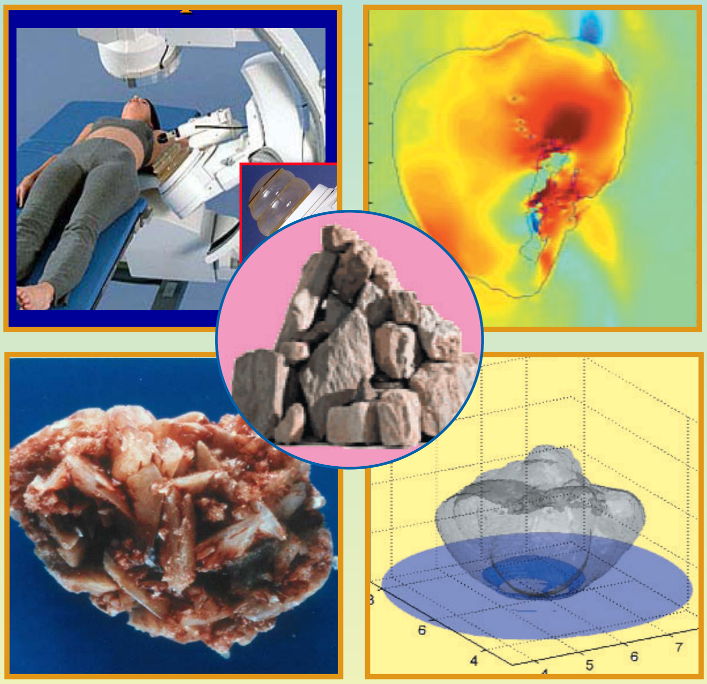
STONE DISEASE

EDITORS

JOHN DENSTEDT - SAAD KHOURY



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FOREWORD

Over the past three decades tremendous changes have occurred in the management of urolithiasis. In the developed world, extracorporeal shockwave lithotripsy and endoscopic techniques have almost completely replaced open surgery as the treatment method for patients with surgical stone problems. Advances continue to occur with the ongoing improvement in endoscopic techniques and technology.

Digital fiber-optic endoscopes, the advent of the holmium laser, and improvement in ancillary devices such as nitinol baskets, access sheaths, and novel guidewires are but some examples of improvements that have occurred as a result of the march in surgical technology.

The goal of the Second International Consultation on stone disease was to bring together global leaders in urolithiasis each of whom, were tasked to examine in detail different aspects of stone disease. This included a wide range of areas from epidemiology and economics, lithotripsy technology, methods of management for ureteral and renal stones, to the latest state-of-the-art in diagnosis and medical strategies for urolithiasis.

Similar to the first international consultation, this endeavour has taken a global perspective to stone disease achieved by populating the various committees with experts from throughout the world.

This volume reflects the current state-of-the-art for urinary stones and proves a useful reference for urologists involved in assessing and managing patients with urinary stone disease.

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Preface

The second International Consultation on Stone Disease represents a considerable achievement building, as it does, on the pioneering work of the first Consultation. This volume will be regarded as "The Bible", that is the reference book for clinicians involved in the management of patients with urinary tract stones. The use of the ICUD methodology for Evidence Based Medicine is a very valuable development on the first volume [1]. This methodology gives the series of recommendations greater authority and allows greater confidence when treating patients.

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The faculty has fulfilled its obligation to the communities of both the developing and developed world and the chapters on epidemiology and bladder stone point the way forward for those communities in which the prevalence of stone disease is at its highest. The International Consultation on Urological Diseases (ICUD), supported as it is by the world's major urological associations and societies, is trying to develop ways of raising the standards of urological practice worldwide. In part, this is being achieved through the production of high quality publications such as this, but also by seeking ways to support our colleagues in developing countries, enabling them to make available first class care, delivered by well-trained urologists, to the maximum n umber of patients suffering from urological diseases.

The ICUD would like to congratulate John Denstedt and his colleagues for the excellence of this publication.

1. Abrams P, Khoury S, Grant A. Evidence-based medicine overview of the main steps for developing and grading guideline recommendations. Prog Urol 2007 May; 17 (3) : 681-4

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Epidemiology of Stone Disease

David Goldfarb, Alberto Trinchieri, Gary Curhan

I. INTRODUCTION

The First International Consultation on Stone Disease met in 2001 and the proceedings were published in 2003 [1]. A thorough review of the epidemiology of nephrolithiasis was presented at that time, along with a discussion of the many methodologic issues related to studying stone disease today. Recommendations were made regarding an approach to dealing with those issues in future studies [2]. We do not intend to repeat here what was previously written, but we will focus on the epidemiologic findings that have been presented in the ensuing years. In **Table 1**, we briefly summarize the recommendations made at that time, which should serve as a template for evaluating the current literature [1].

II. GEOGRAPHIC VARIATION OF INCIDENCE AND PREVALENCE OF NEPHROLITHIASIS

The most recent data regarding prevalence (the proportion with a history of nephrolithiasis) and incidence (rate of new onset of nephrolithiasis) of stones, divided by continent, are summarized in **Table 2**. The focus is on studies published since 2000, to emphasize data not included in the last International Consultation. Most studies contain only prevalence and not incidence data. Very small studies, reflecting only the experience of a single hospital or practitioner, are not presented here. For that reason, reports from Africa did not have sufficient power to present meaningful results. We found no studies reporting the prevalence or incidence of stones in Australia.

Several studies suggest an increasing prevalence of stones around the world. In the United States, two periods were compared in the large nationally representative National Health and Nutrition Examination Surveys (NHANES) [3]. Disease prevalence among 20 to 74 year-olds was greater in the later period,1988 to 1994, than in the earlier period, 1976 to 1980 (5.2% vs. 3.8%). A more modest increase in prevalence was noted in Germany, where it increased from 4.0 to 4.7% from 1979 to 2001 [4]. In a village in Italy, 6.8% of males and 4.9% of females had a history of stone disease in 1986 compared to 10.1% of males and 5.8% of females in 1998 [5]. Whether these observed increases in stone prevalence are accounted for by more frequent occurrence of calcium stones or uric acid stones is not known.

Few studies have examined incidence rates of stone formation. In Japan, the age-adjusted annual incidence of first-episode upper urinary tract stones in 1995 was 68.9 per 100,000, an increase from 54.2 in 1965. The annual incidence increased in all age groups except the first three decades, more than doubling from 43.7 in 1965 to 110.9 in 1995 [6]. In Minnesota, the age-adjusted annual incidence rate of new onset symptomatic stone disease appeared to decrease for men from 155.1 per 100,000 population per year in 1970 to 105.0 in 2000. The annual rates for women appeared to have increased from 43.2 per 100,000 in 1970 to 68.4 in 2000. The incidence rate ratio of men to women decreased from 3.1 to 1.3 during the 30 years [7].

The cause of increasing stone prevalence is also not clearly established. Other data, summarized below (“Associated Diseases”), indicate that obesity and diabetes are both significant risk factors for stones. Since the prevalence of these conditions has also been shown to be increasing in the western world [8, 9], a reasonable speculation, not yet supported by adequately controlled, prospective data, would suggest that increasing prevalence of obesity and diabetes could be in part responsible for the increasing prevalence of stones [10]. The possible role of *Oxalobacter formigenes* in stone formation and more widespread prevalence is described

Table 1. Recommendations for Epidemiologic Studies of Stone Disease (adapted from First ICUD[1]).

1. Subject selection

a. characteristics are fully delineated

b. underlying source population is described

c. if controls are being chosen, they should be identical to cases except have no history of stone disease

2. Measurement instruments

a. reproducibility should be known

b. validation technique is described

3. Study design

a. retrospective study designs are not optimal because exposures may change as a result of the disease

b. outcome ideally would be stone formation and care should be used when extrapolating from studies of urine composition to stone formation

4. Statistical Methods

a. appropriate and sophisticated statistical methods are needed

b. error correction should be applied if possible

c. variables may be continuous or categorical

d. justification for definitions and cutpoints for continuous variables is necessary

e. justification for different definitions based on gender are needed

5. Exposures

a. careful study of current and past exposures is needed

b. new dietary factors for study are needed (e.g. fatty acids, phytic acid)

c. other environmental factors are not adequately studied

1. geographic factors
2. stress

d. genetic epidemiology studies needed

1. Genome wide association studies should be performed on carefully phenotyped individuals
2. detection of important interactions with environmental factors

6. Potential confounders

a. adjustment for other risk factors is essential to identify independent associations

7. Subgroups

a. Risk factors for stone formation may vary according to age, gender and race.

8. Less common stones

a. need to study epidemiology of less common stone composition:

1. uric acid
2. struvite
3. cystine

Table 2. Prevalence and Incidence of Stones by Continent

South America

Nation (city)	Author (year)	Prevalence	Incidence	Notes
Argentina (Buenos Aires)	Pinduli (2006)[56]	All: 4.0% (2.8–5.1) Male: 4.4% (2.6–6.1%) Female: 3.6% (CI 2.1–5.1%) Over 19 Yrs Of Age: 5.1% Men: 6.0% (3.4–8.6%) Women: 4.5% (CI 2.6–6.4%).		N = 1,086
Brazil	Heilberg I; unpublished (personal communication)		Hospitalizations were 2-3000 per month in 1996; and 6-7000 per month in 2006	More hospitalizations for women than men; more in the southeast of Brazil than other regions

Asia

Nation (city)	Author (year)	Prevalence	Incidence	Notes
China (Shenzhen)	Peng (2003)[57]	Men: 8.0% Women: 5.1%		
Korea (Seoul)	Kim H (2002)[58]	Standardized lifetime prevalence rate 3.5%; Men: 6.0% Women: 1.8% Point prevalence rate 0.9% Men: 1.9% Women: 0.3%		N = 2,643
Taiwan	Lee YH (2002)[29]	Ovearll 9.6% Men: 14.5% Women: 4.3%		N = 4588
Iran	Safarinejad (2007)[59]	Overall 5.7% (4.2–5.4). Adults 15–29 years 0.9% 60–69 years 8.2% Men: 6.1% Women: 5.3%.	2005: $145.1/10^5$	N = 7649

Europe

Nation (city)	**Author (year)**	**Prevalence**	**Incidence**	**Notes**
Germany	Hesse (2003)[4]	1979: 4% 2001: 4.7% Men 50-64 yr in 2000: 9.7% Women 50-64 yr in 2000: 5.9%	1979: 0.5% 2000: 1.5%	N = 4000 Recurrence 42% Spontaneous passage 40%
Iceland	Indridason (2006)[60]	Men: 4.3% Women: 3.0%	Men: $562/10^5$ Women: $197/10^5$	
Italy	Trinchieri (2000)	Men 1986: 6.8% 1998:10.1% Women 1986: 4.9% 1998: 5.8%	All: 0.4% Men: 0.6% Women: 0.2%	

North America

Nation (city)	**Author (year)**	**Prevalence**	**Incidence**	**Notes**
United States	Stamatelou (2003) [3]	1979 - 1980: 3.8% 1988 - 1994: 5.2%		1976 – 1980 : N = 15,364 1988 – 1994 : N = 16,115
United States (Rochester, MN)	Lieske (2006) [33]		(per 10^5 per year) Men: 1970: 155.1 2000: 105.0 Women: 1970: 43.2 2000: 68.4	

briefly below. It is also possible that rather than a true increase in prevalence, the above findings represent the detection of more asymptomatic stones found incidentally due to more widespread application of computed tomography (CT) and ultrasound, imaging modalities more sensitive for stone detection than plain radiography.

III. DIET

1. CALCIUM

Since the 1990's epidemiologic data have consistently shown that higher dietary calcium intake is associated with a lower prevalence and incidence of kidney stones [11], [12]. Among twin pairs discordant for stones, those who drank at least 1 cup of milk per day were half as likely to report kidney stones [13]. Newer analyses of databases with longer follow-up have also confirmed earlier findings [14, 15]. The basis of these associations may be that higher dietary calcium intake reduces oxalate excretion by making ingested oxalate insoluble and unabsorbable. Alternatively, dairy products may contain other anti-lithogenic properties.

These epidemiologic data are supported by a randomized controlled trial of a high calcium diet in 120 men with hypercalciuria and recurrent calcium oxalate stones [16]. Men assigned to the high calcium diet (30 mmol or 1200 mg per day), which also had restricted intake of salt, animal protein and oxalate, were compared to men who received a low calcium (10 mmol, 400 mg per day) and low oxalate diet. The high calcium diet group had a 51% lower risk of stone recurrence compared to the low calcium diet group. Calcium supplements on the other hand have not been consistently associated with the same reductions in stone prevalence seen with dietary calcium intake. Epidemiologic data have not shown a risk of calcium supplements [15], while one randomized controlled trial of calcium supplements in post-menopausal women was associated with a 17% higher risk for incidence of stones [17].

2. OXALATE

In three large prospective cohort studies of both men and women, dietary oxalate was only modestly associated with risk of stone formation in men and older women, compared to those individuals in the lowest quintile of oxalate intake, those in the highest quintile were 20% more likely to form a stone [18]. This association was almost completely due to differences in spinach consumption. There was no association between oxalate and stone risk in younger women. Thus, even though urinary oxalate is an important risk factor for calcium oxalate stone formation, dietary oxalate does not appear to be a major risk factor.

3. PROTEIN

Increased dietary protein intake has often been linked to increased stone prevalence though this effect has not been observed uniformly in epidemiologic studies. Short term studies of urine chemistry offer sufficient possible mechanisms to explain such a link: after decreased protein ingestion, stone formers demonstrate increases in urinary citrate excretion and pH, and decreases in calcium and uric acid excretion [19, 20]. A significant proportion of stone formers also have increases in urine oxalate excretion after protein meals [21]. However, in the Health Professionals Follow-up Study, which included 45,619 men without a history of nephrolithiasis followed for up to 14 years, animal protein intake was associated with risk only in men with a body mass index <25 kg/m^2. Animal protein intake was also not significantly associated with stones in the Nurses Health Study II, which included 96,245 women age 27 to 44 years old [15]. A cotwin study in twin pairs discordant for stones did not show protein intake to be a significant risk factor for stone formation in a multivariate analysis [13]. Randomized controlled trials of low protein diets have not to date demonstrated a benefit with respect to prevention of stone formation. Reduced animal protein intake was a component of the diet that reduced stone recurrence in patients who followed a higher, compared to a lower, calcium intake but its importance to that effect could not be independently affirmed [16]. The types of individual protein (dairy, non-dairy, animal, and vegetable) likely have different impacts on stone risk.

5. CARBOHYDRATE

Acute carbohydrate loads had previously been shown to cause increased urine calcium excretion in normal subjects, calcium stone formers and their relatives [22]. Increased intake of sucrose was associated with stone risk in the Nurses Health Studies, both in younger and older women [12, 15], but there was no association in men [14]. More recently, associations between diabetes, obesity and stone formation have also been demonstrated, reviewed below.

6. PHYTATE

One benefit of more vegetable intake may be a resultant increase in dietary phytate content. Phytate (inositol hexaphosphate) may reduce crystallization of calcium salts and reduce urine calcium excretion [23]. Phytate intake was inversely associated with stone formation in younger women [15] but not in men [14].

IV. FLUID INTAKE

One randomized controlled trial demonstrated that higher fluid intake was associated with fewer stone recurrences [24]. Although this study was recently criticized for omission of some methodologic details by the Cochrane review, which called for further research [25], the study is credible and well-performed. Given the nature of the intervention, its cost and basis in chemistry, it is unlikely to be repeated. Results from observational studies also strongly support the protective role of higher fluid intake [6,7,9].

There is no evidence to date that definitively links greater water hardness with increased stone prevalence. Although data demonstrate that drinking hard water is associated with increased urine calcium excretion, no increase in stone prevalence has been demonstrated [26].

V. CLIMATE AND SEASONAL FACTORS

Regional differences in stone prevalence may be attributed to climate but dietary and racial factors may be difficult to separate from geographic variables. Within most countries, warmer climates are associated with more stones. Within the United States, higher prevalence was noted in the southern region [3]. Corresponding to seasonal temperature, hospitalizations for stones in Brazil were more common in the summer than in the winter (**Figure 1**) (Personal communication, Dr. Ita Heilberg). We did not find any European studies addressing geography.

VI. OCCUPATIONAL FACTORS

Few correlations between work place activities or behavior and kidney stones has been established. Stones have been repeatedly associated with “hot” or outdoor occupations such as lifeguards.

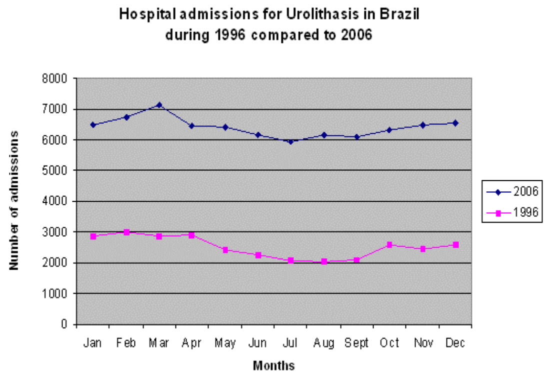

Figure 1. Hospitalizations in Brazil for stones increased from 1996 to 2006. Hospitalizations were more frequent during the summer months than during the winter.

No comprehensive survey has linked stones with other types of work, but one might suspect a higher prevalence of stones in those who can void only infrequently, such as long-distance drivers and teachers.

VII. INHERITANCE AND GENETICS

Stone disease is caused by heritable factors in addition to a variety of environmental influences. The number of people with known genetic causes of stones is quite small. Such patients are affected by disorders such as primary hyperoxaluria, cystinuria, Dent disease, 2,8-dihydroxyadeninuria and others. The rarity of these disorders precludes an important genetic contribution to the relatively high prevalence of stones in the general population. One previous study demonstrated that as many as 40% of patients in a stone clinic had a first degree relative with a history of stones [27]. In men followed prospectively in the Health Professionals Study, the risk of incident stone formation in men with a positive family history was more than doubled compared with those without [28]. In a nation-wide survey in Taiwan, compared with the general population, the odds ratios for stone disease in participants whose father, mother or both parents had a history of stone disease were 3.44, 4.79 and 10.40 respectively [29].

Further demonstration of stone heritability is a twin study in which concordance (both members of a twin pair affected) for stones in monozygotic twins

(32.4%) was nearly twice that of dizygotic twins (17.3%) [13]. Based on these data, heritability was estimated to account for 56% of stone prevalence.

However, the genetic basis for this strong heritable component remains uncertain. Examination of a number of candidate genes for calcium stones has failed to elucidate the responsible molecular mechanisms. Since the most common urinary abnormality in many populations of calcium stones is hypercalciuria, a number of candidate genes that might lead to hypercalciuria have been examined. A partial list of genes that do not account for hypercalciuria includes the vitamin D receptor, the interleukin 1 receptor and TRPV5 channels.

Recently a gene for a soluble adenylate cyclase has been associated with patients with hypercalciuria and low bone mineral density, but the prevalence of this gene in the general population has not been established nor has its role in normal renal physiology been described [30, 31]. A polymorphism in the calcium sensing receptor was associated with hypercalciuria in a cohort of Italian women with hypercalciuria referred for treatment of osteoporosis [32]. This group did not have a history of stone disease. The same allelle, however, had previously been associated with hypercalciuria in stone formers and with primary hyperparathyroidism and stone formation [33].

VIII. AGE AND SEX

Most studies of gender distribution among patients with stones have shown that men outnumber women by ratios roughly between 1.5-2:1 or more. Within this range, the male predominance among stone formers has been seen consistently around the world. Recently an American sample of more than one million hospitalizations between 1997 and 2002 showed an increased number of hospital discharges in women of 21.0% for renal calculi and 19.2% for ureteral calculi, while the number of discharges for men did not change [34]. This finding represented a change in the male:female ratio of for treated stone disease from 1.7:1 to 1.3:1 during the short study period. It may reflect variations in the underlying prevalence by gender of stone disease. Although this study did not have data regarding the concomitant ratio of obesity, the authors noted that the change in stone prevalence among women parallels a similar, more rapid increase in the prevalence of obesity in women than in men [35].

Another study demonstrated increases of kidney stone prevalence in both American men and women, maintaining a ratio of approximately 2:1 in time periods of 1976 to 1980 and in 1988 to 1994 [3]. In the Mayo Clinic's data from Rochester, Minnesota, the overall male:female ratio decreased from 3.1 to 1.3 between 1970 and 2000 [7]. In fact, this change in ratio was partially due to a reduction in kidney stone prevalence for men of 1.7% per year while rates for women increased by about 1.9% per year.

Data from the American database NHANES indicate that stone prevalence increased in all age groups from 1980 to 1994 though despite more than 15,000 participants at each time point, the increase was statistically significant only for men aged 60-74 [3].

In Italy hypercalciuria was more frequent in patients age 20-39 years (50.3%) than in older patients (36%) and hyperuricosuria was lower in the younger patients (5%) than in the older patients (10%) [36]. Similarly, younger Taiwanese stone formers have higher rates of calcium stones and older people have more uric acid and struvite stones [29]. In France, the proportion of uric acid stones rose with age in both genders [37].

IX. ASSOCIATED DISEASES

Recent data have shown important associations of stones with obesity, diabetes, hypertension and gout. The first three of these disorders are themselves linked under the umbrella of "metabolic syndrome", a disorder whose definition, like its pathophysiology, is still the subject of debate. Gout, although not a feature of the metabolic syndrome, is itself linked to obesity and hypertension. Studies have begun to elucidate the multiple mechanisms by which these disorders may increase the prevalence of nephrolithiasis and while we review the epidemiology, we will not attempt to review the putative pathophysiologies in detail here.

1. OBESITY

In both men and women greater body mass index was associated with higher risk for stone formation [38]. After multivariate adjustment, the relative risk for stone formation in men weighing more than 100.0 kg vs less than 68.2 kg was 1.4. The effect was somewhat greater in older and younger women: the relative risk for the same weight categories was 1.9. There was a greater risk for both men and women who gained more than 15.9 kg since age 21 compared with those whose weight did not change: 1.4 for men, 1.7 for older women and 1.8 for younger women. Body mass index was also associated with stones.

These effects of obesity on stone risk, coupled with data demonstrating the increase in prevalence of obesity worldwide [8] could plausibly account in part for the observed increase in stone prevalence.

Among the sample of participants in the above studies who performed 24 hour urine collections, participants with greater BMIs excreted more oxalate, uric acid, sodium and phosphate than participants with lower BMIs [39]. Higher BMI was inversely associated with urine pH. BMI was not associated with urine calcium excretion in the adjusted analysis or with higher urinary supersaturation of calcium oxalate. Urinary supersaturation of uric acid, however, did increase with BMI. These studies did not have data on stone composition.

Other studies have shown that obese stone formers (BMI≥30 kg/m^2) are more likely to have lower urine pH, hyperuricosuria and hypocitraturia in comparison to nonobese stone formers [40]. Increases in BMI appear to be inversely and linearly associated with decreased urine pH in stone formers (though this study did not control or adjust for diabetes) [41].

These alterations in urine chemistry are in turn associated with effects on stone composition. As expected with lower urine pH, uric acid stones constituted 63% of stones among obese subjects as compared with 11% among the non-obese stone formers [40]. Another study confirmed this finding in France [37].

Excluding patients known to have diabetes, they studied 1,931 patients with calcium or uric acid calculi. The proportion of uric acid stones increased from 7.1% in men with normal BMI (< 25 kg/m^2) to 28.7% in obese subjects (≥ 30 kg/m^2). Uric acid stones became more frequent as well in women, constituting 6.1% of stones in women with normal BMI and 17.1% in obese subjects.

These effects of obesity on stone prevalence and composition may in part be associated with insulin resistance, though this hypothesis remains unproven, particularly in patients with obesity who are not affected by diabetes. Increased BMI has also been associated with increased oxalate excretion [42] though an increased risk of calcium oxalate stones has not yet been shown to be associated with obesity.

2. DIABETES

Diabetes has recently been shown to be a risk for stones in epidemiologic studies. Women and men in the Nurses' Health Studies and the Health Professionals Follow-up Study were prospectively studied to determine the association between diabetes and nephrolithiasis [43]. The multivariate relative risk of a history of stone disease in individuals with DM compared to individuals without was 1.3 in older women, 1.6 in younger women, and there was no association in men. The multivariate relative risk of incident kidney stone formation in participants with diabetes compared to participants without was 1.3 in older women, 1.6 in younger women, and there was no association in men.

In all three cohorts there was also an increased multivariate relative risk of incident diabetes in participants with a history of kidney stones compared to participants without. These studies did not include data on stone composition to confirm the supposition that diabetics, like the obese, have an increased proportion of uric acid stones relative to calcium stones. Other data confirm that diabetics have more uric acid stones [44]. In this study from France, uric acid was the dominant constituent of stones in 35.7% of patients with type 2 diabetes and 11.3% in non-diabetics. Conversely, 27.8% of uric acid stone formers were diabetic as compared to 6.9% of calcium stone formers. The association of diabetes and stones has been suggested to be related to lower urine pH resulting from effects of insulin resistance on ammoniagenesis [45].

3. HYPERTENSION

Numerous older epidemiologic studies have linked hypertension to kidney stones. Larger studies have also suggested that a history of kidney stones increases the risk of development of hypertension. The direction of this association is therefore uncertain. Most recently, the NHANES data were used to explore the association of a history of stone disease and a history of hypertension [46]. Female stone formers, but not male, had a 69% increase in odds of self-reported hypertension compared to non-stone formers. Mean systolic BPs in female stone formers in the top 2 quintiles of BMI were 7.6 mm Hg and 4.4 mm Hg greater than those in non-stone formers with similar BMI.

Whether these associations of hypertension and stones are due to effects of the metabolic syndrome, such as associated insulin resistance, changes in renal handling of calcium, dietary salt intake or alterations in GFR [47] has not been determined. Among 3 cohorts of subjects with and without stones, who collected urine for 24 hours, citrate was the only urinary factor consistently related to hypertension. Those in the lowest quartile of urinary citrate excretion had multivariate odds ratios of prevalent hypertension, compared to the highest quartile of 0.4 in older women, 0.5 in younger women, and 0.3 in men [48].

4. GOUT

Gout has been associated with an increased risk of nephrolithiasis in a cross-sectional study [49]. Of individuals with at least 2 episodes of kidney stones, 8.6% had a history of gout, while in subjects with reported gout, 13.9% had a history of stones. After adjustment for sex, race, body mass index, and presence of hypertension, the odds ratio for previous kidney stones in individuals with gout was 1.5. These results were confirmed in men in the prospectively conducted Health Professionals Follow-up Study [50]. A history of gout was significantly associated with kidney stone disease (OR=1.9). This association persisted after adjusting for body mass index and dietary factors. In men who had never had a stone, gout was associated with a multivariate relative risk of incident kidney stones of 2.1.

5. POSSIBLE ROLE OF OXALOBACTER FORMIGENES

Oxalobacter formigenes is a colonic anaerobe which constitutes a normal component of the human microbiota. Its only substrate is oxalate. It may both degrade ingested oxalate present in the intestinal lumen and induce secretion of oxalate from blood into the intestinal lumen [51]. Its presence in the colon may be associated with diminished intestinal absorption of oxalate resulting in diminished urine oxalate excretion. Its absence in patients with stones has been correlated with increased urine oxalate excretion compared with stone-forming patients colonized by the organism [52]. Antibiotic use is associated with reduction in colonization with O. formigenes [53]. Absence of the organism may contribute to hyperoxaluria seen in patients with cystic fibrosis [54] and inflammatory bowel disease [55]. Despite these suggestive associative data relating the organism's presence or absence with less or more urinary oxalate excretion, no prospective study data on the relation between the presence of this organism and risk of incident stones is available. More widespread use of antibiotics throughout the world could be a contributing factor to the increased prevalence of stones discussed above, but again, convincing evidence is lacking.

SUMMARY

Epidemiologic studies can provide important information on patterns of nephrolithiasis and relevant risk factors. Future studies of nephrolithisis will look at the interplay between common genetic variability and environmental factors.

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Economics of Stone Disease

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CONTENTS

Economics of Stone Disease

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I. INTRODUCTION

The lifetime prevalence of stone disease has been estimated at 13% for adult men and 7% for adult women in the United States. (1, 2) Due to the high prevalence, the health care costs associated with nephrolithiasis significantly impact overall health care costs. In the US alone, increases in disease prevalence and health care costs have resulted in total annual medical expenditures for urolithiasis to be estimated at $2.1 billion in 2000. (3) These figures included $971 million for inpatient services, $607 million for physician office and hospital outpatient services and $490 million for emergency room services. (3) Since the incidence of nephrolithiasis peaks between ages 20 and 60, there are additional costs to society associated with loss of productivity. (4, 5)

While much of the published economic data is based in the U.S., the economic impact of stone disease is international. The purpose of this chapter will be to evaluate the financial impact of stone disease in different health care systems. We will also discuss potential means for reducing stone-related health care costs.

II. COST CONSTITUENTS

The overall financial burden can be divided into direct and indirect costs. Direct costs are easier to quantify as they consist of those attributable to inpatient or outpatient care as well as medications. Indirect costs are more difficult to quantify since they include loss of work and productivity. This chapter will focus primarily on direct costs. The chapter will be further divided into treatment related costs and those related to prevention (i.e. evaluation and medical management). When one considers treatment related costs, it is important to consider those costs associated with an acute stone episode as well as inpatient and outpatient care including procedures. Furthermore, we will discuss differences between countries as variations in management and health care systems result in significant differences in cost.

III. INTERNATIONAL PERSPECTIVE

One goal of this International Consortium is to evaluate the impact of stone disease in a variety of countries, and as such, it is important to recognize up front the difficult challenge that this presents. From one perspective, it seems that costs should be relatively homogenous. The majority of stone-related treatment costs result from surgical intervention and relatively few companies produce shock wave lithotripters and endoscopes. As such, one would expect that procedures should "cost" the same no matter what country provides the service. However, in an International Economic Survey by Chandhoke, costs for shock wave lithotripsy (SWL) and ureteroscopy (URS) were widely disparate in different countries. (6) Indeed, a nearly 20-fold difference was demonstrated in the costs of SWL, ureteroscopy with laser lithotripsy and medication among different countries. Even within countries such as India, there were significant regional differences in costs. Does this mean that equipment such as an ureteroscope or lithotripter has vastly different costs in different countries? According to the survey, the cost of ureteroscopy in Germany is $160 and in Switzerland is $1900. (6) One would assume that the Swiss should import their ureteroscopes or drive across the border. More likely, the actual costs of capital equipment such as the ureteroscope or lithotripter are not calculated into the cost equation equally giving the appearance of a cheaper procedure. The only realistic difference in costs across countries would be if there were local production leading to less expensive equipment or if there were a significant difference in physician and nursing salaries leading to lower overhead costs. In some countries such as the U.S., surgery and physician reimbursement are heavily regulated. Insurers and government-run and subsidized health care agencies like the Centers for Medicare and Medicaid (CMS) dictate reimbursement rates for services associated with hospitalization and surgical procedures and for physician fees.

It is also likely that there are costs which are difficult to obtain and quantify in certain countries resulting in inaccurate estimation.

A significant impediment to understanding the financial burden associated with nephrolithiasis is the wide disparity in the cost of stone treatment between health care systems. Although cost studies from different countries may be useful in assessing the cost-effectiveness of a particular treatment or management strategy within that country, conclusions may not be uniformly applicable across nations. It would be helpful if there was a standard international format to assess the cost for the same procedures in every country.

IV. ACUTE MANAGEMENT

Cost related to management of the acute stone event generally encompasses outpatient emergency room or office visits. Patients who seek medical attention are often symptomatic and require intravenous fluid and analgesic administration and occasionally admission to the hospital. Furthermore, evaluation of these patients includes radiographic imaging and laboratory studies, further contributing to the overall cost. In the U. S., the National Hospital Ambulatory Medical Care Survey estimated that there are 226 emergency room visits per 100,000 populace per year. (3)

The need for inpatient versus outpatient treatment for acute management of stone disease impacts the overall cost of the disease. Most patients with stones in the U.S. are managed on an outpatient basis, while there is more variability in admission rates worldwide. The U.S. and Sweden have relatively low admission rates (29% and 38%, respectively) while in Germany approximately 69% of patients with urolithiasis receive inpatient hospital care. (7-9) The admission rate in Western General Hospital, Edinburgh is 43.5%. This has important implications since one study of 4895 patients admitted for stone disease who were not treated surgically, found that the average hospital length of stay was 2.65 days and the mean charge was $2153. (10) The previous study was over 10 years old, but a more recent study from the Urologic Diseases of America project found that in the year 2000 the mean hospital length of stay for stones was 2.2 days. (3) Even when patients are admitted, only 25% end up undergoing a definitive surgical procedure during that admission. (5, 10)

One way to reduce costs would be to limit admissions and determine early in the hospital stay who will require surgery.

There are additional cost implications resulting from the decision whether to observe a stone, with the hope of spontaneous passage, or to intervene surgically. From a financial standpoint, the cheapest course is for a patient to pass a stone spontaneously but choosing observation risks repeated emergency room visits, the possibility of future surgery in those patients who fail to pass their stone and potential risks of waiting such as infection and ureteral stricture. In a meta-analysis of 2704 patients, spontaneous passage rates were higher for distal ureteral stones (45%) compared with middle (22%) and proximal ureteral stones (12%). (11) In the same study, stone size also had a significant impact and two-thirds of stones passed spontaneously within 4 weeks of the onset of symptoms. Lotan and co-workers used a cost-effectiveness model taking factors such as likelihood of spontaneous passage, stone location, stone size and success rates for SWL or URS into account and found that observation was the most cost effective approach to ureteral stones, demonstrating a $1200 cost advantage for distal ureteral stones and a $400 cost advantage for proximal ureteral stones despite low spontaneous passage rates for proximal ureteral stones. (12) Additional emergency room visits and indirect costs of missed work can lower the cost-effectiveness of observing proximal stones which are unlikely to pass.

Strategies to increase the likelihood of spontaneous stone passage will, however, benefit the cost-effectiveness of observational strategies. There is increasing evidence that the use of pharmacological therapy, including combinations of corticosteroids and alpha-adrenergic antagonists or calcium channel blockers, may increase the likelihood of spontaneous ureteral stone passage. (13-16) A meta-analysis of nine trials (number of patients=693) evaluating the benefits of medical expulsive therapy was recently published. (17) In this study, patients given calcium-channel blockers or alpha blockers had a 65% (pooled risk ratio 1.65, 95% CI 1.45-1.88) greater likelihood of stone passage than those not given such treatment.

This increase in likelihood of spontaneous stone passage using medications with low toxicity will reduce the cost of managing acute stones by decreasing the need for expensive surgical intervention.

V. SURGICAL THERAPY

Due to the high prevalence of stone disease and the lack of effective medications to eradicate most stones, surgery is required for a large percentage of patients with resultant high costs. Data from the Centers for Medicare and Medicaid Services (CMS) and Center for Health Care Policy and Evaluation (CHCPE) found that surgery for stone disease was required for 339 to 486 patients for every 100,000 population depending on region of the U.S. (3) The distribution of procedures for stones is similar for CMS and CHCPE with identical rates of SWL (54%) and similar rates for URS (41% and 42% for CMS and CHCPE, respectively) and percutaneous nephrolithotomy (PCNL) (4% and 6% for CMS and CHCPE, respectively). The choice of surgical approach depends on a number of factors including stone characteristics (size, location and composition), the anatomy of the kidney/ureter, patient and physician preference and available technologies (ureteroscopes, holmium laser). The overall cost of stone care depends not only on the initial cost of treatment but also on costs associated with retreating failures, the need for ancillary procedures or hospitalization and indirect costs.

There are many difficulties in generalizing economic conclusions for surgical stone management. The success rates and costs for procedures vary for renal and ureteral stones and by stone size. Furthermore, there is considerable variation in cost of procedures across countries so comparing costs between countries is both impractical and inaccurate. An international economic survey of 10 countries by Chandhoke found that charges for SWL varied from $373 to $9924 and those for URS from $491 to $8108. (6) SWL was determined to be more costly than URS in 5 countries (Australia, Germany, Japan, UK, U.S), equivalent in 3 countries (Canada, Italy, Sweden) and less costly in 2 countries (Switzerland, Turkey) . As such, conclusions for the most cost-effective approach depend on the individual costs within a health care system.

1. RENAL CALCULI

There have been significant changes in the management of renal stones with the conclusions of AUA guidelines that PCNL is the primary treatment for staghorn stones. (18) Furthermore, several studies have compared SWL with URS and PCNL for management of stones in the lower pole of the kidney. A multi-institutional study randomizing patients with <1 cm lower pole stones to URS or SWL revealed stone-free rates at 3 months of 35% and 50% (p not significant), respectively. (19) Likewise, in a randomized trial comparing SWL and PCNL for the treatment of symptomatic lower pole stones ≤ 30 mm, PCNL stone-free rates were far superior to SWL (95% versus 37%, respectively, p <0.001). (20) Since overall treatment costs depend heavily on stone-free rates, differences in success rates have a significant impact overall cost-effectiveness.

There are few studies evaluating the cost of different treatment strategies for treatment of renal calculi. The only prospective, randomized trial comparing the cost of SWL and PCNL for the treatment of renal calculi compared 21 patients with PCNL and 28 patients with SWL for "medium" sized renal stones between 4 and 30 mm in diameter. (21) Although the mean total cost for SWL as primary therapy was less than that for primary PCNL, the cost difference narrowed after 1 year of follow-up as retreatment of some SWL patients was required. Another small study of 30 patients evaluated "tubeless" PCNL, "mini-PCNL" and standard PCNL and found the tubeless approach to be the most cost-effective. (22)

Due to the paucity of prospective studies, several models have been utilized to estimate projected costs of particular treatment strategies based on treatment efficacy and procedure cost. These models have preceded recent studies and are limited by the fact that they are based on studies that did not evaluate stone-free rates uniformly. If one bases stone-free rates of SWL using a plain X-ray rather than computed tomography, then the results are significantly better. Nevertheless, May and Chandhoke compared SWL and PCNL treatment of solitary lower pole renal calculi(23) using charge data from their institution ($8213 for SWL and $26,622 PCNL including retreatment and complication rates) and success rates for SWL and PCNL derived from a published meta-analysis (24).

In their model, all treatment failures were salvaged with secondary PCNL. For lower pole stones <1 cm and 1-2 cm, SWL was less costly than PCNL when PCNL charges exceeded $11,099 and $12,258, respectively. For stones >2 cm in size, PCNL was less costly than SWL, provided PCNL charges remained under $21,059. Since the charge for uncomplicated PCNL was <$15,000 at their institution, the authors concluded that for a solitary lower pole stone greater than 2 cm, PCNL is the most cost-effective approach, while SWL is more cost-effective for lower pole stones <2 cm in size despite lower initial stone free rates.

Chandhoke and associates also compared the cost-effectiveness of SWL and PCNL for the treatment of staghorn calculi using a decision analysis model. (25) Based on their model, the cost of SWL and PCNL-based therapy (combination PCNL/SWL) was comparable for stones < 500 mm^2, but combination therapy was more cost effective than SWL alone when the stone burden exceeded 500 mm^2.

At this time, there is a scarcity of good cost comparisons between PCNL and other techniques. Furthermore, balancing cost-effectiveness with patient preference is an important consideration.

There are unpublished data from Maneesh Sinha, K.R. John, and Ganesh Gopalakrishnan from the Department of Urology at the Christian Medical College, Vellore, India where they compared the cost of open versus percutaneous approaches to stone management of large staghorn calculi greater than 6 cm in size. The period of study was from January 1998 to December 2002. Patients were excluded if they had confounding factors in terms of cost such as additional surgical or medical procedures, were children or had complications unrelated to surgery. A period of 5 years was taken as the time in which capital costs were to be earned back. This was done keeping in mind that technological advancements were likely to render current instruments obsolete in this period. In the actual costing the clinical pathway was followed, i.e. the patients were followed from the time they presented to the outpatient until they were discharged and the costs involved at each stage were computed. The decision to proceed with either open surgery or percutaneous surgery was that of the individual consultants. The analysis included 13 patients in the open group and 19 patients in the PCNL group. Patients in both groups required shock wave lithotripsy to achieve better clearance. The preoperative workup in both groups was Rs.3252.

Anaesthesia costs were Rs.2816 and Rs.2219 in the open and PCNL groups respectively. The expense for instruments was Rs.4765 in the PCNL group and Rs. 1557 in the open group. The overall cost of surgery was Rs.10040 in the open and Rs.13172 in the PCNL group. The final cost in both groups was Rs. 23126 and Rs.28752 in the open and PCNL groups. The costs of treatments in this study do not reflect the national figures but only provide a ballpark figure.

2. URETERAL CALCULI

As discussed previously, the stone size and location are critical factors in determining the most cost-effective management approach. **For ureteral stones in particular, the treatment efficacy needs to be balanced by the cost of the approach and type of anesthesia utilized.** A review of the literature found that the average retreatment for URS was only 2.2% compared with 12.1 percent for ESWL, but the need for general/regional anesthesia was 94.3% and 28.3% in the two groups, respectively. (26) **Furthermore, the ability to perform a procedure on an outpatient basis can significantly decrease the overall costs.** In the U.S. where both URS and SWL are performed routinely on an outpatient basis, URS is more cost effective than SWL for the treatment of ureteral stones primarily because of the wide disparity in stone free rates favoring URS, and the high cost of retreatment for SWL. (27-29).

As mentioned previously, the large variability in cost between SWL and URS in different countries drives the cost-effectiveness analyses. In several countries such as Greece and the Netherlands, URS was performed on an inpatient basis driving up the cost of this treatment approach. (30, 31)

There are relatively few studies evaluating the costs associated with treatment of proximal ureteral stones. Parker and colleagues found that in the U.S., URS was less costly than SWL by $6205 because of an initial treatment success of 91% for URS and 55% for SWL (32). Similarly in Taiwan, Wu et al. found that URS was more cost-effective due to a higher stone-free rate achieved after one treatment with URS compared with SWL (83.2%

(84 of 101) vs. 63.9% (76 of 119), respectively). (33)

Several decision analysis models have been utilized to compare treatment costs for ureteral stones. While these analyses are based on a number of assumptions, they are nonetheless useful because they can be used with the results from combined series, thereby avoiding the bias of single institution data. Wolf and colleagues used decision tree modeling to compare the cost of treating distal ureteral stones with SWL or URS, taking into account success rates, cost and patient preference. (34)

They estimated mean success rates for URS and SWL using published series between 1988 and 1994, yielding stone free rates of 92% for URS and 74% for SWL. The average cost of SWL was 21% higher than URS. Their model took into account the cost of complications and also assumed a standard retreatment arm for patients who failed initial therapy, which consisted of SWL, followed if necessary by URS and then open surgery. By this analysis, the cost of SWL would have to drop by $1107 to reach cost equivalence with URS.

Another decision analysis by Lotan and associates evaluated the most cost-effective treatment for stones located in the proximal, middle or distal ureter. (12) Mean success rates for each of 3 treatment strategies (observation, SWL and URS) were calculated from published series, and procedure costs were derived from their institution. URS was less costly than SWL ($2645 vs. $4225) and based on the literature review was more effective for distal and middle ureteral stones and slightly less effective for proximal ureteral stones.

Observation was determined to be the least costly pathway, provided no cost (e.g. emergency room visits) was incurred when observation failed. However, URS was less costly than SWL for the treatment of stones at all locations in the ureter, cost differences between the two surgical modalities of approximately $1440, $1670, and $1750 for proximal, middle and distal ureteral calculi, respectively, were found. The cost advantages for URS, however, would not be as great in countries where SWL is less costly or equivalent to URS.

VI. MEDICAL EVALUATION AND MANAGEMENT

There is much debate on the merits of medical evaluation and management to reduce the stone recurrence rates. **From a cost-effectiveness standpoint, the cost of evaluation and the medications taken daily is balanced by the direct and indirect costs of surgery that is prevented by reducing recurrences.** A major impact, of course, is the cost of the medication and surgery in each country. In some countries such as the U.S., surgical costs are closely monitored and by and large covered by insurance companies and Medicare. On the other hand, medication costs are often unregulated, and therefore costly medications involve a large out-of-pocket expense for the patients themselves. This leads to a disproportionately higher cost for medication than surgery, particularly when taking into account the relative frequency of medication use (daily) compared with the relative infrequent need for surgery. In the U.S. yearly medication costs ($508) are nearly 10% of the mean cost of a one time URS ($4,185) or SWL ($6,697). (35) There are other countries were medications are subsidized such as the UK with yearly costs of $98 as compared with surgical costs for URS ($3442) and SWL ($1462) or approximately 4% of the mean of these procedures.

According to data from the Medical Expenditure Panel Survey (MEPS), estimated total annual expenditures for outpatient prescription drugs for the treatment of urolithiasis in the U.S. between 1996 and 1998 ranged from $4 million to $14 million. (3) While conservative measures such as increased fluid intake and dietary modification have been shown to reduce stone recurrence, drug treatments provide further risk reduction beyond what can be achieved with diet alone. (36) Unfortunately, the cost, inconvenience and morbidity of medication remain significant impediments to patient compliance with medical therapy.

Several studies have concluded that medical therapy for nephrolithiasis is cost-effective, however, their conclusions rely on key assumptions regarding stone recurrence rates and medication risk reduction. (6, 9, 37-39) There are important factors that have not always been taken into consideration. First, dietary modification alone is effective in reducing stone formation rates, and most medical management regimens include dietary measures in addition to medications. (40) Second, only a fraction of patients (10-20%) actually become symptomatic from a new stone each year and only half of symptomatic patients ultimately require surgical intervention. (41-43) Furthermore, empiric medical therapy without metabolic evaluation has been shown in some randomized trials to reduce the risk of stone recurrence in unselected recurrent calcium stone formers. (44) Thus, previous evaluations have suffered from inherent biases against conservative therapy and in favor of metabolic evaluation and medical treatment. In order to evaluate the cost-effectiveness of medical evaluation and management strategies in different health care systems, a decision tree model(45) utilizing a previously published international cost survey(6) was created. (35) For first time stone-formers, conservative therapy was the most cost effective approach.

For recurrent stone formers (0.3 stones/patient/year), dietary modification alone was the most cost effective approach followed by empiric therapy (drug treatment not based on metabolic evaluation) and directed medical therapy (drug treatment targeted to underlying metabolic defects) in most countries evaluated in the International Cost Survey (US, Italy, Germany, Japan, Turkey, Australia, Canada, Sweden, Switzerland) except the United Kingdom where empiric therapy was the most cost effective strategy as a result of the low cost of drug therapy. Of note, despite their higher cost, drug treatment strategies were associated with significantly lower stone recurrence rates.

VII. INDIRECT COSTS

Due to the fact that most stone patients present to physicians, the direct costs of stone disease are relatively easy to obtain. However, there is a significant impact on society related to loss of productivity. Using a dataset of medical and pharmacy claims from 25 large U. S. employers covering over 300,000 beneficiaries, workers with a claim for nephrolithiasis had approximately $3500 more in medical expenses compared with matched workers without a stone ($6532 versus $3038, respectively).

Of the $6532 average expenditure for workers with nephrolithiasis, approximately 18% was accounted for by prescription drug expenses. (5) Overall, 30% of individuals missed work as a result of nephrolithiasis, with a mean loss of 19 hours per year. The high prevalence of stone disease in younger patients leads to a significant impact on productivity when compared to a disease such as prostate cancer which impacts many men after retirement.

VIII. ISSUES RELATED TO STONE TYPE

Most of the literature related to cost issues focuses on calcium based stones which represent the majority of stones in Western Europe and the U.S. The impact of different stone types has not been addressed from a financial standpoint. Uric acid stones could potentially be treated with medical dissolution strategies but there is a question as to the effectiveness for larger stones, patient compliance and costs related to medications and follow-up. In the UK, ultrasound costs more than 3 times as much as a plain X-ray (KUB) ($170 vs. $51). For cystine stones, chemolysis is not cost-effective as it requires in-patient care and has significant complications. Dietary modification and medications may reduce recurrences and should be considered. Surgical options such as SWL tend to be less effective, but PCNL is a more expensive approach. For infectious (struvite) stones, prevention of recurrent infections is the most cost-effective approach. PCNL is the main surgical treatment and in view of the limited effectiveness of SWL in infectious renal stones, PCNL should probably be the first treatment option.

CONCLUSIONS

The economics of nephrolithiasis are complex but are of singular importance due to the high prevalence and recurrent nature of the disease. Because of significant differences in the cost of surgery, medical evaluation and medication between countries, conclusions based on studies from one country or institution cannot be readily applied to other countries or health care systems. However, cost modeling may allow different institutions or health-care systems to input their cost and efficacy components to determine the most cost-effective treatment strategy for their own particular situation.

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Committee 2

Evaluation of the Stone Former

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CONTENTS

Evaluation of the Stone Former

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INTRODUCTION

The evaluation of patients with nephrolithiasis is influenced by several factors including patient age, the acute or chronic nature of the stone problem, and associated or pre-existing medical conditions. The evaluation process has not been directly subjected to the rigors of high level evidence-based studies. However, there are high quality studies that can be linked to the evaluation process and thus by inference add to the validity of the recommendations made by this panel.

There are various steps in the evaluation process, some of which are done in every case and others which are undertaken selectively. These include patient history, imaging, stone analysis, urine studies, blood tests, and genetic testing. Discussions on each of these domains are provided in separate sections of this document. Recommendations generated based on these reviews are provided at the end of each section. Levels of evidence utilized to make these various recommendations are appended to each respective policy.

A. HISTORY AND PHYSICAL EXAMINATION

Dean G. Assimos

The first component of evaluation is patient history as it directly influences the course of this process. Questions pertaining to the stone problem are asked initially and information regarding the patient's general medical condition (review of symptoms, medical and surgical history) is obtained. ***Dietary and family history*** is then elicited. A ***focused physical examination*** is then undertaken. A review of the aforementioned steps is subsequently provided.

The sequence of initial questioning is dependent on the acuity of the problem. For those with acute colic, the most important initial factors to determine are the duration, intensity and location of the pain, the existence of associated symptoms such as nausea and emesis, and the presence of clinical signs or symptoms suggesting sepsis. Information regarding prior stone events including timing, frequency, stone composition and medical or dietary interventions for stone prevention should be obtained from all stone patients.

A comprehensive review of symptoms is advised as the patient may have an unknown or a known poorly controlled disease process which may promote stone formation or be associated with it. A review of some conditions is subsequently provided.

