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Guideline

The Urological Association of Asia clinical guideline for urinary stone disease

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Abbreviations & Acronyms
AUA = American Urological Association
BMI = body mass index
CI = confidence interval
CT = computed tomography
EAU = European Association of Urology
ECIRS = endoscopic combined intrarenal surgery
Flex = flexible
GR = grade of recommendation
HU = Hounsfield unit
INR = international normalized ratio
IVU = intravenous urography
JUA = Japanese Urological Association
KUB = kidney ureter bladder
LE = level of evidence
MET = medical expulsive therapy
mPCNL = miniaturized percutaneous nephrolithotripsy
MRI = magnetic resonance imaging
NCCT = non-contrast computed tomography

Abstract: The Urological Association of Asia, consisting of 25 member associations and one affiliated member since its foundation in 1990, has planned to develop Asian guidelines for all urological fields. The field of stone diseases is the third of its guideline projects. Because of the different climates, and social, economic and ethnic environments, the clinical practice for urinary stone diseases widely varies among the Asian countries. The committee members of the Urological Association of Asia on the clinical guidelines for urinary stone disease carried out a surveillance study to better understand the diversity of the treatment strategy among different regions and subsequent systematic literature review through PubMed and MEDLINE database between 1966 and 2017. Levels of evidence and grades of recommendation for each management were decided according to the relevant strategy. Each clinical question and answer were thoroughly reviewed and discussed by all committee members and their colleagues, with suggestions from expert representatives of the American Urological Association and European Association of Urology. However, we focused on the pragmatic care of patients and our own evidence throughout Asia, which included recent surgical trends, such as miniaturized percutaneous nephrolithotomy and endoscopic combined intrarenal surgery. This guideline covers all fields of stone diseases, from etiology to recurrence prevention. Here, we present a short summary of the first version of the guideline – consisting 43 clinical questions – and overview its key practical issues.

Key words: grade recommendation, guideline, level of evidence, urolithiasis, Urological Association of Asia.

Introduction

Aims and scope

Asia is the largest continent and accounts for approximately 60% of the world's population. The UAA includes many countries with diverse backgrounds in medicine, climate, insurance

nephro = nephroscopy
NHANES = National Health and Nutrition Examination Survey
NLR = neutrophil-to-lymphocyte ratio
NSAIDs = non-steroidal anti-inflammatory drugs
PCNL = percutaneous nephrolithotripsy
PT = prothrombin time
RCT = randomized controlled trial
RIRS = retrograde intrarenal surgery
SFR = stone-free rates
S-ReSC = Seoul National University Renal Stone Complexity
SWL = shock wave lithotripsy
UAA = Urological Association of Asia
UPJ = ureteropelvic junction
URS = ureteroscopy
US = ultrasonography
UTI = urinary tract infection

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systems, equipment, and access to hospitals and facilities. We are required to establish a consensus on treatment. The UAA Clinical Guidelines for Stone Disease have been prepared to help urologists apply evidence-based management to stones/calculi and incorporate recommendations into clinical practice. The document covers most aspects of the disease, which is still a cause of significant morbidity despite technological and scientific advances. The Work Group is aware of the geographical variations in the provision of healthcare. Diverse treatment alternatives might be possible depending on the social environment of the relevant case(s); however, the best treatment also depends on the circumstances of each individual case and is not uniform. This guideline aims to obtain a consensus on the treatment approach for urinary stone disease. The entire version of this guideline is available on the UAA website. Here, we present a short summary of the first version of the guideline and overview its key practical issues.

Diversity of treatment strategies among the UAA

Due to the different climates, and social, economic and ethnic environments, there is huge diversity in clinical practice for urinary stone disease among Asian countries. Table 1 summarizes treatment strategies for each UAA representative for different stone cases. In accordance with other guidelines, SWL and endoscopic lithotomy, such as RIRS, URS and PCNL are preferred choices in Asia; however, some countries in the Middle East and Southeastern Asia still apply open/laparoscopic pyelolithotomy and ureterolithotomy as surgical options for treatment of renal staghorn and ureteral impacted stones, respectively. Another interesting treatment option often chosen in Korea, Japan and Turkey is ECIRS. For pediatric renal stone cases, SWL is still the standard in the majority of the associations, but RIRS and minimally invasive PCNL are also accepted as reasonable options.

Methods

Data identification

The Guideline for Stone Diseases was developed by committee members recommended by the UAA. The members meticulously reviewed the relevant references retrieved via the PubMed and MEDLINE databases published between 1966 through 31 July 2017.

The search strategy included the following medical subject headings (MeSH) for stone diseases: “Stone” [MeSH], “Urolithiasis” [MeSH], “Nephrolithiasis” [MeSH] and “Calculi” [MeSH]. Other key words for searching references were selected by each committee.

Other sources of information included: (i) JUA clinical guidelines for urolithiasis; (ii) EAU Guidelines on Urolithiasis 2017, published by the EAU; (iii) Medical Management of Kidney Stones: AUA Guidelines, published by the AUA; and (iv) Surgical Management or Stones: AUA/Endourological Society Guidelines.

LE and GR

The LE and GR for each treatment were made based on the following strategy. The recommendations for treatment were based on a non-structured literature search, which has been previously published, and labeled with a LE score according to a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence, ranging from LE:1 (highest evidence level) to LE:5 (case study or expert opinion; Table S1).[1]

Clinical questions and answers

Etiology

CQ 1. Is the prevalence of urinary stone disease increasing?

- The prevalence and incidence of urinary stone disease have increased in many countries in recent years (LE:2, GR:A).
- There is growing evidence of an increasing incidence of stones in the USA (LE:2).
- The increase in the prevalence is less marked, or stable, in Europe (LE:3).
- An upward trend in urinary stone disease has been noted in Asia (LE:3).

Table 1 Treatment approaches of different stone cases among different UAA representatives

	47-year-old man, left partial staghorn stone (40 mm)	65-year-old man, left renal pelvic stone (18 mm)	75-year-old woman, right lower calyx stone (10 mm)	50-year-old women, right mid-ureter stone (13 mm) with moderate hydronephrosis	8-year-old boy, right renal pelvic stone (8 mm)
Cambodia	1: Pyelo-nephrolithotomy 2: PCNL (+stenting)	1: Pyelolithotomy (+stenting)	1: PCNL	1: URS (+pre-stenting) 2: Ureterolithotomy (+stenting)	1: Pyelolithotomy (+stenting)
China	1: PCNL	1: RIRS or mini-PCNL (HU >500) 2: SWL (HU <500)	1: Observation 2: RIRS 3: Micro to mini-PCNL or 1: Ultra-mini-PCNL	1: URS 2: Antegrade URS	1: SWL 2: RIRS (+pre-stenting) or 1: Ultra-mini-PCNL
Hong Kong	1: PCNL	1: PCNL	2: SWL	1: URS	1: SWL
India	1: PCNL 2: Robotic/laparoscopic pyelolithotomy 3: Pyelolithotomy/extended pyelolithotomy	1: PCNL (>1000 HU) 2: SWL (<1000 HU) 3: RIRS	1: SWL (favorable anatomy and stone density) 2: RIRS 3: Mini-PCNL	1: URS 2: Laparoscopic ureterolithotomy	1: SWL 2: Micro-PCNL 3: RIRS
Indonesia	1: Standard/mini-PCNL 2: RIRS 3: Pyelolithotomy	1: Standard/mini-PCNL 2: RIRS 3: SWL 4: Pyelolithotomy	1: SWL (infundibulum is wide and angle of calyx >30) 2: RIRS 3: Standard/mini-PCNL	1: URS 2: Ureterolithotomy	1: SWL 2: RIRS 3: Mini-PCNL
Iran	1: PCNL 2: Multitract mini-PCNL	1: SWL 2: RIRS or mini-PCNL	1: SWL 2: RIRS or mini-PCNL	1: URS 2: Laparoscopic ureterolithotomy	1: SWL
Japan	1: ECIRS by mini-PCNL	1: RIRS 2: Mini-PCNL (+RIRS)	1: SWL 2: RIRS 3: Observation (depends on infundibular length, width)	1: URS (+pre-stenting or nephrostomy tube placement) 2: SWL (+pre-stenting)	1: SWL 2: RIRS (+pre-stenting)
Korea	1: PCNL (prone > supine) 2: ECIRS	1: RIRS 2: Mini-PCNL 3: PCNL	1: Observation 2: URS 3: SWL (if stone is not so hard)	1: URS (+pre-stenting or nephrostomy tube placement) 2: Antegrade URS 3: Laparoscopic ureterolithotomy	1: RIRS 2: SWL 3: Mini-PCNL
Kuwait	1: PCNL 2: Staged RIRS	1: RIRS (+pre-stenting) 2: Mini-PCNL (+stenting)	1: RIRS (+pre-stenting) 2: SWL	1: URS	1: SWL 2: RIRS
Malaysia	1: PCNL	1: PCNL 2: RIRS (+pre-stenting)	1: Observation (asymptomatic) 2: RIRS 3: SWL 4: Mini-PCNL with JJ stent (asymptomatic)	1: URS	1: SWL 2: Mini-PCNL
Nepal	1: PCNL	1: RIRS (HU <1100) or PCNL (HU >1100)	1: Observation (symptomatic) 2: RIRS	1: URS	1: SWL
Singapore	1: PCNL	1: RIRS 2: SWL	1: SWL or RIRS (depends on patient's preference)	1: URS	1: SWL
Taiwan	1: PCNL 2: ECIRS	1: SWL 2: RIRS 3: Mini-PCNL (HU >500 + severe hydro)	1: RIRS	1: URS	1: SWL 2: Mini-PCNL
Thailand	1: PCNL	1: SWL or RIRS	1: SWL or RIRS	1: URS (+pre-stenting)	1: SWL
Turkey	1: PCNL 2: ECIRS	1: RIRS (+stenting) 2: SWL (HU < 500)	1: Ultra-mini-PCNL	1: URS 2: Laparoscopic ureterolithotomy	1: SWL 2: RIRS

Countries are indicated in alphabetical order. Numbers in each column indicate the preference order of treatment options.

