THE UAA CLINICAL GUIDELINE FOR URINARY STONE DISEASE

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The Urological Association of Asia (UAA)

The UAA clinical guideline for urinary stone disease

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1. Introduction

1.1. Foreword

The Urological Association of Asia (UAA) has planned to develop Asian guidelines for all urologic fields, and the first and second such guidelines focusing on lower urinary tract symptoms on urinary tract infections (UTIs) and sexually transmitted diseases were published in 2013 and 2016, respectively. The field of stone diseases is the third of the UAA guideline projects. The first meeting for this project was held on August 3rd, 2017, in Hong Kong. The Guideline Development Work Group (Work Group) was established and initiated the guideline development project.

In April 2018, the Work Group met again at the UAA Congress in Kyoto, and this led to the drafting of the guidelines. All committee members reviewed and made significant contributions for completing this guideline.

1.2. 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 systems, equipment, and access to hospitals and facilities. We are required to establish a consensus on treatment. The *UAA Clinical Guidelines for Stone Disease* has 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 health care.

It must be emphasised that clinical guidelines present the best evidence available to experts, but solely following the guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus these decisions, which also should take into account personal values and preferences/individual circumstances of patients. It must be emphasised that clinical guidelines might present the best evidence available to the urologists, although as stated above, the following guideline recommendations will not necessarily result in the best outcome but will provide a basis for informed decision-making.

Diverse treatment alternatives may 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.

1.3. Diversity of treatment strategies among members of the UAA

Since the foundation of the UAA in 1990, it now consists of 25 member associations and 1 affiliated member. Due to the different climate, social, economic, and ethnic environments, there is huge diversity in clinical practice for urinary stone disease among Asian countries. Thus, we performed a surveillance study to collect information regarding the treatment options for each guideline committee member when we started this project to better understand the differences among those representatives and respect their patient management strategies and limitations imposed by their individual country's health insurance systems.

Table 1.1 summarises treatment strategies for each UAA representative for different stone cases. In accordance with other guidelines, shock wave lithotripsy (SWL) and endoscopic lithotomy, such

Table 1.1 Treatment approaches of different stone cases among different UAA representatives

	47-Year-old male, left partial staghorn stone (40 mm)	65-Year-old male, left renal pelvic stone (18 mm)	75-Year-old female, right lower calyx stone (10 mm)	50-Year-old female, right mid-ureter stone (13 mm) with moderate hydronephrosis	8-Year-old male, right renal pelvic stone (8 mm)
Cambodia	1: Pyelonephrolithotomy 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: Ultramini-PCNL	1: URS 2: Antegrade URS	1: SWL 2: RIRS (+pre-stenting) or 1: Ultramini-PCNL
Hong Kong	1: PCNL	1: PCNL	2: SWL	1: URS	1: SWL
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
India	1: PCNL 2: Robotic/laparoscopic pyelolithotomy 3: Pyelolithotomy/ extented pyelolithotomy	1: PCNL (>1,000 HU) 2: SWL (<1,000 HU) 3: RIRS	1: SWL (favourable anatomy and stone density) 2: RIRS 3: Mini-PCNL	1: URS 2: Laparoscopic ureterolithotomy	1: SWL 2: Micro-PCNL 3: RIRS

Table 1.1 Treatment approaches of different stone cases among different UAA representatives—con't

	47-Year-old male, left partial staghorn stone (40 mm)	65-Year-old male, left renal pelvic stone (18 mm)	75-Year-old female, right lower calyx stone (10 mm)	50-Year-old female, right mid-ureter stone (13 mm) with moderate hydronephrosis	8-Year-old male, right renal pelvic stone (8 mm)
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 and 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	1: URS	1: SWL 2: Mini-PCNL

Nepal	1: PCNL	1: RIRS (HU<1,100) or PCNL (HU>1,100)	1: Observation (asymptomatic) 2: RIRS	1: URS	1: SWL
Singapore	1: PCNL	1: RIRS 2: SWL	1: SWL or RIRS (depends on the 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: Ultramini-PCNL	1: URS 2: Laparoscopic ureterolithotomy	1: SWL 2: RIRS

Countries are indicated in alphabetical order.
Numbers in each row indicate the preference order of treatment options.
ECIRS=endoscopic combined intrarenal surgery; HU=Hounsfield unit; PCNL=percutaneous nephrolithotomy; RIRS=retrograde intrarenal surgery; SWL=shock wave lithotripsy; UAA=Urological Association of Asia; URS=ureteroscopy.

as retrograde intrarenal surgery (RIRS), ureteroscopy (URS), and percutaneous nephrolithotomy (PCNL), are preferred choices in Asia; however, some countries in the Middle East and Southeast 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 endoscopic combined intrarenal surgery (ECIRS). For paediatric 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.

1.4. Work Group composition

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.

1.5. Methodology

1.5.1. Data identification

1) The *Guideline for Stone Diseases* was developed by committee members recommended by the UAA.
2) The members meticulously reviewed the relevant references retrieved via the PubMed and MEDLINE databases published between 1966 and July 31st, 2017.
3) 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.
4) Other sources of information included the (1) Japanese Urological Association (JUA) Clinical Guidelines for Urolithiasis; (2) EAU Guidelines on Urolithiasis 2017, published by the EAU; (3) Medical Management of Kidney Stones: AUA Guidelines, published by the AUA; and (4) Surgical Management of Stones: AUA/Endourological Society Guidelines.

1.5.2. Level of evidence (LE) and grade of recommendation (GR)

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 labelled with an LE score according to a classification system modified from the *Oxford Centre for Evidence-based Medicine Levels of Evidence*,[1] ranging from LE: 1 (highest evidence level) to LE: 5 (case study or expert opinion).

LE	Type of evidence
1	Evidence obtained from multiple large-scale RCTs
2	Evidence obtained from a single RCT or a low-quality RCT
3	Evidence obtained from non-randomised controlled studies
4	Evidence obtained from observational studies
5	Evidence obtained from case studies or expert opinions

LE = level of evidence; RCT = randomised controlled trial.

For each clinical question (CQ) below, the conclusions drawn from the relevant papers and evidence levels have been judged using a GR, ranging from a strong recommendation (grade A) to not recommended (grade D) as indicated below.

GR	Nature of recommendation
A	Highly recommended
B	Recommended
C	No firm evidence for recommendation
C1	May be considered
C2	Not recommended
D	Recommended not to do

GR=grade of recommendation.

1.5.3. Review

The *UAA Clinical Guidelines for Stone Disease* was subjected to peer review prior to publication.

1.6. Guideline development group

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2. Aetiology

Q1. 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 United States (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).

Commentary

Urinary stone disease is a highly prevalent disease worldwide with rates ranging from 7% to 13% in North America, 5% to 9% in Europe, and 1% to 5% in Asia; however, there is significant variation in rates based on geography, climate, diet, fluid intake, genetics, sex, occupation, and age.[2-4] 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.

North America

Growing evidence indicates an increasing incidence of stones in the United States with recent data finding an overall prevalence of urinary stone disease in 8.8% of the population (men 10.6%, women 7.1%), which is higher than the 5.2% prevalence of kidney stone disease reported from 1988 to 1994.[5,6]

Europe

Since 2010, the development of stones in the United Kingdom has been stable at approximately 85,000 cases/year.[7] The prevalence of stone formers among both men and women increased from 1986 to 1998 (from 6.8% to 10.1% in men and from 4.9% to 5.8% in women) in Italy.[8] The rise in Germany was only from 4.0% to 4.7% from 1979 to 2001.[9] Iceland has documented an increase in prevalence, from 7 to 24 per 100,000 for men >40 years, and from 7 to 21 per 100,000 for women >50 years of age during a 24-year period.[10]

Asia

Asia comprises multiple disparate climates and cultures as in Europe, making characterisation of the prevalence and incidence of urolithiasis challenging. An increase in prevalence was also documented across a 40-year period in Japan, where the estimated annual incidence of first-episode upper urinary tract stones in 2005 was 134.0 per 100,000 (192.0 in men and 79.3 in women) compared with 54.2 per 100,000 in 1965, although this steady increase plateaued in 2015.[11] The incidence rate was 457 per 100,000 Koreans in 2002, higher than that in most of Asia.[12] The prevalence of urolithiasis in China was 6.5% in 2015; however, there is a difference in the incidence of urinary stone disease between coastal provinces in the southern and northern parts of the country.[13]

Australia and other parts of the world

The overall increase in stone treatment, and particularly of endoscopic stone treatment, could indicate an increased prevalence of stone disease in Australia.[14] There is a scarcity of studies

characterising the prevalence of urinary stone disease in Africa and Latin America; however, 15% of white men in South Africa have calcium stones, compared with 5% of white women, rates that are comparable with other industrialised nations. The study found that the black South African population was less susceptible to these stones, with a prevalence of < 1%.[15]

Q2. How can stones be classified?

○ Stones can be categorised by aetiology, 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 with other parts in the world (LE: 3, GR: A).
○ Stone composition is often associated with metabolic and/or genetic abnormalities (LE: 3, GR: B).

Commentary

Etiopathogenetic categorisation of stones may include the following: non-infectious stones (calcium oxalate, calcium phosphate, and uric acid), infectious causes (struvite, carbonate apatite, and ammonium urate), genetic-based stones (cystine, xanthine, and 2,8-dihydroxyadenine), or drug-induced stones[16] (LE: 4).

Stone composition is the basis for further diagnostic and management decisions. Stones are often formed from a mixture of stone-forming minerals. For instance, stone composition of uric acid, cystine, or struvite implicates specific metabolic or genetic abnormalities, and knowledge about stone composition may help in taking efficient preventive measures. Calcium phosphate stone composition is more likely to be associated with certain medical conditions or medications, such as renal tubular acidosis (RTA) type 1, primary hyperparathyroidism, medullary sponge kidney, and the use of carbonic anhydrase inhibitors[17,18] (LE: 3).

Table 2.1 lists the clinically most relevant substances and their mineral components.

Some unique trends have been reported from each country around Asia. As the most common stone type, calcium oxalate stones count for an average of one-third of all stones diagnosed in this region, although some Asian countries reported a much higher prevalence of calcium oxalate. In particular, studies performed in India and Israel also demonstrated a higher percentage of calcium oxalate monohydrate stones over calcium oxalate dihydrate stones. In addition, there was a high prevalence of cystine stones reported in a few countries[19-24] (LE: 4).

Q3. 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 body weight and obesity have been shown to increase the risk of urinary stone formation. In an observational study,[25] there was a positive relationship between body mass

Table 2.1 List of variety of stone components

Chemical name	Mineral name	Chemical formula
Calcium oxalate monohydrate	Whewellite	$CaC_2O_4 \cdot H_2O$
Calcium oxalate dehydrate	Wheddelite	$CaC_2O_4 \cdot 2H_2O$
Basic calcium phosphate	Apatite	$Ca_{10}(PO_4)6 \cdot (OH)_2$
Calcium hydroxyl phosphate	Carbonite apatite	$Ca_5(PO_3)_3(OH)$
β-Tricalcium phosphate	Whitlockite	$Ca_3(PO_4)_2$
Carbonate apatite phosphate		$Ca_5(PO_4)_3OH$
Calcium hydrogen phosphate	Brushite	$PO_4 \cdot 2H_2O$
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; sulpha medications; triamterene; ephedrine, melamine; and indinavir)		
Foreign body calculi		

index (BMI) and urinary uric acid, sodium, and phosphate excretion. No correlation could be demonstrated between BMI and inhibitors of stone formation, such as magnesium, citrate, and urine volume.

A recent study on Taiwanese has shown that there is a significant correlation between metabolic syndrome and nephrolithiasis.[26] The most significant component of metabolic syndrome closely associated with nephrolithiasis was elevated blood pressure after adjusting for age and testosterone levels.

Visceral fat was shown to be predictive of stone composition[27] in a Korean population. An increased amount of visceral fat was found to have greater predictive value than urinary pH or BMI for uric acid stones.

A higher fluid intake volume was associated with reduced stone formation rates. A meta-analysis of two randomised controlled trials (RCTs)[28-31] showed that higher water intake resulted in a reduced rate of stone recurrence in patients with a previous episode of calcium stones.