The next step is obtaining a ***complete medical history.*** As mentioned, a number of medical conditions are associated with stone formation. Some of these associations are bi-directional. For example, those with hypertension or diabetes are at higher risk for developing stones and stone formers are more apt to develop these disease processes. [1-3] Obesity, an epidemic problem, increases stone risk and this may be related to insulin resistance. The latter is linked to lower urinary pH and the development of uric acid stones. [4, 5] Subjects with anatomic or functional bowel disease including cystic fibrosis are at risk for stone formation. [6, 7] The etiology of stone formation in this setting may be due to multiple factors including dehydration, hypocitraturia, low urinary pH, hypocitraturia, and enteric hyperoxaluira. Patients with sarcoidosis are more apt to develop stones and this is attributed to hypercalciuria from increased intestinal calcium absorption. [8] The associations of gout and primary hyperparathyroidism are well chronicled. [9-12] Other hyperuricemic conditions such as Lesch-Nyhan syndrome and the administration of systemic chemotherapy to those afflicted with myeloproliferative diseases may be associated with stone formation.[13, 14] Immobilization and other conditions resulting in bone resorption may promote stone formation thought to be due to resultant hypercalciuria and hyperphosphaturia. [14, 15] Type I distal renal tubular acidosis is associated with the development of calcium phosphate stones attributed to an increase in calcium excretion and urinary pH and hypocitraturia. [16] There are a number of hereditary diseases associated with stone formation including cystinuria, the primary hyperoxalurias, the chloride channel disorders, Lesch-Nyhan syndrome, adenine-phospho-ribosyl transferase deficiency and hereditary xanthinuria. [13, 17-20] A number of urologic conditions can influence stone formation. Urinary tract infection with urease producing organisms may result in the development of struvite/carbonate apatite stones. Patients with an abnormal lower urinary tract, especially those with urinary diversion, may be at more risk for such an occurrence. [21] While some have proposed that abnormalities of the upper urinary tract such as medullary sponge kidney, calcyceal diverticula, uretero-pelvic junction obstruction and horseshoe kidney may play a significant role in stone formation, underlying metabolic factors are thought to be more influential. [22-28]

Surgical history is subsequently elicited. The queries regarding stone removing procedures should include associated complications and as to whether a stone free state was achieved. The latter is important as presence of residual stone material may impact stone activity. [29-31] Non-urologic procedures such as contemporary bariatric surgery may promote stone formation. This is attributed to the development of hyperoxaluria. [32, 33]

Information regarding the patient's utilization of medications is obtained. The use of certain medications may promote stone formation. Stones composed of the drug or its metabolites may form or alternatively, the drug(s) may promote changes resulting in 'metabolic stone formation". [34, 35] A list of these agents is provided in **Table 1.**

Information regarding the patient's dietary habits should be obtained as there is compelling evidence that this is an important environmental factor influencing stone formation. Moreover, randomized prospective studies have demonstrated that dietary modifications can attenuate stone activity. [36, 37] Information should be obtained regarding the consumption of fluids, and dietary sodium, animal protein, calcium and oxalate, intake of citrus fruit and supplements. There is robust evidence from epidemiologic studies that reduced consumption of fluid as well as calcium containing foods increases stone risk. There is also evidence from these epidemiologic studies that increased consumption of sodium, animal protein and most recently oxalate is associated with higher stone risk. [38-45]

Table 1.

Induce Changes to Promote Metabolic Stone Formation
Acetazolamide
Allopurinol
Ammonium chloride
Furosemide and other loop diuretics
Glucocorticoids
Indapamide
Laxatives
Phenylbutazone
Potassium bicarbonate
Potassium citrate
Probenicid
Sodium bicarbonate
Sodium citrate
Sulfonylureas
Systemic chemotherapy
Thiazide diuretics
Topiramate
Zonisamide
Stone Formed from Drug or Drug Metabolite
Acyclovir
Allopurinol
Alpha-methyl-dopa
Ceftriaxone
Ciprofloxacin
Diclofenac
Ephedrine
Guaifenesin
Indinavir and other protease inhibitors
Phenazopyridine
Silicate
Sulfadiazine
Tetracycline
Triamterene
Trimehoprim-sulfamethoxazole

Deleterious effects on stone risk parameters with consumption of the latter three have been shown in metabolic studies. [46, 47] Certain specific dietary regimens are known to increase stone risk parameters including the ketogenic and Atkin's diets. [48-49] Supplement utilization is also queried. The consumption of calcium and vitamin D supplements have been demonstrated to be associated with kidney stone risk in epidemiologic cohorts as well as well as a recent fracture prevention trial. [40, 50] In addition, the intake of large quantities of vitamin C has been demonstrated to increase oxalate excretion which is a know risk factor for the development of kidney stones. [51-54] There are various methods of capturing dietary information including dietary recall, food frequency questionnaires and dietary records. The latter two are more accurate while more labor intensive.

Genetic factors can play a role in stone formation, thus, a family stone history should be obtained. Idiopathic calcium oxalate stone disease is a polygenic disorder. While family members may have susceptibility genes, they may not develop stones. [55-57] The majority of the monogenic stone forming disorders are either autosomal recessive or X-linked which may impact which family members manifest with the disease. Genetic counseling and screening of family members is a consideration for the latter patient group.

Physical examination is the last step of this process, typically a focused exam. Digital rectal examination of the prostate in males and vaginal examination in females is undertaken if a lower urinary tract problem is thought to contribute to stone formation.

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STATEMENTS : HISTORY AND PHYSICAL EXAMINATION

A focused history and physical examination should be done in all cases.

• Level 4 Evidence, Grade C Recommendation

Dietary history should be elicited.

• Level 1 Evidence, Grade A Recommendation

Family history should be elicited.

• Level 2 Evidence, Grade B Recommendation

A query for stone inducing drugs should be made.

• Level 2 Evidence, Grade B Recommendation

B. COMPUTED TOMOGRAPHY

JAMES WILLIAMS

I. ROLE OF CT

Helical CT (computed tomography) has become the de facto standard for diagnosis in cases of acute abdominal pain in many countries, and its use is increasingly common for planning urological procedures related to urinary stones. Unenhanced helical CT imaging has been shown to be superior to other imaging modalities both in its ability to identify the presence of urinary calculi and in its value for revealing other causes of abdominal pain when no stone is found. When a stone is found, helical CT can also provide excellent information about the size of a stone, its anatomical location, and even its composition, providing the physician with critical information for planning treatment. The CT imaging procedure takes very little time, and unenhanced CT requires no injections; these two features make it attractive for patients. In many parts of the world, the costs for CT are comparable to or even less than for other imaging modalities for stones. The one criticism of CT is related to the radiation dose received by the patient, and this difficulty, along with the other topics mentioned, are described in more detail below.

As first described by Smith et al. [1] over 10 years ago, non-contrast-enhanced helical CT is excellent for finding stones in patients—even small, ureteral stones in difficult places. In that prospective study, Smith et al. reported that CT had sensitivity of 97%, specificity of 96%, accuracy of 97% for urinary stones. The success of CT in correctly identifying the presence of stones has been confirmed by many other studies, and the improvements in CT technology have simply increased its abilities to distinguish urinary stones from other structures, such as abdominal phleboliths. [2]

Using prospective studies, several groups have examined the ability of CT to identify stones, typically comparing CT with one or more other methods of evaluating patient pain. Sheafor et al. [3] enrolled 45 patients and found CT was superior to ultrasound imaging. Liu et al. [4] enrolled 60 patients who received both low-dose CT and traditional intravenous contrast urography (IVU), and found that CT was far superior to IVU in revealing existing stones; for their settings, the radiation dose for CT was about twice that of IVU. Myers et al. [5] found CT to be better than ultrasound for finding stones in children with reconstructive surgery. Sudah et al. [6] compared CT with magnetic resonance urography (MRU) and IVU in 49 patients, and found CT to be superior to both of the other methods. Wang et al. [7] studied 82 patients, and also found CT to be superior to IVU for revealing stones. Regan et al. [8] examined 64 patients who had been imaged both with MRU and CT, and again, CT revealed more stones.

Thomson et al. [9] randomized 224 patients to either CT or IVU, and found CT to be superior, in part by the ability of CT to provide non-stone diagnoses, and thereby avoid additional tests that were required with IVU. Catalano et al. [10] randomized 96 patients to either CT or ultrasound plus plain x-ray, and also studied another 181 patients using all of those methods; again, CT was found to be the most accurate modality for determining the presence of a stone. Mendelson et al. [11] randomized 200 patients into either CT or IVU for study, and also found CT to be better than IVU for making a definitive diagnosis of a urinary stone.

The data from prospective study of unenhanced helical CT overwhelmingly support CT as the best method for diagnosing the presence of urinary stones. Other advantages of CT cited by the studies against alternative methods include the ability of CT to reveal the exact stone burden of the patient, including its capability of disclosing even small renal stones in the calyces. Moreover, CT almost always took less time to perform than other methods, and in many centers the cost of CT was quite similar to that of the other methods tested.

The use of CT for diagnosing urinary stones does not require the services of a trained radiologist. Both urologists and emergency physicians have been shown to be able to correctly read and interpret CT images for diagnosing stones [12,13]. However, the ability of these specialists to identify alternative diagnoses for abdominal pain was less than that of radiologists in both these studies.

The immediate provision of alternative diagnoses for pain, when stones are not found, has been recognized to be one of the advantages of CT over other methods [1]. In a prospective study, Abramson et al. [14] found alternative diagnoses in 18% of patients entering their emergency department with suspected renal colic. Several retrospective studies have also found high percentages of alternative diagnoses for patients imaged with unenhanced helical CT [37].

It may also be possible for CT scan to indicate stone composition, so that the physician can know if the patient has stones made of calcium oxalate or uric acid, for example, a difference that can significantly affect treatment. The ability of CT to distinguish stone types by x-ray attenuation (Hounsfield units) has been amply demonstrated in vitro [38], but in vivo studies have been less supportive of this role of CT [39]. Part of the difference between in vitro and in vivo studies thus far has clearly been that of resolution, with the in vitro studies using thinner slice-width on CT. This difference in resolution could easily account for the problems of the in vivo studies in resolving differences in stone composition, as clinically relevant stone sizes require slice width of 1 mm or so to accurately show Hounsfield unit values [15].

Overall, the above lists of valuable information offered through the use of helical CT for persons suspected of having urinary stones is very compelling. It is for these reasons, no doubt, that the use of abdominal CT in emergency rooms has increased by over 70% in the US in the years between 2001 and 2005 [16].

This increase in the use of CT has not been seen in all countries, however. Otite et al. [17] recently reported a survey of urologists in the UK and Ireland in which they found that IVU was used for diagnosis of flank pain in 85% of institutions. This usage of IVU was attributed primarily to a lack of CT facilities, but also to greater familiarity of physicians with IVU or ultrasound over CT. Kartal et al. [18] reported a prospective study in Turkey that verified the validity of the existing system of physician use of ultrasound for diagnosing renal colic, and they saw no reason for change. Similarly, Lindqvist et al. [19] carried out a randomized, prospective trial that verified the validity of the tradition in Sweden of not performing immediate radiological workup on patients whose renal colic was relieved by analgesic injection.

The studies just cited also mentioned radiation dose as a reason for avoiding CT for patients suspected of renal colic due to stones. The exact risk of cancer added by a CT scan is difficult to know [20,21]—Therefore, it seems wise to be cautious. Consequently, the work by several groups to develop low-dose protocols for stone detection using CT is welcome [4,22-25]. It seems that CT technology can be improved to reduce radiation dosage while maintaining quality of imaging for diagnosing stones [23], which is a direction that all facilities should strive for as equipment is available.

Information generated by CT can be used to predict treatment results with shockwave lithotripsy. A skin to renal stone distance of greater than 10 cm is predictive of residual fragments [40]. In addition, stones with higher attenuation (>1000 Hu) are less apt to fragment [41].

II. FUTURE OF CT AND THE IMAGING OF STONES

The rapid development of helical CT technology and its equally rapid adoption by the medical community for patient imaging has been a surprise to many [26], and thus it is difficult to predict what may come in the future. However, already dual-source CT has been shown to provide superior resolution and detection for the imaging of coronary plaques without increasing radiation dosage [27,28]. Because urinary stones are also small, high x-ray-density structures, it seems likely that this technology will be advantageous for stone imaging as well. Other technical developments are difficult to predict, but history suggests that we have not reached the end of development of CT imaging, almost all of which is likely to improve the imaging of stones and urological structure.

Do we need improved imaging of urinary stones? Present technology does provide virtually 100% detection of stones, with excellent localization of them within the urinary system. However, it may be useful for CT to have improved estimation of stone size, and for some applications it may also be useful for the physician to be able to visualize the internal structure of stones [15,29,30], rather than simply their presence or size. As mentioned above, CT shows the promise of being able to give the composition of stones and this ability is likely to be improved with technology such as dual-source scanning [31].

One other technology is worthy of mention in this context. Micro CT is also under rapid development, and the earliest forms of this method have shown remarkable ability to reveal stone composition and structure in vitro [32]. Thus it would seem that micro CT may be able to add information about stone composition and morphology that may be useful in understanding a patient's particular form of stone disease. The array of stone morphologies and compositions, and their possible relationship to etiology, is much greater than that presently analyzed by most clinical laboratories [33,34], and micro CT may provide a way for clinical laboratories to gain this information in a comprehensive and objective manner. It is clear that micro CT will also be of value in research on stone disease by providing high-resolution images of the internal structure of stones collected from patients under controlled conditions [35]. The impact of this sort of information on studies of calculus etiology is likely to be great.

It may also be true that micro CT provides a prediction of the quality of patient imaging in the future. At least one paper has proposed a method for gaining significantly higher resolution of clinical CT imaging [36], and the rapid growth of CT technology, referred to above, suggests that such developments are not outside of possibility in the near term.

In sum, CT already provides the best imaging for diagnosis, localization, and characterization of urinary stones in patients, and this position of technical superiority is likely to only increase with time. Nevertheless, issues of availability and radiation dosage will limit use of CT in some venues. Work on reducing radiation dosage for CT is likely to help allay some of these concerns.

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STATEMENTS ON THE ROLE OF CT

Non-contrast l CT is the imaging modality of choice for evaluating the majority of patients with suspected renal colic.

• Level 1 Evidence, Grade A Recommendation

Non-contrast CT may help predict results of shock wave lithotripsy.

• Level 2 Evidence, Grade B Recommendation

Non-contrast CT may identify those with uric acid stones.

• Level 2 Evidence, Grade B Recommendation

Non-contrast CT identifies relationships with surrounding structures which is important for certain surgical planning (percutatneous stone removal).

• Level 4 Evidence, Grade C Recommendation

Non-contrast CT provides accurately defines stone volume and orientation of the stone within the kidney.

• Level 4 Evidence, Grade C Recommendation

Contrast CT defines collecting system anatomy and provides some index of renal function.

• Level 4 Evidence, Grade C Recommendation

C. OTHER IMAGING MODALITES (NON-CT IMAGING)

J. STUART WOLF JR

A Medline search, limited to English language and publication date 1996 through June 2007, was performed using the following search strategy (all MESH terms except where indicated): "kidney calculi or urinary calculi or urolithiasis" AND "ultrasonography," "plain [text string] and radiography," "intravenous [text string] and urography," "radioisotope imaging," OR "magnetic resonance imaging." Selected bibliographies of retrieved articles were reviewed as well. A total of 303 titles and/or abstracts was reviewed. Based upon content of the abstract, a total of 78 articles was selected for detailed review, and of these 55 were used in the preparation of this section.

Although NCCT is the preferred imaging modality in most cases for detecting urinary calculi, both before and after treatment, [1-18] other imaging modalities, including plain abdominal radiography, intravenous urography, ultrasonography, dynamic renal scintigraphy, and magnetic resonance urography still play an important role in specific situations.

Plain abdominal radiography detects only about half of urinary calculi seen on NCCT. [15,19-23] The plain abdominal radiograph, however, is superior to the "scout" NCCT view for detecting urinary calculi. [19-23] The scout NCCT view, formatted to look like a plain abdominal radiograph is obtained with a greater kV than that used to obtain the plain abdominal radiograph (120 – 140 kV, versus 65 – 75 kV), and as such has a greater penetration that fails to detect smaller calculi. In general, about one-half to two-thirds of calculi seen on plain abdominal radiograph are detected on the scout NCCT view. In studies that reported subgroups by size, the inaccuracy of the scout NCCT increases as the stone size decreases; the limitation of scout NCCT is most significant with stones < 5 mm. To facilitate follow-up of a calculus detected on NCCT, a plain abdominal radiograph should be obtained when the stone is not visible on the scout NCCT view.

An in-vitro study demonstrated that the overall actual dimensions of urinary calculi are more accurately determined on NCCT, owing to magnification on plain abdominal radiography. [24 In clinical practice, however, plain abdominal radiography and NCCT vary only slightly in their estimate of the transverse or antero-posterior dimensions of urinary calculi, with no consistent positive or negative trend (-12% to +15%). [25-28] These differences are not clinically significant. The cranio-caudal dimension of urinary calculi is overestimated by NCCT, given the limitation of the cranio-caudal resolution of the reconstruction by the axial slice thickness used in clinical practice. [25-27]

The density of urinary calculi on plain abdominal radiography may be useful for predicting efficacy of shock wave lithotripsy for renal calculi. [29-32] The correlation appears less exact than for NCCT, but is still useful. Stones that appear rough and less dense on plain radiography are more responsive to shock wave lithotripsy compared to stones that appear smooth and dense. In a recent study, Krishnamurthy and associates found that stone density on plain abdominal radiograph was potentially useful only for renal calculi > 10 mm in diameter, with a 60% stone free rate after shock wave lithotripsy when the stone was denser than the ipsilateral 12th rib, compared to 71% when the stone was less dense. [32]

The utility of intravenous urography as a diagnostic technique is becoming limited in centers that have NCCT routinely available. Nonetheless, intravenous urography, which provides information about calyceal anatomy that is relevant to management considerations, is still useful in some cases for planning surgical treatment, especially shock wave lithotripsy, percutaneous nephrostolithotomy and open surgery. [33-36]

Retrograde pyelography may provide similar or better anatomic detail than intravenous urography. It is routinely performed at the time of ureteroscopic stone removal. In addition, it defines ureteral and collecting system anatomy as well or better than intravenous urography. It can also be used for this purpose in those who are not able to receive intravenous contrast.

Although intravenous urography appears to be superior to ultrasonography alone for detecting urinary calculi, [2,13] the expensive labor-intensive process of obtaining an intravenous urogram and the risk of intravenous contrast administration discourage its routine use for diagnosis. The addition of color Doppler to ultrasonography, in order to determine resistive indices, improves the ultrasonographic detection of obstruction by urinary calculi. [17,37-39] Moreover, obtaining a plain abdominal radiograph at the time of ultrasonography improves sensitivity for ureteral stones. In the studies of Ripoles and associates, [15] and Catalano et al, [10] all stones not detected by this combination (with NCCT as the reference standard) passed spontaneously. Thus, this combination of ultrasonography and plain film radiography appears to be a practical and useful one. The combination of ultrasonography and plain film radiography has not been compared to intravenous urography for the detection of renal calculi, so a high-grade recommendation cannot be made, but the preponderance of indirect evidence and consensus opinion suggests that the combination of color Doppler ultrasonography and plain film radiography should be the second choice to NCCT for the detection of urinary calculi when the latter is not available or is contraindicated. This is especially true for children where this combination may approach the sensitivity of NCCT [56].

Distal ureteral calculi are the most difficult stones to diagnose on NCCT, especially when secondary signs (ureteral thickening, ureteral dilation, etc.) are not present. Transrectal or transvaginal ultrasonography allows close approximation of the transducer to the distal ureter. These endo-ultrasound techniques are superior to plain abdominal radiography, intravenous urography, and abdominal ultrasonography for the detection of distal ureteral calculi. [40-43] Direct comparisons with NCCT have not been reported, but it would appear reasonable to consider transrectal or transvaginal ultrasonography when NCCT is negative but a distal ureteral stone is still suspected.

Management decisions in patients presenting with acute urinary calculi are based on clinical, laboratory, and radiographic parameters. The presence or absence of upper urinary tract obstruction is an important consideration. Dynamic renal scintigraphy in the acute setting has been sparingly reported, but may be a useful adjunct to NCCT in determining obstruction by urinary calculi. [44-46] Similarly, magnetic resonance urography can detect obstruction by urinary calculi, and has the advantage of no radiation dose and the ability to detect extra-renal pathology. [18,47-53]

Nonetheless, even when combined with plain abdominal radiography, magnetic resonance urography is still inferior to NCCT for the detection of urinary calculi. [18] Importantly, comparative data of dynamic renal scintigraphy and magnetic resonance urography to each other and to other modalities for detecting obstruction (e.g., color Doppler ultrasonography) are limited.

In the special setting of pregnant women, minimization of radiation is a priority. Controlled trials in this population are not available, but first principles, extrapolation from other studies, and consensus opinion suggest that ultrasonography with color Doppler is the preferred modality for the evaluation of suspected urinary calculi in pregnant women. [36,54,55] “Single shot” intravenous urography or magnetic resonance urography is recommended if the initial test is negative and urinary calculi are still suspected. [36,55]

The methods of follow-up imaging in patients with metabolic stone disease have not been subjected to critical analysis. Follow-up imaging is not recommended for a first time calcium oxalate or calcium phosphate stone former who is rendered stone free and does not have a systemic disease increasing stone risk. A yearly KUB x-ray is recommended for the majority of adult patients with asymptomatic, radio-opaque renal stones whether they are a first time or a recurrent stone former. A yearly KUB is also recommended for adult recurrent calcium oxalate or calcium phosphate stone formers who are stone free. Renal ultrasonography is the preferred follow-up imaging modality for children, and those with uric acid or cystine stones. Stones in the latter 2 cohorts are typically not visible or minimally opaque on plain film imaging while detectable with ultrasonography. This approach limits radiation exposure which is especially important in patients who start forming stones at a younger age and are subject to recurrence. More frequent or different imaging may be required for those who develop symptoms or increasing metabolic activity.

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STATEMENTS FOR NON-CT IMAGING

Non contrast computed tomography (NCCT) is the preferred imaging modality in most cases for detecting urinary calculi.

• Level 1 evidence, Grade A recommendation.

Plain abdominal radiography is superior to scout NCCT for detecting urinary calculi.

• Level 2 evidence, Grade A recommendation.

Plain abdominal radiography and NCCT vary slightly in their estimate of the transverse and antero-posterior dimensions of urinary calculi, but there no consistent positive or negative trends and the differences usually are not clinically significant. The cranio-caudal dimension of urinary calculi is overestimated by NCCT.

• Level 3 evidence, Grade B recommendation

Plain abdominal radiography may be useful for predicting efficacy of shock wave lithotripsy for some renal calculi.

• Level 3 evidence, Grade C recommendation

Intravenous urography may be useful in some cases for planning treatment of urinary calculi.

• Level 3/4 evidence, Grade C recommendation.

The addition of color Doppler to ultrasonography, in order to determine resistive indices, improves the ultrasonographic detection of renal obstruction by urinary calculi.

• Level 2/3 evidence, Grade B recommendation.

Ultrasonography plus plain abdominal radiography is the second choice, after NCCT, for detecting urinary calculi.

• Level 2/4 evidence, Grade C recommendation.

Dynamic renal scintigraphy may be a useful adjunct to NCCT in determining obstruction by urinary calculi, but comparative data to other modalities are limited.

• Level 2 evidence, Grade C recommendation

Magnetic resonance urography can detect obstruction by urinary calculi, but comparative data to other modalities are limited.

• Level 2 evidence, Grade C recommendation

In pregnant women, ultrasonography with color Doppler is the preferred modality for evaluation of suspected urinary calculi. "Single shot" intravenous urography or magnetic resonance urography is recommended if the initial test is negative and urinary calculi are still suspected.

• Level 3/4 evidence, Grade C recommendation

Follow-up imaging is not recommended for a first time calcium oxalate or calcium phosphate stone former who is rendered stone free and does not have a systemic disease increasing stone risk.

• Level 4 evidence, Grade C recommendation

A yearly KUB x-ray is recommended for the majority of adult patients with asymptomatic, radio-opaque renal stones whether they are a first time or a recurrent stone former.

• Level 4 evidence, Grade C recommendation

A yearly KUB is also recommended for adult recurrent calcium oxalate or calcium phosphate stone formers who are stone free.

• Level 4 evidence, Grade C recommendation

Renal ultrasonography is the preferred follow-up imaging modality for children, and those with uric acid or cystine stones.

• Level 4 evidence, Grade C recommendation

More frequent or different imaging may be required for those who develop symptoms or increasing metabolic activity during follow-up.

• Level 4 evidence, Grade C recommendation

D. INITIAL BLOOD STUDIES

Dean G. Assimos

Non-complex blood tests are performed during the initial evaluation. A basic metabolic profile (BUN, serum creatinine, glucose, electrolytes and calcium), serum uric acid and phosphorus are obtained. The basic metabolic profile screens for renal dysfunction including renal tubular acidosis and diminished glomerular filtration, and hyperparathyroidism. While the latter diagnosis is rare, less than 1 % of stone formers in community practice and 2-5% in metabolic stone centers, the potential benefit to the patient is great. [1-3] Serum uric acid is obtained to assess for gouty diathesis. [4] Serum phosphorus aids in the diagnosis of hyperparathyroidism and renal phosphate leak. [5-7] Other studies are needed for the diagnosis of primary hyperparathyroidism and are described elsewhere in this document. A complete blood count with differential is obtained if the patient has signs of sepsis. In addition, blood culture is performed in this setting.

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STATEMENTS ON INITIAL BLOOD STUDIES

Initial blood studies should include a basic metabolic profile (BUN, serum creatinine, electrolytes, calcium, glucose) serum uric acid and phosphorus.

• Level 3 Evidence, Grade C Recommendation.

Complete Blood Count with differential and blood cultures should be obtained if the patient has signs of sepsis.

• Level 3 Evidence, Grade C Recommendation

E. STONE ANALYSIS

Dean G. Assimos

Stone analysis is the most important component of the metabolic evaluation as it directs further testing. There are numerous techniques for stone analysis including X-ray powder diffraction crystallography (XRD), infrared spectroscopy, Raman spectroscopy, Fourier transform infrared spectroscopy (FTIR), transmission electron microscopy with energy dispersive microanalysis, transmission electron microscopy , micro-computed tomography, wet chemical analysis, optical crystallography, density gradient columns, X-ray coherent scatter, and thermal gravimetric analysis. The most commonly utilized are FTIR and XRD. [1-4] These techniques focus on the identification of the crystalline components of the stone and not on macromolecular or other non-crystalline parts. XRD is a semi-quantitative technique where the relative amounts of the stone components are listed in rank order whereas the relative percentage of the stone component is defined with FTIR. Both techniques are accurate but this is dependent on the quality and completeness of the standards library, and the experience of the laboratory. The utilization of both techniques is sometimes warranted for the analysis of multi-component stones. Experienced laboratories can perform these studies quickly and at low cost to the consumer.

Stone composition has some predictive value in diagnosing medical conditions associated with stone formation. Calcium apatite stones and mixed calcium stones (calcium oxalate/calcium apatite) are associated with renal tubular acidosis and primary hyperparathyroidism. [5, 6]. A positive correlation of these diagnoses and the phosphate content of the stone has been reported. [5] There is also a strong positive correlation with uric acid stones and gouty diathesis. [5, 6]

Stone analysis should be performed at the time of the initial stone event if the calculus is available. Stone analysis should be performed in recurrent stone formers even if the initial stone composition is known as changes in stone content are reported in recurrent stone formers. Mandel and associates reported a strong trend for the conversion of calcium oxalate to calcium phosphate in recurrent stone formers. [7] This could influence the progression and severity of the stone disease. [8]

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STATEMENTS ON STONE ANALYSIS

Stone analysis should be obtained for first time and recurrent stone formers.

• Level 2 Evidence, Grade B recommendation.

F. URINE EVALUATION

DEAN G. ASSIMOS

Urinalysis is recommended for all stone patients. While it is the simplest study, it yields important information. Both microscopic and dipstick analyses are performed. While hematuria and pyuria may be due to the presence of stones, other conditions may cause these findings and prompt further evaluation at the discretion of the clinician. Crystalluria may be present in this population, but can also be seen in normal subjects; the exception being cystine crystals. Presence of the latter is indicative of cystinuria. Patients with infection as well as metabolic stones may have bacteruria. Urinary pH and specific gravity are the most important dipstick parameters for this population. Specific gravity is a surrogate for the patient's state of hydration. Urine pH may be an important factor for patients with metabolic and infection stones. While the accuracy of dipstick pH has been questioned, we have recently demonstrated that this may be product dependent. [1, 2] Urine culture and sensitivity testing is recommended if infection is suspected based on urinalysis or clinical findings.

Twenty four hour urine studies while the patient is consuming a self selected diet are highly recommended for recurrent stone formers and those with cystine stones. They are also considered for certain first time stone formers including children, those with a solitary kidney or renal insufficiency, patients with multiple remaining stones, in individuals afflicted with bowel disease, and commercial airline pilots who must remain stone free to work. The justification for such testing is based on the high probability of identifying metabolic abnormalities that are documented risk factors for stone formation such as hypercalciuria and hyperoxaluria, and the existence of effective treatments for these disorders to reduce stone activity [3-9] The similar spectrum, and high prevalence of metabolic abnormalities in first time and recurrent stone formers supports the utility of such studies in select first time stone formers. [10, 11]

Containers for the urine specimens should have a capacity of at least 4 liters. The following parameters should be measured: volume, pH, creatinine, calcium, uric acid, citrate, magnesium, phosphorus, sodium, potassium, ammonia, urea nitrogen and sulfate. Creatinine is assessed to determine the accuracy of the collection; 20-27 mg/kg/day for males and 14-21 mg/kg/day for females. [12] Calcium, citrate, oxalate, uric acid and pH are obtained for the detection of hypercalciuria, hypocitraturia, hyperoxaluria and gouty diathesis. Magnesium and sodium are indices of salt and magnesium intake. Urea nitrogen, sulfate, phosphorus and uric acid are indicators of protein consumption. Cystine excretion is measured in those with cystine stones. Normal values vary with gender, age and body weight. [13]

Measuring the supersaturation of stone forming salts may be a useful tool to assess the effectiveness of dietary and or medical therapy for stone prevention as a reduction in the urinary supersaturation of the targeted stone forming salt is reported to be associated with a decrease in stone activity.[8] In addition, while therapy may reduce the supersaturation of the targeted stone forming salt, an increase in the supersaturation of other stone forming salts may develop. For example, calcium oxalate superasaturation may decrease and supersaturation with calcium phosphate may increase and prove to be deleterious. Such shifts in the supersaturation profile have been demonstrated to parallel the development of admixtures in stones.[14]

Therefore, measuring the supersaturation of urine with calcium oxalate, calcium phosphate, and uric acid should be considered when 24 hour urine studies are analyzed. [15]

Several indices have been developed for measuring urinary saturation. One of the most comprehensive indices is the EQUIL analysis. [16, 17] Using the dissociation constants for the binding of most of the major ions in urine, this software program provides estimates of the relative supersaturation of urine with calcium oxalate monohydrate, calcium oxalate dehydrate, and the various insoluble salts of calcium phosphate. The relative supersaturation is the estimation of the concentration product of these ions in urine relative to their solubility product in an aqueous solution. Concentrations of ions in urine may rise above that where crystallization should occur due to the presence of macromolecules and potent crystallization inhibitors such as citrate. This analysis requires the measurement of 13 ions and is therefore laborious. Tiselius developed an abbreviated calculation that included the measurement of only the major contributors to the saturation calculations which suffices in most circumstances. [18]

A truly abbreviated measurement that shows strong potential is the Bonn Risk Index, which is simply calculated as the ratio of the ionized calcium concentration in urine to the concentration of oxalate. The analysis of 201 urine samples indicated that this index appears to produce equivalent estimates of risk to those estimated by EQUIL and by the Tiselius Risk Index. [19-21]

Another proposed technique is the joint expert speciation system (JESS). This is based on an extensive data base of physiochemical constants and compares favorably with the EQUIL method. However, more study of the utility of this index is needed. [22]

The choice of the method utilized for estimating supersaturation may be influenced by the equipment available and the sophistication of the laboratory. Employing proper quantitative techniques is mandatory. In addition, uniform methodology should be used for estimating supersaturation over time.

The collection of two 24 hour specimens is recommended based on an improved ability to detect an abnormality. [11, 23-26] The latter is due to significant day to day variability which is most influenced by environmental factors. This practice has been challenged by Pak and colleagues who reported that significant positive analyte correlations exist between 2 collected urine specimens. These investigators suggest that a single collection is sufficient for evaluation. [27] However, Parks and associates report that while there are significant correlations of urine values between 2 collections, the standard deviations were large enough that by chance 1 urine collection would differ from the other by a clinically significant amount. This study contained two population sets; private urology practice and university stone research clinic. [24]

A significant number of patients with calcium oxalate and calcium phosphate stones have hypercalciuria. [28] Supplemental testing to elucidate the cause of hypercalciuria such as assessing the responses to a low calcium diet, fasting and calcium loading is not necessary as the therapeutic approach is usually the same for the whole group; initial dietary modifications and if unsuccessful administration of a thiazide agent or indapamide. It is important to screen for the rarer causes of hypercalciuria such as primary hyperparathyroidism and renal tubular acidosis which is done by measuring serum calcium for the former and urine pH, and serum electrolytes for the latter. Serum electrolytes and calcium are also monitored during diuretic therapy as primary hyperparathyroidism is sometimes unmasked and electrolyte abnormalities may develop. In addition repeat 24 hour urine testing is advised with non-selective therapy of hypercalciuria because of potential attenuation of the hypocalciuric action of these diuretics over time. [29]

Ammonium chloride load testing to diagnose incomplete renal tubular acidosis has been described. [30] Such testing is not necessary as these patients have low urinary citrate excretion. Thus treatment would be similar to those with idiopathic hypocitraturia; the administration of alkali agents such as potassium citrate.

Stone analysis may influence selection of urine testing. If the patient has pure struvite stone, 24 hour urine testing is not required as the diagnostic yield is low. The primary goal for these patients is a stone free status and prevention of recurrent urinary tract infection. However, patients with struvite stones mixed with metabolic components should undergo such testing as a significant percentage may have abnormalities and benefit from treatment. [31] The parameters measured in a 24 hour urine study are tailored in a patient with pure cystine stones and limited to volume, pH, cystine and creatinine. However, some of these patients have cystine stones mixed with other metabolic components and a complete panel should be measured. [32] The parameters are also abbreviated in those with pure uric acid stones; volume, pH, creatinine and uric acid. If the patient has a uric acid stone mixed with other metabolic components, a complete panel should be assessed. [33, 34]

A significant proportion of children with stones have underlying metabolic abnormalities. [35-37] Therefore, 24 hour urine testing is warranted. These studies are recommended with the first stone event as this may be an opportunity for early diagnosis of a significant disorder such as primary hyperoxaluria which typically manifests in childhood. [38] Several factors need to be considered when evaluating 24 hour urine studies in children. The excretions for normal children when adjusted to urinary creatinine are distinctly different than for non-stone forming adults. DeFoor and colleagues reported that normal children had higher calcium, oxalate and citrate excretion indexed to creatinine than adults. They also found that the supersaturation of calcium oxalate and calcium phosphate were higher in normal children. [39] The normal values for these urinary parameters in children are influenced by age, gender and race and this must be considered when prescribing treatment for this cohort. [40] There have been few studies which have addressed the latter issue and more are warranted to improve the treatment of the pediatric stone former.

Twenty four hour collections may be difficult to obtain in younger children. Some have advocated analysis with spot urine studies indexing the analyte to creatinine [41, 42] Spot urinary oxalate testing has been demonstrated to discriminate those with primary hyperoxaluria. [43] However, these studies have certain limitations. Results may vary with the time during the day that the specimen is obtained, gender and age. In addition, urinary creatinine is influenced by body weight and protein intake which could lead to intra as well as inter-individual variability. [44] The aforementioned issues limit the utility of this test.

Follow-up 24 hour urine studies are recommended for patients who are treated with dietary modifications or medical therapy. The first follow-up collection is recommended at 6 to 8 weeks after institution of therapy as this provides more than adequate time for the intervention to demonstrate its impact. If beneficial urinary changes do not occur, an alteration in dosing or the agent can be made. If drug adjustments are enacted, another 24 hour urine specimen is collected 6 to 8 weeks later. Yearly 24 hour urine specimens are assessed once the desired changes are achieved. More frequent studies may be necessary if stone activity accelerates or stone composition changes. Specialized urinary studies should be considered in patients with cystinuria receiving treatment with thiol agents as most cystine assays do not reliably discriminate cystine from thiol-cysteine complexes. A technique which measures cystine supersaturation and cystine capacity has been developed and is a reliable index for assessing the response of patients on thiol drugs. [45]

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STATEMENTS ON URINE EVALUATION

Urinalysis should be performed on all patients.

• Level 4 Evidence, Grade C Recommendation

Urine culture should be obtained if infection is suspected.

• Level 4 Evidence, Grade C Recommendation

Twenty four hour urine testing is suggested for recurrent stone formers, cystine stone formers, children, those with solitary kidneys or renal insufficiency, patients with multiple remaining stones, commercial air-line pilots and individuals with bowel disease.

• Level 1-4 Evidence, Grade A-C Recommendation

Urine is collected while the patient is consuming a random diet.

• Level 2 Evidence, Grade B Recommendation

The choice of analytes tested is based on stone analysis. (see text)

• Level 2 Evidence, Grade B Recommendation

The collection of two 24 hour urine specimens is recommended.

• Level 2 Evidence, Grade B Recommendation

Defining the cause of hypercalciuria with fasting calcium and calcium load testing is not indicated for the majority of patients.

• Level 2 Evidence, Grade B Recommendation

G. EVALUATION OF HYPEROXALURIA

Ross P. Holmes

I. INTRODUCTION

An elevated urinary excretion of oxalate is a risk factor for calcium oxalate stone disease. [1] This association is not absolute as there are individuals with high urinary excretions of oxalate who do not form stones or form them infrequently, and conversely there are individuals who form stones with a below normal oxalate excretion. Such occurrences testify to the multi-factorial nature of stone disease. Further complexities arise when evaluating urinary oxalate excretion as there are contributions from both the ingestion of dietary oxalate and endogenous synthesis. [2]

II. MEASUREMENT

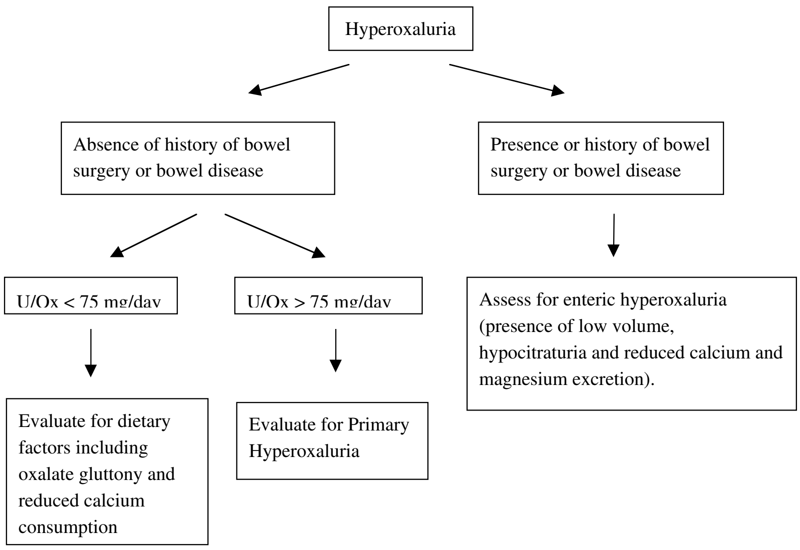
Urinary oxalate measurement is a complex test and must be performed by a specialty laboratory. Most laboratories use an oxalate oxidase technique employing a kit provided by Trinity Biotech (Bray, Ireland). This kit can be adapted for use on most chemical analyzers. Alternatively, ion chromatography can be used. [3] A 24 hour urine collection is currently the best method of determining oxalate excretion due to its dependence on dietary factors. Urinary oxalate excretion also varies from day to day because of variable dietary influences. [4] Therefore, more than one 24 hour urine collection is advised. Two factors that can affect the oxalate content of urine are oxalogenesis and calcium oxalate precipitation. The first is due to the conversion of ascorbic acid and possibly other compounds to oxalate during storage or shipping. This can be limited by acidifying the urine. The formation of calcium oxalate crystals in sufficient amounts to significantly decrease the oxalate content of urine can also be prevented by acidification. The formation of such crystals is also potentially induced by cold storage.

III. NORMAL RANGE

A normal excretion of oxalate is usually accepted to be below 42 mg/day for adults. [5] Normal values for children vary with age and range in random urine samples from < 0.29 mg/mg creatinine for infants less than 6 months of age, to < 0.63 mg/mg creatinine in children 6 – 12 years of age. [6] If only one collection demonstrates increased oxalate excretion, the patient should be counseled regarding methods of reducing this parameter. Further testing may be necessary if the subject has consistently increased oxalate excretion, especially at high levels.

ALGORITHM

An algorithm describing recommended approaches for diagnosing the causes of hyperoxaluria is shown below.



IV. EVALUATION FOR PRIMARY HYPEROXALURIA

The first step is measuring urinary glycolate and L-glycerate. Normal values for urinary glycolate < 50 mg/g creatinine and L-glycerate < 25 mg/g creatinine. [7] Individuals with the Type 1 disease have a deficiency in peroxisomal alanine:glyoxylate aminotransferase (AGT) activity and usually an elevated glycolate excretion, whereas those with the Type 2 disease have an increased L-glycerate excretion and a deficiency in tissue glyoxylate reductase (GR) activity. Some individuals with Type 1 and Type 2 disease have normal excretions of glycolate and L-glycerate. [6, 7] Testing of DNA extracted from whole blood has emerged as a promising new diagnostic approach and is the next recommended step. A search for the known disease mutations in chromosomal DNA is being undertaken. [8,9] The mutations that produce this disease have been identified in about 90% of the alleles of affected individuals. Such screening of DNA from the blood of individuals with presumptive pH results in a sensitivity of 40% and a specificity of 90% when the 3 most common mutations are screened. This increases to 75% sensitivity and 94% sensitivity when the 3 most commonly affected exons are sequenced, and to 94% sensitivity and 98% specificity when the entire gene is sequenced. Using a tiered approach to the analysis, beginning with the analysis of common mutations, followed by the analysis of the most affected exons before moving to whole gene sequencing limits the effects of the time required and the cost of whole gene sequencing. A liver biopsy and the measurement of AGT and GR activities may be required for a definitive diagnosis if the DNA analysis is not confirmatory. If the biopsy indicates that these enzyme levels are normal, the most likely diagnosis is that of unclassified pH. [6, 10]

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STATEMENTS ON EVALUATION OF HYPEROXALURIA

Patients with extremely high levels of hyperoxaluria who do not have bowel disease should be evaluated for primary hyperoxaluria.

• Level 2 Evidence, Grade B Recommendation

Urinary glycolate and L-glycerate are measured in those suspected of having primary hyperoxaluria.

• Level 2 Evidence, Grade B Recommendation

Testing of DNA extracted from whole blood is used to confirm the diagnosis of primary hyperoxaluria.

• Level 2 Evidence, Grade B Recommendation

Liver biopsy and measurement of AGRT and GR activity are used if genetic testing is not confirmatory.

• Level 2 Evidence, Grade B Recommendation

H. EVALUATION FOR PRIMARY HYPERPARATHYROIDISM

Ben Chew

A small percentage of patients with stones have primary hyperparathyroidism. [1] Despite the low prevalence of this disorder, simple screening for this disorder by measuring serum calcium is recommended. This is supported by the reduction in stone activity after surgical correction of primary hyperparathyroidism. Jabbour and colleagues reported on 120 stone patients who underwent parathyroid surgery. Thirty-six (30%) were without stones at the time of surgery and remained stone free during follow-up. Eighty-four patients had stones or nephrocalcinosis at the time of parathyroidectomy. Eighty-eight percent of those with stones and 77% of those with nephrocalcinosis had their stones dissolve or disappear within ten years. The frequency of renal colic was 0.66 per patient per year prior to parathyroidectomy, which reduced significantly following surgery to 0.02 episodes per patient per year. [2] Mollerup and Lindewald followed patients with primary hyperparathyroidism after parathyroidectomy and found that the rate of new stone formation was significantly lower than before this operation. [3] A randomized prospective study demonstrated that patients with primary hyperparathyroidism and nephrolithiasis subjected to parathyroidectomy did not have further stone activity while those assigned observation suffered from stone recurrence.[4]

If the serum calcium is elevated, an intact serum parathyroid hormone (PTH) level and phosphorous are measured. If the serum calcium is normal, serum albumin abnormal or the patient has osteoporosis, ionized calcium is checked. [5] The current standard assays (immunoradiometric [IRMA] or immunochemiluminometric [ICMA]) of measuring "intact" PTH in actual fact measures fragments (e.g. PTH[7-84]) as well as the entire PTH molecule; hence, this method can overestimate the amount of PTH present. A new and more sensitive method using IRMA measures the entire PTH molecule (1-84) but has not yet become widely clinically available. [6-7] These studies are also considered for patients with high normal serum calcium levels, especially if they have calcium phosphate stone components or are recurrent stone formers. The findings of an increased serum PTH and hypercalcemia is indicative of primary hyperparathyroidism. If the patient is hypercalcemic and the intact PTH is not suppressed, this diagnosis is also strongly considered. There is a group of patients with "normocalcemic primary hyperparathyroidism" in whom PTH levels are elevated in conjunction with normal serum calcium levels. [8] Confirming the diagnosis in this setting may be challenging. Vitamin D deficiency must be ruled out. Since "renal leak" hypercalciuria is also a diagnostic consideration, assessing the patient's response to thiazide or indapamide therapy is advised.

Technetium scintigraphy (sestamibi scan) is a consideration in this setting if secondary causes of hyperparathyroidism are excluded. Tordjman and associates performed this study in 22 such patients and identified an adenoma in 16 (73%).[9]

There other etiologies for hypercalcemia in stone formers and include malignancy, sarcoidosis, endocrine disorders, medications, and excessive intake of calcium or vitamin D. PTH is suppressed in the majority of these other entities. [10,11]

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STATEMENTS ON EVALUATION FOR PRIMARY HYPERPARATHYROIDISM

Screening for hyperparathyroidism with serum calcium testing is recommended for patients with calcium oxalate or calcium phosphate containing stones.

• Level 2 evidence, Grade B recommendation

Measurement of serum parathyroid hormone is recommended in patients with hypercalcemia, and for those with high normal serum calcium who are recurrent stone formers or have calcium phosphate containing calculi.

• Level 1-2 evidence, Grade B recommendation

Parathyroidectomy is recommended for patients with stones and primary hyperparathyroidism.

• Level 1 evidence, Grade A recommendation

Committee 3

Medical Management of Urolithiasis

Chairman

MARGARET S. PEARLE

Members

JOHN R. ASPLIN

FREDRIC L. COE

ALLEN RODGERS

ELAINE M. WORCESTER

CONTENTS

Medical Management of Urolithiasis

MARGARET S. PEARLE,
FREDRIC L. COE, ALLEN RODGERS, ELAINE M. WORCESTER

INTRODUCTION

Despite substantial recent progress elucidating the pathogenesis and pathophysiology of renal calculi, treatment regimens have changed relatively little over the years. Furthermore, the number of randomized, clinical trials (RCTs) evaluating the efficacy of medical and dietary treatment regimens is disappointingly few. Indeed, since the last Stone Consultation in 2000, no new randomized trials have been published in this area.

In part, the reluctance to perform RCTs is due to the relative infrequency of the event being measured (i.e., stone recurrence), necessitating a minimum study duration of 2 years to reliably assess recurrence rates. Likewise, the need for long periods of study has prompted investigators to use surrogate endpoints for stone recurrence, typically levels of urinary analytes, rather than actual stone recurrence. Unfortunately, no studies have directly linked urinary parameters with stone formation rates, thereby validating this approach.

Furthermore, among published trials, lack of uniformity of study inclusion/exclusion criteria, endpoints, duration and medication dosing and interval makes comparison among even RCTs evaluating the same drug problematic. Nevertheless, there is high level evidence (level 1a) supporting the overall use of drug and dietary therapy for the prevention of recurrent stones. A meta-analysis of randomized medical therapy trials showed a 22.6% reduction in risk of recurrence (95% confidence interval –29.0% to –16.3%) with the initiation of drug and dietary regimens. [1]

Our committee reviewed the literature pertaining to medical and dietary therapies aimed at stone prevention and compiled the strongest available evidence in support of specific treatment regimens. As in the previous Stone Consultation, we have divided our chapter into calcium and non-calcium containing stones since treatment goals and therapeutic regimens are quite different.

A. CALCIUM STONES

Calcium stones form as a result of a combination of environmental risk factors and metabolic abnormalities that change the urinary environment and increase supersaturation of stone-forming calcium salts. Identification of the underlying metabolic derangements and the environmental risk factors provides the basis for a targeted approach to medical therapy whereby measures aimed at correcting the urinary abnormalities and reducing urinary supersaturation can be initiated. It is important to note, however, that a strategy of empiric medical therapy, whereby treatment is initiated without regard to metabolic background, has not been proven ineffective. Indeed, several successful medical therapy trials were based on non-selective treatment of recurrent calcium stone formers. [2,3] For the purposes of this consensus paper, the use of targeted medical and dietary treatments aimed at correcting specific abnormalities will be addressed.

I. DIETARY MEASURES

The impact of dietary measures on stone formation has long been recognized. Hosking coined the term “stone clinic effect” to describe the benefit of dietary measures, including a high fluid intake and avoidance of “dietary excesses” on stone prevention. [4] Indeed, a prospective, multicenter, randomized trial compared the effect of specific dietary recommendations based on comprehensive metabolic evaluation and close follow up with non-specific dietary recommendations and limited follow-up in first-time stone formers and found a 3-fold higher rate of stone recurrence in the latter group compared with the former. [5]

A variety of dietary factors have been implicated in calcium stone formation, including low fluid intake, high calcium and low calcium diet, overindulgence in animal protein and excess intake of salt and oxalate-rich foods. Unfortunately, few prospective, randomized clinical trials have evaluated the benefit of dietary modification on actual stone formation. Rather, the effect of most dietary measures has been assessed by way of metabolic studies using urinary stone risk factors as a surrogate for stone risk. As such, level 1 evidence in support of most dietary measures is limited.

1. FLUIDS

The protective effect of a high fluid intake against stone formation has been ascribed to the dilutional effect on crystallization of stone-forming salts. In 2 large observational studies, the risk of incident stone formation was found to be inversely proportional to fluid intake. [6, 7] In both a large male and female cohort, comparison of subjects in the highest quintile of fluid intake (mean 2167 ml/day in men and 2312 ml/day in women) to the lowest (mean 1789 ml/day in men and 1802 ml/day in women) resulted in a relative risk of stone formation of 0.71 (95% CI 0.52 to 0.97) in the male cohort and 0.61 (95% CI 0.48 to 0.78) in the female cohort.

In the only prospective RCT assessing the effect of fluid intake on stone recurrence, 199 first-time idiopathic calcium stone formers were randomized to a high fluid intake (enough to produce a urine output of at least 2 liters daily) or received no specific recommendations. [8] At the conclusion of the 5 year trial, urine volume was more than 2.5-fold higher in the high fluid group compared to the control group, and this difference translated into a recurrence rate less than half that of the control group (12% versus 27% respectively, p=0.008) and a longer time to recurrence (mean 39 months versus 25 months, respectively).

