments undoubtedly can develop into new stones, but several reports have shown that this risk is reasonably low. It is still necessary, however, to have a follow-up programme because of the inherent tendency to new stone formation that characterizes patients with stone disease.

Residual fragments of infection stones, associated with the most pronounced risk of recurrent stone formation, can be eliminated with PNL, with or without percutaneous chemolysis. Such a step might also be used as an auxiliary procedure in the treatment of cystine stones.

For uric acid stones, oral chemolysis is the first choice of treatment for stone elimination. However, an increased rate of dissolution can be obtained by combining stone disintegration and chemolysis, and treatment in this way may be considered for removal of large uric acid stones. The approximate estimates of surface area corresponding to oval stone projections with certain diameters are given in Appendix 2.

An overview of treatment recommendations according to size and stone type as discussed above is shown in Tables 18-23.

Table 18: Active removal of radiopaque (calcium) renal stones with a largest diameter ≤ 20 mm (surface area ~ ≤ 300 mm²)

Preference	Procedure	LE	GR
1	ESWL, also including piezolithotripsy	1b	A
2	Percutaneous nephrolithotomy	1b	A
3	Retrograde intrarenal surgery	2a	C
4	Laparoscopic surgery	2a	C
5	Open surgery	4	C

ESWL = extracorporeal shock-wave lithotripsy.

Infection stones are also radiopaque and usually contain calcium in the form of carbonate apatite and hydroxyapatite. These stones should be treated in the same way as sterile calcium stones, provided there is no obstruction and that a symptomatic infection has been adequately treated.

For all patients with infection stones, recent history of urinary tract infection or, bacteriuria antibiotics should be administered before the stone-removing procedure for at and continued least 4 days afterwards	**LE = 4** **GR = C**

Table 19: Active removal of uric acid renal stones with a largest diameter ≤ 20 mm (surface area ~ ≤ 300 mm²)

Preference	Procedure	LE	GR
1	Oral chemolysis	2a	B
2	ESWL + oral chemolysis	2a	B

ESWL = extracorporeal shock-wave lithotripsy, also including piezolithotripsy.

For patients with uric acid stones and a percutaneous nephrostomy catheter in place, stone disintegration with ESWL can advantageously be combined with percutaneous chemolysis (see Section 7.5).

Table 20: Active removal of cystine stones with a largest diameter ≤ 20 mm (surface area ~ ≤ 300 mm²)

Preference	Procedure	LE	GR
1	ESWL	2a	B
1	Percutaneous nephrolithotomy	2a	B
2	Retrograde intrarenal surgery	4	C
3	Laparoscopic surgery	4	C
4	Open surgery	4	C

ESWL = extracorporeal shock-wave lithotripsy, also including piezolithotripsy.

Table 21: Active removal of radiopaque (calcium) renal stones with a largest diameter > 20 mm (surface area > 300 mm²)

Preference	Procedure	LE	GR
1	Percutaneous nephrolithotomy	1b	A
2	ESWL	1b	A
3	Percutaneous nepholithotomy + ESWL	2b	B
4	Laparoscopic surgery	4	C
4	Open surgery	4	C

ESWL = extracorporeal shock-wave lithotripsy, also including piezolithotripsy.

Table 22: Active removal of uric acid renal stones with a largest diameter > 20 mm (surface area ~ > 300 mm²)

Preference	Procedure	LE	GR
1	Oral chemolysis	2a	B
2	ESWL + oral chemolysis	2a	B
3	Percutaneous nephrolithotomy	3	C
3	Percutaneous + chemolysis	3	C

ESWL = extracorporeal shock-wave lithotripsy, also including piezolithotripsy.

For patients with uric acid stones and a percutaneous nephrostomy catheter in place, stone disintegration with ESWL combined with percutaneous chemolysis is a good alternative to quickly dissolve the stone material (see Section 7.5).

Table 23: Active removal of cystine stones with a largest diameter > 20 mm (surface area > 300 mm²)

Preference	Procedure	LE	GR
1	Percutaneous nephrolithotomy	2a	B
1	Percutaneous nephrolithotomy + ESWL	2a	B
1	Percutaneous nephrolithotomy + chemolysis	3	C
2	ESWL + chemolysis	3	C
3	Laparoscopic surgery	4	C
3	Open surgery	4	C

ESWL = extracorporeal shock-wave lithotripsy, also including piezolithotripsy.

Patients, who are planned for ESWL-treatment of stones with a diameter exceeding (20 mm ~300 mm²), should have an internal stent to avoid problems related to Steinstrasse	**LE = 3** **GR = B**

8. STAGHORN STONES

A staghorn stone is defined as a stone with a central body and at least one caliceal branch. Whereas a partial staghorn stone fills up only part of the collecting system, a complete staghorn stone fills all the calices and the renal pelvis.

Patients with staghorn stones can usually be treated according to the principles given for large stones (diameter > 20 mm / 300 mm²) (see Chapter 7)	**LE = 1b** **GR = A/B**

In patients with small staghorn stones and a non-dilated system, repeated ESWL sessions with a stent can be a reasonable treatment alternative. Nephrectomy should be considered in the case of a non-functioning kidney. In selected cases with infection, cystine, uric acid and calcium phosphate stones, the combined use of ESWL or other stone-removing procedures and chemolysis may be useful. The principles of chemolytic treatment are discussed in Chapter 7.

9. MANAGEMENT OF PATIENTS WITH STONES IN THE URETER.

2007 GUIDELINE FOR THE MANAGEMENT OF URETERAL CALCULI

EAU/AUA Nephrolithiasis Guideline Panel

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THE MANAGEMENT OF URETERAL CALCULI: DIAGNOSIS AND TREATMENT

RECOMMENDATIONS

9.1 Introduction

The American Urological Association (AUA) Nephrolithiasis Clinical Guideline Panel was established in 1991. Since that time, the Panel has developed three guidelines on the management of nephrolithiasis, the most recent being a 2005 update of the original 1994 *Report on the Management of Staghorn Calculi (1)*. The European Association of Urology (EAU) began their nephrolithiasis guideline project in 2000, yielding the publication of *Guidelines on Urolithiasis*, with updates in 2001 and 2006 (2). While both documents provide useful recommendations on the management of ureteral calculi, changes in shock-wave lithotripsy (SWL) technology, endoscope design, intracorporeal lithotripsy techniques, and laparoscopic expertise have burgeoned over the past five to ten years.

Under the sage leadership of the late Dr. Joseph W. Segura, the AUA Practice Guidelines Committee suggested to both the AUA and the EAU that they join efforts in developing the first set of internationally endorsed guidelines focusing on the changes introduced in ureteral stone management over the last decade. We therefore dedicate this report to the memory of Dr. Joseph W. Segura whose vision, integrity, and perseverance led to the establishment of the first international guideline project.

This joint EAU/AUA Nephrolithiasis Guideline Panel (hereinafter the Panel) performed a systematic review of the English language literature published since 1997 and a comprehensively analyzed outcomes data from the identified studies.

Based on their findings, the Panel concluded that when removal becomes necessary, SWL and ureteroscopy (URS) remain the two primary treatment modalities for the management of symptomatic ureteral calculi. Other treatments were reviewed, including medical expulsive therapy (MET) to facilitate spontaneous stone passage, percutaneous antegrade ureteroscopy, and laparoscopic and open surgical ureterolithotomy. In concurrence with the previously published guidelines of both organizations, open stone surgery is still considered a secondary treatment option. Blind basketing of ureteral calculi is not recommended. In addition, the Panel was able to provide some guidance regarding the management of pediatric patients with ureteral calculi. The Panel recognizes that some of the treatment modalities or procedures recommended in this document require access to modern equipment or presupposes a level of training and expertise not available to practitioners in many clinical centers. Those situations may require physicians and patients to resort to treatment alternatives.

This article will be published simultaneously in *European Urology* and *The Journal of Urology*. The Panel believes that future collaboration between the EAU and the AUA will serve to establish other internationally approved guidelines, offering physician and patient guidance worldwide.

9.2 Methodology

The Panel initially discussed the scope of the guideline and the methodology, which would be similar to that used in developing the previous AUA guideline. All treatments commonly employed in the United States and/or Europe were included in this report except for those that were explicitly excluded in the previous guideline or newer treatments for which insufficient literature existed. In the analysis, patient data were stratified by age (adult versus child), stone size, stone location, and stone composition. Later, however, the data were found to be insufficient to allow analysis by composition. The outcomes deemed by the Panel to be of particular interest to the patient included the following: stone-free rate, number of procedures performed, stone-passage rate or probability of spontaneous passage, and complications of treatment. The Panel did not examine economic effects, including treatment costs.

Outcomes were stratified by stone location (proximal, mid, and distal ureter) and by stone size (dichotomized as $\leq$10 mm and >10 mm for surgical interventions, and $\leq$5 mm and >5 mm for medical interventions and observation where possible; exceptions were made when data were reported, for example as <10 mm and $\geq$10 mm). The mid ureter is the part of the ureter that overlies the bony pelvis, i.e., the position of the ureter that corresponds to the sacroiliac joint; the proximal ureter is above and the distal ureter is below. Treatments were divided into three broad groups:
1.   Observation and medical therapy
2.   Shock-wave lithotripsy and ureteroscopy
3.   Open surgery, laparoscopic stone removal, or percutaneous antegrade ureteroscopy.

The review of the evidence began with a literature search and data extraction. Articles were selected from a database of papers derived from MEDLINE searches dealing with all forms of urinary tract stones. This database was maintained by a Panel chair. The abstract of each paper was independently reviewed by an American and a European Panel member, and articles were selected for data extraction if any panel member felt it might have useful data. Additional articles were suggested by Panel members or found as references in review articles. In total, 348 citations entered the extraction process. An American and a European Panel member each independently extracted data from each article onto a standardized form. The team members reconciled the extractions, and the data were entered into a Microsoft Access® (Microsoft, Redmond, WA)

database. The Panel scrutinized the entries, reconciled the inconsistencies in recording, corrected the extraction errors, and excluded some articles from further analysis for the following reasons:

1. The article was included in the previous guideline.
2. The article did not provide usable data on the outcomes of interest.
3. Results for patients with ureteral stones could not be separated from results for those with renal stones.
4. The treatments used were not current or were not the focus of the analysis.
5. The article was a review article of data reported elsewhere.
6. The article dealt only with salvage therapy.

A total of 244 of the 348 articles initially selected had extractable data. Articles excluded from evidence combination remained candidates for discussion in the text of the guideline.

The goal was to generate outcomes tables comparing estimates of outcomes across treatment modalities. To generate an outcomes table, estimates of the probabilities and/or magnitudes of the outcomes are required for each intervention. Ideally, these are derived from a synthesis or combination of the evidence. Such a combination can be performed in a variety of ways depending on the nature and quality of the evidence. For this report, the Panel elected to use the Confidence Profile Method (3), which provides methods for analyzing data from studies that are not randomized controlled trials (RCTs). The Fast*Pro computer software[4] was used in the analysis. This program provides posterior distributions from meta-analyses from which the median can be used as a best estimate, and the central 95% of the distribution serves as a confidence interval (CI). Statistical significance at the $p < 0.05$ level (two-tailed) was inferred when zero was not included in the CI.

Because of the paucity of controlled trials found on literature review, however, the outcome for each intervention was estimated by combining single arms from various clinical series. These clinical series frequently had very different outcomes, likely due to a combination of site-to-site variations in patient populations, in the performance of the intervention, in the skill of those performing the intervention, and different methods of determining stone-free status. Given these differences, a random-effects, or hierarchical, model was used to combine the studies.

Evidence from the studies meeting the inclusion criteria and reporting a given outcome was combined within each treatment modality. Graphs showing the results for each modality were developed to demonstrate similarities and differences between treatments.

The available data for procedures per patient would not permit a statistical analysis using these techniques. Unlike the binary outcome of stone-free status (the patient either is or is not stone free), the number of procedures per patient is a discrete rate. In some cases discrete rates can be approximated with a continuous rate, but in order to meta-analyze continuous rates, a measure of variance (e.g., standard deviation, standard error) is needed in addition to the mean. Unfortunately, measures of variance were rarely reported in the studies reviewed. As a result, numbers of procedures per patient were evaluated by calculating the average across studies weighted by the number of patients in each study. Procedures per patient were counted in three totals: primary procedures, secondary procedures, and adjunctive procedures. Primary procedures were all consecutive procedures of the same type aimed at removing the stone. Secondary procedures were all other procedures used to remove the stone. Adjunctive procedures were defined as additional procedures that do not involve active stone removal. One difficulty in estimating the total number of procedures per patient is that secondary and adjunctive procedures were not reported consistently. Since the Panel had decided to analyze primary, secondary, and adjunctive procedures separately, only studies that specifically reported data on a type of procedure were included in estimates for that procedure type. This approach may have overestimated numbers of secondary and adjunctive procedures because some articles may not have reported that procedures were not performed.

It is important to note that, for certain outcomes, more data were reported for one or another treatment modality. While resulting CIs reflect available data, the probabilities for certain outcomes can vary widely within one treatment modality. In addition, the fact that data from only a few RCTs could be evaluated may have somewhat biased results. For example, differences in patient selection may have had more weight in analyses than differing treatment effects. Nevertheless, the results obtained reflect the best outcome estimates presently available.

Studies that reported numbers of patients who were stone free after primary procedures were included in the stone-free analysis. Studies that reported only the combined number of patients who either were stone free or had "clinically insignificant fragments" were excluded. Many studies did not indicate how or when stone-free status was determined. The stone-free rate was considered at three time points: after the first procedure, after all consecutive procedures using the primary treatment, and after the total treatments.

Initially, the Panel divided complications into three broad categories: acute, long-term, and medical; however, after examining the available evidence, the Panel determined that this breakdown was not useful.

Several factors caused inaccuracy in the estimates, but did so in opposite directions, thereby reducing the magnitude of inaccuracy. For example, including studies that did not specifically mention that there were no occurrences of a specific complication may have led to overestimates of complication rates when meta-analyzed. By combining similar complications, the Panel also potentially mitigated the overestimate by making it more likely that a complication in the class was reported. The probability that a patient will have a complication may still be overstated slightly because some patients experienced multiple complications. Since the grouping of complications varies by study, the result of the meta-analysis is best interpreted as the mean number of complications that a patient may experience rather than as the probability of having a complication. Moreover, since reporting of complications is not consistent, the estimated rates given here are probably less accurate than the CIs would indicate. There were insufficient data to permit meaningful meta-analyses of patient deaths.

Data analyses were conducted for two age groups. One analysis included studies of patients ages 18 or younger (or identified as pediatric patients in the article without specifying age ranges). The adult analysis included all other studies even if children were included.

After the evidence was combined and outcome tables were produced, the Panel met to review the results and identify anomalies. From the evidence in the outcome tables and expert opinion, the Panel drafted the treatment guidelines.

In this guideline the standard, recommendations, and options given were rated according to the levels of evidence published from the U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research (5):

Ia.   Evidence obtained from meta-analysis of randomized trials
Ib.   Evidence obtained from at least one randomized trial
IIa.   Evidence obtained from at least one well-designed controlled study without randomization
IIb.   Evidence obtained from at least one other type of well-designed quasi-experimental study
III.   Evidence obtained from well-designed nonexperimental studies, such as comparative studies, correlation studies, and case reports
IV.   Evidence obtained from expert committee reports, or opinions, or clinical experience of respected authorities

As in the previous AUA guideline, the present statements are graded with respect to the degree of flexibility in application. Although the terminology has changed slightly, from the original AUA reports, the current three levels are essentially the same. A "standard" is the most rigid treatment policy. A "recommendation" has significantly less rigidity, and an "option" has the largest amount of flexibility. These terms are defined as follows:

1.   **Standard:** A guideline statement is a standard if: (1) the health outcomes of the alternative interventions are sufficiently well known to permit meaningful decisions, and (2) there is virtual unanimity about which intervention is preferred.
2.   **Recommendation:** A guideline statement is a recommendation if: (1) the health outcomes of the alternative interventions are sufficiently well known to permit meaningful decisions, and (2) an appreciable, but not unanimous majority agrees on which intervention is preferred.
3.   **Option:** A guideline statement is an option if: (1) the health outcomes of the interventions are not sufficiently well known to permit meaningful decisions, or (2) preferences are unknown or equivocal.

The draft was sent to 81 peer reviewers of whom 26 provided comments; the Panel revised the document based on the comments received. The guideline was submitted first for approval to the Practice Guidelines Committee of the AUA and the Guidelines Office of the EAU and then forwarded to the AUA Board of Directors and the EAU Board for final approval.

The guideline is posted on the American Urological Association website, www.auanet.org, and on the European Association of Urology website, www.uroweb.org. Chapter 1 will be published in *The Journal of Urology* and in *European Urology*.

9.3   Results of the Outcomes Analysis

The results of the analysis described in this chapter provide most of the evidentiary basis for the guideline statements. Further details and tables corresponding to the figures in this section are found in Chapter 3 and the Appendixes.

The panel's attempt to differentiate results for pediatric patients from those for adults was not completely successful as most studies included both adults and children. Where possible, the panel performed two analyses, one including all studies regardless of patient age, and a second including only those studies or groups of patients that were comprised entirely of pediatric patients.

9.3.1 Observation and Medical Therapies
Stone-passage rates

Only limited data were found on the topic of spontaneous passage by stone size. For stones ≤5 mm, meta-analysis of five patient groups (224 patients) yielded an estimate that 68% would pass spontaneously (95% CI: 46% to 85%). For stones >5 mm and ≤10 mm, analysis of three groups (104 patients) yielded an estimate that 47% would pass spontaneously (95% CI: 36% to 59%). Details of the meta-analysis are presented in Appendixes 8 and 9.

Two medical therapies had sufficient analyzable data: the calcium channel blocker nifedipine and alpha-receptor antagonists. Analyses of stone-passage rates were done in three ways. The first combined all single arms evaluating the therapies. Using this approach, meta-analysis of four studies of nifedipine (160 patients) yielded an estimate of a 75% passage rate (95% CI: 63% to 84%). Six studies examined alpha blockers (280 patients); the meta-analysis yielded a stone-passage rate of 81% (95% CI: 72% to 88%).

The second method was a standard Bayesian hierarchical meta-analysis of the available RCTs that compared either nifedipine or alpha blockers to control therapies. The results for nifedipine showed an absolute increase of 9% in stone-passage rates (95% CI: -7% to 25%), which was not statistically significant. Meta-analysis of alpha blockers versus control showed an absolute increase of 29% in the stone-passage rate (95% CI: 20% to 37%), which was statistically significant.

The Panel also attempted to determine whether alpha blockers provide superior stone passage when compared to nifedipine. Two randomized controlled trials were identified. When hierarchical meta-analysis was performed on these two studies, tamsulosin provided an absolute increase in stone-passage rate of 14% (95% CI: -4% to 32%) which was not statistically significant. When nonhierarchical methods were used, the stone-passage improvement increased to 16% (95% CI: 7% to 26%) which was statistically significant. Finally, the Panel used the results of the meta-analyses versus controls (second method above) to determine the difference between alpha blockers and calcium channel blockers. This method allows the use of more data but is risky since it depends on the control groups having comparable results. The analysis yielded a 20% improvement in stone-passage rates with alpha blockers, and the 95% CI of 1% to 37% just reached statistical significance.