In addition, soft drink and ascorbic acid were shown to increase the risk of stone formation in small randomised studies.[29,30]

Q4. 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 should be encouraged to reduce the risk of stone formation (LE: 2, GR: B).
○ Dietary fibre content should be increased and oxalate content should be restricted in recurrent calcium oxalate stone-forming cases (LE: 4, GR: B).

Commentary

Patients with recurrent stone disease should be evaluated in detail for possible metabolic abnormalities potentially amenable to dietary or pharmacologic measures for prevention.

The Nurses' Health Study in the United States found an inverse relationship between dietary calcium intake and renal calculus formation. The relative risk of stone formation in women in the highest quintile of calcium intake was 0.65 compared to those in the lowest quintile.[32]

In a single randomised prospective study,[33] hyperoxaluria was shown to be significantly associated with dietary ascorbic acid intake and inversely associated with calcium intake. A randomised controlled study comparing men on a normal calcium, low animal fat diet and a low-calcium, normal animal fat diet found reduced stone recurrence rates in the arm with the low animal fat diet.[34] The effect appeared to be due to decreased urinary oxalate levels in the intervention arm, as urinary calcium levels decreased in both populations, whereas oxalate levels increased in the low-calcium diet group.

A recently published paper described the trend observed in metabolic features over 20 years in over 4,000 Korean patients. Over time, an increase in the prevalence of uric acid stones with a decrease in the prevalence of calcium oxalate and phosphate stones has been reported, which may be related to metabolic syndrome associated with increased fat and meat in the diet.[35]

Q5. What is the role of genetic factors in urinary stone disease?

○ Genetic factors are highly associated with both 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 and idiopathic calcium stones (LE: 3).

Commentary

Genetic factors are highly associated with both pathogenesis and clinical outcomes of urinary stone disease (LE: 3).

Patients with urinary stone disease have a higher prevalence of positive family history of the disease, which has been reported to be between 30% and 50%.[36-40] Studies have demonstrated that 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%).[42] Family history of urolithiasis is also associated with an earlier onset coupled with a higher risk of recurrence.[37,40] These lines of evidence suggest that genetic factors for urolithiasis play a pivotal role in its aetiology (LE: 3).

Inherited metabolic disorders, such as adenine phosphoribosyltransferase (APRT) deficiency, cystinuria, Dent disease, familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC), and primary hyperoxaluria (PH), cause urinary hypersaturation of insoluble mineral salts, which can inevitably increase the risk of kidney stone formation. All of these disorders are often associated with cases of paediatric urolithiasis.[43] These disorders have been associated with the following specific gene mutations: APRT deficiency (*APRT* gene)[44]; cystinuria (*SLC7A9* and *SLC3A1*)[45-47]; Dent disease (*CLCN5* and *OCRL1*)[48,49]; FHHNC (*CLDN16* and *CLDN19*)[50,51]; PH (*AGXT*, *GRHPR*, and *HOGA1*)[52-54] (LE: 4).

In addition to hereditary-based cases of urolithiasis, a large number of reports in the literature have focused on the association of gene single-nucleotide polymorphism (SNP)/mutations with idiopathic calcium stone development.[55] Genome-wide association studies revealed that SNPs and mutations of following genes increase the risk of urolithiasis: stone matrix (*SPP1*[56-60]), calcium regulation (*CASR*,[61-64] *CLDN14*,[61] and *ORAI1*[65]), phosphate regulation (*VDR*,[66,67] *KL*,[68,69] *NHERF1*,[70] *FGF23*,[71] and *CALCR*[72]), and urinary inhibitor of stone formation (*SLC13A2*[73] and *F2*[74]) (LE: 3).

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

○ There is a clear geographical variation in stone incidence worldwide (LE: 3).
○ The 'stone belt' (areas where stones are frequent) includes Southeast Asia and West Asia (LE: 2).
○ Ethnic differences in the incidence of stone disease have been observed (LE: 3).

Commentary

There is a clear geographical variation in stone incidence worldwide. Furthermore, incidence may vary considerably even in different parts of the same country. The variation in incidence and prevalence is influenced by many factors with varying degrees of impact on stone formation.

The prevalence of urinary stone disease varies widely in different regions of the world and depends greatly on the geographical area, racial distribution, socio-economic status, and dietary habits. The geographical distribution of stone disease tends to roughly follow that of environmental risk factors. Thus, a higher prevalence of stone disease is found in hot, arid, or dry climates, such as the mountains, desert, or tropical areas. However, genetic factors and dietary influences may outweigh the effects of geography.

Comparison of the accurate prevalence of the disease is difficult because of the differences in the evaluation methodology used. Generally, the risk of adult urolithiasis seems to be higher

in the western hemisphere (5-9% in Europe, 12% in Canada, and 13-15% in the United States) than in the Eastern hemisphere (1-5%).[75] However, the highest lifetime risk of calculus formation is found in the United Arab Emirates and in Saudi Arabia, with an approximate prevalence of 20%. The stone belt (areas where stones are frequent), which includes Southeast Asia from West Asia, extends around the world.

Racial differences in the incidence of stone disease have also been observed. Although it is difficult to find racial differences among Asian countries, the highest prevalence of stone disease has been reported in the white population, followed by Hispanics, Asians, and African-Americans in the United States, with a prevalence of 70, 63, and 44% of whites, respectively, among American men. Among American women, however, the prevalence was highest among whites but lowest among Asian women.[76] According to the National Health and Nutrition Examination Survey (NHANES) data set, Hispanics [odds ratio (OR) 0.60, 95% confidence interval (CI) 0.49-0.73, $P < 0.001$] and black non-Hispanics (OR 0.37, 95% CI 0.28-0.49, $P < 0.001$) were significantly less likely to report a history of stone disease compared with white non-Hispanics.[77]

Q7. 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 demonstrated in various geographical areas, including Japan,[78] Taiwan,[79] Iran,[80] Korea,[81] New Zealand,[82] Australia, Saudi Arabia,[83] the United States,[84] and Italy. In many countries, seasonal trends in monthly urinary stone attack rates exist, with the incidence peaking in the summer, which corresponds to July to September and January to March in the northern and southern hemispheres, respectively; these trends have been demonstrated to exist regardless of patients' age, sex, and race. Seasonal variation in stone disease is likely related to temperature by way of fluid losses from perspiration[85] and perhaps by sunlight-induced increases in the synthesis of 1,25-dihydroxyvitamin D3 (vitamin D).[82] The mechanism of stone formation due to dehydration involves an increase in urinary crystallisation and stone formation due to the low volume of urine because of insufficient liquid intake to compensate for sweating in hot climates.[86] Alternatively, increased exposure to sunlight causes increased production of vitamin D and increased urinary calcium excretion.[82] Serum levels of vitamin D and urinary calcium excretion and oxalate have been shown to be significantly higher from May to October than from November to April.[87] In addition, the serum vitamin D level has been reported to be significantly higher throughout the year in hypercalciuric than normocalciuric stone formers.[87] A population-based study indicated there were sex differences between the hormonal and dietary control of urinary calcium excretion. Serum calcium level was positively correlated with urinary calcium excretion in women but not in men.[88]

The tendency for increasing incidence of renal colic, in parallel with the rise in ambient temperature, has been well documented in many countries.[82,89] In addition, humidity could influence the onset of renal colic.[78,85] An association between the onset of renal colic and exposure to hot and dry weather, particularly when temperatures rise above 27°C and relative humidity falls below 45%, has been reported.[85]

Comparison of the prevalence of renal colic in Ramadan (the month of fasting for Moslems) with other months has indicated that higher temperature rather than fasting is the main cause of increased renal colic attacks.[90]

Trends in global warming will likely result in shifting and expansion of areas at increased risk of stone formation.[84] Conversely, other studies have indicated that the prevalence of urolithiasis is not related to season in Northern Europe and Western Australia, where the climate is stable.[91-93]

3. Diagnosis

Q8. 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 (ionised) calcium, phosphorus, uric acid, and magnesium, as well as urinary calcium, phosphate, uric acid, magnesium, citrates, and cystine levels, are investigated at least one time (LE: 3, GR: B).

Commentary

If an intervention is planned, then prothrombin time (PT), international normalised ratio (INR), and blood group testing should be performed.

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 performed 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.[94-98]

Q9. 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 disease (LE: 4, GR: B).

○ Ultrasonography is the recommended choice for detection of most renal stones and ureteric stones, particularly in children (LE: 4, GR: B).

○ Non-contrast computerised tomography (NCCT) has the best sensitivity and specificity for the detection of renal stones and is superior to ultrasound (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 minimise radiation risk to patients (LE: 4, GR: B).

Commentary

Traditionally, plain radiography (kidney-ureter-bladder [KUB] view) has been the basic investigation for stone detection. Nevertheless, the accuracy of KUB for the detection of urinary stones is low: about 80-90% of stones are radiopaque, in particular during diagnostic settings[99] (LE: 4, GR: B). Digital acquired KUB, which is becoming increasingly popular, has been considered to be less optimal for stone detection[100] (LE: 5 GR: C1).

US has the advantage of being radiation-free, contrast-free, and readily available. It is suitable for renal stones and also for some ureteric stones located at pelviureteric and vesicoureteric junctions. However, the sensitivity/specificity for diagnosing ureteric stones is lower[99] (LE: 4, GR: B).

NCCT has high sensitivity and specificity for the detection of both renal and ureteric stones. The sensitivity and specificity for detecting ureteric stones have been reported to be 98 and 97%,

respectively[101,102] (LE: 4, GR: B). However, radiation exposure is a main concern. Therefore, low-dose NCCT (with doses < 4 mSv) is recommended for the detection of ureteric stones in patients with BMI < 30 kg/m^2.[101] However, for obese patients (BMI > 30 kg/m^2), standard dose NCCT should be used for better image quality.

A study funded by the Agency for Healthcare Research and Quality in the United States suggested the use of US during the initial assessment of acute loin/abdominal pain suggestive of renal calculi. Ultrasonography could help avoid performance of a computed tomography (CT) scan in some patients and hence result in less overall radiation exposure than NCCT for all patients[103] (LE: 2 GR: A). Moreover, the use of US did not result in significant missing of significant pathology or in the increase in pain experienced by patient. Therefore, US will still have a role in the initial assessment of patients suspected to have ureteric stones.

Q10. 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 colour, discomfort on urination, and previous stone episodes (LE: 1, GR: A).
○ Obtaining habitual behaviour regarding diet and physical activity, family history, age of onset, and previous stone episodes is also helpful to predict the risk and recurrence of stones (LE: 1, GR: A).

Commentary

Medical history is very important when a patient is suspected of having urinary stones. Although 70% of patients have asymptomatic stones on US, haematuria, flank/abdominal pains, prior stone episodes, nausea, and vomiting are common signs to suspect stone existence[104,105] (LE: 1). Pain that is constant in the acute phase can indicate a more severe obstruction, whereas intermittent pain is more commonly associated with an incomplete obstruction. Haematuria is most common on the first day of symptoms, with a sensitivity of 95%, but decreases to 65% by days 3-4. Urgency, dysuria, frequency, and pain during urination are common for urinary tract infection (UTI), whereas fevers, chills, and rigors are usually not present in uncomplicated cases and should raise concern for an infected stone[104] (LE: 1, GR: A).

In addition, studies have been suggesting that habitual behaviour, including larger amounts of diet and alcohol consumptions, positive family history, and less physical activity are associated with the risk of urinary stone disease[30,37,106-109] (LE: 3, GR: A). In addition, positive family history, younger age at onset, and having two or more previous stone episodes increase the prevalence of stone recurrence[37,109-111] (LE: 1, GR: A).

Q11. How we should diagnose urinary stones in specific situations, such as in children and in pregnant patients?