The benefit of particular beverages other than water in preventing stone formation is controversial. Unfortunately, no RCTs have evaluated specific beverages for their role in promoting or preventing stone formation. Observational studies have found that coffee, tea and alcoholic beverages are associated with a reduced risk of stone formation. [9-11] Evaluation of soda consumption on stone risk has yielded conflicting results. However, after controlling for other dietary factors, observational studies no showed associated increased stone risk in those consuming higher amounts of soft drinks.

Citrus juices have been thought to decrease the risk of stone formation due to their high content of citrate, a known inhibitor of calcium stone formation. However, observational studies showed no association of stone risk with orange juice and a 40% *increased* risk with grapefruit juice [10], despite metabolic studies showing a reduction in urinary stone risk factors and urinary saturation of calcium oxalate with orange juice [12, 13] and no net effect [14] or a decrease in urinary saturation with grapefruit juice [13].

The effect of lemonade on stone risk is likewise controversial. A retrospective study of 11 hypocitraturic patients on lemonade therapy (2 liters daily) revealed a mean increase in urinary citrate of 383 mg/day and a reduction in stone formation rate from 1.0 to 0.13 stones/patient/year at a mean follow-up of 44 months. These findings are consistent with a short-term metabolic study that demonstrated a mean increase of 204 mg citrate/day in 11 of 12 hypocitraturic stone formers. However, in a recent 3-phase metabolic study in 13 normal subjects and stone formers on a controlled metabolic diet, orange juice but not lemonade, resulted in an increase in urinary citrate and pH over water. [15] Overall, only orange juice consumption was associated with a reduction in urinary saturation of calcium oxalate.

From the available literature, there is level 1b evidence supporting a high fluid intake as a protective measure against stone formation. Citrus juices have not been shown unequivocally to reduce stone recurrence rates, although evidence from short-term metabolic studies shows a beneficial effect of some but not all citrus juices on urinary stone risk factors. Randomized clinical trials in this area are sorely needed.

2. CALCIUM

The role of dietary calcium in stone prevention is controversial. Traditionally, a high calcium intake has been thought to increase stone risk by raising urinary calcium and urinary saturation of stone-forming calcium salts. However, a high calcium intake may lower urinary oxalate by binding intestinal oxalate and reducing intestinal oxalate absorption, thereby reducing urinary saturation of calcium oxalate. The net effect of these opposing influences depends in part on the state of intestinal calcium absorption and on dietary oxalate intake. For example, a metabolic study comparing the effect of a high and low calcium diet during restricted oxalate intake showed no difference in urinary oxalate on the 2 diets, suggesting that a restricted oxalate intake averts the rise in urinary oxalate associated with low calcium intake. [16] Likewise, a retrospective study of 28 hypercalciuric calcium stone formers advised to adhere to moderate dietary calcium and oxalate restriction, along with initiation of a thiazide diuretic and potassium citrate, showed no increase in urinary oxalate during a mean duration of follow-up of 3.7 years. [17]

In several large observational studies, however, a high calcium intake was found to be protective against incident stone formation. In both male and female cohorts, even after adjusting for a variety of factors, individuals in the highest quintile of calcium intake were associated with the lowest risk of incident stone formation. [6,7,18,19] However, this association did not hold true in the subgroup of men aged 60 years or older, in whom no association between dietary calcium intake and stone formation was found. [18] One explanation for this finding of a protective effect of a high calcium intake against stone formation may be the co-ingestion of stone protective factors, such as alkali or fluids, along with calcium-containing foods that counteract the increased stone risk associated with increased urinary calcium. [16]

Despite the intense interest in the role of calcium in stone formation, only a single RCT has addressed calcium intake and long term stone recurrence rates in calcium stone formers. Borghi and colleagues randomized 120 hypercalciuric calcium oxalate stone formers to a low calcium diet (400 mg daily) or a diet normal in calcium intake (1200 mg/daily) but restricted in sodium and animal protein. [20] At the end of the 5 year study, the low calcium group had a higher stone recurrence rate (38%) than the normal calcium, low sodium and animal protein group (20%), despite comparable urinary calcium levels in the both groups. The authors accounted for the difference in recurrence rates by the difference in urinary oxalate, which was reduced in the latter group and increased in the former. Despite the important implications of this study, the question of the independent role of calcium on stone formation has still not been addressed, as the randomized trial did not examine the role of calcium independent of other variables.

While it is generally agreed that severe calcium restriction should be avoided in all individuals because of the risk of bone loss, modest calcium restriction may be advisable in hypercalciuric stone formers who demonstrate a marked and sustained increase in urinary calcium with increased calcium intake. On the other hand, in normal individuals or stone formers with normal intestinal calcium absorption, the initial rise in urinary calcium with an increased calcium intake is subsequently attenuated by the process of intestinal adaptation by which a compensatory reduction in vitamin D synthesis reduces the fractional absorption of calcium and subsequent urinary calcium excretion. In these individuals, a normal or high calcium intake is unlikely to increase urinary calcium or promote stone formation. As such, calcium restriction is unnecessary and ill-advised in this population. Indeed, review of a large number of calcium stone formers found that calcium restriction failed to reduce urinary calcium or urinary saturation of calcium oxalate in normocalciuric patients [21]. In contradistinction, in patients with moderate or severe hypercalciuria and intestinal calcium hyperabsorption, modest calcium and oxalate restriction reduced urinary calcium and saturation of calcium oxalate without an associated increase in urinary oxalate.

The type of calcium supplementation, whether from food or supplements, as well as the timing of calcium consumption (with meals or between meals) also influences urinary calcium and oxalate excretion. Curhan and colleagues found that older women consuming calcium supplements were 20% more likely to forms stones than those who did not [6], but that association did not hold true in younger women [19] or men [7]. In contrast, a short-term controlled metabolic study showed that calcium citrate supplementation in non-stone forming post-menopausal women increased urinary calcium and citrate and reduced urinary oxalate and phosphate without a change in urinary saturation of calcium oxalate or brushite, suggesting no increased stone risk with calcium citrate supplementation in healthy post-menopausal women. [22]

In conclusion, although a high calcium intake may have little effect or even decrease the risk of stone formation in normal subjects or in stone formers with normal intestinal calcium absorption, in patients with absorptive hypercalciuria modest calcium restriction or normal calcium intake, perhaps with the addition of a thiazide, is still advisable. Dietary calcium intake can then be increased as guided by urinary calcium and bone mineral density.

3. OXALATE

Urinary oxalate contributes to urinary saturation of calcium oxalate. The relative contribution of dietary oxalate versus endogenously produced oxalate on urinary oxalate excretion is controversial, but Holmes and co-workers found that dietary oxalate accounted for 24-50% of urinary oxalate, depending on dietary calcium and oxalate intake. [23] Because of intestinal calcium-oxalate interaction, the rise in oxalate associated with a high oxalate diet can be averted by instituting a high calcium intake. [24] Although dietary oxalate restriction in the setting of dietary calcium restriction has been shown to prevent the induced rise in urinary oxalate, definitive studies assessing the independent impact of dietary oxalate restriction on stone formation are lacking. Despite limited available evidence, calcium oxalate stone formers, particularly those with hyperoxaluria, should be instructed to reduce their intake of nuts, chocolate, brewed tea and dark roughages such as spinach and broccoli.

Because vitamin C is oxidized to oxalate *in vivo*, ingestion of ascorbic acid poses a potential risk for calcium oxalate stone formation. Although the literature is replete with conflicting reports of the effect of ascorbic acid on urinary stone risk factors and overall stone risk, 2 recent metabolic studies showed a 34-41% increase in urinary oxalate in stone formers ingesting 1-2 grams of vitamin C daily. [25, 26] Likewise, in a recent observational study, Taylor and colleagues reported a 40% increased risk of stone formation in those consuming in excess of 1000 mg of vitamin C daily compared to those ingesting less than 90 mg daily. [18] As such, calcium oxalate stone formers should be advised to limit heir intake of vitamin C to less than 1 gram daily.

4. PROTEIN

A diet rich in animal protein has been implicated in stone formation owing to the high content of sulfur-containing amino acids that confer an acid load which reduces urine pH and citrate and induces renal calcium excretion. In addition, animal protein increases urinary uric acid by way of its high purine content that serves as a substrate for urate synthesis. A study evaluating the metabolic effects of a high protein, low carbohydrate diet, typified by the Atkin's Diet confirmed a reduction in urine pH and citrate and an increase in urinary calcium during the stringent induction phase and less rigid maintenance phases of the diet. [27] A large epidemiological study in men also showed a positive correlation between animal protein consumption and incident stone formation in men but not women. [6,7,19]

Despite known favorable changes in urinary stone risk factors associated with a reduction in animal protein intake, there have been no clinical trials investigating the isolated effect of animal protein restriction on stone risk. Indeed, Hiatt and associates failed to observe a beneficial effect of a low protein diet in conjunction with high fiber and high fluid intake in a randomized trial of 102 first-time calcium oxalate stone formers. [28]At the conclusion of the 4-year trial, the stone recurrence rate was 6-fold *higher* in the low protein group compared with the control group (24% versus 4%, relative risk 5.6, 95% CI 1.2 to 26.1). Of note, however, mean urinary volume in the control group exceeded that of the intervention group at 2 of the 3 follow-up visits, potentially confounding the outcomes.

In the randomized trial by Borghi and associates, however, comparing a low calcium diet with a normal calcium, low protein, low sodium diet, the latter group experienced fewer stone recurrences than the low calcium group, although the effect of reduced protein intake cannot be distinguished from the effect of the other variables. [20]

In the absence of good level I evidence to the contrary, and ample support from metabolic studies, modest restriction of animal protein (limiting meat intake—red meat, fish and poultry— to no more than 2 meals daily, approximately 6-8 ounces) is advisable for most calcium stone formers.

5. SODIUM

A high salt intake has been associated with an increased risk of stone formation through a variety of effects. First it decreases renal calcium reabsorption and increases calcium excretion. It also reduces urinary citrate resulting in reduced inhibitory activity against the crystallization of stone-forming calcium salts. Finally it increases monosodium urate formation which promotes calcium oxalate crystallization. Curhan and colleagues confirmed a positive correlation between sodium consumption and risk of first-time stone formation in women but not in men. [6,7]No prospective clinical trials have investigated the role of sodium restriction as an independent variable in reducing the risk of stone formation, although the Borghi trial found a lower rate of recurrent stones in men adhering to a normal calcium, low animal protein, low sodium (50 mmol/day) diet than men on a low calcium diet. [20]

Calcium stone formers should be advised to avoid adding salt to foods and to limit their intake of sodium to 2000 to 3000 mg daily. For hypercalciuric stone formers taking thiazide diuretics, sodium restriction is particularly critical as high urinary sodium attenuates the hypocalciuric action of these drugs.

II. PHARMACOLOGIC INTERVENTION

1. THIAZIDES

The rationale for the treatment of calcium stone formers with thiazide diuretics is that this class of drugs reduces urinary calcium directly, by enhancing calcium reabsorption in the distal renal tubule, and indirectly by stimulating sodium-dependent calcium reabsorption in the proximal tubule by way of extracellular volume depletion.

In renal hypercalciuria, by which hypercalciuria is due to impaired renal tubular calcium reabsorption, thiazides act directly to correct the calcium leak and prevent secondary hyperparathyroidism. On the other hand, the mechanism of enhanced intestinal calcium reabsorption (absorptive hypercalciuria, AH), the most common cause of hypercalciuria, is unknown; as such, thiazide treatment in AH is empiric and aimed at reducing calcium excretion without affecting intestinal calcium reabsorption.

The clinical benefit of thiazides in reducing stone formation has been amply demonstrated in RCTs, despite a lack of uniformity in the type, dosage or dosing interval of thiazide administration among the various trials (**Table 1**). Among 9 RCTs [3,29-36] comparing thiazide or thiazide-like diuretics with placebo or no treatment, 7 trials demonstrated a benefit of therapy in reducing stone recurrence [3,29-32,34,35]. In the 2 trials not showing a reduction in recurrence rates, the mean duration of follow-up was less than 2 years, a study period generally considered insufficient for a stone trial because of the relative infrequency of stone events. Indeed, a meta-analysis of 8 randomized thiazide trials with appropriately expressed data revealed a risk difference in the active treatment groups compared to the placebo/no treatment group of 21.3% (95% confidence interval –29.2% to –13.4%, p=0.000014). [37] Overall, the treatment arms demonstrated a post-treatment stone rate of 0.13 stones/pt/year compared with 0.3 stones/pt/year in the placebo arms, representing a 57% risk reduction.

Interestingly, only 2 of the 9 thiazide RCTs limited enrollment to patients with hypercalciuria [29,31]; in the other 7 trials, patients were enrolled nonselectively, without regard to metabolic background.

The recommended dosages of commonly used thiazide diuretics for an average sized adult are hydrochlorothiazide (25-50 mg twice daily), benzoflumethazide (2.5 mg twice daily) and trichlormethiazide (2-4 mg daily). Alternatively, the nonthiazide diuretics Indapamide (1.25-2.5 mg daily) and Chlorthalidone (25-50 mg daily) have similar mechanisms of action to thiazides. Thiazide use may be limited by side effects in up to 30-50% of patients, including fatigue, light-headedness, hypotension, erectile dysfunction and gastrointestinal effects. In addition, thiazide-induced hypokalemia, glucose intolerance, hyperuricemia and dyslipidemia have been reported. [38] The degree of hypokalemia is dose-dependent and more pronounced with longer-acting thiazides.

The intracellular acidosis associated with thiazide-induced hypokalemia promotes citrate reabsorption in the proximal renal tubule, leading to hypocitraturia which can offset the beneficial effect of thiazides. As such, potassium supplementation is recommended in patients taking thiazides. Although both potassium citrate and potassium chloride can replete potassium and avert many of the adverse metabolic effects of thiazides, potassium citrate has a greater citraturic response, further increasing urinary inhibitory activity. [39] Potassium magnesium citrate, a new, but not yet commercially available drug for stone prevention, increases urinary citrate excretion and corrects thiazide-induced hypomagnesemia, thereby facilitating potassium repletion. [40,41] The choice of potassium citrate versus potassium chloride supplementation in conjunction with thiazides should be driven by urinary pH and citrate, as the increase in urinary pH with potassium citrate supplementation may enhance the propensity for calcium phosphate stone formation.

2. CITRATE

Citrate inhibits calcium stone formation by several mechanisms. First, citrate complexes with calcium, thereby reducing urinary saturation of calcium salts. [42] In addition, citrate directly prevents or inhibits the process of crystallization, growth and/or aggregation of calcium oxalate and calcium phosphate. Compelling evidence justifying the use of citrate as a therapeutic or prophylactic agent in

Table 1. Randomized, controlled "thiazide" trials for prevention of recurrent calcium stone formation, (level 1b).

Author	Treatment	Selection	Duration of Study (yrs)	No. pts.	Stones/pt/yr	Remission rate (%)	p-value
Borghi et al	Indapamide	Hypercalciuria	3	19	0.06	84.2	<0.05
[29]	No tx			21	0.28	57.1	
Brocks et al	BFMZ	Non-selective	4	33	0.09	84.8	NS
[32]	Placebo			29	0.11	82.8	
Ettinger et al	Chlorthalidone	No-selective	4	23	0.05	87.0	<0.05
[3]	Placebo			31	0.22	54.8	
Mortensen et al	BFMZ	Non-selective	2	12	-	100.0	<0.1
36	Placebo			10	-	60.0	
Laerum and Larsen [34]	HCTZ Placebo	Non-selective	3	23 25	0.07 0.18	78.3 52.0	0.05
Ohkawa et aL [31]	Triclorme-thiazide	Hypercalciuria	2	82	0.13	86.5	<0.05
	No Tx			93	0.31	55.9	
Robertson	BFMZ	Non-selective	3	13	0.22	-	"sig"
[75]	No Tx			9	0.58	-	
Scholz et al	HCTZ	Non-selective	1	25	0.20	76.0	NS
[33]	Placebo			26	0.20	76.9	
Wilson et al	HCTZ	Non-selective	3	23	0.15	-	<0.05
[30]	No Rx			21	0.31	-	

BFMZ=bendroflumethiazide

the management of calcium oxalate urolithiasis abounds in the literature. The evidence derives from two main sources: measurement of urinary citrate levels in normal and stone-forming subjects and determination of *in vitro* crystallization inhibition. Regarding the first of these, several studies have demonstrated hypocitraturia in stone patients [43-48] thereby indicating a causal link. Further support for hypocitraturia as a significant risk factor for calcium oxalate stone formation has been provided by *in vitro* crystallization studies in which citrate has been shown to modulate all three mechanisms associated with stone development, including nucleation [49-51], growth [52,53] and aggregation [53-56]. As such, several different citrate-containing preparations have been developed and tested in clinical trials for their efficacy in reducing stone formation and recurrence rates.

The 3 preparations that have been best studied are potassium citrate, sodium potassium citrate and potassium magnesium citrate. Details of the clinical trials involving these medications are summarized in **Tables 2 and 3**. In collating the data for these tables, two inclusion criteria were imposed: trials should involve stone formers, not healthy subjects, and the determination of stone recurrence, remission or rate of stone formation must be provided. Studies which presented alterations in urinary risk factors only were not included.

The tables reveal that the number of trials involving potassium citrate far outweighs those involving the other two citrate preparations. Notwithstanding the shortcomings and limitations associated with quantitative determination of remission rates [57], it is evident that stone recurrence and/or remission rates were determined in the potassium citrate trials with greater rigor than in those involving the other preparations.

Among the potassium citrate studies, a single placebo-controlled RCT was reported, thereby pro-

Table 2. Uncontrolled clinical trials evaluating potassium citrate therapy in preventing stone recurrence

Author	Patients	Duration of Trial	Dosage	Effects on Urine Risk Factors	Effects on Stone Formation and Remission Rates
Preminger *et al* (1985)	n=5M, 4F (*RTA*)	34 months	60-80 mEq/day	pH↑, cit↑, Ca↓, RS CaOx↓	Zero recurrence
Pak *et al* (1985)	n=89 (*HCN* or *HAL*)	1-4.3 years$^{\varnothing}$	60 mEq/day	pH↑, RS CaOx↓	•stone formation ↓'d in 97.8% of patients •remission obtained in 79% of patients
Pak and Fuller (1986)	n=31M, 6F, (*HC CaOx N*)	2.13 years	30-80 mEq/day^{+}	pH↑, cit↑, RS CaOx↓	•stone formation ↓'d in 89.2% g patients •stone formation rate ↓'d from 2.11 to 0.28 stones/patient years
Pak, Sakhee and Fuller (1986)	n=14M, 4F (*UAL*)	1-5 years	60 mEq/day^{+}	pH↑, cit↑, uric acid↓, RS CaOx↓	•stone formation rate ↓'d (1.20 to 0.01 stones/patient years) •remission obtained in 94.4% of patients •group stone formation rate ↓'d by 99.2%
Khanniazi *et al* (1993)	n=12M, 5F	7 days	56.7mEq/day	pH↑, cit↑, UA↑, Ca↓	•crystalluria ↓'d in 71% of patients
Abdulhadi *et al* (1993)	n=7M, 3F (*HC CaOxN*)	9-43 months	20-40 mEq/day^{+}	cit↑	•stone formation rate ↓'d from 1.17 to 0.45 stones/patient years •remission achieved in 80% of patients
Whalley *et al* (1996)	n=11M, 4F (*HC CaOxN*)	4 years	90 mEq/day	cit↑	•rate ↓'d from 0.7 to 0.13 stones/patient-years •remission rate of 93% obtained
Lee *et al* (1999)	n=237M, 76F	24-42 months$^{\varnothing}$	90 mEq/day		•stone recurrence reduced by 92%
Soygur *et al*(2002)	n=90 (*SWL*)	12 months	60 mEq/day		•zero recurrence in group which were initially stone free

RTA: renal tubular acidosis, *HCN*: hypocitraturic calcium nephrolithiasis, *UAL*: uric acid lithiasis, *HC CaOxN*: hypocitraturic calcium oxalate nephrolithiasis, *RCU*: recurrent calcium urolithiasis, *SWL*: shock wave lithotripsy patients, *RS CaOx*: relative supersaturation calcium oxalate

$^{+}$UrocitK (Mission Pharmacal), $^{-}$Ferrer Pharma Int, $^{\varnothing}$minor gastro-intestinal side effects

Table 3. Randomized, controlled trials evaluating alkali citrate therapy in preventing stone recurrence (level 1b).

Author	Treatment	Selection	Duration of Study (yrs)	N	Stones/pt/yr	Remission (%)	p-value
Barcelo et al [58]	K-cit	Hypocitraturia	3	18	.01	73.23	<0.05
	Placebo			20	1.1	20	
Hofbauer et al [57]	Na-K-cit	Non-selective	3	16	0.9	31.3	NS
	No Rx			22	0.7	27.3	
Ettinger et al [2]	K-Mag-C	Non-selective	3	16	-	87.1	rr=0.06
	Placebo			25	-	36.4	

viding high level (1b) evidence in support of potassium citrate therapy for the prevention of recurrent calcium stones. [58] Barcelo and colleagues prospectively randomized 57 patients with active stone disease (2 or more stones during the preceding 2 years) and idiopathic hypocitraturia to treatment with 45-60 mEq potassium citrate daily or placebo. A significantly higher remission rate was seen with potassium citrate (72%) than placebo (20%) and a corresponding significant increase from baseline in urinary citrate, pH and potassium was found in the treatment but not placebo group. The other, uncontrolled trials also uniformly showed a benefit of therapy compared to baseline stone formation rates or historical controls.

With the exception of one study [59], all the trials involved both male and female patients. On the other hand, Schwille and co-workers specifically included only male patients because of the potential influence the menstrual cycle might exert on citrate metabolism. [59] Unfortunately, no attempt was made to distinguish between the genders in the studies involving both males and female patients.

Although most trials investigated efficacy for the prevention of calcium stones, potassium citrate has also been used successfully in the management of uric acid calculi presenting either alone or in combination with calcium stones. [60] However, use of potassium citrate for this indication has not been investigated in a placebo-controlled, randomized trial.

Several studies failed to demonstrate convincingly the efficacy of sodium potassium citrate in favorably altering urinary risk factors for calcium oxalate or uric acid nephrolithiasis. [61-63] However, Berg and colleagues reported some favorable urinary changes in groups of healthy and stone-forming subjects treated with sodium potassium citrate, although these results were somewhat tempered by unfavorable urinary changes as well. [64] In a more recent study of both healthy controls and stone-formers, the beneficial effects of sodium potassium citrate were enhanced when it was co-administered with magnesium oxide. [65]

In the only RCT, Hofbauer and co-workers randomized a group of 50 active stone formers to dietary measures alone or dietary measures plus sodium potassium citrate. [57] Despite a significantly higher urinary citrate in the treatment group compared with the control group, a comparable decline in stone formation rates (from 1.8 to 0.7 stones/per patient/year versus 2.1 to 0.9 stones/per patient/year, respectively) was observed in the 2 groups. Consequently, when all the studies are considered and with special consideration given the RCT, the preponderance of evidence is not to recommend sodium potassium citrate as a therapeutic agent in the management of stones (levels 1b and 2), perhaps because the benefit of a higher citrate level is offset by the unfavorable effect of the sodium load.

Potassium magnesium citrate was developed to combine the beneficial effects of alkali citrate with the additional inhibitory action of magnesium. Potassium magnesium citrate was shown to have a greater citraturic response than either potassium citrate or magnesium citrate in healthy subjects. [66] In a study involving groups of healthy and stone-forming subjects, potassium magnesium citrate increased urinary pH, citrate and magnesium to a greater extent than was achieved with potassium citrate, while reducing the amount of undissociated uric acid. [67] Thus, the authors concluded that potassium magnesium citrate is more effective than potassium citrate in inhibiting the crystallization of uric acid and calcium oxalate. In a recent study comparing potassium chloride, sodium potassium citrate, magnesium glycine and potassium magnesium citrate on urinary risk factors in stone patients, the latter preparation was found to induce the most favorable response with regard to raising urinary pH, citrate and magnesium and decreasing urinary calcium. [68]

In the only placebo-controlled randomized trial evaluating the efficacy of potassium magnesiuim citrate in preventing stone recurrence, a group of 64 active calcium oxalate stone formers was randomized to potassium magnesium citrate or placebo and followed for 3 years. New stones formed in 63.6% of the control group compared with 12.9% of the potassium magnesium citrate group (relative risk 0.16, 95% CI 0.05 to 0.46). [2] Of note, there was a relatively high drop-out rate (24% in the placebo group and 48% in the treatment group) in the trial primarily due to gastrointestinal side effects. Interestingly, in contrast to the potassium citrate RCT which was limited to hypocitraturic calcium stone formers, potassium magnesium citrate was used non-selectively, without regard to metabolic background.

Despite strong evidence (level 1b) supporting the clinical efficacy of potassium magnesium citrate, the drug remains investigational. Consequently, potassium citrate is the drug of choice for the long term treatment of hypocitraturic calcium oxalate stone patients as it decreases the rate of stone formation and enhances urinary citrate levels. [69] Despite this optimisim for this drug, however, Mattle and Hess point out that all of the current sound evidence on the therapeutic effect of alkali citrate is derived from only 227 randomly treated patients. [70]

Potassium citrate is administered in starting doses of 40-60 mEq daily in divided doses. Potassium citrate can be used for treatment of patients with hypocitraturia or for normocalciuric calcium stone formers regardless of other associated abnormalities. In patients with hypercalciuria treated with thiazides, potassium citrate is additionally prescribed to prevent thiazide-induced hypokalemia and hypocitraturia. For patients with enteric hyperoxaluria, potassium citrate can raise urine pH and citrate. However, dosages higher than those used for idiopathic calcium nephrolithiasis (up to 120 mEq daily) may be required. Because of the rapid intestinal transit associated with chronic diarrheal syndromes, a liquid form of potassium citrate may be better absorbed.

3. ALLOPURINOL

Allopurinol is a xanthine oxidase inhibitor that prevents the conversion of hypoxanthine to xanthine, the precursor of uric acid, thereby reducing uric acid production and urinary uric acid excretion. Uric acid promotes calcium oxalate stone formation by increasing urinary saturation of monosodium urate, a promoter of calcium oxalate crystallization through heterologous nucleation. At pH<5.5, the sparingly soluble undissociated form of uric acid predominates leading to uric acid crystallization and uric acid and/or calcium oxalate stone formation. At pH>5.5, uric acid promotes calcium oxalate stone formation by way of monosodium-urate-induced calcium oxalate crystallization. [71] In addition, uric acid reduces the effectiveness of naturally occurring inhibitors of calcium oxalate crystallization. [72]

The rationale for the use of allopurinol for the prevention of calcium oxalate stones is that it reduces serum and urinary uric acid levels, thereby preventing calcium oxalate crystallization. The effectiveness of allopurinol has been tested in 4 RCTs in which groups of calcium oxalate stone formers treated with allopurinol were compared with placebo-treated or untreated control groups. [30,73-75] All trials utilized the same daily dosage of allopurinol (300 mg), although some differed in the dosing interval. Only one of the 4 trials demonstrated a benefit of allopurinol therapy in preventing stone recurrence; Ettinger and colleagues demonstrated a reduction from 0.26 to 0.12 stones/patient/year with drug treatment. [73] Of note, only the Ettinger trial among the 4 RTCs limited enrollment to patients with hyperuricosuria, while the remaining 3 trials enrolled patients unselectively without regard to metabolic background. As such, allopurinol cannot be recommended as an empiric treatment for stone prevention, but instead is recommended for patients with hyperuricosuric calcium oxalate nephrolithiasis. Indeed, most patients with hyperuricosuria can be managed with dietary measures, namely reduced intake of animal protein. However, for patients with hyperuricosuria despite dietary measures, those with hyperuricemia and gout or those who are unable to sufficiently reduce their animal protein intake, allopurinol is an effective therapy.

Allopurinol is typically prescribed at a dosage of 300 mg daily. Although the drug is generally well-tolerated, rare side effects include reversible elevation of liver enzymes and occurrence of a rash that can progress to Stevens-Johnson syndrome. Either of these side effects should prompt immediate discontinuation of the drug.

For the occasional hyperuricosuric patient who is unable to tolerate allopurinol, potassium citrate has been shown to be effective in reducing stone recurrence. [76] Potassium citrate not only reduces urinary saturation of calcium oxalate but also inhibits urate-induced heterologous nucleation of calcium oxalate.

4. MAGNESIUM

Several lines of evidence support the use of magnesium in preventing calcium stones. First, magnesium decreases the crystallization of calcium oxalate by complexing with oxalate ions to form soluble magnesium oxalate, thereby reducing the amount of free oxalate ions in the urine. [77,78] Second, *in vitro* crystallization experiments demonstrated that it inhibits calcium oxalate nucleation, growth and aggregation. [77,79,80] In addition, magnesium oxalate is more soluble than calcium oxalate. [77,81] Some studies have also reported lower levels of urinary magnesium in stone formers compared with healthy controls. [82-84] Finally, magnesium supplementation has been shown recently to reduce intestinal oxalate absorption. [85,86]

Not all studies, however, have corroborated these findings. Some workers have found that magnesium does not inhibit calcium oxalate crystallization [81,87], and others have failed to demonstrate relative hypomagnesemia in stone formers [88-91]. Furthermore Takasaki and colleagues found no relationship between stone recurrence and urinary magnesium. [92] Finally, decreases in oxalate absorption following magnesium supplementation do not agree with results from earlier studies in which this effect was not demonstrated. [93,94]

Despite conflicting empirical and experimental evidence on the effect of magnesium on urinary stone risk, preparations containing this ion, primarily magnesium oxide and magnesium hydroxide, have been tested in clinical trials. Details of these trials are summarized in Tables 4-6. The inclusion criterion for compilation of these tables was that the studies must have evaluated only stone-forming patients.

Only one large, long-term trial [95] and no RCTs have evaluated the efficacy of magnesium oxide in preventing stone recurrence (**Table 4**). **Table 5**, showing magnesium hydroxide trials, contains only one RCT involving 82 patients treated with magnesium oxide or placebo for which no difference in recurrence rates was demonstrated. [3]

Although combination therapy involving magnesium oxide and either pyridoxine or sodium potassium citrate has achieved favorable changes in urine risk factors and recurrence rates in uncontrolled trials (**Table 6**), compelling evidence supporting this strategy for calcium oxalate stone management is lacking.

Massey suggested that magnesium oxide and magnesium hydroxide are ineffective as monotherapies in the treatment of calcium urolithiasis due to their poor gastrointestinal absorption. [96] These forms of magnesium are the least bioavailable of the magnesium salts, with magnesium complexes with chloride, citrate, gluconate and aspartate being more soluble. The use of the mixed salt potassium magnesium citrate is an example of a preparation that attempts to exploit this physicochemical property of magnesium salts. [2] Interestingly, in a study by Schwille and associates using a commercially unavailable magnesium-alkali-citrate preparation, the authors concluded that successful inhibition of calcium oxalate crystallization was due to the action of the citrate rather than magnesium. [51] Another example of a more soluble magnesium salt is magnesium hydrogen aspartate which was shown in a metabolic study to successfully reduce oxalate absorption in healthy individuals. [86]

Overall there is little evidence to support the use of either magnesium oxide or magnesium hydroxide as a therapeutic option for the treatment of calcium oxalate nephrolithiasis. The development and testing of more soluble magnesium salts, possibly incorporating citrate, may show greater promise in effectively reducing stone recurrence rates.

B. NON-CALCIUM STONES

I. URIC ACID STONES

The primary determinants of uric acid stone formation are urine volume, urinary uric acid level and urine pH. Although low urine volume predisposes to all types of stone formation by increasing urinary saturation of stone-forming salts, it is rarely the only risk factor in uric acid stone formation. Hyperuricosuria contributes to uric acid stone formation, but is a relatively rare finding in idiopathic uric acid stone formers. In contrast, acidic urine is the predominant feature in idiopathic uric acid stone formation. In an acidic urinary environment, the sparingly soluble, undissociated form of uric acid predominates, leading to uric acid crystallization and uric acid or calcium stone formation.

The etiology of low urine pH is unknown in most

Table 4. Uncontrolled clinical trials evaluating the efficacy of magnesium oxide

Authors	No. Pts.	Duration of Trial	Dosage	Effects on Urine Risk Factors	Effects on Stone Formation and Remission Rates
Albuquerque et al [182]	19M, 5F *(RCaOx)*	14 days	450 mg/day	Ox↓, crystalluria↓	not measured
Moore et al [183]	2M *(RCaOx, RCaP)*	1 year	420 mg/day	Ca↓, P↓, Mg↑	•zero recurrence
Koher et al [184]	3M, 2F (*RSF*)	14 days	500-1500 mg/day	no statistical differences	not measured
Melnick et a [l95]	142 (*RCaOx*)	2-4 years	1200 mg/day	Mg↑	•recurrence rate↓
Fetner et al [185]	4M (*RCaOx-CaP*)	15 days	1680 mg/day	pH↑, Ca↑, Mg↑, P↓, AP(Bru)↑	not measured
Tiselius et al [94]	15 (*RSF*)	6-12 months	400 mg/day	Ca↑	not measured
Musialik et al [186]	6 (*RCA*)	10 months	600 mg/day		•recurrence rate↓

RCaOx: recurrent calcium oxalate stone formers; *RSF:* recurrent stone formers;
RCaP: recurrent calcium phosphate stone formers; *RCa*: recurrent calcium stone formers
AP (Bru): activity product brushite

Table 5. Clinical trials evaluating the efficacy of magnesium hydroxide

Authors	No. Pts	Duration of Trial	Dosage	Effects on Urine Risk Factors	Effects on Stone Formation and Remission Rates
Johansson et al [187]	42M, 14F (*RCa*)	2 years	960 mg/day	Mg↑	•zero recurrence in 80% of patients •recurrence rate reduced from 0.8 to 0.3 stones/patient years
Ettinger et al [3*]	82 (*RSF*)	2 years	650-1300 mg/day	Mg↑	•no change in recurrence rate relative to placebo
Vagelli et al [188]	7M, 2F (*R Ca*)	18 months	500 mg/day	Mg↑, Ox↓	•recurrence rate decreased from 0.75 to 0.11 stone/patient years

RCa: recurrent calcium stone formers; *RSF*: recurrent stone formers

*: placebo –controlled design

Table 6. Uncontrolled clinical trials evaluating the efficacy of combination therapy with magnesium oxide

Author	No. Pts.	Treatment and Dosage	Duration of Trial	Effect on Urinary Risk Factors	Effect on Stone Formation and Stone Remission Rates
Gershoff et al [189]	36 (*R CaOx*)	200 mg MgO+ 10 mg vit B6 per day	5 years	Ca↑, cit↑	•zero recurrence rate in 83% of patients
Prien et al [172]	265 (*R CaOx*)	300 mg MgO + 10 mg vit B6 per day	4.5-6 years		•recurrence rate decreased from 1.3 to 0.10 stones/patient years
Rattan et al [173]	16 (*R CaOx*)	300 mg MgO + 10mg vit B6 per day)	120 days	Mg↑, cit↑, Ox↓	not measured
Kato et al [65]	10M, 4F (*R CaOx*)	500 mg MgO + KNaCit (463 mg KCit and 390 mg NaCit)	7 days	Mg↑, Cit↑, Ox↓	not measured

R CaOx: recurrent calcium oxalate stone formers

uric acid stone formers, although secondary causes of acidic urine, such as chronic diarrhea, strenuous exercise or overconsumption of animal protein (which provides an acid load) may lead to uric acid stone formation. The pathophysiologic mechanism of an unduly acidic urine in uric acid stone formers is thought to be an acidification defect resulting from increased endogenous acid production or impaired production or transport of renal ammonium. [97] Insulin resistance has been implicated as a possible link between uric acid stone formation and low urine pH, as studies have demonstrated that urine pH directly correlates with glucose disposal rate, a measure of insulin resistance. [98]

1. DIETARY MEASURES

Treatment of uric acid stones is aimed at correcting the pathophysiologic factors associated with stone formation. Dietary measures, including increased fluid intake and reduced animal protein consumption, should be recommended to all stone formers in order to reduce urinary saturation of uric acid. The goal is to achieve a urine volume of at least 2 liters daily and to limit intake of animal protein to approximately 6-8 ounces daily (1-2 servings).

2. PHARMACOLOGIC CORRECTION OF HYPERURICOSURIA

Pharmacologic correction of hyperuricosuria can be achieved with the administration of allopurinol, which is a xanthine oxidase inhibitor that prevents the conversion of hypoxanthine to xanthine and ultimately to uric acid. Allopurinol is reserved for patients with persistent hyperuricosuria despite dietary measures to reduce purine intake or for those with genetic or myeloproliferative disorders and those with chemotherapy-related tumor lysis. Allopurinol is used at a dosage of 300 mg daily and is generally well tolerated. However the occurrence of a rash or detection of elevated liver enzymes should prompt cessation of the dug.

Several new investigational drugs have been developed that have shown to be efficacious in reducing serum uric acid. Febuxostat is a nonpurine xanthine oxidase antagonist that has been used in the treatment of hyperuricemia in patients with gout. [99] At daily oral doses of 80 or 120 mg, Febuxostat was shown to be more effective than a daily dose of 300 mg of allopurinol in lowering serum uric acid and reducing the frequency of gouty attacks (68). Another new xanthine oxidase inhibitor, Y700, has also been shown to be superior to allopurinol in lowering serum uric acid levels. Like Febuxostat, Y700 is eliminated through the liver and can therefore be used in patients with renal insufficiency. Neither agent is FDA-approved and the efficacy of each in preventing uric acid stones has not yet been investigated. Rasburicase, a recombinant form of uricase that converts uric acid to the more soluble allantoin, was shown to be more effective than allopurinol in lowering serum uric acid levels in patients with high tumor cell turnover. However, use of Rasburicase is limited by its high level of immunogenicity and need for intravenous administration.

3. ALKALINIZATION THERAPY

Correction of the underlying acidic urine is accomplished with either potassium citrate or sodium alkali (sodium citrate or sodium bicarbonate), both of which have been shown to achieve urinary alkalinization and in some cases stone dissolution. Potassium citrate has the advantage of also reducing urinary calcium, thereby decreasing the risk of calcium stone formation, since low urine pH is also a risk factor for calcium oxalate stone formation. However, for patients with renal insufficiency or those who are unable to tolerate potassium citrate, sodium citrate and sodium bicarbonate are effective alternatives, although the sodium load may increase urinary calcium excretion.

No prospective, randomized clinical trials have evaluated the use of alkalinizing agents in the prevention or dissolution of uric acid stones. However, 2 case series assessed the efficacy of alkali therapy in preventing recurrent uric acid stones. Pak and colleagues treated 18 patients (6 patients with uric acid stones and 12 patients with a combination of uric acid and calcium stones) with 30-80 meq of potassium citrate daily for a mean of 2.78 years. [60] Mean urine pH increased from 5.3 to 6.19 and urinary undissociated uric acid declined significantly with treatment. Mean stone formation rate dropped from 1.2 to 0.1 stones/patient/year (p>0.001), representing a remission rate of 94%.

Rodman also reported on 17 patients with a history of uric acid stones or recurrent colic due to gravel who were treated with single dose, alternate day potassium alkali (citrate or bicarbonate) for an average of 2.5 years. Patients monitored their urine pH with narrow range pH paper with the goal of achieving a urine pH of 6.8. No recurrences occurred in any of these patients

The goal of therapy is to achieve a urine pH between 6.0 and 7.0. Above pH 6.1, the amount of undissociated, uric acid is substantially reduced, and a pH below 7.0 will reduce the likelihood of predisposing to calcium phosphate stones. The recommended starting dosage of alkali is 20-40 mEq daily in 2 or 3 divided doses. A less desirable alternative to potassium citrate or sodium alkali, is acetazolamide, a carbonic anhydrase inhibitor that reliably increases urine pH, but additionally reduces urinary citrate by inducing a metabolic acidosis.

Potassium citrate and sodium alkali are generally well tolerated. However, side effects are primarily gastrointestinal, consisting of nausea, bloating and/or diarrhea. Taking the medication on a full stomach can sometimes alleviate these symptoms. Hyperkalemia occurs rarely with potassium citrate, primarily in the setting of renal insufficiency which is a relative contraindication for potassium alkali.

II. CYSTINURIA

Cystine is a dibasic amino acid formed by the linkage of two cysteine molecules via a disulfide bond. Cystine has a much lower solubility than cysteine, which leads to the clinically relevant feature of cystinuria, cystine stone formation. Cystine stone formation is directly related to the level of cystine saturation of the urine. Cystine saturation is a function of cystine solubility, cystine excretion, and urine flow rate; the last two factors determine the urine cystine concentration. Therapy to reduce stone formation is focused on lowering urinary cystine concentration or increasing cystine solubility.

There are no controlled prospective trials using stone formation as an endpoint for any therapy for cystine stones. However, studies using endpoints of cystine excretion and studies of stone passage using patients as their own historical controls provide reasonable data on which to base therapeutic choices.

1. DIET THERAPY

a) Fluids

Cystinuric patients are routinely instructed to increase fluid intake and maintain a high urine flow rate in order to lower urine cystine saturation. The level of urine flow required is dependent on the patient's cystine excretion, but most patients need to produce at least 3 liters of urine per day. It is usually recommended that the patient awaken at least once per night to void and drink additional water.

b) Sodium

Amino acids are freely filtered by the glomerulus and reabsorbed in the proximal tubule. Proximal tubule reabsorption of sodium and water provide the energy and chemical driving force for the reabsorption of cystine. High dietary intake of sodium, as assessed by urine sodium excretion, is associated with increased urine cystine excretion. [100] Low sodium diets, which lead to slight volume depletion and subsequent increased proximal tubule reabsorption of sodium, have been used to lower urine cystine excretion. [101-104] These studies are summarized in **Table 7**.

c) Protein

Cystine is a non-essential amino acid that can be obtained from a normal diet, or can be produced endogenously using sulfur derived from the essential amino acid methionine. There is a correlation between urine cystine excretion and dietary protein intake, as judged by urine urea nitrogen excretion. [100] Thus, restricting dietary protein intake is a potentially attractive therapy for cystinuric patients. There has been only a single study of low protein diet in cystinuria. Rodman et al studied seven patients maintained for 5 days each on a low protein (mean of 54 grams per day) and high protein diet (mean of 140 grams per day) and found a 20% reduction in cystine excretion on the low protein diet. [105] The effectiveness and safety of long term low protein diets in cystinuria has not been established. The reduction in urine cystine in the Rodman study is modest despite a large change in dietary protein. Lowering the intake of the essential amino acid methionine in patients who already have a defect in sulfur amino acid metabolism could theoretically lead to a nutritional deficiency. Rather than placing patients on low protein diets, it seems prudent to have patients maintain normal protein intake and avoid protein gluttony. An additional benefit of avoiding high protein diets is lowering dietary acid load, thus increasing urine pH and cystine solubility.

2. PHARMACOLOGIC THERAPY

a) Urinary alkalinization

One of the main factors controlling cystine solubility is urine pH. Unfortunately, solubility does not begin to increase significantly until pH is above 7 to 7.5, a level that requires significant and frequent dosing of alkali. In addition, the effect on solubility varies considerably amongst individuals, making

Table 7. Effect of urinary sodium on cystine excretion in cystinuric patients

Study	N	Urine Na and cystine on high sodium diet	Urine Na and cystine on low sodium diet	p value	Comment
Norman et al [102]	5	Na 122 ± 8 mmol/g creat Cystine 1.6 ± 0.7mmol/g creat	Na 76 ± 9 mmol/g creat Cystine 1.0 ± 0.3mmol/g creat	For Na <0.001 For cystine <0.05	-
Peces et al [103]	3	Na 227 ± 36 mmol/d Cystine 1.7 ± 0.3mmol/g creat	Na 51 ± 11 mmol/d Cystine 0.7 ± 0.3mmol/g creat	For Na <0.01 For cystine <0.02	-
Lindell et al [101]	13	Na 129 ± 48 mmol/g creat Cystine 2.3 ± 0.7 mmol/g creat	Na 37 ± 16 mmol/g creat Cystine 1.7 ± 0.7 mmol/g creat	For Na <0.001 For cystine <0.05	7 of the 13 subjects were also treated with tiopronin.
Rodriguez et al [104]	5	Na 6.0 ± 2.1 mmol/kg/d Cystine 19 ± 7 mg/kg/d	Na 1.5 ± 0.5 mmol/kg/d Cystine 1.0 ± 0.2 mg/kg/d	For Na 0.03 For cystine 0.02	Patients were children between the age of 6 to 10 years.

it difficult to determine the optimal dose of alkali in any given patient. [106,107] If possible, urine saturation should be directly measured rather than relying on simplified nomograms relating urine pH and cystine solubility. [100]

Sodium and potassium salts have been used to increase urine pH. Because of the concern that high sodium diets can increase urine cystine excretion, potassium citrate is generally favored over sodium bicarbonate, unless the patient develops hyperkalemia due to inability to excrete the potassium load. Fjellstedt et al have shown that potassium citrate is as effective as sodium bicarbonate in alkalinizing urine and also showed a correlation between urine sodium and cystine excretion in patients also treated with tiopronin. [108]

b) Thiol-binding drugs

Tiopronin, d-penicillamine, and captopril are drugs that contain thiol groups. When present in solution with cystine, a disulfide exchange reaction occurs and a drug-cysteine complex forms. The drug-cysteine complexes for all three of these thiol-binding drugs are much more soluble than cystine, effectively increasing cystine solubility. These medications have been shown to lower urine cystine saturation when studied in vitro and clinically. [109-112] Tiopronin and d-penicillamine have been studied the most extensively, although no RCTs have been reported. The drugs do appear to lower cystine stone formation as judged by stone formation rates pre and post-treatment. [107,113-116] However, the significant level of side effects of the drugs generally restricts their use to patients who are unable to control stone formation with high fluid intake, dietary modification and urine alkalinization. Common side effects include nausea, rash, fatigue, fever, and proteinuria. The side effects appear to be dose related and tiopronin is reported to have lower rates of side effects than d-penicillamine. [115]

Captopril has received considerable attention as a potential therapy. There are a few uncontrolled studies that show reduction in stone recurrence rates with captopril. [117,118] However, there are conflicting results as to the effect of captopril on urine cystine excretion in these patients. [117-120] Captopril is generally better tolerated than tiopronin and d-penicillamine, but that is likely due to the much lower dose used, 150 mg per day (0.7 mmol/day) versus 1000 to 2000 mg/day (6 to 12 mmol/day) for thiola and d-penicillamine. In fact, the low dose of captopril brings into question the proposed mechanism of action of the drug and its effectiveness in preventing stone formation. At a dose of 0.7 mmol/day and an estimated absorption of 70%, only 0.5 mmol/day would be excreted in the urine, an amount insufficient to solubilize the cystine present in the urine of most patients. In contrast, 3 to 6 mmol per day of tiopronin and d-penicillamine are excreted in the urine during therapy. If captopril is effective in reducing cystine stone formation presumably there is an alternate mechanism to formation of a drug-cysteine complex. Until better studies are available, captopril should not be considered the preferred thiol binding drug, unless the patient also has hypertension. Cysteamine and 2,3 dimercaptosuccinic acid (DMSA) are thiol-containing drugs that might be effective for treatment of cystinuria, but at this time they have not been adequately studied. [121,122]

III. INFECTION STONES

Infection stones are comprised of magnesium ammonium phosphate alone or in combination with calcium carbonate apatite, and they form as a result of urinary infection with urease-producing organisms which leads to increased ammonia production and elevated urine pH. In an alkaline environment, phosphate solubility is reduced, thereby leading to urinary supersaturation with respect to magnesium ammonium phosphate and calcium carbonate apatite.

The primary treatment for infection stones is surgical. Eradication of infection is rarely possible without complete clearance of stone from the collecting system. For patients with recurrent infection stones, a variety of preventative measures have been investigated, with treatment aimed at reducing urinary saturation by increasing urine volume or restricting substrate, increasing urinary solubility through reduction in urine pH and elimination of the offending organisms with long-term antibiotics.

a) Diet

Early attempts to treat struvite and other phosphate-containing stones with dietary modification based on a low calcium, low phosphorus, high fluid (3 liter/day) diet, along with aluminum gel and estrogen supplementation met with some success. [123-125] However, the aluminum gel, which binds phosphate in the intestinal lumen, was subsequently found to be associated with a variety of adverse effects, including constipation, anorexia, lethargy, bone pain, and hypercalciuria. [125,126] Although dietary measures aimed at limiting phosphorus- and magnesium-containing supplements or foods may have a limited benefit, evidence in support of this approach is scant (limited to level 2 and 3).

b) Urinary Acidification

Because infection stones form only in an alkaline urinary environment (pH>7.2), urinary acidification has been utilized for the prevention of infection stones. Neither ascorbic acid [25] nor ammonium chloride has been shown to successfully achieve a sustained reduction in urinary pH. L-Methionine administered orally is absorbed in the small intestine and metabolized in the liver to sulfate and hydrogen ions, thereby providing an alkalinizing effect. Short-term metabolic studies confirmed a reduction in urinary pH to 6.0-6.2 with the administration of a single oral dose of 1500 mg L-methionine. [127], and a long term clinical trial of 19 recurrent infection stone formers revealed a reduction in mean urinary pH from 7.5 to 5.5, with only 10% of patients experiencing a stone recurrence over a 10 year period of observation [128]. No published RCTs, however, have directly compared L-methionine with placebo or no treatment.

Urinary acidification is contraindicated in patients with metabolic acidosis of any etiology. Additionally, urinary acidification risks bone demineralization. Consequently, this form of treatment has not been widely adapted.

c) Antibiotics

Long-term antibiotic administration has been advocated for the prevention of struvite stones to eradicate infection and remove the source of urease. Unfortunately, no RCTs have evaluated the utility of chronic antibiotic therapy in the prevention of infection stones. However, a few retrospective studies have shown lower rates of stone recurrence in patients rendered stone and infection free following definitive surgery for infection stones. [129] Beck and Riehle treated a group of 33 patients with 3 months of culture-specific antibiotics following SWL monotherapy and found that at a mean follow-up of 27 months, 78% of 9 kidneys with ≥5 mm residual fragments but only 20% of 20 kidneys initially rendered stone free demonstrated stone regrowth.[130]Furthermore, among 16 stone free patients, only 1 patient experienced a recurrent infection compared with 47% experiencing recurrent infections among the 17 patients with stable or progressive residual fragments. This study emphasizes the importance of a stone free state after surgery in reducing the occurrence of new stones and repeated infection, as well the benefit of long-term culture-specific antibiotics in preventing stone and infection recurrence.

Although no level 1 evidence supports the use of long term antibiotic therapy to prevent recurrent stone formation, level 3 evidence is compelling enough to recommend suppressive antibiotics in patients rendered stone free by surgery in order to maintain sterile urine and prevent the morbidity of recurrent stones and infection. The choice of antimicrobial agent is best directed at the organism grown from the stone removed at the time of surgery, as it has been shown that the results of urine cultures obtained pre-operatively do not always correspond to the organism isolated from the stone [131].

d) Urease Inhibitors

The only preventative treatment for infection stones that has been subjected to RCTs is the use of urease inhibitors. Urealysis catalyzed by urease is essential for the production of struvite stones in humans. Consequently, inhibition of urease should eliminate the conditions predisposing to struvite stone formation. Although there is ample clinical and experimental evidence demonstrating the effectiveness of urease-inhibiting drugs such as acetohydoxamic acid, the high side effect profile of urease-inhibitors has limited it use in clinical practice.