9.3.1.1 Shock-wave Lithotripsy and Ureteroscopy

Stone-free rates were analyzed for a number of variant methods of performing SWL and URS. The Panel attempted to differentiate between bypass, pushback, and in situ SWL as well as differences between lithotripters. Most differences were minimal and did not reach statistical significance. For that reason, the data presented in this Chapter compare the meta-analysis of all forms of SWL to the meta-analysis of all forms of URS. The Panel also attempted to differentiate between flexible and rigid ureteroscopes. Details of the breakdowns by type of SWL and URS are given in Chapter 3. Data were analyzed for both efficacy and complications. Two efficacy outcomes were analyzed: stone-free rate and procedure counts. Complications were grouped into classes. The most important classes are reported herein. The full complication results are in Appendix 10.

Analyses were performed for the following patient groups where data were available.
1.   Proximal stones ≤10 mm
2.   Proximal stones >10 mm
3.   Proximal stones regardless of size
4.   Mid-ureteral stones ≤10 mm
5.   Mid-ureteral stones >10 mm
6.   Mid-ureteral stones regardless of size
7.   Distal stones ≤10 mm
8.   Distal stones >10 mm
9.   Distal stones regardless of size

Analyses of pediatric groups were attempted for the same nine groups, although data were lacking for many groups.

9.3.1.2 Efficacy Outcomes
Stone-free rates

The Panel decided to analyze a single stone-free rate. If the study reported the stone-free rate after all primary procedures, that number was used. If not and the study reported the stone-free rate after the first procedure, then that number was used. The intention of the Panel was to provide an estimate of the number of primary procedures and the stone-free rate after those procedures. There is a lack of uniformity in the literature in reporting the time to stone-free status, thereby limiting the ability to comment on the timing of this parameter.

The results of the meta-analysis of stone-free data are presented for the overall group in Table 1 and

Figure 1. The results are presented as medians of the posterior distribution (best central estimate) with 95% Bayesian CIs (credible intervals [CIs])

Overall Population	AUA / EAU Ureteral Stones Guideline Panel Stone Free Rate - Primary Treatments or First Treatment			
	SWL		URS	
	G/P	Med / 95% CI	G/P	Med / 95% CI
Distal Ureter	50 6981	74% (73-75)%*	59 5952	94% (93-95)%*
Distal ureter < 10 mm	17 1684	86% (80-91)%	13 1622	97% (96-98)%
Distal ureter > 10 mm	10 966	74% (57-87)%	8 412	93% (88-96)%
Mid Ureter	31 1607	73% (66-79)%	30 1024	86% (81-89)%
Mid ureter < 10 mm	5 44	84% (65-95)%	5 80	91% (81-96)%
Mid ureter > 10 mm	2 15	76% (36-97)%	5 73	78% (61-90)%
Proximal Ureter	41 6428	82% (79-85)%	16 2242	81% (77-85)%
Proximal ureter < 10 mm	14 886	90% (85-93)%	9 243	80% (73-85)%
Proximal ureter > 10 mm	11 293	68% (55-79)%	8 230	79% (71-87)%

G = Number of Groups/Treatment arms extracted; P = Number of Patients in those groups

Table 1. Stone-Free Rates for SWL and URS in the Overall Population
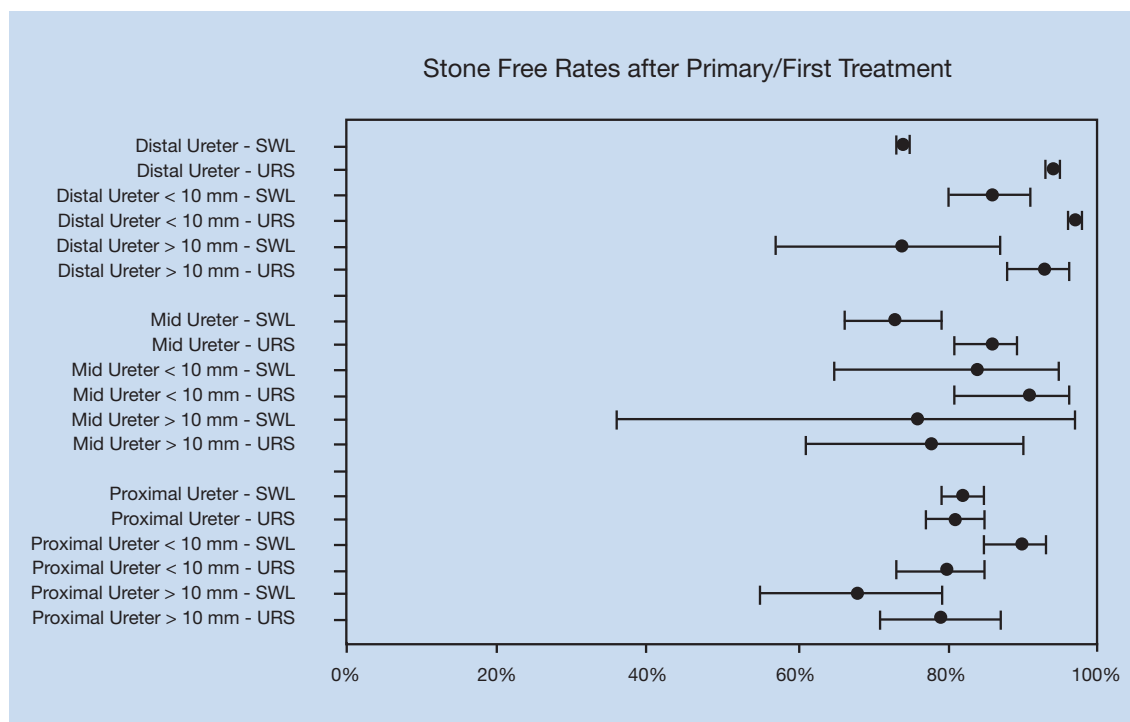
Figure 1. Stone-Free Rates for SWL and URS in the Overall Population
Estimated Occurrence Rate with 95% CI
CI=confidence interval

This analysis shows that overall, for stones in the proximal ureter (n=8,670), there was no difference in stone-free rates between SWL and URS. However, for proximal ureteral stones <10 mm (n=1,129), SWL had a higher stone-free rate than URS, and for stones >10 mm (n=523), URS had superior stone-free rates. This difference arises because the stone-free rate for proximal ureteral stones treated with URS did not vary significantly with size, whereas the stone-free rate following SWL negatively correlated with stone size. For all distal stones, URS yields better stone-free rates overall and in both size categories. For all mid-ureteral stones, URS appears superior, but the small number of patients may have prevented results from reaching statistical significance.

Unfortunately, RCTs comparing these treatments were generally lacking, making an accurate assessment impossible. However, the posterior distributions resulting from the meta-analysis can be subtracted, yielding a distribution for the difference between the treatments. If the CI of this result does not include zero, then the results may be considered to be statistically significantly different. This operation is mathematically justifiable but operationally risky: if the patients receiving different treatments are different or if outcome measures are different, results may be meaningless. Nonetheless, the Panel performed the comparison and found that URS stone-free rates were significantly better than SWL rates for distal ureteral stones ≤10 mm and >10 mm and for proximal ureteral stones >10 mm. The stone-free rate for mid-ureteral stones was not statistically significantly different between URS and SWL. The results with URS using a flexible ureteroscope for proximal ureteral stones appear better than those achieved with a rigid device, but not at a statistically significant level.

Stone-free results for pediatric patients are shown in Table 2 and Figure 2. The very small number of patients in most groups, particularly for URS, makes comparisons among treatments difficult. However, it does appear that SWL may be more effective in the pediatric subset than in the overall population, particularly in the mid and lower ureter.

Table 2. Stone-Free Rates for SWL and URS, Pediatric Population

PediatricPopulation	AUA / EAU Ureteral Stones Guideline Panel Stone Free Rate - Primary Treatments or First Treatment			
	SWL		URS	
	G/P	Med / 95% CI	G/P	Med / 95% CI
Distal Ureter	8 229	80% (68-90)%	9 151	92% (86-96)%*
Distal ureter < 10 mm	5 135	86% (78-92)%	2 29	86% (72-98)%
Distal ureter > 10 mm	2 26	83% (58-97)%		
Mid Ureter	6 33	82% (63-94)%	3 11	80% (52-96)%
Mid ureter < 10 mm	4 16	80% (41-98)%		
Mid ureter > 10 mm	1 6	96% (67-100)%	1 5	78% (37-99)%
Proximal Ureter	7 101	81% (69-90)%	5 18	57% (25-85)%
Proximal ureter < 10 mm	5 43	89% (72-98)%		
Proximal ureter > 10 mm	3 16	63% (21-94)%		

G = Number of Groups/Treatment arms extracted; P = Number of Patients in those groups

Figure 2. Stone-Free Rates for SWL and URS, Pediatric Population
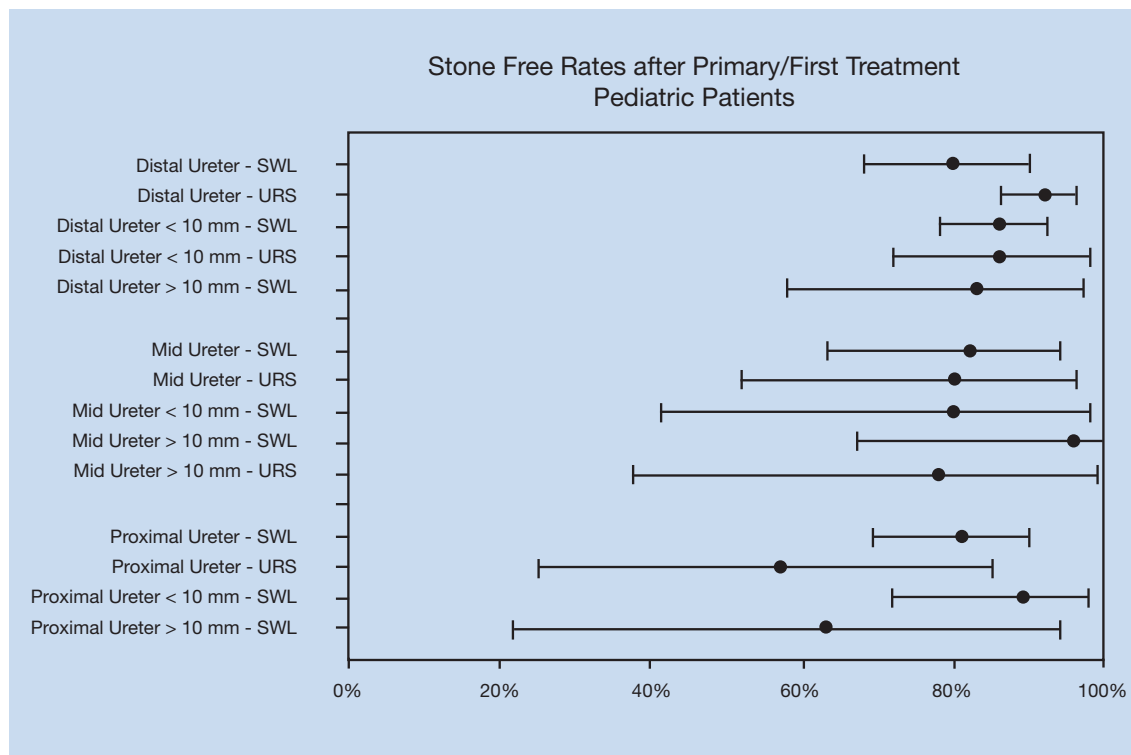
Estimated Occurrence Rate with 95% CI
CI=confidence interval

9.3.1.3   Procedure Counts
Procedure counts were captured as three types:
1.   Primary procedures – the number of times the intended procedure was performed.
2.   Secondary procedures – the number of times an alternative stone removal procedure(s) was performed.
3.   Adjunctive procedures – additional procedures performed at a time other than when the primary or secondary procedures were performed; these could include procedures related to the primary/secondary procedures such as stent removals as well as procedures performed to deal with complications; most adjunctive procedures in the data presented represent stent removals. It is likely that many stent-related adjunctive procedures were underreported, and thus the adjunctive procedure count may be underestimated.

As mentioned in Chapter 2, it was not possible to perform a meta-analysis or to test for statistically significant differences between treatments due to the lack of variance data, and only weighted averages could be computed. The procedure count results for the overall population are shown in Table 3 and Figure 3. Figure 3 results are presented as stacked bars.

Table 3. Procedure Counts for SWL and URS in the Overall Population

Overall Population	Procedure Counts											
	Grps/Pts	# Procs	Grps/Pts	# Procs	Grps/Pts	# Procs	Grps/Pts	# Procs	Grps/Pts	# Procs	Grps/Pts	# Procs
	SWL						URS					
	Primary		Secondary		Adjunctive		Primary		Secondary		Adjunctive	
Distal Ureter	48/7117	1.22	30/5069	0.12	15/3875	0.03	56/5308	1.04	25/5124	0.03	24/2848	0.36
Distal ureter < 10 mm	16/1618	1.34	5/170	0.12			12/1117	1.01	6/492	0.05	4/305	0.88
Distal ureter > 10 mm	11/951	1.44	3/1026	0.10			5/231	1.02	1/69	0.14	1/110	1.00
Mid Ureter	10/291	1.11	9316	0.18	4/241	0.23	25/686	1.04	15/934	0.07	8/357	0.09
Mid ureter < 10 mm	2/31	1.29					4/32	1.00	2/34	0.34	1/7	1.14
Mid ureter > 10 mm	3/53	1.76					2/18	1.00	1/35	0.31	1/5	0.02
Proximal Ureter	37/5902	1.31	20/2131	0.07	13/1329	0.24	42/1634	1.02	27/1831	0.26	14/1159	0.17
Proximal ureter < 10 mm	16/1243	1.26	5/150	0.14	3/114	0.77	6/68	1.00	4/62	0.39	3/27	0.52
Proximal ureter > 10 mm	10/409	1.49	5/83	0.21	4/45	0.56	5/137	1.07	1/130	0.13	1/11	0.21

Figure 3. Procedure Counts for SWL and URS in the Overall Population
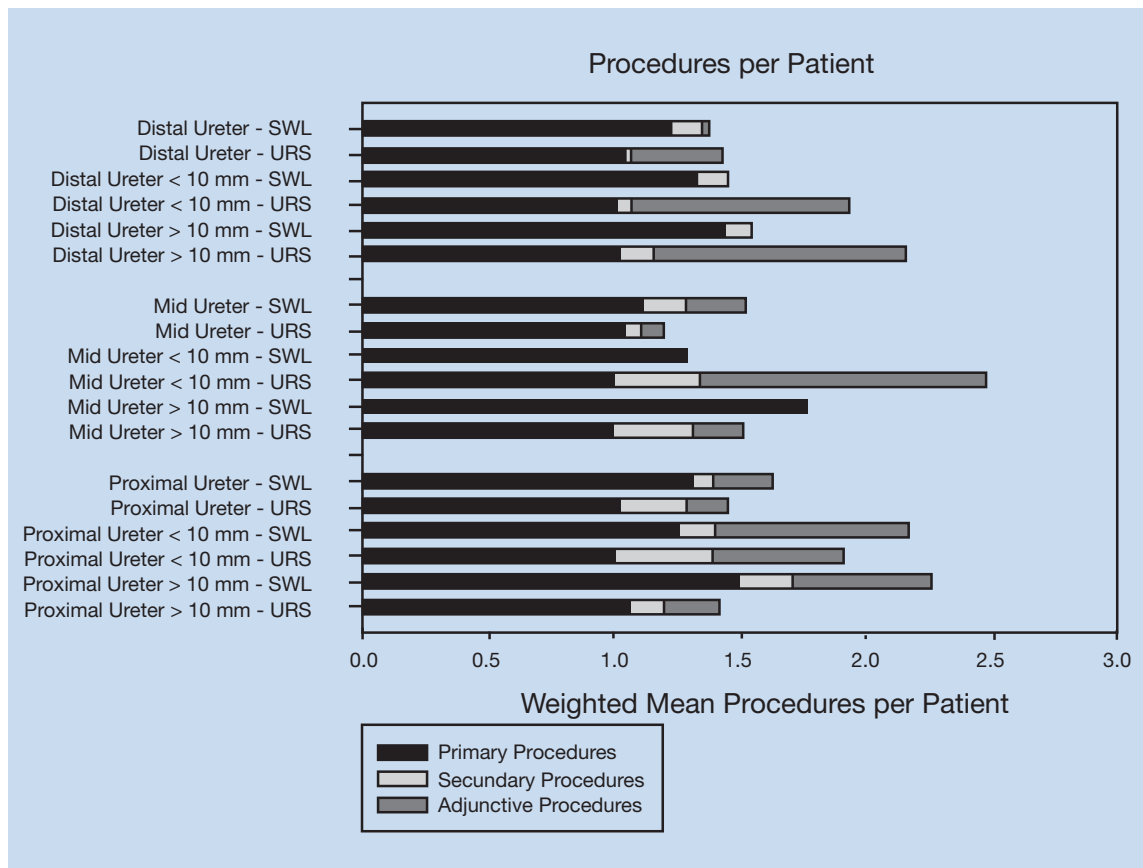
Procedure count results for pediatric patients are shown in Table 4 and Figure 4. Again, the numbers of patients with available data were small and did not support meaningful comparisons among treatments.