○ In pregnant women, use US as a first-line imaging modality and magnetic resonance imaging (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 detection of urinary stones in pregnant patients, major concerns are the effects of radiation exposure, which are classified as non-stochastic (deterministic) or stochastic effects.[112,113] Non-stochastic effects, such as teratogenesis, are dose dependent above a baseline threshold dose (<50 mGy is considered safe) and depend on the gestation age (minimum risk prior to the 8th week and after the 23rd week). Stochastic effects, such as carcinogenesis, are possible at any level of radiation and do not depend on gestation age. Table 3.1 shows the radiation doses absorbed by a foetus following common imaging modalities.[112] While the majority of radiographic investigations involve fetal radiation doses far below the safety threshold of 50 mGy, the physician has to justify the need for any investigation resulting in an absorbed dose to the foetus of >0.5 mGy.[112]

US is the initial imaging modality for pregnant patients suspected of renal colic, because it has the potential for diagnosis without any risk of radiation.[112,113] However, it has inherent disadvantages, such as operator dependency and the difficulty in differentiation between physiologic hydronephrosis of pregnancy and acute ureteral obstruction. Certain signs are suggestive of obstruction over physiologic hydronephrosis, and these include dilation of the infrailiac ureter, high-grade left-sided hydronephrosis, absence of ureteral jets, and an elevated renal resistive index.[114] Transvaginal US has also been shown to improve sensitivity in the detection of distal ureteral stones.[115]

MRI is used as a second-line procedure to differentiate physiologic from obstructive hydronephrosis during pregnancy.[112,113] Compared with CT scans, disadvantages in using MRI, such as expense, limited availability, and inferior diagnostic sensitivity in detecting urinary stones, are counterbalanced by the lack of radiation exposure.[116] Three-tesla MRI has not been evaluated in pregnancy, and the use of gadolinium is not recommended to avoid toxic effects to the foetus.

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%).[117] Based on such studies and successful reduction of radiation exposure, it is recommended that low-dose CT be used as a second-line imaging modality for women in the second and third trimesters. However, it is generally recommended for judicious use in pregnant women as a last-line option.

For the detection of urinary stones in children, cumulative and long-term effects of radiation exposure are again the major concerns.[118] Carcinogenic risk may be even greater in the paediatric population because of the longer life expectancy, the greater sensitivity of developing

Table 3.1 Radiation-absorbed doses to the foetus for common imaging modalities

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

CT=computed tomography; IVU=intravenous urography; KUB=kidney ureter bladder; MRI=magnetic resonance imaging.

tissues/organs to radiation effects, and the cumulative doses by repeated investigations due to a high risk of recurrence in these patients. As in pregnant patients, US is the initial imaging modality for children suspected of having renal colic.[118] It has been reported that US has 70% sensitivity and 100% specificity for the detection of urinary stones in patients aged <18 years.[119] Furthermore, most stones that were not visualised on US were clinically insignificant. Given the concerns of radiation exposure with CT and the relatively high sensitivity and specificity of US in detecting urinary stones of clinical importance, low-dose CT should be reserved as a second-line imaging modality for children for whom US is not diagnostic despite being highly suspected of having urinary stones.[118]

Q12. What type of imaging work-up is necessary before surgery?

○   Use of nomograms of NCCT results can predict the stone clearance rate and therefore may guide optimal treatment options (LE: 2, GR: B).
○   CT scan is also useful for clinicians in the pre-operative planning of PCNL by allowing the best and safest access for stone clearance (LE: 4, GR: B).
○   Clinicians should perform functional radionuclide studies to assess the function of the affected kidney in any doubt of a non-functioning kidney (LE: 5, GR: C).

Commentary

Before performing any intervention for urinary stone disease, it is important to ascertain the size and the location of the stone, the anatomy of the renal collecting system, any obstruction, radiologic characteristics, the composition of the stone, and the function of the kidney. Traditionally, an intravenous urogram is used for diagnosis and planning of stone treatment. The introduction of NCCT not only may help in the diagnosis of stone disease, but also many other stone parameters, such as mean stone density, skin-to-stone distance, may also be assessed. These factors have been found to be useful for the prediction of treatment outcomes. Therefore, currently, NCCT is the main imaging for work-up before surgery. For kidneys suspected of poor renal function, a radioisotope renogram should be used to document the differential kidney function.

To facilitate clinical applications, nomograms have been developed to predict the stone clearance rate by any treatment modality. By using NCCT, different nomograms have been developed by different groups for the prediction of stone clearance after shock wave lithotripsy (SWL), RIRS, or PCNL.

For SWL, factors affecting the stone-free rates (SFRs) include stone density and skin-to-stone distance values[120] (LE: 4, GR: B). The stone density can be measured using Hounsfield units (HU). Clinical algorithms for 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[121,122] (LE:4, GR:B).

For PCNL, Okhunov *et al.* developed a novel surgical classification system for kidney calculi, namely, S.T.O.N.E.[123] (LE: 4, GR: B), which correlates post-operative stone-free status, estimated blood loss, operative time, and length of hospital stay. A nomogram was also developed by the Clinical Research Office of the Endourological Society (CROES) PCNL Study Group in 2013 to predict the SFR after PCNL, which showed an area under curve of 0.76[124] (LE: 4, GR: B). In Asia, the Modified Seoul National University Renal Stone Complexity (S-ReSC) Score was developed by Jeong *et al.* in 2013, which assigned a score of 1-9 based on the number of sites involved in the renal collecting system[125] (LE: 4, GR: B). This score was also extrapolated for the prediction of SFRs after RIRS[126] (LE: 4, GR: B).

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. The use of CT angiography was investigated retrospectively and has been shown to reduce bleeding in patients undergoing mini-PCNL, which showed a lower reduction in haemoglobin level[127] (LE: 4, GR: C1).

(Q)13. How can we determine the renal function of each kidney?

○   Differential function of the kidneys can be attained by 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).

○   The use of ultrasonography 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

There is little evidence on the importance as well as the necessity of differential renal function assessment in urolithiasis, and this is extrapolated from paediatric urology and also from the assessment of renal cell carcinoma. The least invasive method for determining differential function is the use of radionuclide renal scan, such as 99m-technetium (99mTc) dimercaptosuccinic acid or 99mTc diethylenetriaminepentaacetic acid.[128]

However, in patients with ureteral stones causing hydronephrosis, there is a concern that the estimated differential function by conventional nuclear scan may not be accurate and requires conjugate views for accurate evaluation[129] (LE: 4, GR: B).

Alternatively, more invasive methods include the use of creatinine clearance from urine collected from percutaneous nephrostomy, compared with urine collected from the contralateral percutaneous nephrostomy or the self-voided urine. This raises a concern as the stone may not be completely obstructing and therefore may underestimate the function of the concerned kidney.

Ultrasonography or NCCT can also be used as an alternative for the measurement of the differential function of the kidneys. Performing cortical thickness or parenchymal volumetric measurement by using US or NCCT can help provide a reasonable prediction of the differential creatinine clearance in obstructed kidneys[130] (LE: 4, GR: C1).

4. Metabolic evaluation

Q14. Is metabolic evaluation necessary for patients with stone disease?

○   Basic evaluation is recommended for all patients presenting with stones (LE: 4, GR: B).
○   Metabolic evaluation is recommended for patients at high risk of stone recurrence or formation (LE: 4, GR: B).

Commentary

For patients presenting with a first stone episode, the initial evaluation is targeted at defining patients who are at high risk of recurrence or complications. The recommended basic work-up is defined elsewhere in this guideline.

Metabolic evaluation of stone disease can reveal abnormalities, which are amenable to medical treatment. In recurrent stone formers, metabolic evaluation showed significant serum and urinary abnormalities in contrast to first-time stone formers in an observational study.[131] Medical treatment of stone disease has been shown to reduce the risk of stone recurrence in a meta-analysis of RCTs.[132]

Q15. Is it necessary to identify stone components?

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

Commentary

Two main physical methods are currently used for stone analysis: X-ray diffraction and Fourier transform infrared spectroscopy. Semiquantitative evaluation of the stone components is possible with these methods. Older chemical analysis methods for stone analysis are usually qualitative and are no longer recommended.[133]

Stone analysis is an important part of the complete evaluation in a patient with stone disease. Potential aetiologies for stone formation can be determined from the stone composition, and pharmacologic treatment can then be instituted for recurrence prevention based on the information obtained from stone composition. 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.[134] Uric acid stones can be treated with urinary alkalinisation.

For patients with recurrent stone disease, the stone composition may change over time, which can have an impact on the efficacy of preventive treatments.[97] For this reason, all stone particles passed spontaneously or obtained in different interventions should routinely be sent for analysis to monitor possible changes in stone formation, particularly in cases unresponsive to a certain medical treatment modality. Failure of the pharmacologic prevention of stone disease may also signify a change in stone composition. Hence, a repeat stone analysis is recommended in such cases.

Q16. Are biochemical tests by 24-hour urine necessary? And when?

○ Twenty-four-hour urine tests are recommended in patients deemed at high risk of stone formation (LE: 3, GR: B).

○ Two separate 24-hour collections should be performed for a complete biochemical work-up (LE: 4, GR: B).

○ Collection of samples should be performed in patients who have been stone-free for at least 20 days (LE: 4, GR: B).

○ Repeat evaluation is recommended in patients on pharmacologic treatment for recurrence (LE: 4, GR: B).

Commentary

The epidemiology of stone disease varies geographically and is a result of many complex factors, including climate, genetics, and lifestyle. Therefore, the prevention and treatment of stone disease should be individualised based on the results of metabolic testing and stone analyses where available.[4]

The list of characteristics that classify a patient as a high-risk stone former is extensive.[135] High-risk stone formers include those with stone formation at an early age (paediatric age group), with associated diseases such as hyperparathyroidism, genetic diseases such as xanthinuria, and anatomical abnormalities such as horseshoe kidneys. High-risk stone formers should be counselled for 24-hour urine evaluation as the results can guide medical prevention.[136,137]

Spot urine tests have been used as an alternative in patients who are not willing or are unable to perform 24-hour urine collection.[138] However, the results are less reliable than 24-hour collections as the results may vary with time and patient factors, such as weight and age.

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 pharmacologic therapy. Repeat urine analysis allows titration of drug doses as necessary.[139]

5. Medical management

Q17. What is the recommended treatment for ureter stone pain management?

○ Use non-steroidal anti-inflammatory drugs (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

Renal colic is an acute syndrome involving unilateral flank pain, linked to an obstruction in the upper urinary tract. The pain is often intense. After having considered other diagnoses and checking for signs of complications (fever or oligoanuria), the first step is to control the pain.

NSAIDs are effective in patients with acute stone colic and have better analgesic efficacy than opioids[140,141] (LE: 3). In a three-treatment group, double-blind RCT, adult participants (aged 18-65 years) with moderate to severe renal colic (Numerical Pain Rating Scale ≥4) were recruited and were assigned (1:1:1) to receive diclofenac (75 mg/3 mL intramuscularly), morphine (0.1 mg/kg intravenously), or paracetamol (1 g/100 mL intravenously). In the patients with ureteric calculi, diclofenac and paracetamol were more effective than morphine in achieving at least a 50% reduction in initial pain score at 30 minutes after analgesia. Significantly lower numbers of adverse events were recorded in the diclofenac group and the paracetamol group than in the morphine group. During the 2-week follow-up, no additional adverse events were noted in any group. Intramuscular NSAIDs offer the most effective sustained analgesia for renal colic and seem to have fewer side effects[142] (LE 2). For patients with ureteral stones that are expected to pass spontaneously, NSAID tablets or suppositories (e.g., diclofenac sodium, 100-150 mg/day, 3-10 days) may help reduce inflammation and the risk of recurrent pain[143,144] (LE 1).

Medical expulsive therapy (MET) refers to the administration of drugs (e.g., tamsulosin or nifedipine) that expedite the passage of stones without the need for surgical intervention.[145,146] Alpha1-blockers have the potential to inhibit ureteral spasm and uncontrolled contraction, theoretically reducing pain and promoting spontaneous stone passage. Calcium channel blockers also suppress smooth muscle contraction by inhibiting the influx of extracellular calcium into smooth muscle cells.[146] Meta-analysis studies have clearly shown that the number of pain episodes, the need for analgesic medication (diclofenac), and hospitalisation can be reduced in patients with ureteral stones treated with alpha1-blockers[147] (LE 1). 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 in facilitating ureteric stone expulsion[148,149] (LE 1).

Pathan *et al.*[149] compared the epidemiology, clinical presentations, management, and outcomes of renal colic presentations in two major academic centres from two geographically diverse populations: Qatar (a country in the Afro-Asian stone belt) and South-Eastern Australia (not within a stone belt). Their findings suggest that the benefits of treatment, including medical expulsion therapy, varied between the two populations. Differences in epidemiology and patient mix should be considered while tailoring strategies for effective management of patients with renal colic in a given setting.[150] Therefore, patients with renal colic should have individualised treatment.