Commentary

Urinary stone disease is a highly prevalent disease worldwide, with rates ranging from 7–13% in North America, 5–9% in Europe and 1–5% in Asia; however, there is significant variation in rates based on geography, climate, diet, fluid intake, genetics, sex, occupation and age.[2–14] It is difficult to evaluate the precise prevalence and incidence worldwide, because there are differences in assessment methods across countries. It should be noted that nationwide comparative studies are rare in developing countries.[15]

CQ 2. How can stones be classified?

Stones can be categorized by etiology, chemical/mineral names, size and location (LE:3, GR:A).

The most common stone type is calcium oxalate, and some Asian countries have a higher percentage of this chemical composition compared to other parts of the world (LE:3, GR:A).

Stone composition is often associated with metabolic and/or genetic abnormalities (LE:3, GR:B).

Commentary

Etiopathogenetic categorization of stones can include the following: non-infection stones, infectious causes, genetic-based stones or drug-induced stones (LE:4).[16]

Stone composition is the basis for further diagnostic and management decisions. Calcium phosphate stone composition is more likely to be associated with certain medical conditions or medications, such as renal tubular acidosis type 1, primary hyperparathyroidism, medullary sponge kidney and the use of carbonic anhydrase inhibitors (LE:3).[17,18]

Table 2 lists the clinically most relevant substances and their mineral components. Some unique trends, including calcium oxalate and cystine stones, have been reported from each country throughout Asia (LE:4).[19–24]

Table 2 List of variety of stone components

Chemical name	Mineral name	Chemical formula
Calcium oxalate monohydrate	Whewellite	$CaC_2O_4H_2O$
Calcium oxalate dehydrate	Wheddelite	$CaC_2O_42H_2O$
Basic calcium phosphate	Apatite	$Ca_{10}(PO_4)6(OH)_2$
Calcium hydroxyl phosphate	Carbonite apatite	$Ca_5(PO_3)_3(OH)$
β-Tricalcium phosphate	Whitlockite	$Ca_3(PO_4)_2$
Carbonate apatite phosphate	Dahllite	$Ca_5(PO_4)_3OH$
Calcium hydrogen phosphate	Brushite	PO_42H_2O
Calcium carbonate	Aragonite	$CaCO_3$
Octacalcium phosphate		$Ca_8H_2(PO_4)_6{\cdot}5H_2O$
Uric acid	Uricite	$C_5H_4N_4O_3$
Uric acid dehydrate	Uricite	$C_5H_4O_3{\cdot}2H_2O$
Ammonium urate		$NH_4C_5H_3N_4O_3$
Sodium acid urate monohydrate		$NaC_5H_3N_4O_3{\cdot}H_2O$
Magnesium ammonium phosphate	Struvite	$MgNH_4PO_4{\cdot}6H_2O$
Magnesium acid phosphate trihydrate	Newberyite	$MgHPO_4{\cdot}3H_2O$
Magnesium ammonium phosphate monohydrate	Dittmarite	$MgNH_4(PO_4){\cdot}1H_2O$
Cystine		$[SCH_2CH(NH_2)COOH]_2$
Xanthine		$C_5H_4N_4O_2$
2,8-Dihydroxyadenine		$C_5H_5N_5O_2$
Drug stones (magnesium trisilicate; ciprofloxacin; sulfa medications; triamterene; ephedrine, melamine; and indinavir)		
Foreign body calculi		

CQ 3. What is the role of lifestyle in urinary stone disease?

- Metabolic syndrome is associated with stone formation (LE:4, GR:B).
- Fluid intake volume has been shown to be inversely related to urolithiasis (LE:1, GR:A).
- Soft drink consumption should be discouraged to reduce new stone formation (LE:2, GR:B).

Commentary

Increased bodyweight and obesity have been shown to increase the risk of urinary stone formation.[25] A recent study in Taiwanese men showed there was a significant correlation between metabolic syndrome and nephrolithiasis.[26] Visceral fat was shown to be predictive of stone composition in a Korean population.[27] A higher fluid intake volume was associated with reduced stone formation rates. Higher water intake resulted in a reduced rate of stone recurrence in patients with a previous episode of calcium stones.[28–31] In addition, soft drink and ascorbic acid were shown to increase the risk of stone formation.[29,30]

CQ 4. What is the role of metabolic components in urinary stone disease?

- Calcium intake should not be restricted, as there is an inverse relationship between dietary calcium and stone formation (LE:4, GR:A).
- High sodium intake is associated with an increased risk of stone formation (LE:4, GR:A).
- Increased dietary ascorbic acid intake is associated with hyperoxaluria (LE:3, GR:A).
- A low animal protein diet should be encouraged to reduce the risk of stone formation (LE:2, GR:B).
- Dietary fiber content should be increased, and oxalate content should be restricted in recurrent calcium oxalate stone-forming cases (LE:4, GR:B).

Commentary

The Nurses' Health Study in the USA found that the relative risk of stone formation in women in the highest quintile of calcium intake was 0.65 compared with those in the lowest quintile.[33] In a single randomized prospective study, hyperoxaluria was shown to be significantly associated with dietary ascorbic acid intake and inversely associated with calcium intake.[32] A low animal fat diet was reported to reduce stone recurrence rates.[34] Recent East Asian studies reported a decreased incidence of calcium-containing stones and increased incidence of uric acid stones in Korea,[35] and a decreased incidence of uric acid stones in Japan,[11] during a 20-year observation period.

CQ 5. What is the role of genetic factors in urinary stone disease?

- Genetic factors are highly associated with both the pathogenesis and clinical outcomes of urinary stone disease. Clinicians should consider patients' genetic background, including family history (LE:3, GR:A).
- Positive family history of urinary stone disease is associated with earlier disease onset and a higher risk of recurrence (LE:3, GR:B).

- The association of gene mutations with disease development has been reported for both rare inherited disorders causing urolithiasis, as represented by cystine stones, and idiopathic calcium stones (LE:3).

Commentary

Patients with urinary stone disease have a higher prevalence of positive family history of the disease, which has been reported to be between 30–50%.[36–40] A family history of urolithiasis increases the relative risk of stone disease by 2.57-fold in men.[41] In addition, the concordance rate of the disease in monozygotic twins is higher compared with dizygotic twins (32.4 *vs* 17.3%; LE:3).[42]

Inherited metabolic disorders are often associated with pediatric urolithiasis cases.[43] Adenine phosphoribosyltransferase deficiency,[44] cystinuria,[45–47] xanthinuria,[48] Dent disease,[49,50] familial hypomagnesemia with hypercalciuria and nephrocalcinosis,[51,52] and primary hyperoxaluria[53–55] cause urinary hypersaturation of insoluble mineral salts, which can inevitably increase the risk of kidney stone formation (LE:4).

In addition, a large number of reports in the literature have focused on the association of gene single-nucleotide polymorphism/mutations with idiopathic calcium stone development (LE:3).[56]

CQ 6. What is the role of regional or ethnic differences in urinary stone disease?

- There is a clear geographic variation in stone incidence worldwide (LE:3).
- The "stone belt" (areas where stones are frequent) includes South-East Asia and West Asia (LE:2).
- Ethnic differences in the incidence of stone disease have been observed (LE:3).

Commentary

The prevalence of urinary stone disease varies widely in different regions of the world, and depends greatly on the geographic area, racial distribution, socioeconomic status and dietary habits. The geographic distribution of stone disease tends to roughly follow that of environmental risk factors. Comparison of the accurate prevalence of the disease is difficult because of the differences in the evaluation methodology used.[57]

Racial differences in the incidence of stone disease have also been observed.[58] According to the NHANES dataset, Hispanic (OR 0.60, $P < 0.001$) and black non-Hispanic people (OR 0.37, $P < 0.001$) were significantly less likely to report a history of stone disease compared with white non-Hispanic people.[59] A Canadian study reported that the relative risk of calcium nephrolithiasis was higher in individuals of Arabic, West Indian and Asian descent, but lower in those of East Asian descent than in those of European and Latin American descent.[60]

CQ 7. What is the role of seasonal variation in urinary stone disease?

- Seasonal variations are related to urinary calculi pain attacks (LE:3).
- It has been suggested that there is an association between the rise of the ambient temperature and the occurrence of urolithiasis (LE:3).
- Seasonal variation in stone disease is likely related to temperature by way of fluid losses from perspiration and by sunlight-induced increases in vitamin D (LE:2).