The molecular structure of hydroxamic acid is similar to that of urea, thereby accounting for the specific inhibition of urease at low concentrations with these agents. [132]Currently, the only two FDA-approved urease inhibitors are acetohydroxamic acid (AHA) and hydroxyurea. [133] Although hydroxyurea is an irreversible urease inhibitor, it has been shown *in vitro* to be less effective than AHA as a urease ihhibitor. [134] In addition, hydroxyurea is broken down by urease, liberating ammonia, while AHA is inactive as a substrate. [135] AHA is the most commonly used and best-studied urease inhibitor. It has been shown to effectively lower urinary pH and ammonia levels and to cause stone dissolution. [136,137] A total of 3 RCTs have shown a benefit of AHA in retarding stone growth (**Table 8**). [138-140] However, the high attrition rate and need to stop or reduce medication due to side effects exceeded 22% in all 3 trials (range 22 to 62%).

Table 8. Randomized, controlled trials evaluating the effect of Acetohydroxamic Acid (AHA) on recurrent stone formation (level 1b)

Author	Study Group	Treatment	No. Pts.	Duration of Study/Time to endpoint	Outcome	Dropout or Severe Side Effects
Williams et al [140]	Pts with infection stones	AHA	18	100% increase in stone size Mean 15.8 mo.	None reached endpoint	47% (9/19)
		Placebo	19	100% increase in stone size Mean 19.6 mo.	37% (7/19) reached endoint	5.5% (1/18)
Griffith et al [138]	Spinal cord pts with chronic UTI and stones	AHA		Stone growth by 24 mo.	33%	62%
		Placebo		Stone growth by 24 mo.	60%	31%
Griffith et al [139]	Pts with chronic UTI and stone	AHA		Time to stone growth	17%	22% intolerable side effects
		Placebo		Time to stone growth	46%	4.1% intolerable side effects

For patients who have demonstrated aggressive, recurrent infection stones, a trial of AHA, at a starting dosage of 250 mg twice daily is recommended. If tolerated, the dosage can be increased to 250 mg three times daily. AHA is contraindicated in patients with renal insufficiency (serum creatinine greater than 2 mg/dL), as therapeutic urinary concentrations are unlikely to be achieved and the risk of toxicity is increased. [141] Use of AHA is also contraindicated in pregnant women due to teratogenicity shown in animals. [142]For patients with a poorly functioning, stone-bearing kidney, use of AHA is relatively contraindicated because of the potential for increased excretion of AHA on the contralateral side and sub-therapeutic levels in the stone-bearing kidney. [143]

Although the evidence in support of AHA for the prevention of recurrent struvite stones is good (level 1b), widespread use of the medication is limited by a high side effect profile.

C. IMPORTANCE OF FOLLOW-UP

The importance of periodic follow-up for patients actively treated with medical therapy for stone prevention cannot be overemphasized. When prescribing treatments aimed at achieving some measurable change, it is imperative to ascertain whether or not the beneficial change has occurred. Although stone disease does not command the urgency of cancer or vascular disease, treatment without follow-up is no less intolerable.

Our main treatments for calcium stone prevention, thiazides, potassium citrate, allopurinol, high urine volume, and control of dietary sodium and protein intakes, are supported by prospective randomized trials of sufficient power to draw conclusions of merit. In addition, surgery for primary hyperparathyroidism, alkali for uric acid stones, high fluid, alkali, and thiol agents for cystinuria are obvious treatments with no formal trials. Likewise, the patchwork of remedies for enteric hyperoxaluric states for which there is fragmentary evidence, and liver transplantation for primary hyperoxaluria complete the summary of what can be offered to a patient by way of stone prevention. As a rule, all of these treatments in one way or another aim to reverse pathogenetic factors of stone formation, have a rationale in science and are meant to be long lasting in their effects.

It is impossible to gauge response to treatment if we do not carefully monitor reversal of the pathogenetic factors we have set out to reverse. A variety of factors may alter the expected response to treatment; patients have different dose requirements, compliance is variable, high dietary sodium may offset the hypocalciuric effect of thiazide and worsening obesity may offset potassium alkali. Furthermore, time may alter responses, such that what was effective at one time may no longer be so.

What we look for in response depends upon the treatment. For thiazides, urinary calcium and sodium, serum potassium and urinary supersaturations of calcium oxalate and calcium phosphate are obvious choices. For potassium citrate, one expects an increase in urine potassium and decline in urine ammonia (proof of use and that dose is adequate to titrate an important fraction of net acid production, respectively), an increase in urine citrate and a modest increase in urine pH without an increase calcium phosphate supersaturation. For allopurinol, a fall in urine and serum uric acid is expected, and monitoring liver function tests is necessary. For uric acid stones, an increase in urine pH sufficient to reduce uric acid supersaturation to near 1 is sought. For fluids and dietary sodium and oxalate, we strive for increases in urine volume and reduction in urinary sodium and oxalate. With reduced protein intake, a fall in protein catabolic rate to the normal range is expected. Post-parathyroidectomy for primary hyperparathyroidism, normal values for blood and urine calcium should be seen. The level strived for in each case is a complex matter, but an appropriate trend is sought.

Follow-up should occur at about 6-12 weeks of treatment to be sure dosing is appropriate, that patients are compliant and that no adverse effects are evident. An approximately 90% success is achieved in initial follow-up testing, although at one year of treatment, that drops to 80%, with subsequent loss of about 20% of patients yearly thereafter. At a national kidney stone testing laboratory, first follow-up 24 hour urine collections during treatment are considerably below the standard for a university program, and longer term follow-up is even less reliable.

On the clinical side, new stones and changes in stone size will vary with the initial stone tempo and stone burden. Follow-up imaging likely occurs more regularly than urine or serum chemistries, although there is no clear evidence for either. However, it is changes in the laboratory values that reveal the early response to treatment, occurring before the next stone makes clear the failure of treatment, hence the emphasis on close laboratory follow-up.

D. FUTURE DIRECTIONS

There are a limited number of therapies that have been proven to be effective in treating calcium kidney stones. Thaizides, citrate, allopurinol, water and low sodium, low protein, normal calcium diet have all demonstrated efficacy in randomized prospective trials. Unfortunately, progress continues to be slow in identifying new therapies and testing these therapies under the most rigorous scientific conditions. Treatment of calcium kidney stone patients has not changed significantly in the last 20 years. In order to for the field to progress, treatments which are in use but of unclear value need to be rigorously tested to determine if they are effective. In addition, new pharmacologic agents need to be studied and brought to market to help treat this very common disorder. Summarized below are a few of the therapies that show promise as treatment for calcium stones. The list is representative and not meant to be an exhaustive list of all potential therapies in stone disease.

Pharmacologic treatment of calcium oxalate stones has focused on lowering urine calcium excretion or altering the excretion of inhibitors (citrate) or promoters (uric acid) of crystallization. Unfortunately, there has not been a controlled trial of any drug to reduce urine oxalate excretion, and therapy to reduce urine oxalate has largely consisted of dietary advice to avoid foods with high oxalate content. However, two new therapies show considerable promise as treatment for hyperoxaluria, pyridoxamine and oxalate-degrading bacteria.

Pyridoxamine is a derivative of vitamin B6. It is present in human plasma at low levels and has been shown to be non-toxic when given in pharmacologic doses to humans. In vitro, pyridoxamine forms adducts with the carbonyl precursors of oxalate synthesis (glyoxylate and glycoaldehyde), reducing the amount of glyoxylate remaining for conversion to oxalate in the liver. Pyridoxamine reduces urine oxalate excretion when fed to normal rats. [144] In rats made hyperoxaluric by treatment with ethylene glycol, pyridoxamine significantly lowered urine oxalate and reduced the amount of crystallization in the kidney. [144] Obviously this therapy holds most promise for patients in whom hyperoxaluria is due to endogenous overproduction of oxalate, such as patients with primary hyperoxaluria. There are no published studies of the effect of pyridoxamine on urine oxalate excretion in humans but there is an NIH sponsored trial underway to determine the efficacy in patients with primary hyperoxaluria and in patients with idiopathic calcium oxalate stone disease.

Recent advances in our knowledge of intestinal handling of oxalate may provide a new way to lower urine oxalate. Studies in null mice for the oxalate transporter Slc26a6 gene have shown marked hyperoxaluria which is due to increased net absorptive flux of oxalate across the intestine. [145,146] This appears to be due to a loss of oxalate secretion from knock out of the transporter, leaving an unopposed absorption of oxalate. That the gut can be such a powerful secretor of oxalate was not appreciated and provides an alternative avenue for oxalate excretion. Any treatment that can lower intestinal oxalate concentration could improve the driving forces for secretion or absorption. Oxalate degrading bacteria provide such a mechanism. Oxalobacter formigines is an anaerobic bacterium that is part of the normal intestinal flora. [147] Various cross-sectional studies have shown that stone formers have lower rates of colonization than non-stone formers; however it is not possible to tell from these studies if this is the cause or effect of stone disease. [148,150]

The potential of oxalate degrading bacteria as a therapy for hyperoxaluria and calcium oxalate stones has been an area of active investigation. In a rat model of hyperoxaluria, Sidhu et al showed that treatment with oxalobacter lowered urine oxalate excretion. [151] Hatch et al showed that not only administration of bacteria can increase intestinal oxalate secretion by lowering luminal oxalate concentration, but also that bacterial homogenates can stimulate intestinal secretion of oxalate by up-regulating transporters. [152] Studies in humans are limited, but one uncontrolled trial in patients with primary hyperoxaluria showed that urine oxalate excretion was lowered in some of patients. [153] We await formal trials of oxalobacter in common calcium oxalate stone formers.

Lactic acid bacteria also have the capacity to degrade oxalate, although it is not their sole energy source and as such, they tend to be less efficient at oxalate degradation than oxalobacter. An uncontrolled trial of a probiotic preparation of lactic acid bacteria in 6 patients showed a significant reduction in urine oxalate. [154] In addition, a trial of escalating doses of lactic acid preparation showed a modest reduction in urine oxalate excretion in patients with enteric hyperoxaluria. [155] However, a recent RCT of the same probiotic did not show lowering of urine oxalate in patients with hyperoxaluria and calcium oxalate stones. [156] Whether the lactic acid bacteria are effective in a subgroup of patients remains to be seen.

Idiopathic hypercalciuria is a systemic disease that involves the kidneys, intestine and bone, and it is the most common metabolic abnormality found in calcium stone formers. Low bone mineral density is a frequent finding in patients with idiopathic hypercalciuria and patients with a history of kidney stones have an increased rate of fractures. [157-159] However, the optimal therapy to improve bone mineral in stone formers has not been studied. There is limited data showing that thiazides increase bone mineral in patients with idiopathic hypercalciuria. [160] The role of bisphosphonates, which increase bone mineral content by reducing osteoclast-mediated bone resorption, has not been thoroughly studied in the stone forming population. Many early studies of bisphosphonate therapy used etidronate, which is no longer in common use. Wesinger et al showed a reduction in urine calcium and an increase in bone mineral density in 18 patients with idiopathic hypercalciuria treated for 1 year with daily alendronate. [161] In a recent study, Heller et al reported an improvement in urine calcium and markers of bone turnover when patients with hypercalciuria were treated with alendronate. [162]

Bisphosphonates may also have a beneficial role in preventing stone formation by lowering urine calcium and by acting as a crystallization inhibitor in the urine. [163,164] Whether bisphosphonates are safe and effective for long term treatment of hypercalciuria and hypercalciuric bone disease remains to be determined. [165] An alternative therapy for osteopenia associated with hypercalciuria is potassium citrate which has been shown to increase bone mineral density during therapy, presumably by neutralizing the dietary acid load that is buffered by the bone. [166] The relative effectiveness of thiazides versus alkali versus bisphosphonates is unknown at this time.

Sodium thiosulfate is a drug used for its anti-oxidant activity that is used as a substrate for reactions requiring sulfur groups. Currently the two major clinical uses of sodium thiosulfate are for treatment of cyanide toxicity and as a neutralizing agent to reduce the toxicity of the cancer chemotherapy agent, cisplatin. In 1985 Yatzidis reported an uncontrolled trial of sodium thiosulfate in 34 patients with calcium kidney stones, comparing stone rates pre- and post-therapy. [167] The author reported a reduction in stone recurrence rate from 0.98 in the pretreatment period to 0.11 stones/patient/year after initiation of the drug ($p<0.001$). The subjects were not chosen on the basis of any metabolic subtype. Despite the reported success of sodium thiosulfate, no further studies on stone prevention have been published nor has it become a common stone treatment. However, recent publications showing a beneficial effect of sodium thiosulfate on soft tissue calcifications in patients with kidney failure have led to a renewed interest in the drug. [168,169] Currently studies are underway using a genetic hypercalciuric rat model to determine if sodium thiosulfate can reduce stone formation and to determine the mechanism of action. If these studies are encouraging, further trials in humans will be warranted.

In addition to these relatively new therapies, there are a number of treatments that are commonly used today but have not received adequate study to confirm their effectiveness. Well-controlled trials, with stone formation as a primary endpoint, are required to prove these therapies effective. In addition, identification of sub-groups of patients who would most benefit from these therapies is also needed. Even though these treatments are currently used and generally considered to be of low toxicity, formal trials are still warranted to prove their effectiveness.

Pyridoxine is frequently recommended as a treatment of hyperoxaluria, since pyridoxine is a co-factor for the enzyme AGT, which converts glyoxylate to glycine, reducing formation of oxalate. There are a number of trials of pyridoxine in stone disease, although none have prospectively determined, using an adequate control group, whether stone formation improves. Some have shown that urine oxalate falls during therapy but this is not a universal finding. [170-173] In addition, some studies of pyridoxine also included use of magnesium supplements, making it difficult to isolate an effect of pyridoxine. Two large prospective cohort studies found a relationship between low pyridoxine intake and incident stone formation in women, but not in men. [174,175]

Magnesium has been mentioned as a therapy for stone disease since it may lower urine oxalate by complexing oxalate in the intestine and reducing oxalate absorption [81], as well as by acting as a calcium oxalate crystal inhibitor in the urine [176]. As noted previously, only one RCT of magnesium supplements in calcium stone disease has been reported and it failed to show a benefit of therapy [3]. Unanswered is whether patients who have low urine magnesium [177] represent a subset of patients who may respond to magnesium supplements, since no trials have considered magnesium excretion as an entry criteria.

Neutral phosphate salts are frequently recommended as a therapy for calcium stone disease in which no urine metabolic abnormality is found. The single prospective trial of phosphate salts used an acid phosphate salt which did not reduce stone formation. [178] Neutral phosphate has been proposed to reduce stone formation by suppressing vitamin D production, thereby reducing calcium absorption and excretion. Phosphate supplementation increases urine excretion of pyrophosphate, an inhibitor of calcium crystallization. [179,180] Neutral phosphate is a recommended therapy for patients with primary hyperoxaluria [181], but more detailed studies are needed to define its role in routine calcium stone disease.

The above therapies have all focused on calcium oxalate stones. There are no other randomized prevention trials for recurrent non-calcium stone disease except for struvite stones. Prospective clinical trials have not been performed for uric acid stones and are unlikely to be performed, as alkali therapy is well tolerated, inexpensive and clearly lowers urine uric acid saturation. It is unreasonable to expect alkali therapy to be compared to placebo for uric acid stones. Any new therapies for uric acid stones likely will not be studied compared to placebo but rather studied in equivalence trials with alkali as the standard therapy. Calcium phosphate stones have not been specifically studied. Although they may be included in studies of calcium stones, they comprise a distinct minority of stones and therefore the findings of any study performed for calcium stone formers may not be specifically applicable to calcium phosphate stones. Trials to determine optimal therapy for calcium phosphate stones would be very useful. Uncommon stone types such as cystine are unlikely to have prospective trials in the near future except those that use surrogate end points such as reduction in saturation rather than a hard end point such as stone formation.

E. CONCLUSION

The high prevalence of stone disease, high rate of recurrence and substantial cost attributable to the diagnosis and treatment of stones makes a medical prophylactic program attractive. However, medical and dietary treatment regimens should be validated by prospective randomized clinical trials before subjecting patients to the inconvenience of life-style changes, the morbidity of adverse events and the expense of treatment. Accordingly, in the future, uniform and well-defined entry criteria and clearly defined outcome measures in well-designed randomized clinical trials should answer questions about efficacy of current and future treatments and make comparisons among trials and treatments meaningful. Furthermore, the question of whether selective or non-selective therapy provides superior metaphylaxis has not been systematically addressed in randomized trials and awaits further study.

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Committee 4

Stone Technology: Shock Wave and Intracorporeal Lithotripsy

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CONTENTS

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INTRODUCTION

The introduction of shock wave lithotripsy (SWL) and endourologic techniques such as ureteroscopy (URS) and percutaneous nephrolithotomy (PNL) radically changed the treatment paradigm for upper urinary tract calculi. That is, stones that once required an open surgical procedure to effect cure could be treated with a minimally invasive approach (URS, PNL) or in a completely non-invasive manner (SWL). Within 5 years of its introduction, SWL became the most common intervention for patients suffering from renal or ureteral calculi [1]. SWL remains very popular, however, where shock waves (SW's) were once considered the treatment of choice for virtually all stones, it is now recognized that SWL has practical limitations. Some urologists are now less likely to turn to SWL, and some no longer see SW's as a first line option [2].

This shift understandably follows advancements in technology and technique, as significant improvements have been made in hand-held devices such as rigid and flexible lithotrites and flexible scopes, and more urologists have come to master particularly challenging endourologic procedures. However, it would be shortsighted to conclude that SWL is ineffective or is being replaced. Indeed, recent advances in SWL have introduced significant improvements in the safety and efficacy of SW's. Urologists now have more options at their disposal, better tools and better choices. Here we assess these options and take a fresh look at the technology available for stone removal.

A. SHOCK WAVE LITHOTRIPSY

I. CURRENT STATUS AND PREDICTION FOR SWL AS A VIABLE TREATMENT OPTION

Following the introduction of the first widely distributed clinical lithotriptor, the Dornier HM3, SWL was rapidly adopted as the treatment of choice for renal calculi. At that time, success rates were reported to be exceedingly high regardless of stone size, composition, or location. In fact, a number of SWL centers claimed overall success rates of greater than 90% [1]. More recent studies of the efficacy of SWL have found that treatment results are extremely variable; success rates even with the same lithotriptor can vary substantially (e.g. from 53% to 91% for the Storz Modulith SL20) [3, 4]. Consequently, efforts have been devoted to defining which stones will respond best to SWL, with the goal of identifying prognostic features that may be able to predict treatment outcome (**Table 1**). Several criteria have been identified with body habitus, stone burden, stone composition, and anatomical location all generally accepted as parameters that may have predictive value. Recent research has also demonstrated that stones having CT visible internal structural features are more fragile than stones that appear homogeneous, suggesting that CT data may be particularly valuable in treatment planning [5, 6].

Table 1. Clinical Parameters that May Affect Outcome of SWL

- **Patient habitus**
  - Skin to stone distance greater than 10 cm predictive of treatment failure
  - As body mass index increases the likelihood of success decreases
- **Stone burden**
  - Lower pole stones greater than 1 cm unlikely to be discharged from kidney
  - SWL of non-lower pole stones should be restricted to stones less than 2 cm
- **Stone composition**
  - Favorable
    - Calcium oxalate dihydrate
    - Hydroxyapatite
    - “Rough” cystine
  - Unvavorable
    - Calcium oxalate monohydrate
    - Brushite
    - “Smooth”cystine
    - Matrix
- **Renal Anatomy**
  - Hydronephrosis
    - Sign of distal obstruction, which will impede stone passage
  - Calyceal diverticula
    - Optimally treated with PNL
    - SWL only for those with a wide, functionally patent diverticular neck
  - Horseshoe kidney
    - SWL outcomes best for stones in middle and upper calyces
  - Ureteral stones
    - SWL a reasonable treatment option. However, URS is associated with high immediate success rate with minimal morbidity

1. PATIENT HABITUS

The morbidly obese patient may be more likely than a non-obese patient to experience a poor treatment outcome following SWL. Ackermann and associates reported a multivariate analysis finding that body mass index was a significant negative predictor of a stone-free outcome following SWL [7]. Portis and associates have reported similar findings [8]. Furthermore, morbid obesity may make SWL impractical or technically impossible, due to weight limitations on the lithotripter table or gantry, inability to radiographically target the stone, or a skin to stone distance that exceeds the maximum allowable focal distance of the lithotripter. In situations where the increased distance from the skin surface to the stone renders positioning of the stone at the focus of the shock wave impossible, a “blast path” technique that relies upon high pressures produced at a point located coaxially beyond F2 may be required [9].

2. STONE BURDEN

Early in the clinical use of SWL, large kidney stones, and even staghorn stones were treated with SW’s. Although there were reports of successful outcomes when treating staghorn stones, it is now recognized that such an extensive stone burden predicts a poor outcome. In particular, patients harboring staghorn calculi should not be treated with SWL as the primary treatment modality. The 2005 American Urological Association’s Nephrolithiasis Guideline Panel has published recommendations for the management of patients with staghorn calculi based on a meta-analysis of outcome data from published, peer-reviewed articles [10]. In the panel’s estimation, SWL of staghorn calculi is associated with a high risk of residual fragments, a high probability of unplanned procedures, and a high likelihood of multiple SWL procedures. Stone burden proves to be an important factor in predicting the outcome of SWL even for patients with non-staghorn calculi; as the amount of stone to be treated increases, the likelihood of a successful outcome decreases. In particular, stones greater than 2 cm in size are unlikely to respond well to SWL treatment, and may best be approached through an alternative means such as PNL [11].

3. STONE COMPOSITION

Stone fragility in SWL is variable among stones of different composition, and even stones of the same composition may respond to SW’s differently [12]. For example, SWL, when used unselectively to treat patients with cystine stones, yields poor results. Hockley and colleagues reported on 43 cystinuric patients treated with SWL and PNL, and found that stone-free rates with SWL were 70.5% for calculi 20 mm or less and 41% for stones greater than 20 mm [13]. Kachel and associates similarly reviewed 18 patients with cystine stones and recommended SWL monotherapy only for cystine stones less than 15 mm [14]. Chow and Streem, too, reported on SWL treatment outcome in 31 cystinuric patients, finding an overall stone-free rate of 86.9% [15]. Therefore, SWL for cystine stones should be reserved for those patients with a small stone burden.

Brushite calculi respond to SWL almost as poorly as cystine stones. Klee and associates reported on 30 patients with a total of 46 brushite stones [16]. The overall success rate for patients treated by SWL monotherapy was 65% (success defined as fragments less than 4 mm), with a mean of 1.5 SWL sessions required per stone. However, only 11% of patients became stone free. Of 20 kidneys with residual fragments less than 4 mm, 12 had rapid re-growth to significant size within 3 to 12 months. Parks and associates found that SWL use was more frequent among brushite stone formers than among a similar cohort of calcium oxalate stone formers, suggesting that multiple treatments may have been required to fragment the targeted stone [17]. A treatment paradigm similar to cystine stone formers, then, may be most reasonable, whereby only patients with brushite stones of a small size undergo SWL.

It is not just stones that are commonly thought of as exceptionally “hard” or “dense” that respond poorly to SWL; very soft matrix calculi, which are composed of as much as 65% organic matter (compared with 2% to 3% organic matter in most non-infected urinary calculi), also respond poorly to SWL [18]. Also, fragility is variable even for stones of the same composition. Such variability may be due to internal structural features, including variable amounts of secondary mineral in the stone, variation in the spatial arrangement of the secondary mineral within the stone, and variation in the layer structures of the primary and secondary minerals [12]. Variability in structural features may affect the type of fragments produced. Cystine and calcium oxalate monohydrate stones, in addition to being difficult to fragment, also tend to produce relatively large pieces which may be difficult to clear from the collecting system [19, 20]. Generally, patients with such hard to break stones (i.e., brushite, cystine, calcium oxalate monohydrate) should be treated with SWL only when the stone burden is small.

Taken together, there are certain stones, defined by their composition, that respond poorly to SWL. Specifically, patients with cystine, brushite, and matrix calculi do not generally experience a stone-free outcome following SWL. Matrix calculi should not be treated with SWL. Although stones of cystine or brushite composition are not a contraindication to SWL, the treating urologist should take this factor into consideration when developing a treatment plan for these patients, and treatment with SWL should only be contemplated if the stone burden is minimal.

4. STONE LOCATION

Regardless of its location in the body, if a stone sits proximal to a site of obstruction in the urinary tract, the outcome with SWL will likely be poor. With this in mind, stone-free rates for patients with hydronephrosis or obstruction are poor, as the patient is unlikely to clear stone fragments unless the obstruction is alleviated [21]. If both obstruction and infection are present, SWL may result in life-threatening urosepsis [22]. On a broader scale, there are certain considerations such as calyceal diverticuli and peculiarities in the anatomy of the lower pole that can hinder stone clearance following SWL and should be considered when deciding the suitability of SWL for the case at hand.

Although stones located within calyceal diverticula may be treated with SWL, this issue is controversial. The stone-free rate for patients with calculi located within calyceal diverticula who are treated by SWL averages only 21% (range 4-58%) [23]. However, an average of 60% (range 36 to 86%) of patients will become symptom free following SWL. It should be noted that series showing the highest symptom free rates involve a relatively short follow-up (three to six months), and when patients are followed over a longer time, some patients initially rendered symptom free will subsequently become symptomatic and require retreatment [24].

The SWL highest success rate for stones within calyceal diverticuli was reported by Streem and Yost who treated a series of 19 patients harboring calyceal diverticular calculi less than 1.5 cm and with a functionally patent diverticular neck [25]. They described an initial stone-free rate of 58% and a symptom-free rate of 86%. Such an outcome was likely the result of careful patient selection; all of the diverticula filled with contrast on preoperative intravenous pyelogram, the ostia were well visualized, and the aggregate stone size was less than 1.5 cm.

Although SWL can be used to treat patients with calyceal stones in a horseshoe kidney, the reported results of SWL treatment for such cases are variable [19, 26-30]. Theiss and colleagues stratified stones by location and found that the clearance rate for lower calyceal stones was inferior to that of middle and upper calyceal stones [27]. Patients with renal calculi in horseshoe kidneys treated with SWL not only required a higher number of SW's per treatment, but also experienced a higher retreatment rate (30% versus 10%) than similar stones in orthotopic renal units [1, 21].

Calculi in ectopic renal units can often be initially approached with SWL, although data on this subject are limited [31, 32]. If the bony pelvis shields the targeted stone from the shock wave of the lithotriptor, a prone position may be necessary. Tunc reported that in a series of 14 patients with calculi in pelvic kidneys that, although successful fragmentation was achieved for most patients at the time of treatment, the stone-free rate at 3 months was only 57% [30].

There is considerable controversy concerning the management of patients with lower pole calculi, an issue that was first noted in a meta-analytic study by Lingeman and associates who reported that when stratified according to stone size, patients with stones smaller than 10 mm had a stone-free rate of 74% when treated by SWL and patients with stones 10-20 mm had a stone-free rate of 56% for the SWL group [33]. A regression analysis demonstrated that increasing stone burden was associated with progressively less successful stone-free outcomes for patients treated with SWL. This study has prompted a number of groups to assess the impact of lower calyceal anatomy, with subsequent studies reporting stone-free rates for calculi 10 mm or smaller, 11 to 20 mm, and 20 mm or larger of 67.8%, 54.6%, and 28.8%, respectively [30, 34, 35].

As the results of SWL of lower pole calculi are poor, and significantly dependent on stone size, Albala and associates performed a multicenter, randomized, prospective study (Lower Pole I) that compared the treatment outcomes for patients with lower pole calculi following either PNL or SWL [36]. The stone-free rate at 3 months post-treatment, as measured by nephrotomograms, was 95% of those undergoing PNL and 37% for those undergoing SWL. Of note, stone clearance from the lower pole following SWL was especially poor for stones greater than 10 mm. For patients with stones less than 10 mm, 20 of 20 (100%) patients treated with PNL were stone free, whereas 12 of 19 (63%) treated with SWL were stone free. For those patients with calculi 11 to 20 mm in size, 26 of 28 (93%) treated with PNL were stone free, whereas 6 of 26 (23%) treated with SWL were stone free. Finally for patients with calculi 21 to 30 mm in size, 6 of 7 (86%) treated with PNL were stone free, whereas 1 of 7 (14%) treated with SWL was stone free. The main advantage of SWL was the lower associated morbidity. Recognizing subsequent advances in URS technology, the Lower Pole Stone Study Group later went on to compare SWL and URS for lower pole stones less than 10 mm, and reported that there was no significant difference in stone-free rates between the two techniques [37].

Although the optimal approach for managing patients with lower pole stones is still evolving, SWL is a reasonable consideration for individuals with lower pole stones of 1 cm or less in aggregate size. That is, there is a good chance of achieving a stone-free status with minimal attendant morbidity using SWL in this setting. The best treatment for patients with intermediate-sized (1–2 cm) lower pole calculi has not been established. Patients with lower pole stones greater than 2 cm are not best served with SWL, as they are unlikely to experience a successful outcome.

The role of SWL in the treatment of ureteral stones is an area of some controversy, as both SWL and URS are effective therapies for this clinical situation. The American Urological Association Ureteral Stones Clinical Guidelines Panel has found both modalities to be acceptable treatment options based on the stone-free results, morbidity, and retreatment rates for each respective therapy [38]. However, costs and patient satisfaction or preference were not addressed, and the report was based on data derived from older endoscopic and lithotripsy technology. In 2001, the European Association of Urology published Guidelines on Urolithiasis, which included an analysis of the relevant literature for the three years following the AUA publication [39].

This group noted that in the intervening years there had been dramatic advances in endoscopic technology, giving rise to significant improvements in stone-free rates, such that in many cases, ureteroscopy may be the optimal treatment approach, as success rates were 90 to 100% stone-free rate for distal ureteral calculi and 74% for proximal ureteral calculi. In addition, 95% of patients could be successfully treated with only one endoscopic procedure, and the best results were achieved with Ho:YAG laser lithotripsy in the proximal ureter. A complete analysis of this clinical scenario must note that both SWL and URS have advantages and disadvantages, and both may be reasonable treatment options for patients with ureteral calculi. Whereas SWL is less invasive, the high, immediate success rate with minimal morbidity and decreased cost are important positives of URS.

5. HOW SWL IS DELIVERED

As lithotriptors have become more portable and transportable, the proportion of SWL procedures performed in a hospital inpatient setting had declined, and the proportion of SWL procedures performed in ambulatory surgery centers and outpatient centers has risen. In the United States, in Medicare patients with a diagnosis of renal calculi, the rate of SWL has remained fairly stable over the years 1992, 1995, and 1998. However, the rates of SWL performed at ambulatory surgery centers, hospital outpatient centers, and hospital inpatient centers have shown distinct trends [37]. There is a declining utilization of SWL in hospital inpatient settings, as 5,580 procedures were performed in this setting in 1992, declining to 3,700 in 1995 and then to 2,960 in 1998. In the face of this decline, the SWL was increasingly performed in ambulatory surgery centers, moving from 1,000 in 1992 to 1,160 in 1995, to 1,400 in 1998. Similarly, SWL in hospital outpatient settings also rose, from 15,300 in 1992 to 22,100 in 1995, to 23,680 in 1998.

The changes observed in the Medicare population were remarkably similar to those observed in a population of commercially insured patients, which also demonstrated a steady increase in the proportion of SWL procedures performed in an ambulatory surgery setting. Although current data are not readily available it is widely appreciated that in the United States there has been a substantial rise in the presence of mobile lithotripsy companies that provide lithotriptors and lithotripsy expertise to hospitals and clinics that do not own their own equipment. In many cases this means that much of the hands-on procedure of lithotripsy is performed by technicians and not by the subscribing urologist. This may be no different than what occurs in some established stone centers, where a highly trained and experienced staff is responsible for the more routine aspects of treatment. This does, however, suggest a trend away from stone experts taking greater responsibility for all the critical steps of a protocol that are necessary to achieve a successful outcome.

6. HOW UROLOGISTS ARE TRAINED IN SWL

One of the advantages of SWL relative to other surgical techniques for the treatment of patients with stone disease is its short learning curve. Indeed, SWL may be performed following a short training period for urologists, and there are even reports of SWL being successfully administered by medical technicians [40]. However, when SWL was first introduced, the training was rigorous and a typical training program consisted of the management of 25 consecutive patients for 5 to 10 working days [41]. Such experience was mandated to include pre-treatment evaluation and post-treatment patient care. The director of the SWL center was further required to have personal experience with at least 200 patients. A more recent survey of Canadian Urological Association members found that 70% of respondents rated SWL training as useful and relevant to practice [42]. However, at present there is no formal curriculum in SWL training, and organizations such as the American Urological Association do not have a formal didactic in this technology. We contend that SWL should not be viewed as routine, and that proper practice demands that the person in charge have a good grasp of the scientific basis of lithotripsy and an up-to-date understanding of the mechanisms of SW action. In this regard, a greater emphasis on the training of urologists and lithotripsy technicians would be welcomed.

7. SUMMARY AND PERSPECTIVE

The evolution of SWL is no different than the evolution of any other surgical technology: as experience with the technology increases, a better understanding of which patients will respond to that technology will develop. In general, it is now well recognized that the larger the stone burden, the less likely SWL is to provide an optimal treatment outcome. Cystine, brushite, and certain calcium oxalate stones are also known to be less susceptible to SW's , and patients with a large burden of these stones should undergo an alternative treatment modality. Stones within calyceal diverticula and the lower pole of the kidney in many cases will not be effectively expelled from the renal unit, and may also be best accessed, fragmented, and removed by endoscopic means. Horseshoe kidneys and ectopic kidneys harboring minimal stone burdens may respond well to SWL. The implication of the transition of SWL from a hospital setting to an outpatient and even ambulatory setting is unclear.

However, the minimal requirements for physician education and didactic training with regards to SWL, is worrisome. As technologists take greater responsibility for conducting the procedural aspects of lithotripsy, it is not inconceivable that there could come a time when the economics of medicine deem it too costly for a physician to perform SWL, and instead rely on a lower level provider to perform SWL treatment. It is, therefore, imperative that a more formal training program in SWL be developed, so the urologist becomes intimately familiar with the mechanisms of SW action, the optimal clinical situation where SWL should be used, the factors that contribute to collateral tissue damage, and current treatment strategies that can be used to improve efficacy and minimize adverse effects.

Take Home Message (Status and Prediction for SWL as a Viable Treatment Option):

- SWL is a viable option, particularly well suited to treatment of solitary upper tract calculi.
- A variety of factors can contribute to poor outcomes with SWL, and include;
  - Obesity
  - Stone burden >2 cm
  - Stone composition is predominantly brushite, cystine or matrix
  - Stone located in lower pole calyx or calyceal diverticulum
- Proper delivery of lithotripsy requires a thorough understanding of the mechanisms of SW action yet, at most institutions, training in SWL is only cursory.
- As the majority of lithotripsies have moved to the outpatient setting, urologists have less control over these procedures.

II. LITHOTRIPTOR TECHNOLOGY: PAST, PRESENT AND FUTURE

1. LOOKING BACK- THE EVOLUTION OF MACHINE DESIGN

Traditionally lithotriptors have been categorized as first-, second- or third generation (an unfortunate and confusing classification system) devices. The Dornier HM3 is the first generation lithotriptor. It features an electrohydraulic source (see below) mounted at the floor of a large water bath in which the patient is placed, and which provides for optimal coupling to deliver SW energy to the body. Stone localization is via biplanar fluoroscopic imaging. Depending upon the case at hand, local sedation, regional, or general anesthesia is applied.

Second generation lithotriptors feature an electrohydraulic, electromagnetic or piezoelectric shock wave source (see below). Coupling is provided by a water cushion or partial water bath. The machines are further equipped with either ultrasonic or fluoroscopic imaging and have lessened anesthesia requirements. Limited multifunctional and/or multidisciplinary use is possible. These devices generate peak pressures similar to or lower than the HM3 but with smaller focal zones.

Third generation lithotriptors are equipped with a combined targeting system consisting of fluoroscopy and ultrasound to be used alternately or, in the ideal situation, simultaneously. They also have lessened anesthesia requirements and the integration of both fluoroscopy and ultrasound in an endourologic treatment table facilitate multi-functional and multidisciplinary use. These devices typically have higher peak pressures and smaller focal zones than the HM3.

a) Electrohydraulic lithotriptors (EHL-SWLs)

An electrohydraulic shock wave source consists of a spark plug placed underwater with a gap of approximately 1 mm between the two electrode tips. A capacitor is charged to a voltage between 12 and 30 kV and then abruptly discharged causing the explosive formation of an underwater plasma channel in the gap. The resulting rapid evaporation of the water surrounding the electrode tips releases a spherical (unfocused) shock wave. The spark plug is positioned at the first focus (F1) of an ellipsoidal bowl and the spherical shock wave reflects from the surface of the ellipsoidal bowl and converges (focuses) at the second focus (F2) [43]. The process causes erosion of the electrode tips leading to irregularities in the resulting spark and the shock wave originating from it. The erosion of the electrode tips thus limits the lifetime of the spark plug to several thousand shocks per spark plug. The Dornier HM3 had a complete water bath, which provided optimal coupling but subsequent EHL-SWLs have the shock wave source mounted in a sealed therapy head which is coupled to the body using gel or oil.

b) Electromagnetic lithotriptors (EMLs)

Electromagnetic shock wave generators are available in several geometries. In one case an electric coil is formed on a flat surface and a conductive membrane placed on top. A capacitor is then discharged through the coil which produces a magnetic field that repels the membrane resulting in the generation of a plane (unfocused wave) which is focused with an acoustic lens. In another geometry the coil is wrapped around a cylinder (about the size of a soup can) and the wave spreads out cylindrically (unfocused) from the coil. The coil is placed within a parabolic reflector which acts to focus the cylindrical wave. In a third approach the coil is formed on the inner surface of a spherical cap. When the coil is excited the wave generated has the same curvature as the spherical cap and therefore starts off as a focused wave propagating toward the centre of the radius of curvature of the spherical surface [44]. In all cases the initial wave is not a true shock wave but as it propagates towards the focus it evolves into a shock wave [43]. All electromagnetic shock wave sources are in a sealed therapy head, which is coupled to the body using gel or oil, except for the Storz devices which couple the sealed therapy head via a small, shallow water bath. Electromagnetic shock wave sources are more consistent and reproducible than EHL-SWL spark-gap sources and have a lifetime of about two million SW's.

c) Piezoelectric lithotriptors (PELs)

A piezoelectric shockwave generator consists of a concave spherical cap lined on the inner surface with piezoceramic elements—typically hundreds or thousands are employed. Piezoceramic elements rapidly change shape in response to an electric current. A capacitor is discharged through these elements, which because of the geometry of the sphere, produces an acoustic wave with a spherically converging wavefront. The pressure wave focuses at the centre of the sphere. As with the EMLs the wave does not start as a shock wave but rather develops into a shock wave due to non-linear propagation. Typically PELs are mounted in the therapy head like other SW sources. One notable exception was the original Wolf Piezolith which was equipped with a partial water bath bringing the patient in direct contact with the water.

Although piezoelectric shockwave sources develop high focal pressures this technology generally is considered to be less effective than other devices, as the clinical data shows a high re-treatment rate [45].

• Assessment of Lithotriptor Performance

Comparison of the performance of different lithotriptors presents a difficult challenge. From a basic science perspective one should appreciate that there are no agreed upon metrics by which to compare the acoustic output of different machines, no straightforward means to operate any particular lithotriptor so that it is equivalent to another [43]. As discussed below (see Section D.) lithotriptors all produce SW's with similar waveforms, but each machine generates an acoustic field having unique properties in regards to the amplitude and spatial distribution of acoustic pressure and energy density that characterize its focal volume.

Whereas, it may be possible to operate different machines, for example, to give the same peak positive pressure, they will not deliver the same energy. This reality has made it very difficult to devise adequate comparisons of different modes of shock generation, or compare different devices of any given type.

In the clinical setting investigators have adopted a variety of methods to compare lithotriptors based on clinical outcomes. Denstedt and colleagues established the Effectiveness Quotient (EQ), which takes into account stone free rate, retreatment rate and auxiliary procedure rate post-SWL [255]. Others have modified the EQ to include all auxiliary procedures, both pre- and post-SWL, and have defined the extended EQ (EQ_B) [256]:

$$EQ_B = \frac{\%\text{stone free patients}}{100\% + \%\text{Re-treatment} + \%\text{Aux. Proc pre- and post-ESWL}} \times 100$$

The Modified EQ (EQ_{mod}) makes a further distinction between adjuvant and therapeutic post-ESWL procedures [256].

Apart from the parameters in these formulae, which are difficult to precisely define and measure, several additional factors are likely to play an important role in outcomes. These include the parameters of SW delivery (SW-rate, power setting, number of SW's), the acoustics of the shock source (mentioned above), the quality of imaging, stone burden and types of stones, stone location, method of anesthesia, and body habitus.

Table 2 shows reported EQ_B for a selection of electrohydraulic and electromagnetic lithotripters. It can be seen that even for a specific lithotripter (e.g. HM3, Lithostar), there is typically a wide range in EQ_B's reported by different investigators. As such, where one may see apparent trends in performance it is wise to remember that such data are often quite difficult to interpret.

Table 2. Effectiveness Quotients Comparing the Clinical Performance of Lithotriptors

	EFFECTIVENESS QUOTIENTS (EQ_B)		
ELECTROHYDRAULIC LITHOTRIPTERS			
MACHINE	**AUTHOR**	**EQ**	**REMARKS**
DORNIER HM3	Frick (257)	25	
	Cass (267)	33	Ureteral calculi
	Cass (261)	35	
	Selli et al (264)	44	Lower ureteral calculi in situ
	Tiselius et al (259)	47	Mid-ureteral stones in situ
	Petterson (258)	47	
	Cole et al (263)	62	Distal ureteral stones in situ
	Danuser et al (265)	62	Ureteral stones
	Politis et al (262)	65	
	Erturk et al (266)	65	Distal ureteral stones
	Lingeman et al (260)	67	
MEDSTONE STS	Cass (267)	38	Ureteral calculi
	Lipson et al (268)	40	
	Cass (261)	63	
TECHNOMED SONOLITH	Tan et al (46)	26	
	Martin et al (269)	44	
HEALTHTRONICS LITHOTRON	Fuselier et al (270)	55	
ELECTROMAGNETIC LITHOTRIPTERS			
DORNIER LITHOTRIPTER S	Tailly (271)	74	Ureteral stones in situ
	Tailly (272)	80	Ureteral stones in situ
STORZ MODULITH SL20	Liston et al (274)	58	
	Rassweiler et al (273)	65	
SIEMENS LITHOSTAR	Andersen et al (277)	31	
	Bierkens et al (280)	31	
	El-Damanhouri et al (275)	43	
	Mobley et al (279)	46	
	Clayman et al (276)	56	
	Netto et al (278)	59	

2. NEW AND EMERGING LITHOTRIPTORS

a) Wide focal zone machines

What makes one lithotriptor different from the next is its acoustic output, in particular the dimensions and pressures of the focal volume or focal zone (see Section D). It should be noted that few lithotriptors have undergone independent assessment and for those that have the values are not always in agreement. For example, published values for focal width for the Dornier HM3, the lithotriptor that has been studied the most, run from 8 to 15 mm with peak pressures of the order of 40 MPa. Lithotriptors that employ electromagnetic sources typically have smaller focal widths around 5 mm and peak pressures on the order of 100 MPa [43].

Historically, the development of a smaller focal zone with high peak pressure was accompanied by loss of disintegrative capacity [43]. There is now evidence to support the argument that a wide focal zone provides for more efficient fragmentation, and it appears that the energy incident on the stone may be a better metric than peak pressure for predicting fragmentation. There is also evidence that high peak pressures (high energy flux densities) result in increased tissue injury [46, 47]. This may explain in part why the Dornier HM3, which has a wide focal zone and moderate peak pressures, was such an effective lithotriptor.

The concept of employing a broad focal zone with low peak pressures was pioneered with the CS-2012A XX-Es (XiXin Medical Instruments Co) lithotriptor introduced in 2002 [44]. The XX-Es employs a self-focusing electromagnetic source that in independent testing has been characterized to generate a focal width of ~18 mm (at 9.3 kV) with a peak pressure of ~17 MPa [48]. We know of only one published report of clinical experience with this lithotriptor [44]. Laboratory studies with pigs showed no detectable renal injury when 1500 SW's (a clinical dose) were applied at settings (9.3 kV, ~17 MPa, 27 SW/min) recommended for patient treatment [48]. For comparison, a somewhat higher dose of 2000 SW's (24 kV, ~40 MPa, 120 SW/min) with the HM3 produced a lesion measuring 6.1% of functional renal volume (FRV), but slowing the SW-rate to 30 SW/min reduced the lesion to 0.1% FRV. Thus, the observation of minimal to no injury with the XX-ES may be because the SW rate was very slow, and may not be related to the broad focal width of this lithotriptor. Since recent studies have shown stone breakage to be improved when the focal zone is wider than the stone (see below), a wide focal zone lithotriptor operated at low pressure and slow SW-rate may provide the conditions necessary to achieve better stone breakage with less tissue injury.

Most new lithotriptors entering the market are described as having wide focal zones. Siemens reports that their Pulso EM source, used in the Lithoskop, as having a focal width between 12 mm (low power setting) and 8 mm (high power setting) with a peak pressure varying from 8 MPa to 75 MPa. The Dornier EMSE 220X-XXP source has a reported diameter of 5.4 mm at the highest power setting, which is larger than the 2.5 to 3 mm diameter of most of the other Dornier electromagnetic SW sources. The peak pressure at the highest power setting is 90 MPa. The Storz Modulith SLX-F2 has two selectable focal zones: large focus and small focus. The idea is to allow the doctor to select the appropriate focal width dependent on the anatomical location of the stone. Storz promotes the small focus for the treatment of ureteral stones and the large focus for kidney stones. The manufacturer reports the "large" focal zone as 4.8 mm in diameter and 42 mm long and the "small" focal zone as 2mm in diameter and 20 mm long. We note however that the "large" focal zone in this instance is much narrower than other "wide" focal zone devices on the market, and so it is debatable as to whether the SLX-F2 truly results in a "wide" focal zone. By way of comparison, the LithoGold (Tissue Regeneration Technologies, LLC) is a recently introduced EHL-SWL reported by the manufacturer to have a focal width of ~16-17 mm.

b) Dual head lithotriptors

Lithotriptors with two treatment heads have recently been developed for clinical use. The use of dual shock sources has the potential advantage of reducing treatment time, as SW's can be delivered along separate paths. Also, twin sources can be a means to manipulate the acoustic field with the potential to improve stone breakage [49]. One such machine, the Direx Duet (Direx Corp., Natick, MA, USA) can be operated so that SW's are fired at the same time (synchronous or simultaneous mode) or in sequence (alternating mode). In alternating mode each head can be fired at a rate of 120 SW/min, thereby delivering 240 SW/min to the target. Independent studies of the Duet fired in simultaneous mode have shown that timing of the pulses degrades over the lifetime of the electrodes [50]. That is, the measured delay between pulses increased as more shots were fired. When timing was very close ($\leq$ 2 µs) acoustic pressures at the focal point were about twice that produced by just one electrode. Increase in the delay time separated the pulses, such that with a delay of ~4 µs there was no constructive interference at the focal point. The delay between pulses created a spatial shift in their position of overlap such that a delay of 6 µs shifted the axis of the focal volume by ~ 1 cm. Assessment of renal injury in pigs treated with 1200 paired SW's (1200 from each head, 120 SW/min per head) fired in simultaneous mode showed damage similar to, but more variable than the injury produced by 2400 or 4800 SW's from an HM3 lithotriptor fired at the same rate. This suggests that delivery of SW's with dual heads may be no more damaging than SW's from a conventional lithotriptor. However, because variability in the timing of pulses shifts their location of coincidence, and since tissue damage is dose-dependent, it seems likely that the timing delay in the firing of SW pairs created movement of the focal volume that distributed acoustic energy over a much larger region of the kidney. Such movement would also be expected to carry the focal volume off a targeted stone and reduce the efficiency of stone breakage. Thus, there may be considerable promise in dual head lithotripsy, but further work needs to be conducted to determine the potential advantages, pitfalls and problems.

c) Improved electrodes for electrohydraulic machines:

One of the important technological advances in SWL was the development of electromagnetic shock wave sources. Electromagnetic lithotriptors (EML's) have the advantage that their acoustic output is very consistent from shot to shot and there is no need to change electrodes between or during cases. A potential disadvantage is that, except for the XX-ES, all EML's have somewhat narrow focal zones. Although EML's are very popular, there is still an important place for electrohydraulic lithotriptors. The Dornier HM3, long since out of production but still in use, employs a caged electrode with a lifetime of ~2000 SW's (depending on voltage/power-level). Various other electrode designs have been used. One approach has been to enclose the spark gap within a plastic housing filled with electrolyte. Such encapsulated electrodes can be long-lived. An example is the NewTrode™ electrode used with the HealthTronics LithoDiamond. In independent in vitro testing the NewTrode was found to have stable acoustic output and consistent stone breakage for up to 17,500 SW's [51].

Another new concept in electrode design is the SmartTrode™ used with the LithoGold lithotriptor manufactured by TRT—Tissue Regeneration Technologies. The SmartTrode™ is a self-advancing electrode in which the spark gap remains constant, and is intended to provide improved consistency with less shot-to-shot variability over a lifetime of 6,000 SW's. To date there have been no published reports of the performance or characteristics of this electrode.

Technical advances such as seen with the NewTrode™ encapsulated electrode and the SmartTrode™ self-advancing electrode appear to be positive steps. But because electrodes are not interchangeable between different lithotriptors, new electrodes end up being just another new feature of a given machine. Also, because each lithotriptor can only be operated with one style of electrode it is impossible to directly compare the performance of different electrodes. It would be valuable to know, for example, if the concept of the encapsulated electrode as developed for a specific machine (e.g. NewTrode for the LithoDiamond) would offer an advantage with other lithotripters.

d) Improved imaging/targeting systems

Treatment strategies in SWL are to a great extent influenced by the imaging system available with a lithotriptor. Early lithotriptors were typically equipped either with ultrasound or fluoroscopy alone. Newer machines often have both imaging modalities. In general, fluoroscopic imaging (X-ray) allows targeting of radiopaque stones in the entire urinary tract, while ultrasound imaging (US) allows targeting of both radiopaque and radiolucent stones in the renal pelvis and calyceal system, in the UPJ and upper proximal ureter, and in the distal ureter when the bladder is used as an acoustic window. In machines where only X-ray is available radiolucent stones cannot be detected, while radiopaque stones in the entire urinary tract can be targeted (**Table 3**). For stones in certain areas such as the distal ureter, special positioning techniques may be necessary. In machines where only US is available the direct targeting of ureteral stones can be extremely difficult, with a low probability of success. Also, the quality of US imaging is often poor with obese patients.