If analgesia cannot be achieved with appropriate medical agents, drainage of the collecting system, using either a ureteral stent or percutaneous nephrostomy or emergency stone removal, should be planned.

Q 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 (SSP) (LE: 1, GR: A).
○ The use of external physical vibration lithecbole is a treatment option (LE: 1, GR: B).

Commentary

In a double-blind placebo-controlled study of 3,296 patients with distal ureteral stones, 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[149] (LE: 1). The benefits of tamsulosin include a higher stone expulsion rate (86% vs. 79%, $P < 0.001$) for distal ureteral stones and a shorter time to expulsion for distal ureteral stones, defined as below the level of the sacroiliac joint, with a dimension of 5-7 mm (148.3 vs. 248.7 hours, $P < 0.001$), than those in placebo. No improvement in stone passage rates was observed in patients with ≤ 5-mm distal ureteral stones treated with tamsulosin[149] (LE: 1). While an RCT does not recommend the use of tamsulosin for symptomatic stones < 9 mm,[151] a similar result was shown by another RCT trial.[152-154] However, several well-designed, randomised, double-blind, placebo-controlled studies have recently produced contradictory results, showing no overall benefit of MET.[152-154] These trials were parallel in design, whereby each group of participants was exposed to one of the study interventions (alpha1-blocker vs. placebo)[152-155] (LE: 2) or alpha1-blocker vs. calcium channel blocker vs. placebo[156] (LE: 2). Patients with stones located in any part of the ureter[155,156] or with distal ureteral stones[152-154] were enrolled. The stone size was pre-specified in all (4-10 mm,[155] ≤ 7 mm,[154] < 8 mm,[153] and < 10 mm[152,156]). The primary endpoints of the studies were the stone passage rate,[153-155] the stone passage rate and time to stone passage,[152] and the necessity for interventional stone removal.[156] The study by Pickard et al.[156] had 90% power for the most conservative hypothesis that the proportion of participants experiencing stone passage would be 10% higher in the tamsulosin than in the nifedipine group. In the study by Furyk et al.,[152] there was no difference in stone passage rate between the placebo and the tamsulosin groups. However, the sample size calculation was based on improving passage for stones of 5-10 mm in diameter. Only the subgroup analysis for stones of 5-10 mm revealed a higher passage rate in the tamsulosin group. Instead, Pickard et al.[156] observed overall stone passage in almost 80% of the patients, regardless of the treatment. The study by Pickard et al. was not sufficiently powered to assess the efficacy of MET for stones of > 5 mm in the upper or middle ureter. In addition, there were no significant differences in pain scores or in the number of rescue pain medications. These were secondary outcomes assessed with patient surveys, which suffered from lower follow-up rates compared with those for the primary outcome.

Tamsulosin is thought to induce spontaneous stone passage by relaxing the ureteral smooth muscle and decreasing the ureteral wall tone[157] (LE: 1). Young et al. evaluated the factors responsible for stone distribution and expulsion and found that the upper ureter and ureterovesical junction are two peak sites at which stones lodge. For stones ≤ 10 mm in size, the initial stone lodge site is not a significant predictor of MET failure in patients who have no previous history of active stone treatment in the ureter[158] (LE: 4). Furyk et al. assessed the efficacy

and safety of tamsulosin compared with placebo as MET in patients with distal ureteric stones ≤10 mm in diameter, and found no benefit overall of 0.4 mg of tamsulosin daily for patients with distal ureteric calculi ≤10 mm in terms of spontaneous passage, time to stone passage, pain, or analgesia requirements. In the subgroup with large stones (5-10 mm), tamsulosin did increase passage and should be considered a treatment option[152] (LE 1).

Physical examination, urinalysis, complete blood count, serum chemistry, and inflammatory markers, plain radiographs, and NCCT at initial presentation were reviewed to determine predictors of future SSP. Low neutrophil-to-lymphocyte ratio (NLR) (<2.3) may predict SSP in patients with ureter stones less than 10 mm in size. Our results suggest that ureteral inflammation plays an important role in SSP. Early intervention may be considered for patients presenting with high NLR (≥2.3)[152] (LE: 4).

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[159-163] (LE: 1-3).

Q19. 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 alkalinisation of urine (LE: 2, GR: A).

Commentary

Uric acid stone formation is frequently associated with obesity, metabolic syndrome, and diabetes type 2 and also presents with low urine pH values.[164] It is necessary to determine the stone composition prior to treatment.[165] The uric acid (2,6,8-trioxypurine) calculus composition is confirmed by calculus analysis, urinary pH measurement, and X-ray characteristics.

Uric acid is the final product of purine metabolism. 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.[166] Oral alkaline citrate or sodium bicarbonate is used for chemolysis through alkalinisation of the urine.[167] 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. Patients should be informed on how to modify the dosage of alkalising medication according to urine pH, which is a direct consequence of such medication, and morning urine must be included.

Q20. 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).
○ Removal and cure of the lithiasis after the treatment of UTI, which is the main aetiologic factor in this pathology (LE: 1, GR: A).

Commentary

Pyonephrosis is the accumulation of pus in the hydronephrotic collecting system and is associated with suppurative destruction of the renal parenchyma[168] (LE: 3). Risk factors include

urinary stone disease, immunosuppression, and poorly controlled diabetes mellitus. If it is not diagnosed early, it can worsen rapidly and cause the death of the patient, with the development of septic shock[169] (LE: 2).

The accumulation of purulent exudate in the hydronephrotic collecting system and abscess formation constitute the pathophysiology of pyonephrosis. Pyuria is seen very commonly in pyonephrosis and may sometimes be nonspecific. The treatment approaches of pyelonephrosis accompanying urinary stone should be individualised based on age, the general condition of the patient, and patient compliance[170] (LE: 1). Sometimes retrograde ureteral catheterisation is appropriate for drainage pyuria. This approach was later modified as a result of the advances made in antibiotic therapy and included vigorous antibiotic treatment and prompt drainage of the kidney[171] (LE: 2). The choice of antibiotic therapy should be based on the result of urinary culture. However, sometimes antibiotics have no effect on pyonephrosis unless the pus is surgically drained. Thus, percutaneous nephrostomy provides a means of draining off pus and determining possible residual renal function.[171] Thus, percutaneous nephrostomy and ureteral catheter insertion are therefore necessary. If performed properly, percutaneous drainage is a fast, reliable, and quickly effective therapeutic method in one session[172] (LE: 1). Nephrectomy can be the preferred treatment for a kidney that has lost most of its function if the contralateral kidney is normal; this approach has been found to have fewer complications compared with other treatments. Treatment of pyelonephrosis frequently consists of nephrectomy to remove the non-functional kidney, which represents a potentially dangerous source of systemic infection[173,174] (LE: 3, LE: 1).

Nephrectomy is advocated as a treatment option in the case of a damaged kidney, which seems to be difficult to preserve by conservative and endourologic treatment, with a normally functioning contralateral kidney. Conservative treatment should be envisaged particularly in the case of a single kidney or if the patient's health status is poor. The best treatment consists of the removal and cure of the lithiasis, which is the main aetiologic factor in this pathology[171] (LE: 2).

6. Surgical management

Q21. When can SWL be the first option for patients with renal stones?

○ Although 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 (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 favourable factors, such as high mean stone density, located in calices with poor anatomy, the treatment outcome will be less favourable. Therefore, the pros and cons of each treatment modality should be discussed in detail with the patient before a joint decision on the treatment plan can then be taken (LE: 5, GR: B).

○ SWL is highly effective in paediatric patients due to its non-invasive nature and higher SFRs compared with adult patients (LE: 2, GR: B).

Commentary

In principle, all urinary calculi can be treated with SWL. Two issues should be considered before recommending SWL to patients as the first treatment option.

First, there should be no contraindications for SWL, which include

1) untreated active UTI;
2) uncontrolled hypertension;
3) uncollected coagulopathy;
4) unresolved distal obstruction, which might affect stone fragment clearance;
5) pregnancy; and
6) close approximation of aortic/main artery aneurysm.

For patients with no contraindications for SWL, the second issue that should be considered is whether SWL will provide an effective and safe treatment to the patient. Factors to be considered include the following:

1) Stone factors: the stone size, composition, and site.
2) Patient factors: patient fitness for endoscopic procedures and patient body's habitus.

According to EAU Guidelines, for patients with a non-caliceal stone < 20 mm in size and a caliceal stone < 10 mm in size, SWL is a first-line treatment. However, recent studies also suggest that lower caliceal stones < 20 mm in size could still be treated by SWL.[175] Therefore, we suggest SWL as a treatment option for all renal stones < 20 mm in size, after consideration of other factors that could affect SWL treatment outcomes, such as stone composition and caliceal anatomy.

Calcium oxalate monohydrate, brushite, or cystine stones are poorly fragmented by SWL, and therefore alternate treatments should be considered. With the increase usage of CT scan for detection of renal stone, additional CT parameters should be used to predict SWL outcome.[121] In general, stones with HU > 1,000, with long skin-to-stone distance, are less responsive to SWL. Algorithms with a combination of these parameters are also available to guide clinical decisions[121,122] (LE: 4).

3) Anatomical factors: unfavourable anatomy of the lower calyx, including a steep infundibular-pelvic angle, long lower pole calyx (> 10 mm), and narrow infundibulum (< 5 mm)[176] (LE: 4). In addition, for stones in a kidney with abnormal anatomy, such as horseshoe kidney, the treatment result might be less favourable. Obese patients or stones with long skin-to-stone distance would also affect treatment outcomes, and alternative treatment, in particular RIRS, should be considered[121,122] (LE: 4).

Nevertheless, adequate information, including the treatment results, potential advantages, and complications of various treatments, should be provided to patients, and a joint decision on the treatment plan should be made.

In summary, SWL might be considered as the first treatment option for the index patient who has no contraindication for SWL, with stones < 20 mm in size in general or < 10 mm for lower caliceal stones with favourable anatomy and composition (non-cystine, non-calcium monohydrate stone, or stone CT HU < 1,000). For a patient with contraindication for SWL, an abnormal body habitat, hard stones, and an unfavourable renal anatomy, other treatment options should be considered.

Q22. What are the complications of SWL?

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

Commentary

Complications of SWL may be divided into three types: intraprocedural complications,[177] early complications, and long-term complications (Table 6.1).

Intraprocedural complications

Patients may have side effects related to the use of sedatives. In addition, SWL may trigger cardiac dysrhythmia (11-59%).[177] Occasionally, the patient may develop severe pain due to renal haematoma or may develop sepsis during the procedure.

Early complications

The incidence of complications after SWL is low and most complications are mild[177-179] (LE: 4, GR: B). Haematoma formation is one of the most serious complications related to SWL. In a recent report including 320 subjects, the incidence of symptomatic and asymptomatic haematoma rates were 1.3 and 7.69%[180] (LE: 2, GR: B). Other common complications included sepsis, ureteric colic, and steinstrasse. Rare complications included hepatic haematoma[181] (LE: 5, GR: C1).

Long-term complications

Currently, there is strong evidence suggesting long-term complications related to SWL[182,183] (LE: 4, GR: B). However, residual stone fragments may be a cause for stone recurrence[177] (LE: 4, GR: B).

Q23. 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 6.1 Common complications after SWL

Complications	EAU Guidelines (%)	Sun *et al.* (Chinese group)[178] (LE: 4) (%)	Jagtap *et al.* (Indian group)[179] (LE: 4) (%)
Intraprocedural complication			
Dysrhythmia	11-59	–	–
Early complications			
Haematoma, symptomatic	< 1	–	0.48
Haematoma, asymptomatic	4-19	–	–
Renal colic	2-4	1.3-3.7	1.02
Steinstrasse	4-7	–	1.96
Sepsis	1.0-2.7	4.0-7.4	2.05
Long-term complications			
Regrowth of residual fragments	21-59	–	–

EAU=European Association of Urology; LE=level of evidence; SWL=shock wave lithotripsy.

○ The following complications are the most relevant (Table 6.2):
   1) sepsis,
   2) ureteral stricture,
   3) ureteral injury, and
   4) 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%.[184] Most complications are minor and do not require intervention. The most relevant intraoperative and post-operative 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).