Table 4. Procedure Counts for SWL and URS in the Pediatric Population, All Locations

Pediatric Population	Procedure Counts											
	Grps/Pts	# Procs	Grps/Pts	# Procs	Grps/Pts	# Procs	Grps/Pts	# Procs	Grps/Pts	# Procs	Grps/Pts	# Procs
	SWL						URS					
	Primary		Secondary		Adjunctive		Primary		Secondary		Adjunctive	
Distal Ureter	7/212	1.38	4/98	0.08	2/43	0.07	10/185	1.05	7/190	0.09	5/96	0.72
Distal ureter < 10 mm	5/135	1.42	1/14	0.36			2/63	1.00	4/131	0.11	1/5	0.78
Distal ureter > 10 mm	4/26	1.42										
Mid Ureter	4/32	1.44	1/9	0.11			4/18	1.00	2/12	0.17	2/12	0.75
Mid ureter < 10 mm	3/16	1.50					1/7	1.00	1/7	0.14	1/7	0.71
Mid ureter > 10 mm	1/6	1.33					1/5	1.00	1/5	0.20	1/5	0.20
Proximal Ureter	5/83	1.28	3/38	0.05	1/5	0.00	6/27	1.00	7/38	0.34	1/9	1.00
Proximal ureter < 10 mm	5/43	1.19	1/3	0.00	1/3	0.00	1/9	1.00	2/18	0.33	1/9	1.00
Proximal ureter > 10 mm	4/16	1.38	2/2	0.00	2/2	0.00						

Figure 4. Procedure Counts for SWL and URS in the Pediatric Population, All Locations

Procedures per Patient - Pediatric Patients

Weighted Mean Procedures per Patient

Primary Procedures
Secundary Procedures
Adjunctive Procedures
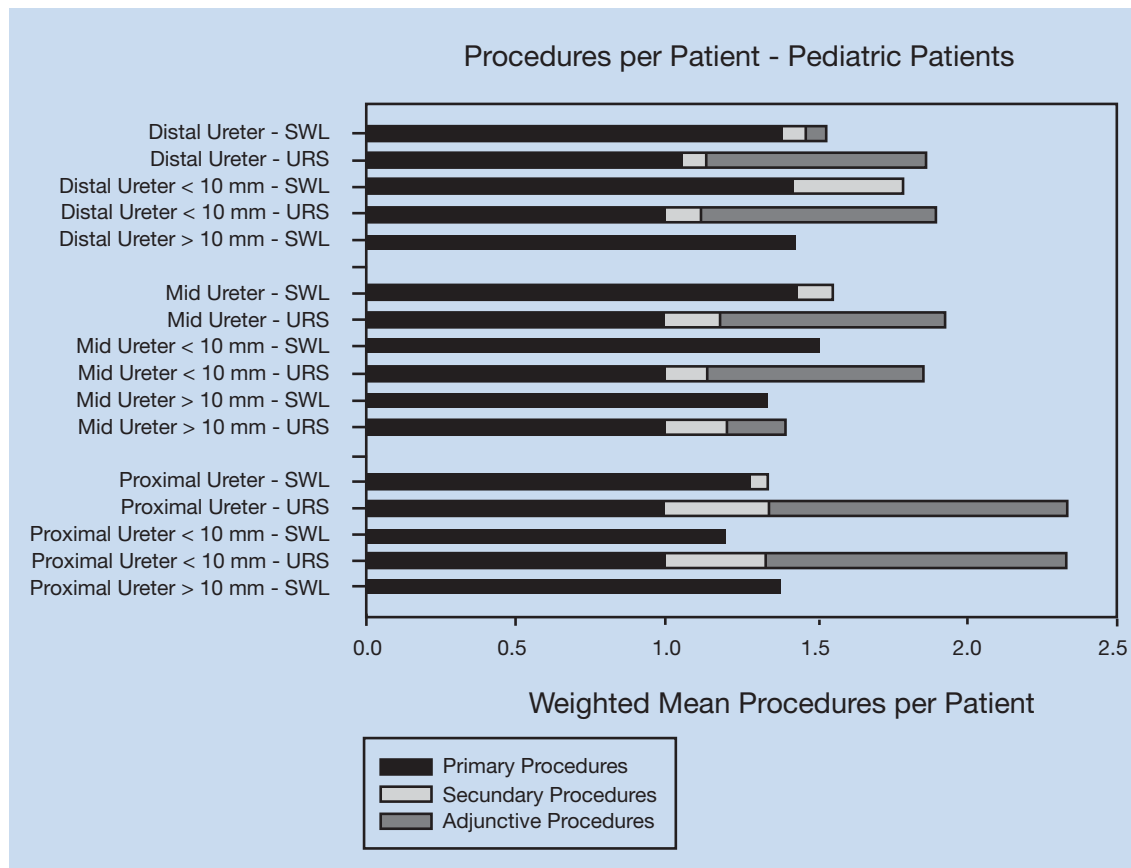
9.3.1.4   Complications

The articles were extracted for various complications; however, the Panel believes the following are the most relevant:
1.   Sepsis
2.   Steinstrasse
3.   Stricture
4.   Ureteral injury
5.   Urinary tract infection (UTI)

Serious complications, including death and loss of kidney, were sufficiently rare that data were not available to estimate their rates of occurrence. Other complications are listed in Chapter 3.

The complication rates for the overall population by treatment, size, and location are shown in Table 5.

Table 5. Complications Occurrence Rates with SWL and URS, Overall Population

	SWL		URS	
	Groups/Patients	Med/95% CI	Groups/Patients	Med/95% CI
Distal Ureter				
Sepsis	6 2019	3% (2 - 5)%	7 1954	2% (1 - 4)%
Steinstrasse	1 26	4% (0 - 17)%		
Stricture	2 609	0% (0 - 1)%	16 1911	1% (1 - 2)%
Ureteral Injury	1 45	1% (0 - 5)%	23 4529	3% (3 - 4)%
UTI	3 87	4% (1 - 12)%	3 458	4% (2 - 7)%
Mid Ureter				
Sepsis	2 398	5% (0 - 20)%	4 199	4% (1 - 11)%
Steinstrasse	1 37	8% (2 - 20)%		
Stricture	1 43	1% (0 - 6)%	7 326	4% (2 - 7)%
Ureteral Injury			10 514	6% (3 - 8)%
UTI	1 37	6% (1 - 16)%	1 63	2% (0 - 7)%
Proximal Ureter				
Sepsis	5 704	3% (2 - 4)%	8 360	4% (2 - 6)%
Steinstrasse	3 235	5% (2 - 10)%	1 109	0% (0 - 2)%
Stricture	2 124	2% (0 - 8)%	8 987	2% (1 - 5)%
Ureteral Injury	2 124	2% (0 - 8)%	10 1005	6% (3 - 9)%
UTI	5 360	4% (2 - 7)%	2 224	4% (1 - 8)%

Table 6 summarizes complications for all pediatric groups. Since there are few groups and patients, it was not possible to stratify data by stone size or location. The reported frequencies of pain may be inaccurate because of inconsistent reporting.

Table 6. Complication Occurrence Rates - Overall, Pediatric Population

Complications of Treatment- PEDIATRIC	SWL		URS	
	Groups/Patient	**Med / 95% CI**	**Groups/Patient**	**Med / 95% CI**
Bleeding	2	**5%**	1	**17%**
	206	(0-24)%	66	(9-27)%
Overall Significant complications	1	**1%**	5	**5%**
	38	(0-6)%	65	(1-14)%
Pain	3	**18%**	3	**5%**
	106	(9-30)%	98	(1-13)%
Retention	1	**2%**	1	**4%**
	63	(0-7)%	26	(0-17)%
Sepsis	2	**4%**	3	**3%**
	101	(1-12)%	73	(0-9)%
Skin	1	**0%**		
	168	(0-1)%		
Stricture	1	**1%**		
	25	(0-9)%		
Ureteral Obstruction	4	**2%**		
	283	(1-6)%		
UTI	2	**2%**		
	63	(0-9)%		
Infection			2	**6%**
			91	(2-13)%
Stent Migration			1	**5%**
			25	(0-17)%
Ureteral Injury			6	**6%**
			216	(3-10)%
Ureteral Obstruction			1	**1%**
			26	(0-9)%
UTI			1	**2%**
			12	(0-19)%
Stricture			5	**5%**
			106	(2-11)%
Other Long Term CX			1	**12%**
			43	(5-24)%

G = number of groups/treatment arms extracted; P = number of patients in those groups.

9.3.1.5 Other Surgical Interventions

Small numbers of studies reported on open surgery, laparoscopic stone removal, and percutaneous antegrade ureteroscopy. Because these procedures are usually reserved for special cases, the reported data should not be used to compare procedures with each other or with SWL or URS. As expected, these more invasive procedures yielded high stone-free rates when used.

A single pediatric report provided procedure counts for two patients who had one open procedure each. Two studies reported stone-free rates for children with open procedures (n=five patients); the computed stone-free rate was 82% (95% CI: 43% to 99%).

9.4   The Index Patient

In constructing these guidelines, an "index patient" was defined to reflect the typical individual with a ureteral stone whom a urologist treats. The following definition was created.

The index patient is a nonpregnant adult with a unilateral noncystine/nonuric acid radiopaque ureteral stone without renal calculi requiring therapy whose contralateral kidney functions normally and whose medical condition, body habitus, and anatomy allow any one of the treatment options to be undertaken.

9.5 Treatment Guidelines for the Index Patient

9.5.1 For All Index Patients

Standard: Patients with bacteriuria should be treated with appropriate antibiotics.
[Based on Panel consensus/Level IV]

Untreated bacteriuria can lead to infectious complications and possible urosepsis if combined with urinary tract obstruction, endourologic manipulation, or SWL. Urine culture prior to intervention is recommended; screening with dipsticks might be sufficient in uncomplicated cases (2). In case of suspected or proven infection, appropriate antibiotic therapy should be administered before intervention (6).

Standard: Stone extraction with a basket without endoscopic visualization of the stone (blind basketing) should not be performed.
[Based on Panel consensus/Level IV]

Before the availability of modern ureteroscopes, extraction of distal ureteral stones with a basket with or without fluoroscopy was common. This procedure is, however, associated with an obvious risk of injury to the ureter. It is the expert opinion of the Panel that blind stone extraction with a basket should not be performed, and that intraureteral manipulations with a stone basket should always be performed under direct ureteroscopic vision. Fluoroscopic imaging of the stone alone is not sufficient.

9.5.2 For Ureteral Stones <10 mm

Option: In a patient who has a newly diagnosed ureteral stone <10 mm and whose symptoms are controlled, observation with periodic evaluation is an option for initial treatment. Such patients may be offered an appropriate medical therapy to facilitate stone passage during the observation period.
[Based on review of the data and panel opinion/Level 1A]

The Panel performed a meta-analysis of studies in which spontaneous ureteral stone passage was assessed. The median probability of stone passage was 68% for stones ≤5 mm (n=224) and 47% for those >5 and ≤10 mm (n=104) in size (details previously discussed and provided in the appendixes). The Panel recognized that these studies had certain limitations including nonstandardization of the stone size measurement methods and lack of analysis of stone position, stone-passage history, and time to stone passage in some. A meta-analysis of MET was also performed which demonstrated that alpha blockers facilitate stone passage and that the positive impact of nifedipine is marginal. This analysis also indicates that alpha blockers are superior to nifedipine and, hence, may be the preferred agents for MET (details provided in the Appendixes). A similar benefit of MET was demonstrated in a recently published meta-analytic study (7). The methods of analysis used in this study were somewhat different as the absolute improvement in stone passage was calculated in our study and the relative improvement in the latter. The vast majority of the trials analyzed in this and our analysis were limited to patients with distal ureteral stones. The majority of stones pass spontaneously within four to six weeks. This was demonstrated by Miller and Kane (8), who reported that of stones ≤2 mm, 2 to 4 mm and 4 to 6 mm in size, 95% of those which passed did so by 31, 40, and 39 days, respectively. In a choice between active stone removal and conservative treatment with MET, it is important to take into account all individual circumstances that may affect treatment decisions. A prerequisite for MET is that the patient is reasonably comfortable with that therapeutic approach and that there is no obvious advantage of immediate active stone removal.

Standard: Patients should be counseled on the attendant risks of MET including associated drug side effects and should be informed that it is administered for an "off label" use.
[Based on Panel consensus/Level IV]

Standard: 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.
[Based on Panel consensus/Level IV]

> **Standard: Patients should be followed with periodic imaging studies to monitor stone position and to assess for hydronephrosis.**
>
> [Based on Panel consensus/Level IV]

> **Standard: Stone removal is indicated in the presence of persistent obstruction, failure of stone progression, or in the presence of increasing or unremitting colic.**
>
> [Based on Panel consensus/Level IV]

9.5.3   For Ureteral Stones >10 mm

Although patients with ureteral stones >10 mm could be observed or treated with MET, in most cases such stones will require surgical treatment. No recommendation can be made for spontaneous passage (with or without medical therapy) for patients with large stones.

9.5.4   For Patients Requiring Stone Removal

> **Standard: A patient must be informed about the existing active treatment modalities, including the relative benefits and risks associated with each modality.**
>
> [Based on Panel consensus/Level IV]

Specifically, both SWL and URS should be discussed as initial treatment options for the majority of cases. Regardless of the availability of this equipment and physician experience, this discussion should include stone-free rates, anesthesia requirements, need for additional procedures, and associated complications. Patients should be informed that URS is associated with a better chance of becoming stone free with a single procedure, but has higher complication rates.

> **Recommendation: For patients requiring stone removal, both SWL and URS are acceptable first-line treatments.**
>
> [Based on review of the data and Panel consensus/Level 1A-IV (details provided in Chapter 3)]

The meta-analysis demonstrated that URS yields significantly greater stone-free rates for the majority of stone stratifications.

> **Recommendation: Routine stenting is not recommended as part of SWL.**
>
> [Based on Panel consensus/Level III]

The 1997 AUA guideline, *Report on the Management of Ureteral Calculi*, stated that "Routine stenting is not recommended as part of SWL (9)." The 1997 guideline Panel noted that it had become common practice to place a ureteral stent for more efficient fragmentation of ureteral stones when using SWL. However, the data analyzed showed no improved fragmentation with stenting (9). The current analysis demonstrates similar findings. In addition, studies assessing the efficacy of SWL treatment with or without internal stent placement have consistently noted frequent symptoms related to stents (10-13).

> **Option: Stenting following uncomplicated URS is optional.**
>
> [Based on Panel consensus/Level 1A]

Several randomized prospective studies published since the 1997 AUA guideline document have demonstrated that routine stenting after uncomplicated URS may not be necessary (10,14-19). It is well documented that ureteral stenting is associated with bothersome lower urinary tract symptoms and pain that can, albeit temporarily, alter quality of life (15-17,20-26). In addition, there are complications associated with ureteral stenting, including stent migration, urinary tract infection, breakage, encrustation, and obstruction. Moreover, ureteral stents add some expense to the overall ureteroscopic procedure and unless a pull string is attached to the distal end of the stent, secondary cystoscopy is required for stent removal (27).

There are clear indications for stenting after the completion of URS. These include ureteral injury, stricture, solitary kidney, renal insufficiency, or a large residual stone burden.

> **Option: Percutaneous antegrade ureteroscopy is an acceptable first-line treatment in select cases.**
>
> [Based on Panel consensus/Level III]

Instead of a retrograde endoscopic approach to the ureteral stone, percutaneous antegrade access can be substituted (28). This treatment option is indicated:

- in select cases with large impacted stones in the upper ureter
- in combination with renal stone removal
- in cases of ureteral stones after urinary diversion (29)
- in select cases resulting from failure of retrograde ureteral access to large, impacted upper ureteral stones (30).

Option: 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.
[Based on Panel consensus/Level III]

The 1997 AUA guideline stated that "Open surgery should not be the first-line treatment (9)." The invasiveness and morbidity of open surgery can be avoided. In very difficult situations, however, such as with very large, impacted stones and/or multiple ureteral stones, or in cases of concurrent conditions requiring surgery, an alternative procedure might be desired as primary or salvage therapy. Laparoscopic ureterolithotomy is a less invasive alternative to open surgery in this setting. Comparative series indicate that open surgical ureterolithotomy can be replaced by laparoscopic ureterolithotomy in most situations (31,32). From the 15 case series of laparoscopic ureterolithotomy included in the Panel's literature review, the median stone-free rate was 88% for the primary treatment. It is notable that this success was achieved when virtually all of the procedures were for large and/or impacted calculi.

9.6   Recommendations for the Pediatric Patient

Option: Both SWL and URS are effective in this population. Treatment choices should be based on the child's size and urinary tract anatomy. The small size of the pediatric ureter and urethra favors the less invasive approach of SWL.
[Based on review of data and Panel consensus/Level III]

9.7   Recommendations for the Nonindex Patient

Standard: For septic patients with obstructing stones, urgent decompression of the collecting system with either percutaneous drainage or ureteral stenting is indicated. Definitive treatment of the stone should be delayed until sepsis is resolved.
[Based on Panel consensus/Level III]

The compromised delivery of antibiotics into the obstructed kidney mandates that the collecting system be drained to promote resolution of the infection. The choice of drainage modality, whether percutaneous nephrostomy or ureteral stent, is left to the discretion of the urologist, as both have been shown in a randomized trial to be equally effective in the setting of presumed obstructive pyelonephritis/pyonephrosis (33). Definitive treatment of the stone should be delayed until sepsis has resolved and the infection is cleared following a complete course of appropriate antimicrobial therapy.

9.8   Discussion
There are two significant changes in treatment approach that distinguish the present document from the guideline published by the AUA in 1997. The most significant change is the use of retrograde URS as first-line treatment for middle and upper ureteral stones with a low probability of spontaneous passage. This change reflects both the vast technological improvements that have been made during the last decade and the experience and facility that surgeons now have with the procedure. The other change is the establishment of effective MET to facilitate spontaneous stone passage. These advances, the current status of other technologies and procedures, issues related to nonindex patients, and future directions and research germane to this condition will be subsequently discussed.

9.8.1   Medical Expulsive Therapy
There is growing evidence that MET, the administration of drugs to facilitate stone passage, can be efficacious. Studies have demonstrated that this approach may facilitate and accelerate the spontaneous passage of ureteral stones as well as stone fragments generated with SWL (34-38). Our meta-analysis demonstrated the effectiveness of MET. Nine percent (CI: -7% to 25%) more patients receiving nifedipine passed their stones than did controls in our meta-analysis, a difference that was not statistically significant. In contrast, a statistically significant 29% (CI: 20% to 37%) more patients passed their stones with alpha blocker therapy than did control patients. These findings indicate that alpha blockers facilitate ureteral stone passage while nifedipine may provide a marginal benefit. Therefore, the Panel feels that alpha blockers are the preferred

agents for MET at this time. Similar findings have been reported by Hollingsworth and associates (7), who recently performed a meta-analysis of studies involving alpha blockers or nifedipine in patients with ureteral stones. The differences in methodology from our study have been previously mentioned. Patients given either one of these agents had a greater likelihood of stone passage than those not receiving such therapy. The pooled-risk ratios and 95% CIs for alpha blockers and calcium channel blockers were 1.54 (1.29 to 1.85) and 1.90 (1.51 to 2.40) (7). The benefit of adding corticosteroids was reported to be small (7,37). Tamsulosin has been the most common alpha blocker utilized in these studies. However, one small study demonstrated tamsulosin, terazosin, and doxazosin as equally effective in this setting (39). These studies also demonstrated that MET reduces the stone-passage time and limits pain. The beneficial effects of these drugs are likely attributed to ureteral smooth muscle relaxation mediated through either inhibition of calcium channel pumps or alpha-1 receptor blockade. Further prospective and randomized studies are warranted to determine the patients who best respond to MET. A large, multicenter, randomized, placebo-controlled study has recently been funded in the United States for this purpose. Patients with ureteral stones in all segments of the ureter will be randomized to tamsulosin or placebo.