Commentary

A close relationship between seasons and the incidence of ureterolithiasis has been shown in various geographical areas.[61–67] Seasonal trends in monthly urinary stone attack rates exist, with the incidence peaking in the summer, which is likely related to the high temperature that leads to fluid losses due to perspiration,[68,69] and perhaps by sunlight-induced increases in the synthesis of 1,25-dihydroxyvitamin D_3 (vitamin D).[65,70] The tendency for increasing incidence of renal colic in parallel with the rise in ambient temperature has been well documented in many countries.[65,71] Conversely, other studies have shown that the prevalence of urolithiasis is not related to season in Northern Europe and Western Australia, where the climate is stable.[72–74]

Diagnosis

CQ 8. What basic clinical work-up is necessary for the diagnosis of urinary stone disease?

- Urine routine and microscopic investigations (red blood and white blood cell counts, nitrites, urinary pH and culture, and sensitivity tests (LE:3, GR:B).
- Blood samples for total and differential counts, serum urea, creatinine, Na and K are investigated in first-time stone-former patients (LE:3, GR:B).
- If the patient is a recurrent stone former, then stone analysis, serum (ionized) calcium, phosphorus, uric acid, magnesium, as well as urinary calcium, phosphate, uric acid, magnesium, citrates and cystine levels are investigated at least once (LE:3, GR:B).

Commentary

If an intervention is planned, then PT, INR and blood group testing should be carried out. All retrieved fragments or collected stone material in voided urine should be examined by X-ray diffraction or infrared spectroscopy methods. Stone analysis should be carried out in recurrent stone formers during each stone episode, even if the initial stone composition is known, as changes in stone content have been reported in recurrent stone formers.[75–79]

CQ 9. What is the recommended imaging modality for the diagnosis of stone disease?

- Plain radiography is not sensitive and specific enough for the diagnosis of stone (LE:4, GR:B).
- US is the recommended choice of diagnosis for most renal stones and ureteric stones, particularly in children (LE:4, GR:B).
- NCCT has the best sensitivity and specificity for the detection of renal stones, and would be superior to US, in particular for ureteric stones. However, risks of radiation exposure should be considered (LE:4, GR:B).
- If possible, a low-dose NCCT protocol should be used for patients with BMI <30 kg/m^2, to minimize radiation risk to patients (LE:4, GR:B).

Commentary

The accuracy of KUB for the diagnosis of urinary stones is low, approximately 80–90% of stones are radiopaque, in particular during diagnostic settings (LE:4, GR:B).[80,81]

US has the advantage of being radiation-free, contrast-free and readily available; however, the sensitivity/specificity for diagnosing ureteric stones is low (LE:4, GR:B).[80]

NCCT has high sensitivity and specificity for the detection of both renal and ureteric stones (LE:4, GR:B).[82,83] As radiation exposure is a main concern, low-dose NCCT (with doses <4 mSv) is recommended for the detection of ureteric stones in patients with BMI <30 kg/m^2.[82] A study funded by the Agency for Healthcare Research and Quality suggested the use of US during the initial assessment of acute loin/abdominal pain suggestive of renal calculi, avoiding carrying out a CT scan in some patients and hence resulting in less overall radiation exposure than NCCT for all patients (LE:2, GR:A).[84]

CQ 10. Is an interview necessary for the diagnosis of stone disease?

- Medical history is very important to diagnose stone disease. Physicians should ask detailed questions regarding symptoms, including pain, nausea/vomiting, urine color, discomfort on urination and previous stone episodes (LE:1, GR:A).
- Obtaining information on habitual behavior regarding diet and physical activity, family history, age of onset, and previous stone episodes are also helpful to predict the risk and recurrence of stones (LE:1, GR:A).

Commentary

Although 70% of patients have asymptomatic stones on US, hematuria, flank/abdominal pains, prior stone episodes, nausea and vomiting are common signs to suspect stone existence (LE:1, GR:A).[85,86] In addition, habitual behavior, including a larger amount of diet and alcohol consumption, positive family history, and less physical activity, is associated with the risk for urinary stone disease (LE:3, GR:A).[30,37,87–90] Positive family history, younger age at onset and having two or more previous stone episodes increase the prevalence of stone recurrence (LE:1, GR:A).[37,90–92]

CQ 11. How should we diagnose urinary stones in specific situations, such as in children and pregnant patients?

- In pregnant women, use US as a first-line imaging modality and MRI as a second-line approach (LE:2, GR:B).
- In pregnant women, reserve low-dose CT as a last-line option (LE:2, GR:B).
- In children, US is a first-line imaging modality, and low-dose CT is an alternative option if US cannot exclude urinary calculi (LE:2, GR:B).

Commentary

For the diagnosis of urinary stones in pregnant patients, major concerns are the effects of radiation exposure.[93,94] Table 3 shows the radiation doses absorbed by a fetus after common imaging modalities.[91] The physician has to justify the need for any investigation resulting in an absorbed dose to the fetus of >0.5 mGy.[93]

US is the initial imaging modality for pregnant patients suspected of renal colic;[93,94] however, it has inherent disadvantages, such as operator dependency and the difficulty in differentiation between physiological hydronephrosis of pregnancy and acute ureteral obstruction.[95] Transvaginal US has also been shown to improve sensitivity in the diagnosis of distal ureteral stones.[96] MRI is used as a second-line procedure, to differentiate physiological from obstructive hydronephrosis during pregnancy.[93,94,97]

Low-dose CT for the detection of urinary stones during pregnancy has been associated with a higher positive predictive value (95.8%) compared with MRI (80%) and US (77%).[98] Cumulative and long-term effects of radiation exposure are again the major concerns for children; therefore, US is the initial imaging modality for children suspected of renal colic.[99] US has 70% sensitivity and 100% specificity for the detection of urinary stones in patients aged <18 years.[100]

Table 3 Radiation absorbed doses to the fetus for common imaging modalities

	Fetal dose (mGy)	
Modality	Mean	Maximum
Ultrasound	None	
MRI (<1.5 Tesla)	None	
KUB radiography	1.4	4.2
IVU	1.7	10
CT	8.0	49

CQ 12. What type of imaging work-up is necessary before surgery?

- Use of nomograms of NCCT results can predict the stone clearance rate, and therefore might guide optimal treatment options (LE:2, GR:B).
- CT scan is also useful for clinicians in the preoperative planning of PCNL by allowing the best and safest access for stone clearance (LE:4, GR:B).

Commentary

For SWL, factors affecting the SFR include stone density and skin-to-stone distance values (LE:4, GR:B).[101] The stone density can be measured using HU. Clinical algorithms for the prediction of upper ureteric stone and renal stones, such as the Triple D scoring system, have been developed to define the most appropriate cases for SWL application (LE:4, GR:B).[102,103] For PCNL, Okunov *et al.* developed a novel surgical classification system for kidney calculi, namely S.T.O.N.E. (LE:4, GR:B).[104] A nomogram was also developed by the CROES PCNL Study Group in 2013 to predict the SFR after PCNL, which showed an area under curve of 0.76 (LE:4, GR:B).[105] In Asia, the Modified S-ReSC Score was developed, which assigned a score of 1–9 based on the number of sites involved in the renal collecting system (LE:4, GR:B).[106,107] The use of NCCT can provide most information required for an appropriate and successful intervention. However, the use of contrast-enhanced CT is sometimes required (LE:4, GR:C1).[108]

CQ 13. How can we determine renal function of each kidney?

- Differential function of the kidneys can be attained by a radionuclide renal scan (LE:3, GR:B).
- A more invasive investigation of differential function includes determining the creatinine clearance of urine obtained during percutaneous nephrostomy with or without self-void urine (LE:5, GR:C).
- Use of US or NCCT for the assessment of cortical thickness or cortical volume of the kidneys for the prediction of differential kidney function has also been described (LE:4, GR:C).

Commentary

The least invasive method for determining differential function is the use of radionuclide renal scan.[109] However, in

patients with ureteral stones causing hydronephrosis, there is a concern that the estimated differential function by conventional nuclear scan might not be accurate and requires conjugate views for accurate evaluation (LE:4, GR:B).[110] Alternatively, more invasive methods include the use of creatinine clearance from urine collected from percutaneous nephrostomy, compared with urine collected from contralateral percutaneous nephrostomy or self-voided urine (LE:5, GR:C). Carrying out cortical thickness or parenchymal volumetric measurement by using US or NCCT could help provide a reasonable prediction of the differential creatinine clearance in obstructed kidneys (LE:4, GR:C1).[111]

Metabolic evaluation

CQ 14. Is metabolic evaluation necessary for stone disease patients?

- Basic evaluation with serum chemistry and urinary analysis is recommended for all patients presenting with stones (LE:4, GR:B).
- Metabolic evaluation including 24-h urine collection is recommended for patients at high risk of stone recurrence or formation (LE:4, GR:B).

Commentary

Metabolic evaluation of stone disease can reveal abnormalities, which are amenable to medical treatment. In recurrent stone formers, metabolic evaluation, including serum mineral, parathormone and 24-h urine chemistry, showed significant serum and urinary abnormalities in contrast to first-time stone formers in an observational study.[112] Medical treatment of stone disease has been shown to reduce the risk of stone recurrence in a meta-analysis of RCTs (LE:4, GR:B).[113]

CQ 15. Is it necessary to identify stone components?