In lithotriptors where ultrasonic imaging is combined with an adaptable fluoroscopic C-arm, either fluoroscopy or ultrasound can be used separately. Ultrasound then can be used for kidney stones and very proximal or very distal ureteral stones, while most ureteral stones can be targeted with X-ray.

Technically, two different approaches are available for X-ray and ultrasound: imaging through the center of the shock source (also referred to as "inline" or coaxial) and "outline" imaging (**Table 4**). The configuration of the SW reflector employed in EHL-SWLs means that in-line imaging is impossible. Instead, isocentric/outline X-ray and US are used for localisation and real-time monitoring during shock wave treatment.

The use of an isocentric arm for the US transducer provides a convenient way for the probe to be handled while maintaining the geometric focus of the lithotriptor in the field of view. Outline ultrasound can be used to monitor stone comminution in real time. However, outline US is difficult to use for most ureteral stones.

Inline fluoroscopy requires a port in the shockwave source so that the x-ray beam can pass through the source without significant attenuation. The geometry of the Storz SLX EM source allows for either X-ray beams to pass or for an ultrasound probe to be inserted along the axis of the shock wave path. Certain other EML sources now also offer inline ultrasound, which is achieved by placing an ultrasound transducer in the centre of the shock wave source (e.g. Dornier FarSight, Siemens Lithoskop).

Table 3. Advantages and Disadvantages of SWL Imaging Systems

FLUOROSCOPY	**ULTRASOUND**
ADVANTAGES	
- in situ treatment of ureteral stones in all parts of the ureter	- easy targeting of radiolucent stones - easier targeting of smaller renal stones
- shorter learning curve	- real-time image : easier, faster focusing
- automatic positioning mode available on some systems	- no exposure to radiation
DISADVANTAGES	
- no direct targeting of radiolucent stones - small stones sometimes difficult to locate	- in situ treatment of ureteral stones is possible only for very proximal and very distal ureteral calculi
- no real-time image	- longer learning curve
- exposure to radiation	- poor imaging with obese patients

Table 4. Comparison of Ultrasound Imaging Systems for SWL

IN-LINE SCANNER	OUT-LINE SCANNER
ADVANTAGES	
- easier to distinguish between multiple stones	- most appropriate window can be chosen for kidney stones: avoids rib shadows
- easier targeting of very proximal and very distal ureteral stones	- better appraisal of fragmentation - use as diagnostic scanner - can be exchanged for 5 MHz scanner to improve imaging in children
DISADVANTAGES	
- rib shadows may hide stones from view - poorer image quality	- very proximal ureteral stones sometimes more difficult to find
- some systems: difficult to monitor disintegration during SW delivery (retracted transducer)	- patient positioning for prevesical stones more difficult

Automatic positioning mode is available with some lithotriptors and in this mode the urologist marks the position of the stone on the monitor by moving the cross-hairs or pointing a light pen. The computer then determines the position of the stone relative to the focal point and initiates movement of the patient table appropriately.

Take Home Message (Lithotripter Technology: Past, Present and Future):

- Since the introduction of the Dornier HM3, lithotripters have become compact and transportable. This evolution has made lithotripsy more accessible but has introduced new problems such as the challenge of achieving good coupling with a dry treatment head.
- Lithotripters have employed three modes of SW generation: electrohydraulic, electromagnetic, and piezoelectric. Electromagnetic lithotripters deliver more consistent pulses than do electrohydraulic machines, and the shock sources have a much longer lifetime (millions of SW's).
- Electrohydraulic lithotripters tend to have a wider focal zone than do electromagnetic lithotripters, and generate lower acoustic pressures and lower energy densities.
- Most new lithotripters either have a measurably wide focal zone on the order of 17-18 mm, or they have settings that produce a relatively wide focal zone. There is considerable latitude to what lithotripter manufacturers may consider to be a "wide" focal zone.
- Lithotripters with two treatment heads (dual head lithotripters) have the potential to reduce treatment time by firing SW's on separate acoustic axes (alternating mode). Research shows that dual SW's can suppress or enhance cavitation to advantage, depending on timing of the pulses. Simultaneous pulses double acoustic pressures only in the focal volume, but shot timing is critical and difficult to control.
- Electrodes for EHL-SWLs wear down and must be replaced. New designs to dramatically improve electrode lifetime have been lithotripter specific as, so far, electrodes are not interchangeable.
- Imaging for stone localization is very effective, but imaging quality is rarely sufficient to determine when stone breakage is complete.
- Diagnostic US is available with many lithotripters but most urologists choose to use fluoroscopy for stone localization and monitoring during treatment.
- Acoustic coupling in dry-head lithotripsy is prone to failure. Handling and application of gel can introduce substantial defects that block SW energy. Patient movement and repositioning the patient can further introduce defects. Variability in coupling likely contributes to variability in outcomes.

III. PROBLEMS IN SWL THAT CALL FOR NEW TECHNOLOGY

The basic concept of SWL is very simple—stones can be reduced to gravel by treating them with SW's generated outside the body—and the ideal outcome is elimination of the stone without causing untoward collateral damage. This has proven to be harder to achieve than one might expect. Shock waves can cause tissue injury (see below) and when the dose is too great the injury can be severe. The challenge is to treat with as few SW's as possible, to maximize stone breakage while minimizing tissue damage. This problem is made difficult by a number of factors including poor and variable acoustic coupling, stone motion during treatment, the inability of current imaging methods to determine when stones are completely broken, and lack of an indicator that injury is occurring. All are problems that could be addressed with new technology.

1. ACOUSTIC COUPLING

It is difficult to achieve good acoustic coupling between the treatment head and the patient's skin. Air pockets get caught at this interface, reducing transmission of SW energy into the patient. Coupling is highly variable from attempt to attempt, and the quality of coupling is easily disrupted if the patient moves or is repositioned. In vitro studies have shown that defects in the coupling interface of only about 2% of the contact area can reduce the breakage of model stones by 20-40% [52]. This means that when coupling is poor it can take a significantly greater number of SW's to break stones. Coupling is extremely variable and in tests under controlled conditions the common method of applying gel produced defects ranging from 1.5% to 19% of the coupling area. It seems reasonable that poor coupling may be one reason why dry-head lithotriptors have not achieved the success rates reported for the water tub style Dornier HM3. Also variability in coupling could be a factor affecting variability in outcomes. At the present time there is no way to judge the quality of coupling during treatment. This may be a problem that could be solved using ultrasound imaging. As more lithotriptors become equipped with inline diagnostic US this technology could be used to assess coupling as well as targeting and monitoring of the stone. There may be other potential solutions as well, but regardless of the approach it would be welcome to see progress in this area.

2. STONE TRACKING

Stones are moving targets, and movement due to normal respiratory excursion is in the range of 2-5 cm and not in alignment with the acoustic axis. This can have a substantial effect on the ability to hit the stone. One in vitro study determined that for a lithotriptor with a focal width of 3-4 mm, operated at a SW-rate of 120 SW/min, stones measuring ~8 mm and moving through a 20 mm excursion cycle (8 cycles/min) were hit by fewer than 50% of the SW's that were fired [53]. This suggests that because of stone movement the overall treatment dose is at least twice what it needs to be, and that during a typical treatment session the kidney would be hit by a substantial number of SW's that are not contributing to stone breakage but may be contributing to collateral damage. It would be valuable to have a tracking system that permits SW's to be fired only when the stone is within the focal zone of the lithotriptor. Several targeting systems that include complex imagers and algorithms to track the stone, even lithotriptors designed to move the focal zone as the stone moves have been proposed, but none are currently used [54-56]. Piezoelectric lithotriptors (PEL) have the potential advantage that individual piezoceramic elements can be fired, and this has led to development of a PEL-based tracking system [57]. However, this lithotriptor did not break stones effectively. A new approach for real-time tracking has recently undergone in vitro testing and uses the principle of vibroacoustography to detect when the stone has entered the focal volume of the lithotriptor [58]. Such a system has the advantage of a high signal to noise ratio and US exposure levels below FDA safety guidelines. Thus, several methods for stone tracking have been developed and tested. Hopefully further progress in this area will result in a technique that has practical application.

3. DETECTION OF STONE BREAKAGE

In addition to the inherent ineffectiveness of lithotriptors due to poor coupling and because stones move with each breath, it is also likely that most patients are over-treated because the urologist has no reliable means to determine when the stone has been broken to completion. Imaging systems on lithotriptors tend to be excellent for localizing and targeting the stone, but with fluoroscopy or US it is very difficult to know when the stone has broken into fragments small enough to pass through the ureter. It is often possible to see an effect of treatment. Stones can sometimes be seen to move or jump upon being hit by SWs, and in some cases stones will appear less dense as the treatment progresses, suggesting that the stone is fragmenting into smaller pieces, which are beginning to disperse about the renal collecting system. However, the treatment endpoint is difficult to determine, as conventional imaging cannot distinguish between sizeable fragments and clusters of small fragments. With this limitation the urologist is left with the classic dilemma of whether to extend the session and risk over-treatment, or end the session and possibly have to re-treat. Also, one cannot rely too heavily on estimates of stone burden to determine the dose that will be needed, because SWL fragility is highly variable from stone to stone [12].

Some research has been conducted to find alternative methods to assess stone breakage. An effort has been made to correlate Doppler ultrasound with breakage, and it has been proposed that cavitation noise might be used to monitor breakage [59]. These in vitro studies are encouraging, as they document progress using a broadband receiver to detect resonant scattering when the stone is hit by SW's. When the stone fractured, the frequency of vibration increased and was inversely proportional to the size of the fragments. Early test results were highly repeatable, showing a spectral energy shift to higher frequencies as the stone broke into smaller fragments. Such a system will require further refinement, but would not be difficult to adapt to a clinical lithotriptor. Hopefully, this or some other method can be developed to help determine when stone fragments have been reduced to a critical size. This could be a tremendous benefit to improving the safety of SWL.

4. DETECTION OF TISSUE INJURY DURING TREATMENT

Current understanding of the mechanisms responsible for damage to the kidney during SWL (see below) implicates cavitation as a key player in the rupture of blood vessels. Cavitation may not act alone in initiating vessel breakage, shear stress may be involved, but animal studies have demonstrated that cavitation occurs at sites of hemorrhage in the kidney. Renal injury in SWL is dose-dependent—the more SW's delivered, the greater the damage. Whereas injury is cumulative, it appears that damage is not strictly additive. That is, damage does not initiate with the beginning of treatment and there appears to be a threshold for trauma to occur. A study in pigs treated with the Dornier HM3 (24 kV, 120 SW/min) has shown that quantifiable hemorrhage jumps dramatically between 1000 SW's (0.2% FRV) and 2000 SW's (~6% FRV) [60]. Where the injury threshold lies may depend on multiple factors including the acoustic output of the lithotriptor, the settings used for treatment, and the health of the patient. It would be valuable to have a means to detect injury as it is occurring, to know when the injury threshold has been reached.

A recent study describes an acoustic detection system that seems well suited to this task. The approach was to use focused directional transducers to listen for cavitation bubble noise and to correlate these signals with cavitation echogenicity visualized by diagnostic ultrasound [61, 62]. An important outcome of this work was the finding that B-mode ultrasound alone was a sensitive and accurate tool to detect cavitation in the kidney during treatment. More research needs to be done to characterize the severity of injury at the onset of cavitation within tissue, but this could be a very practical tool to help the urologist follow the progression of injury. Since some lithotriptors are already equipped with B-mode ultrasound for stone localization, this may be a realistic technique to pursue.

5. RADIATION PROTECTION

Although low dose x-ray exposure is available on some newer lithotriptors, patients and potentially the clinical team are exposed to ionizing radiation when fluoroscopic targeting is used. This is an area where improvements are needed.

6. ADAPTATIONS FOR TREATMENT OF OBESE PATIENTS

The increasing number of obese patients will make it necessary to provide devices that are designed for higher patient weight. The increased skin to stone distance presented in obesity also affects the penetration depth of the SW source and the quality of imaging, and the quality of acoustic coupling. Improvements are needed in all these areas.

Take Home Message (Problems in SWL that Call for New Technology):

- It is difficult to achieve good acoustic coupling between the treatment head and the patient, as air caught at this interface interferes with the transmission of SW energy. Coupling is variable and will degrade if the patient moves, but, unfortunately there is no method currently available to assess the quality of coupling during treatment.
- New technology is being developed to address several important issues in SWL.
  - It is feasible to actively track stones so that SW's are fired only when the focal zone is on target.
  - An US-based system that can detect when a stone has fractured has the potential to determine when stones have broken to completion.
  - Real-time acoustic monitoring to detect cavitation in tissue may soon be able to determine the injury threshold during SWL treatment.

IV. MECHANISMS OF SHOCK WAVE ACTION

1. THE ACOUSTIC FIELD OF SHOCK WAVE LITHOTRIPTORS

The principle physical property of a lithotriptor is the spatial and temporal distribution of the acoustic pressure field it produces. A typical shock wave measured in a Dornier HM3 lithotriptor is shown in **Figure 1**. The SW consists of a leading compressive phase, with about 40 MPa peak pressure and duration of 1 µs. The rise time (time for pressure to increase from 10% to 90% of peak amplitude) of the shock front is less than 5 ns in water and is much longer (around 70 ns) after passage through the body wall [43, 63]. The positive pressure phase of the SW is followed by a tail of negative pressure with peak amplitude of about –10 MPa and duration of 4 µs.

All lithotriptors produce waveforms that are strikingly similar, consisting of a leading compressive phase followed by a tensile tail [64, 65]. What dis-

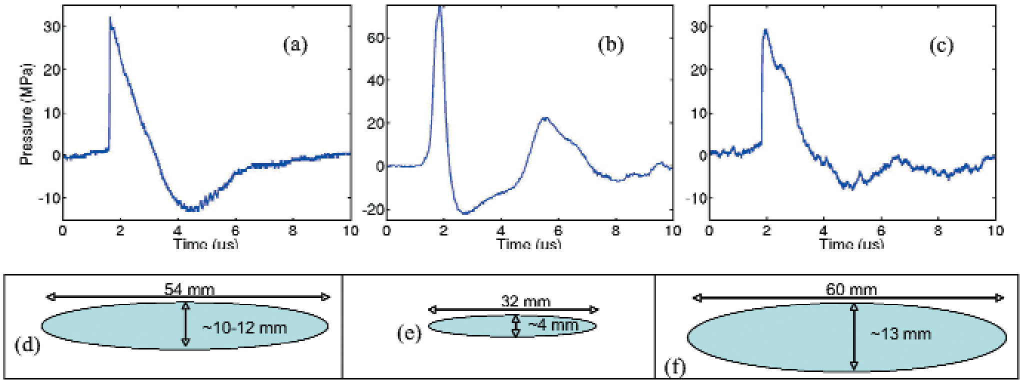


Figure 1. Measured waveforms at the focus of (a) HM3 (b) Storz SLX at E7 (c) LithoDiamond at 20 kV and scaled representations of the focal volumes for (d) Dornier HM3 (e) Storz SLX (f) LithoDiamond.

tinguishes one lithotriptor from another is the peak pressures it produces and the spatial extent of the acoustic field (Fig. 1). The measurements shown in Fig. 1 (a-c) were taken at the geometric focus of the lithotriptor. The physics of acoustic focusing is such that the pressure field is not focused to a single point but rather is distributed in space. A common method used to report the spatial extent is to determine the volume in which the pressure is above 50% of the peak pressure – commonly referred to as the -6 dB volume because in the decibel scale -6 dB corresponds to a 50% reduction in pressure. In lithotriptors this volume is typically cigar shaped, long in the direction of the acoustic axis and narrow in the lateral direction. In Fig. 1 (d,e,f) the approximate focal volumes are shown to scale. Thus, focal volumes can differ considerably in size, a feature that can have an important effect on stone breakage (discussed below).

The definitions of peak pressure and -6 dB focal volume do not provide a complete picture of the acoustic impact on a stone. The peak pressure represents only a single point on the waveform at one location in space. The -6 dB focal volume is a relative measure based on the peak pressure, rather than a specific threshold. As shown in Fig.1, the -6 dB focal zone of the Storz SLX is the volume where the pressure achieves or exceeds ~32 MPa but for the Dornier HM3 none of the waveforms (not even those at the focus) have enough amplitude to be included in the -6 dB focal zone of the Storz lithotriptor. Therefore although the -6 dB zone gives an indication of where a stone should be placed to achieve good breakage it does not show the limits of the region of high pressure. That is, for most lithotriptors acoustic pressures do not fall abruptly off axis, and in vitro studies have shown that stones can be broken even when they sit outside the focal volume. At present there is no metric available to determine the working volume of a lithotriptor. However, one metric that captures the entire waveform and its distribution in space is the acoustic energy. To determine the energy one must first calculate the pulse intensity integral (PII which has units J/m2) which is obtained by squaring the pressure waveform (Fig. 1) and integrating in time over the length of the pulse. The energy is then calculated by integrating the PII over an area in space. For example, if one considers the case of centering the focal zone of the Dornier HM3 (focal width ~10-12 mm) or the Storz SLX (focal width ~4 mm) on a stone that is 6.5 mm in diameter, even though the peak pressures generated by the two machines is different (HM3 ~32 MPa, SLX ~65 MPa) the energy incident on the stone is almost the same (HM3 5.3 mJ, SLX 4.8 mJ) [66]. Therefore just comparing peak pressures of a lithotriptor does not necessarily translate into the energy delivered into the stone.

2. MECHANISMS OF STONE COMMINUTION

Presently there is no consensus on precisely how shock waves fragment stones, but research suggests that a number of mechanisms are likely involved, and these can be broadly divided into ***direct stress*** and ***cavitation***.

Direct stress refers to the impact of the shock wave on the stone and the subsequent evolution of stress inside the stone. **Figure 2** shows a simulation of the stress waves resulting from the passage of a lithotripsy shock wave through a natural stone. The acoustic waves in the fluid surrounding the stone

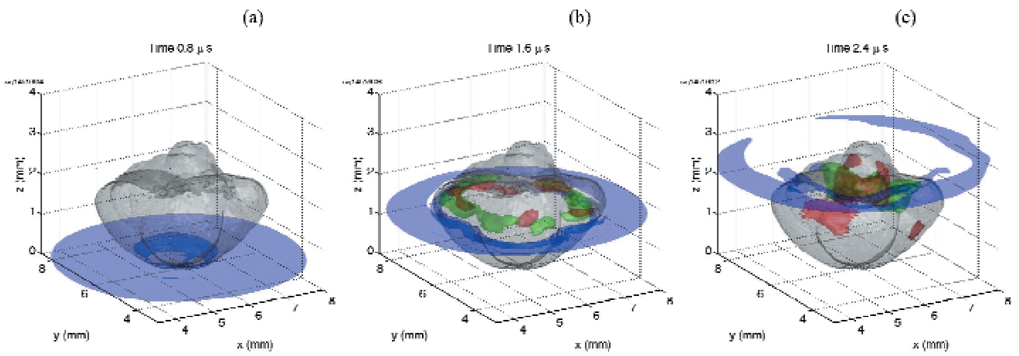


Figure 2. Snapshots from a 3D computer simulation of the passage of a shock wave through a kidney stone. The stone is predominantly calcium oxalate monohydrate with some focal spots of apatite. Blue shows the compressive phase of the incident shock wave. Green shows maximum shear stress in the stone (55 MPa). Red shows principal tensile stress in the stone (80 MPa). (a) The shock wave is just incident on the stone from below. (b) The shock wave in the fluid has reached to the middle of the stone. There is no indication of tension due to spall (red) at the distal surface of the stone however there is generation of shear (green) and tension (red) at the outer edges. (c) The shear waves have propagated to the centre of the stone to produce a large region of tension near the distal surface.

are also referred to as compressive waves because physically their effect is to compress the fluid. The stone can support two types of waves: compressive waves (known as P waves in seismology) which travel quickly, and shear waves (called S waves in seismology) that propagate more slowly. Although the incident wave in a fluid is purely compressive it can excite both compressive and shear waves when it passes into the stone. This depends on the properties of the stone and angle of the surface.

Most brittle solids, like kidney stones, are much weaker in tension than in compression and so regions of large tensile stress can be expected to make the material fail. Both the compressive and shear waves can produce tensile stress in a kidney stone. Early work suggested that the compressive wave may have played a dominant role through a process of spallation. The spall (or Hopkinson) effect occurs when the compressive wave in the stone reflects at the distal stone/urine surface. The reflection causes the leading positive pressure wave to invert in phase, and this large tensile wave is joined by the tensile phase of the incoming SW to create a very large tensile stress near the distal side of the stone [67-70]. This makes great sense in concept, however, the irregular geometry of most natural stones disrupts the constructive interference necessary to create a focus of tensile stress, and this is not conducive to spallation. In particular, for the simulation in Fig. 2 one would expect the spall effect to be present in the middle frame but there is no indication of large tensile stress near the distal surface.

Recent studies indicate that shear waves generated at the outer surface of the stone play a much greater role in the development of tensile stress inside a stone than does a mechanism such as spallation [71]. Shear waves are most efficiently produced at surfaces of the stone that create angles greater than about 20 degrees relative to the axis of the incoming SW and are generated by two mechanisms. First, the passage of the shock wave in the fluid surrounding the stone can be thought of as squeezing the stone from the outside and second, internal waves launch from points along the stone surface [71, 72]. In Fig. 2(b) the region of shear stress around the equator of the stone is due to these processes. The shear waves propagate toward the center of the stone where they combine to yield large tensile stresses. The last frame of Fig. 2 shows a region of high tensile stress in the middle of the stone due to the shear waves. In vitro experiments demonstrate that both types of shear waves (those that squeeze from the outside, and those that originate from the surface of the stone) are important in the fracture of artificial stones, and it appears that the spall effect contributes very little to this process [73].

We note that many materials fail readily under stress from shear, particularly if they consist of layered structures, as the bonding strength of the matrix often has a low ultimate shear stress. The compressive waves and shear waves can both result in shear stress inside the stone and therefore fragmentation of kidney stones may be a result of shear stress rather than tension [67, 68, 74-76].

a) Cavitation

refers to small bubbles/cavities that grow in the urine surrounding the stone due to the large negative pressure tail of the acoustic pulse. The bubbles can collapse with great violence and generate intense shock waves or very powerful microjets of fluid [77, 78]. Cavitation is principally a surface acting mechanism, and experiments indicate that it acts most strongly on the proximal (shock wave incident) surface of the stone [69, 79-81]. **Figure 3** shows high-speed movie images of the bubble cloud induced on the proximal surface of an artificial stone in response to a lithotripsy shock wave. Numerous studies indicate that cavitation plays a role in stone fragmentation, and there is strong evidence to show that cavitation is particularly important in grinding up small fragments that may not be conducive to fragmentation by direct stress effects [82].

One drawback of cavitation is that bubble growth pulls energy from the tensile phase of the SW [83, 84]. The more bubbles that form in the fluid surrounding the stone, the lower the amplitude and duration of the negative pressure in the pulse. This reduces the driving force for bubble activity that causes erosion at the stone surface. Since minute bubbles spawned by cavitation can persist between SW's, more cavitation occurs at faster SW-rates. This may explain why stone breakage is reduced at fast clinical SW-rate (120 SW/min) compared to slow rate (30-60 SW/min) [85, 86]. The increase in cavitation activity with rate may also explain why tissue damage increases dramatically when shock waves are delivered at a higher rate [87, 88]. The presence of cavitation in lithotripsy is likely an important contributor to the fragmentation process but it also acts as a limiter as to how fast shock waves should be delivered as too much cavitation reduces fragmentation and increases tissue damage.

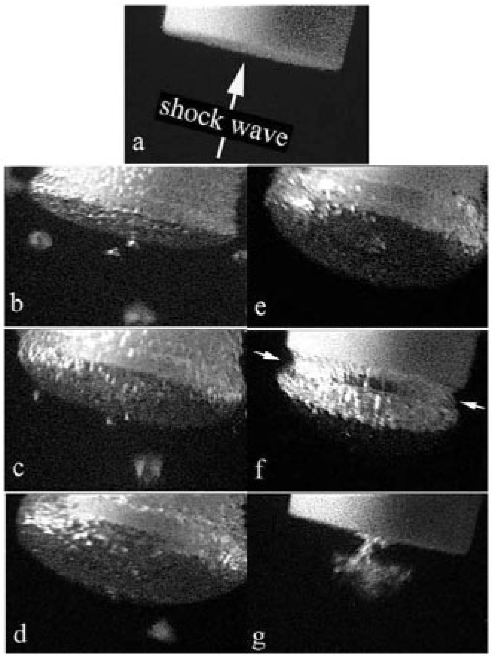


Figure 3. High-speed movie images of cavitation on the proximal surface of an artificial kidney stone.

We comment that, regardless of the mechanism(s) by which SWs impact stones, it is likely stones fragment through a fatigue process. ***Fatigue*** refers to the progressive development of cracks in a material over subsequent loading; in this case hundreds to thousands of shock waves [89]. The cracks are nucleated at sites of small imperfections that occur in almost all materials. The imperfections amplify stresses many fold and cause the imperfections to grow into microcracks. With an increasing number of shock waves the microcracks grow into macrocracks and eventually produce cracks large enough to induce failure [89]. Any of the mechanisms discussed above could drive fatigue.

b) The importance of focal width to the mechanisms of stone breakage

Recent studies suggest that the focal width generated by a lithotriptor plays an important role in stone breakage. The original clinical lithotriptor, the Dornier HM3 has long been considered to be a very effective machine. The HM3 has a relatively large focal zone (~8-12 mm depending on method of measurement) and moderate peak pressure (37 MPa at 18 kV). Subsequent lithotriptors have tended to be more tightly focused. At first view a tighter focal zone may seem advantageous as this should allow for more energy to be focused on the stone, with less acoustic impact on the surrounding tissue. A second advantage is that lithotriptors with narrower focal zones tend to produce less discomfort for the patient. This is because the diameter of the shock wave source is larger, spreading the area of SW entry at the skin. **Figure 4** shows how the focal width and the pressure at the skin vary as a function of diameter of the shock wave source. By making a larger diameter source the acoustic pressure at the

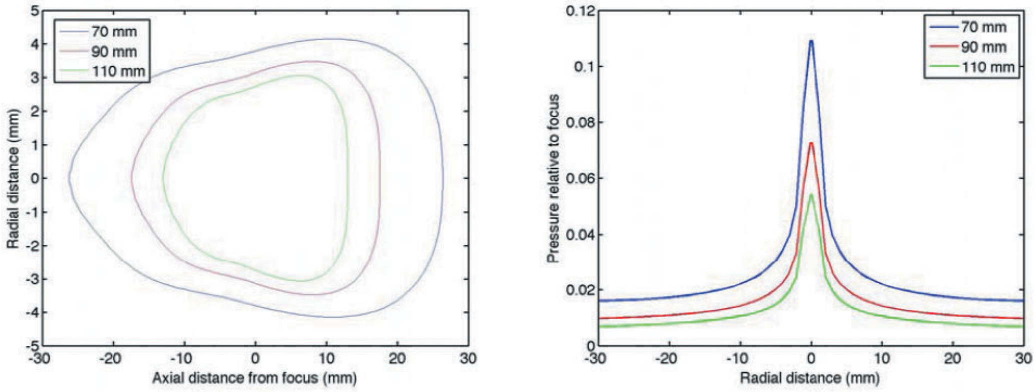


Figure 4. Calculations of the effect of the diameter of the shock wave source on the size of the focal zone and pressure at skin. Left: The -6 dB contour showing the size of the focal zone for source radii of 70, 90 and 110 mm. The focal zone decreases as the source is made larger. Right: Pressure distribution at the skin (taken to be 11 cm from the focus). For the larger aperture the pressure is less than half that of the smaller source.

skin is reduced and general anesthesia can be avoided.

However, there are potential drawbacks with a narrow focal zone. Since the kidney moves due to respiratory motion the stone tends to move in and out of the focal zone. **Figure 5** shows in vitro fragmentation in a broad and a narrow focal zone lithotriptor for the case where the stone is in motion. For the narrow focal zone lithotriptor even 10 mm of motion resulted in a 50% reduction in fragmentation whereas the broader focus lithotriptor tolerated more than 35 mm of motion before performance was reduced equivalently [53].

Another potential drawback with a narrow focus lithotriptor is that for larger stones the energy deposited into the stone can be low. **Figure 6** shows the energy deposited into a stone as a function of focal size of the lithotriptor. For a 4 mm diameter stone the energy deposited into the stone is about 5 mJ but drops dramatically for focal widths less than the size of the stone. For a 10 mm diameter stone the energy deposited by a 10 mm focal width is about 5 times that of a 4 mm focal width. A further issue with narrow focus lithotriptors is that the shear wave mechanism described above requires that the outer surface of the stone be subject to high-pressure waves to generate large stresses inside the stone [71]. **Figure 7** compares the simulated tensile stress inside a natural kidney stone for a focal zone (4 mm) that is about the same size as the stone and a focal zone (8 mm) much larger than the stone. The tensile stress is much higher and spread over a larger volume for the case of the wider focus.

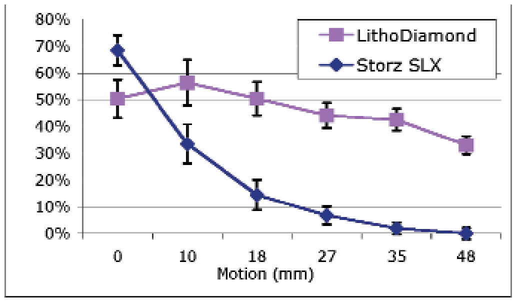
Recent research has provided sound physical evidence as to why a lithotriptor with a broader focal zone should fragment stones more effectively. The community appears to have responded because, as described in Section B, a number of lithotriptors recently released onto the market have a broader focus.

3. THE PHYSICS OF TISSUE DAMAGE

Given that the shock wave is a mechanical insult to the tissue presumably all bioeffects have a mechanical genesis to them. The thermal effects associated with a clinical dose of SW's results in a temperature elevation of less than 1ºC and is considered negligible [90]. The mechanical mechanisms by which shock waves induce tissue damage are the same as in stone fragmentation: direct stress and cavitation.

It is generally accepted that cavitation plays a significant role in tissue damage in shock wave lithotripsy. Cavitation activity in the kidney has been detected in both animal models and in patients during shock wave lithotripsy [62, 80, 91]. Studies that have attempted to enhance cavitation have seen increases in tissue damage, for example, when shock waves have been administered to animals after the injection of contrast agents, which act as cavitation nuclei, widespread tissue damage has been reported [92]. Likewise studies that have attempted to suppress cavitation by modifying the waveform or using overpressure or SW timing to interrupt the bubble growth and collapse cycle have seen a reduction in tissue damage [93-95].

However, cavitation may not be the whole story.



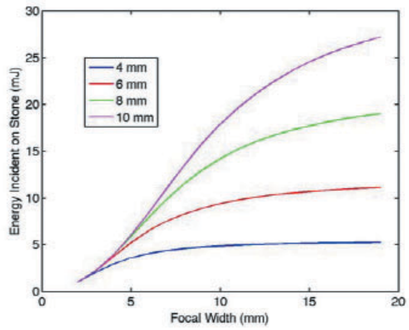


Figure 5. Effect of stone motion on fragmentation efficiency of a LithoDiamond (EHL with broad focus) and a Storz SLX (EML with narrow focus). The fragmentaion efficiency of the SLX is better at the focus but drops of dramatically even for 10 mm of motion. The fragmentation performance of the LithoDiamond is robust to stone motion.

Figure 6. Calculation of the energy deposited into a stone as a function of focal width of the lithotripter. For these calculations it was assumed that the pulse intensity integral at the focus was constant at 0.4 mJ/mm2. For the 4 mm stone it can be seen that the energy is about 5 mJ for focal widths greater than about 5 mm, that is the wave is completely enveloping the stone for focal widths greater than 5 mm. However, for a 10 mm stone the energy only starts to asymptote for focal widths of 20 mm.

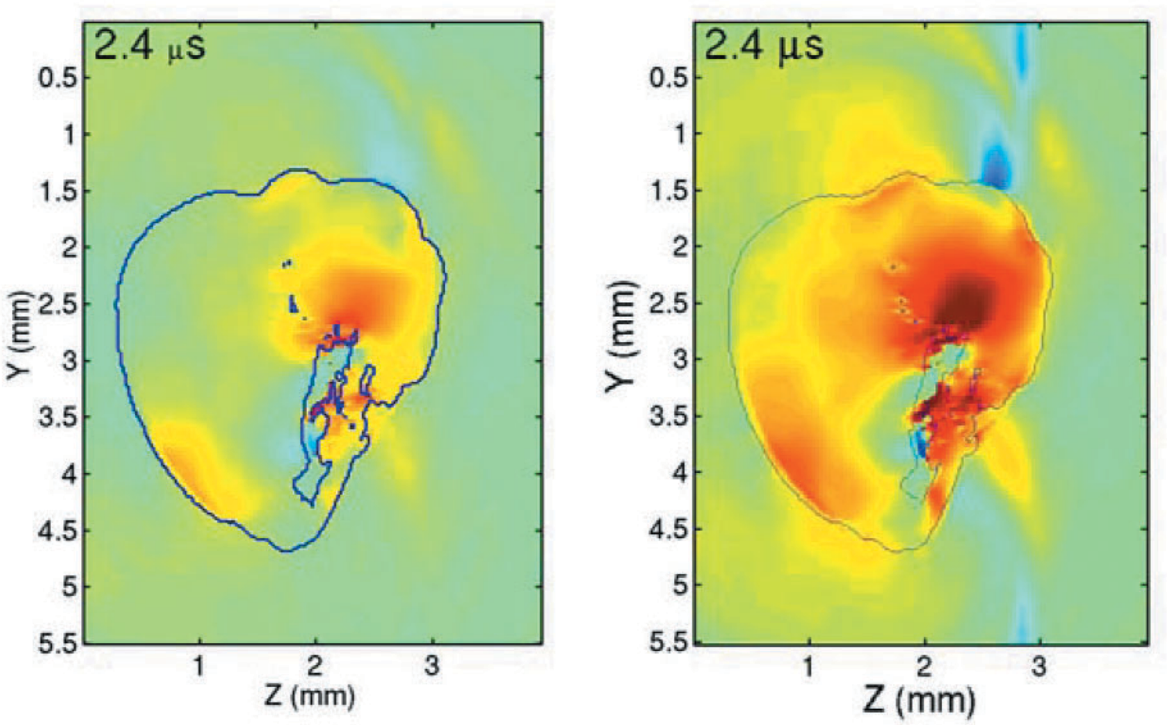


Figure 7. Comparison of the tensile stress generated inside a natural stone for a focal width of 4 mm (left) and 8 mm (right). The larger focal width produced much higher tension due to the presence of shear waves generated at the outer surface of the stone. The volume of stone with tensile stress greater than 80 MPa is 3.8 % for the 8 mm focal width but is only 0.04% for the 4 mm focal width. For the 4 mm focal width to generate the same volume of high stress as the 8 mm case the peak pressure would need to be 74 MPa - a factor of two higher.

Studies using a pig model have shown that damage is initiated in the small capillaries of the renal medulla. The classic model of cavitation damage is that the cavities exist in an infinite fluid and grow to diameters of the order of 1 mm before collapsing violently. It is the violence of the collapse that results in damage to the tissue. The small capillaries are less than 10 µm in diameter and do not provide a sufficient fluid space to allow for large expansions of bubbles.

Therefore it appears that some other mechanism may be required to produce the initial damage to the capillaries. Rupture of the vessels will result in pools of blood in the tissue in which cavitation bubbles can grow and collapse violently leading to significant tissue damage. One possibility for the initiating mechanism is cavitation related. Studies have shown that the initial growth of the bubbles can strain an artificial vessel wall and eventually lead to rupturing of the vessel [96]. A second possibility is shear stress induced by the shock wave. The shear stress could be induced by the presence of inhomogeneities in the tissue [89]. Another shear stress argument relies on-individual shock waves to leave a small amount of net deformation of the tissue, that is, after the passage of a shock wave the tissue has not returned to its initial position. The elastic response of the tissue means that it will return to its initial condition but this depends on the time scale of the tissue and this appears to be on the order of 1 second for kidney tissue. Numerical modeling suggests that if shock waves are delivered fast enough the shear strain in the tissue can accumulate until a critical level is reached where capillaries rupture and blood pools, creating conditions ripe for cavitation and further injury [97].

In conclusion, current evidence indicates that cavitation dominates the mechanical side-effects observed in tissue damage, however, cavitation may require a direct stress mechanism (e.g. cumulative shear) to initiate bleeding before cavitation can commence.

Take Home Message (Mechanisms of Shock Wave Action)

- All lithotriptors are basically the same—they all produce a similar signature waveform.
- What makes one lithotripter different from the next is the dimensions of its acoustic field, and the peak pressures it generates.
- Peak pressure as a measure of acoustic output can be misleading. A better metric is the energy delivered to the stone (or tissue).
- The dimensions of the focal zone do not define the limits of high pressure of the shock pulse, and tissue can be damaged or stone breakage can occur outside the focal zone.
- SW's break stones through a combination of direct stress and cavitation.
- A critical form of direct stress is shear produced as acoustic waves strike irregularities at the stone surface and propagate as inwardly directed waves (internal waves) to generate high tensile stress within the stone.
- Urinary stones are brittle solids that fail in tension or under stress from shear.
- Cavitation bubbles form at the stone surface and collapse with great force, generating powerful secondary SW's or fluid micro-jets.
- Cavitation is most effective in breaking up stone fragments too small to be broken by direct stress.
- More cavitation bubbles form at fast SW rate than at slow rate.
- SW's fired at fast rates (e.g. 120 SW/min) are less effective in stone breakage than SW's at slower rate because the greater cavitation at fast rate pulls energy from the SW. Stones break significantly better when SW's are fired at slow rate.
- Stones break better when the focal zone is wider than the stone.
- Because stones move due to respiratory excursion, a wider focal zone lithotripter will subject the stone to more incident SW energy, and breakage will be more effective than with a narrow focal zone machine.
- Cavitation within blood vessels is believed to cause vascular trauma.
- Shear stress has the potential to cause vessels to rupture, particularly when SW's are fired at 60 SW/min and faster.

V. LITHOTRIPSY ADVERSE EFFECTS: RENEWED CONCERN FOR LONG-TERM CONSEQUENCES

It is now firmly established that tissue injury can be a consequence of SWL, and this has been the topic of numerous reviews [60, 98-101]. We know that SW's can rupture blood vessels in the kidney, can damage renal glomeruli and tubular epithelial cells, and that this injury leads to focal inflammation and scar formation with subsequent loss of functional renal volume. It has also been shown that whereas SW trauma tends to be localized to the region in and around the focal volume of the lithotriptor, injury is not always limited to the focal zone and can occur in surrounding organs.

Acute SW injury tends to be well tolerated by most patients but in some individuals this damage can be severe. Reports include the occurrence of unmanageable parenchymal hemorrhage and the formation of massive subcapsular hematomas leading to acute renal failure, even kidney loss [102-107]. Such catastrophic events are likely very rare, but the fact that SWL can have such undesirable consequences is still cause for concern.

Perhaps a more pressing issue is the realization that lithotripsy has the potential to lead to long-term adverse effects. In particular there is concern that SWL may exacerbate existing hypertension or lead to new-onset hypertension, that a history of multiple lithotripsies could promote the development of diabetes mellitus, and that repeated SWL damage to the renal papilla might affect a progression in the pathology of stone disease [60, 101]. The link between SWL and hypertension was first observed nearly 20 years ago and has been followed by numerous reports including a prospective study showing a significant increase in intrarenal resistive index in patients 60 years of age and older [108, 109]. Although hypertension is most often readily manageable, this is clearly a serious unwanted complication and the finding that age is a risk factor could affect treatment planning for older patients.

A potentially more difficult situation for chronic stone patients is the possibility of an association between lithotripsy and the development of diabetes mellitus. In 2006 the Mayo Clinic group reported findings of a retrospective case-control study evaluating long-term effects for patients treated in 1985 using the Dornier HM3 lithotriptor (a 19 yr follow-up) [110]. It was observed that patients treated by SWL were significantly more likely to develop diabetes mellitus than non-SWL controls. The occurrence of diabetes in this group was also associated with the treatment dose, both the number and intensity of SW's. The study had several noteworthy limitations including retrospective and self-report design, a larger stone burden in the SWL group and no consideration for family history for diabetes. Clearly, more research is needed in this area, but the results suggest the sobering possibility that SWL could result in a serious, life-altering condition.

A recent study suggests the possibility that multiple lithotripsies may further complicate or exacerbate stone disease [111]. Parks et al looked for factors that might explain the confirmed increase in calcium phosphate stones over the past three decades [111, 112]. Their analysis showed a positive correlation between the calcium phosphate content of stones and the number of SWL sessions per patient. Calcium phosphate stone formers underwent more lithotripsies than did calcium oxalate stone formers and the number of SWL sessions was highest for patients with brushite stones. The implication is that a history of multiple treatment sessions may be creating tissue injury that affects stone formation, resulting in the production of a stone type that is more difficult to treat, and a background pathology (i.e. tubular atrophy and papillary fibrosis) that is more deleterious to the kidney [113].

FURTHER PERSPECTIVE ON ADVERSE EFFECTS

Lithotripsy remains a very important treatment option that is well suited for the removal of otherwise uncomplicated upper tract stones. The fact that SWL can cause injury and that multiple lithotripsies have been linked to potentially serious long-term effects cannot be ignored. Shock wave injury is a reality. The challenge is to find ways to minimize adverse effects, and do this without neutralizing the effectiveness of shock waves. It should be appreciated that considerable progress is being made on this front (See Section VI-2, below).

Take Home Message (Lithotripsy Adverse Effects)

- Lithotripter SW's cause tissue injury—the damage is primarily a vascular lesion.
- SWL injury is not limited to the region of the focal volume, and can affect adjacent organs.
- SWL injury to the kidney is dose-dependent, so it makes sense to minimize the number and energy of SW's during treatment.
- Acute SW injury to the kidney can initiate an inflammatory response that progresses to scar formation and loss of functional renal volume.
- Acute injury involving frank hemorrhage can lead to severe adverse effects including acute renal failure or kidney loss, but such complications are rare.
- SWL has the potential to lead to long-term adverse effects, and evidence suggests several possible outcomes, including:
  - New-onset hypertension in elderly patients
  - Exacerbation of stone disease (linked to multiple lithotripsies)
  - Increased likelihood of developing diabetes mellitus

VI. IMPROVING "BEST PRACTICE" IN SWL

1. THE STANDARD FOR CURRENT TREATMENT

Although SWL continues to be widely used as a first or second line treatment modality for urolithiasis around the world, there are currently no globally accepted published guidelines regarding the pre-operative, intra-operative and post-operative assessment and management of patients undergoing SWL. A suggested clinical care pathway is offered in **Figure 8**, although this may call for modification based on local health system resources and biases.

a) Pre-SWL Assessment

A focused medical history and physical examination are essential in any patient being considered for SWL therapy. A history of urolithiasis and previous SWL treatment is assessed, along with urologic disorders and renal disease. Bleeding disorders, including a family history of bleeding problems, should be assessed. All co-morbidities should be evaluated to determine if the patient is fit enough to undergo SWL therapy. Physical examination needs to include vital signs including blood pressure measurement. Systemic examination of the cardiopulmonary systems should be completed and abdominal examination assesses for a pulsating abdominal aortic aneurysm, a renal arterial bruit and costovertebral angle tenderness.

Pre-SWL investigations are required to ensure the risk of intra- and post-operative complications is

PRE-OP SWL ----------------------------------	INTRA-OP SWL --------------------------------------	POST-OP SWL
History	IV access for analgesia and appropriate anesthesia	Observation with vitals q15mins x 1 hour
Previous stones and SWL treatment	Monitor for HR, BP and O_2 saturation	D/C home with instructions:
Patient/family Hx of bleeding disorders	SW-rate 60-90 SW/min	Increase fluid intake
Patient/family Hx of renal disease	Total shock waves: few as possible to minimize injury	Analgesics PRN
Symptoms and signs of recent UTI	Use pulse progressive fluoroscopy	Strain urine & collect fragments
		Admit to hospital PRN only
Physical examination		
Blood pressure		
Pulsating abdominal mass or bruit		*Follow-up*
		Routine imaging @ 3 months
Investigations		KUB & U/S, *or*
Urinalysis		CT scan (radiolucent stone)
Urine culture		Early imaging @ 2 weeks PRN
KUB x-ray & U/S abdomen, *or*		
CT scan abdomen/pelvis		
ECG (M > 40 years, F > 50 years)		

Figure 8. Recommended clinical care pathway for "Best Practice" in SWL

minimized. It is particularly important to determine that SWL is an appropriate form of therapy for the patient and stone, and that the patient does not have a concurrent urinary tract infection or a bleeding disorder. As such, mandatory investigations include urinalysis and appropriate imaging for all patients. Urine culture is required if urinalysis shows pyuria. Pre-SWL imaging will depend on available modalities and may include KUB, renal ultrasound, computed tomography (CT) scan of the abdomen/ pelvis, or intravenous pyelogram (IVP). CT is recommended, as the presence of CT visible internal structure within stones is a valuable indicator of stone fragility [5, 6]. Blood work studies, including complete blood count, coagulation parameters and renal function, are performed as indicated by the patient's history.

Electrocardiogram should be done in male patients over the age of 40, female patients over the age of 50 and any patient with a history of any kind of cardiac disease. All investigations should be performed no more than 2 or 3 months before SWL and need to be repeated if clinically indicated.

Patients should restrict their diet and fluid consumption at least 4-6 hours pre-SWL in the rare event that a general anesthetic is required. Many lithotripsy units have a surgical care pathway that includes taking a laxative the day before SWL. All patients need to arrange transportation to and from the lithotripsy unit by a responsible adult. Patients who live more than a few hours by car from the lithotripsy unit or hospital need to arrange an overnight stay in same city before returning home the next day.

Table 5. Contraindications to SWL

- Absolute (worldwide, do not vary from center to center)
- Pregnancy
- Uncorrected bleeding disorder
- Active sepsis or untreated urinary tract infection
- Untreated obstruction distal to the stone

- Relative (may vary from center to center)
- Stone Factors

- Size: large stones > 2cm maximum diameter or staghorn
- Location: lower calyceal, especially if > 1cm
- Number: more than 1, especially if large or in different locations
- Composition: hard stones such as calcium oxalate monohydrate, calcium phosphate or cystine
- Previous failed SWL for same stone
- Patient Factors
- Obesity
- Uncontrolled hypertension
- Proximate aneurysms
- Cardiac pacemakers
- Significant cardiopulmonary disease
- Inability to be properly positioned (ie. orthopedic deformity)
- Severe gastrointestinal disease
- Impaired cognitive ability

Contraindications to SWL are listed in **Table 5**. Absolute contraindications are widely maintained and do not vary from center to center. Women of childbearing age have been historically excluded from SWL of middle and distal ureteral calculi because it was thought that the effect of shock wave energy on the ovary might be deleterious. This has been investigated in animal models and clinical studies. McCullough and colleagues reported that shock wave energy did not have a significant impact on rat ovarian function and did not cause teratogenic effects in offspring [114]. Vieweg and associates performed a clinical retrospective study on the possible adverse effects of SWL on the female reproductive tract and found that SWL of lower ureteral calculi did not affect female fertility [115]. Erturk and associates also reported that SWL was a safe treatment modality for women of reproductive age with distal ureteral calculi [116]. However, the aforementioned studies are limited by small numbers of subjects, so it is difficult to draw generalizable conclusions. The use of SWL in the pediatric population is a similarly unresolved issue, as there are no prospective studies evaluating the effect of SWL on the pediatric kidney. In a porcine model, the relative size of the SWL-induced lesion in a juvenile kidney is significantly larger than the relative size of the SWL-induced lesion in an adult kidney [117]. Therefore, the safety of treating women of childbearing age and younger with SWL has not been established.

There are several relative contraindications to SWL and these may vary somewhat from center to center, country to country or lithotriptor to lithotriptor.

Certain stone factors must be considered pre-SWL, including stone composition, stone location, stone size and number of stones. Any patients with a known history of hard stones (calcium phosphate, calcium oxalate monohydrate or cystine) are not good candidates for SWL. Results of SWL therapy for lower calyceal stones, especially if greater than 1cm in diameter, are poor. Larger renal stones (staghorn or diameter greater than 2.5 cm) should not be treated with SWL. If a stone has previously failed SWL therapy, especially if there was no fragmentation despite good stone localization, another treatment should be pursued. Relative contraindications may also be related to patient factors. Obesity may render stone localization or targeting difficult or impossible. Poorly controlled hypertension may result in an increased incidence of post-SWL perirenal hematomas.

Although most centers are now able to perform SWL safely in patients with most types of cardiac pacemakers, SWL is still contraindicated in this patient population in some centers. Regardless, any patient with a pacemaker should have a formal cardiology consult before their SWL treatment. Any patient with severe cardiac or pulmonary disease, or any patient in whom a general anesthetic in not safe, should not undergo SWL therapy because of the small chance of requiring conversion to a general anesthetic during SWL therapy. There are differing views on the discontinuation of anti-platelet agents such as aspirin and non-steroidal anti-inflammatory drugs (NSAIDS) before SWL, and for this reason, some centers will treat patients on these agents but most centers insist on them being discontinued for a minimum 7-10 day period pre-SWL in order to ensure normal platelet function at time of SWL to minimize the risk of hemorrhage [118-121].

Any kind of arterial aneurysm (renal, splenic, aortic) that is in the vicinity of the F2 will contraindicate SWL in many centers. Any congenital or acquired disorder that prevents proper patient positioning for SWL (orthopedic or spinal deformity) may prevent SWL from being possible. Any congenital or acquired renal disorder (ie. horseshoe kidney, ectopic kidney) may be associated with a low success rate with SWL due to abnormal renal drainage and prohibition of prompt clearance of stone fragments. Patients with gastrointestinal disorders, especially inflammatory bowel disease, may not be suitable candidates for SWL because of the risk that SWL will exacerbate their condition and symptoms. SWL therapy may not be suitable for cognitively impaired patients who cannot understand and cooperate during the procedure.

Renal drainage by ureteral stent or percutaneous nephrostomy is required before SWL when there is renal obstruction or impacted stone(s) associated with significant hydronephrosis, the stone is large (ie. greater than 1.5cm in the kidney or 1.0cm in the ureter), there is evidence of pyonephrosis, stone localization is difficult due to poor visualization of the stone, or if SWL is being undertaken in a solitary or transplanted kidney.

Antibiotics are required before SWL when the patient has symptoms or signs of a UTI with pyuria, a positive urine culture, or both [122]. There are no published guidelines about the use of specific antibiotics pre-SWL and therefore antibiotic therapy must be directed to the culture and sensitivity report. SWL therapy should be deferred until the urine is sterile.

b) Intra-operative Management

All patients undergoing SWL should be adequately monitored during the procedure with oxygen saturation, blood pressure and heart rate measurements. Intravenous access is required for anesthesia and analgesia. Although SWL is usually done under neurolept anesthesia, in some centers it is still done with a general anesthetic. The use of prophylactic antibiotics is somewhat controversial due to conflicting studies in the literature [123-126]. Most urologists and lithotripsy units do not routinely use prophylactic antibiotics in patients with a sterile urine pre-SWL.