9.8.2   Shock-wave Lithotripsy

Shock-wave lithotripsy was introduced to clinical practice as a treatment for ureteral stones in the early 1980s. Today, even with the refinement of endourologic methods for stone removal such as URS and PNL, SWL remains the primary treatment for most uncomplicated upper urinary tract calculi. The meta-analysis published by the AUA Nephrolithiasis Guideline Panel in 1997 documented that the stone-free rate for SWL for proximal ureteral stones overall was 83% (78 studies, 17,742 patients). To achieve this result, 1.40 procedures were necessary per patient. The results were very similar in the distal ureter, with a stone-free rate of 85% (66 studies, 9,422 patients) necessitating 1.29 primary and secondary procedures per patient. There was no significant difference between various SWL techniques (SWL with pushback, SWL with stent or catheter bypass, or SWL in situ). Consequently, the Panel suggested that the use of a ureteral stent to improve stone-free rates was not warranted. This observation is also confirmed by the present analysis. However, there may be circumstances such as when the stone is small or of low radiographic density where a stent or ureteral catheter (sometimes using a contrast agent) may help facilitate localization during SWL. The Panel considered complications of SWL for ureteral stones to be infrequent.

The current meta-analysis analyzed SWL stone-free results for three locations in the ureter (proximal, mid, distal). The SWL stone-free results are 82% in the proximal ureter (41 studies, 6,428 patients), 73% in the mid ureter (31 studies, 1,607 patients), and 74% in the distal ureter (50 studies, 6,981 patients). The results in the 1997 guideline, which divided the ureter into proximal and distal only, reported SWL stone-free results of 83% and 85%, respectively. The CIs for the distal ureter do not overlap and indicate a statistically significant worsening of results in the distal ureter from the earlier results. No change is shown for the proximal ureter. The cause of this difference is not clear. Additional procedures also were infrequently necessary (0.62 procedures per patient for proximal ureteral stones, 0.52 for mid-ureteral stones, and 0.37 for distal ureteral stones). Serious complications were again infrequent. As expected, stone-free rates were lower and the number of procedures necessary were higher for ureteral stones >10 mm in diameter managed with SWL.

The outcomes for SWL for ureteral calculi in pediatric patients were similar to those for adults, making this a useful option, particularly in patients where the size of the patient (and ureter/urethra) may make URS a less attractive option.

The newer generation lithotriptors with higher peak pressures and smaller focal zones should, in theory, be ideal for the treatment of stones in the ureter but instead have not been associated with an improvement in stone-free rates or a reduction in the number of procedures needed when this treatment approach is chosen. In fact, the SWL stone-free rates for stones in the distal ureter have declined significantly when compared with the 1997 AUA analysis. The explanation for the lack of improvement in SWL outcomes is unknown.

Although ureteroscopic stone removal is possible with intravenous sedation, one clear advantage of SWL over URS is that the procedure is more easily and routinely performed with intravenous sedation or other minimal anesthetic techniques. Therefore, for the patient who desires treatment with minimal anesthesia, SWL is an attractive approach.

Shock-wave lithotripsy can be performed with the aid of either fluoroscopy or ultrasound (US). While some stones in the proximal and distal ureter can be imaged with US, this imaging modality clearly limits SWL application in the ureter when compared to fluoroscopy. However, a combination of both fluoroscopy and US can facilitate stone location and minimize radiation exposure.

As documented in the 1997 AUA report, there appears to be little, if any, advantage to routine stenting when performing SWL for ureteral stones.

Concerns have been raised, too, regarding the use of SWL to treat distal ureteral calculi in women of childbearing age because of the theoretical possibility that unfertilized eggs and/or ovaries may be damaged.

To date, no objective evidence has been discovered to support such concerns, but many centers require that women age 40 or younger be fully informed of the possibility and give their consent before treatment with SWL (40-44).

9.8.3   Ureteroscopy

Ureteroscopy has traditionally constituted the favored approach for the surgical treatment of mid and distal ureteral stones while SWL has been preferred for the less accessible proximal ureteral stones. With the development of smaller caliber semirigid and flexible ureteroscopes and the introduction of improved instrumentation, including the holmium:YAG laser, URS has evolved into a safer and more efficacious modality for treatment of stones in all locations in the ureter with increasing experience world-Wide (45,46). Complication rates, most notably ureteral perforation rates, have been reduced to less than 5%, and long-term complications such as stricture formation occur with an incidence of 2% or less (47). Overall stone-free rates are remarkably high at 81% to 94% depending on stone location, with the vast majority of patients rendered stone free in a single procedure (Figure 1 and Chapter 3).

In 1997, the AUA Nephrolithiasis Clinical Guideline Panel recommended SWL for <1 cm stones in the proximal ureter and either SWL or URS for >1 cm proximal ureteral stones.9 With improved efficacy and reduced morbidity currently associated with ureteroscopic management of proximal ureteral stones, this modality is now deemed appropriate for stones of any size in the proximal ureter. Indeed, the current analysis revealed a stone-free rate of 81% for ureteroscopic treatment of proximal ureteral stones, with surprisingly little difference in stone-free rates according to stone size (93% for stones <10 mm and 87% for stones >10 mm). The flexible ureteroscope is largely responsible for improved access to the proximal ureter; superior stone-free rates are achieved using flexible URS (87%) compared with rigid or semirigid URS (77%). These stone-free rates are comparable to those achieved with SWL.

The middle ureter poses challenges for all surgical stone treatments; the location over the iliac vessels may hinder access with a semirigid ureteroscope, and identification and targeting of mid-ureteral stones for SWL has proved problematic due to the underlying bone. Despite the limitations, ureteroscopic management is still highly successful; a stone-free rate of 86% was demonstrated in the current analysis, although success rates declined substantially when treating larger stones (>10 mm) compared with smaller stones (78% versus 91%, respectively).

Ureteroscopic treatment of distal ureteral stones is uniformly associated with high success rates and low complication rates. An overall stone-free rate of 94% was achieved with either a rigid or semirigid ureteroscope, with little drop off in stone-free rates when treating larger stones. On the other hand, flexible URS was less successful than rigid or semirigid URS for distal ureteral stones, particularly those >10 mm, likely due to difficulty maintaining access within the distal ureter with a flexible ureteroscope.

A number of adjunctive measures have contributed to the enhanced success of ureteroscopic management of ureteral calculi. Historically, stones in the proximal ureter have been associated with lower success rates than those in the mid and distal ureter, in part because the proximal ureter is more difficult to access and stone fragments often become displaced into the kidney where they may be difficult to treat. Improved flexible ureteroscopes and greater technical skill, along with the introduction of devices to prevent stone migration (48,49) have improved the success of treating proximal ureteral stones.

Although the efficacy of URS for the treatment of ureteral calculi has been amply shown, the need for a ureteral stent with its attendant morbidity has biased opinion towards SWL in some cases. Clearly, SWL is associated with fewer postoperative symptoms and better patient acceptance than URS. However, a number of recent prospective, randomized trials have shown that for uncomplicated URS, the ureter may be left unstented without undue risk of obstruction or colic requiring emergent medical attention (10,14-19).

Ureteroscopy can also be applied when SWL might be contraindicated or ill-advised. Ureteroscopy can be performed safely in select patients in whom cessation of anticoagulants is considered unsafe (50). In addition, URS has been shown to be effective regardless of patient body habitus. Several studies have shown that morbidly obese patients can be treated with success rates and complication rates comparable to the general population (51,52). Finally, URS can be used to safely simultaneously treat bilateral ureteral stones in select cases (53-55).

9.8.4   Percutaneous Antegrade Ureteroscopy

Percutaneous antegrade removal of ureteral stones is a consideration in selected cases, for example, for the treatment of very large (>15 mm diameter) impacted stones in the proximal ureter between the ureteropelvic junction and the lower border of the fourth lumbar vertebra (30,56). In these cases with stone-free rates between 85% and 100%, its superiority to standard techniques has been evaluated in one prospective randomized (57) and in two prospective studies (28,30). In a total number of 204 patients, the complication rate was low, acceptable, and not specifically different from any other percutaneous procedure.

Percutaneous antegrade removal of ureteral stones is an alternative when SWL is not indicated or has

failed (58) and when the upper urinary tract is not amenable to retrograde URS; for example, in those with urinary diversion (29) or renal transplants (59).

9.8.5   Laparoscopic and Open Stone Surgery

Shock-wave lithotripsy, URS, and percutaneous antegrade URS can achieve success for the vast majority of stone cases. In extreme situations or in cases of simultaneous open surgery for another purpose, open surgical ureterolithotomy might rarely be considered (60,61). For most cases with very large, impacted, and/or multiple ureteral stones in which SWL and URS have either failed or are unlikely to succeed, laparoscopic ureterolithotomy is a better alternative than open surgery if expertise in laparoscopic techniques is available. Both retroperitoneal and transperitoneal laparoscopic access to all portions of the ureter have been reported. Laparoscopic ureterolithotomy in the distal ureter is somewhat less successful than in the middle and proximal ureter, but the size of the stone does not appear to influence outcome.

Although highly effective, laparoscopic ureterolithotomy is not a first-line therapy in most cases because of its invasiveness, attendant longer recovery time, and the greater risk of associated complications compared to SWL and URS.

9.8.6   Special Considerations
9.8.6.1   Pregnancy

Renal colic is the most common nonobstetric cause of abdominal pain in pregnant patients requiring hospitalization. The evaluation of pregnant patients suspected of having renal colic begins with ultrasonography, as ionizing radiation should be limited in this setting. If the US examination is unrevealing and the patient remains severely symptomatic, a limited intravenous pyelogram may be considered. A typical regimen includes a preliminary plain radiograph (KUB) and two films, 15 minutes and 60 minutes following contrast administration. Noncontrast computed tomography is uncommonly performed in this setting because of the higher dose of radiation exposure. Magnetic resonance imaging can define the level of obstruction, and a stone may be seen as a filling defect. However, these findings are nonspecific. In addition, there is a paucity of experience with using this imaging modality during pregnancy (62).

Once the diagnosis has been established, these patients have traditionally been managed with temporizing therapies (ureteral stenting, percutaneous nephrostomy), an approach often associated with poor patient tolerance. Further, the temporizing approach typically requires multiple exchanges of stents or nephrostomy tubes during the remainder of the patient's pregnancy due to the potential for rapid encrustation of these devices.

A number of groups have now reported successful outcomes with URS in pregnant patients harboring ureteral stones. The first substantial report was by Ulvik, et al (63) who reported on the performance of URS in 24 pregnant women. Most patients had stones or edema, and there were no adverse sequelae associated with ureteroscopic stone removal. Similar results have been reported by Lifshitz and Lingeman (64) and Watterson et al (65) who found that the ureteroscopic approach was both diagnostic and therapeutic in pregnant patients with very low morbidity and the need for only short-term ureteral stenting, if at all, afterwards. When intracorporeal lithotripsy is necessary during ureteroscopic treatment of calculi in pregnant patients, the holmium laser has the advantage of minimal tissue penetration, thereby theoretically limiting risk of fetal injury.

9.8.6.2   Pediatrics

Both SWL and URS are effective treatment alternatives for stone removal in children. Selection of the most appropriate treatment has to be based on the individual stone problem, the available equipment and the urologist's expertise in treating children. Children appear to pass stone fragments after SWL more readily than adults (66-71).

Ureteroscopy may be used as a primary treatment or as a secondary treatment after SWL in case of poor stone disintegration. Less efficient SWL disintegration might be seen in children with stones composed of cystine, brushite and calcium oxalate monohydrate or when anatomic abnormalities result in difficulties in fluoroscopic or ultrasonographic visualization of the stone (72-74).

One of the main problems with pediatric URS is the size of the ureteroscope relative to the narrow intramural ureter and the urethral diameter. This problem has lately been circumvented by the use of smaller ureteroscopes, for example, mini or needle instruments as well as small flexible semirigid or rigid ureteroscopes and pediatric (6.9 Fr) cystoscopes. With the availability of 4.5 and 6.0 Fr semirigid ureteroscopes, a 5.3 Fr flexible ureteroscope and a holmium:YAG laser energy source, instrument-related complications have become uncommon (73-75). However, the utilization of proper technique remains the most important factor for generating successful outcomes in this population. Percutaneous stone removal is also possible in pediatric patients with comparable indications to those in adults. Such an approach might be considered for stone removal in children with a malformation of the lower urinary tract.

9.8.6.3 Cystine Stones

Individuals with cystinuria are considered nonindex patients by the Panel for a variety of reasons. There are limited data regarding treatment outcomes in this group (76-83). In vitro studies also show that these stones are commonly resistant to SWL, although the degree of resistance may be variable (77,78). The structural characteristics of these stones are thought to contribute to their decreased SWL fragility. In addition, some of these stones may be barely opaque on standard imaging or fluoroscopy, potentially compromising shock-wave focusing. In contrast to SWL, technology currently utilized for intracorporeal lithotripsy during URS, including the holmium laser, ultrasonic and pneumatic devices, can readily fragment cystine stones (81).

Certain imaging characteristics may predict SWL outcomes for this patient group. Bhatta and colleagues reported that cystine stones having a rough-appearing external surface on plain film imaging were more apt to be fragmented with shock-wave energy than those with a smooth contour (82). Kim and associates reported that the computed tomography attenuation coefficients of the latter were significantly higher than the rough-type stones (83). Other types of stones with higher attenuation values have also been demonstrated to be resistant to shock-wave fragmentation (84).

Patients with this rare genetic disorder typically have their first stone event early in life, are prone to recurrent stones, and are consequently subject to repetitive removal procedures. In addition, patients with cystinuria are at risk for developing renal insufficiency over time (85,86). Prophylactic medical therapy and close follow-up can limit recurrence.

9.8.6.4 Uric acid Stones

Uric acid calculi are typically radiolucent, thus limiting the ability to treat such patients using in situ SWL. However, this approach may be possible with devices that use US if the stone can indeed be localized. When properly targeted, these stones fragment readily with SWL. Uric acid stones have lower computed tomography attenuation values, and can usually be distinguished from calcium, cystine, and struvite calculi (87). The presence of a low attenuation or a radiolucent stone, particularly in a patient with a low urinary pH, should lead the clinician to suspect this diagnosis. Manipulation of the urinary pH with oral potassium citrate, sodium citrate, or sodium bicarbonate to a level ranging from 6.0 to 7.0 may obviate the need for surgical intervention. Moreover, this medical treatment may allow stone dissolution in patients whose symptoms are controllable, should prevent the development of future uric acid stones, and has also been shown to enhance stone clearance with SWL (88). Medical expulsive therapy may be administered concomitantly. Ureteroscopy is a very effective method of treating patients who are not candidates for observation (89).

9.9   Research and Future Directions

Ten years have elapsed since the last publication of the AUA guidelines, and one year since the EAU recommendations on ureteral stones. Extensive cooperation between AUA and EAU Panel members has produced this unique collaborative report. This venture should provide the foundation for future collaborative efforts in guideline development.

The Panel encountered a number of deficits in the literature. While the management of ureteral stones remains commonly needed, few RCTs were available for data extraction. The data were inconsistent, starting from the definition of stone sizes and ending with variable definitions of a stone-free state. These limitations hinder the development of evidence-based recommendations.

To improve the quality of research, the Panel strongly recommends the following:
- conducting RCTs comparing interventional techniques like URS and SWL
- conducting pharmacological studies of stone-expulsion therapies as double-blinded RCTs
- reporting stone-free data without inclusion of residual fragments
- using consistent nomenclature to report stone size, stone location, stone-free rates, time point when stone-free rate is determined, or method of imaging to determine stone-free rate
- reporting data stratified by patient/stone characteristics, such as patient age, stone size, stone location, stone composition, gender, body mass index, and treatment modality
- reporting all associated treatments including placement of ureteral stents or nephrostomies
- using standardized methods to report acute and long-term outcomes
- developing methods to predict outcomes for SWL, URS, and MET
- providing measures of variability such as standard deviation, standard error, CI, or variance with corresponding average patient numbers
- reporting raw data to facilitate meta-analyses

The Panel suggests focusing on the following issues in future investigations:
- investigating the proposed current efficacy problems of second and third generation shock-wave machines and developing approaches to improve SWL

- determining the safety of each technique with respect to acute and long-term effects
- investigating the promising medical stone expulsion in basic research studies and in clinical trials to unravel the underlying mechanisms and to optimize the treatment regimens
- addressing issues such as patient preferences, quality of life, and time until the patient completed therapy when evaluating treatment strategies. To date, only a few studies have addressed patient preference.90-92
- although largely dependent on different health systems, addressing cost-effectiveness

9.10 Acknowledgements and Disclaimers

The supporting systematic literature review and data analysis, and the drafting of this document were conducted by the EAU/AUA Nephrolithiasis Guideline Panel (hereinafter the Panel). Each association selected a Panel chair who in turn appointed the Panel members, urologists with specific expertise in this disease.

The mission of the Panel was to develop either analysis- or consensus-based recommendations, depending on the type of evidence available and Panel processes to support optimal clinical practices in the management of ureteral calculi. This document was submitted to 81 urologists and other health care professionals for peer review. After revision of the document based upon the peer review comments, the guideline was submitted for approval to the Practice Guidelines Committee of the AUA and the Guidelines Office of the EAU. Then it was forwarded to the AUA Board of Directors and the EAU Board for final approval. Funding of the Panel and of the PGC was provided by the AUA and the EAU, although Panel members received no remuneration for their work. Each member of the PGC and of the Panel furnished a current conflict of interest disclosure to the AUA.

The final report is intended to provide medical practitioners with a current understanding of the principles and strategies for the management of ureteral calculi. The report is based on an extensive review of available professional literature as well as clinical experience and expert opinion. Some of the medical therapies currently employed in the management of ureteral calculi have not been approved by the US Food and Drug Administration for this specific indication. Thus, doses and dosing regimens may deviate from that employed for the Food and Drug Adminstration-approved indications, and this difference should be considered in the risk-versus-benefit assessment.

This document provides guidance only, and does not establish a fixed set of rules or define the legal standard of care. As medical knowledge expands and technology advances, this guideline will change. Today it represents not absolute mandates but provisional proposals or recommendations for treatment under the specific conditions described. For all these reasons, the guideline does not preempt physician judgment in individual cases. Also, treating physicians must take into account variations in resources, and in patient tolerances, needs and preferences. Conformance with the guideline reflected in this document cannot guarantee a successful outcome.

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10. GENERAL RECOMMENDATIONS AND PRECAUTIONS FOR STONE REMOVAL

10.1 Infections

A test for bacteriuria should be carried out in all patients in whom stone removal is planned. Screening with dipsticks might be sufficient in uncomplicated cases. In others, urine culture is necessary. In cases with clinically significant infection and obstruction, several days of drainage procedures by a stent or a percutaneous nephrostomy should precede the active intervention for stone removal.

10.2 Aspects of anticoagulation and stone treatment

Patients with bleeding diathesis or medical anticoagulation should be referred to an internist for appropriate therapeutic measures prior to, and during, the stone-removing procedure. In patients with an uncorrected bleeding diathesis, the following treatments are generally contra-indicated:
- Extracorporeal shock-wave lithotripsy (ESWL)
- Percutaneous nephrolithotomy with or without lithotripsy (PNL)
- Open surgery (1,2).

Although several authors have demonstrated that ESWL is feasible and safe after correction of the underlying coagulopathy (3-5), ureterorenoscopy may offer an approach with less morbidity. The holmium (Ho:YAG) laser in combination with contemporary small-calibre ureteroscopes has been demonstrated as being safe in these patients. Furthermore, ureteroscopic Ho:YAG laser lithotripsy, without the need for pre-operative correction of the haemostatic parameters, limits the risk of thromboembolic complications and avoids the costs associated with an extended hospital stay.