- Stone analysis should be carried out for all first-time stone formers (LE:4, GR:C).
- Stone analysis should be repeated at every attack or intervention for patients with early stone recurrence after intervention, or late recurrence after a stone-free period (LE:3, GR:C).

Commentary

Stone analysis is an important part of the complete evaluation for a patient with stone disease. For example, calcium oxalate monohydrate stones can be associated with intermittent hyperoxaluria from high oxalate intake, decreased diuresis or inherited diseases, such as primary hyperoxaluria.[114] For patients with recurrent stone disease, the stone composition might change over time, which can impact on the efficacy of preventive treatments.[78]

CQ 16. Are biochemical tests by 24-h urine necessary? And when?

- Twenty-four hour urine tests are recommended for patients deemed at high risk of stone formation (LE:3, GR:B).
- Two separate 24-h collections should be carried out for a complete biochemical work-up (LE:4, GR:B).
- Collection of samples should be carried out for patients who have been stone-free for at least 20 days (LE:4, GR:B).
- Repeat evaluation is recommended for patients on pharmacological treatment for recurrence (LE:4, GR:B).

Commentary

The list of characteristics that classify a patient as a high-risk stone former is extensive.[115] High-risk stone formers should be counseled for 24-h urine evaluation including pH, minerals, oxalate, citrate and amino acids, as the results can guide medical prevention.[116,117] Spot urine tests have been used as an alternative for patients who are not willing or unable to carry out 24-h urine collection.[118] There is limited evidence for the timing of repeat urine collections, but most consensuses recommend a repeat collection at 8–12 weeks after commencement of pharmacological therapy. Repeat urine analysis allows titration of drug doses as necessary.[119]

Medical management

CQ 17. What is the recommended treatment for ureter stone pain management?

- Use NSAIDs to control the colic pain (LE:2, GR:A).
- Use alpha1-blockers (e.g. tamsulosin) as a treatment option for distal ureteral stones of >5 mm in size (LE:1, GR:A).

Commentary

NSAIDs are effective for patients with acute stone colic, and have better analgesic efficacy than opioids (LE:3).[120,121] Intramuscular NSAIDs offer the most effective sustained analgesia for renal colic, and seem to have fewer side-effects (LE:2).[122] For patients with ureteral stones that are expected to pass spontaneously, NSAID tablets or suppositories (e.g. diclofenac sodium, 100–150 mg/day, 3–10 days) might help reduce inflammation and the risk of recurrent pain (LE:1).[123,124]

MET refers to the administration of drugs (e.g. tamsulosin or nifedipine) that expedite the passage of the stone without the need for surgical intervention.[125,126] Meta-analysis studies have clearly shown that patients with ureteral stones treated with alpha1-blockers can reduce the number of pain episodes, the need for analgesic medication (diclofenac) and hospitalization (LE:1).[127] Administration of tamsulosin and nifedipine in MET was determined to be safe and effective for distal ureteric stones with renal colic; tamsulosin was significantly better than nifedipine in relieving renal colic and facilitating ureteric stone expulsion (LE:1).[128,129]

CQ 18. What promotes spontaneous passage of urinary stone?

- Small stones (ureteral stones of <10 mm in size) are highly likely to pass spontaneously (LE:2, GR:A).
- Stone location at the lower ureter with no obstruction (LE:4, GR:B).
- Anti-inflammatory drugs. Inflammatory changes in the ureter provoke a reduction in the rate of spontaneous passage of urinary stones; therefore, anti-inflammatory drugs, such as NSAIDs and steroids, are generally considered to increase spontaneous passage of urinary stone rates (LE:4, GR:B).
- Alpha1-blockers have been recommended for muscle relaxation of the lower ureter and to promote spontaneous ureter stone passage (LE:1, GR:A).
- Use of external physical vibration lithecbole is a treatment option (LE:1, GR:B).

Commentary

Tamsulosin significantly facilitated the passage of distal ureteral stones in patients with well-controlled pain, no infections, abnormal anatomy, renal insufficiency or high-grade obstruction (LE:1).[129] No improvement in stone passage rates was observed in patients with ≤5-mm distal ureteral stones treated with tamsulosin (LE:1).[129] While one RCT does not recommend the use of tamsulosin for symptomatic stones <9 mm,[130] a similar result was shown by another RCT trial.[131–133] However, several well-designed, randomized, double-blind, placebo-controlled studies have recently produced contradictory results, showing no overall benefit of MET.[131–135] Only the subgroup analysis for stones of 5–10 mm showed a higher passage rate in the tamsulosin group, by relaxing ureteral smooth muscle and decreasing the ureteral wall tone (LE:1).[136,137]

Low NLR (<2.3) might predict spontaneous stone passage in patients with ureter stones <10 mm in size, suggesting that ureteral inflammation plays an important role in stone passage (LE:4).[131] External physical vibration lithecbole was found to be efficacious in assisting the discharge of lower pole renal stone fragments, and can be used as an adjunctive method of minimally invasive stone treatment (LE:1–3).[138–142]

CQ 19. What is the role of medical chemolysis in uric acid stone?

- Uric acid stones can be dissolved by medical chemolysis using oral alkaline citrate or sodium bicarbonate through alkalinization of urine (LE:2, GR:A).

Commentary

Urinary concentration of uric acid depends on urine pH, urine volume and excretion of uric acid. Urinary pH is the most important factor in uric acid solubility.[143] Oral alkaline citrate or sodium bicarbonate is used for chemolysis through alkalinization of the urine.[144] Although the efficiency of chemolysis is directly proportional to higher pH, the pH should be adjusted in the range of 7.0–7.2 to prevent formation of calcium phosphate calculus.

CQ 20. What medical treatment is appropriate for pyelonephritis accompanying urinary stone?

- Active antibiotic treatment and timely drainage of kidney if necessary (LE:1, GR:A).
- Percutaneous nephrostomy and ureteral catheter insertion (LE:2, GR:A).
- Nephrectomy is advocated as the treatment of choice for a kidney that has lost most of its function and the contralateral kidney is normal (LE:1, GR:A).
- Remove and cure of the lithiasis after the treatment of UTI, which is the main etiological factor in this pathology (LE:1, GR:A).

Commentary

The treatment approaches of pyelonephrosis accompanying urinary stone should be individualized based on the age, general condition of the patient and patient compliance (LE:1).[145] Retrograde ureteral catheterization is appropriate for drainage of hydronephrosis (LE:2).[146] In addition, percutaneous nephrostomy provides a means of draining off pus and determining possible residual renal function.[146] If carried out properly, percutaneous drainage is a fast, reliable, and quickly effective therapeutic method in one session (LE:1).[147] The combination of medical management and percutaneous drainage decreased the mortality rate of obstructive emphysematous pyelonephritis to 13.5%, compared with 50% with medical management alone.[148] Nephrectomy is advocated as a treatment option in the case of a damaged kidney, which seems difficult to be preserved by conservative and endourological treatment, with a normally functioning contralateral kidney (LE:3, LE:1).[149,150] The best treatment consists of the removal and cure of the lithiasis, which is the main etiological factor in this pathology (LE:2).[146]

Surgical management

CQ 21. When can SWL be the first option for patients with renal stones?

- While SWL is an option for most renal stones, it should not be applied to patients who are contraindicated for SWL or have abnormal renal anatomy, such as caliceal diverticulum and so on (LE:5, GR:A).
- For renal stones <20 mm, SWL is a recommended first-line treatment for patients (LE:3, GR:A).
- For stones >20 mm or for renal stones presenting less favorable factors, such as high mean stone density or located in calices with poor anatomy, the treatment outcome will be less favorable. Therefore, the pros and cons of each treatment modality should be discussed in detail with the patient before a joint decision on treatment plan can then be taken (LE:5, GR:B).
- SWL is highly effective in pediatric cases due to its non-invasive nature and higher SFRs compared with adults (LE:2, GR:B).

Commentary

SWL might be considered as the first treatment option for the index patient who has no contraindication for SWL, with stones sized <20 mm in general[151] or <10 mm for lower caliceal stones with favorable anatomy and composition (non-cystine, non-calcium monohydrate stone or stone CT HU <1000; LE:4).[100,101,152] For a patient with contraindication for SWL, abnormal body habitat, hard stone or unfavorable renal anatomy, other treatment options should be considered.

CQ 22. What are the complications of SWL?

- In general, the incidence of complications of SWL is low, and the majority are clinically not severe (LE:4, GR:B).
- The most severe complication, symptomatic hematoma, is detected in <1% of cases (LE:4, GR:B).
- There is no evidence suggesting SWL has long-term side-effects for patients (LE:4, GR:B).

Commentary

The incidence of complications after SWL is low and most are mild (LE:4, GR:B).[153–155] Complications of SWL can be divided into three types: intraprocedure,[150] early complications[156,157] and long-term complications (Table 4).[158,159] Major contraindications are pregnancy, uncontrolled UTI and/or coagulation disorders, and the presence of an aortic or renal aneurysm.[160]

CQ 23. What are the complications of lithotripsy by URS?

- The overall complication rate after URS is 9–25%. Most complications are minor and do not require intervention (LE:1, GR:A).