The urologist controls three treatment parameters during SWL: the total number of shock waves administered; the rate of delivery of shock waves; the voltage (or energy) of the shock wave generator. The total number of shock waves administered varies between centers but most centers administer between 1500 and 3500 shock waves per treatment. Concern over the potential for SWL-induced adverse effects (discussed above) is good reason to keep the SW dose as low as possible. Shock waves are usually delivered at a rate of 60-120 SW/min. Slow rate is preferable, as patient studies have shown improved outcomes at reduced SW-rate (see below) [85, 86, 137, 138]. The power setting should be set low and gradually increased to the working setting (rarely the highest setting). Such a ramping protocol is often done to help the patient adapt to treatment, but recent research in experimental animals has shown that SW-intensity-ramping has a significant tissue protective effect (see below) [139].

Stones in the kidney or proximal ureter can be targeted using fluoroscopy or ultrasound and mid-ureteral and distal ureteral stones require fluoroscopic targeting. Pulse progressive fluoroscopy can be used to minimize ionizing radiation exposure. The process of stone comminution or fragmentation is monitored by fluoroscopy or ultrasound, and treatment should be terminated when it is estimated that fragments are small enough to be voided in the urine or when the maximum number of shock waves has been administered.

c) Post-SWL Treatment Plan

Immediately following SWL, patients should remain monitored for at least 1 hour with serial vital signs. Some centers routinely obtain a KUB x-ray before discharge to assess fragmentation. Patients are normally discharged home with instructions to increase their daily fluid intake and a prescription for an analgesic such as ketorolac tromethamine, acetaminophen with codeine, or morphine. As mentioned earlier, antibiotics are not universally prescribed post-SWL but are still routinely used in many centers on a prophylactic basis despite clear lack of evidence-based medicine to support their use. There are still some centers in which SWL is an inpatient procedure, but for the vast majority of centers, SWL is done on an outpatient basis.

Since the recent advent of medical expulsive therapy for ureteral calculi, the role of medical expulsive therapy post-SWL to improve spontaneous passage of stone fragments has been the subject of clinical trials [127]. Micali et al showed a significant increase in stone free rates in patients treated with medical expulsive therapy (nifedipine and tamsulosin) versus control patients [128]. However, at the present time, there is insufficient evidence in the literature to recommend routine use of medical expulsive therapy post-SWL.

There are no widely accepted guidelines regarding post-SWL imaging and follow-up. For radiopaque stones, most urologists order a KUB x-ray and for radiolucent stones a CT scan or ultrasound is required. The timing of post-SWL imaging varies widely from center to center. Some centers routinely obtain post-SWL imaging 2 weeks post-SWL but many endourologists feel that there is no role for routine imaging less than 3 months post-SWL because stone fragments may take several weeks to pass after SWL. Of course, when clinically indicated, imaging is done at any time post-SWL.

Determining stone free rates following SWL has been challenging because of the conflicting definitions and significance of "clinically insignificant residual fragments" (CIRFs) in the literature. Some studies adhere to a strict definition of a stone free state that counts any fragment of any size as a residual fragment, while other authors have allowed fragments up to 3, 4 or 5mm to not count as residual fragments. Some experts believe that any residual fragment of any measurable size should be considered clinically significant, while others believe that any fragment less than or equal to 5mm is clinically insignificant. The significance of CIRFs in the literature is controversial, with some studies showing that CIRFs usually pass spontaneously without significant complications, while other studies show that almost one-half of patients with CIRF's run into problems [129-131]. Indications for ancillary treatment depend on fragment size, location and patient symptomatology. Ancillary treatment modalities include repeat SWL, retrograde ureteroscopy, and percutaneous antegrade nephrolithotripsy.

2. NEW TREATMENT STRATEGIES TO IMPROVE OUTCOMES

Advances in lithotriptor technology may eventually deliver substantive improvements in hardware that make lithotripsy safer and more effective. However, recent advances in basic research point to strategies that can be used to improve outcomes with our existing machines.

a) Shock Wave Rate

The initial work addressing the effect of shock wave rate on stone fragmentation was performed by Vallancien et al, who utilized an *in vitro* piezoelectric model and reported that stones treated at a slower rate fragmented better than did stones treated at a faster rate [132]. Subsequent in vitro and in vivo experiments have confirmed this finding [84, 133-135]. Interestingly, the initial clinical evaluations of slow versus fast shock wave treatment rate were randomized controlled trials [85, 86, 136, 137]. These four randomized controlled trials were conducted in four different countries, inclusion criteria varied among studies, stone size could not be compared across studies, the lithotriptors used were different in all studies, and the definition of success varied. Three of the studies reported improved outcomes at slower rate. One study found no effect of SW-rate [136]. Nonetheless, a meta-analysis of these studies demonstrated a 10% greater likelihood of a successful treatment outcome when SWL is performed at a rate of 60 shocks per minute rather than 120 shocks per minute [138]. Despite the heterogeneity of data, there was no consistent source of bias among the studies detected by the meta-analysis. Thus it can be concluded that stone breakage is improved by slowing the rate of SW delivery.

A recent study with experimental animals indicates that SW injury to the kidney is dramatically reduced when the rate of SW delivery is slowed [88]. Pigs treated with 2000 SW's at 120 SW/min (24 kV) using the Dornier HM3 had a lesion measuring 4.6±1.7% of functional volume, while treatment at 30 SW/min reduced the lesion to less than 0.1% FRV (0.08±0.02%, $p<0.005$). A similar result was observed when injury was assessed using the XX-Es lithotriptor. In that study pigs treated with the recommended clinical dose for the XX-Es (1500 SW, 17 MPa at 9.3 kV, 27 SW/min) showed no significant alteration in renal hemodynamic function, and no morphologically detectable tissue injury [48]. Pigs treated with the same number of SW's at comparable settings (37 MPa at 18 kV, 30 SW/min) with the HM3 lithotriptor showed a modest fall in glomerular filtration rate and renal plasma flow, and lesion size measured only 0.1%FRV.

Thus, reducing the rate of SW delivery had a significant protective effect on the kidney. The slow SW-rate (~30 SW/min) used in these studies was considerably slower than is typically used (120 SW/min) by most urologists and further studies are needed to determine if reducing the rate to 60-90 SW/min is also beneficial. Since clinical studies have shown that stone breakage is better at slower rates, it appears that reducing SW-rate is a sensible strategy to improve both the safety and the efficacy of SWL.

b) "Pre-treatment" at low Shock Wave Energy

SWL induces a vasoconstrictive response within the renal vasculature, and recognizing this phenomenon Willis and associates reported a practical way to protect the treated kidney from the lesion that generally results from a clinical dose of shock wave energy [139]. Prior to administering a clinical dose of SW energy with a Dornier HM-3 lithotriptor, a pre-treatment dose of 100 to 500 SW's at low energy is applied (12 kV, 120 SW/min). Following this short exposure to low energy SW's, the full clinical dose is given to the same site. Under these conditions, the normal lesion produced by SWL, which in their porcine model occupied ~6% of the renal parenchyma, was reduced to 0.3%, a highly significant change. Possible hypotheses for the mechanism of this effect include the ideas that vasoconstriction induced by the initial, priming dose of SW's may make certain vessel walls less susceptible to cavitation or shear, or may suppress cavitation.

c) Attention to the quality of acoustic coupling:

In vitro studies modeling the interface between the treatment head of the lithotripter and the skin of the patient suggest that it is difficult to achieve good acoustic coupling [52]. Air pockets can get trapped at the coupling interface, reducing the transmission of SW energy and increasing the number of SW's needed for stone comminution.

De-coupling and re-coupling to simulate repositioning the patient during treatment introduces more air pockets, further degrading the quality of coupling. There is currently no way to monitor coupling during treatment, but simple steps can be taken to reduce the introduction of defects to the coupling interface. Coupling can be improved by minimizing the handling of the coupling medium. Dispensing gel from a squirt bottle introduces air pockets and rubbing the gel by hand to cover the treatment head and skin further degrades the coupling interface. Improved coupling can be achieved by delivering a large volume of gel (~250 ml) as a mound dispensed from the stock jug (not a squirt bottle) to just the treatment head (not to the skin) and allowing the gel to spread upon contact between the treatment head and the skin.

d) Summary and Perspective

Most simple upper urinary tract calculi can be treated with SWL. The recommended clinical care pathway for "best practice" in SWL is presented in Figure 1, and adherence to this plan minimizes the morbidity of SWL while maximizing stone free rates worldwide. Although there are few parameters within lithotripsy that the urologist may manipulate (i.e. SW number, power setting, SW rate), recent evidence suggests that administering shock waves at a rate of 60 per minute (or slower), ramping up of SW energy, and close attention to the process of coupling could significantly improve outcomes.

Take Home Message (Improving "Best Practice" in SWL):

- Currently there are no globally accepted guidelines for pre-, intra-, and post-operative management of patients undergoing SWL. Governing bodies such as the AUA and EUA should consider investing effort in this direction.
- Outcomes assessment for SWL has not been standardized, and the absence of uniform criteria for judging stone-free rate and success rate hinders critical analysis comparing various treatment protocols and different stone technologies.
- The proven potential for adverse effects in SWL demands that success in lithotripsy is judged not only on efficacy, but on safety.
- Research suggests several strategies that can be followed to improve the efficiency of stone breakage, and reduce adverse effects.
  - Stone breakage is significantly improved by slowing the SW rate.
  - Renal injury in pigs was virtually eliminated when treatment was performed at ~30 SW/min.
  - Initiating treatment using low energy SW's before increasing the power setting has a remarkable protective effect to reduce renal injury.
  - Quality of coupling between the treatment head and skin can be improved significantly by minimizing handling of the coupling gel.

B. INTRACORPOREAL LITHOTRIPSY

Broadly, intracorporeal lithotripsy can be divided into two categories: rigid and flexible. Both types of systems have proven to be valuable for specific applications suited to their unique design characteristics.

I. RIGID INTRACORPOREAL LITHOTRITES

Three distinct types of rigid intracorporeal lithotrites are available, including ultrasonic, ballistic (pneumatic and electrokinetic), and combination (ultrasonic-pneumatic) systems (**Table 6**).

1. ULTRASONIC LITHOTRITES

Ultrasonic lithotripsy was first used in an experimental setting in the early 1950s [140, 141]. It was not until two decades later, though, that an ultrasonic lithotrite was first put to clinical use when Terhorst successfully fragmented a bladder stone in vivo [142]. In 1977, Kurth expanded the indications of ultrasonic lithotripsy to the fragmentation of renal stones during PNL [143]. While ultrasonic lithotrites have been used to treat stones at all locations within the urinary tract, their most important present application is during PNL [144, 145].

a) Mechanism of Action (Ultrasonic Lithotrites)

Ultrasonic lithotripsy has changed little since its inception over five decades ago. Typically, the ultrasonic lithotrite is used under direct visualization with a rigid endoscope. In order to fragment stones, the device relies on the vibrational energy of ultrasonic waves—typically around 20 kHz. When ultrasound is applied to a rigid object such as a stone, the crystal lattice of the stone is fractured, and the stone breaks up into small fragments. The probe of the lithotrite has a hollow core, which can be connected to suction so that small stone particles can be continuously removed.

There are three components to an ultrasonic lithotrite: the generator, the transducer handpiece, and the ultrasound probe (**Figure 9**). The generator, typically powered at 100 watts, provides electrical energy to the transducer. Within the transducer is a piezoceramic element that emits ultrasonic waves. The ultrasound energy is transformed into trans-

Table 6. Comparison of Rigid Intracorporeal Lithotrites

Lithotriptor	Examples	Mechanism of Action	Risk of Tissue Injury	Treatment Characteristics	Probe Size	Reusable
Ultrasonic	Various companies	Vibrational ultrasound waves from piezoelectric generator	Low	Power = 100 W Frequency = 20-27 kHz	2.5-12F	Yes
Pneumatic: Compressed Air	Swiss Lithoclast	Pneumatic jack hammer, Purely mechanical by compressed air	Low	Pressure = 3 Atmospheres Frequency = 12 Hz	2.5-9.5F	Yes
Pneumatic: Electrokinetic	Combilith/ Compact	Pneumatic jack hammer, Purely mechanical by electromagnet source	Low	Power settings = 11-14.3	2.4-6F	Yes
Pneumatic: CO2 Cartridges	Stonebreaker	Pneumatic jack hammer, Purely mechanical by compressed air	Low	Pressure = 30 Atmospheres No electrical power	10F	Yes
Combination: Ultrasonic/ Pneumatic	Lithoclast Ultra	Vibrational ultrasound + pneumatic jack hammer	Low	Combination of ultrasonic and pneumatic	10F	Yes
Combination: Dual Ultrasonic	Cyberwand	Vibrational ultrasound at two set frequencies	Low	Inner probe = 21 kHz Outer probe = 1 kHz	11.25	Yes

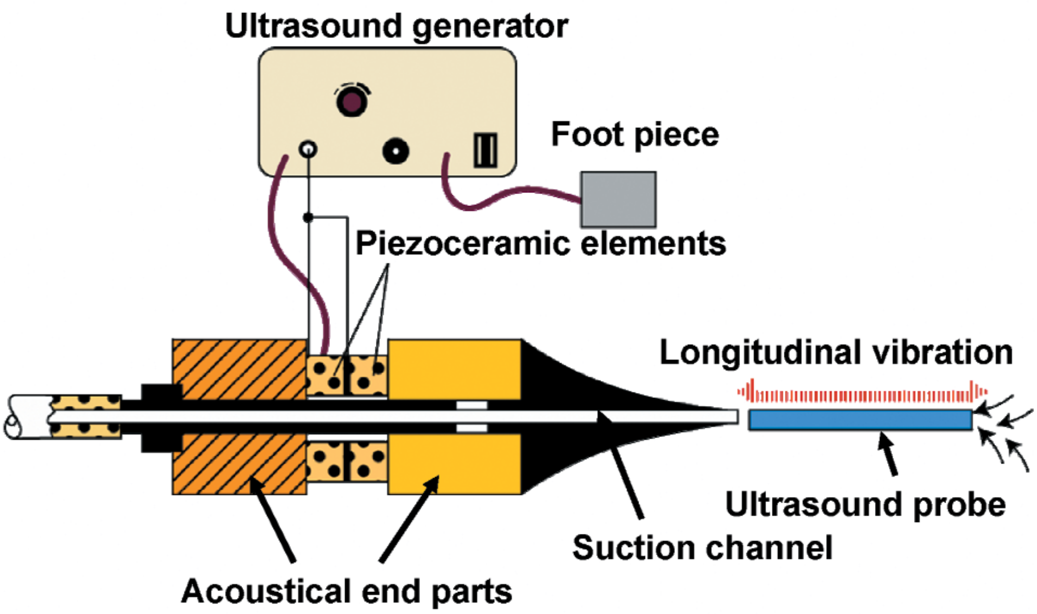


Figure 9. Key components and assembly of an ultrasonic lithotripsy system

verse and longitudinal vibrations that propagate along the hollow metal ultrasound probe. The length of the probe is determined by the acoustic parameters of the system. Stone fragmentation occurs when the probe contacts the stone surface. The efficiency of fragmentation is related to the stone size, density, and surface characteristics. Stones, that are small, less dense, or have a rough surface fragment more rapidly than do larger, denser, smoother surfaced stones [144, 146]. Stone fragmentation is influenced by the degree of manual pressure applied to the stone. As manual compression is increased, the size of the stone fragments tends to increase. Stone treatment may require periods of more intense manual pressure early in the procedure followed by more delicate handling later in the procedure to evacuate smaller fragments. Temptation to apply excessive pressure should be avoided, as calculi can be easily pushed through the urothelium.

Bending the probe can result in heating at the site of flexure, and continuous flow of irrigant through the probe is needed to cool the probe and handpiece [144, 146-148]. Heating of the probe can be a sign that the probe lumen is clogged. Clogging is more common with use of small-diameter probes in the ureter, and differences in commercially available ultrasound probes may also influence heat generation at the probe tip. For example, Terhorst et al noted the addition of a burr head to the ultrasound probe significantly decreased local heating during prolonged use [149, 150].

b) Bioeffects (Ultrasonic Lithotrites)

Ultrasonic lithotripsy is a generally safe technology, but there is risk of perforating the renal pelvis or ureter particularly when pushing against a small or rough surfaced stone [144]. Adverse effects to the underlying urothelium, renal parenchyma, and surrounding soft tissues are rare [151]. In normal operating conditions, both in vivo and in vitro, ultrasonic lithotripsy causes negligible damage to soft tissues. Rathert et al. applied ultrasonic lithotripsy in vivo to sections of the bladder wall in rabbits and failed to produce significant trauma and observed no perforation with continuous exposures up to 5 minutes in duration [152]. Histologically, the treated tissues showed nonspecific inflammatory changes. Grocela and Dretler similarly showed that the placement of the probe on compliant tissue (i.e urothelium) results in minimal damage [151]. The explanation for the relatively atraumatic nature of the ultrasonic device rests on the compliant nature of tissue which does not resonate with the vibrational energy of the probe [144].

Injury, including perforation of the collecting system with irrigation extravasation and/or hemorrhage, can occur during ultrasonic lithotripsy. Such events are most often a consequence of incorrect handling of the probe. Poor technique can also lead to injury of the treating surgeon, as prolonged hand contact with the metal probe can cause burns.

Ultrasonic lithotripsy has the potential to damage the hearing of the operator. Although there have been no reports of hearing loss among OR staff using these devices Teigland et al found that during clinical cases, sound measurements approached 100 decibels. However, auditory tests among urologists enrolled in the study were normal [153].

c) Indications and Outcomes in Ultrasonic Lithotripsy

Although ultrasonic lithtotripsy was initially applied to the treatment of patients with bladder stones, this technology has achieved widespread usage in the treatment of large and complex renal calculi by PNL. In fact, based on the efficacy and safety of treatment, the American Urological Association recommends PNL with intracorporeal lithotripsy as the treatment of choice for patients with staghorn stones [146]. Given the advances in other types of intracorporeal lithotripsy, such as the Holmium laser, the use of ultrasonic lithotripsy for ureteral stones and bladder calculi has greatly diminished. Nevertheless, ultrasonic lithotripsy remains useful for select patients with ureteral stones, especially those with larger stone bulk such as Steinstrasse after SWL [154]. Clinical disadvantages for ultrasonic lithotripsy, particularly for treatment of stones in the ureter, include the relatively large probe size, rigid structure, and potential for over-heating. The reported fragmentation and stone free rates are 97- 100% and 94%, respectively [145].

2. BALLISTIC LITHOTRITES

Ballistic lithotripsy based on the principle of stone fragmentation upon repeated mechanical impact was first described in 1832 when Baron de Heurteloup used a metallic rod to fragment bladder stones [146]. Modern ballistic lithotrites were developed and widely introduced in the 1990s, and devices are now produced by many companies and marketed for treatment of stones in all locations of the urinary tract. Ballistic lithotripsy is considered to be effective for all types of stones regardless of composition and is considered to be a cost-effective treatment modality.

a) Mechanism of Action (Pneumatic-ballistic Lithotrites)

The general concept of ballistic lithotripsy is similar to the function of a jackhammer, in which either a moveable probe is driven into direct contact with the stone, or a projectile is accelerated to hit the base of a fixed probe, which transfers the energy of contact to the stone (**Figure 10**). Most ballistic lithotrites use compressed air to accelerate the projectile and as such are called pneumatic lithotrites. In the Lithoclast, the projectile hits the base of the probe with a pressure of 3 atmospheres and at a frequency of 12 Hz [155]. The Stonebreaker uses compressed air from disposable carbon dioxide cartridges to generate probe pressures of 30 atmospheres [156]. The Browne Pneumatic Impactor also uses compressed air, but in this case the probe is moveable and is made of flexible nitinol [157, 158]. Electrokinetic lithotrites are similar in principle to other ballistic lithotrites, but use electromagnetic energy rather than compressed air to propel the projectile into contact with the metal probe [159-163].

Mechanical stone fragmentation occurs when energy from the probe overcomes the tensile strength of the stone. Ballistic lithotripsy is most effective when the probe is in direct contact with the stone, and fragmentation is further enhanced when the probe remains straight. While flexible probes have been developed, at the current time these appear to be less effective than rigid probes [164, 165]. The jackhammer fragmentation mechanism makes ballistic lithotripsy effective for all stone types, although harder stones typically require more pulses and attention to optimal contact to ensure successful fragmentation [155]. Stone retro-pulsion during treatment is a concern with these devices [159, 160]. As such ballistic lithotrites prove to be most effective for fixed stones and large stone burdens.

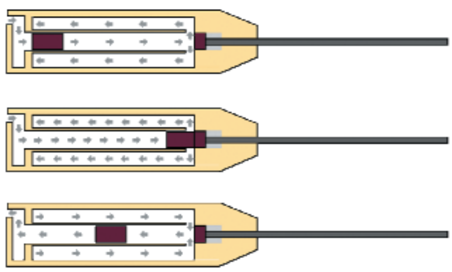


Figure 10. Mechanism of action of a pneumatic-ballistic lithotrite. (A) Projectile in resting position within hand piece. (B) Compressed air accelerates the projectile into contact with the base of the probe. Energy of contact transmitted along the probe to reach the stone (not shown). (C) Air pressure in the outer channel of hand piece acts as pneumatic spring forcing projectile back toward base of hand piece.

One potential drawback of some pneumatic-ballistic lithotrites is that they have only a solid metal probe and as such are not configured to evacuate fragments. To overcome this, devices have been introduced (Lithovac and Lithoclast Ultra, EMS, Kaufering, Germany) that incorporate a central pneumatic-ballistic solid probe and an outer tubular suction channel [166, 167].

Pneumatic-ballistic lithotrites have multiple firing modes. For example, the Lithoclast can deliver single pulses or be used in continuous firing mode. Investigators recommend using higher energy and continuous firing when treating fixed stones and lower energy and single shot firing when treating mobile stones. Hemal et al. prospectively evaluated the fragmentation properties of single shot versus multiple shot pulse settings for patients undergoing PNL, finding that the single shot mode was associated with significantly less mean operative time, less residual stone fragments, and fewer secondary procedures [168].

b) Bioeffects of Ballistic Lithotrites

Although the potential exists for damage to the urothelium and surrounding tissues, injury with pneumatic-ballistic lithotrites has been found to be minimal [169]. The risk of perforation of the ureter is lower for these devices than for intracorporeal electrohydraulic, ultrasonic and laser lithotrites. In a study by Teh et al, continuous delivery of pneumatic-ballistic pulses for 1 minute directly to the ureter did not perforate the wall and was associated with only a minimal risk of hematoma [170]. Denstedt et al. similarly evaluated the tissue effects of the Lithoclast in a porcine model, and found that treatment produced very little trauma [169]. Local effects such as bleeding were rarely observed, and tissue changes, such as edema and mucosal denudation resolved completely within 3 to 6 weeks as assessed by gross inspection, radiologic imaging, and histologic analysis.

Piergiovanni et al compared tissue effects associated with four classes of intracorporeal lithotripsy devices including pneumatic-ballistic lithotrites [171]. They found few tissue effects with pneumatic-ballistic and ultrasonic lithotrites. Treatment by intracorporeal electrohydraulic lithotripsy and holmium laser lithotripsy was associated with a higher risk of tissue damage, including thermal injury.

c) Indications and Outcomes with Ballistic Lithotrites

Given the variety probe sizes available, ballistic lithotrites have the potential to be used for stones throughout the urinary tract (**Tables 7, 8**). However, they tend to be most effective in cases involving rigid endoscopes and are particularly helpful when treating hard stones during PNL. Pneumatic-ballistic lithotripsy is less popular nowadays for the treatment of ureteral and bladder stones given the advances in flexible intracorporeal lithotriptors. Fragmentation rates for pneumatic lithotripsy have been reported to be 84-100% and the overall stone free rates are approximately 70% for upper ureter, 90% for middle ureter and 83-98.6% for distal ureteral stones with few complications [145]. Despite the variety of devices that have been proposed and clinically introduced, most of the data come from experience with the Lithoclast [146, 155, 158, 159, 168, 169, 290].

Stone migration (stone retro-pulsion) is potentially a major disadvantage when treating stones with a ballistic lithotrite and has been observed in 2-17% of ureteral stone cases, where failure is usually attributed to the inability to trap the stone in a capacious ureter [144, 151].

3. COMBINATION LITHOTRITES

The newest class of rigid intracorporeal lithotrite incorporates two modes of stone breakage into one device [145]. Two such systems have been introduced, one that uses both ultrasonic and pneumatic-ballistic probes (Lithoclast Ultra, EMS), and one having a fixed ultrasound probe plus a movable probe also driven by ultrasound (Cyberwand, Cybersonics).

a) Mechanism of Action (Combination Lithotrites)

The first combination lithotrite was the Lithoclast Ultra, which incorporates a standard Lithoclast pneumatic device in conjunction with an ultrasonic hand piece. Multiple treatment probes are available for the Lithoclast portion of the device (0.8 mm, 1.0 mm, 1.6 mm, and 3.2 mm). The Lithoclast ultra is set up such that the standard Lithoclast probe is positioned through the hollow metallic ultrasonic lithotripsy probe. The hollow ultrasound probe is available in two sizes (3.3 mm and 3.8 mm) [145]. The Lithoclast Ultra is designed such that the tip of the Lithoclast pneumatic probe extends approximately 1 mm beyond the hollow ultrasonic lithotripsy probe. The mechanism of action for the combination device is the same as either of the components used individually, and a feature exists that allows the surgeon to activate the ballistic or ultrasonic components separately or in combination. In vitro and clinical studies have shown that use of the Lithoclast Ultra was superior to ultrasonic lithotripsy alone from a standpoint of stone penetration time, overall fragmentation time, and effectiveness of stone fragmentation [172, 173].

Another combination lithotrite system, the Cyberwand (Gyrus/ACMI, Maple Grove, MN) utilizes two ultrasound probes (inner and outer) that operate at different frequencies (**Figure 11**). The inner probe (2.77 mm outer diameter) is fixed to

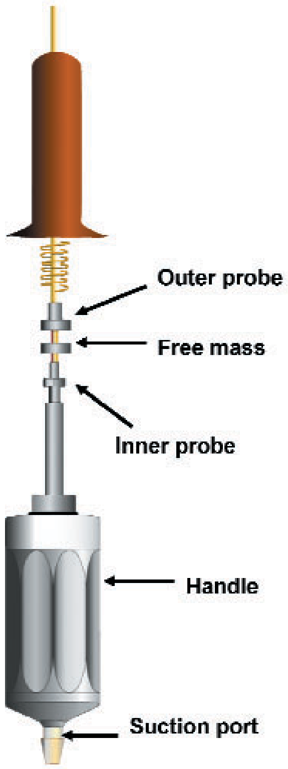


Figure 11. Inner workings of the Cyberwand probe assembly

Table 7. Ureteral Stone Outcomes Using Pneumatic-ballistic Lithotrites

Ureteral Stones								
Author	**Year**	**N**	**Device**	**Stone size, mean**	**OR time, mean**	**Complications, %**	**Fragment, %**	**Stone Free %**
Tawfiek (157)	1997	7	BPI	10.1 mm	80	11	89	100
Kok (281)	1998	74	SLC	58 mm2	NR	5 (4/74)	91	96
Knispel (288)	1998	143	SLC	6.8 mm	NR	NR	72	NR
Teh (170)	1998	30	SLC	12 mm	NR	3.3	95	93
Keeley (161)	1999	121	EKL	11.5 mm	NR	2	99	80%, 1 treatment
Menezes (282)	2000	23	SLC	69 mm2	54	14	74	87
Menezes (282)	2000	22	EKL	72 mm2	50	14	86	77
Delvecchio (167)	2000	21	SLC +LV	84 mm2	42	0	100	95%
Nutahara (283)	2000	66	SLC	NR	90	NR	NR	97%
Sun (284)	2001	145	CUT	11 mm	35	3.4	69.7	Mean, 31 days
Sozen (285)	2003	500	SLC	8.7 mm	32	6.4	96.8	94.6
Aghamir (286)	2003	340	SLC	10.4 mm	NR	11.5	88.7	89.5
Akhtar (287)	2003	529	SLC	NR	NR	14	98	100
De Sio (162)	2004	19	SLC	10.2	46	36.3	89.4	95
De Sio (162)	2004	19	EKL	10.6	55	26	78.9	89
Jeon (233)	2005	26	SLC	11	77	8	73	85
Gonen (250)	2006	23	CUL	8.9	42	13	100	100
Mohseni (252)	2006	16	SLC	11.6	41.5	12.4	NR	93.7
Mohseni (252)	2006	18	SLC	13.1	40.6	44	NR	83.3
TOTALS	1997-2006	2142 patients	Various	Range: diameter, 6.8-13.1 mm, area, 30-84 mm2	Range: 32-90 minutes	0-44%	Range: 69.7-98%	Range: 77-100%

BPI = Browne Pneumatic Impactor, SLC = Swiss Lithoclast, EKL = electrokinetic lithotriptor, LV = lithovac, CUT = Calcutript, CUL = Calculith

Table 8. Renal Stone Outcomes Using Pneumatic-ballistic Lithotrites

Renal Stones									
Author	**Year**	**N**	**Device**	**Stone size, mean**	**OR time, mean**	**Complications, %**	**Fragment, %**	**2nd Procedure, %**	**Stone Free %**
Denstedt (155)	1993	45	SLC	12 stones >2 cm = D, 16 partial staghorn 17 complete staghorn	137	0	100	33	86
Haupt (159)	1996	68	SLC			1	98		
Desai (289)	1999	39	SLC	2.0 cm	75	38	91	NR	91
Hemal (168)	2003	69	SLC	Mostly staghorn	123	30.4	100	20.2	100
Hemal (168)	2003	84	SLC	Mostly staghorn	141	36.9	100	26	99
TOTALS	1993-2003	305 patients	SLC	Mostly staghorn	Range: 75-141 min	Range: 0-38%	Range: 91-100%	Range: 20-33%	Range: 86-100%

SLC = Swiss Lithoclast

the hand piece and the frequency is set at 21 kHz. The outer probe (3.75 mm outer diameter), also called the floating probe, moves in a reciprocating fashion dependent on the vibrational energy of the inner probe. Vibration of the inner probe sets a sliding piston (free mass) in motion, which pushes the outer probe forward. Resistance from a coil spring forces the outer probe back toward the hand piece. Excursion of the outer probe is determined by the free mass, which serves as a frequency coupler limiting vibration of the outer probe to about 1 kHz. Similar to the Lithoclast Ultra, the probes are offset by about 1 mm. Unlike the Lithoclast, however, the movable probe of the Cyberwand does not project past the position of the fixed probe. This minimizes its jackhammer effect, in that it only strikes a stone when the fixed probe has already penetrated it. Like the Lithoclast, the Cyberwand is highly effective in breaking hard stones, and both devices are effective in evacuating fragments.

b) Bioeffects of Combination Lithotrites

Clinical studies with the Lithoclast Ultra reveal a safety profile similar to that of ultrasonic lithotrites [174, 175]. The potential for urothelial trauma would seem greater, however, as the narrow pneumatic-ballistic probe of the Lithoclast Ultra extends beyond the larger blunt outer probe. At the time of publication there were no data concerning the safety of the Cyberwand in clinical practice, and no experimental studies to assess injury with either of these devices.

c) Indications and Outcomes for Combination Lithotrites

Two experimental studies have been performed with LithoClast Ultra, comparing its two modalities in isolation and together [145, 176]. The combination mode proved to be significantly more efficient, as the time required to completely fragment and clear the stone material ranged between 5.9 and 7.4 minutes versus 23.8 and 12.3 min, for pneumatic-ballistic and ultrasound modes respectively. Moreover, the average size of the largest stone fragments was significantly smaller with the combination probe. Clinical studies with the LithoClast Ultra have documented an overall stone free rate of 80-97% with no complications reported [145].

Kim et al recently compared the efficacy of the Cyberwand device to the LithoClast Ultra in a hand-free in vitro test system using gypsum artificial stones [177]. The mean penetration time for the Cyberwand was statistically faster than for the LithoClast Ultra, but the difference amounted to just a few seconds. There were no noteworthy issues with overheating, occlusion, or other malfunction with either lithotrite.

SUMMARY AND PERSPECTIVE REGARDING RIGID INTRACORPOREAL LITHOTRITES

Rigid intracorporeal lithotripsy is expected to remain important, especially for patients undergoing PNL for large renal and proximal ureteral stones. Although it is conceivable that novel rigid lithotripsy systems will be introduced, a more likely scenario will be the continued advancement of combination systems, which improve efficiency by incorporating the best attributes of the individual lithotripsy systems. While ultrasonic lithotrites are excellent for simultaneous fragmentation and removal of most urinary stones, some stones (i.e. cystine and calcium oxalate monohydrate) may not be as easily fragmented with a solely ultrasonic device. Pneumatic-ballistic lithotrites are effective in fragmenting essentially all stone types, but the conventional device does not permit immediate fragment evacuation. These types of treatment concerns are overcome, and the efficacy of treatment is improved, with the use of combination devices.

Take Home Message (Rigid Intracorporeal Lithotrites):

- The great advantage of rigid intracorporeal lithotrites is the efficiency with which they fragment and remove a stone burden. The rigid devices are a mainstay of PNL, and should be used in the treatment of renal calculi whenever a rigid nephroscope will permit their passage.
- An obvious shortcoming of rigid lithotrites is that they cannot be used with flexible endoscopes. The concept of an effective ballistic-style probe capable of fragmenting hard mineral via flexible access would be an attractive development.
- Stone migration (propulsion/retropulsion) is a problem with typical ballistic-pneumatic devices, and ancillary tools to block or limit migration can be worthwhile.
- The suction capability of a lithotrite is a particularly valuable feature.
- Combination lithotrites utilize both ultrasonic and jackhammer mechanisms and are effective in fragmenting and clearing large stone burdens of even the hardest mineral types.

II. FLEXIBLE INTRACORPOREAL LITHOTRITES

1. INTRACORPOREAL ELECTROHYDRAULIC LITHOTRIPSY

The idea of using spark-gap generated (electrohydraulic) shock waves to disintegrate stones inside the human body was first employed by Yutkin in 1955 at the University of Kiev. Ten years later the “Urat-1” (also known as the “Soviet Apparatus”) was developed and reports describing this device began to appear in Russian and East European journals [151].

The components used in these early designs had poor conductivity and high resistance, and thus required high energy to produce the desired spark. The probes were 9-10F in diameter and were basically two isolated wires. Probe failure occurred after less then 50 shocks [178]. The principle was to create a large cavitation bubble to produce a SW that would impact the stone. But if the voltage was too high, bubble expansion would not occur and the discharge energy would generate heat. Direct contact with the mucosa, or repeated firing near tissue could cause perforation of the bladder wall. Still, relative to contemporary devices the intracorporeal electrohydraulic lithotrite was considered a technological advance [179, 180].

Further improvements included smaller probes and shorter pulse duration, in the microsecond range. The procedure became safer, and was extended into the upper urinary system. At first, the distal ureter was approached blindly, using a 9F probe, with up to 90% success [181]. However, perforation and extravasation occurred in 40% of cases. The technique was further improved with direct endoscopic visualization allowing passage of 5F probes [182].

As ureteroscopes and EHL probes became smaller, retrograde and antegrade techniques improved success rates. Flexible mini scopes, with 1.6F probes, were found particularly useful, especially for stones at the lower pole of the kidney, and are probably the most commonly used nowadays. Further improvements were introduced, such as the plasma shield consisting of a hollow spring and a metal-end cap, in an attempt to minimize tissue damage without adversely affecting stone fragmentation rates [183-186].

a) Mechanism of action of Intracorporeal EHL

Application of high voltage (3-6 kV) across the electrode leads of the EHL probe tip generates a spark creating a plasma. The plasma expands at supersonic speed, propagating a spherically expanding SW that impacts the stone. Plasma expansion produces a cavitation bubble and collapse and rebound of this bubble generates SW’s that impact the stone. If bubble collapse is asymmetric a damaging fluid micro-jet is generated. [187-189]

b) Tissue effects and safety of Intracorporeal EHL

The diameter of the cavitation bubble produced depends on the quantity of energy used: at levels greater than 1,300 mJ, the bubble expands to more than 1.5 cm; at levels lower than 400 mJ the diameter is less than 4 mm. The size of the probe has little effect on the amount of energy that reaches the tip. Therefore, smaller probes do not necessarily mean safer application of energy. Vorreuther et al. demonstrated that when an EHL probe was placed in direct contact with the mucosal layer, an energy discharge of 100mJ caused mucosal damage, 500mJ damaged the underlying muscularis, and 1,000mJ caused perforation of the wall [187]. Furthermore, repeated discharges in the same place, at any energy level, result in perforation. Pseudoaneurysm with arteriovenous fistula is a rare but possible complication. Steps to minimize the risk of complications should be taken, including maintaining good visibility to ensure that the probe is not in contact with the mucosa, avoiding multiple or rapidly repeated shocks at the same location, and using the lowest possible intensity setting to obtain good fragmentation. Depending on bubble size, the ureteral wall may be distended or disrupted, even when the probe is not in direct contact with the mucosa. The maximal size of this bubble depends on the energy applied, and ranges from 3mm (25mJ) and up to over 15mm (1300mJ). In the laboratory setting, a single discharge exceeding 1000mJ has been observed to cause a lesion in the ureter 1 cm in length.

Damage to the ureter with EHL occurs in 10-15% of patients in the form of mucosal denudation, submucosal swelling and hemorrhage and correlates with the energy applied and the number of pulses [187, 190]. Therefore, the goal should be to obtain a low energy pressure pulse with high disintegration efficacy. Most stones can be disintegrated safely by EHL with moderate energies. EHL’s can also generate high pressures in excess of the maximum energy of laser lithotripters. If high energies are used, the urologist must be careful to place the probe visibly at the center of the stone in a wide ureter, and to use only single shot mode. EHL is relatively contraindicated in impacted ureteral stones, due to the danger of damaging the ureteral wall, and is contraindicated in pregnancy.

c) Clinical use of Intracorporeal EHL

There has been a decline in the use of EHL for fragmenting ureteral and renal stones in recent years. Nonetheless, EHL is an efficient and economical method of stone fragmentation (**Table 9**). The advent of probes < 3F allows the use of a small bore flexible ureterorenoscopes with effective flow of irrigant.

Results for the clinical application of EHL are summarized in Table 1. The first description of the treatment of an upper tract stone by EHL was by Reuter and Kern [191]. Initial trials were unfavorable owing to the fact that these treatments involved blind passage of a 9F electrode into the ureter. However, in 1988 Begun et al treated 21 stones with 9F and 13F flexible ureteroscopes resulting in fragmentation in 91% of stones and no significant complications apart from retained stone fragments and small ureteral perforations [192]. Denstedt and Clayman reported similar success using 3F EHL probes in 40 cases with 91% fragmentation and 5% complications limited to ureteral tears in the distal ureter at a point remote from where the EHL was deployed [183].

Feagins reported the use of the 1.9F probe to successfully fragment 90% of intrarenal or ureteral stones in 30 cases [193]. Elahsry et al, again using 1.9F probe confirmed fragmentation in 98% of 45 cases with 89 stones [194]. Basar et al reported on EHL successfully fragmenting 187 out of 207 (90.3%). A total of 119 patients (57.5%) became stone free 3 months after the operation [195]. This increased to 170 cases (82.1%) at a mean follow up of 20 months. However, in this series 6 (2.9%) patients had to be converted to open surgery because of Ureteral perforations and in 7 cases (3.4%) the stone could not be fragmented due to hardness.

In 1996 Elahsry commented that of the available forms of intracorporeal lithotripsy only laser and EHL were malleable enough to be used during flexible ureterorenoscopy [194]. He further argued that none of the laser probes were as malleable as the EHL, precluding the effective delivery of the laser energy into the lower pole calyx. Therefore an EHL lithotriptor may have a place in the management of lower pole calyceal stones, particularly stones where the angle between the lower pole infundibulum and the renal pelvis is acute.

2. HOLMIUM LASER LITHOTRIPSY (HO:YAG)

The role of flexible ureteroscopy in the urologist's armamentarium has undergone a dramatic evolution over the last decade, driven to a great extent by the development of (HO:YAG) laser lithotripsy [145, 196]. Lasers have been utilized as intracorporeal lithotriptors since the introduction of the ruby, coumarin pulsed-dye, alexandrite and neodymium:YAG lasers [197-200]. However, specific shortcomings of these sources regarding safety (ruby), ineffectiveness with some stone types (pulsed-dye, alexandrite, ND:YAG), and cumbersome fiber size (ND:YAG) have been balanced by positive features of the HO:YAG. The HO:YAG is a solid state laser operating in the infrared portion of the electromagnetic spectrum [201]. It is effective on all stone types, and because its output is effectively absorbed by fluid media the HO:YAG presents little risk of collateral tissue damage.

Table 9. Intracorporeal Electrohydraulic Lithotripsy for Ureteral Stones: Outcomes and Complications

Author	Patients	Probe Size (French)	Perforation (%)	Successful Fragmentation (%)	Stone Free (%)
Hofbauer (291)	34	2.4	17.6	85.3	89.5
Basar (195)	198	3, 4.5	39	90.3	57.5
Elashry (184)	45	1.9	0	98	92
Teichman (229)	23	1.9	13	N/A	87
Kupeli (290)	33	5	12.1	N/A	90.9
Weighted Average	465		8.5	90	84

a) Mechanism of Action (HO:YAG laser)

Holmium lasers release a burst of pulsed light at a wavelength of 2140 nm. The primary mechanism of action is photothermal; fragmenting the stone by direct stone absorption of laser energy and thermal combustion [202, 203]. Zhong et al. demonstrated using high speed photography that acoustic emissions generated by HO:YAG were weaker than in EHL due to the irregular geometry of the cavitation bubbles generated [203]. Others have confirmed the primary importance of the photothermal effect, and also quantified the impact of cavitation bubbles and pressure waves with increasing fiber size [204]. The absence of significant photoacoustic effects was demonstrated using needle hydrophone monitoring of pressure transients [205].

Vassar et al confirmed the photothermal mechanism by demonstrating the generation of end-products of thermo-chemical reactions: cystine and free sulfur from cystine stones, ammonium carbonate and magnesium carbonate from struvite stones, and cyanide from uric acid stones [202, 205].

b) Tissue Effects and Safety of HO:YAG

Collateral tissue injury from a thermal effect is unlikely as the energy is effectively absorbed in a fluid medium. While EHL can cause damage even if fired several millimeters away from tissue, the holmium laser is safe at a distance of 0.5-1 mm from the ureteral wall without fear of perforation [206]. However, if the fiber is placed in direct contact and perpendicular to the ureter, it can create a thermal lesion 0.5-1mm in depth, and is capable of generating a full-thickness perforation in less than 1 second (1-2 pulses), even at low energy (0.2J, 5Hz). Clinical studies report a 3-4% rate of ureteral perforation [207-209]. The laser perforates most commonly when it is advanced out of the working channel in the setting of an impacted stone, before it is activated. Damage can be minimized by withdrawing the scope to an area of normal ureter, maneuvering the endoscope upwards to move the exit point of the fiber away from the ureter, then advancing onto the impacted stone. Similarly, painting the surface of the stone rather than drilling through the stone until the fiber tip is no longer visible will minimize the risk of ureteral perforation.

c) Clinical Experience with HO:YAG

The HO:YAG laser is an effective intracorporeal lithotriptor for distal ureteral calculi (**Table 10**). Two large published series report success rates of 93-96%, with a complication rate of 14% and secondary procedure rate of 4-5% [207, 210]. Indeed, more recent studies report success rates of 97-100% for ureteral calculi and 84% for intrarenal calculi. Fragmentation was incomplete in 6% of cases and secondary intervention was required in 6%. The overall complication rate was 4%. New onset ureteral stricture developed postoperatively in 0.35% of patients [211].

Success rates for distal ureteral stones are independent of stone size: 100% for <1 cm, and 92% for >1 cm [212]. When all ureteral calculi are considered, success rates for distal ureteral calculi are superior to those for proximal ureteral calculi (96% vs. 78%). Larger stone size (odds ratio 1.2) and proximal ureteral location (odds ratio 4.8) are independent predictors of treatment failure [210]. Other investigators have reported superior success rates for proximal ureteral calculi managed by ureteroscopic HO:YAG lithotripsy, ranging from 88-97% with a 3-11% secondary procedure rate [207, 213].

The HO:YAG laser has been used successfully to treat lower pole calculi as well. Kourambas et al. reported a 85% success rate for lower pole stones,

Table 10. Holmium:YAG Laser Ureteroscopic Lithotripsy for Ureteral Calculi

Author	Patients	Perforation (%)	Stricture (%)	Successful Fragmentation (%)	Stone Free (%)
Devarajan (207)	265	4	3	100	93
Yip (292)	69	0	1.4	91	N/A
Biyani (293)	48	2	N/A	100	98
Grasso and Chalik (294)	109	0	0	100	100
Sofer (211)	598	0.1	1.1	97	97
Weighted Average	1466	1.1	1.2	97.3	95.3

with a mean operative time of 50 minutes [214]. If active deflection to address a lower pole calculus is impeded with the 200μm laser fiber, the stone can be entrapped in a nitinol stone basket and displaced into the renal pelvis or an upper pole calyx for treatment [214, 215]. As such, this technique may help prolong the longevity of the flexible ureteroscope [216].

Outcomes in the lower pole are dependent on stone size, with a 95% success rate for stones smaller than 2 cm, but a 45% success rate for stones larger than 2 cm. [217]. A two-staged ureteroscopic approach to large calculi increases the success rate for intrarenal calculi to 91%, and improves the success rate for lower pole stones greater than 2 cm to 82% [217, 218]. Recently, the efficacy of flexible ureteroscopy for the management of intermediate size lower pole renal calculi has been confirmed, with stone-free rates of 75% for patients with calculi 10-20 mm in the lower pole [219].

Understanding of the impact of spatial anatomy of the lower renal pole on success with SWL has helped urologists select patients who might benefit from a ureteroscopic approach [220]. Patients with a lower infundibulopelvic angle <40 degrees, especially if combined with an infundibular length >3 cm or infundibular width <5 mm would be better served by a ureteroscopic or percutaneous procedure [220]. While the success of flexible ureteroscopy appears to be largely unaffected by the infundibular angle, other investigators have reported that an infundibular length of >3 cm increases the risk of ureteroscopic failure about 8-fold [217].

Flexible ureteroscopy with HO:YAG provides an attractive option for treatment of complicated stone patients, such as the morbidly obese, those on anticoagulation, patients with pelvic kidneys or other anatomical abnormalities, cystine stone formers and patients with a recurrent large (>2cm) stone burden [221-223]. This technology also appears to have an important role in the stratified management of ureteral calculi in pregnancy, minimizing maternal and fetal morbidity and radiation exposure while expeditiously and definitively treating the calculus while obviating the need for prolonged ureteral stenting [224-226].

Flexible ureteroscopy with intrarenal laser unroofing of submucosal papillary calculi may be utilized in patients with symptomatic nephrocalcinosis [227]. Taub et al. recently reported a retrospective series evaluating the durability of response to ureteroscopic laser papillotomy for the treatment of painful papillary calcifications [228]. Holmium laser ablation of superficial papillary tissue was performed using 8 to 10W at 10Hz energy settings [228]. Ablation was performed to unroof obstructed collecting tubules until all visible calculi were vaporized. «Much less pain» was reported by 85% of patients with a durable response reported by 60% at a mean follow-up of 18 months, and dramatic improvements in narcotic usage, pain scores, and impact on daily activities were demonstrated [228]. Though promising, further refinement in patient selection and determination of the maximum number of papilla that should be treated in one session is needed. The impact of this technique on viability of the treated papilla and renal function deserves further study.

The majority of prospective studies have evaluated the role of ureteroscopic HO:YAG versus SWL. No prospective clinical trials exist to our knowledge comparing intracorporeal lithotriptor modalities for ureteroscopy. In a retrospective cohort study, the stone-free rates both at the end of the ureteroscopy and 3-months post-procedure were significantly higher for the holmium laser than for EHL [229]. For ureteral calculi less than 15 mm., fragmentation by EHL was more rapid than HO:YAG and though stone-free rates were lower with EHL at the completion of ureteroscopy (65% vs. 97%) stone-free rates at 3-months were comparable. However, HO:YAG was more efficient for fragmentation of ureteral calculi ≥15 mm and resulted in higher stone-free rates at 3-months (100% vs. 67%).

There have been recent reports of the treatment of large renal calculi with a combination of HO:YAG laser and EHL applied through a ureteroscopic approach [230, 231]. Although success was reported in up to 92% of patients, stone-free measures were not strictly defined and multiple treatment sessions were required. It was concluded that staged ureteroscopic nephrolithotripsy of large renal calculi is feasible with low morbidity and clearance rates comparable to percutaneous nephrolithotripsy. Before widespread adoption, this hypothesis should be subject to a randomized controlled trial.

When contrasted with use of pneumatic-ballistic lithotrites for treatment of upper ureteral calculi, the holmium laser gave higher stone-free rates (92 versus 42%), lower incidence of secondary procedures (8 versus 58%), and less stone migration

[232]. A retrospective cohort study supports the observation of higher immediate stone-free rates (96% vs. 73%), shorter operative times (50 vs. 77 min) and shorter hospitalizations (1 day vs. 2.5 days) with HO:YAG lithotripsy as compared to the Lithoclast pneumatic-ballistic device [233]. In vitro analyses have demonstrated that not only does the holmium laser fragment all compositions of urinary calculi (calcium oxalate, calcium phosphate, cystine, struvite, uric acid), it produces smaller stone fragments than pneumatic-ballistic, EHL and pulsed-dye (Candela) lithotripsy [234].