Avoiding electrohydraulic lithotripsy seems to be crucial to decrease bleeding complications (6,7)	**LE = 4** **GR = C**

10.3 Pacemaker

Although the rule is that patients with a pacemaker can be treated with ESWL, it is recommended that the patient's cardiologist is consulted before undertaking ESWL treatment. Patients with implanted cardioverter defibrillators need to be treated with special care because some of these devices need deactivation during ESWL. Such a step might, however, not be necessary with new-generation lithotripters (8).

10.4 Hard stones

Stones composed of brushite or calcium oxalate monohydrate are characterized by particular hardness. This may be a factor in favour of percutaneous removal of such stones, particularly if they are large. The possibility of chemolytic treatment of brushite stone fragments is noteworthy in view of the high recurrence rate seen with this type of stone.

Cystine stones are of two types: those responding well to ESWL and those responding poorly (9). For large ESWL-resistant stones, PNL is the best alternative for efficient removal, thereby avoiding too much shock-wave energy to the renal tissue.

10.5 Radiolucent stones

Uric acid concrements can be localized with US, or with intravenous or retrograde administration of contrast medium. It should be noted that only uric acid stones, not sodium urate or ammonium urate stones, can be dissolved by oral chemolysis.

10.6 Recommendations for special considerations

Table 24 summarizes recommendations for special considerations.

Table 24: Recommendations for special considerations

Special considerations	LE	GR
Treatment with antibiotics should precede stone-removing procedures in case of a positive urine culture, positive dip-stick test or suspicion of an infective component	3	B
Treatment with salicylates should be stopped 10 days before the planned stone removal	3	B
ESWL and PNL are contraindicated in pregnant women	4	C
ESWL is possible in patients with a pacemaker	4	C
ESWL = extracorporeal shock-wave lithotripsy; PNL = percutaneous nephrolithotomy.		

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11. MANAGING SPECIAL PROBLEMS

Caliceal diverticulum stones are treated using ESWL, PNL (if possible) or retrograde URS (RIRS). An optional method for removal of diverticular stones is video-endoscopic retroperitoneal surgery. The principles of video-endoscopic surgery are outlined elsewhere (1-5). In the case of a narrow communication between the diverticulum and the renal collecting system, well-disintegrated stone material will remain in the original position. These patients may become asymptomatic as a result of stone disintegration only.

Horseshoe kidneys may be treated according to the principles of stone treatment presented above (6). It needs to be emphasized, however, that according to the anterior position of the kidney, it is commonly necessary to carry out ESWL treatment with the patient in the prone position (i.e. with shock-wave entrance from the abdominal side).

Stones in transplanted kidneys: Recommended procedures for the removal of stones in transplanted kidneys are ESWL and PNL. For pelvic kidneys, ESWL or video-endoscopic laparoscopic surgery is recommended. For obese patients, the options are ESWL, PNL or open surgery.

Stones formed in a continent reservoir present a varied and often difficult problem (7-14). General directions for the management of this problem cannot be given. Each stone problem has to be considered and treated individually.

Patients with obstruction of the ureteropelvic junction: Stones can be removed at the same time as the outflow abnormality is corrected either with percutaneous endopyelotomy (15-35) or with open reconstructive surgery. Transureteral endopyelotomy with Ho:YAG laser endopyelotomy is another alternative to correct this abnormality. Incision with an Acucise balloon catheter may also be considered provided the stones can be prevented from falling down into the pelvo-ureteral incision (36-39).

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12. MANAGEMENT OF STONE PROBLEMS DURING PREGNANCY

Urolithiasis during pregnancy, though rare, is a challenging condition from diagnostic as well as therapeutic aspects. Although the rough incidence of the pathology varies widely from 1 in 200 to 2,000 pregnancies; the true incidence has been reported to be between 0.026% and 0.53%. When compared to non-pregnant age-matched controls, pregnant women do not have an elevated incidence of urolithiasis. No major differences in stone composition have been found when comparing pregnant women to the general population (1-6).

Stones may be present in both kidneys with an equal frequency and ureteral stones are twice as common as renal calculi. Symptomatic stone disease presents in the second or third trimester in 80-90% of women. Stones affect the two kidneys with equal frequency, even though physiological hydronephrosis of pregnancy more commonly affects the right side (7).

The management of such patients can pose significant and multiple challenges to the patient, obstetrician and urologist, but fortunately a considerable amount of the symptomatic stones (70-80%) pass spontaneously. Taking all these facts into account, the obstetricians should be aware of the symptoms, the practical diagnosis and the associated risks of urolithiasis (8).

12.1 Symptoms

Generally, pregnant women present with symptoms of urolithiasis in the second or third trimesters of pregnancy. In the presence of appropriate signs, such as flank pain with tenderness, haematuria and/or unresolved bacteriuria, it is important that physicians in charge consider the presence of urinary calculi. This is largely because of the possible obstetric complications associated with urolithiasis, including preterm labour and preterm premature rupture of membranes. Failure to promptly diagnose and manage the urinary stones during pregnancy may have adverse consequences for mother and child (9).

12.2 Diagnostic evaluation

Correct diagnosis of urolithiasis during pregnancy is often difficult and can be a real challenge as a result of the normal physiological changes occurring during this special period. As well as maternal renal functional status and stone-related factors (number, size, location and configuration), proper imaging is a very crucial factor for diagnosis and appropriate treatment planning. The most important factor complicating the radiological evaluation of stone disease in pregnancy is the risk of radiation exposure to the fetus, which includes possible teratogenesis, carcinogenesis, and mutagenesis. The risk is critically dependent on the gestational age and the amount of radiation delivered.

Ultrasonography (using the change in resistive index and transvaginal US when necessary) has become the primary radiological diagnostic tool	**LE = 1a** **GR = A**

However, ultrasonography is of limited value in cases of acute obstruction because of poor sound transmission through gas and bone and the operator-dependent ability of US to differentiate between physiological dilation of pregnancy and ureteral. A limited excretory urogram or magnetic resonance imaging may be performed in particularly complicated cases. Other diagnostic modalities used to try and diagnose the presence of the stone(s) and assess the degree of obstruction in pregnant women include:
- Transvaginal/endoluminal ultrasonography (evaluation of possible stones at the vesicoureteral junction)
- Magnetic resonance urography (MRU), avoiding ionizing radiation and administration of iodinated contrast medium that should be reserved for complex cases when ultrasonography fails to afford a diagnosis
- More recently, gadolinium-enhanced breath-hold gradient-echo MR excretory urography (MREU).

12.3 Management of the stone problem

Following establishment of a correct diagnosis:

In 70-80% of patients, the stones will pass spontaneously	**LE = 1a** **GR = A**

Preference 1	Conservative management with bed rest, appropriate hydration and analgesia should be the first-line treatment for all pregnant women with non-complicated urolithiasis	LE = 4 GR = C

If spontaneous passage does not occur or if complications develop (commonly the induction of premature labour), some certain established treatment options should be considered:

Preference 2	The placement of an internal stent or a percutaneous nephrostomy catheter are suggested first-line treatment alternatives	LE = 4 GR = C

Preference 3	Ureteroscopy, although more invasive, has been accepted as a minimally invasive treatment alternative (9-13)	LE = 1b GR = A

With respect to stone-related pain management during pregnancy, among the drugs used so far, acetaminophen and narcotic analgesics are the medications with no known teratogenic effects. Although no drug is absolutely free of risk during pregnancy, these drugs appear to have a minimal risk when used judiciously in usual doses under medical supervision. Also, aspirin and NSAIDs may be used while being aware of their non-teratogenic adverse effects (14,15).

Alternatively, in recent years, epidural blocks have been commonly used to reduce maternal pain and their safety for mother and fetus are well accepted, provided maternal hypotension is avoided. Although this approach is infrequently used, it may be helpful for selected patients who fail more conservative expectant management and when operative intervention is not possible because of patient refusal or the lack of equipment or endourological expertise (16).

12.3.1 Surgical management
Despite the commonly accepted success of conservative management, surgical intervention may ultimately be required in the presence of certain indications such as f.i. febrile urinary tract infection, pyelonephrosis, sepsis, obstruction of a solitary kidney, intractable pain, nausea, or vomiting. Depending on the experience and capability of the institution, a team including a urologist, obstetrician and anaesthesiologist should make a proper management plan based on the patient's wishes together with her comfort level.

12.3.2 Temporary urinary diversion
Decompression of the renal collecting system by placing a percutaneous-nephrostomy tube or an internal ureteral stent was first suggested by Meares in 1978. Although the efficacy of these procedures has been firmly established, today each procedure has its own advantages and disadvantages.

12.3.2.1 Percutaneous nephrostomy catheter
This procedure is a widely accepted approach being routinely performed with local anaesthesia under US guidance. Increasing experience has shown that the percutaneous approach has certain advantages over retrograde stent placement, which may be summarized as follows:
- In most cases, local anaesthesia will be sufficient to place the tube under US guidance in acutely ill or septic patients, providing immediate urine drainage and culture to determine organism-specific antibiotic therapy.
- This approach may provide access for subsequent PNL in patients with a stone burden requiring PNL in the post-partum period and at the same time manipulation of the obstructed ureter. The potential risk of perforation and infection is avoided
- The percutaneous approach enables immediate confirmation and continuous supervision of drainage. Failure to drain is easily identified and appropriately managed.
- Moreover, subsequent percutaneous chemolytic irrigation of the renal collecting system might be useful for dissolution of uric acid, cystine, or struvite stones (17).

The disadvantages of external tubes are the inconvenience of dealing with a collection device, the risk for accidental dislodgement and bacterial colonization. Moreover, the insertion of a percutaneous nephrostomy catheter may be complicated by significant bleeding because of tract creation and dilatation.

12.3.2.2 Internal ureteral stent
Drainage of the obstructed renal collecting system can be accomplished by an internal ureteral stent inserted under local or general anaesthesia with transabdominal US guidance or limited fluoroscopy, or without any of these imaging procedures. Stent insertion is routinely performed by most urologists and the equipment should be readily available at most centres (18).

However, stent-related irritative lower urinary tract symptoms and rapid encrustation, which may be

attributed to hypercalciuria, hyperuricosuria or infection that occur during pregnancy, are among the well-known problems of this approach. Internal stents may also be associated with increased analgesic requirements and decreased overall quality of life.

Some investigators therefore recommend hydration, dietary calcium restriction and antibiotics as well as frequent stent replacement at intervals of 4-8 weeks. Infection and migration are other complications of internal stents and because of these difficulties, reservation of ureteral stent placement for the later stages (> 22 weeks) of pregnancy has been advocated.

The choice between these two alternative methods is based on the factors discussed above (21-23).

When conservative management fails and urinary diversion is desired, both nephrostomy tube placement and internal ureteral insertion are appropriate alternatives	**LE = 3** **GR = B**

12.3.2.3 Ureteroscopy
The use of flexible and thin ureteroscopes for diagnostic and therapeutic purposes in a less invasive and traumatic manner has led several urologists to consider this method as a first-line treatment for pregnant women who have failed conservative management. However, it is clear that ureteroscopic management during pregnancy should be planned and performed at an experienced urological centre under close obstetric and anaesthetic surveillance.

The procedure may require general anaesthesia and one must always be aware of the potential risk of ureteral perforation and sepsis. The intervention should be performed by an experienced urologist. The anatomical distortion of the bladder as well as the distal ureter, particularly during the third trimester, may make semi-rigid URS more difficult. Therefore, stone manipulation at or near term should be discouraged. Most distal-ureteral stones can be retrieved with a stone basket, but some may require fragmentation, which can be accomplished safely with a pulsed-dye laser, Ho:YAG laser or pneumatic lithotripsy (24,25).

The most important contraindications to URS during pregnancy are inexperience and inadequate endoscopic instruments, stones with a diameter exceeding 1 cm, multiple calculi, transplanted kidney and sepsis (because of the higher risk of complications).

Again, caution must be exercised when performing URS during pregnancy with a solitary kidney. Ureteroscopy in experienced hands can be an effective treatment alternative to removal of ureteral stones during pregnancy (LE = 1b; GR = B).

Due to the established risks of radiation exposure on the growing fetus, SWL and percutaneous nephrolithotripsy (PNL) are contraindicated in pregnancy	**LE = 4b** **GR = C**

12.4   Conclusions
Urolithiasis in pregnancy remains a diagnostic and therapeutic challenge. Although US is the method of choice for the practical and safe evaluation of a pregnant woman, a limited intravenous urography, isotope renography or MREU is useful for delineating the level and grade of obstruction in case of hydronephrosis.

Depending on the stage of the pregnancy, degree of the pain and the presence of certain complications, such as obstruction, urosepsis and renal functional deterioration, conservative management with bed rest, hydration and analgesia will result in spontaneous passage of the stone in two-thirds of patients. If conservative treatment fails, temporary urinary diversion with percutaneous nephrostomy or an internal stent may be appropriate.

However, developments in diagnostic technology, as well as in endoscopic instrumentation during the last 5 years, have made it possible to use high-quality imaging and small-calibre ureteroscopes. In this way, the endoscopic approach has become feasible and safe both for diagnostic and therapeutic purposes. However, this type of management should be performed only in centres with sufficient experience. SWL in pregnancy remains an absolute contraindication.

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13. MANAGEMENT OF STONE PROBLEMS IN CHILDREN

Besides a global increase in the rates of urolithiasis in developed countries, a shift has been noted in the age group experiencing the first stone episode (1-3). More than 1% of all urinary stones have been registered in patients under the age of 18 years. In developing countries, however, the situation differs. Due to malnutrition and racial factors, paediatric urolithiasis still is an endemic disease in certain parts of the world such as Turkey and the Far East, whereas other regions demonstrate similar rates as those observed in developed countries (4-7).

13.1   Investigations

Paediatric patients with urinary stones are considered to be a high-risk group for developing recurrent stones.

Therefore, investigations for stone diagnosis, as well as metabolic abnormalities, are crucial (8)	**LE = 2a** **GR = B**

The investigations may be divided into the following categories:
* Those related to the diagnosis of stones, including anatomic and functional information about the urinary tract ('imaging')
* Those related to metabolism.
    Infants and children may present with a wide range of uncharacteristic symptoms in the presence of urinary stones. All investigations start with an evaluation of the patient's personal and family history, including nutritional habits and fluid intake, physical investigation, and laboratory tests of blood and urine.

A urine culture is mandatory (8)	**LE = 2** **GR =A**

13.1.1 Imaging

When selecting diagnostic procedures to identify urolithiasis in paediatric patients, the investigator must consider the fact that the patients may be uncooperative, require anaesthesia for some modalities, or be sensitive to ionizing rays. Therefore, ultrasound (US) is of great significance in this setting. More than one imaging study or combinations of various procedures will be required in most cases (9). Besides US, several optional procedures such as plain films (KUB), intravenous urography (IVU), helical CT, magnetic resonance urography (MRU), or nuclear imaging may be used.

13.1.1.1 Ultrasound

Ultrasound is the most popular imaging study. Its advantages in paediatric patients are the absence of irradiation and anaesthesia.

Ultrasound evaluation should include the kidney, the filled bladder, and adjoining portions of the ureter (10)	**LE = 4** **GR = B**

In addition, colour-Doppler US showing **differences in the ureteric jet** (11) (LE = 4; GR = C) and **differences in the resistive index of the arciform arteries of both kidneys are indicative of the grade of obstruction** (12) (LE = 4; GR = C).

Thus, US is able to provide information about the presence, size and location of a stone, the grade of dilatation and obstruction. It is also able to indicate signs of abnormalities that facilitate the formation of stones. Ultrasound also is a part of the metaphylactic work-up.

Nevertheless **US fails to identify stones in more than 40% of paediatric patients** (13,14) (LE = 4) and provides no information about renal function.

13.1.1.2 Plain films (KUB)

In combination with US or MRU, KUB may serve as a useful aid to identify stones and their radiopacity as well as facilitate follow-up.

13.1.1.3. Intravenous urography (IVU)

Intravenous urography is an important diagnostic tool. With this procedure, it is possible to demonstrate nearly all stones in the collecting system and to provide anatomical and functional information. Post-interventional KUB may be easily compared with previous IVPs in cases of radiopaque stones. However, it requires the injection of contrast dye. The radiation dose for IVU is comparable to that used for a voiding cystourethrogram (dose range, 49.06 to 83.33 cGy/cm^2).

Recently developed CT protocols may further reduce the radiation exposure (18) (LE = 4; GR = C). However, the radiation dose and the extent of information about renal function must be considered when using non-enhanced helical CT.

Conventional imaging models are indispensable in some cases (15,16)	**LE = 4** **GR =C**

13.1.1.4 Helical computed tomogram (CT)

Non-enhanced helical CT is a well-established procedure for diagnosing urolithiasis in adults. It has the highest sensitivity and specificity among all diagnostic procedures.

In paediatric patients, only 5% of stones escape detection by non-enhanced helical CT (4,14,17)	**LE = 4**

Sedation or anaesthesia is rarely needed when a modern high-speed CT apparatus is used (10)	**LE = 4**

13.1.1.5 Magnetic resonance urography (MRU)

Magnetic resonance urography is unable to demonstrate a urinary stone. However, it may provide detailed information about the anatomy of the urinary collecting system, the location of an obstruction or stenosis in the ureter, and the morphology of renal parenchyma (19) (LE = 4).

13.1.1.6 Nuclear imaging

The DMSA scan (^{99m}Tc-dimercaptosuccinyl acid) provides information about cortical abnormalities such as scarring, but is of no help in the primary diagnosis of urolithiasis. A diuretic renogram with injection of a radiotracer (MAG$_3$ or DPTA) and furosemide are able to demonstrate renal function, identify obstruction in the kidney after injection of furosemide, as well as indicate the anatomical level of the obstruction (10) (LE = 4; GR = C or B).

13.1.2   Metaphylactic investigations

Paediatric urinary stone patients are deemed a high-risk group for developing recurrent urinary stones and therefore require specific metaphylaxis for effective stone prevention. The risk may arise from anatomical or functional disorders of the urinary collecting system, or metabolic failures including genetic disorders.

The most common non-metabolic disorders are vesico-ureteral reflux, ureteropelvic junction obstruction, a neurogenic bladder, or other voiding difficulties (9)	**LE = 4**

If suspected, suitable investigations must be performed (see appropriate chapter).

Metabolic investigations are based on a proper stone analysis. According to the current standard, infrared spectroscopy or X-ray diffraction are mandatory for adult patients. A wet chemistry analysis is insufficient (20)	**LE = 2b** **GR = B**

Based on the composition of stones (see also the appropriate Chapter 16 in this document).

Additional serum chemistry and 24-hour urine collections may be required (8)	**LE = 2** **GR = A**

13.2   Stone removal

In principle, the same treatment modalities are used for adults and children. However, the specific circumstances of paediatric therapy must be taken into account when treating children.