Serious complications, including death and loss of kidney function, were sufficiently rare, such that data were not available to estimate their incidence rates (LE: 1, GR: A).

Q24. 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).

Table 6.2 Common complications with URS compared with SWL

	SWL			URS		
	Groups	**Patients**	**Med (95% CI)**	**Groups**	**Patients**	**Med (95% CI)**
Distal ureter						
Sepsis	6	2,019	3% (2-5%)	7	1,954	2% (1-4%)
Ureteral stricture	2	609	0% (0-1%)	16	1,911	1% (1-2%)
Ureteral injury	1	45	1 (0-5%)	23	4,529	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%)
Ureteral 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%)
Ureteral stricture	2	124	2% (0-8%)	8	987	2% (1-5%)
Ureteral injury	2	124	2% (0-8%)	10	1,005	6% (3-9%)
UTI	5	360	4% (2-7%)	2	224	4% (1-8%)

CI=confidence interval; SWL=shock wave lithotripsy; URS=ureteroscopy; UTI=urinary tract infection.

Table 6.3 Perioperative complications of percutaneous nephrolithotomy (n=11,929)

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
Embolisation	0.4	0-1.5
Organ injury	0.4	0-1.7
Urinoma	0.2	0-1
Death	0.05	0-0.3

○ The most common post-operative 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. The minimally invasive PCNL is at least as efficacious and safe as the 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%.[185] The minimally invasive PCNL is at least as efficacious and safe as the standard PCNL (LE: 1).[186] Due to the advancements in endoscopic instruments and the development of surgical techniques, one Asian study indicated that the complication rate of PCNL improved from 21.3% between 1997 and 2005 to 10.3% between 2006 and 2014[187] (LE: 3).

According to the largest of meta-analysis to date and the EAU Guidelines, the most common post-operative complications associated with PCNL are fever and bleeding, urinary leakage, and problems due to residual stones (Table 6.3)[188] (LE: 1).

Clavien 1 complications, which include deviations from the normal post-operative course without the need for pharmacologic treatment or interventions, were observed in 88.1% of cases. In addition, Clavien 2 complications, including blood transfusion and parenteral nutrition, occurred in 7%; Clavien 3 complications requiring intervention in 4.1%; Clavien 4 life-threatening complications in 0.6%; and Clavien 5 complications or mortality in 0.04%.[188]

With regard to procedure position, a meta-analysis of 13 studies (6 RCTs and 7 retrospective studies) with 6,881 patients revealed that the post-operative complication rate was 20.5% in the prone position vs. 18.1% in the supine position. Pooled data showed similar overall complication rates in both supine and prone groups (OR 0.88, 95% CI 0.76-1.02, $P=0.10$)[189] (LE: 1).

Given the recent trend in expansion of ECIRS cases in Asia,[190] the possible types and incidence of complications associated with this approach when compared with that of PCNL alone should be considered. One RCT has compared ECIRS with minimally invasive PCNL and demonstrated that no significant difference in perioperative complications, including blood transfusion, was observed between the two groups ($P=0.409$)[191] (LE: 2).

Q25. What situations require open/laparoscopic/robotic-assisted stone surgery?

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

Commentary

Recently, endoscopic management has become a gold standard treatment for the majority of stones requiring surgical removal since it offers comparable outcomes but faster recovery and less morbidity. However, open/laparoscopic/robotic-assisted surgery may be offered to selected patients or in clinical situations. For example, for large stones or stones with complex configuration, open/laparoscopic/robotic-assisted surgery may clear all stone burden within a

single session. These surgical modalities can be offered for stones with concomitant urinary tract anatomical abnormalities that require reconstruction, such as in ureteropelvic junction (UPJ) obstruction or ureteral stricture.

Besides open stone surgery, successful laparoscopic and robotic-assisted operations to remove stones have also been reported. Several reports in the literature indicate the simplicity of the procedure and excellent outcomes resulting from laparoscopic pyelolithotomy with or without concomitant pyeloplasty.[192,193] Both the transperitoneal and retroperitoneal approaches resulted in similar SFRs.[194] Laparoscopic management of symptomatic caliceal diverticular stone is effective in diverticula with thin overlying renal parenchyma or anterior lesions inaccessible by endourologic techniques.[195] Laparoscopic anatrophic nephrolithotomy can be performed selectively in large staghorn stones requiring complete removal in a single surgical session.[196] Nevertheless, an effective method for protective hypothermia is still debatable. Lastly, laparoscopic ureterolithotomy, either with the transperitoneal or the retroperitoneal approach, may be an alternative for impacted large proximal ureteral stones.[197]

Q 26. What urinary stones are eligible for endoscopic combined intrarenal surgery (ECIRS)?

○ Possible indications requiring combined approaches to the kidney or ureter (LE: 2, GR: B) include
  - 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, such as malrotation of the kidney, horseshoe kidney with a highly inserted ureter, or renal pathology with a severe ureteral stenosis, etc.[190,191,198,199] (LE: 2).

Complicated stones and difficult anatomy may affect the surgical outcomes, defined by the SFR,[190,200] and may also cause more damage to the flexible ureteroscope because of excessive stress on the scope (Figure 6.1).

ECIRS can be performed in either the supine or the prone position. However, there has been no randomised controlled study examining the patients' position[198,201,202] (LE: 4). ECIRS contains two different concepts of location (bidirectional) and time (simultaneous).[201,203] Selection of the combined bidirectional or simultaneous bidirectional approach depends on the location and size of the renal stones (Figure 6.2).

Figure 6.1 Development of stone surgery in the era of flexible ureteroscopy
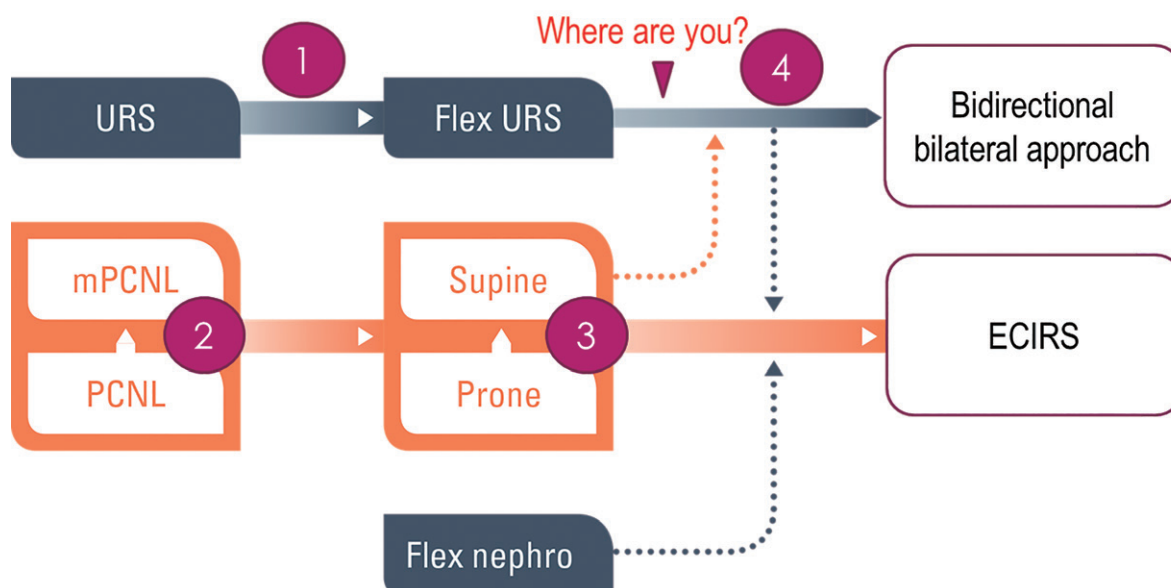
ECIRS = endoscopic combined intrarenal surgery; Flex = flexible; mPCNL = miniaturized percutaneous nephrolithotripsy; nephro = nephroscopy; PCNL = percutaneous nephrolithotripsy; URS = ureteroscopy.

Numbers 1-4 represent the turning point where a surgeon needs to select a surgical option. (1) Rigid, or semirigid ureteroscopic surgery was developed to flexible ureteroscopic surgery to remove renal stones; (2) use of miniaturized nephroscopes became one of the good options to remove large renal stones in conjunction with 30-Fr conventional percutaneous nephrolithotomy; (3) percutaneous nephrolithotomy in supine position is increasing; (4) endoscopic combined intrarenal surgery using flexible ureteroscopes and percutaneous nephroscopes in a single session is gaining more and more attention worldwide.

Ⓠ27. What urinary stones are eligible for miniaturised PCNL?

○ Miniaturised 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

Conventional PCNL using 30-Fr tract size has been the gold standard to treat renal stones > 2 cm.[204] Although the terminology related to the tract size has remained poorly defined, miniaturised PCNL usually describes the access sheaths of size < 20 Fr. Miniaturised PCNL becomes increasingly used with technical development of 'miniperc with an outer diameter of 14-20 Fr', 'ultraminiperc with an outer diameter of 11-13 Fr', and 'microperc with 4.85-Fr all-seeing needle or micro-miniperc with 8-Fr metallic sheath'.[204-210]

The acceptable criteria on stone burden of the miniaturised PCNL has been medium-sized renal stones < 3.0-3.5 cm, and ultraminiperc or microperc may be suitable for stones < 1.5 cm.[208-211] Miniaturised PCNL may be considered when there are diverticular stones, as well as paediatric medium-sized stones[208,209,212] (LE: 4).

Figure 6.2 Combined approach to removal of stones simultaneously
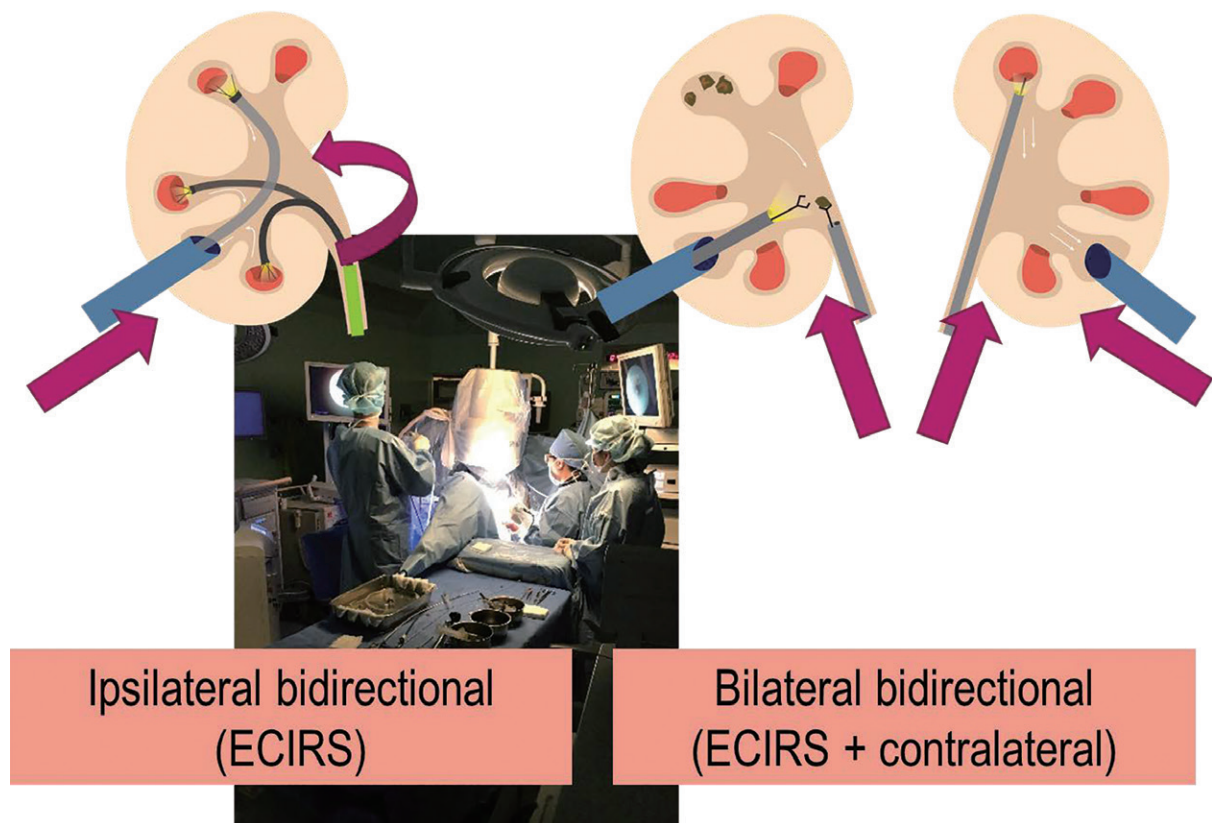
ECIRS=endoscopic combined intrarenal surgery.
Endoscopic combined intrarenal surgery can be considered for multiple approaches with flexible scopes and rigid nephroscopes to remove renal stones in an ipsilateral kidney. Bilateral renal stones can be removed in a single session in some cases.