Investigators have evaluated the impact of holmium laser pulse width (pulse duration) on stone migration [235]. Pulse width is independent of the energy setting and rate that are used. Most holmium laser machines have a set pulse width. The Convergent Odyssey 30W holmium laser has the option of adjusting the pulse width from 350 µs (standard) to 700 µs (long). In vitro testing demonstrated that there was significantly more stone movement with standard pulse width compared to the longer pulse width and, therefore, more energy could be delivered using long pulse width before the stone model migrated away from the tip of the laser. The artificial stones tested were heavier (50-400 mg) than typical natural stones (5-20 mg). One might predict that lighter stones would migrate more than heavier models - therefore this study may understate the difference between the two pulse width settings. An important observation was that migration did not occur at either pulse width until energy settings of 1.4J or higher were utilized, irrespective of the mass of the model stone. This confirms the observation that stone propulsion is not a factor with the holmium laser, and if one limits the energy to 1J, stone migration can be eliminated altogether.

d) Practical Considerations in the Use of the HO:YAG Laser:

- Laser settings for stone disintegration range from 0.5-1.5J and 5 to 20 Hz for an energy output of 2.5 to 30W [236]. Typical settings are 0.8J and 8Hz, and it is uncommon to exceed 1.0J and 15 Hz. By utilizing low energy ($\leq$1.0J) and increasing the frequency one achieves smaller stone fragments, less stone migration and less degradation of the laser fiber tip [237, 238].
- Typically the 200µm fiber is utilized to fragment intrarenal calculi, and especially lower pole calculi; while the 365µm fiber is used for ureteral, renal pelvis or upper pole calculi. The 365µm fiber is more durable than the 200µm fiber.
- What is gained in fiber durability is lost in visibility and deflection. In comparison to 365 µm fibers, one can gain up to 26° more deflection using the 200 µm fiber. Only 7-16% of maximum deflection (-9 to -19 degrees) is lost with the 200µm fiber compared to 18-37% (-24 to -45 degrees) of maximum deflection with the 365 µm fiber [236, 239].
- Though one would predict that for a given power output (e.g. 1.0W) the greatest energy density (J/cm^2) delivered would be with the smallest laser fiber, in vitro studies have demonstrated that the best stone fragmentation efficiency is seen with the 365µm fiber [240]. The 200-272µm fiber is inefficient and prone to damage at energies >1.0J, therefore it is recommended to increase the frequency (e.g. 15-20) rather than energy if the stone does not fragment at 1.0J [236, 241].
- The delivery of holmium laser energy depends on output through reusable quartz fibers from 200 - 400 µm in size. Performance and safety studies of commercially available laser fibers showed that the Dornier Lightguide 200 was the most likely of small fibers to fracture and cause damage to a flexible ureteroscope. The Lumenis 272 and the Innova Quartz 400 were the most durable in their size class [242].
- Passage of the fiber 1-2 mm beyond the tip of the ureteroscope with the tip of the ureteroscope straight is recommended to avoid damage to the lens or the working channel.
- Caution should be used to avoid inadvertent transection of guide wires or baskets with the holmium laser. In vitro testing has demonstrated that a 0.035” safety wire will transect after 90 seconds while a 1.9F Nitinol basket will transect after 4 seconds, and on occasion as quickly as 1 second when targeted directly with 0.8 and 5Hz [243]. If this occurs, careful inspection of the device should be performed to confirm that no fragments have been left behind that might serve as a nidus for stone formation.
- Use of a 2F laser catheter in the working channel decreases the chance of damaging the channel during passage of the 200µm fiber, however this also decreases irrigant flow by 80%, impacting endoscopic vision [244].

- The Storz Flex-X^2 flexible ureteroscope contains Laserite™, a laser resistant ceramic coating that is marketed to protect the distal tip from laser damage, however this claim has yet to be substantiated by independent in vitro or clinical evaluations, and the impact on scope durability remains to be elucidated.

Take Home Message (HO:YAG Laser):

- The Holmium:YAG laser is the intracorporeal lithotripter of choice when a flexible device is required. Its superior safety profile and ability to fragment stones of all compositions has helped advance the technique of flexible ureteroscopic treatment of stone disease.

III. NEW AND INNOVATIVE DEVICES TO IMPROVE INTRACORPOREAL LITHOTRIPSY

1. OTHER INTRACORPOREAL LASER SYSTEMS

The Erbium:YAG (Er:YAG) laser fragments stones by photothermal effect. Stone fragmentation is more efficient than the HO:YAG laser as the optical energy is better absorbed at the 294 nm wavelength of the Er:YAG [245, 246]. For all stone compositions, HO:YAG created wider, more irregular craters while Er:YAG created deeper craters and greater ablated stone volume. However, challenges in the development of optical fibers capable of delivering sufficient energy through current endoscopes have stalled further development of this device. Silica fibers degrade rapidly with this wavelength, fluoride fibers are too brittle and sapphire fibers are costly and too fragile for clinical applications.

The frequency doubled double-pulse Nd:YAG (FREDDY) laser is a potential option for intracorporeal lithotripsy. Although in vitro studies have demonstrated that stone fragmentation is more efficient with the FREDDY laser than with the holmium laser, stone retropulsion was significantly greater with the FREDDY [247]. In addition, the FREDDY does not fragment all stone compositions, and does not have soft tissue applications [248].

2. MINIMIZING STONE MIGRATION AND IMPROVING ACCESS WITH INTRACORPOREAL DEVICES

One of the challenges in performing intracorporeal lithotripsy is keeping stones and fragments in check. That is, dealing with the tendency of lithotrites to push stone material away from the working tip of the device. Stone migration (propulsion, retropulsion) can occur when working in either the ureter or the kidney and can be an important factor that increases intra-operative time and the urologist's frustration level. Three occlusion devices have been developed to prevent stone migration in the ureter. The N-Trap (Cook Urological) is a 2.8F deployable «backstop» composed of 24 interwoven nitinol wires that has been shown in ex-vivo pig ureters to prevent the migration of plastic beads as small as 1.5 mm. The 3F Stone Cone Retrieval Coil (Boston Scientific, Natick, MA) may also be deployed beyond a stone and has been shown to prevent the migration of fragments ~2.5 mm or larger [249-251]. Another device (Accordian from Percsys Inc) has recently been introduced that can function to blockade the lumen of the ureter or close off the UPJ to restrict stone migration, but, there is no published information about its effectiveness for this application.

Proximal placement of Lidocaine jelly has been successfully used to prevent retrograde stone displacement [252]. The same concept was recently evaluated by Sacco et al, using a thermosensitive polyoxyalkylene copolymer that is liquid at low temperature and turns into a viscous gel at body temperature [253]. The polymer was delivered above a stone phantom surgically placed in the pig ureter. Following lithotripsy the gel was dissolved with cold saline and residual gel dissolved in the urine. Such a strategy seems reasonable and warrants further investigation.

At times, stone extraction is attempted but is unsuccessful due to the size of the stone. Traditionally the basket is disassembled and lithotripsy is performed alongside the basket. Certain devices have been developed that may permit laser treatment of an entrapped stone (1.5 F Halo tipless basket from Sacred Heart Medical (Minnetonka, MN); Escape Stone Basket from Boston Scientific (Natick, MA). It is important to emphasize that stone capture with subsequent laser lithotripsy should be considered the exception, to be used only in the situation of an entrapped stone. Otherwise, laser lithotripsy prior to stone capture is advocated as a safer approach.

If active deflection to address a lower pole calculus is impeded with the 200 µm laser fiber, a novel temperature-activated deflectable laser fiber sheath (Powerflex; Optical Integrity, Panama City, Florida) can be utilized to maximize deflection. This Nitinol sheath (1.83 F) actively deflects after a rapid flush of 10 cc of hot water (60° C) through the irrigation side-port, resulting in deflection angles up to 20° beyond maximum deflection of the ureteroscope [254].

Newer generation flexible ureteroscopes also promote access to the lower renal calyces, as they are uniformly designed with exaggerated deflectability. In many cases, grasping devices can be placed through the working channel with the scope in full deflection and a stone can be manipulated into an upper pole calyx for treatment.

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Treatment of Renal Stone

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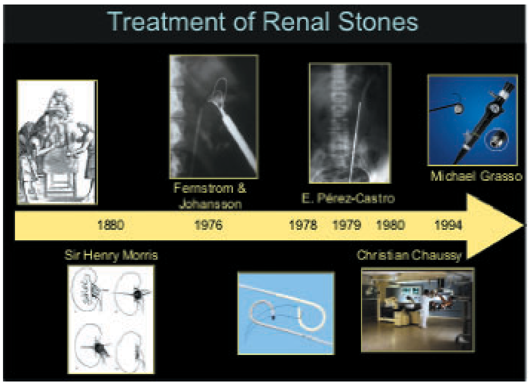
A. INTRODUCTION

Percutaneous nephrolithotomy (PCNL) was established as a minimal invasive treatment option for removal of kidney stones in the seventies and was further developed in the following years [1-3]. However, PCNL-frequency diminished with the introduction of extracorporeal shock wave lithotripsy (ESWL) in the early eighties [4]. In recent years, as clinical experience with ESWL revealed its limitations, the role of PCNL for treating urolithiasis was redefined[5-7]. Today, PCNL should be the first line treatment of large or multiple kidney stones, and stones in the inferior calyx [8]. Furthermore, improvements in instruments (i.e. mini-nephroscopes, flexible pyeloscopes and ureteroscopes) as well as lithotripsy technology (i.e. ultrasound / pneumatic devices, Holmium-YAG-laser) increased the efficacy of percutaneous stone disintegration yielding stone free rates of >90% [9-10]. The milestones of renal stone treatment are summarized in **figure 1.**

Currently there is a tendency to develop specialized medical centers for centralization of diseases with a low incidence or diseases with complicated procedures, in order to gain expertise on certain areas and to reduce complications. The latter is often underestimated and therefore classifications are developed. The registration and classification of perioperative complications is currently studied using the Clavien Grading System. This is a next step to better understand treatment outcomes and improve treatment strategies in renal stone management.



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B. TREATMENT OPTIONS

I. ACTIVE MONITORING

While most of the renal stones are diagnosed because of symptoms, asymptomatic stones (i.e.calyceal stones, stones in calyceal diverticulum, staghorn calculi) are found incidentally during abdominal imaging for other reasons. Any calyceal stone was not used to be operated when open surgery was the only way for treatment of urinary calculi. Today, there is tendency to treat any stone regardless the size and location by extracorporeal shock wave lithotripsy (ESWL), percutaneous nephrolithotripsy (PNL) and ureteroscopy (URS). The overall success rate of ESWL is 70% for all renal calculi while PCN provides 90% success rate with higher morbidity.

In a prospective randomized study the stone free rate was 37% for ESWL and 95% for PCN in the treatment of lower pole calyceal stone [1]. Stone free rate for retrograde ureteroscopic lithotripsy is differs from 50% to 80% for renal stones smaller than 2 cm. Recently, laparoscopy is being performed for special conditions such as larger or impacted ureteral stone and pelvic stone which is not suitable for PCN and URS. The goal of any treatment is to render the patient stone free after the procedure, because of the residual fragments can be the precursor of new stone formation. There is no doubt any symptomatic urinary stone shoud be treated accordingly, but it is still controversial which asymptomatic stone should be treated or not. In this chapter active monitoring of stone patients, early diagnosis and management of any residual fragment after the treatment will be discussed.

1. STAGHORN STONES

When the open surgery was the only choice for treatment of urinary calculi, staghorn calculi were better left untreated because of high morbidity and poor results. However, conservative treatment resulted with loss of renal function and subsequent renal insufficiency. Blandy and Singh reviewed 185 patients with staghorn calculi. Sixty patients were treated conservatively while 125 underwent open surgery for removal of the stone[2]. The mortality rate was 7.2% and 28% for observation and treatment group, respectively over a 10 year period. In another study, Koga et al followed 167 patients with staghorn calculi and one third of those developed chronic renal failure while 7 died because of uremia [3]. Similarly, Vargas et al followed 22 patient with staghorn calculi conservatively and half of those patients developed either renal deterioration or urinary tract infection while 2 died of urosepsis [4]. These findings are enough for that any staghorn stone should be treated surgically unless the patient is not fit for the procedure. (**Evidence Level II/B**).

2. ASYMPTOMATIC AND/OR INCIDENTALLY DIAGNOSED RENAL STONES :

Incidentally diagnosed asymptomatic urinary calculi are getting more and more in our practice. It was reported that the incidence of calyceal stones smaller than 10 mm. treated by ESWL increased from 36% to 50% [5, 6]. In a retrospective study, an increase in the size of asymptomatic renal stones was observed in 45% of the patients within 7.4 year follow up [7]. Sixty-eight percent of those patients developed urinary infection. The authors concluded that majority of those patients would require intervention within the first 5 years. Glowacki et al reviewed the records of 107 patients with asymptomatic calculi with a mean 31.6 months follow-up [8]. Of the patients, 32% became symptomatic and spontaneous passage occurred in 15% while 53% needed intervention. They concluded that the risk of symptomatic episode or need for intervention was nearly 10% per year with a cumulative 5-year event probability of 48.5%. In a prospective randomized study, Burgher et al reviewed 300 male patients who were followed for a mean of 3.26 years for asymptomatic renal calculi [9]. The mean stone size was 10.8 mm and 56% were lower pole calyceal stones. Disease progression was observed in 77% of the patients while 26% required surgical intervention. They observed that stones larger than 4 mm. have more risk to be symptomatic, and upper or middle calyceal stones have less risk for growth than those in lower pole. They also pointed out that the targeted medical therapy may be protective for stone growth but does not decrease the intervention rate, even in uric acid stone patients. In a prospective randomized study recently, Inci and colleagues reported the results with long-term follow-up of asymptomatic lower pole calyceal stones in 24 patients [10]. Disease progression was observed in one third of the patients and 3 needed surgical interventions. These studies revealed that approximately one third of asymptomatic renal stones might be symptomatic in 2-3 years requiring intervention while some of those would pass spontaneously. (**Evidence Level III/B**). Keeley et al treated a group of patients with asymptomatic calyceal stones by ESWL. Of the 200 patients, stone free rates were 28% and 17% in the treatment and observation group, respectively [11]. However 10 patients in the observation group required invasive procedures. In this study, 72% of the patients had lower pole calyceal stones and the conclusion was ESWL did not improve the clinical outcome in patients with small asymptomatic calculi (**Evidence Level II/B) (Table 1).**

3. POST-PROCEDURAL RESIDUAL STONES

Before the availibility of ESWL and endourological procedures, presence of stone fragments was considered evidence of failure after the open surgery. The number of asymptomatic calyceal stone patients resulting from ESWL or other endourological procedures are increasing. Residual fragments should be followed for occurrence of urinary obstruction, persistent infection and regrowth. The presence of asymptomatic, nonbstructive, noninfectious residual fragments smaller than 4-5 mm termed clinically insignificant residual fragment (CIRF) . In several studies it was reported that residual fragments are still present in 24% to 36% of patients 3 months after ESWL treatment [5, 12, 13]. Demirkesen and colleagues treated 2566 renal unit with ESWL and 68 renal units (2.7%) had congenital upper tract abnormalities [14]. The stone free rates were 56% and 78% for anomalous kidney group and normal group, respectively. Clinically insignificant fragments were detected in 37% and 18.5% of patients with anomalous kidney and normal anatomy, respectively. They concluded that the fragmentation rate is similar, but clearance rate of the fragments was lower in patients with congenital abnormalities. If the patient is not rendered stone free, a 50-80% incidence of stone growth or new stone formation will be observed in those patients [15, 16, 17]**.** There has been concern about the fate of CIRF in the long term both for becoming symptomatic and/or larger. Streem prospectively followed 160 patients who had CIRFs after ESWL for a mean of 23 months and 18.1% regrowth rate was detected. Symptomatic episodes or need for intervention occurred in 43.1% of the patients with a mean of 26 months follow-up [18]. They concluded that the term clinically insignificant fragment is a misnomer. In two similar studies in which the fate of CIRFs were evaluated, the authors concluded that this term shouldn't be employed to describe residual fragments after ESWL and efforts should be performed to obtain stone free status after the procedure [19, 20]. Recently, Osman and colleagues showed that 78% of CIRFs passed spontaneously, and only 21.4% of patients with CIRF had recurrent stones requiring treatment after ESWL within the 5 year follow-up. They noted that close follow-up and adequate metaphylaxis were required [21]. Rassweiler et al reviewed the literature consisting almost 14,000 patients for long-term results of ESWL on renal stones comparing with two major center in Germany. They underlined that newer ESWL technology has increased the CIRF rate and in the series 25% to 55% of those fragments passed spontaneously or remained clinically insignificant within 2 years. The authors indicated that any endoscopic procedure for the treatment of residual fragments is over treatment in asymptomatic patients

Table 1. Studies for follow-up of asymptomatic renal stones

	Number of patiens	Type of study	Follow-up Mean (months)	Stone Size (mm)	Stable %	Symp+ or Disea progr %	Spontan. passage %	Interven. Required %
Hubner et al, 1990	62	Retrospt	88.8		55		16	40
Glowacki et al, 1992	107	Retrospt	31.6		68	32	15	53
Keeley et al, 2001	99	Prospect	26.4	< 15			17	15
Burgher et al, 2004	300	Retrospt	39	10.8		77		26
Inci et al, 2007	24	Prospect	52.3	8.8		33.3		11

[22]. They suggested the appropriate medical therapy would control the active stone formation following shock wave lithotripsy. Zanetti et al reviewed the long-term outcomes and therapeutic implications of selected group of patients with asymptomatic residual fragments, 3 months after ESWL. A total of 129 patients with residual fragments less than 4 mm at 3 months were re-examined at 12 months. At the 12 months follow up, 60 patients (46,5%) were stone free and 56 still had CIRF. Stone regrowth occurred in 13 patients [23]. Recently, El-Nahas et al followed 154 patients with fragments smaller than 5 mm after ESWL treatment, by noncontrast CT every 6 months or when symptoms developed [24]. Struvite stones excluded from the study because of high rate of stone progression. They reported that 48.7% of those fragments became clinically significant stones requiring ESWL in 50 , percutaneous nephrolithotomy in 2 and medical treatment for symptomatic episodes in 23 patients. They concluded that the term CIRF is not appropriate for all post-ESWL fragments as almost half of these fragments become clinically significant (**Evidence Level III/B**).

Some studies concerning medical treatment of recurrent stones after the procedure showed satisfactory results [25]. Metabolic evaluation is recommended in patients who have risk of recurrent stone disease. In a randomized study, Cicerello et al evaluated the effectivity of citrate intake and antibiotic (when infection is present) treatment in patients who had residual calcium and struvite stones after ESWL [26]. They found that the stone free rate was 32% and 40% in untreated calcium stone and infection stone patients, respectively at 12 months. In the treated group, the stone free rate was 74% and 86% in the same order, at 12 months. In a retrospective nonrandomized study, Fine et al reported that the patients with CIRF after ESWL who did not continue on medical therapy were under the higher risk for recurrence and regrowth [27]. Soygur et al designed a randomized prospective study including 56 patients who were stone free (Group I) and 34 patients who had residual fragments (Group II) after ESWL treatment for lower pole calyceal stone [281]. Both group were randomized for no treatment and potassium citrate intake. In group I the recurrence rate was 0% and 28.5% in treated and untreated patients, respectively. In group II who had residual fragments after ESWL, the recurrence rate was 12.5% and 44.5% in treated and untreated patients, respectively (**Evidence Level II/B**). Contrary to this Osman et al found no relation between metaphylaxis and stone regrowth [21]. Although most of the studies suggested that metaphylaxis after ESWL reduces the risk of recurrence or stone regrowth, further randomized controlled studies should be performed with a standardized imaging method.

One of the important issue is the imaging method used in determining of residual fragments. All imaging modalities have different sensitivities. Denstendt et al reported the endoscopic and radiological evaluation of residual fragment rates following PNL and ESWL. They found that plain abdominal radiographs and renal tomography overestimated stone free rates by %35 and %17 respectively, compared with flexible nephroscopy [29]. Use of plain abdominal films alone are the most difficult to interpret, resulting in the highest uncertainty about the presence of residual stones [30, 31].

Several reports evaluated the sensitivity of ultrasound in the detection of urolithiasis to be between %65 and %95 [32, 33]. Ultrasound is inadequate for determining the stone burden and also differentiation of intact stones from fragmented ones [9]. The sensitivity of computerized tomography (CT) has shown to be superior to plain radiography and USG in detecting post procedural residual stones [34] **(Evidence Level III/B)**. These findings are also presented in **Table 2.**

Table 2. Studies for follow up of post ESWL residual fragments

	Number of patiens	Type of Study	Follow-up Mean (months)	Stable %	Inc size or Disea prog %	Stone Free %	Interven. Required %	Type of interven. (n)
Streem et al, 1996	160	Prospect	23	41.9	18.1	23.8	27.5	ESWL:35 PNL:1 RIRS:1
Zanetti et al, 1997	129	Retrospt	12	43.5	10	46.5	14.7	
Buchholz et al, 1997	55	Retrospt	30	12.7	2	87.3	2	
Candau et al, 2000	97	Retrospt	40.6	29	37	33	22	ESWL:13 PNL:3 RIRS:1
Khaitan et al, 2002	75	Prospect	15	17	58	24	30	ESWL:16 PNL:3 RIRS:4
Osman et al, 2005	76	Prospect	57	27.3	21.4	51.3		
El-Nahas et al, 2006	154	Prospect	31	52.6	33.8	13.6	48.7	ESWL:50 PNL:2

RECOMMENDATIONS

Recommendation	*Level of Evidence*
Any asymptomatic renal pelvic stone or staghorn calculi in a good functioning kidney should be treated to prevent the loss of renal function and occurence of urinary infection. Observation without any treatment should be reserved for unfit patients for intervention.	**III/B**
Asymptomatic small renal stones should be followed for possibility of disease progression and urinary infection.	**II/B**
Invasive treatment is not recommended for CIRF because some of those will pass spontaneously or will not require treatment.	**II/B**
Fragments larger than 4-5 mm have greater risk to become symptomatic.	**III/B**
The prophylactic ESWL treatment of asymptomatic renal stones or CIRFs is not superior to observation. However ESWL is the first choice of treatment for those patients when required.	**II/B**
Targeted medical treatment may prevent stone growth but does not improve the fate of any asymptomatic stone.	**III/C**

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II. RESIDUAL STONE FRAGMENTS: AN EVIDENCE BASED APPROACH TO MEDICAL TREATMENT

1. INTRODUCTION AND DEFINITIONS

In 1986, Lingeman et al reported a 96% successful result with shock wave lithotripsy (SWL) using an unmodified Dornier HM-3 lithotripter. However, 25% of the successfully treated patients had "clinically insignificant residual fragments", defined as residual calculi less than 5mm in diameter which were asymptomatic and not composed of struvite or associated with infection (1). Since then, residual stone fragments represent a common and still controversial problem of SWL, percutaneous nephrolithotomy (PNL) or ureterolithotripsy (URS). Still, the definition of residual fragments has not been well established. In the era of open stone surgery, residual fragments of any size suggested a failed procedure. With the advent of SWL, all fragments remaining in the kidney 3 months after the last session of SWL are defined as residual fragments. Those fragments larger than 5 mm are generally considered to indicate a failure for SWL (2) **(Evidence level III/B).** By extent any fragments remaining following PNL or URS are considered as residual fragments. The issue of residual fragments becomes more complicated with the advent of the term "clinically insignificant residual fragments (CIRF)". The definition of CIRF which has prevailed describes post treatment stones that are smaller than 4-5 mm, asymptomatic, non-obstructive, non-infectious, and associated with sterile urine (3, 4) **(Evidence level III/B).** By extension this term also defines stones of similar characteristics left behind after percutaneous nephrolithotomy or ureteroscopic procedures (2, 3) **(Evidence level III/B).** The choice of size limit of <4-5mm has not been based on solid statistical observations from previous studies **(Evidence level III/B).**

In patients with infection related calculi, the consequence of residual fragments is particularly harmful. Residual fragments may harbour the offending bacteria and thus perpetuate postoperative bacteriuria and persistent infection. Furthermore, stone regrowth has been reported in up to 75% of such patients after SWL, compared with 10% of patients who experienced complete stone removal (5, 6) **(Evidence level III/B).** For patients with metabolic stone disease, complete stone removal does not prevent stone recurrence, but it does prolong treatment intervals (7) **(Evidence level IIb/B).** Thus residual stones, including small stones, in these categories, may not have an immediate clinical relevance but are likely to affect patient's well being in the long term. In these situations, it is important to select a treatment approach that is more likely to render the patient stone free.

2. OUTCOME OF CLINICALLY INSIGNIFICANT RESIDUAL FRAGMENTS (CIRF)

Residual stone fragments may be important for several reasons. They may act as a nidus for recurrent stone growth, especially when underlying metabolic abnormalities persist, they can become dislodged acutely and cause significant obstruction with pain, or they may be the source of persistent infection (3). Several studies have stressed the fate of residual stone fragments after SWL (**Table 1**) (5, 6, 8-15).

Table 1. Fate of residual stone fragments following SWL

Series	No of patients	Mean follow-up in months (range)	Stable (%)	Regrowth (%)	Stone free (Spontaneous passage) (%)
Beck	53	26.6	11	78	11
Moon	248	6	-	-	92.7
Streem	160	23 (1.6-88.8)	43.5	10	46.5
Buchholz	55	54	12.7	2	85.3
Zanetti	129	12 (3-12)	43.5	10	46.5
Candau	83	40.6 (7-96)	29	37	34
Khaitan	81	15 (6-60)	17.3	58.7	24
Afshar*	26	46	31	69	-
Osman	76	57 (52-63)	27.3	21.4	51.3
El-Nahas	154	31 (7.3-80.2)	52.6	33.8	13.6

* Paediatric population

For a mean follow-up range between 6 and 57 months spontaneous stone passage noted in 11-92.7% of cases. The spontaneous clearance rate was highest for stones located in the ureter and lowest for the lower pole stones. Stone remained stable in a rate of 11% to 52.6%, while stone re-growth was encountered in 2% to 78%. The wide spectrum of the above results is attributed to the nature of the studies. Most of these studies presented the retrospective experience of the respective authors **(Evidence level III/B).** In addition, different methods of reporting treatment results, different radiologic evaluation of residual stones, different site and size of the residual stones and record of patients' follow-up data at different times (1 versus 3 months) after the last session of SWL, were the main restrains of these studies **(Evidence level III/B).** Rassweiler et al in an extensive review of the literature depicted that 25% and 55% of patients with CIRF would be stone-free or remain clinically insignificant during follow-up, respectively (4). 20% of CIRF would become clinically significant and 4-25% of patients would require a secondary intervention which mostly would consist of a repeat SWL. The authors concluded that if there are no clinical symptoms, any endoscopic procedure should be considered as over-treatment (4) **(Evidence level III/B).**

The natural history and clinical significance of small, asymptomatic, non-infection related stone fragments after SWL were prospectively evaluated in four studies (9,10, 12,14) **(Evidence level IIb/B).**

In total, 463 patients with CIRF <5mm in diameter were prospectively followed for a mean period of 15 months (12) to 4.9 years (14). Stone-free status or a stable or increased amount of residual stone ranged from 23.8% to 78.9%, 10.7% to 41.9% and 2% to 58.6%, respectively. 41.4-100% of patients remained asymptomatic, while 0-58.6% had a symptomatic episode or required intervention 1.6 to 85.4 months after SWL. The intervention required was relatively non-invasive and consisted of either repeat SWL or retrograde endoscopy. As the stone burden and number of stone fragments increased, and when the fragments were located in the lower calyces, the risk of CIRF becoming clinically significant increased (9, 12, 14). Also, as the duration of follow-up increased, the rate of complications increased (12). Metabolic defects, when treated adequately, did not increase the re-growth rate (12, 14). The results of these studies indicate that while patients with small CIRF after SWL could be followed expectantly, a significant number would require intervention or have symptomatic episodes during follow-up **(Evidence level IIb/B).** As a consequence the term CIRF after SWL may not be appropriate.

3. SURGICAL MANAGEMENT OF RESIDUAL FRAGMENTS

In the past, several authors have not recommended systematic SWL re-treatment for all asymptomatic patients with residual stone fragments after an initial session of SWL (4, 6, 10, 16) With the exception of the study performed by Buchholz et al (10) **(Evidence level IIb/B)**, the above recommendation emerged from the results of reviews or retrospective studies **(Evidence level III/B).** Buchholz et al (10), in a study of 55 patients with CIRF showed that only 12.7% of the residual fragments had not passed spontaneously after a mean follow up of 2.5 years. All of them were clinically silent and only in 2% of the cases stone re-growth was shown. No stone recurrences were observed within the follow-up period. The authors concluded that more invasive procedures to clear all minor fragments are not warranted **(Evidence level IIb/B).** However, with emerging evidence (9, 10, 12, 14) **(Evidence level IIb/B)** showing that the term of CIRF could be a misnomer, mainly due to the fact that a great proportion of patients will require an intervention as the follow-up increases, several authors addressed the issue of early re-treatment of residual fragments after an initial intervention (8, 17-20).

Parr et al (17) in a retrospective study showed that additional extracorporeal lithotripsy for CIRF remaining after a mean of two (range 1-9) initial SWL sessions, promoted stone clearance only in those patients with non-dilated calyces. The small number of patients included in the study (n=22), the minor number of patients benefited from re-treatment (n=3) and the nature of the study do not allow for definitive conclusions to be drown **(Evidence level III/B).** In a retrospective study of Moon et al (8), the stone-free rate of 248 cases of CIRF was 32.7% by 1 month, 73.0% by 3 months, and 92.7% by 6 months of follow-up. Of 16 patients who had residual stone fragments at 6 months and underwent an additional session of SWL, 12 (75%) became stone free by another 6 months of follow-up. The authors suggested that repeated SWL, even for stone fragments of 3 to 4 mm in diameter, might promote clearance of the CIRF **(Evidence level III/B).** This was confirmed in a prospective randomized study conducted by Krings et al (18) **(Evidence level 1b/A).** Piezoelectric SWL re-treatment was compared to surveillance only in 50 patients with persistent caliceal stone fragments after primary SWL for renal calculi. After a 3-month follow-up significant decreases in residual debris were observed in the retreated group, while changes in the control group were negligible. The authors suggested that considering the low morbidity of outpatient SWL with a pain-free, second generation lithotripter, SWL re-treatment of completely fragmented but persistent stone debris appears to be justified to render the kidney stone-free. Still, the advantages of a higher stone-free rate by SWL re-treatment must be weighted against potentially higher side effects and the additional cost.

Recently, an adjunct to the clearance of lower pole calculi after SWL emerged in the form of the mechanical percussion and inversion with or without diuresis (21). In a study of Chiong et al (21), 108 patients with lower pole calculi ≤ 2 cm were prospectively randomized to undergo SWL alone or SWL followed by mechanical vibration, inversion and diuretic therapy. The radiologically documented complete stone clearance rate at 3 months for the first group was 35.4% while for the second group was 62.5% ($p = 0.006$) **(Evidence level Ib/A).** The same treatment modality has been applied in a prospective randomized manner for CIRF after SWL (19). Pace et al compared the effectiveness of mechanical percussion and inversion with observation for 1 month, for eliminating caliceal fragments of less than 4mm 3 months after shock-wave lithotripsy. The mechanical percussion and inversion group had a substantially higher stone-free rate (40% versus 3%, $p<0.001$) and a greater improvement in total stone area (-63.3 versus + 2.7%, $p<0.001$) than the observation group **(Evidence level Ib/A).** No significant adverse effects were noted in either two groups. The authors stated that mechanical percussion and inversion is a safe and effective treatment option for residual lower pole calculi.

4. MEDICAL TREATMENT FOR RESIDUAL FRAGMENT

Metabolic evaluation and stone analysis should be offered to patients who require surgical stone removal. Pearle and associates have emphasized the importance of the administration of medical therapy in reducing stone recurrences after treatment (22). In their meta-analysis of randomized trials for medical prevention of nephrolithiasis, they showed a significant benefit of drug therapy for calcium oxalate stones. This was mainly attributed to the benefit of using thiazides compared to placebo or no treatment. The design variability of the analyzed studies precluded adequate analysis of other drug therapies such as alkali citrate or allopurinol **(Evidence level 1a/A).**

Apart from preventing stone recurrences, medical therapies to ease urinary-stone passage have been reported (23). Hollingsworth and associates have recently published the results of a meta-analysis of all randomized controlled trials in which calcium-channel blockers or alpha blockers were used to treat urinary stone disease (23) **(Evidence level 1a/A).** Authors' findings extracted from nine trials encompassing 693 patients, suggested that medical therapy is an option for facilitating urinary stone passage for those patients amenable to conservative management, potentially obviating the need for surgery. Patients given calcium-channel blockers or alpha blockers had a 65% greater likelihood of stone passage than those not given such treatment. The pooled risk ratio for alpha blockers was 1.54 (1.29-1.85) and for calcium-channel blockers with steroids was 1.90 (1.51-2.40). The proportion of heterogeneity not explained by chance alone was 28%. The number needed to treat was 4.

In the venue of these results several authors have addressed the issue of medical therapy in the management of residual stone fragments after SWL or PNL (24-28) (**Table 2**). Fine et al in a retrospective non-randomized study evaluated the fate of residual stone fragments after SWL in regard to whether the patients were or were not put on medical therapy after the procedure (24). 49 patients with residual fragments after SWL were identified. Of them, 36 received medical therapy in the form of thiazide diuretics, sodium cellulose phosphate, allopurinol, potassium citrate and a-mercaptopropionylglycine, based on specific indications. 13 patients chose to stop medical treatment within 4 months after SWL. Patients on medical therapy experienced a significant decrease in the stone-formation rate from a median of 1.17 to 0.00 stones per patient per year ($p<0.001$). In those patients not on medical therapy there was only a minimal decrease in the stone-formation rate from a median of 1.33 to 0.77 stones per patient per year. The medically treated patients had a significantly greater stone remission rate than the untreated patients (63.9% versus 23.1%, $p<0.05$). 27.8% of the patients showed an increase in stone burden during medical treatment compared to 61.6% without medical treatment. Moreover, while 13.9% of the treated patients demonstrated a decrease in stone burden, none of the untreated patients showed decreased stone mass. The authors

Table 2. Medical therapy effect on residual stone fragment activity.

Reference	Stone free		Stone size unchanged or decreased		Stone size increased**	
	Medical therapy	Control	Medical therapy	Control	Medical therapy	Control
Cicerello*	80.5%	36%	75%	52.6%	5%	47%
Soygur*	44.4%	12.5%	56.6%	25%	-	62.5%
Sarica*†	-	-	81.8%	27.2%	18.2%	72.8%
Fine	58.3%	38.4%	13.9%	0%	27.8%	61.6%
Kang* **	77%	21%				

*Randomized controlled studies

**Re-growth and/or recurrence rate included

***Stone remission rates after PNL.

†Study in children

specifically assessed the significance of clinically insignificant residual stone fragments (CIRF; stones <5mm in diameter). Among the 49 patients, 36 had CIRF. 25 of them received medical therapy while 11 did not. 16% of those treated medically demonstrated fragment growth compared to 54.5% of the untreated patients ($p<0.05$). This retrospective study **(Evidence level III/B)** early indicated that medical therapy may control active stone formation in patients with residual stone fragments following SWL (24).

These results were confirmed by three prospective randomized trials. Cicerello et al showed that citrate intake reduced growth or agglomeration and increased the clearance rate of residual fragments after SWL in calcium oxalate and in infection stone patients **(Evidence level Ib/A)** (25). The authors prospectively randomized 40 sterile calcium and 30 struvite stone patients with residual fragments <5 mm in diameter after SWL, into two groups: one on citrate therapy (6 to 8 gm per day) and the other on hygienic measures only, served as the control group. Infection stone patients also received adequate antibiotic therapy throughout the study. After one year of follow-up residual fragments disappeared in up to 74% of the citrate treated calcium oxalate patients and in up to 86% of the citrate treated infection stone patients. In the control group the percentages were 32% and 40%, respectively. During the 12-month follow-up, residual fragment growth or re-aggregation occurred in 47% of the calcium oxalate control patients compared to 5% of the calcium oxalate citrate treated patients. None of the treated or control infection stone patients in whom stone fragments persisted at the end of follow-up had growth or re-aggregation of residual fragments (25).

Similar results were found in the study of Soygur et al, who prospectively randomized 34 patients with lower pole residual stone fragments after SWL into two subgroups that were matched for sex, age, and urinary values of citrate, calcium and uric acid (26) **(Evidence level 1b/A)**. One group was given oral potassium citrate 60 mEq per day, and the other group served as controls. The stone recurrence rate at 12 months in the group who were on citrate therapy was significantly less than in the control group (56.6% versus 87.5%, respectively). Stone fragments disappeared in 8 of the 18 patients (45.5%) and remained the same size in 10 of the 18 patients (54.5%) who continued medical therapy. In the control arm, only 2 patients (12.5%) demonstrated disappearance of residual stone fragments. In 4 patients (25%), residual fragments remained unchanged (26).

Medical treatment seems to prevent stone regrowth or stone formation in children with residual stone fragments after SWL. Sarica et al randomized 44 children, in whom stones <5mm in diameter persisted after SWL, into two groups (27). Group I (n=22) received potassium citrate 1 mEq/Kg/day for 12 months under close follow-up. Group II (n=22) received no specific medication or preventive measure and constituted the control group. Children on medication showed significantly lower re-growth and recurrence rates compared to children in group II (4/22; 18.1% vs 16/22; 72.7%, respectively). Moreover, the mean size of the residual fragments in patients receiving no therapy demonstrated a significant increase to baseline compared with the children on medication. Whereas the mean size of the residual fragments in Group II was 3.6mm a month after SWL, it was 5.4mm after a year ($p<0.05$). There was no significant change in children undergoing potassium therapy, with values of 4.0mm before and 4.4mm at one year, respectively ($p>0.05$) (27) **(Evidence level Ib/A).**

Finally, there is some evidence **(Evidence level III/B)** suggesting that medical management can control active stone formation in patients with residual stone fragments after PNL (28). Kang et al retrospectively reviewed the medical records of 40 patients who had residual stone fragments after percutaneous lithotripsy (28). Of those patients, 26 received medical therapy as follows: potassium citrate for hypocitraturia, renal tubular acidosis, chronic diarrheal calciuria; and allopurinol for hyperuricosuria. Some patients were prescribed more than 1 medication. Stone formation rate (SFR) was calculated for each patient. New stone formation was assessed by stone passage without change in the number of residual fragments, surgical removal of newly formed stones, the appearance of new stones, or an increase in size of stone fragments on abdominal radiographs. Remission rates were assessed following initiation of medical therapy and were calculated as the percentage of patients with no further evidence of active stone disease throughout the length of their follow-up. Patients on medical therapy exhibited a lower median SFR (0.02 versus 1.00 stones per patient per year) and a higher remission rate (77% versus 21%) compared to patients not on medical therapy, supporting the role of medical treatment in inhibiting new stone formation or growth in patients with residual fragments following PNL (28).

5. CONCLUSION

The definition of "clinically significant residual stone fragment" is based on arbitrarily set criteria. There is some evidence supporting that as the burden and number of clinically insignificant residual fragments increases the risk of becoming clinically significant also increases. Moreover, as the duration of follow-up increases, the rate of complications and the need for intervention due to symptomatic episodes also increase. SWL re-treatment, with or without patient inversion, of completely fragmented but persistent stone debris appears to be justified to render the kidney stone-free. Medical therapy can control active stone formation, reduce growth or agglomeration and increase the clearance rate of residual fragments after SWL. Medical therapy may control active stone formation and growth in patients with residual stone fragments after PNL.

RECOMMENDATIONS

Recommendation	*Level of Evidence*
Clinical Insignificant Residual Stone fragment" (CIRF) is based on arbitrarily criteria	**III/B**
As the burden and number of CIRF increase the risk of becoming clinically significant increases.	**IIb/B**
As the duration of follow-up increases, the rate of complications and the need for intervention for symptomatic episodes due to CIRF increases.	**IIb/B**
ESWL re-treatment of completely fragmented but persistent stone debris appears to be justified to render the kidney stone-free	**Ib/A**
Medical therapy can control active stone formation, reduce growth or agglomeration and increase the clearance rate of residual fragments after SWL.	**Ib/A**
Medical therapy may control active stone formation and growth in patients with residual stone fragments after PNL.	**III/C**

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III. EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY FOR RENAL STONES

The progresses in minimal invasive techniques due to the advances in technology have greatly reduced the number of patients with renal stone requiring open surgery. The current concept is to provide the maximum benefit with minimal morbidity to the patient when treating the renal stones. Extracorporeal shock wave lithotripsy (ESWL) has become established as the preferred treatment modality for renal stones up to 2 cm [1]. ESWL is characterized by a low complication rate and by a few absolute contraindications. Currently, the contraindications to ESWL are limited to pregnancy, aortic and/or renal aneurysms and coagulation disorders [2]. However, treatment outcome following ESWL depends on several factors. The type of lithotriptor, stone characteristics (i.e. number, size, composition and location), renal anatomy and function are important parameters in determining treatment characteristics and outcome. Auxiliary procedures used before and after treatment, complications, and cost effectiveness are also considered when evaluating the treatment efficacy. Additionally, the evaluation the results of ESWL with the different imaging methods may alter the stone free and residual stone rates [3,4,5].

First-generation lithotriptors required epidural or general anesthesia. With the development and introduction of second and third generation lithotriptors, ESWL treatment has become more feasible with minimal analgesia or without anesthesia on outpatient setting [6]. These changes has led to treatment with lower complications and expanding indications (i.e. treatment of large or staghorn stones). However, loss of stone fragmentation efficacy with second and third generation lithotriptors, and improvement of endourologic instruments (i.e. flexible ureteroscopes, holmium laser lithotripsy, nitinol basket) have led to controversies regarding the first-line treatment choice [7].

Recently, numerous studies have focused on the equipments (i.e. electrohydraulic, electromagnetic and piezoelectric) [8,9,10,11,12] and modifications in shockwave delivery method (i.e. duration, frequency of shocks wave and twin-pulse technique) [13-18] to improve the effectiveness of ESWL monotherapy. Furthermore, the recent reports have demonstrated that modern imaging [19-22] and statistical methods (i.e. artificial neural network) [23-25] may provide more effective assistance for identification of the best and worst candidates for ESWL 7.

1. RESULTS

Not only the results, but also the complications and re-treatment rates of ESWL may vary with the type of the machine mentioned above. Over the years, many authors have reported their results with major differences regarding the machines, stone and treatment characteristics, stratification for stone size and definition of the results. There is no consensus on ESWL terminology [26]. Hence, comparison of the studies is almost impossible.

In clinical practice, one of the most useful way to compare performance of the lithotriptors has been described by Denstedt et al as the efficiency quotient (EQ) [27]. EQ is a more objective means of evaluating treatment outcome since factors such as re-treatment rate and auxiliary procedures in addition to stone free rate are assessed during the first 3 months of follow-up.

EQ is calculated by the following formula:

$$EQ : \frac{\text{Stonefree \%}}{\text{Stonefree \%100 + \% re-treatment rate+ \% auxiliary procedures}} \text{ x } 100$$

In the European Guidelines on Urolithiasis [xxviii], active treatment was suggested for all stones greater than 6– 7 mm.. For renal stones smaller than 2 cm, ESWL in situ is considered the first-line treatment for all radio-opaque stones **(Evidence Level IA)**, with the addition of antibiotics for infectious stones. **(Evidence Level IIB**). ESWL is the recommended treatment for cystine stones up to 2 cm. **(Evidence Level IIB)**. Uric acid stone is the only one that oral chemolysis is the preferred treatment **(Evidence Level IIB)**. Percutaneous nephrolithotomy (PNL) is the first-line treatment for stones greater than 2 cm. **(Evidence Level IB)**.

For staghorn stones (either partial or complete), the preferred treatment modality is again PNL and the role of ESWL remains as a part of the combination with PNL **(Evidence Level IA)**. Only in patients with smaller staghorn stone and a nondilated system, ESWL monotherapy should be considered as a reasonable alternative **(Evidence Level IIIC)**. The combination of PNL and ESWL appears to be superior to ESWL and subsequent PNL **(Evidence Level IA)**.

2. SPECIAL SITUATIONS

a) Lower pole calyceal stones

The relative incidence of isolated lower pole calyceal stone (LPS) has been increasing in the last decade and has reached a plateau since 1990 [29,30]. The optimal management of lower pole stone disease remains controversial. The clearance rather than stone disintegration of LPS after ESWL is significantly inferior comparing to other localizations of the kidney. Although the role of ESWL for the management of LPS has been questioned in some studies [29,31,32], many have suggested its use as a primary treatment modality for stones smaller than 2cm. [33-35]. Lingeman et al performed a meta-analysis of 13 studies published on the management of LPS with ESWL. They reported a stone-free rate of 59% in a meta-analysis of 2927 patients. When stratified according to stone size, the stone free rates for stones smaller than 10mm., 10 to 20mm., and greater than 20mm. were reported to be 74%, 56% and 33%, respectively29. Obek et al compared the results of isolated LPS with those of isolated middle and upper calyceal calculi and found that the stone free rate was 70%, 57% and 53% in the same order35. May and Chandoke reported stone free rates of 76%, 74% and 33% in a single session in solitary lower pole stones, less than 10mm., 10-20mm., and greater than 20mm., respectively33. These results seem to be good enough to still choose ESWL as a least invasive treatment for LPS smaller than 2 cm. **(Evidence Level IIIB)**

Recently, three prospective randomized trials for the treatment of LPS were reported. In a multi-center study comparing PNL to ESWL for LPS, Albala and colleagues found that the overall stone-free rate was 95% after PNL and only 37% after ESWL, whereas stone-free rate for stones 2 cm or less was 96% and 40% for PNL and ESWL, respectively. They suggested that PNL might be the preferred treatment modality for decreasing cost of treatment and avoiding additional procedures especially in patients with LPS greater than 1cm. 32. Another prospective, randomized study comparing ESWL and retrograde ureteroscopic stone removal for LPS up to 1 cm. in 67 patients showed a stone-free rate of 35% and 50% for ESWL and ureteroscopy, respectively. They did not reveal a statistically significant difference and stated that ESWL should be offered first because of greater patient acceptance and shorter convalescenc [36]. The third prospective multi-institutional randomized trial comparing ESWL, PNL, and flexible URS for lower calyx stones was published by Preminger. In this study, stone-free rate for stones less than 1 cm. in diameter was 67% and 100% for SWL and PNL, respectively. However, stone free rate for stones between 1.1 and 2 cm. were 21 and 92% for ESWL and PNL, respectively. Additionally, the author noted that ureteroscopic management of renal stones appeared as a reasonable alternative for patients with bleeding diatheses, renal anomalies, solitary kidneys or morbid obesity [37]. (Level IIIB)

The other controversy regards the geometrical features of the lower calyx anatomy. While some authors reported that calyceal anatomy was predictive of stone clearance after ESWL for LPS [38-42] contrary to this others found that anatomic parameters did not have a significant impact on stone clearance [32,36,43]. Sampaio and Aragao first described the impact of lower pole spatial anatomy on stone clearance [39]. They stated that a lower pole infundibulopelvic angle less than 90 degrees, lower pole infundibular width less than 4 mm. and multiple lower pole calyces may decrease stone free rate41. Elbahnasy and colleagues used a different method to measure the lower pole infundibulopelvic angle [42]. They found three unfavorable parameters: lower pole infundibulopelvic angle less than 90 degrees, infundibular width less than 5 mm. and infundibular length greater than 3 cm. In addition, Tuckey et al described pelvic calyceal height as an important parameter for stone clearance [44]. On the contrary, Madbouly et al reported that the lower pole renal anatomy had no influence on stone clearance44. Similar results were also declared by Albala and colleagues32. Recently, Danuser et al published a newsworthy study regarding the anatomic features of lower calyceal system. In their logistic regression analysis, they did not find any of the anatomic factors to have a significant influence on stone clearance and underlined the current opinion of the European Association of Urology (EAU) guidelines on urolithiasis36. **(Evidence Level IIIB)**

b) The use of stents prior to ESWL

In a survey among American urologists, despite the lack of scientific evidence regarding the frequent use of internal ureteral stents, routine stent placement before ESWL for patients with renal pelvic calculi 1, 1.5 and 2 cm. was preferred by 25.3%, 57.1% and 87.1% of urologist, respectively [45]. Previous studies suggested that ureteral stents might reduce the number of complications after

ESWL such as obstruction, sepsis and pain [46]. In addition, another study reported that ureteral stents contributed to the successful passage of fragments in the treatment of renal stones larger than 2.5 cm. [47]. Anderson et al advocated the percutaneous debulking before ESWL or ESWL with prophylactic ureteral stenting for stones larger than 3 cm in diameter [48].

However, the use of ureteral stents in patients undergoing ESWL for renal calculi is still controversial. Low et al retrospectively reviewed the results of 179 patients with solitary renal stones treated with ESWL and found that there was no difference in stone-free rates at 1 and 3 months and need for retreatment with or without stent placement [49]. In a similar study, Sulaiman et al reported that the use of ureteral stents had no effect on the incidence of steinstrasse for patients with stones smaller than 2 cm [50]. Preminger et al also found no relationship between the use of a stent and an increased rate of free of stones following ESWL [51] (**Evidence Level IIIB**).

Two randomized study published by Pryor et al and Bierkens et al focused on the ureteral stent prior to ESWL [52,53]. Two studies underlined that stone-free rates in stented patients did not differ from those in non-stented. In addition, they concluded that ureteral stents should not be used in patients with large renal calculi, since they did not reduce post ESWL morbidity and they clearly had side effects of their own. **(Evidence Level IIB)**

Complications associated with ureteral stents include migration, infection, pyelonephritis, breakage, encrustation and stone formation [54,55]. In 290 patients with ureteral stents treated with ureteroscopy or ESWL, El-Faqih et al found an increasing stent encrustation rate of %76.3 beyond 12 weeks, %3.7 incidence of stent migration and %0.3 rate of stent breakage566. Joshi et al also reviewed the stent- related symptoms; a significant proportion of patients (%60) with ureteral stents had symptoms of increased frequency and urgency with or without urge incontinence. They also pointed that the stent-related symptoms were similar as described for an overactive bladder and the presence of a stent might unmask or exacerbate pre-existing, subclinical detrusor instability [56]. Recently, El-Assmy et al evaluated the outcome of ureteral stents prior to ESWL in patients with moderately and marked hydronephrosis. In this prospective, randomized, controlled clinical study, 93 stented patients were compared with 93 non-stented patients who had solitary ureteral stones 2 cm or less. All stented patients significantly complained of side effects attributed to the stent, but did not have a better stone-free rate (84.9% vs 91.4%) [57]. **(Evidence Level IIA).** In addition, Sighinolfi et al recently published a prospective study that ureteral stents impaired the quality of sexual life in male and female subjects [58].

3. CIRF

Asymptomatic, nonobstructive, noninfectious, residual fragments post-ESWL up to 4 or 5 mm associated with sterile urine termed clinical insignificant residual fragments (CIRF) [59]. CIRFs are commonly seen after ESWL, most frequently presenting in the lower calyx especially if the stone is larger. Notably, second and third generation lithotriptors have increased the CIRF rates. Residual stone fragments are less frequently visible on abdominal plain films than in conventional or spiral computed tomography scans [3,4]. As questioned by Danuser et al, if these CIRFs have no need for intervention, is it really necessary to evaluate stone-free rate using these more sensitive tools, with more radiation exposure? [36]. The study, with 5 year follow-up, recently published by Osman et al showed that 78% of CIRF pass spontaneously, and only 21.4% of patients with CIRF had recurrent stones requiring treatment. They noted that close follow-up and adequate metaphylaxis were required [61]. Rassweiler et al [60] reviewed almost 14,000 patients for long-term results of ESWL on renal stones. They underlined that small asymptomatic calyceal stones can be treated by lithotripsy and showed that passage of fragments may continue up to 2 yr post-ESWL. Authors indicated that any endoscopic procedure for the treatment of residual fragments is overtreatment in asymptomatic patients [60].