Spontaneous passage of a stone is more likely to occur in children than in adults (21)	**LE = 4** **GR = C**

However, there is no evidence to demonstrate the safety and efficacy of nifedipine or alpha-blockers in paediatric patients, both being very common in adults.

For invasive stone removal in paediatric patients, both ESWL and endourologic procedures are effective alternatives. Several factors must be considered when selecting the therapeutic procedure:
- Compared to adults, children pass fragments more rapidly after ESWL.
- For endourological procedures, the smaller organ size must be considered when selecting instruments for PNL or URS.
- Use of US for localization during ESWL in order to eliminate radiation exposure.
- Anticipated stone composition (cystine stones are more resistant to ESWL).
- Co-morbidity involving the use of concomitant treatment.
- The need for general anaesthesia for ESWL (depending on the patient's age and the lithotripter used).

13.2.1   Endourological procedures

The improvement of intracorporeal lithotripsy devices and the development of smaller instruments facilitate both PNL and URS in children. For PNL, nephroscopes that are sized 15F or less are available (22,23) (LE = 4; GR = C). Smaller 'needle ureteroscopes' and flexible scopes are also available.

During URS, dilatation of the ureteral orifice is rarely needed (24)	**LE = 4** **GR = C**

As in adults (see Chapters 7 and 9):

The holmium:yttrium aluminium garnet (Ho:YAG) laser is the preferred device for intracorporeal lithotripsy (25)	**LE = 4** **GR = C**

For PNL or URS with larger instruments, US or pneumatic lithotripsy are appropriate alternatives (26)	LE = 3 GR = C

13.2.2 ESWL

Considering the use of SWL in paediatric population (following the first publication by Newman et al. in 1986), the number of reports has increased tremendously emphasizing the efficiency and safety of ESWL in paediatric urolithiasis. With its minimal invasive nature and, of course, satisfactory stone-free rates, ESWL has been found to render the patients stone-free over a short period with reasonable number of shock waves and limited auxiliary procedures. Again, despite the increasing application of PNL, the development of smaller-diameter flexible ureteroscopes and ancillary instruments, ESWL is still the least-invasive alternative (23,27,29).

It should be kept in mind, however, that the higher incidence of metabolic and anatomical abnormalities (when compared with the adult population) is a major concern in stone formation and may influence the management options and the ultimate effectiveness of the selected treatment. Despite a successful disintegration, residual fragments after ESWL should be followed closely with regular examinations and it has clearly been shown that residuals may predispose to recurrent urolithiasis (28,29).

The indications for ESWL are similar to those in adults. Children with renal pelvic stones or caliceal stones with a diameter up to 20 mm (~ 300mm^2) are ideal cases for this form of stone removal. The success rates tend to decrease as the stone burden increases	LE = 1a GR = A

Stone-free rates ranging between 67% and 93% in short-term and between 57% and 92% in long-term follow-up studies have been reported in the literature. It has also been shown that more effective disintegration of even larger stones, together with swifter and uncomplicated discharge of larger fragments, can be achieved with ESWL in children. Stones located in calices, as well as in abnormal kidneys and larger stones, have been found harder to be disintegrated and also cleared. Additionally, the likelihood of urinary obstruction is higher in such cases and children should be followed closely for the prolonged risk of urinary tract obstruction. Depending on the stone-related factors, the re-treatment rate ranges from 13.9% to 53.9% and ancillary procedures and/or additional interventions ranged from 7% to 33% (27,28,30).

A general anaesthetic is demanded in 30% to 100% of children treated by ESWL. However, this demand together with the method of anaesthesia varies strongly depending on the age of the child, and on the type of lithotripter in use. General anaesthesia is generally performed except possibly for older children. However, sedation is usually needed to relieve the discomfort caused by the procedure (23,28).

On the other hand, despite its effective and minimal invasive character, theoretical concerns have been raised regarding the safety and bioeffects that ESWL might have on the immature, growing kidney and surrounding organs. However, no irreversible functional and morphological side effects of high-energy shock-wave have been demonstrated during both short- and long-term follow-up. In addition, when the potential deterioration of renal function is taken into account (although it is transient), restriction of the number of shock waves and the energy used during each treatment session will help to protect the kidneys (31,32).

In contrast to the effective results of ESWL in renal stones, ureteral stones with a diameter of < 5 mm are likely to pass spontaneously in up to 98% of cases. Intervention will be required for large-sized, as well as impacted, stones. Although ESWL is the first treatment modality for most stones located in the upper urinary tract in children, the success rates decrease as the stone passes to the more distal parts of the ureter. The overall stone-free rates have ranged from 80% to 97% in different series and the success rates for proximal and distal ureteral stones ranged from 75% to 100%, respectively (23,27,33,34).

Despite the definitive removal of ureteral stones by endoscopic procedures, acceptable success rates by ESWL had made it a favourable first-line treatment modality for most proximal ureteral stones. Currently, ESWL is likely to be unsuccessful in larger stones (largest diameter > 10 mm) as well as impacted stones, calcium oxalate monohydrate and cystine stones, stones in children with unfavourable anatomy and in whom localization difficulties exist. Compared to adults, children pass stone fragments easily and the need for a stent is rare. If the stone burden is so large, that a ureteral stent is required, alternative procedures should be considered. Although internal stents are seldom needed following ESWL-treatment of upper tract stones, ureteral pre-stenting appeared to have decreased the stone-free rate after the initial treatment and re-treatments between 12% and 14% were recorded (23,35,36).

13.2.3 Conclusions

Among the available treatment strategies in paediatric urinary calculi, ESWL is the method of choice for smaller stones (diameters < 20 mm, surface area ~ < 300 mm^2). The successful stone-free rates emphasize the efficacy

of this treatment modality when combined with judicious use of the auxiliary procedures. Accordingly ESWL is a safe and highly effective treatment alternative for the management of appropriate stones in children. However, satisfactory outcomes with reasonable low complications can only be achieved with adequate experience. Particular attention should be paid to residual fragments, especially in children with predisposing metabolic as well as anatomical disorders.

13.2.4 Open or laparoscopic surgery
The rate of open procedures in stone patients has dropped significantly in all age groups. Open surgery, if required, may be replaced by laparoscopic procedures. Indications for surgery include failure of primary therapy for stone removal (37), abnormal position of the kidney (38), or an additional target of therapy apart from stone removal, such as the treatment of stones in a primary obstructive megaureter (39) (LE = 4; GR = C).

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14. RESIDUAL FRAGMENTS

Residual fragments are commonly seen after ESWL, most frequently presenting in the lower calyx following the disintegration of large stones. However, residual fragments may occur following ESWL for all sizes of stones.

Different imaging techniques have variable degrees of sensitivity. Thus, CT or tomographic examinations both demonstrate small fragments better than a standard film (KUB). A CT scan also has the capacity to demonstrate uric acid concrements, which are otherwise radiolucent. Reports on residual fragments therefore vary from one institution to another, depending on which imaging method is used. However, there is no data in the literature demonstrating the clinical value of being able to detect small tiny concretions visible only on CT scan. Moreover, CT examinations still cannot be carried out everywhere.

It is our recommendation that the results of a stone-removing procedure are based on the findings of a good-quality KUB and that CT examination is only necessary for uric acid stones.

Stone residuals with a largest diameter of 4 mm should be termed residual fragments. Residuals with a diameter of 5 mm or more should be termed residual stones.

The clinical problem of asymptomatic stone residuals in the kidney is related to the risk of developing new stones from such nidi.

Patients with residual fragments or stones should be regularly followed up to monitor the course of their disease	**LE = 4** **GR = C**

Identification of biochemical risk factors and appropriate stone prevention is particularly indicated in patients with residual fragments or stones (35)	**LE = 1b** **GR = A**

In symptomatic patients, it is important to rule out obstruction and to treat this problem if present. In other cases, necessary therapeutic steps need to be taken to eliminate symptoms. In asymptomatic patients where the stone is unlikely to pass, treatment should be applied according to the relevant stone situation.

For well-disintegrated stone material residing in the lower calix, it might be worthwhile considering inversion therapy during high diuresis and mechanical percussion (38)	**LE = 1a** **GR = A**

The risk of recurrence in patients with residual fragments after treatment of infection stones is well recognized. In a 2.2 year follow-up of 53 patients, 78% of patients with stone fragments 3 months after treatment experienced stone progression. The corresponding stone-free rate was 20% (1).

The term 'clinically insignificant residual fragments' (CIRF) was introduced for calcium stone residual fragments. The role of CIRF has been a matter of debate and concern for some time (2-13). Most studies on the long-term course of the disease in patients with residual fragments are restricted to periods between 1 and 6 years. The longest follow-up period was reported by Yu et al. (14). After 6.3 years, stone growth was observed in 26% of patients and recurrent stone formation in 15%. During a follow-up of between 7 and 96 months, with an average follow-up of 3.4 years, the residual fragments increased in size in 37% of patients. A new stone-removing procedure was undertaken in 22% of patients (15). In data on 104 patients with residual fragments, 40% showed decreased disease or remained stable, while 5% progressed during a mean follow-up of 1.2 years (16), with further intervention necessary in 9.3% of patients by 2 years of follow-up. In a follow-up of patients with < 4 mm residual fragments during a 4-year period, there was obvious increase in size in 37% and a need for retreatment in 12% (17).

New stone formation is another aspect to consider in ESWL-treated patients because of the assumption that the fraction of stone-free patients is overestimated. Stone recurrences were thus reported to be 8.4% after 1 year, 6.2% after 1.6 years, 9.7% after 3.3 years, 20% after 3.5 years and 7% after 3.6 years (18). In a Japanese report, the recurrence rates were 6.7%, 28.0% and 41.8% after 1, 3 and 5 years, respectively (19). For a group of Swedish patients with calcium stones, a 20% risk of recurrent stone formation was recorded during the first 4 years after ESWL. Twenty-five per cent of patients with infection stones had formed new stones after 2 years. The greatest risk was seen in patients with stones containing a high content of calcium phosphate (20). In a neural network analysis, an increased stone size was noted in 48% of patients with residual fragments followed up for 3.5 years, but none of the identified risk factors for stone growth was found to be individually predictive for the continuing stone formation (37).

For a kidney with stones or fragments in the lower caliceal system and with no functioning parenchyma in that part, lower pole resection is an alternative treatment to be considered (21). For stones in the upper and middle calyces, URS with contact disintegration is another treatment option. Percutaneous chemolysis is an alternative treatment for stone fragments composed of magnesium ammonium phosphate, carbonate apatite, uric acid, cystine and brushite. Internal ureteral stenting before ESWL is recommended for

stones with a largest diameter of more than 20 mm (~300 mm^2).

This step is recommended to avoid problems with an accumulation of stones obstructing the ureter, known as a Steinstrasse (see Chapter 15) (22-34). The risk of developing a Steinstrasse is particularly pronounced for stones located in the renal pelvis (36). Table 25 summarizes the recommendations for the treatment of residual fragments.

Table 25: Recommendations for the treatment of residual fragments

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

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15.   STEINSTRASSE

A Steinstrasse or fragment column in the ureter is an accumulation of gravel that does not pass within a reasonable period of time and that interferes with urine passage (1). The frequency of this complication has decreased with the liberal insertion of double-J stents before ESWL of large renal stones.

In all patients with signs of infection, it is necessary to give antibiotics and to provide adequate drainage as soon as possible.

Insertion of a percutaneous nephrostomy catheter usually results in passage of the fragments (2). For distally located accumulations of fragments, URS might be useful to remove the leading stone fragment by contact disintegration.

Treatment recommendations are summarized in Table 26.

Table 26: Recommendations for treatment of Steinstrasse

Position of stone	Unobstructed	Obstructed and/or symptomatic	LE	GR
Proximal ureter	1. ESWL 2. URS	1. PN 1. Stent 1. URS 1. ESWL	4	C
Mid-ureter	1. ESWL 2. URS	1. PN 1. Stent 1. URS 1. ESWL	4	C
Distal ureter	1. ESWL 1. URS	1. PN 1. Stent 1. URS 1. ESWL	4	C
LE = level of evidence; GR = grade of recommendation; ESWL = extracorporeal shock-wave lithotripsy; PN = percutaneous nephrostomy catheter; URS = ureteroscopy.				

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16. INTERNAL STENTING – WHEN AND WHY

16.1 Introduction

Stents were introduced into clinical urological practice nearly three decades ago (1,2). Made of flexible, synthetic polymers and constructed and designed to be retained in situ, the internal ureteral stent has become an expedient device in the urologist's armamentarium to assist and maintain drainage of the upper urinary tract in the face of obstruction or anticipated obstruction (3).

As the renal calculus is the commonest cause of upper urinary tract obstruction, the ureteric stent has become almost a *sine qua non* in the surgical management of upper tract renal and ureteral calculi in conjunction with extra and intra-corporeal stone removal/disintegration. Whereas stent insertion for the immediate relief of significant and serious obstruction due to a calculus is unquestionable, and its placement in the ureter following ureteroscopic procedures was considered to be mandatory, a revised approach in some circumstances is now being considered on the basis of later experience.

No stent is ideal and it is the responsibility of the surgeon to be familiar with indications for usage, selection, modes of insertion and potential complications. Even though retrograde insertion of the stent is the usual method, a percutaneous antegrade approach through the loin under X-ray or US control may, in some circumstances, be undertaken. Although both techniques are within the expertize of a competent, trained urological surgeon, the percutaneous antegrade method is often and most commonly performed by radiologists.

16.2 The use of stents in the management of stones in the kidney

Extracorporeal shock-wave lithotripsy and PNL is the treatment of choice for renal calculi (see Chapter 7 for principles for active removal). Most simple renal calculi (80-85%) can be treated with SWL, while PNL is the treatment of choice for complex renal calculi (4,5). With stones > 20 mm in diameter, the placement of a stent prior to ESWL was recommended to obviate the possible obstruction by a Steinstrasse. It was reported that the peri-operative placement of double-J stents can significantly reduce post ESWL morbidity and does not impede passage of the disintegrated stone fragments (6). In any case, this becomes almost obligatory when treating stones in a solitary kidney, where the avoidance of risk of obstruction by even small fragments has greater relevance.

There is little or no reason to leave a stent in situ after PNL since all disintegrated stone material is captured and removed at operation and the kidney drained by a nephrostomy tube. However, with bimodal

therapy for staghorn stones, where PNL is followed by ESWL for residual fragments, internalized stenting prevents obstruction if stone fragments fall into the ureter prior to ESWL and prevents formation of an obstructing Steinstrasse thereafter.

Technological advances with flexible, miniaturized ureteroscopes enables treating simple renal calculi with these instruments, with similar stone-free rates to shock-wave lithotripsy and without the morbidity that accompanies PNL. The placement of a stent may well be indicated in this situation and is a matter of clinical judgement and individual circumstances.

16.3 The use of stents in the ureter

The size, character and location of stones in the ureter determine management. The criteria that apply to the spontaneous passage of a stone are well documented and form the basis of expectant treatment. Likewise, ureteral obstruction by a stone, unlikely to pass, calls for intervention that will involve the use of a means to remove the stone and relieve obstruction. There are two competing approaches to the interventional management of stones in the ureter: ESWL and/or ureteroscopic (URS) stone removal/disintegration. The relative advantages, benefits and results of the two are discussed elsewhere. The indications for the insertion of a stent together with SWL or URS and the relief of obstruction need to be defined (7).

16.3.1 Indications for stenting for urgent relief of obstruction
The indications for stenting for urgent relief of obstruction are:
- Presence of infection with urinary tract obstruction
- Urosepsis
- Intractable pain or vomiting or both
- Obstruction in a solitary or transplanted kidney
- Bilateral obstructing stones
- Relief of ureteral calculus obstruction in pregnancy, pending definitive therapy in the post-partum period.

A randomized controlled trial showed that ureteral catheters, ureteral stents and percutaneous nephrostomy tubes were equally effective for decompressing the urinary tract (8; Chapter 9).

For decompression of the renal collecting system ureteral catheters, stents and percutaneous nephrostomy catheters are apparently equally effective	**LE = 1b** **GR = A**

16.4 Stents in conjunction with ESWL therapy for ureteral stones

The assumption that a stent in the ureter contributed to more efficient fragmentation of the stone with ESWL led to the routine pre-treatment placement of an internal stent. Several studies, including randomized controlled trials, in large numbers of patients have now shown that there was no difference in stone-free rates between stented and non-stented patients (9). In fact, stenting was seen to be significantly associated with a decreased stone-free rate (10).

Indeed, stenting has several disadvantages. It makes a non-invasive procedure into an invasive one, causes undesirable side effects, and increases the cost of treatment. The recommendation, therefore, is that stent insertion prior to SWL for obstructing ureteral stones 2 cm or less provides no advantage and is unnecessary.

16.5 Stents in conjunction with ureteroscopy (URS)

The routine placement of a stent was once considered to be an integral adjunct to URS. It was done as a precautionary measure to prevent:
- Obstruction
- Renal pain due to oedema from balloon dilatation
- Trauma of instrumentation
- Stone manipulation and disintegration.

Several prospective, randomized, controlled trials comparing non-stented versus stented ureteroscopic lithotripsy have shown significantly more morbidity in respect of haematuria, flank and abdominal pain, dysuria and hospital stay in the stented patients (11-13). In a non-randomized study, up to 80% of participants experienced urinary symptoms and pain associated with indwelling ureteral stents, which interfered with daily activites and resulted in a reduced quality of life (14). A recent study has also reported that an indwelling ureteral stent can impair the quality of sexual life in both male and female subjects (15). In a meta-analysis of nine randomized controlled trials of stenting versus non-stenting after URS in 831 patients, Nabi et al. (16) reported that the incidence of irritative lower urinary tract symptoms was significantly higher in the stented patients, while there were no differences in stone-free rates, urinary tract infection rates, requirements

for analgesia or long-term ureteric stricture formation.

The recommendation, therefore, is that ureteric stents are not necessary following uncomplicated URS for stones.

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17.   RECURRENCE PREVENTIVE TREATMENT

17.1   Recurrence preventive treatment of patients with calcium stone disease

Table 27 summarizes various therapeutic tools, which aim to reduce the risk of recurrent calcium stone formation. The levels of evidence (LE) and the grades of recommendation (GR) refer to the effects on stone formation reported in the literature. The description of biochemical effects enables the most appropriate treatment to be selected in patients with known abnormalities in urine composition.