Table 4 Common complications after SWL

Complications	EAU guidelines	Sun and Zhang (Chinese group)[154] (LE:4)	Jagtap *et al.* (Indian group)[155] (LE:4)
Intraprocedure			
Dysrhythmia	11–59%	–	–
Early complications			
Hematoma (symptomatic)	<1%	–	0.48%
Hematoma (asymptomatic)	4–19%	–	–
Renal colic	2–4%	1.3–3.7%	1.02%
Steinstrasse	4–7%	–	1.96%
Sepsis	1–2.7%	4.0–7.4%	2.05%
Long-term complications			
Regrowth of residual fragments	21–59%	–	–

- The following complications are the most relevant (Table 5): sepsis; ureteral stricture; ureteral injury; and UTI.
- Serious complications, including death and loss of kidney, were sufficiently rare that data were not available to estimate their rates of occurrence (LE:1, GR:A).

Commentary

The overall complication rate after URS is 9–25%.[161] The most relevant intraoperative and postoperative complications are sepsis, ureteral stricture, ureteral injury and UTI. Ureteral avulsion and strictures are rare (<1%). Previous perforations are the most important risk factors for complications (LE:1, GR:A).

CQ 24. What are the complications of PCNL?

- The complication rate of PCNL was reported to range from 10% to 20%, and most of the complications were not severe (LE:1, GR:A).
- The most common postoperative complications associated with PCNL are fever and bleeding, and urinary leakage (LE:1, GR:B).
- The complication rates of standard PCNL and minimally invasive PCNL were reported to be 15.9% and 12.8%, respectively. Minimally invasive PCNL is at least as efficacious and safe as standard PCNL (LE:1, GR:A).

Commentary

The complication rate of standard PCNL was reported to be 15.9%, whereas that of minimally invasive PCNL was reported to be 12.8% (LE:1).[162,163] The complication rate of PCNL improved from 21.3% between 1997 and 2005 to 10.3% between 2006 and 2014 (LE:3).[164] The most common postoperative complications associated with PCNL are fever and bleeding, urinary leakage, and problems due to residual stones (LE:1; Table 6).[165] Clavien 1, 2, 3, 4 and 5 complications were observed in 88.1%, 7%, 4.1%, 0.6% and 0.04% of cases, respectively.[165] One RCT has compared ECIRS with minimally invasive PCNL, and showed that no significant difference in perioperative complications including blood transfusion was observed between the two groups (P = 0.409; LE:2).[166]

Table 5 Common complications with URS compared with SWL

	SWL		URS	
	Groups/ patients	Median/ 95% CI	Groups/ patients	Median/ 95% CI
Distal ureter				
Sepsis	6	3%	7	2%
	2019	2–5%	1954	1–4%
Ureteral stricture	2	0%	16	1%
	609	0–1%	1911	1–2%
Ureteral injury	1	1%	23	3%
	45	0–5%	4529	3–4%
UTI	3	4%	3	4%
	87	1–12%	458	2–7%
Mid ureter				
Sepsis	2	5%	4	4%
	398	0–20%	199	1–11%
Ureteral stricture	1	1%	7	4%
	43	0–6%	326	2–7%
Ureteral injury			10	6%
			514	3–8%
UTI	1	6%	1	2%
	37	1–16%	63	0–7%
Proximal ureter				
Sepsis	5	3%	8	4%
	704	2–4%	360	2–6%
Ureteral stricture	2	2%	8	2%
	124	0–8%	987	1–5%
Ureteral injury	2	2%	10	6%
	124	0–8%	1005	3–9%
UTI	5	4%	2	4%
	360	2–7%	224	1–8%

Table 6 Perioperative complications of percutaneous nephrolithotomy

Complication	Frequency (%)	Range
Fever	10.8	0–32.1
Transfusion	7	0–20
Thoracic complications	1.5	0–11.6
Sepsis	0.5	0.3–1.1
Embolization	0.4	0–1.5
Organ injury	0.4	0–1.7
Urinoma	0.2	0–1
Death	0.05	0–0.3

Total n = 11 929.

CQ 25. What situation(s) require(s) open/laparoscopic/ robotic-assisted stone surgery?

- Although endoscopic management is a standard approach for most stone removal surgery, open/laparoscopic/ robotic-assisted surgery might be alternatives in selected situations, such as stones requiring complete removal within a single session (infection stones) or stones with urinary tract anatomical abnormalities requiring simultaneous reconstruction (LE:5, GR:C1).

Commentary

For large stones or stones with complex configuration, open/laparoscopic/robotic-assisted surgery might clear all stone burden within a single session. Several reports showed the simplicity of the procedure and excellent outcomes resulting from laparoscopic pyelolithotomy with or without concomitant pyeloplasty.[167,168] Both the transperitoneal and retroperitoneal approach resulted in similar SFRs.[169] Laparoscopic management of symptomatic caliceal diverticular stone is effective in diverticula with thin overlying renal parenchyma or anterior lesions inaccessible by endourological techniques.[170] Laparoscopic anatrophic nephrolithotomy can be carried out selectively in large staghorn stones requiring complete removal in a single surgical session.[171] Finally, laparoscopic ureterolithotomy might be an alternative for impacted large proximal ureteral stones.[172]

CQ 26. What urinary stones are eligible for ECIRS?

- Possible indications requiring combined approaches to the kidney or ureter (LE:2, GR:B):
  - large and complex stones;
  - large renal and concomitant ureteral stones or strictures;
  - ipsilateral medium-to-large renal stones and contralateral small renal stones;
  - diverticular stones with a difficult angle to the infundibulum or a narrow infundibulum;
  - difficulty of angle to approach from the calyx of the percutaneous puncture to other calyces to avoid multiple tracts;
  - impacted UPJ stones with complete obstruction; and ureteral strictures that require an antegrade incisional procedure.

Commentary

The retrograde approach using a flexible ureteroscope has shown good surgical outcomes. However, the antegrade approach using a flexible ureteroscope or nephroscope can increase the SFRs in cases of acute infundibulopelvic angle or narrow infundibulum, musculoskeletal deformities, or anatomical abnormalities (LE:2).[166,173–175] ECIRS can be carried out in either the supine or prone position. However, there has been no randomized controlled study examining the patients' position (LE:4).[173,176,177] ECIRS contains two different concepts of location (bidirectional) and time (simultaneous; Fig. 1).[176,178] Selection of the combined bidirectional or simultaneous bidirectional approach depends on the location and size of the renal stones (Fig. 2).

CQ 27. What urinary stones are eligible for miniaturized PCNL?

- Miniaturized PCNL can be recommended to treat medium-sized renal stones with promising good surgical outcomes with comparable SFRs and reduced risk of morbidity (LE:1, GR:B).

Commentary

The acceptable criteria on stone burden of the miniaturized PCNL has been medium-sized renal stones <3.0–3.5 cm, and ultraminiperc or microperc might be suitable for stones <1.5 cm.[179–182] Miniaturized PCNL can be considered when there are diverticular stones, and pediatric medium-sized stones as well (LE:4).[179,180,183] Miniaturized PCNL has shown comparable surgical outcomes to conventional PCNL in terms of SFRs with lower probability of complications;[184,185] however, it seems to have longer operative times and higher intrarenal pressure than conventional PCNL during surgery.[186,187] The surgical outcomes of miniaturized PCNL are promising, with good SFRs, shorter hospital stay and reduced risk of morbidity, such as bleeding, adjacent organ injury and so on (LE:1).[186] Miniaturized PCNL and RIRS have similar indications for medium-sized renal stones <3 cm;[188] however, safety concerns regarding the higher bleeding risk, larger hemoglobin drop or longer hospital stay of miniaturized PCNL compared with RIRS arose (LE:1).[189,190]

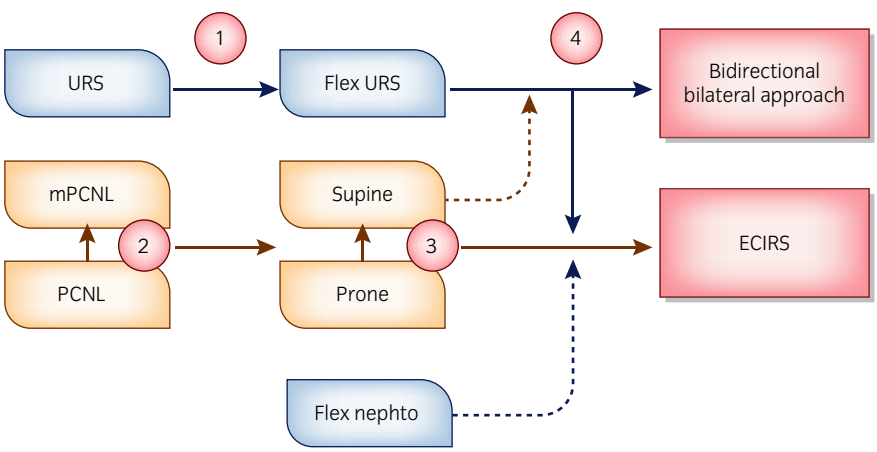

Fig. 1 Development of stone surgery in the era of flexible ureteroscopy. Numbers 1–4 represent the turning point where a surgeon needs to select a surgical option. (1) Rigid or semi-rigid ureteroscopic surgery was developed for flexible ureteroscopic surgery to remove renal stones. (2) The use of a miniaturized nephroscope became one of the good options for removal of large renal stones in conjunction with 30-Fr conventional percutaneous nephrolithotomy. (3) Percutaneous nephrolithotomy in the supine position is increasingly used. (4) The bidirectional approach with a flexible ureteroscope for bilateral renal stones became more common due to development of the procedure with device innovation. Furthermore, ECIRS using flexible ureteroscopes and percutaneous nephroscopes in a single session is gaining increasing attention worldwide.