Miniaturised PCNL has shown comparable surgical outcomes to conventional PCNL in terms of SFRs with lower probability of complications.[213,214] However, miniaturised PCNL seems to have longer operative times and higher intrarenal pressure than conventional PCNL during surgery.[214-216] The surgical outcomes of miniaturised PCNL are promising, with good SFRs, shorter hospital stay, and reduced risk of morbidity, such as bleeding and adjacent organ injury[214] (LE: 1).

Miniaturised PCNL and RIRS have similar indications for medium-sized renal stones <3 cm.[217] Previous studies showed similar outcomes compared to RIRS for medium-sized renal stones. However, they raised safety concerns in terms of higher bleeding risk, larger haemoglobin drop, or longer hospital stay of miniaturised PCNL compared with RIRS.[218,219] (LE: 1).

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

○ Considering its low SFR for stones >15 mm, RIRS could be performed 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- to 20-Fr tracts is accumulating more evidence regarding reliability and safety considerations (LE: 1, GR: B).

○　　However, ultramini-, micro-PCNL, or the ancillary use of miniaturised nephroscopes and flexible ureteroreno- or nephroscopes has shown limited evidence based on observational or retrospective studies (LE: 4, GR: C1).

Commentary

The summarised flow chart for the treatment algorithm for adult patients with symptomatic renal stones is shown in Figure 6.3.

Other unspecified renal stones	< 10 mm	10-15 mm	15-20 mm	20-30 mm	> 30 mm
Renal stone without large lower pole burden	Ultramini- and micro-PCNLs, RIRS, SWL	Ultramini- and micro-PCNLs, RIRS, SWL	Mini-, ultramini-, and micro-PCNLs; RIRS; SWL	Standard and mini-PCNLs (ECIRS)*	Standard PCNL (ECIRS)*
References	190, 191, 199, 200, 202, 204-210, 213, 214, 218, 220-232				
Renal stone with large lower pole burden		Ultramini- and micro-PCNLs, RIRS	Mini-, ultramini-, and micro-PCNLs; RIRS	Standard and mini-PCNLs (ECIRS)*	Standard PCNL (ECIRS)*
References	190, 191, 199, 200, 202, 204-210, 213, 214, 217, 218, 220-232				
Renal stone with concomitant ureter stone	RIRS, ECIRS, SWL	RIRS, ECIRS	RIRS, ECIRS	ECIRS with standard and mini-PCNLs	ECIRS with standard PCNL
References	201, 203				
Anatomical abnormalities such as diverticular stones and horseshoe kidney stones	RIRS, ultramini- and micro-PCNLs	RIRS, ultramini- and micro-PCNLs (ECIRS)*	RIRS, mini-PCNL (ECIRS)*	ECIRS with standard and mini-PCNLs	Standard PCNL (ECIRS)*
References	233-235				

*Limited evidence and availability, performed by experts in high-volume centres; standard PCNL (24-30 Fr).
ECIRS=endoscopic combined intrarenal surgery; PCNL=percutaneous nephrolithotomy; RIRS=retrograde intrarenal surgery; SWL=shock wave lithotripsy.

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

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

Figure 6.3 Flow chart for treatment of adult patients with symptomatic renal stones
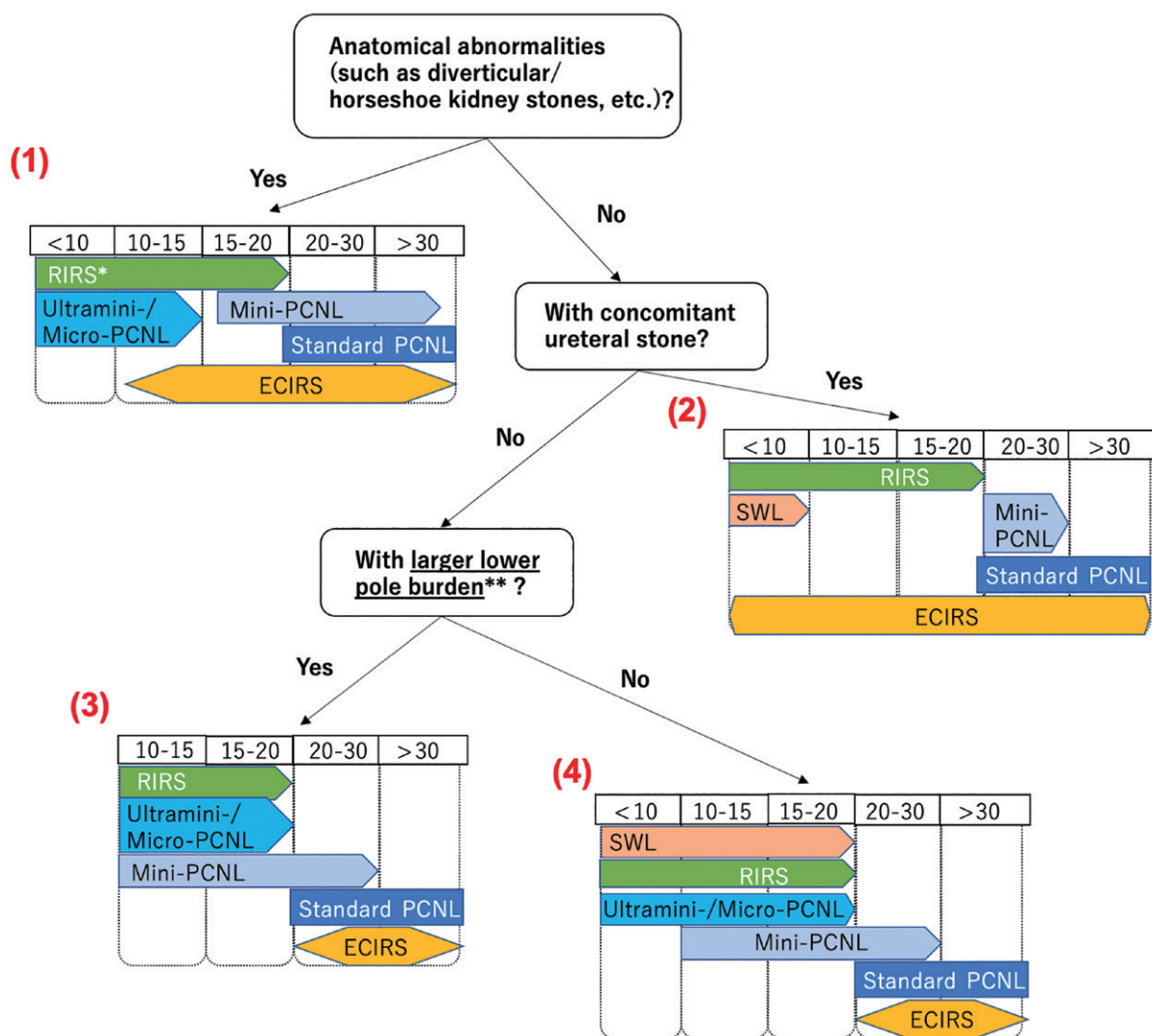
ECIRS=endoscopic combined intrarenal surgery; PCNL=percutaneous nephrolithotripsy; RIRS=retrograde intrarenal surgery; SWL=shock wave lithotripsy.
*There are some limitations/exceptions depending on anatomical difficulties in the flexible ureteroscope approach.
**Cases predominantly having lower caliceal stones > 10 mm.

Commentary

The summarised flow chart for the treatment algorithm for adult patients with ureteral stones is shown in Figure 6.4.

Stone-related and patient factors should be considered when treating adult patients with ureteral stones. Small stones or those located in the distal ureter have a higher probability of passing spontaneously. The rate of spontaneous passage is 38% for stones < 4 mm compared with 1.2% for those > 6 mm. Similarly, stones in the distal ureter have a passage rate of 45%, whereas those in the proximal ureter have a passage rate of 12%.[236] Generally, stones < 10 mm

Figure 6.4 Flow chart for treatment of adult patients with ureteral stones
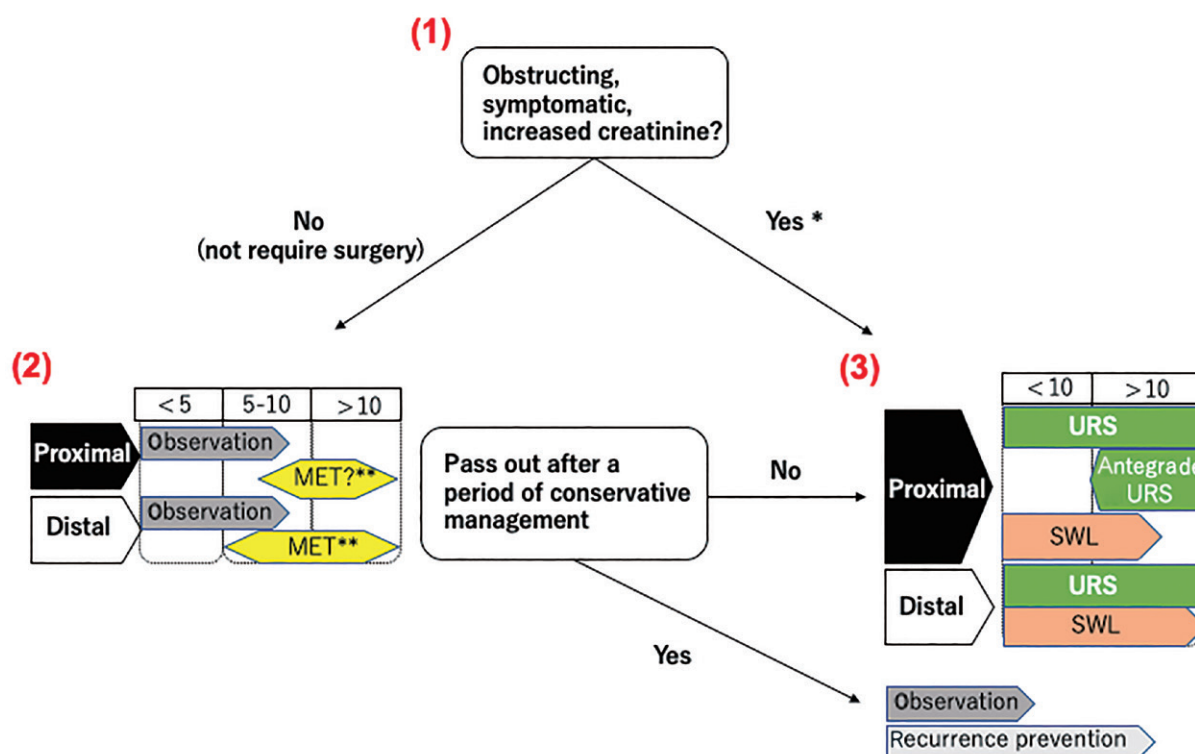
MET=medical expulsive therapy; SWL=shock wave lithotripsy; URS=ureteroscopy.
*These conditions may require ureteral stent insertion or percutaneous nephrostomy tube placement prior to removal of stones.
**Should consider early intervention in parallel during the medical treatment.

at the greatest dimension can be managed expectantly for 4 weeks if the renal function is still preserved and the patient is in good condition. In addition, MET using smooth muscle relaxant agents, including tamsulosin or nifedipine, can be used to aid stone passage.[237] However, recent RCTs have questioned this approach.[156]

If surgical stone removal is clinically indicated, URS, either the retrograde or the antegrade approach, and SWL are usually used. For proximal ureteral stones, a recent systematic review reveals that URS is associated with a better SFR compared with SWL at 1 month following the procedures, and the difference is more evident for stones >10 mm. Furthermore, the retreatment rate and the need for secondary procedures was also lower in patients undergoing URS.[238] This high success rate of URS is attributed to the use of flexible ureteroscopes, retropulsion devices, and lithotripsy with holmium:yttrium-aluminium-garnet (Ho:YAG) laser fibre, which allows surgeons to reach and treat proximal ureteral stones more effectively. However, URS has higher complication rates and longer hospital stays when compared with SWL. In a limited setting without available flexible ureteroscopes, treatment can still be reasonably achieved using small-calibre, semirigid URS, especially in female patients.[239]

Treatment of distal ureteral stones with URS demonstrates a slightly higher immediate SFR than SWL, and distal ureteral stones are less likely to require retreatment.[240,241] Furthermore, results of treating larger ureteral stones favour URS. However, both modalities are generally accepted as a first-line treatment since SWL is less invasive and may not always require general anaesthesia.[242] Thus, costs, patient satisfaction, and preference should be considered when selecting an appropriate treatment.[243]

Q 30. How can we manage urinary stones in specific situations such as those in 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, and PCNL) are acceptable treatment options for children with renal stones (LE: 2, GR: B).