Table 27: Dietary and pharmacological treatment regimens for prevention of recurrent calcium stone formation

Treatment	Biochemical effects	References	LE	GR
Increased fluid intake	Dilution of urine	6,7	1b	A
Reduced intake of oxalate	Reduced excretion of oxalate			
Reduced intake of animal protein	Reduced excretion of: • Calcium • Oxalate • Urate Increased excretion of: • Citrate • Increased pH	28	1b	A
Reduced intake of sodium	Reduced excretion of calcium Increased excretion of citrate	28	1b	A
Increased intake of fibres		12,13	2b	B
Increased intake of vegetables, provided there is a simultaneous adequate intake of calcium		36	3	B
Avoid excessive intake of vitamin C	Reduced urinary oxalate	18	2b	B
Thiazide	Reduced excretion of calcium	52-63, 67	1a	A
Potassium citrate	Increased excretion of citrate Inreased urine pH Increased inhibition of crystal growth and crystal agglomeration.	70,71	1b	A
Potassium magnesium citrate	Inreased urine pH Increased excretion of citrate Increased inhibition of crystal growth and crystal agglomeration Reduced supersaturation with	73	1b	A

	CaOx as a result of increased urinary magnesium Increased inhibition of CaP crystal growth and aggregation			
Allopurinol (in patients with hyperuricuric calcium oxalate stone formation)	Reduces urinary urate Decreased risk of calcium oxalate crystal formation	98	1b	A
Pyridoxine	In patients with primary hyperoxaluria: reduced excretion of oxalate	103	3	C

Abnormal crystalluria is a common finding in patients with recurrent calcium stone disease. Compared to non-stone formers, stone-forming patients have been shown to have more, larger, and aggregated crystals (1). Moreover, crystalluria found in early morning urine samples seems to predict the risk of recurrent stone formation (2). The abnormal crystalluria can cause:

- A small urine volume
- Increased excretion of urine variables important for increasing the ion-activity products of calcium oxalate/calcium phosphate, or,
- Reduced activity of inhibitors of crystal growth and crystal agglomeration.

These factors have been extensively reported in a large number of articles and the issue has been previously comprehensively summarized (3-5).

It is axiomatic that without sufficiently supersaturated urine there can be no crystal formation and accordingly no stone formation. It therefore seems essential to make the relevant corrections of urine composition in order to counteract critical supersaturation and pathological crystallization. The treatment recommendations, which are based on assumed or demonstrated abnormalities, should be adapted to the severity of the disease to avoid overtreatment and obtain reasonable patient compliance.

17.1.1 Drinking recommendations
An inverse relationship between high fluid intake and stone formation has been demonstrated (6,7). The general recommendation for calcium stone formers is to maintain a high urine flow by a generous intake of fluids. The aim should be to obtain a 24-hour urine volume of at least 2 L (LE 1b; GR A).

Although most beverages can be drunk to increase fluid intake and help prevent stone formation, grapefruit juice has been shown to be associated with an increased risk of stone formation (8) (LE 3; GR C). The presence of citrate appears to be the important determinant of the effect of fruit juices. In the presence of hydrogen ions, the net result is neutralization. However, with potassium, pH and citrate are increased. For this reason, orange juice is beneficial but not cranberry juice (9,10). Although grapefruit juice has a high potassium content, its effect on calcium oxalate supersaturation is counteracted by a high supply of oxalate (11).

17.1.2 Dietary recommendations
Diet should be of a 'common sense' type, i.e. a mixed balanced diet with contributions from all food groups, but without excesses of any kind (12).

Fruits, vegetables and fibres: Fruit and vegetable intake should be encouraged because of the beneficial effects of fibre (13). The alkaline content of a vegetarian diet also gives rise to a desirable increase in urinary pH (12).

Oxalate: An excessive intake of oxalate-rich products, should be limited or avoided to prevent an oxalate load. This includes fruit and vegetable rich in oxalate such as wheat bran, This is particularly important in patients in whom an high oxalate excretion has been demonstrated. The following products have a high content of oxalate (14):

- Rhubarb, 530 mg oxalate/100 g
- Spinach, 570 mg oxalate/100 g
- Cocoa, 625 mg oxalate/100 g
- Tea leaves, 375-1450 mg oxalate/100 g
- Nuts, 200-600 mg oxalate/100 g.

Vitamin C is a precursor of oxalate, but its role as a risk factor in calcium oxalate stone formation remains controversial. Some studies have shown that a daily intake of up to 4 g might be allowed without risk (15-17). However, a recent study demonstrated a significantly increased risk in stone formation for men taking 1 g/day or more of vitamin C compared to men taking less than 90 mg (18). It therefore seems justified to advise calcium oxalate stone formers to avoid excessive intake of vitamin C. The allowed amount is not obvious but a

daily intake of more than 500 mg (11) to 1 g (18) should probably be avoided.

Animal protein should not be ingested in excessive amounts (19-25), and it is recommended that animal protein intake is limited to to 0,8-1 g/kg body weight. An excessive consumption of animal protein gives rise to several unfavourable effects on stone formation, such as hypocitraturia, low pH, hyperoxaluria and hyperuricosuria. Moreover, an increased resorption of bone increases urinary calcium (26).

Calcium intake should not be restricted unless there are very strong reasons because of the inverse relationship between dietary calcium and calcium stone formation (27). The minimum daily requirement for calcium is 800 mg and the general recommendation is 1,000 mg/day.

Calcium supplements are not recommended except in cases of enteric hyperoxaluria, when additional calcium should be ingested with meals to bind intestinal oxalate.

Sodium: A high consumption of sodium brings about several changes in urine composition. Calcium excretion is increased by reduced tubular reabsorption. Urinary citrate is reduced due to loss of bicarbonate. The risk of forming sodium urate crystals is increased and the effect of thiazide in reducing urinary calcium is counteracted by a high sodium intake. The combined restriction of sodium and animal protein in a randomized study resulted in a reduced rate of calcium stone formation (28). The daily sodium intake should not exceed 3 g.

Urate: The intake of food particularly rich in urate should be restricted in patients with hyperuricosuric calcium oxalate stone disease (29-34), as well as in patients with uric acid stone disease. The intake of urate should not exceed 500 mg/day. Examples of food rich in urate (21) include:
- Calf thymus, 900 mg urate/100 g
- Liver, 260-360 mg urate/100 g
- Kidneys, 210-255 mg urate/100 g
- Poultry skin, 300 mg urate/100 g
- Herring with skin, sardines, anchovies, sprats, 260-500 mg urate/100 g.

In patients with an expected low risk of recurrent stone formation (S or Rm), advice on fluid intake and diet may be sufficient to prevent stone recurrence. The positive effect of such a regimen has been referred to as the 'stone clinic effect'.

17.1.3 Pharmacological treatment

The general opinion is that any treatment aiming at correction of abnormalities in urine composition and elimination of risk factors of pathological crystallization should always start by giving patients advice regarding dietary and drinking habits. In case pharmacological treatment is considered (following prior unsuccessful therapeutic approaches) adequate patient education regarding drinking and dietary recommendations is even more imminent since treatment outcome will largely depend on patient compliance. In this respect, it is essential to choose the most appropriate form of treatment. The ideal pharmacological agent should halt the formation of calcium stones, be free of side effects and be easy to administer. These aspects are all of utmost importance in order to achieve a reasonably good compliance.

The recommendations given in this guideline document are based on what has been published in this field. An extensive review and interpretation of literature results were carried out by the European Urolithiasis Research group at a Consensus Conference in Mannheim, Germany in 1996, and have subsequently been referred to in several publications (37-41). The ensuing recommendations are to a large extent still highly relevant.

It seems logical and theoretically most attractive to administer pharmacological agents in a selective way with the aim of correcting one or several biochemical abnormalities. It needs to be emphasized, however, that there is no absolute consensus on such a view (42,43,11).

The pharmacological agents most commonly used for patients with recurrent calcium stone formation are thiazides, potassium citrate, orthophosphate, magnesium and allopurinol. The scientific basis of these forms of treatment is briefly summarized below.

17.1.3.1 Thiazides and thiazide-like agents

Hydrochlorothiazide, bendroflumethiazide, trichlorothiazide and the non-thiazide indapamide have been used for recurrence prevention in patients with calcium stone disease. The purpose of thiazide treatment is to reduce the excretion of calcium in hypercalciuric patients, but it has been stated that calcium reduction is also seen in patients with normocalciuria (20). The hypocalciuric action of thiazides is thought to be mediated by increased reabsorption of calcium in the proximal as well as in the distal parts of the nephron (20,44). It has, moreover, been suggested that thiazides might decrease the excretion of oxalate, possibly by a reduced intestinal absorption of calcium (45-47), but recent studies have shown that such an effect is unlikely to occur. However,

a thiazide-induced reduction in urinary oxalate is not a consistent finding in the clinical studies.

There is more than 35 years of clinical experience with thiazides as a method for stone prevention. Following the initial report by Yendt in 1970 (48), a large number of reports have been published, most of which support a reduced rate of recurrent stone formation.

The clinical effect of thiazide treatment has accordingly been evaluated in 10 randomized studies, four of which included placebo-treated patients. Although two short-term placebo-controlled studies (49,50) failed to confirm a positive effect of thiazides, a significantly reduced recurrence rate was recorded in three 3-year follow-up studies (51-55). A similar result was also obtained in three groups of patients treated with thiazides between 2.3 and 4.3 years, in comparison with conservatively treated patients (56,57). A significantly reduced rate of stone formation was also noted when a thiazide was given intermittently to recurrent stoneformers (58).

A reduced rate of recurrence was also observed in several other studies which compared treated patients with those not given any pharmacological agent (58-62). In some other studies, the results were less convincing (63,64).

The convincing positive effect of thiazide treatment was further supported by a meta-analysis based on randomized trials. This analysis showed significantly better results with active treatment than with placebo or no treatment ($p < 0.02$) (65).

The major drawback of thiazide treatment is the occurrence of side effects. The unmasking of normocalcaemic hyperparathyroidism, development of diabetes and gout, as well as erectile dysfunction, contribute to a limited tolerance and a high drop-out rate. Compliance is usually in the range of only 50-70%.

Whether or not thiazide treatment should be reserved only for patients with hypercalciuria, or used also in patients without this abnormality, cannot be definitely concluded from the various studies. Suffice it to mention that of the randomized studies, three studies selected hypercalciuric patients (55-57) and all three showed a significantly positive effect of thiazides.

In the other seven randomized trials, in which no selection was made, a significant effect was reported in five. Due to the frequent occurrence of hypercalciuria also in an unselected group of stone formers, there is no strong scientific basis for a recommendation in this regard. It is our opinion, however, that the major indication for choosing a thiazide or a thiazide-like agent should be hypercalciuria. In the absence of high calcium excretion, other forms of treatment may be better first-choice alternatives. As in all situations when pharmacological treatment is considered, a judgment must be made between the benefits and risks of the medication. According to these considerations, treatment with thiazide is usually reserved for patients with a high excretion of calcium (i.e. more than 6.5-7 mmol/24 hours or more than 4.5-5 mmol/16 hours).

Hydrochlorothiazide is usually administered at a dosage of 25-50 mg once or twice daily. The thiazide-induced loss of potassium should be substituted by giving either potassium citrate 3.5-7 mmol twice daily or another potassium salt. It has been shown, however, that potassium citrate was superior to potassium chloride in this regard (66). Hypocitraturia associated with hypokalaemia is thought to explain therapeutic failures in thiazide-treated patients.

17.1.3.2 Alkaline citrate

Treatment with alkaline citrate is commonly used as a method to increase urinary citrate in patients with hypocitraturia. A low citrate excretion is a well-recognized and common finding in patients with calcium stone disease. The role of citrate is important because of its complex formation with calcium. This chelation reduces the ion-activity products of both calcium oxalate and calcium phosphate. Moreover, citrate is an inhibitor of growth and aggregation/agglomeration of these crystals (67). Administration of an alkaline salt brings about an increased pH and an increased excretion of citrate. There are also reports of favourable clearance of residual fragments during treatment with alkaline citrate (see below).

Although the general principle is to give citrate preparations, it is the alkalinization of the tubular cells that is the most important factor that results in an increased citrate excretion, with only a small fraction of the administered citrate being excreted in urine.

The alkalinizing agents used to prevent recurrent calcium stone formation are sodium potassium citrate, potassium citrate, sodium citrate, potassium magnesium citrate, potassium bicarbonate and sodium bicarbonate.

Alkaline citrate has been used in four randomized studies. Potassium citrate was used in two studies (68,69), sodium potassium in one study (70) and sodium magnesium citrate in another study (71). In the two studies of potassium citrate, a significantly reduced recurrence rate was recorded. A favourable effect was also reported with potassium magnesium citrate, whereas no effect was noted with sodium potassium citrate compared with an untreated group.

Other non-randomized studies with alkaline citrate have shown a variable outcome. However, the general impression is that potassium citrate (68,69,72-77) has a greater potential for preventing recurrence than sodium potassium citrate (39,70,78,79). This observation is also supported by the different effects of potassium citrate and sodium citrate on urine composition (80).

Although potassium magnesium citrate appears efficient in prevention of recurrent stone formation, this agent is not yet generally available. Further studies are necessary to show whether this preparation is superior to potassium citrate.

Whether or not alkaline citrate preparations should be reserved for patients with hypocitraturia or used in a non-selective way has not been appropriately addressed in any study. An attempt to compare literature data has suggested a trend towards selective treatment (81). In a meta-analysis of randomized trials, it was not possible to adequately analyse the therapeutic outcome (65).
The usefulness of alkaline citrate as a way of increasing stone clearance after SWL has been studied by several groups. It was accordingly shown that sodium potassium citrate (82), as well as potassium citrate (77,83), increased the clearance of stone fragments. According to preliminary and unpublished data from a European multicentre investigation, this effect has not been confirmed.

The frequency of side effects is fairly high and compliance with alkaline citrate administration was shown to be no better than approximately 50%.

Because of the many effects on calcium oxalate and calcium phosphate crystallization and stone formation, treatment with alkaline citrate, nevertheless, can be recommended as a treatment for preventing recurrent stones. The recommended agent is potassium citrate. Although it is likely that this form of treatment is most beneficial for patients with a low citrate excretion, so far there is no solid evidence in the literature to support this assumption and further studies are necessary. The risk of forming calcium phosphate stones as a result of the increased pH is theoretical, but there are only occasional reports of such an outcome.

17.1.3.3 Orthophosphate
The theoretical rationale for giving orthophosphate to patients with recurrent calcium oxalate stone formation is to reduce the excretion of calcium and increase the excretion of pyrophosphate. Pyrophosphate is an inhibitor of both calcium oxalate and calcium phosphate crystal growth. The effect on urinary calcium is assumed to be mediated by formation of 1,25 (OH)2-vitamin D with an associated decreased absorption of calcium and reduced bone resorption. Administration of orthophosphate (neutral) has been reported to also increase urinary citrate.

There are only a few studies in the literature that deal with the effect of orthophosphate on stone formation. In a randomized, placebo-controlled study on potassium *acid* phosphate given during a period of 3 years, stone formation increased in the orthophosphate-treated group (84).

The rate of stone formation during 3 years of treatment with phosphate was also studied in two randomized studies (52,53). The number of patients in each of these studies was small and there were no statistically significant differences between treated and untreated patients. In some, less well-controlled, studies (85,86), it was also not possible to confirm a reliable effect of phosphate treatment. A reduced rate of stone formation was, however, noted by others (87,88). In reviews of the literature results, there is a lack of scientific evidence that phosphate is effective in preventing calcium stone formation (65,89).

Although patient compliance with treatment is reported as good, side effects such as diarrhoea, abdominal cramps, nausea and vomiting are common. Moreover, a possible effect on parathyroid hormone must be considered. It is possible that the pattern of side effects is favourably affected by slow-release potassium phosphate (90). The effect of phosphate administration on calcium phosphate stone formation has not been elucidated.

In conclusion, there is only very weak evidence that orthophosphate significantly reduces calcium oxalate stone formation. Although this form of treatment may be a possible option in patients with absorptive hypercalciuria, so far there is insufficient evidence to recommend its use.

17.1.3.4 Magnesium
An increased excretion of magnesium might reduce the ion-activity product of calcium oxalate and inhibit the growth of calcium phosphate crystals. There are also observations of an increased excretion of citrate following administration of magnesium (91). Magnesium is also considered important for the transformation between various calcium phosphate crystal phases. A high urinary concentration of magnesium is thus thought to decrease the risk of brushite formation.

Magnesium oxide, magnesium hydroxide, potassium magnesium citrate and magnesium aspartate have been used. The effect of potassium magnesium citrate is discussed above regarding alkaline citrate.

There are two randomized studies on the clinical effects of magnesium, one in which treatment with magnesium hydroxide was compared with a placebo control group (92) and one with magnesium oxide and untreated controls (52). None of them showed a statistically significant effect on stone formation despite follow-up periods of 4 and 3 years, respectively.

The positive effects of magnesium administration reported previously (93,94) have not been confirmed by recent controlled studies (65,89). Thus, there is insufficient evidence to recommend magnesium as monotherapy in calcium stone prevention.

17.1.3.5 Allopurinol
Treatment with allopurinol to counteract the formation of calcium oxalate stones was introduced following demonstration of a relationship between hyperuricosuria and calcium oxalate stone formation (95). The effect of allopurinol on calcium oxalate stone formation may be mediated through:
•   Reduced salting-out effect
•   Decreased risk of uric acid or urate crystals as promoters of calcium oxalate precipitation
•   Complex formation between colloidal urate and macromolecular inhibitors, and/or
•   Reduced excretion of oxalate.
It should also be mentioned that allopurinol may influence crystallization by its antioxidative properties.

Allopurinol has been used clinically to treat patients both with, and without, hyperuricosuria. In a placebo-controlled randomized study of allopurinol-treated, hyperuricosuric, calcium-oxalate stone formers, 75% of patients given allopurinol were free of recurrent stone formation compared with 45% in the placebo group (96). This effect was statistically significant. Three other randomized studies compared treatment with allopurinol and placebo or no treatment (96-98) in patients not selected because of hyperuricosuria. No significant difference was found between treated and untreated patients in any of these studies.

In a long-term follow-up of non-selected, calcium oxalate stone formers treated with 300 mg of allopurinol daily, no effect was found on stone formation (97). A similar result was recorded in another Swedish study (98). These results are in contrast to those obtained in patients treated for hyperuricosuria (99,100).

Allopurinol tolerance is usually good, but severe side effects have been reported with high doses. There is no information on compliance. The results indicate that allopurinol might be useful for treating patients with hyperuricosuric calcium oxalate stone formation. However, it cannot be recommended for patients with other biochemical abnormalities.

17.1.3.6 Pyridoxine
Theoretically, administration of pyridoxine (vitamin B6) might favourably influence the endogenous production of oxalate. This may be explained by an increased transamination of glyoxylate due to the action of the co-enzyme pyridoxal phosphate.

Pyridoxine has successfully been used together with orthophosphate in the treatment of patients with primary hyperoxaluria (101), as well as patients with idiopathic hyperoxaluria (102). There are no controlled studies to support the use of pyridoxine in patients with idiopathic calcium oxalate stone disease.

Due to the rarity, and severity, of primary hyperoxaluria, there are no randomized studies on the efficacy of pyridoxine. Several reports confirm, however, that a fraction of patients with Type 1 hyperoxaluria responds favourably to large doses of pyridoxine. Because of the lack of other effective forms of treatment, it is definitely worthwhile trying pyridoxine therapeutically, with the aim of reducing oxalate excretion in patients with primary hyperoxaluria Type I.