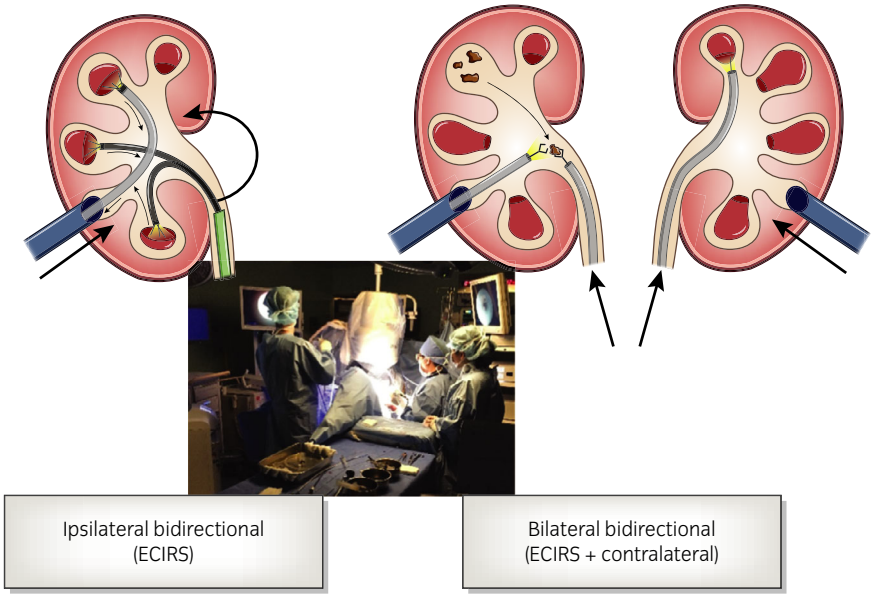

Fig. 2 Combined approach to removing stones simultaneously. Endoscopic intrarenal surgery can be considered using multiple approaches with a flexible scope in combination with a rigid nephroscope to remove renal stones in an ipsilateral kidney. Bilateral renal stones can be removed in a single session in some cases.

CQ 28. What is the algorithm for treatment of adult patients with symptomatic renal stones?

- Considering its low stone-free rate for stones >15 mm, RIRS could be carried out for stones up to 20 mm in size (LE:2, GR:B).
- Although there is limited evidence about the choice of appropriate surgical approach for symptomatic renal stones, mini-PCNL with 14–20-Fr tracts is accumulating more evidence regarding the reliability and safety considerations (LE:1, GR:B).
- However, ultramini-, micro-PCNL, or the ancillary use of miniaturized nephroscopes and flexible ureteroreno- or nephroscopes has shown limited evidence based on observational or retrospective studies (LE:4, GR:C1).

Commentary

The summarized flow chart for treatment algorithm is shown in Figure 3.[166,174–181,184,185,188,189,191–206]

CQ 29. What is an algorithm for treatment of adult patients with ureteral stones?

- Expectant management or MET might be considered for non-obstructing ureteral stones without complications (LE:1, GR:B).
- Once the surgery is indicated, URS or SWL are acceptable (LE:2, GR:B).

Commentary

The summarized flow chart for treatment algorithm is shown in Figure 4.[135,207–214]

CQ 30. How can we manage urinary stones in specific situations, such as children and pregnant women?

- In pregnant patients with uncomplicated urinary stones, offer conservative management as a first-line therapy (LE:4, GR:B).
- URS has emerged as a preferred treatment for pregnant patients who failed conservative management (LE:2, GR:B).
- Placement of a ureteral stent or a percutaneous nephrostomy tube is an alternative option, with frequent stent or tube changes usually being necessary (LE:2, GR:C).
- In children with uncomplicated ureteral stones ≤10 mm, offer conservative management as a first-line therapy (LE:4, GR:B).
- Both SWL and URS are the treatments of choice for children with ureteral stones who are unlikely to pass the stones or who have failed conservative management (LE:2, GR:B).
- All three surgical modalities (SWL, URS, PCNL) are acceptable treatment options for children with renal stones (LE:2, GR:B).

Commentary

The spontaneous stone passage rates for pregnant patients ranges from 48% to 84%.[91] NSAIDs are contraindicated in pregnancy. Frequent small doses of morphine can be used safely for severe pain, and acetaminophen for mild analgesia.[93,94] The use of MET for pregnant patients as "off-label" use remains debatable.[94] When clinical indications for intervention emerges, placement of a ureteral stent or percutaneous nephrostomy tube is an effective option;[94,215,216] however, URS has been identified as a reasonable alternative in these situations.[217–219] SWL is an absolute contraindication, and PCNL should be generally avoided.[93,94]

An initial trial of conservative management should be offered for children with uncomplicated ureteral stones, because spontaneous stone passage is expected in a significant proportion of children.[99,220] SWL provides more effective disintegration of large stones, and rapid and uncomplicated discharge of fragments compared with adult patients.[221] With the development of intracorporeal lithotripsy devices and smaller-caliber instruments, indications for URS and PCNL are similar to those for adult patients.[222,223]

CQ 31. How should asymptomatic small renal stone be managed?

- Asymptomatic stones develop symptomatic events in 31.8–53.6% of patients within 5 years (LE:4).
- Clinicians can offer active surveillance for patients with asymptomatic renal stones due to their low probability for

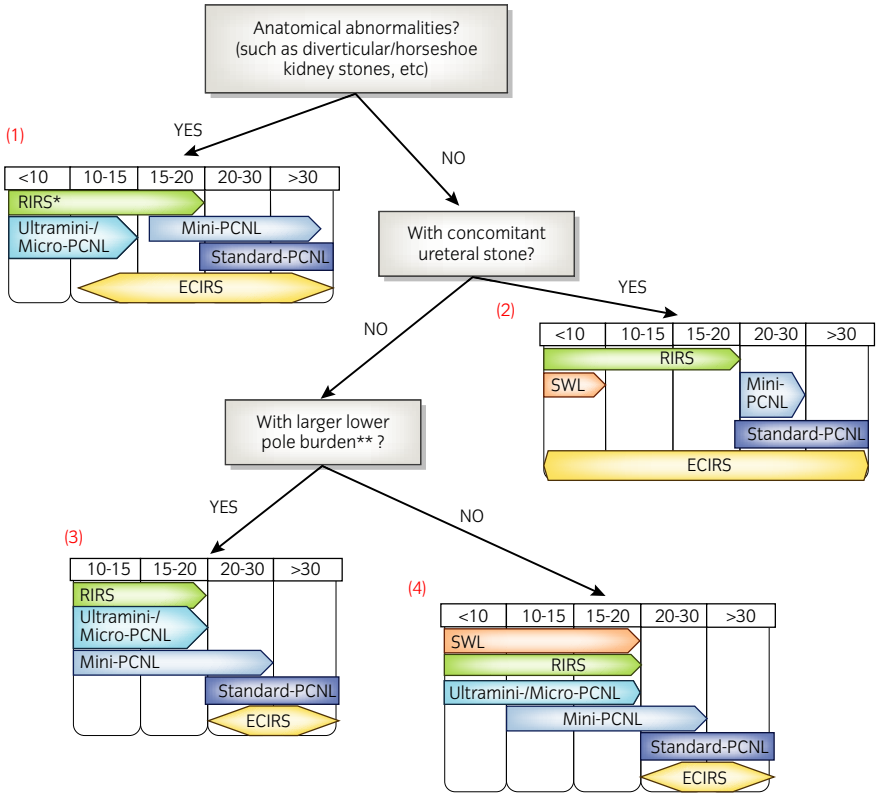

Fig. 3 Flow chart for treatment of adult patients with symptomatic renal stones. The first step in considering surgical intervention for renal stones is to confirm any anatomical abnormalities. (1) Horseshoe kidneys with calyceal diverticula usually have narrow and long infundibula, making SWL ineffective; therefore, either RIRS or PCNL should be considered, depending on the stone burden. In addition, miniaturized PCNL and ECIRS could be an option, depending on anatomical features. (2) A concomitant ureteral stone is more appropriately managed with a retrograde approach, using RIRS or ECIRS. Antegrade lithotripsy with mini- or standard-PCNL is also appropriate for a stone >20 mm. (3) Large lower pole stones measuring ≤20 mm should be treated with RIRS or miniaturized PCNL, and lower pole stones >20 mm should be treated with standard PCNL or ECIRS. SWL is less effective due to potential postprocedure complications and limited evidence for efficacy. (4) Small, simple renal stones are treatable with SWL, RIRS or miniaturized PCNL. Stones >20 mm should be treated using standard PCNL or ECIRS. *There are some limitations/exceptions regarding the anatomical difficulties in approaching the stone with a flexible ureteroscope. **Cases predominantly having lower caliceal stones >10 mm.

developing symptomatic events requiring interventions (LE:2, GR:C).