Commentary

The spontaneous stone passage rates for pregnant patients range from 48% to 84% and do not differ from those of non-pregnant patients,[112] although the rates might be overestimated owing to the difficulty of diagnostic imaging. Thus, conservative management should be offered in uncomplicated cases. NSAIDs are contraindicated in pregnancy. Frequent small doses of morphine can be used safely for severe pain and acetaminophen for mild analgesia.[112,113] Regarding alpha1-blockers as MET, patients should be counselled about conflicting evidence on the efficacy of MET in non-pregnant patients, scarce investigations in the pregnant population, and 'off-label' use.[113]

When clinical indications for intervention emerges (e.g., failure of spontaneous passage, intractable symptoms, severe hydronephrosis, sepsis, or induction of premature labour), placement of a ureteral stent or a percutaneous nephrostomy tube is an effective option.[113,244] However, these temporising treatments are often poorly tolerated due to stent discomfort, bacterial colonisation, and rapid encrustation, which necessitate frequent exchanges during pregnancy[113,245]; URS has emerged as a reasonable alternative in these situations.[246,247] Compared with temporising treatments until after delivery, URS resulted in fewer requirements for stent exchange, less stent discomfort, and better patient satisfaction.[248] In pregnant patients, SWL is an absolute contraindication and PCNL should be generally avoided.[112,113]

An initial trial of conservative management should be offered in children with uncomplicated ureteral stones because spontaneous stone passage is expected in a significant proportion of children, thus avoiding surgical intervention.[249] Although MET seems to be safe and effective in children, care should be taken as this is a controversial area in adult patients.[118]

SWL is the least invasive procedure for stone management in children and provides more effective disintegration of large stones and rapid and uncomplicated discharge of fragments compared with adult patients.[250] General anaesthesia, intravenous sedation, or patient-controlled analgesia are used, depending on the patient's age and the lithotripter used. With the development of intracorporeal lithotripsy devices and smaller calibre instruments, endourologic procedures have become the treatment of choice for medium and larger stones in children. Although delicate and smaller calibre urinary organs in children must be considered when selecting instruments, indications for URS and PNL are similar to those for adult patients.[251,252]

Q31. How should asymptomatic small renal stones be managed?

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

The prevalence of asymptomatic stones is 9.5% (n=565/5,945) and has dramatically increased from 7 to 24 per 100,000 for men and from 7 to 21 per 100,000 for women over two decades. Considering these increases were only significant for men and women above 50 years old, the more frequent use of imaging for older patients resulted in this trend[10] (LE: 4).

A prior retrospective cohort study consisting of 107 patients indicated that 31.8% of patients with asymptomatic stone developed symptomatic stone events in 31.6 months of mean study follow-up.[253] Recent retrospective (n=347) and prospective (n=550) 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.[254,255] Both 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. However, smaller samples size from Singapore also indicated that stones measuring <5 mm were significantly more likely to be passed than larger-size stones[256] (LE: 4).

A Turkish prospective study of patients with asymptomatic lower pole caliceal stones with a mean cumulative stone diameter of 8.8 mm indicated that 33.3% had an increased stone size and 11.1% needed surgical interventions by their long-term follow-up (mean 52.3 months). Spontaneous passage occurred in 18.5% of the patients, with a 40% probability of experiencing pain[257] (LE: 4).

The largest prospective RCT, comparing SWL with observation for 228 patients with asymptomatic caliceal stones <15 mm in total diameter, reported no advantage of SWL for SFR, quality of life, renal function, and symptoms over 2.2 years of mean follow-up.[258] In addition, a Turkish group reported that PCNL had a significantly higher SFR than SWL, whereas 18.7% of the observation group required intervention with their prospective RCT for 94 patients with asymptomatic lower caliceal stones <20 mm in total diameter randomised into observation, SWL, or PCNL groups.[259] In another Turkish prospective study comparing observation, SWL, and URS for 150 patients with asymptomatic lower calyceal stones <10 mm in total diameter, the overall non-eventful ratio of the observation group was 88% during 21 months of mean follow-up and did not statistically differ from the SWL and URS groups (LE: 2).

A patient decision-based survey revealed that 22.8% chose observation, 29.7% chose URS, and 47.5% chose SWL with a hypothetical scenario of an asymptomatic 8-mm lower pole stone. Their decision was more likely to lean towards their previous surgical type, but the patients who had passed larger stones were less likely to choose observation over surgery[260] (LE: 4).

Taken together, clinicians may offer active surveillance for patients with asymptomatic renal stones due to their low probability of developing symptomatic events and requiring interventions (GR: C). Patients should be treated in cases of rapid growth and development of symptoms (GR: A).

7. Recurrence prevention

Q32. 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. Patients with urinary stone should be advised to achieve a goal of 2.0-2.5 L of urine daily (LE: 2 GR: A).

Commentary

Dehydration has been shown to be a risk factor for calcium stone formation. There is a significantly lower urine volume in stone formers compared with healthy subjects.[28] Increased fluid intake, which results in urine dilution, is a widely accepted measure to reduce recurrent stone formation.[261] A randomised prospective study has shown that stone formers who were assigned to increase fluid intake to achieve a urine volume of ≥ 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 2.0-2.5 L of urine daily should be recommended. Although the concept of hydration is simple, it can be difficult to practice in some patients. Successful fluid drinkers are more likely to be aware of their future stone risks and be counselled on prevention by a urologist.[262] Recently, a combination of fluid tracking system and mobile health technology, such as a smart water bottle, has been introduced as a non-invasive fluid tracker. It has considerable potential to help patients with urinary stone achieve high fluid intake.[263]

Q33. What are the components that affect 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).
○ Normalisation 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

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

About 25% of recurrent stone formers experience one lifetime recurrence.[264,265] A highly recurrent disease is observed in slightly >10% of patients. Stone type and disease severity determine low or high risk of recurrence (Table 7.1).[266,267]

All stone formers, independent of their individual risk, should follow the suggested preventive measures, whose main focus is normalisation of dietary habits and lifestyle risks (Table 7.2).[268-273] Stone formers at high risk require specific prophylaxis for recurrence, which is usually pharmacologic treatment based on stone analysis (Table 7.3).

Table 7.1 Examples for high-risk stone formers

General factors
Early onset of urolithiasis (especially children and teenagers)
Familial stone formation
Brushite-containing stones (CaHPO4 · 2H$_2$O)
Uric acid- and urate-containing stones
Infection stones
Solitary kidney (the kidney itself does not particularly increase the risk of stone formation, but prevention of stone recurrence is of more importance)
Diseases associated with stone formation
Hyperparathyroidism
Metabolic syndrome
Nephrocalcinosis
PKD
Gastrointestinal diseases (i.e., jejuno-ileal bypass, intestinal resection, Crohn's disease, malabsorption conditions, and enteric hyperoxaluria after urinary diversion) and bariatric surgery
Sarcoidosis
Spinal cord injury, neurogenic bladder
Genetically determined stone formation
Cystinuria (types A, B, and AB)
PH
RTA 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

PH = primary hyperoxaluria; PKD = polycystic kidney disease; RTA = renal tubular acidosis; UPJ = ureteropelvic junction.

Table 7.2 General preventive measures

Methods	Details
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: < 1,010
Nutritional recommendations for a balanced diet	Balanced diet
	Rich in vegetables and fibre
	Normal calcium content: 1.0-1.2 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

BMI = body mass index.

The effect of fruit juices is mainly determined by the presence of citrate or bicarbonate.[32] If hydrogen ions are present, the net result is neutralisation. However, if potassium is present, both pH and citrate are increased[274-276] (LE: 2, GR: B).

A common-sense approach to diet should be taken, which includes a mixed balanced diet with contributions from all food groups, without any excesses.[29,277,278]

Fruit and vegetable intake should be encouraged because of the beneficial effects of fibre, although the role of the latter in preventing stone recurrences is debatable.[279-282] The alkaline content of a vegetarian diet also increases urinary pH (LE: 1, GR: A).

Excessive intake of oxalate-rich products should be limited or avoided to prevent high oxalate load,[32] particularly in patients who have high oxalate excretion (LE: 3, GR: C).

Although vitamin C is a precursor of oxalate, its role as a risk factor in calcium oxalate stone formation remains controversial.[283] However, it seems wise to advise calcium oxalate stone formers to avoid excessive intake (LE:3, GR:C).

Animal protein should not be taken in excess[30,34] and should be limited to 0.8- to 1.0-g/ kg body weight. Excessive consumption of animal protein has several effects that favour stone formation, including hypocitraturia, low urine pH, hyperoxaluria, and hyperuricosuria (LE: 1, GR: A).

Calcium intake should not be restricted unless there are strong reasons due to the inverse relationship between dietary calcium and stone formation[33,280] (LE: 1, GR: A). Calcium supplements are not recommended except in enteric hyperoxaluria, when additional calcium should be taken with meals to bind intestinal oxalate[30,34,274] (LE: 1, GR: A).

Calcium stone formation can be reduced by restricting sodium and animal protein[30,34] (LE: 1, GR: A). A positive correlation between sodium consumption and risk of first-time stone formation has been confirmed only in women[33,284] (LE: 2, GR: B). There have been no prospective

Table 7.3 Pharmacologic substances used for stone prevention - characteristics, specifics, and dosage

Agent	Rationale	Dose	Specifics and side effects	Stone type
Alkaline citrates	Alkalinisation Hypocitraturia Inhibition of calcium oxalate crystallisation	5-12 g/day (14-36 mmol/day) Children: 0.1-0.15 g/kg/day	Daily dose for alkalinisation depends on urine pH	Calcium oxalate, uric acid, cystine
Allopurinol	Hyperuricosuria Hyperuricaemia	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	1,000 mg/day	Intake 30 minutes 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 Hyperuricaemia	80-120 mg/day	Acute gout contraindicated, pregnancy, xanthine stone formation	Calcium oxalate, uric acid
L-Methionine	Acidification	600-1,500 mg/day	Hypercalciuria, bone demineralisation, systemic acidosis. No long-term therapy	Infection stones, ammonium urate, calcium phosphate
Magnesium	Isolated hypomagnesemia Enteric hyperoxaluria	200-400 mg/day Children: 6 mg/kg/day	Renal insufficiency demands dose correction. Diarrhoea, chronic alkali losses, hypocitraturia	Calcium oxalate
Sodium bicarbonate	Alkalinisation Hypocitraturia	4.5 g/day		Calcium oxalate, uric acid, cystine

Table 7.3 Pharmacologic substances used for stone prevention - characteristics, specifics, and dosage—con't

Agent	Rationale	Dose	Specifics and side effects	Stone type
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: 0.5-1.0 mg/kg/day	Risk of agent-induced hypotonic blood pressure, diabetes, hyperuricaemia, hypokalaemia, followed by intracellular acidosis and hypocitraturia	Calcium oxalate, calcium phosphate
Tiopronin	Cystinuria Active decrease of urinary cystine levels	Initial dose: 250 mg/day Maximum: 2,000 mg/day	Risk of tachyphylaxis and proteinuria	Cystine

clinical trials on the role of sodium restriction as an independent variable in reducing the risk of stone formation.