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

To prevent recurrence, it is essential to reduce the hyperabsorption of oxalate and correct any other urine abnormalities. A restricted intake of oxalate-rich foods should be combined with calcium supplements to enable calcium oxalate complex formation in the intestine (103). Calcium should therefore be given at meal times. Other oxalate-binding agents might also be useful, such as the marine colloid, Oxabsorb (104). An increased fluid intake is of course desirable, but its efficacy is often low because of the intestinal loss of water and increased diarrhoea. Administration of alkaline citrate is recommended to raise urinary pH and citrate (105). The diet should be restricted with regard to fat (106).

17.1.4.   Recommendations
Although there is no place for monotherapy with magnesium salts, a combination with thiazides might prove useful, but there is so far insufficient scientific evidence for this approach (107). Nevertheless, this alternative is mentioned because of its possible role in prevention of brushite stones.

It has been assumed that oxalate is more powerful than calcium in affecting supersaturation with calcium oxalate, but recent observations have indicated that calcium and oxalate influence the supersaturation with approximately equal power (108). It is therefore essential to correct abnormalities of both variables.

In patients with incomplete distal renal tubular acidosis, the treatment of choice appears to be potassium citrate, a regimen that has a positive effect on the acidosis, citrate excretion and stone formation (109).

There is no absolute consensus that a selective treatment is better than a non-selective treatment for recurrence prevention in idiopathic calcium stone disease. An analysis of data from the literature, however, has suggested a slight difference in favour of treatment directed towards individual biochemical abnormalities (43). Recommendations for a selective therapeutic approach are given in Table 28. In the absence of any common biochemical risk factors, it was shown that a water load had a positive effect on supersaturation and crystallization (110).

It is generally considered that dietary and drinking advice should always be considered first and that pharmacological alternatives should be added only if the the first step fails or if there are specific reasons for starting pharmacological treatment from the beginning. It is essential to note, however, that pharmacological treatment always should be combined with appropriate changes in dietary and drinking habits.

For patients with mild recurrent calcium stone disease and without residual stones or fragments (S_o, R_{mo}), it seems sufficient to give the patient general advice regarding dietary and fluid intake. For patients with a similar history of stone formation but with residual stones or fragments in the kidneys (S_{res}, R_{m-res}), it might be worthwhile applying a more aggressive treatment based on urinary findings as this approach has resulted in effective counteraction of active stone formation and growth of residuals (106). For patients in category R_s it is logical to take appropriate steps to stop or efficiently counteract recurrent stone formation, irrespective of whether or not the patient has residual stone-fragments (Table 29).

Table 28: Suggested treatment for patients with specific abnormalities in urine composition

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

Table 29: When should calcium stone formers be offered recurrence preventive treatment and how?

Category	Analysis of urinary risk factors	Recurrence prevention
S_o	No	General advice
S_{res}	Yes*	Specific advice, with or without a pharmacological agent
R_{mo}	No	General advice
R_{m-res}	Yes*	Specific advice, with or without a pharmacological agent
R_s	Yes	Specific advice, with or without a pharmacological agent

* Optional procedure that is recommended if it is likely that the information obtained can be useful for designing the subsequent treatment.

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17.2   Medical treatment of patients with uric acid stone disease

Uric acid stones form in urine highly supersaturated with uric acid. The most common abnormality is a low urine pH often occurring with a small urine volume. These two abnormalities provide the basis for precipitation of uric acid, even in patients with a normal urate excretion. A typical example is the patient with ileostomy with loss of both alkali and fluid. The high excretion of urate seen in patients with disturbed purine metabolism can result in a critical supersaturation with reasonably normal pH and volume (1).

17.2.1   Drinking and dietary recommendations
Fluid intake should be adjusted to allow for a 24-hour urine flow of approximately 2-2.5 L (2-5). The intake of animal protein should not exceed 0.8 g/kg /day (6-7).

17.2.2   Pharmacological treatment
Alkalinization of urine is mandatory and should preferably be carried out with potassium citrate. The pH should be increased to a level above 6.5 and the general recommendation is to obtain a pH in the range 6.5-7.2 (2,3,5). The dose should be adjusted to obtain a pH in the range between 6.1 and 7.0 (3). There might be a risk of calcium phosphate stone formation if the pH is raised to higher levels, although such a complication seems to be less common than expected.

Although both sodium bicarbonate and sodium citrate can be used to obtain an alkaline pH (1 g of sodium bicarbonate corresponds to 12 mmol and the recommended dose is 1 g x 3) the preferred agent is potassium citrate. This is because the solubility of potassium urate is greater than that of sodium urate (10,11) and potassium does not increase the excretion of calcium. For further alkalinization, it has been suggested that acetazolamide or topiratmate might be considered (8,9), but with this therapy the risk of calcium phosphate stones is more pronounced because of the simultaneous decrease in citrate excretion. A reduced excretion of urate is accomplished with allopurinol and this agent should be used when the 24-hour urate excretion exceeds 4 mmol (12). It is interesting to know that a combination of alkali, allopurinol and a high fluid intake can be used to dissolve uric acid stones.

The pharmacological treatment of patients with uric stone disease is outlined in Table 30.

Table 30: Pharmacological treatment of uric acid stone disease

Objective	Therapeutic measures	Ref	LE	GR
Prevention	**Urine dilution**	2-5	3	B
	A high fluid intake; 24-hour urine volume exceeding 2-2.5 L			
	Alkalinization	8-11	2b	B
	Potassium citrate 3-7 mmol x 2-3			
	In patients with a high serum or urine level of urate	12	3	B
	Allopurinol 300 mg x 1			
Medical dissolution of uric acid stones	**Urine dilution**			
	A high fluid intake; 24-hour urine volume exceeding 2-2.5L		4	C
	Alkalinization	13,14	1b	A
	Potassium citrate 6-10 mmol x 2-3			
	Always reduce urate excretion		4	C
	Allopurinol 300 mg x 1			

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17.3 Medical treatment of cystine stone disease

17.3.1 *Dietary recommendations*

Although a diet low in methionine theoretically might be of value for reducing urinary excretion of cystine, such a step is unlikely to result in reasonable compliance by the patient and this regimen is not usually used or recommended.

A restricted intake of sodium is, however, probably more effective in reducing urinary cystine. The recommendation given is to avoid a daily consumption of sodium above 2 g (1).

17.3.2 Drinking advice
A high diuresis is of fundamental importance. The aim is to dilute the urine so that supersaturation with cystine is decreased below the solubility product of cystine, or at least below its formation product. In general, the goal is a 24-hour urine volume of at least 3 L (2,3). To reach this goal, a considerable fluid intake evenly distributed during the day is necessary. A more accurate recommendation of the size of urine volume needed can be obtained by knowing the ion-activity product of cystine, which can be calculated from the cystine concentration and the pH (4).

17.3.3 Pharmacological treatment
The solubility of cystine increases in alkaline urine, but a substantial increment in solubility does not occur unless the pH is above 7.5. The rule of thumb is that the solubility of cystine is approximately 250 mg/L (1 mmol/L) at pH 7, 500 mg (2 mmol/L) at pH 7.5 and 750 mg (3 mmol/L) at pH 8 (2). To alkalinize the urine, potassium citrate is the best alternative. Sodium bicarbonate, sodium citrate or sodium potassium citrate should not be given because of the undesirable effect of sodium on the excretion of cystine (1).

A typical dose of potassium citrate is 20-25 mmol per day given three times a day, but the required dose has to be determined by the effect this regimen has on urinary pH. The administration of acetazolamide can be used to improve the alkalinization (5).

When the combined effects of a high diuresis and alkalinization are not enough to prevent stone formation, complex formation by chelating agents is necessary (2,6,7). Thiol compounds, such as D-penicillamine (8,9) and α-mercaptopropionyl glycine (tiopronin) (8-10), are most commonly used. The latter compound seems to be associated with fewer side effects than penicillamine. The recommended daily dosage is 10-15 mg/kg (or 750 mg/day), but the daily required dose might be in the range 250-2000 mg. For pencillamine, the daily dose is 1-2 g. A third alternative is captopril (an angiotensin-converting enzyme inhibitor). Positive effects on urinary cystine and stone formation have been reported with a daily dose of 75-100 mg (1,11,12). Administration of thiols always should be accompanied by pyridoxine to avoid vitamin B_6-deficiency. The recommended dose is 50 mg/day.

Patients who are treated with thiols should regularly be examined with analysis of blood haemoglobin, white blood cells and thromocytes. Moreover, the urine should be checked for proteinuria.

The treatment of patients with cystine stone disease is outlined in Table 31.

Table 31: Pharmacological treatment of patients with cystine stone disease

Therapeutic measures	References	LE	GR
Urine dilution A high fluid intake should be recommended so that the 24-h urine volume exceeds 3000 mL. To achieve this goal, the intake should be at least 150 ml/h	1-3	3	B
Alkalinization *For patients with a cystine excretion below 3 mmol/24h:* Potassium citrate 3-10 mmol x 2-3 should be given to achieve a pH > 7.5	1-3	3	B
Complex formation with cystine *For patients with a cystine excretion above 3 mmol/24 or when other measures are insufficient* Tiopronin (α-mercapto-propionyl glycine), 250-2000 mg/day **or** Captopril, 75-150 mg	1-7	3	B

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17.4   Management of patients with infection stones

17.4.1   Pharmacological treatment of infection stone disease
The pharmacological treatment of patients with infection stone disease is outlined in Table 32. The definition of infection stones is stones composed of magnesium ammonium phosphate and carbonate apatite. These stones are caused by urease-producing micro-organisms. It is fundamental that the renal collecting system is cleared of stone material to prevent recurrence in patients with infection stone disease.

It is fundamental that the renal collecting system is cleared from stone material	LE = 3 GR = C

Table 32: Pharmacological treatment of infection stone disease

Therapeutic measures	References	LE	GR
Stone removal	1	4	C
Surgical removal of the stone material as completely as possible			
Antibiotic treatment			
Short-term antibiotic course	2	3	B
Long-term antibiotic course		3	B
Acidification			
Ammonium chloride 1 g x 2-3	4	3	B
Methionine 500 mg 1-2 x 3	3	3	B
Urease inhibition	5,6	1b	A
In very selected cases with severe infections, treatment with acetohydroxamic acid (Lithostat) might be a therapeutic option			

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18. ABBREVIATIONS USED IN THE TEXT
This list is not comprehensive for the most common abbreviations

AP_{CaOx}	ion-activity product of calcium oxalate
AP_{CaP}	ion-activity product of calcium phosphate
AP(CaOx) index	approximate estimate of APCaOx
AP(CaP) index	approximate estimate of APCaP
AUA	American Urological Association
Ca	calcium
$CaHPO_4 2H_2O$	calcium hydrogen phosphate
CaOx	calcium oxalate
CaP	calcium phosphate
CI	confidence interval
CIs	credible intervals
CIRF	clinically insignificant residual fragments
Cit	citrate
CT	computed tomography
CY	cystine stone
EAU	European Association of Urology
EHL	electrohydraulic lithotripsy
ESWL	extracorporeal shock-wave lithotripsy, also including piezolithotripsy
GFR	glomerular filtration rate
GR	grade of recommendation
HCl	hydrochloric acid
Ho:YAG	holmium:yttrium aluminium garnet
INF	infection stone
IVP	intravenous pyelography
IVU	Intravenous urography
KUB	plain abdominal film of the kidneys, ureters and bladder
LE	level of evidence
l	length (of stone)
MET	medical expulsive therapy
Mg	magnesium
MREU	MR excretory urography
MRU	Magnetic resonance urography
Nd:	YAG frequency doubled laser
NH_4Cl	ammonium chloride
NSAID	non-steroidal anti-inflammatory drug
Ox	oxalate
PNL	percutaneous nephrolithotomy with or without lithotripsy
RIRS	retrograde intrarenal surgery
R_{mo}	recurrent stone former with mild disease and without residual stone(s) or stone fragments
R_{m-res}	recurrent stone former with mild disease with residual stone(s) or stone fragments
R_s	recurrent stone former with severe disease with or without residual stone(s) or fragments or with specific risk factors irrespective of otherwise defined category
RTA	renal tubular acidosis
SA	stone surface area
S_o	first time stone former without residual stone or stone fragments
S_{res}	first time stone former with residual stone or stone fragments
SWL	shock-wave lithotripsy
THAM	trihydroxymethyl aminomethan
UR	uric acid/sodium urate/ammonium urate stone
URS	ureteroscopy
US	ultrasonography
UTI	urinary tract infection
V	urine volume
w	width (of stone)

19. APPENDICES

APPENDIX 1: Devices for endoscopic disintegration of stones

BALLISTIC LITHOTRIPSY
Ballistic lithotripsy involves a device in which alternating compression caused by air or electromechanical forces is transmitted to a metal rod. Pulses drive a metallic bullet that bumps the end of the rod against the stone. Rods are 2.4-6 F in diameter and can be used through a semi-rigid ureteroscope and all rigid endoscopes. A similar effect is obtained by alternating mechanical displacement.

ULTRASONIC LITHOTRIPSY
These commercially available units consist of a power generator, an US transducer and a probe, forming the sonotrode. A piezoceramic element in the handle of the sonotrode is stimulated to resonate, and this converts electrical energy into US waves (at a frequency of 23,000- 27,000 Hz). The US waves are transmitted along the hollow metal probe to create a vibrating action at its tip. When the vibrating tip is brought into contact with the surface of a stone, the calculus can be disintegrated. The probes, which are available in sizes 10 F and 12 F, are passed through the straight working channel of a rigid ureteroscope or nephroscope. Suction tubing can be connected to the end of the sonotrode.

ELECTROHYDRAULIC LITHOTRIPSY
The electrohydraulic lithotripsy (EHL) unit has a probe, a power generator and a foot pedal. The probe consists of a central metal core and two layers of insulation with another metal layer between them. Probes are flexible and available in many sizes for use in rigid and flexible nephroscopes. The electrical discharge is transmitted to the probe where it generates a spark at the tip. The intense heat produced in the immediate area surrounding the tip results in a cavitation bubble, which produces a shock wave that radiates spherically in all directions. EHL will effectively fragment all kinds of urinary stones, including very hard stones composed of cystine, uric acid and calcium oxalate monohydrate. Recently, a 1.6 F EHL probe was developed. It has been quite successful in fragmenting ureteral and intrarenal stones. It has superior flexibility compared to the laser fibre.

LASER LITHOTRIPSY
Today, neodymium:yttrium-aluminium-garnet (Nd:YAG) or holmium:YAG (Ho:YAG) lasers are used as sources for laser lithotripsy units. The reported results indicate that the Ho:YAG efficacy is superior to the Nd:YAG and does effectively fragment all types of urinary stones, wherever they are located and whatever their composition, including cystine stones. The Ho:YAG system produces light of 2100 nm, with a tissue penetration of less than 0.5 mm and complete absorption in water. The Nd:YAG is used frequency-doubled and produces light of 1064 nm, with a tissue penetration of 4 mm. Fibres for ureteroscopy are available for both lasers at 200 and 365 μm in diameter.
In combination with the actively deflectable, flexible ureteroscope, the Ho:YAG laser has proven to be ideally suited for fragmenting stones in the upper ureter. Potential complications of the Ho:YAG laser when used to fragment ureteral stones include possible perforation of the ureteral wall and consecutive formation of strictures.

APPENDIX 2: Approximate stone surface area with known diameters of the stone

An approximate estimate of the stone surface area (mm²) can be extracted from the length and width on the KUB. The calculated surface area for any combination of stone diameters up to 25 mm is shown in Table A1.

Table A1: Approximate stone surface area (mm²) calculated from the length and width of the stone

Length mm \ Width mm	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1	0.8	1.6	2.4	3.1	3.9	4.7	5.5	6.3	7.1	7.9	8.6	9.4	10.2	11.0	11.8	12.6	13.3	14.1	14.9	15.7	16.5	17.3	18.1	18.8
2	1.6	3.1	4.7	6.3	7.9	9.4	11.0	12.6	14.1	15.7	17.3	18.8	20.4	22.0	23.6	25.1	27	28.3	30	31.4	33.0	34.5	36.1	37.7
3	2.4	4.7	7.1	9.4	12	14	16	19	21	24	26	28	31	33	35	38	40	42	45	47	49	52	54	57
4	3	6	9	13	16	19	22	25	28	31	35	38	41	44	47	50	53	57	60	63	66	69	72	75
5	4	8	12	16	20	24	27	31	35	39	43	47	51	55	59	63	67	71	75	79	82	86	90	94
6	5	9	14	19	24	28	33	38	42	47	52	57	61	66	71	75	80	85	89	94	99	104	108	113
7	5	11	16	22	27	33	38	44	49	55	60	66	71	77	82	88	93	99	104	110	115	121	126	132
8	6	13	19	25	31	38	44	50	57	63	69	75	82	88	94	100	107	113	119	126	132	138	144	151
9	7	14	21	28	35	42	49	57	64	71	78	85	92	99	106	113	120	127	134	141	148	155	162	170
10	8	16	24	31	39	47	55	63	71	79	86	94	102	110	118	126	133	141	149	157	165	173	181	188
11	9	17	26	35	43	52	60	69	78	86	95	104	112	121	130	138	147	155	164	173	181	190	199	207
12	9	19	28	38	47	57	66	75	85	94	104	113	122	132	141	151	160	170	179	188	198	207	217	226
13	10	20	31	41	51	61	71	82	92	102	112	122	133	143	153	163	173	184	194	204	214	225	235	245
14	11	22	33	44	55	66	77	88	99	110	121	132	143	154	165	176	187	198	209	220	231	242	253	264
15	12	24	35	47	59	71	82	94	106	118	130	141	153	165	177	188	200	212	224	236	247	259	271	283
16	13	25	38	50	63	75	88	100	113	126	138	151	163	176	188	201	214	226	239	251	264	276	289	301
17	13	27	40	53	67	80	93	107	120	133	147	160	173	187	200	214	227	240	254	267	280	294	307	320
18	14	28	42	57	71	85	99	113	127	141	155	170	184	198	212	226	240	254	268	283	297	311	325	339
19	15	30	45	60	75	89	104	119	134	149	164	179	194	209	224	239	254	268	283	298	313	328	343	358
20	16	31	47	63	79	94	110	126	141	157	173	188	204	220	236	251	267	283	298	314	330	345	361	377
21	16	33	49	66	82	99	115	132	148	165	181	198	214	231	247	264	280	297	313	330	346	363	379	396
22	17	35	52	69	86	104	121	138	155	173	190	207	225	242	259	276	294	311	328	345	363	380	397	414
23	18	36	54	72	90	108	126	144	162	181	199	217	235	253	271	289	307	325	343	361	379	397	415	433
24	19	38	57	75	94	113	132	151	170	188	207	226	245	264	283	301	320	339	358	377	396	414	433	452
25	20	39	59	79	98	118	137	157	177	196	216	236	255	275	294	314	334	353	373	393	412	432	451	471

Conflict of interest
All members of the Urolithiasis guidelines writing panel have provided disclosure statements of all relationships which they have and which may be perceived as 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.