- Asymptomatic renal stones should be treated in situations of rapid growth and development of symptoms (LE:2, GR:A).

Commentary

A prior retrospective cohort study showed that 31.8% of asymptomatic stone patients developed symptomatic stone events in 31.6 months of mean study follow up.[224] Recent cohort studies reported that the development of symptomatic stone events were 53.6% for 31 months of mean follow up and 42% for 4.7 years of median follow up, respectively.[225,226] Studies suggested that larger stone size, in particular volume, and rapid increase in stone volume appeared to be predictive of future stone events in patients with asymptomatic stones (LE:4).[227,228] Some RCTs reported that observation of asymptomatic renal stone did not affect the patient's follow up compared with SWL or PCNL (LE:2).[229,230] A patient decision-based survey showed that 22.8% chose observation, which revealed that the patients who had passed larger stones were less likely to choose observation over surgery (LE:4).[231]

Recurrence prevention

CQ 32. Is hydration effective for stone prevention and how much fluid intake should be recommended?

- Hydration is clinically useful for secondary stone prevention by a urine dilutional effect. Urinary stone patients should be advised to achieve a goal of 2–2.5 L of urine daily (LE:2, GR:A).

Commentary

Increased fluid intake, which results in urine dilution, is a widely accepted measure to reduce recurrent stone formation.[232,233] An RCT has shown that stone formers who were assigned to increase fluid intake to achieve a urine volume ≥2 L/day had a significantly lower stone recurrence rate compared with controls (12% *vs* 27%, $P = 0.008$).[28] In general, adequate hydration with a goal of at least 2–2.5 L of urine daily should be recommended. A non-invasive fluid tracker, a combination of a fluid tracking system and mobile health technology, has considerable potential to help urinary stone patients achieve high fluid intake.[234]

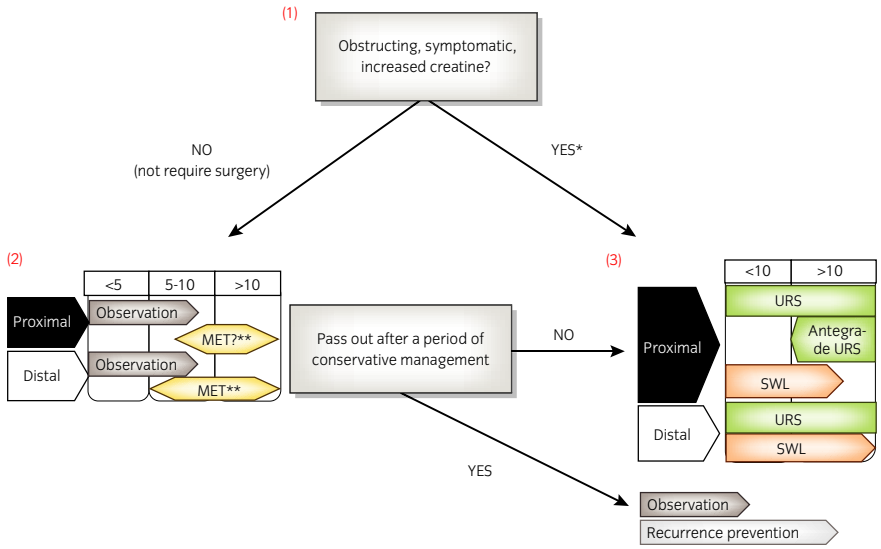

Fig. 4 Flow chart for treatment of adult patients with ureteral stones. Stone-related and patient factors should be considered when treating adults with ureteral stones. (1) The first step is to verify whether the patient has an indication for active stone removal, including significant urinary obstruction, stone-related symptoms and progressive renal deterioration. (2) In the absence of an indication for active stone removal, close observation or MET should be offered. In general, small ureteral stones have a high probability of spontaneous passage, especially when located in the distal ureter. MET can be appropriate for distal ureteral stones >5 mm and proximal ureteral stones larger than 10 mm. (3) If active stone removal is clinically indicated, URS, using either a retrograde or antegrade approach, and SWL are usually considered. Proximal ureteral stones >10 mm can be treated with URS more efficiently than with SWL. *These conditions might require ureteral stent insertion or percutaneous nephrostomy tube placement before removal of stones. **A treating physician should consider early surgical intervention in parallel during the trial of medical treatment.

CQ 33. What are the components that affect the risk of recurrence that are effective for prevention of stone disease?

- Stone type and disease severity determine recurrent risk, including general factors, diseases associated with stone formation, genetically-determined stone formation, drug-induced stone formation, anatomical abnormalities associated with stone formation and environmental factors (LE:2, GR:B).
- Normalization of dietary habits with adequate fluid intake and a balanced diet, adequate physical activity, and maintenance of a normal BMI level are the main strategies for preventing stone disease (LE:1, GR:A).

Commentary

Stone type and disease severity determine a low or high risk of recurrence (Table 7).[235–238]

All stone formers, independent of their individual risk, should follow the suggested preventive measures, whose main focus is normalization of dietary habits and lifestyle risks (Table 8).[239–244] Stone formers at high risk require specific prophylaxis for recurrence,[245,246] which is usually pharmacological treatment based on stone analysis (Table 9).

CQ 34. What foods are effective for preventing the recurrence of calcium stones?

- A common-sense approach to diet should be taken; that is, a mixed balanced diet with contributions from all food groups, without any excesses. Fruit and vegetable intake are encouraged; oxalate-rich products, vitamin C and animal protein should be restricted; and excessive intake of calcium should be limited (LE:2, GR:B).

Commentary

The effect of fruit juices is mainly determined by the presence of citrate, bicarbonate and pottassium.[32,247–249] Potassium increases both pH and citrate (LE:2, GR:B). Fruit and vegetable intake should be encouraged because of the beneficial effects of fiber, although the role of the latter in preventing stone recurrences is debatable (LE:1, GR:A).[250–253] Excessive intake of oxalate-rich products should be limited or avoided to prevent high oxalate load, particularly in patients who have high oxalate excretion (LE:3, GR:C).[32] As its role as a risk factor in calcium oxalate stone formation remains controversial,[254] avoiding excessive vitamin C intake seems wise for calcium oxalate stone formers (LE:3, GR:C).[255] Excessive consumption of animal protein has several effects that favor stone formation, including hypocitraturia, low urine pH, hyperoxaluria and hyperuricosuria, and should be limited to 0.8–1.0 g/kg bodyweight (LE:1, GR:A).[30,34] Calcium intake should not be restricted unless there are strong reasons due to the inverse relationship between dietary calcium and stone formation (LE:1, GR:A).[33,251] Calcium supplements are not recommended except in enteric hyperoxaluria (LE:1, GR:A).[34] Calcium stone formation can be reduced by restricting sodium and animal protein (LE:1, GR:A).[30,34,251,256]

CQ 35. Does salt intake increase the risk of urinary stones?

- Clinicians should provide patients with calcium stones suitable information about restriction of sodium intake and the necessity of appropriate intake of dietary calcium of 1000–1200 mg per day (LE:2, GR:C1).

Commentary

Dietary salt – sodium chloride – is linked to calcium excretion in urine.[257] An RCT showed that a lower salt diet with a

Table 7 Examples for high-risk stone formers

General factors
Early onset of urolithiasis (especially children and teenagers)
Familial stone formation
Brushite-containing stones ($CaHPO_4 \cdot 2H_2O$)
Uric acid- and urate-containing stones
Infection stones
Solitary kidney (the kidney itself does not particularly increase the risk of stone formation, but prevention of stone recurrence is of more importance)
Diseases associated with stone formation
Hyperparathyroidism
Metabolic syndrome
Nephrocalcinosis
Polycystic kidney disease
Gastrointestinal diseases (i.e. jejuno-ileal bypass, intestinal resection, Crohn's disease, malabsorption conditions, enteric hyperoxaluria after urinary diversion) and bariatric surgery
Sarcoidosis
Spinal cord injury, neurogenic bladder
Genetically determined stone formation
Cystinuria (type A, B and AB)
Primary hyperoxaluria
Renal tubular acidosis type I
2,8-Dihydroxyadeninuria
Xanthinuria
Lesch–Nyhan syndrome
Cystic fibrosis
Drug-induced stone formation
Anatomical abnormalities associated with stone formation
Medullary sponge kidney (tubular ectasia)
UPJ obstruction
Caliceal diverticulum, caliceal cyst
Ureteral stricture
Vesico-uretero-renal reflux
Horseshoe kidney
Ureterocele
Environmental factors
Chronic lead exposure

Table 8 General preventive measures

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

target of ≤100 mEq (2300 mg) could reduce calcium excretion in urine for hypercalciuric stone formers (LE:2).[34] Previous interventional studies have reported a linear association between salt intake and urinary calcium excretion.[258,259] Intake of high dietary salt diminishes the efficacy of reabsorption of sodium and water in renal proximal tubules, which prevents calcium reabsorption.[260,261] This hypercalciuric status might facilitate stone formation.[262]

CQ 36. Does animal protein intake increase the risk of urinary stones?

- Animal protein lowers urinary pH and increases uric acid in urine. Intake of excessive animal protein is one of the risk factors for excessive uric acid excretion and calcium stone formation (LE:1, GR:B).