Pharmacologic treatment is necessary in patients at high risk of recurrent stone formation. The ideal drug should halt stone formation, have no side effects, and be easy to administer. Each of these aspects is important to achieve good compliance.

Q34. What foods are effective at 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 intakes 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

Fruit and vegetable intakes should be encouraged because of the beneficial effects of fibre, although the role of the latter in preventing stone recurrences is debatable.[279-282] The alkaline content of a vegetarian diet also increases urinary pH (LE: 1, GR: A).

Excessive intake of oxalate-rich products should be limited or avoided to prevent high oxalate load,[32] particularly in patients who have high oxalate excretion (LE: 3, GR: C).

Although vitamin C is a precursor of oxalate, its role as a risk factor in calcium oxalate stone formation remains controversial.[283] However, it seems wise to advise calcium oxalate stone formers to avoid excessive intake[285] (LE: 3, GR: C).

Animal protein should not be eaten in excess[30,34] and should be limited to 0.8-1.0 g/kg body weight. Excessive consumption of animal protein has several effects that favour stone formation, including hypocitraturia, low urine pH, hyperoxaluria, and hyperuricosuria (LE: 1, GR: A).

Calcium intake should not be restricted unless there are strong reasons due to the inverse relationship between dietary calcium and stone formation[33,280] (LE: 1, GR: A). Calcium supplements are not recommended except in enteric hyperoxaluria, when additional calcium should be taken with meals to bind intestinal oxalate[34] (LE: 1, GR: A).

Calcium stone formation can be reduced by restricting sodium and animal protein[30,34] (LE: 1, GR: A). A positive correlation between sodium consumption and risk of first-time stone formation has been confirmed only in women[280,284] (LE: 2, GR: B). There have been no prospective clinical trials on the role of sodium restriction as an independent variable in reducing the risk of stone formation.

Q35. 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 1,000-1,200 mg/day (LE: 2, GR: C1).

Commentary

There is limited evidence about the relationship between salt intake and stone formation in Asia. Dietary salt, sodium chloride, is linked to calcium excretion in urine.[286] A randomised trial showed that a lower salt diet with a target of ≤100 mEq (2,300 mg), in conjunction with the recommended calcium intake and low consumption of animal protein, could reduce calcium excretion in urine for hypercalciuric stone formers[34] (LE: 2).

Previous interventional studies have reported a linear association between salt intake and urinary calcium excretion. A dietary increase of 6 g (103 mEq) salt in a day would result in a 40 mg (1 mmol) increase of urinary calcium per day.[287] Healthy subjects who consume >10 g (171 mEq) of salt daily had a 21.8% prevalence of hypercalciuria; however, those with a lower salt intake had a prevalence of only 3.9%.[288]

Intake of high dietary salt induces high sodium load and relative hypervolemic status. This condition diminishes the efficacy of reabsorption of sodium and water in renal proximal tubules.[289,290] Therefore, calcium reabsorption becomes less effective because it is passively coupled with sodium and water reabsorption. This hypercalciuric status may facilitate stone formation.[291] Conversely, a low dietary salt intake may induce calcium reabsorption indirectly in the renal proximal tubules and subsequent lower calcium excretion in urine.

Q36. 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,[285,292] and metabolic[293] studies have suggested that excessive consumption of animal protein may induce stone formation[285,294,295] (LE: 4). The acid load derived from sulphur-containing amino acids in animal protein may decrease urinary pH and citrate, in conjunction with hyperuricaemia and resultant hyperuricosuria through purine metabolism.[293]

In patients with recurrent calcium oxalate stones, a limited animal protein intake of 0.8-1.0 g/kg/day reduces stone formation[30] (LE: 1).

Q 37. Does thiazide prevent urinary stones?

○ Clinicians may 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

Previous studies have shown that thiazide may reduce recurrent calcium stone formation by the hypocalciuric effect with a once-daily use of 50 mg hydrochlorothiazide, 25 mg chlorthalidone, and 2.5 mg indapamide[34,296-300] (LE: 1). Restriction of sodium intake should also be considered to maximise the hypocalciuric effect. Potassium citrate or potassium chloride may be necessary to prevent hypokalaemic effects induced by thiazide medication. Potassium-sparing diuretics, such as amiloride, triamterene, or spironolactone, should be avoided during potassium supplementation.

Although there has been no randomised controlled study regarding calcium phosphate stone formers, thiazide medication may be considered for these patients.

Q 38. Does citric acid prevent urinary stones?

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

Commentary

Urinary citrate inhibits calcium stone formation by complexing with urinary calcium and inhibiting calcium oxalate crystal growth and aggregation. Renal citrate excretion is modulated by systemic acid-base balance, and medical conditions leading to metabolic acidosis promote hypocitraturia.[301]

Administration of citrate has been demonstrated to benefit hypocitraturic stone formers. Besides potassium citrate, various citrus juices containing citric acid have been investigated for their favourable effect on urinary citrate levels. Orange juice induces citraturia effectively due to its high concentration of potassium citrate.[302] Lemonade and lime juice show increased urinary citrate in some studies[303] but not in others.[304] Grapefruit juice not only increases urinary citrate but also increases oxalate excretion, so its protective effect is offset.[305] Additional larger scale clinical trials are required to demonstrate whether citrus juice is beneficial to prevent calcium stone formation.[306]

Q39. Does magnesium prevent urinary stones?

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

Commentary

Magnesium inhibits calcium oxalate stone formation through multiple mechanisms. Urinary magnesium complexes with oxalate, which reduces ionic oxalate concentration and calcium oxalate supersaturation. It also inhibits nucleation and growth of calcium oxalate crystals.[307] When taken with oxalate, dietary magnesium decreases oxalate absorption in healthy volunteers.[308] Moreover, recent data have shown that the inhibitory effect of magnesium synergises with citrate and continues to be effective at an acidic pH environment.[309]

Assessment in calcium stone formers demonstrated that magnesium supplement improved lithogenic biochemical parameters.[310,311] To address stone inhibitory effects, most clinical trials used magnesium in combination with various stone inhibitors, such as potassium-sodium citrate and magnesium oxide,[312] potassium-magnesium citrate, and vitamin B6 prophylaxis,[313] and magnesium gluconate. These clinical studies have shown favourable effects of magnesium over calcium stone formation, including increased urinary citrate level and reduced stone recurrence.[314] However, the results should be interpreted carefully as each study used a combination of stone inhibitors and none used magnesium alone. One study compared the effectiveness of magnesium hydroxide with chlorthalidone in protection of recurrent calcium nephrolithiasis and found inferior results.[296] The failure of magnesium as a sole therapy may be related to poor absorption and low rates of magnesium deficiency.[314] Additionally, in one cohort study of recurrent calcium stone formers, increasing magnesium intake was significantly associated with decreasing hyperoxaluria. This finding implies that high magnesium intake may be required to observe its protective effects.[315]

Q40. What prevents uric acid stone formation?

○ Hydration and urine alkalinisation 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 and urinary alkalinisation, and, less importantly, at reducing uric acid excretion.[316] The exact amount of daily fluid to prevent uric acid stone remains unclear. However, a total of 2.5-3.0 L/day is generally recommended.[317] Urinary alkalinisation can be achieved either by diet manipulation or pharmacotherapy with a goal of urine pH of >6.0. A more vegetarian diet and reduction in animal protein intake can increase urine pH and reduce uric acid excretion. Orange- or lemonade-based juice not only increases urine pH and volume but also increases urine citrate.[318] Nevertheless, the protective effect of urine citrate over uric acid stone is still questionable.

Pharmacotherapy to raise urine pH is usually achieved with citrate supplementation, either with potassium citrate or sodium citrate. Bicarbonate supplementation may be used as well with lower gastrointestinal side effects and lower cost compared with potassium citrate supplementation. Periodic monitoring of urine pH is mandatory since hyper-alkalinisation of urine may lead to formation of calcium phosphate stones.[319] Xanthine oxidase inhibitors such as allopurinol can decrease hyperuricaemia and hyperuricosuria but should be used after low urine pH is corrected.

Q 41. What prevents cystine stones?

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

Commentary

Since recurrent stone formation is frequently observed in cystinuria patients, medical prophylaxis is highly recommended.[320] Cystine is poorly soluble at urine pH <7.0, and stone formation occurs when urinary cystine concentration is >250 mg/dL.[321] Thus, preventive measures with adequate hydration and urine alkalinisation are mandatory. 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.[322]

Fluid intake should reach at least 4-5 L/day in adult patients to achieve a urinary cystine concentration below 250 mg/dL.[323] To alkalinise urine, potassium citrate is usually prescribed if not contraindicated. The target urine pH of 7.0-7.5 is recommended because hyper-alkalinisation of urine can lead to calcium phosphate stone formation and UTI.

Dose escalation and close monitoring of urine cystine level are required due to frequent and potentially severe adverse reactions of this agent.[324]

Q 42. What prevents infectious stones?

○   Fluid intake and diet is generally 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 may 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[325] (LE: 2, GR: B), short- or long-term antibiotic treatment,[326] urinary acidification using methionine[327] (LE: 2, GR: B) or ammonium chloride[328] (LE: 2, GR: B), and advice to restrict intake of urease[329,330] (LE: 1, GR: A). For severe infections, acetohydroxamic acid may be an option[329,330] (LE: 1, GR: A) but is not licensed/available in the United States. Phytolysin included in integrated management results in the improvement of general clinical signs and laboratory parameters of blood and urine, leads to a decrease in the

level of leukocyturia and bacteriuria, increases diuresis and urinary alkalinisation, and reduces the number of relapses of UTI and stone formation[331] (LE: 2, GR: B).

ⓆQ43. What is a useful imaging test for follow-up of urinary stone recurrence?

- ○ Plain radiography, nephrotomography, ultrasonography, intravenous urography, 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 performed cautiously and only when necessary (LE: 1, GR: A).
- ○ Imaging plays a critical role in the initial diagnosis, follow-up, and urologic management of urinary tract stone disease (LE: 1, GR: A).

Commentary

Following urologic treatment of patients with stone disease, the main objectives of CT imaging are to (1) ascertain SFS, (2) identify the presence of residual stones, (3) rule out stricture in the urinary system, and (4) detect any complications related to urologic interventions. Multidetector computed tomography (MDCT) is a modality of choice for identifying residual stone burden after interventional procedures such as PCNL and SWL.[332-335] CT aids in accurately localising the residual fragments in the kidney/ureters and thereby facilitates their removal. This is essential because recurrence rates are higher in patients (50-80%) with persistent residual stones compared with those with stone-free status. CT has a definitive role in the follow-up of stones that are lucent on conventional imaging; however, its additional value in stones that are radiopaque on KUB or scout images remains debatable.[332,336]

Imaging has an essential role in the diagnosis, management, and follow-up of patients with stone disease. A variety of imaging modalities are available to the practicing urologist, including conventional radiography (KUB), intravenous urography (IVU), US, magnetic resonance urography, and CT scans, each with its advantages and limitations. Traditionally, IVU was considered the gold standard for diagnosing renal calculi, but this modality has largely been replaced by unenhanced spiral CT scans at most centres. Renal US is recommended as the initial imaging modality for suspected renal colic in pregnant women and children, but recent literature suggests that a low-dose CT scan may be safe in pregnancy. Intraoperative imaging by fluoroscopy or US plays a large role in assisting the urologist with the surgical intervention chosen for the individual patient with stones. Post-treatment imaging of patients with stones 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 minimise cumulative radiation exposure from repeated CT scans. Patients with asymptomatic caliceal stones who prefer an observational approach should have a yearly KUB to monitor progression of stone burden. Current research has focused on the development of a micro-CT scan and coherent-scatter analysis to determine stone composition *in vivo*. This may have a significant impact on the future clinical management of renal calculi by facilitating selection of the most appropriate surgical intervention based on stone composition at the time of presentation[332,334,337] (LE: 2, GR: A).

Abbreviations and Acronyms

BMI: body mass index
ECIRS: endoscopic combined intrarenal surgery

MET: medical expulsive therapy
PCNL: percutaneous nephrolithotomy
RIRS: retrograde intrarenal surgery
SWL: shock wave lithotripsy
URS: ureterorenoscopy
UTI: urinary tract infection

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Conflicts of Interest

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