Commentary

Previous clinical,[34] epidemiological[256,263] and metabolic[264] studies have suggested that excessive consumption of animal protein might induce stone formation (LE:4).[256,264–266] For patients with recurrent calcium oxalate stones, limited animal protein intake of 0.8–1.0 g/kg/day reduces stone formation (LE:1).[30]

CQ 37. Does thiazide prevent urinary stones?

- Clinicians might recommend thiazide medication with or without potassium citrate to patients with high or relatively high urinary calcium, as well as recurrent calcium stone formers without definite evidence of metabolic abnormalities (LE:1, GR:B).

Commentary

Thiazide reduces recurrent calcium stone formation by the hypocalciuric effect with once-daily use of 50 mg hydrochlorothiazide, 25 mg chlothalidone and 2.5 mg indapamide (LE:1).[34,267–271] Potassium citrate or potassium chloride might be necessary to prevent hypokalemic effects induced by thiazide medication.

CQ 38. Does citric acid prevent urinary stones?

- Various citrus juices can be utilized to induce citraturia. However, whether this approach can reduce calcium stone recurrence is still under investigation (LE:4, GR:C1).

Commentary

Administration of citrate has been shown to benefit hypocitraturic stone formers.[272] Orange juice effectively induces citraturia due to its high concentration of potassium citrate.[273] Lemonade and lime juice show increased urinary citrate in some studies,[274] but not in others.[275] Grapefruit juice not only increases urinary citrate, but also increases oxalate excretion, so its protective effect is offset.[276]

CQ 39. Does magnesium prevent urinary stones?

- Magnesium inhibits calcium oxalate stone formation either *in vitro* or *in vivo*, and several studies have shown its protective effects based on urinary parameters. Most clinical trials utilizing magnesium in combination with other stone inhibitors showed promising results. However, magnesium as sole therapy is ineffective and is not recommended (LE:4, GR:D).

Commentary

Urinary magnesium complexes with oxalate, which reduces calcium oxalate supersaturation, inhibit the nucleation and growth of calcium oxalate crystals.[277,278] Furthermore, recent data have shown that its inhibitory effect synergizes with citrate and continues to be effective at an acidic pH environment.[279] Magnesium supplement in calcium stone formers

Table 9 Pharmacological substances used for stone prevention: characteristics, specifics and dosage

Agent	Rationale	Dose	Specifics and side-effects	Stone type
Alkaline citrates	Alkalinization Hypocitraturia Inhibition of calcium oxalate crystallization	5–12 g/day (14–36 mmol/day) Children: 0.1–0.15 g/kg/day	Daily dose for alkalinization depends on urine pH	Calcium oxalate, uric acid cystine
Allopurinol	Hyperuricosuria Hyperuricemia	100–300 mg/day Children: 1–3 mg/kg/day	100 mg in isolated hyperuricosuria Renal insufficiency demands dose correction	Calcium oxalate, uric acid, ammonium urate, 2,8-dihydroxyadenine
Calcium	Enteric hyperoxaluria	1000 mg/day	Intake 30 min before meals	Calcium oxalate
Captopril	Cystinuria Active decrease of urinary cystine levels	75–150 mg	Second-line option due to significant side effects	Cystine
Febuxostat	Hyperuricosuria Hyperuricemia	80–120 mg/day	Acute gout contraindicated, pregnancy, xanthine stone formation	Calcium oxalate, uric acid
L-Methionine	Acidification	600–1500 mg/day	Hypercalciuria, bone demineralization, systemic acidosis No long-term therapy	Infection stones, ammonium urate, calcium phosphate
Magnesium	Isolated hypomagnesiuria Enteric hyperoxaluria	200–400 mg/day Children: 6 mg/kg/day	Renal insufficiency demands dose correction Diarrhea, chronic alkali losses, hypocitraturia	Calcium oxalate
Sodium bicarbonate	Alkalinization Hypocitraturia	4.5 g/day		Calcium oxalate, uric acid, cystine
Pyridoxine	Primary hyperoxaluria	Initial dose 5 mg/kg/day Maximum 20 mg/kg/day	Polyneuropathia	Calcium oxalate
Thiazide (hydrochlorothiazide)	Hypercalciuria	25–50 mg/day Children: 0.5–1 mg/kg/day	Risk for agent-induced hypotonic blood pressure, diabetes, hyperuricemia, hypokalemia, followed by intracellular acidosis and hypocitraturia	Calcium oxalate, calcium phosphate
Tiopronin	Cystinuria, active decrease of urinary cystine levels	Initial dose 250 mg/day Maximum 2000 mg/day	Risk for tachyphylaxis and proteinuria	Cystine

improved lithogenic biochemical parameters.[280,281] Clinical studies that utilized magnesium in combination with various stone inhibitors have shown favorable effects of magnesium over calcium stone formation,[282,283] including increased urinary citrate level and reduced stone recurrence.[284] One study compared the effectiveness of magnesium hydroxide with chlorthalidone in protection of recurrent calcium nephrolithiasis and found inferior results.[267] However, one cohort study of recurrent calcium stone formers reported that increased magnesium intake was significantly associated with decreased hyperoxaluria.[285]

CQ 40. What prevents uric acid stone formation?

- Hydration and urine alkalinization are the mainstays of uric acid stone prevention. The latter can be achieved either by diet manipulation or by pharmacotherapy using citrate supplementation (LE:4, GR:B).

Commentary

The main principles of uric acid stone medical therapy and prevention are aimed at increasing urine volume, urinary alkalinization and, less importantly, the reduction of uric acid excretion.[286] The exact amount of daily fluid to prevent uric acid stone remains unclear. However, a total of 2.5–3 L per day is generally recommended.[287] Urinary alkalinization can be achieved either by diet manipulation or pharmacotherapy with the goal of urine pH >6.0.[274] Periodic monitoring of urine pH is mandatory, as hyperalkalinization of urine might lead to formation of calcium phosphate stones.[288]

CQ 41. What prevents cystine stones?

- In cystine stone formers, prevention with proper hydration and urine alkalinization is generally utilized as first-line prevention. If stone recurrence still occurs, second-line prevention with a cystine-binding agent is offered (LE:4, GR:B).

Commentary

As recurrent stone formation is frequently observed in cystinuria patients, medical prophylaxis is highly recommended.[289] Cystine is poorly soluble at urine pH <7.0, and stone formation occurs when urinary cystine concentration is >250 mg/dL.[290] Fluid intake should reach at least 4–5 L/day for adult patients to achieve a urinary cystine concentration <250 mg/dL.[291] In alkalinized urine, potassium citrate is usually prescribed to target urine pH of 7.0–7.5, if not contraindicated. If these two steps fail to prevent cystine stone recurrence, the next step is to add a cystine-binding agent, such as tiopronin or D-penicillamine.[292,293]

CQ 42. What prevents infectious stones?

- Fluid intake and diet is general recommended (LE:2, GR:B).

- Other treatments, such as short- or long-term antibiotic treatment, methionine or ammonium chloride, restricted intake of urease, or acetohydroxamic acid, might be considered for recurrent or severe infection (LE:1, GR:A).
- Phytolysin improves general clinical signs and laboratory parameters of blood and urine, and reduces the number of relapses of UTI and stone formation (LE:2, GR:B).

Commentary

General preventive measures are recommended for fluid intake and diet. Specific measures include complete surgical stone removal (LE:2, GR:B).[294] Short- or long-term antibiotic treatment,[295] urinary acidification using methionine (LE:2, GR:B),[296] or ammonium chloride (LE:2, GR:B),[297] and advice to restrict intake of urease (LE:1, GR:A).[298,299] For severe infections, acetohydroxamic acid might be an option (LE:1, GR:A).[298,299] Phytolysin leads to a decrease in the level of leukocyturia and bacteriuria, increases diuresis and urinary alkalinization, and reduces the number relapses of UTI and stone formation (LE:2, GR:B).[300]

CQ 43. What is a useful imaging test for follow up of urinary stone recurrence?

- Plain radiography, nephrotomography, US, IVU and CT have all been used to evaluate residual fragments (LE:1, GR:A).
- The routine use of CT scan for follow-up studies should be carried out cautiously and only when necessary (LE:1, GR:A).
- Imaging plays a critical role in the initial diagnosis, follow up and urological management of urinary tract stone disease (LE:1, GR:A).

Commentary

A variety of imaging modalities are available to the practicing urologist, including KUB, IVU, US, magnetic resonance urography and CT scans, each with its advantages and limitations. Post-treatment imaging of stone patients is recommended to ensure complete fragmentation and stone clearance. Plain radiography is suggested for the follow up of radiopaque stones, with US and limited IVU reserved for the follow up of radiolucent stones to minimize cumulative radiation exposure from repeated CT scans. CT is a modality of choice for identifying residual stone burden after interventional procedures,[301–304] and has a definitive role in the follow up of stones that are lucent on conventional imaging.[301,305] Patients with asymptomatic caliceal stones who prefer an observational approach should have a yearly KUB to monitor the progression of stone burden (LE:2, GR:A).[301,303,306]

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Conflict of interest

The Work Group consists of an international group of clinicians with specific expertise in this area. All experts involved in the production of this document have submitted declarations of potential conflict of interest. Individual statements can be viewed on the UAA website.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Level of evidence and grade of recommendation.