RECOMMENDATIONS

Recommendation	*Level of Evidence*
ESWL in situ is considered the first-line treatment for all radio-opaque stones up to 1 cm, with the addition of antibiotics for infectious stones	**IA, IIB**
Ureteral stenting for stones less than 2 cm does not increase the stone free rate or reduce complications	**IB**
Ureteral stenting should be considered for renal stones > 2 cm and in patients with risk factors including solitary kidney, advanced age, immobility, and poor medical condition	**IIIB**

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IV. PERCUTANEOUS NEPHROLITHOTOMY: AN EVIDENCE BASED APPROACH TO INDICATIONS, LIMITATIONS AND TECHNICAL DETAILS.

1. INTRODUCTION

Since Fernstrom and Johansson first removed a renal calculus through a nephrostomy tract in 1976 (1), percutaneous nephrolithotomy (PNL) has significantly changed and is continuing to evolve (2, 3) (**Figure 1**). Certain indications for percutaneous management of renal calculi have been established (4) (**Table 1**). The most important depend on the size and the composition of the stone, the site of the stone and the existence of obstruction distal to the stone, the certainty for the final result, the failure or the contraindication to SWL, and the presence of renal anatomic variation (4-8) **(Evidence level IIa/B, III/B, IV/C).** Apart from the aforementioned "renal" reasons for concern, several patient groups such as children, obese patients and those with a previous renal surgery require specific consideration before choosing PNL as a treatment option. PNL technique has also tremendously evolved over the last two decades. Our aim was to identify the level of the evidence published in literature supporting the indications, contraindications and the various technical details of percutaneous nephrolithotomy.

Figure 1. Percentage of papers on open surgery, PNL and ESWL for treating renal stones recorded in the MEDLINE database from 1980.

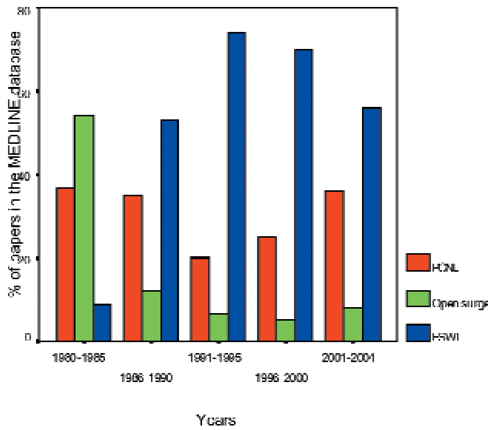

Table 1. Indication for percutaneous management of renal calculi

Stone size
Stone consistency
Lower calyceal stone
Stones associated with obstruction
Infection stones
Certainty of the final result
ESWL failure or contraindication to ESWL
Anatomic variation

2. PNL INDICATIONS AND LIMITATIONS

PNL as monotherapy has advantages in the removal of large stones, achieving excellent results with minimal morbidity (5). The point of transition for the term "large stone" is believed to be the 2cm (5) **(Evidence level IV/C).** Partial or complete staghorn calculi may require multiple punctures or the combination of PNL and SWL followed by repeat PNL (sandwich therapy) (6, 7) **(Evidence level IIa/B, III/B, IV/C).** PNL should be the preferred technique for patients with struvite stones. When these infected stones are removed completely by PNL, the patient has a 90% chance of remaining stone free for at least 3-years (6, 9) **(Evidence**

level IV/C). Compared to SWL (7) **(Evidence level IIa/B, III/B, IV/C)** or open surgery (6, 10) **(Evidence level Ib/A, III/B, IV/C,)** PNL, alone or in combination with SWL, results in higher stone free rates, lower procedures needed per patient rates (6), lower morbidity, shorter operative time, shorter hospital stay and earlier return to work (10). Treatment of lower pole caliceal stones should be guided by the diameter of the stone. In a meta-analysis of 1994, limitations of SWL included lower stone-free rates and higher re-treatment rates compared to PNL (11) **(Evidence level Ia/A)**. Large stones of the lower pole are best managed by PNL as a first treatment option, irrespectively to the anatomy of the lower pole (5, 11, 12). A large multicenter prospective randomized trial comparing PNL and SWL for lower pole calculi greater than 1cm (12) revealed stone-free rates significantly higher with PNL (91%) compared to SWL (21%). Re-treatment rate and ancillary treatments were higher for SWL (16% and 14%) as compared with those for PNL (9% and 2%) **(Evidence level Ib/A).**

However, PNL has a higher success rate in the cost of higher complication rates (6, 13) (**Evidence level IV/C**). As an alternative, flexible ureteroscopy and laser disintegration have been proposed for lower pole stones up to 2 cm (13). Despite recent technological advances, such as the use of ureteral access sheaths (14), which in theory increase irrigant flow and improve visualization, the success rate does not exceed 88% (15). These high rates necessitated two sessions on several occasions (15). These data necessitate the conduction of a randomized prospective trial comparing these two treatment modalities.

Although no prospective randomized trials comparing PNL, laparoscopy and ureteroscopy exist, percutaneous nephrolithotomy is considered the gold standard for managing calyceal diverticula (16) **(Evidence level III/B)**. High rates of stone-clearance (76% to 100%) and diverticular obliteration (61% to 100%) have been published in contemporary series, while complications ranged from 0 to 30% (16). When compared to SWL, PNL achieved a higher stone-free rate with similar recurrence rates and complication rates (17) **(Evidence level III/B).** Ureteroscopic management yielded poor results with regard to stone-free (19 to 58%), symptom-free (35 to 69%) and diverticular obliteration status (20%) (18). Ureteroscopy should be reserved for patients with anterior, mid or upper pole diverticula or for patients who are unable to undergo PNL (16) **(Evidence level III/B)**. The laparoscopic approach, although applied in few patients (19), seems appropriate for those with thin overlying renal parenchyma or with anterior lesions that are too large or not accessible to ureteroscopy **(Evidence level III/B).**

PNL in the horseshoe kidney (20), malrotated and pelvic kidneys (21-23), and transplanted kidneys (24, 25) has been safe and effective, especially when large stones or ureteropelvic junction obstruction existed **(Evidence level III/B).** When compared to SWL, PNL leads to better stone-free rates for stones larger than 2cm (21, 26, 27) **(Evidence level III/B).** Renal access is obtained mostly through an upper pole calyx (20) and vascular injury is less likely in these conditions. This is because the whole blood supply enters the kidney medial in renal congenital anomalies (22-24), and the anterior nature of the transplant kidney in the iliac fossa offers easier access through the anterior abdominal wall for tract dilation (4). However, a second look procedure is occasionally necessary to render the kidney free of stones (20, 24). Currently, there is a growing evidence suggesting that for patients suffering by large or complex stone burden in an ectopic kidney, a laparoscopic-assisted PNL is the optimal treatment, resulting in higher stone free rates and shorter hospital stay compared to standard PNL technique (22, 28) **(Evidence level III/B).**

There are no randomized controlled studies comparing different treatment modalities for pediatric nephrolithiasis (29-31) **(Evidence level III/B).** Standard PNL with the use of adult instruments (32-34) or mini-PNL with specifically designed pediatric instruments (30, 35) are safe and highly effective treatment alternatives for stone disease in infants, preschool or older children **(Evidence level III/B).** Although there is a tendency for using smaller instruments, there is no evidence supporting a better functional outcome or a lower complication rate (29-31) **(Evidence level III/B)**. When specific criteria are followed PNL, SWL and ureteroscopy are all valuable treatment options for pediatric calculi (36) **(Evidence level IIb/ B).** PNL in children is recommended when SWL or ureteroscopy have failed, when a large stone burden is treated, and when anatomical abnormalities, that may impair urinary drainage and stone clearance, exist (29-31, 37) **(Evidence level III/B)**. Stone-free rates with a single session of PNL range from 67% (32) to 100 % (38). Retained calculi are more common with staghorn and multiple stones compared to solitary stones (33). The need for more than one session or for the combination of PNL with SWL or URS has been realized in these situations (33, 34).

Several retrospective studies indicate that PNL in obese patients can be performed with stone-free rates (as high as 100%), complication rates and hospital stays comparable to those achieved in an unselected population (39, 40) **(Evidence level III/B).** In a recent retrospective study, no statistically significant differences were found in decrease in haemoglobin concentration, hospital stay, and complication rate when patients were stratified in four groups according to their body mass index. The need for auxiliary procedures and stone-free rates were comparable (41) **(Evidence level III/B).**

Five specifically designed studies failed to show any statistical difference in the success and complication rates of PNL between the patients who had and those who did not have previous renal surgery (42-46) **(Evidence level III/B).**

Two prospective studies regarding the efficacy and safety of bilateral simultaneous PNL (BSPNL) have been published in the literature (47, 48). BSPNL was succeeded in 87.5% and 96% of the 16 and 25 patients that was tried to, respectively. Stone-free rates were 78.5% and 87.5%, but this was accomplished by a second session in 2.8% and 1.2% of the patients, respectively.

The average operating time in these two studies was 126 and 122 minutes. Both studies reported a low rate of insignificant complications. Unfortunately, the procedure was not compared to the standard unilateral PNL performed in two sessions **(Evidence level IIb/B).** This was retrospectively examined in the series of Holman et al (49).

The stone-free rates, the renal impairment, the hospital stay, the analgesic requirements, and the complication rates, were not significantly different between BSPNL and PNL at two sessions **(Evidence level III/B).** Bilateral simultaneous tubeless PNL appears to be a feasible, safe and effective procedure offering potential advantages of decreased analgesic requirement and hospital stay without increasing the complications when compared to standard bilateral simultaneous PNL (50) **(Evidence level III/B).**

3. POINTS OF PNL TECHNIQUE

a) Patient Positioning

Percutaneous nephrolithotomy is usually performed in the prone position. This approach has some disadvantages, including patient discomfort and circulatory and ventilatory difficulties (51). PNL may be precluded by the presence of associated pulmonary disorders and/or obesity. PNL at the lateral decubitus and supine position has been seen to be a safe and effective alternative (51-53) **(Evidence level III/B)**. In a recently published prospective study of 130 patients, Shoma et al compared the results of PNL in the supine and prone position (54). The study was non-randomized but the two groups of patients did not differ in their preoperative characteristics **(Evidence level IIa/B).** Regardless of the position, the pelvicalyceal system was successfully approached in all patients and the posterior calyces were the most common site of entry. The overall success rate was 89% and 84% in the supine and prone positions, respectively. The complication rates were similar in both groups, and none of the patients experienced injury of adjacent organs.

b) Imaging Modalities

For most patients fluoroscopy or sonography is done to monitor access into the renal collecting system for subsequent PNL (55, 56). There are no prospective randomized studies comparing these two imaging modalities **(Evidence level III/B)**. Several retrospective studies (57-61) **(Evidence level III/B)** and a prospectively designed study (62) **(Evidence level IIb/B)** showed that the use of fluoroscopy for renal access was associated with an increased blood loss during percutaneous nephrolithotomy compared to the use of ultrasound guidance. There are only a few reports regarding the use of CT for percutaneous access guidance (63). Although, CT is a useful adjunct in planning percutaneous nephrolithotomy (64) and successful access even in non-dilated collecting systems has been achieved, the use of CT to guide the kidney puncture is time-consuming, space-demanding and usually needs to be performed on a different session **(Evidence level III/B).** It may be useful in a select group of patients such as those with ectopic kidneys, a retrorenal colon, severe spinal dysraphism and hepatomegaly or splenomegaly. A CT guided puncture may give a better anatomical mapping for a supracostal approach for PNL (65) **(Evidence level III/B).**

c) Combined PNL and Ureteroscopic Access

Landman and associates (66, 67) presented a combined percutaneous and retrograde approach with application of a hydrophilic-coated, kink-resistant ureteral access sheath with a funnel-shaped ergonomic entry port to treat partial or complete staghorn calculi. With a single lower pole access 78% of the cases were cleared of stones. The main advantages of this technique are the capability to place the guide wire through and through out of the patient's body, the rapid and atraumatic passage of a flexible ureteroscope into the collecting system and the benefit of allowing stone fragments to pass safely through the sheath. The authors have shown that the ureteral access sheath resulted in significantly increased irrigant flow and significantly decreased intrarenal pressure when compared to the standard ureteric catheters or the occlusion balloon catheters (66) **(Evidence level IIb/B).** Other authors have confirmed the feasibility of endoscopically guided percutaneous renal access with the use of a flexible ureteroscope (68, 69). However, these improved techniques of the two original techniques of Hunder-Hawkins (70) and Lawson (71) for achieving retrograde percutaneous access, may offer no real advantages over antegrade percutaneous access (55) **(Evidence level III/B)**. A prospective randomized study recruiting a large number of patients is needed to further delineate the advantages of this combined procedure.

d) Robotic percutaneous renal access

In the late 1980's the percutaneous access to the kidney robot (PAKY) was introduced by Wickham et al at Guy's hospital, in London, UK (72). Kavoussi et al subsequently showed the possibility of clinically using this active robotic system for needle puncture in PNL (73). In 2003, the first prospective randomized controlled experimental trial of trans-Atlantic telerobotics with robotic needle punctures during PNL into a kidney model controlled remotely was performed. The robot took longer to carry out the procedure but was significantly more accurate than a human, which may be vital in a procedure such as PNL (74) **(Evidence level Ib/A).** This work was preceded by a non randomized prospective comparison of robotic percutaneous access to the kidney to standard manual access in humans, performed by the same team (75)**.** The number of attempts, the time to access and the blood loss in the robotic arm were comparable to those of standard manual percutaneous access technique **(Evidence level IIa/B).**

e) The site of the kidney puncture

An optimal and atraumatic access to the desired calyx is a crucial step in a successful PNL. In the majority of cases this is possible by a subcostal puncture. However, a supracostal approach is preferable in patients with staghorn, complex renal and proximal ureteral calculi, as it offers direct access to most parts of collecting system and upper ureter (55, 65, 76-78) **(Evidence level III/B)**. There are no prospective randomized controlled studies, enrolling a large number of patients that compare the success and complication rates of these two approaches. In retrospective studies, stone-free rates up to 87% have been reported with a single session of supracostal PNL (79) **(Evidence level III/B).** The disadvantage is the high incidence of intrathoracic complications as well as a higher rate of spleen and hepatic injury (77-79). The overall pleural complication rates in the retrospective studies published in the literature range from 0% to 37% (55, 65, 76, 77) **(Evidence level III/B)**. Munver et al (65) reviewed their complications from supracostal punctures for PNL access in 240 patients. The overall complication rate for supracostal access tracts was 16.3% compared with 4.5% for infracostal access. Punctures above the 11^{th} rib resulted in a tremendously higher intrathoracic complication rate (34.6%) compared to the supra 12^{th}- rib access (1.4%), fact that corroborates the strategy of avoiding this high approach if possible **(Evidence level III/B).** Finally, several retrospective studies (57-61) **(Evidence level III/B)** and a prospectively designed study (62) **(Evidence level IIb/B)** revealed no association between the calyx of puncture and the blood loss during percutaneous nephrolithotomy.

f) One versus multiple tracts

In certain cases multiple accesses may be required during PNL. In general, multiple accesses are considered when calyx contains stone that is larger than 2cm and cannot be approached with rigid instrument via primary access or calyx contains stones of any size that cannot be reached with flexible instrument via primary access (55) **(Evidence level III/B).** Multiple accesses can be performed either through separate skin incisions and separate tracts when excessively large stone burden or complex collecting system is treated or through a Y puncture or a triangular technique when stones located in parallel with or adjacent to the calyx of initial puncture (55, 80) **(Evidence level III/B).** Several retrospective studies (57-61, 81) **(Evidence**

level III/B) and a prospectively designed study (62) **(Evidence level IIb/B)** revealed that multiple renal accesses were related with an increased blood loss during percutaneous nephrolithotomy.

g) Tract Dilation

Nephrostomy tract dilation is most commonly performed with the telescoping dilators of Alken (82), the Amplatz polyurethane progressive fascial dilators (83), or the balloon dilator (84). Several retrospective studies have compared pneumatic dilation with the multi-incremental techniques (85, 86). They have shown that balloon dilation is safer and faster and reduces the x-ray exposure of the patient and operators **(Evidence level III/B).** In addition, several retrospective studies (57-61, 81) **(Evidence level III/B)** and a prospectively designed study (62) **(Evidence level IIb/B)** showed that balloon dilatation was related with a decreased blood loss during percutaneous nephrolithotomy compared to other modalities. In a recently published prospective experimental study comparing the degree of renal trauma in a porcine model no difference was noted between the Amplatz sequential fascial dilators and the balloon dilator (87) **(Evidence level IIa/B).** Thus, for the above reasons, the balloon dilator is regarded as the gold standard.

While a percutaneous access tract is usually achieved via a two-step process, several authors have recently presented their experience with different types of "one-step" renal access (88-91). Frattini et al (88) conducted a randomized study using different dilating techniques, including the "one-shot" technique which was described by them firstly. This method is a single dilation with a 25F or 30F Amplatz dilator performed over an Alken guide or an 8F dilator. This technique required the least amount of fluoroscopy time but the difference was not statistically significant. None of their patients required blood transfusion. As dilation was unsuccessful only in patients undergone this technique and there were no upper pole or multiple punctures performed, the technique warrants more studies to confirm its superiority **(Evidence level Ib/A).**

Pathak et al recently contacted a small prospective randomized controlled study comparing the high-pressure balloon dilator to a novel one step device called the Pathway Access Sheath (PAS). The authors showed that the single-step renal access device was safe and efficacious and resulted in a shorter insertion time for percutaneous nephrolithotomy. Blood loss was also less, but this difference was not statistically significant (90) **(Evidence level Ib/A).**

h) Mini-PNL

Attempts have been made to popularize techniques of mini-percutaneous nephrolithotomy in the hope to decrease the morbidity associated with larger nephroscopes and tubes, especially regarding patient discomfort and potential renal damage (92-96). Chan et al (93) described their experience performing PNL with a 13 F nephroscope followed by placing an 8F nephrostomy tube with a 7F double-pigtail ureteric stent. The stone free rates were impressive, although the stone burden in their series ranged from 0.3 to 2.0 cm^2. A specially designed 12 F nephroscope was successfully used by Lahme et al (94) to treat renal stones of a medium size of 2.4 cm^2. There were no conversions to conventional PNL and no transfusions were necessary. Although a high stone-free rate was achieved, visibility with the smaller nephroscope was hindered with larger stones, and the operating time was significantly longer than for standard PNL. Similarly to the above studies further contemporary retrospective studies failed to show any superiority of mini-PNL over the standard technique (92, 96) **(Evidence level III/B).** More importantly, Feng et al in a prospective randomized study of "mini-PNL", standard PNL and tubeless PNL showed no overall advantage of the 'mini" technique, while the later had a slight disadvantage because of poorer visualization and optics and difficulties with use of the nephroscopic graspers (95) **(Evidence level Ib/A)**.

i) Kidney Drainage after PNL

The use of nephrostomy tubes for kidney drainage is common after PNL. An ideal tube should have excellent biocompatibility and strength, be well tolerated by the patient, resist obstruction or dislodging, and be simple to insert and replace (97). Such a tube does not exist and as a consequence several experts have individualized the type of drainage catheter per case (97, 98) **(Evidence level IV/C).** Smith (97) and associates proposed no tube or the balloon/malecot type nephrostomy tubes following straightforward uncomplicated PNL. For problematic PNL, such as when mucosal perforation, significant hemorrhage, residual stones or edema of the PUJ is anticipated, the specially designed Councill-tip (99) or the Kaye Tamponade (100) catheters are recommended. Drainage after complicated renal surgery, for example when severe hemorrhage or PUJ tear, or injuries to adjacent organs occur, can best be accomplished by using a re-entry tube (101) or an endopyelotomy tube **(Evidence level IV/C).** However, several prospective randomized experimental and clinical studies regarding post-PNL drainage have been published. Canales et al compared four types of catheters in an experimental model, in order to evaluate the impact of catheter configuration on drainage flow and retention strength. Among the Bardex Council 16F (eccentric balloon), Microvasive Flexima 14F (pigtail), Bardex Malecot 16F (flange) and Cook nephrostomy 16F (symmetric balloon) catheters, the later combined strong drainage flow and strong retention strength (102) **(Evidence level Ib/A).** Prospective randomized studies have shown that the use of a smaller drainage catheter leads to no statistically significant benefit to the patient with regard to comfort beyond 6 hours postoperatively (103, 104) **(Evidence level Ib/A).**

On the contrary, when a 7F tail stent with a 18F Councill nephrostomy tube were compared to a 24F re-entry Malecot nephrostomy tube, in a randomized prospective manner, the former were certainly better tolerated by the patients (105) **(Evidence level Ib/A).** Marcovich et al have prospectively compared the functional and subjective outcome following insertion of three different types of drainage tubes: a 24F re-entry tube, an 8F pigtail catheter and a double–J stent. There were no statistically significant differences among the three catheters in terms of change in hematocrit, need for blood transfusion, tube blockage rate, extravasation and presence of perinephric fluid, complication rate, length of hospital stay or persistent leakage after tube removal. All three catheters were equally tolerated by patients (106) **(Evidence level Ib/A).**

There are now several reports of "tubeless" renal surgery (95, 107-110) the largest of which comprised 154 patients (109). All are retrospective in nature and concluded that tubeless surgery may be safe and effective in selected patients. However, importantly, these patients met strict exclusion criteria such as operative time more than 2 or 3 hours, the need for three or more percutaneous accesses, perforation of the collecting system, bleeding, and significant residual stone burden that would necessitate a secondary procedure. Furthermore, the average stone burden treated in these studies was relatively low and the patients were left with common (107) or specifically designed (108) internal ureteral stents, which can cause significant discomfort (111) **(Evidence level III/B).** Two prospective randomized studies have been conducted to compare tubeless nephrolithotomy to other modalities **(Evidence level Ib/A).** Feng et al (95) prospectively randomized 10 patients each to standard PNL, mini-PNL and tubeless PNL. The tubeless technique was associated with the least amount of morbidity and the greatest cost efficiency compared

Table 2. Indications success and complication rates when PNL is used in different patient and "kidney" groups

	Mean stone size (cm)	**% Stone free rate**	**% of ancillary procedures needed[1]**	**Hospital stay (days)**	**% Complication rate**
Lower pole stones	0.5-10	70-100	4-62.5	3-6	13-38
Calyceal Diverticula	0.2-3	76-100	0.04-18	2-15	0-30
Horseshoe kidneys	All sizes	72-87.5	8.3-33	3-10	8-29
Children	All sizes	67-100	0-32	1-11	0-28
Bilateral PCNL	All sizes	76-100	3-81	11-21	3-25
Obesity	All sizes	60-100	14-45	2-10	0-37
Previous surgery	Up to 3	51-92	27-78	3-7	13.6-24
Lateral decubitus and supine position	All sizes	66.6-89	7.5-33.3	2.5[2]	0-17
Mini-PCNL	0.1-10.62[3]	62.5-100	9-68	1-5	0-17.5

[1] % of more than one PNL or additional ESWL/URS procedures needed to render the patients stone free
[2] Average hospital stay
[3]Stone size in cm^2

with the other techniques. Desai et al prospectively randomized 10 patients each to receive conventional large bore (20Fr) nephrostomy drainage, small bore (9Fr) nephrostomy drainage or no nephrostomy drainage (112). Tubeless PNL was associated with the least postoperative pain, urinary leakage and hospital stay. All three groups were similar in terms of operative time, duration of hematuria and decrease in hematocrit **(Evidence level Ib/A).**

A possible adjunct to tubeless PNL could be the placement of a hemostatic agent along the percutaneous tract at the time the tube is removed. The most commonly hemostatic agents currently in use are fibrin glue (113, 114), gelatin matrix hemostatic sealant (115) and oxidized cellulose (116). Several retrospective studies demonstrated that these hemostatic agents are safe and effective for use after tubeless PNL, and are associated with less analgesic requirement and with a shorter hospital stay (113-115) **(Evidence level III/B)**. These findings were partially confirmed by small sized prospective randomized studies. Shah et al (117), depicted that the instillation of fibrin glue in highly selected patients was safe and associated with less postoperative pain and a lower analgesic requirement, while Aghamir et al (116) failed to show any advantage of the oxidized cellulose use **(Evidence level 1b/A)**. These conflicting results together with the high cost of these materials and the possibility of viral transmission to the patient indicate that their use should not be recommended routinely unless a large randomized prospective trial confirms any benefit. Table 2 illustrates the success and complication rates when PNL is employed.

CONCLUSIONS

With the development of techniques for percutaneous access and equipment to disintegrate calculi, PNL is currently used by many endourologists, being the procedure of choice for removal of large renal calculi. Although it is more invasive than SWL and retrograde ureteroscopic lithotripsy, PNL has been successfully performed with high efficiency and low morbidity in difficult renal anatomies and patient conditions. The technique of the procedure has been evolved significantly over the last years. Several technical details still need clarification. The need for well designed prospective randomized trials comparing PNL with alternative treatment modalities arises through the literature review.

RECOMMENDATIONS

Recommendations on PNL indications:

Recommendation	*Level of evidence*
The term “large stone” is applicable > 2cm	**IV/C**
In the treatment of staghorn stones, compared to ESWL or open surgery, PNL alone or in combination with ESWL, results in higher stone free rates, lower rate of ancillary procedures, lower morbidity, shorter operative time, shorter hospital stay and earlier recovery	**Ib/A** **IIa/B** **III/B, IV/C**
Large stones of the lower pole (>1 cm) are best managed by PNL as a first treatment option, irrespective of the anatomy	**Ia/A**
PNL is considered the gold standard for managing caliceal diverticula	**III/B**
PNL in the horseshoe kidney, malrotated, pelvic kidneys and transplanted kidneys is safe and effective	**III/B**
PNL, ESWL and ureteroscopy are all valuable treatment options for pediatric calculi	**IIb/B**
Previous surgery does not contraindicate subsequent PNL	**III/B**
Simultaneous bilateral PNL is a safe and efficacious procedure.	**IIb/B**

Recommendations on PNL technique

Recommendation	*Level of evidence*
PNL is usually performed in the prone position.	**III/B**
PNL at the lateral decubitus / supine position is a safe and effective alternative.	**IIa/B**
Fluoroscopy or US is mainly used to monitor access into the collecting system	**III/B**
Fluoroscopy is associated with an increased blood loss compared to US	**IIb/B, III/B**
CT scan may be useful in a select group of patients	**III/B**
Robotic percutaneous access seems more accurate and safe to human access	**Ib/A, IIa/B**
A supracostal approach is preferable in patients with staghorn, complex renal and proximal ureteral calculi	**III/B**
There is no association between the calyx of puncture and blood loss	**IIb/B, III/B**
Multiple accesses are considered when calyx contains stones larger than 2cm and cannot be approached with the (flexible) instrument	**III/B**
Multiple renal accesses are related with an increased blood loss	**IIb/B, III/B**
The balloon dilator is regarded as the gold standard.	**IIa/B, IIb/B, III/B**
Mini PNL shows no advantages over standard PNL	**Ib/A, III/B**
The size of drainage catheter makes no difference to patients outcome	**Ib/A**
Tubeless surgery may be safe and effective in selected patients	**Ib/A, III/B**
Some hemostatic agents are of benefit to patient during tubeless PNL	**Ib/A, III/B**

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V. RETROGRADE INTRARENAL SURGERY FOR RENAL STONES

Extracorporeal schock-wave lithotripsy (ESWL) is still the first line treatment for renal calculi with success rate of 70% for all renal calculi. The success rates of ESWL for lower pole calyceal stones differs from 63 to 74% and 23 to 56% less than 1 cm and 1 to 2 cm, respectively [1]. Higher failure rate for lower pole calyceal stones (LPS) have been attributed to diminished infindibular width, longer infindibular length and narrow infindibulopelvic angle. Percutaneous removal of renal stones (PNL) is widely use with a success rate of more than 90% with greater morbidity comparing to ESWL and ureteroscopy (URS). Advances in design of flexible ureteroscopes, use of nitinol baskets and graspers, developement of smaller caliber flexible holmium laser (200 microm) and electrohydraulic (EHL) probes (1.6-1.9 F) allowed to treat intrarenal stones retrogradely with higher success rate and minimal morbidity.

Retrograde intrarenal surgery (RIRS) has been mostly used for stones failed with ESWL. In a retrospective study, the records of 81 patients who had RIRS after multiple ESWL sessions were reviewed [2]. Rigid ureteroscope in 8 , flexible in 67 and both in 6 patients were used. The fragmentation was achieved by holmium :YAG laser mostly and EHL occasionally. They reported 67% success rate and 46% stone free rate (SFR) with minor complications, based on KUB or US findings within 3 weeks postoperatively. The procedure was unsuccessful in 13 patients with larger stones or obstructed system in which subsequent ancillary procedures were used. They concluded that RIRS could be used as a salvage therapy in patients with renal stones smaller than 2 cm. that failed with ESWL . Similarly in another study 38 patient underwent RIRS for ESWL-resistant renal stones [3]. Stones were disintegrated by 150-200 micron holmium:YAG laser probes in 32 patients through both semirigid and flexible ureteroscopes. Stone free rate was 58% after a single procedure and overall success rate was 76% after second session. In conclusion they recommended RIRS as a safe porcedure with high successs rate for ESWL resistant renal stones less than 1 cm and stones in anomalous kidney .There is only one study comparing the success rate of RIRS for primary renal stones and ESWL-resistant stones. The major differences from previous studies were the use of access sheath in all cases and 54% of the patients were prestented. Flexible ureteroscopes and holmium laser were used in all patients. In group I who underwent RIRS as a first-line therapy, immediate success rate was 67% versus 51% in group II. Sixty percent of the patients had lower pole calyceal stone[4]. Conversely to previous studies, the authors concluded that RIRS after ESWL failure has lower success rate and much more complications. This was attributed to the presence of embedded stone fragments into the mucosa resulting from multiple ESWL procedures **(Evidence Level III C).**

Extracorporeal shock wave lithotripsy was recommended for 1 cm or less lower pole calyceal stones (LPS) and PNL for larger stones by lower pole study group [1]. However recently effectivity of RIRS for LPS has been investigated by many authors. Lower pole calyx is one of the most difficult location to have an access with flexible ureteroscope. The secondary deflection maneuver and the use of nitinol tipless baskets and graspers, facilitated the access into the lower calyx and subsequently improved the success of stone treatment. There is only one prospective randomized study comparing ESWL and ureteroscopy for 1 cm. or less lower pole calyceal stone. Of seventyeight patients, 67 were entered the study. In this multiinstutitional study, 9 different systems were used for ESWL and ureteroscopic procedures were performed by different surgeons in each center [5]. Computerized axial tomography obtained three months later the procedure, revealed 35%, 50% stone free rates for ESWL and URS respectively. These results seemed as URS was superior to ESWL but there was no difference statistically. In the URS group stones couldn’t be reached in 5 patients and 2 of them underwent ESWL treatment. They noted that there was no difference in both technique regarding success rate but ESWL has lower complication, shorter convalesence and greater patient acceptance. In another retrospective study the records of 95 patients who had 2 cm. or less lower pole calyceal stone were reviewed [6]. The records of 78 patients were available. In 59 patients, in situ fragmentation was performed mostly with 200 micron holmium laser probe or 1.9 F electrohydraulic probe occasionally. Stones were fragmented after relocation with tipless nitinol basket in the remaining 19. In this study SFR was higher in the group that stones were relocated especially in patients who had stones larger than 1 cm. **(Evidence Level IIIB).**

The treatment of renal stones in morbidly obese patients is often associated with problems and complications. Extracorporeal shock wave lithotripsy can not be performed in some morbidly obese patients because of poor imaging, weight limitation of the equipment and the skin to stone distance exceeding the F1 to F2 focal point distance Percutaneous nephrolithotripsy has higher risk of bleeding, anesthetic problems and postoperative thromboembolic complications especially in patients with a BMI greater than 40 kg/m^2 [7-8] Dash et al. compared the results of retrograde ureteroscopic treatment of intrarenal stones in 16 morbidly obese patients (BMI greater than 40 kg/m^2) and 38 normal weight patients [9]. The overall success rate was 83% for morbidly obese and 67% for normal weight group which was not significant statistically. Complication rate was quite low in both group and they concluded that RIRS could be the first-line treatment for renal calculi in morbid obese patients. Similar results were published by Andreoni et al in 8 morbidly obese patients with a BMI greater than 45 kg/m^2. In this retrospective study SFR was 70% after the initial procedure [10]. There was only one minor complication not related to the procedure itself. The conclusion was RIRS is a safe and efficient procedure for renal stones smaller than 1.5 cm. in morbidly obese patients. No transfusion was required in both series. **(Evidence Level IIIC).**

Percutaneous nephrolithotripsy was recommended for renal calculi larger than 500 mm2 by American Urological Association in 2005. The success rate for PNL was ranging from 74% to 83% however this was associated with higher transfusion rate (14% to 24%) and significant complications such as acute renal loss, acute renal failure, colonic injury, vascular injury, pneumothorax, prolonged urine leakage, pyelonephritis, sepsis, deep venous thrombosis and pulmonary embolus [11]. Dretler published the results of ureteroscopic fragmentation followed by ESWL treatment in 8 patients who had renal stones greater than 500 mm^2 [12]. All renal stones were fragmented by pulsed dye laser via 7.2 F semirigid and 10.8 F flexible ureteroscopes. 7 patients were stone free and the other had only a fragment smaller than 5 mm. In 1990, Aso et al reported 50% success rate with flexible ureteroscopy and EHL in patients with staghorn calculi [13]. Then Grasso and et al published their experience with RIRS for renal stones larger than 2 cm. in 51 patients, in which percutaneous surgery was contraindicated for some reasons [14]. In this study, both semirigid and flexible ureteroscopes were used, and stones were disintegrated with 200 micron flexible holmium laser probe if needed. The immediate overall success rate was 93%, based on postoperative KUB findings. Eight patients required second session and one patient had third. The stones couldn't be reached in 3 patients and procedures were converted to percutaneous technique. They concluded that RIRS could be performed safely for large and complex upper tract stones. El-Anany et al. obtained complete fragmentation in 23 of 30 patients (77%) with a renal stone burden of larger than 2 cm [15]. All stones were disintegrated by holmium laser through both semirigid and actively deflectable flexible ureteroscopes. Failures in 7 patients were due to migration of the pelvic stone to an inaccesible calyx, poor visualization or inability to access stone bearing calyx. The conclusion of the study was that RIRS for larger renal stones was a safe and effective alternative to PNL and open surgery. They also mentioned that smaller stone burden the greater success rate with less operating time for the procedure. Recently Mariani reviewed the results of ureteroscopic lithotripsy of renal stones in 16 patients who had branched renal calculi measured between 560 and 2425 mm^2 [16]. Of the patients, 81% were obese and the BMI was greater than 40 kg/m^2 in 38%. Lithotripsy was performed by a single deflection flexible ureteroscope and EHL was used predominantly. Fourty procedures were performed for 17 renal units (mean 2.4 stage). 15 renal units were stone free with a success rate of 88% without any major complication. **(Evidence Level IIIC).**

The increased success rate is not only due to advances in flexible ureteroscopy and intracorporeal lithotripsy technology, but also the use of ureteral access sheath and tipless nitinol baskets (**Table 1**), graspers. Some authors believe that ureteral access sheath facilitates retrograde flexible ureteroscopy and improves the success of treatment. It has been shown that intrarenal pressure decreases during ureteroscopic procedures when ureteral access sheath is used [17]. In a retrospective study, 256 ureteroscopic procedures were reviewed and the stone free rate in ureteral access sheath group and non-ureteral access sheath group was 79% and 67% , respectively [18]. Some other studies revealed that the use of ureteral access sheath facilitates reentry into the ureter and consequently shortens the operating time, provides better visualization, increases the ureteroscope's life span

Table 1. A comprehensive overview of the treatment characteristics regarding RIRS for renal stones in the literature

	Number of the patients	Stone size(mm)	Ureteroscope type	Access sheath	Energy for lithotripsy	Nitinol basketry	Follow-up imaging	Additional procedures
Grasso et al, 1998	45	24.8	Flexible	No	Holmium all	?	KUB+ US	PCNL:3
Schuster et al, 2002	95	8.5	Flexible	No	Holmium+++ EHL+	Yes	KUB	ESWL:3 PCNL:1
Stav et al, 2003	81	9.2	Flexible+++ Rigid+	No	Holmium +++ EHL +	No	KUB+ US	PNL:5 ESWL:6 Open:2
L'esperance et al, 2005	173	8.7	Flexible	Yes	Holmium all	Yes	IVU+	? NCCT
Pearle et al, 2005	35	6.9	Flexible	Yes	Holmium all	Yes	NCCT	ESWL:2
Jung et al, 2006	38	9.0	Flexible+++ Semirigid+	No	Holmium all	No	NCCT IVU	PNL:2 ESWL:1
Holland et al, 2006	93	9.6	Flexible+++ Semirigid+	Yes	Holmium all	Yes	KUB+ US	?
Geavlete et al, 2006	42	?	Flexible	No	EHL all	Yes	KUB+	PNL:5 US+IVU
Mariani et al, 2007	16	>40	Flexible	No	EHL+++ Holmium+	?	KUB+ US+IVU	?

and improves the stone free rate [17,18,19]. The risk of stricture formation and other possible complications with ureteral access sheath have been discussed. However, Delvecchio et al found only one stricture in 71 cases possibly not related to access sheath itself [20]. It is usually accepted that 12/14 F ureteral access sheath has minimal risk of ureteral injury and enough internal channel to work easily. The use of nitinol tipless basket or grasper is another developement enables to reach the stone in any calyx or caliceal diverticulum. Ureteroscope's deflecting capability is not affected by 2.6 or 3.2 F nitinol baskets or graspers [21].The stones located in the lower pole calyx can be easily entrapped with a nitinol basket or grasper. If the stone is larger than 4 mm it is relocated into the mid or upper calyx for further disintegration. Meanwhile irrigating flow through the endoscope is decreased minimally providing good visualization [22]. **(Evidence Level IIIC)**. In some cases relocation of the stone can be difficult even with nitinol basket or grasper. This can be helped by placing the patient to head down or flank position [23] **(Evidence Level IVC).**

Holmium:YAG laser has been widely used for any ureteroscopic lithotripsy. For intracorporeal lithotripsy, 550 and 365 microm holmium:YAG laser fibers can only be used through semirigid ureteroscopes while 200 microm fibers should be used with flexible ureteroscopes. It has been demonstrated that 200 micron laser fiber compromise the flexible ureteroscope tip deflection by 7%-16% [24]. This decreases the success rate if the lower calyceal stone is fragmented in situ . Painting vaporization technique with holmium:YAG laser is described by Preminger which allows to disintegrate the stone into the smaller particles not required active removal [25]. Electrohydraulic lithotripsy is another option that can be used in conjunction with flexible ureteroscopy. Especially, 1.6 or 1.9 F EHL probes are used with no limitation of tip deflection. Electrohydraulic lithotripsy even with smaller probes may cause mucosal injury and destroy the tip of the instrument. In recently published two studies, EHL was used for intracorporeal lithotripsy of renal stones without ureteral access sheath. The results were quite similar : the success rate was 72%, 80% and 50% in the first, 78%, 72%, and 49% in the second study for stones 10 mm or less, 11-20 mm and greater than 20 mm respectively [26,27]. Hematuria was quite often possibly related to EHL in both series and the conclusion was RIRS for stones greater than 20 mm is associated with lower success rate and longer operating time while multiple procedures are needed. **(Evidence Level IIIC).**

Retrograde intrarenal surgery for renal stones is reported that could be used safely in patients with bleeding diathesis [28]. There is no much experience with RIRS for stone in anomalous kidneys. However, Weizer et al reported 88% complete clearance of the stone in 8 patients who had pelvic or horseshoe kidneys [29]. There are few reports combining the RIRS with ESWL and PNL in the same session . In the series that RIRS was combined with ESWL, all 14 patiens were not suitable candidates for PNL because of having risk of bleeding, not to tolerate prone position, anatomic location of the kidney and previous unsuccessful experience with the technique [30]. The stones were fragmented either intracorporeally with 200 micron holmium laser probe or ESWL monitored by flexible ureteroscope with a success rate of 76.9%. One patient underwent percutaneous nephrostomy and subsequent PNL because of urosepsis. The authors reported that there was no damage to the ureteroscope because of the narrow focal zone of the ESWL system. In another two studies in patients who had multiple or branched renal calculi, PNL was combined with retrograde ureteroscopy to decrease the number of percutaneous access without any complication and blood transfusion [31,32]. Simultaneous bilateral flexible ureteroscopic treatment of renal stones has been reported but required more facilities and experience [33]. **(Evidence Level IVC).**

In the review of current literature, holmium:YAG laser seems to be the choice of method for intracorporeal lithotripsy during RIRS for intrarenal stones in most of the series [32,33,34,35].Flexible ureteroscopes are used mostly and semirigid instruments occasionally. **(Evidence Level IIB).** The use of ureteral access sheath is still controversial but there are some data showing that it facilitates the procedure while improving the stone free rates [17,18,19,25,36]. Prospective randomized studies are needed to prove the benefit of ureteral access sheath use. Nitinol baskets and graspers are on routine use either to remove the smaller fragments or relocate the stone into a more accessible calyx for further disintegration. In the current series the success and stone free rates are detected by plain film (KUB), ultrasonography (US) or noncontrast CT (NCCT). NCCT seems to be superior to other methods for detecting smaller fragments [35,36]. **(Evidence Level IIB)**.

Moreover presence of 4 mm and smaller fragments after the procedure is accepted as success by some authors while 2 mm by others. It should be considered that the different imaging modalities can alter the success rate. In some series a number of the patients are prestented. There is no data if prestenting facilitates the procedure or not. Placement of ureteral stent after the procedure is also another issue to study on. Prestenting or poststenting are still based on the surgeon’s experience and choice. There is no study to evaluate the cost effectivity of RIRS. A cost analysis shoud be done and compared to ESWL and PNL treatment.

RECOMMENDATIONS

Recommendation	***Level of Evidence***
RIRS is preferred as a treatment of choice for morbid obesity, bleeding diathesis and anomalous kidney.	**IIIB**
The success rate is higher for 1 cm or smaller stones.	**IIIB**
Use of an access sheath depends on the surgeon’s preference and the use of nitinol baskets or graspers is advised.	**IIIC**
Relocation is recommended if the stone is located in a difficult position for fragmentation.	**IIIB**

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VI. LAPAROSCOPIC RENAL STONE EXTRACTION: AN EVIDENCE BASED REVIEW

1. INTRODUCTION

The management of calculus disease has changed with the advent of extracorporeal shock wave lithotripsy (SWL), percutaneous nephrolithotomy (PNL) and rigid or flexible ureteroscopy (URS) (1). However, despite the technical development and the expanding indications, the new technologies have not been able to completely replace open surgery (2). There are still some situations where open surgery could be the «most suitable option» for treating calculus disease. These are the cases that should be considered for potential management with laparoscopic surgery (3).

Wickham et al. were the first to describe an attempted removal of a ureteral calculus using the laparoscope in the retroperitoneum (4). Since then several studies have been reported on laparoscopic management of calculus disease including ureterolithotomy (3, 5-9), pyelolithotomy (10-14), anatrophic nephrolithotomy (15), nephrectomy and nephroureterectomy (12, 16). Various indications for laparoscopic surgery for calculus disease are summarized in Table 1. However, these indications have not been clearly defined and may vary from center to center depending on the available expertise **(Evidence level IV/C)**. There are few comparative studies between laparoscopic and open stone surgery (5, 17) and laparoscopic and percutaneous surgery (14) **(Evidence level IIa/B)**.

Our aim was to identify the level of the evidence published in literature supporting the laparoscopic approach to stone extraction.

2. LAPAROSCOPIC PYELOLITHOTOMY

Gaur and colleagues introduced the retroperitoneoscopic pyelolithotomy in five patients in 1994 and recommended the procedure for stones not amenable to SWL or PNL or when both the facilities were unavailable (10) **(Evidence level IV/C).** Review of the literature by Hoening et al in 1997 revealed 11 pyelolithotomies with a conversion rate of 27% and an operative time of 2 to 5 hours (11). This review confirmed the feasibility of laparoscopic pyelolithotomy **(Evidence level III/B).**

Since then many authors have reported their experience with laparoscopic pyelolithotomy (1, 12, 13, 18-33). Indications for the laparoscopic approach included: study of the feasibility of the procedure (12, 27-30), preceded failed endourologic approach (20, 21, 26-28), treatment of complex staghorn calculi (22, 27), stone-removal from an anomalous or ectopic kidney (12, 20, 23, 24, 32), assistance of getting access during percutaneous nephrolithotomy (19, 20, 23, 24, 32), concomitant correction of a pelvi-ureteric junction obstruction (1, 13, 27, 29), and finally absence of endourologic facilities in developing countries (10, 18).

The results of these studies indicated that the laparoscopic pyelolithotomy, performed either transperitoneally [1, 19, 20, 13, 24, 27, 29, 30-33] or retroperitoneally [12, 18, 21, 22, 23, 27, 28], is a feasible as well as an effective and a safe procedure for selected cases. Depending on indication, overall success rates and stone-free rates ranged from 71% (12) to 100% (27). Open conversion rates ranged from 0% (27) to 27% (12). Mean operative time, hospital stay and complication rate were all within acceptable rates. However, all these studies were either case reports or retrospective studies enrolling a small number of patients and presented no comparison with other treatment modalities **(Evidence level III/B).**

Goel et al (14) retrospectively compared retroperitoneoscopic pyelolithotomy (n = 16) to PNL (n = 12) in the management of a solitary renal pelvic calculus more than 3 cm in size **(Evidence level III/B).** The two groups were similar regarding patient age and sex. Mean stone sizes were 3.6 cm versus 4.2 cm, respectively. There were two conversions in the laparoscopic group for stone migration into the calyx and dense perirenal adhesions, making dissection difficult. Mean operating time was 142 minutes versus 72 minutes for PNL ($p < 0.0001$). Blood loss was similar: 173 cc versus 141 cc. Mean hospital stay was 3.8 days versus 3 days, although the duration of convalescence was somewhat shorter in the PNL group. Laparoscopic pyelolithotomy was associated with longer operating time, longer recuperation, was more invasive, less cosmetic, and required more skill as compared to percutaneous nephrolithotomy. Advanced endourologic facilities, such as laparoscopic ultrasound, were required for removal of calyceal stones in the event of migration or for localization of stone. The authors concluded that PNL is the best treatment modality for renal stones and laparoscopy should be offered to those who need adjunctive procedures such as pyeloplasty or puncture under vision during PNL **(Evidence level III/B).**

Maria et al (34) retrospectively compared laparoscopic transperitoneal pyelolithotomy to PNL for the treatment of pelvic stones > 20mm in diameter. There was no difference between the two groups regarding the characteristics of patients and stones. Operative time was significantly longer in the laparoscopic group (129 vs 75 min; $p=0.001$) and conversion was required in two patients (12%). Postoperative complication rates (12% vs 18%), hospital stay (6.5 days vs 5.6 days; $p=0.17$) and stone-free rates (88% vs 82%) were comparable. The authors concluded that specific indications of each technique must be determined although PNL remains the gold standard for most large pelvic stones **(Evidence level III/B).**

3. LAPAROSCOPIC NEPHROLITHOTOMY

Current relative indications for laparoscopic nephrolithotomy include the ablation of diverticular mucosa for symptomatic caliceal diverticula with stones and the removal of staghorn calculi via an anatrophic nephrolithotomy performed laparoscopically (**Table 1**).

Table 1. Indications for laparoscopic stone surgery

Organ	Procedure	Indication
Kidney	Pyelolithotomy	Failure of endourologic management
		Complex renal anatomy
		Concomitant repair of PUJ obstruction
	Nephrolithotomy	Failure of endourologic management
		Complex calculi
		Concomitant repair of caliceal diverticula
	Polar nephrectomy	Non-functioning kidney portion
		Duplex system with non-functioning moiety
	Simple nephrectomy-Nephroureterectomy	Non-functioning Kidney
Ureter	Ureterolithotomy	Failure of endourologic management
		Lager or impacted stone
		Stone in megaureter
Bladder	Stone retrieval	Stone retrieval and diverticulectomy

Several authors have explored the role of laparoscopy for caliceal diverticula containing calculi, and 18 cases have been published in literature. Of these, 6 were performed by a transperitoneal (35-37) and 12 by a retroperitoneal approach (38-41). Indications for the laparoscopic approach included a stone located in anterior diverticula, with or without a thin overlying renal parenchyma, need for ablation of the diverticula and previously failed endourologic procedures such as PNL or flexible ureteroscopy. All stones were located in the upper pole, with one exception (37)**.** Stone localization was achieved by palpation and visual contact, especially when the overlying renal cortex was either bulging or depressed because of scarring, and by retrograde injection of indigo carmine, fluoroscopy or ultrasonography. Stones and diverticula were successfully treated without open conversion in all cases. The diverticula were generally managed by fulguration (27), although in some cases, the cavity was closed with perirenal fat (39)**,** gelatine resorcinol formaldehyde glue (40)**,** or suture closure of the diverticular neck (38). Operative times ranged from 60 to 200 minutes (27)**.** These studies indicate that laparoscopic diverticulectomy and stone removal is an efficient and a safe alternative or adjunct to endourologic procedures **(Evidence level III/B).**

Relative contraindications to the laparoscopic approach include failed PNL with perirenal adhesions overlying the site of surgical interest and a thick rim of renal parenchyma obscuring the diverticula and make the localization of its cavity and the stone difficult (27). These cases could be challenging and impose an indication for a limited anatrophic nephrolithotomy (38) **(Evidence level III/B).** The later was shown to be feasible in an animal model (15). Although three cases of successful clinical laparoscopic anatrophic nephrolithotomy have been published (38, 42), more studies on its feasibility, safety and success rate should be performed.

4. CONCLUSION

Shock wave lithotripsy and endourologic approaches are highly successive and constitute the treatment of choice for urinary calculi. Laparoscopic pyelolithotomy is feasible but rarely indicated in the present era. Laparoscopic nephrolithotomy may be indicated to remove a stone from an anterior diverticulum or when PNL or flexible ureteroscopy have failed.

RECOMMENDATIONS

RECOMMENDATIONS ON LAPAROSCOPIC STONE EXTRACTION

Recommendation	*Level of evidence*
Laparoscopic pyelolithotomy is feasible but rarely indicated in the present era.	**III/B**
Laparoscopic nephrolithotomy may be indicated to remove a stone from an anterior divertic ulum or when PNL or flexible ureteroscopy have failed.	**III/B**

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C. SPECIAL STONES

I. COMPOSITION

Nephrolithiasis is estimated to carry a yearly incidence of 0.5% in North America and Europe and is characterized by a continuous increase in prevalence that has reached 5.2%. [1] The kidney stones are composed of a mixture of inorganic and organic crystals in combination with proteins. These compounds are physiologically present in the urine as salts besides inhibitors and complexing agents (e.g. citrate, magnesium, glycoproteins, etc.). Therefore, urine is a complex solution that allows various salts to be held in solution in higher concentration than in other pure solvents, attribute named metastability. For example, in normal urine the concentration of calcium oxalate is four times more than its solubility and precipitation occurs only after supersaturation exceeds 7-11 times its solubility. [2] The sequence of events leading to lithogenesis consists of: supersaturation, crystallization/aggregation, crystal retention, stone formation. The frequency of calculi by composition is led by calcareous amalgams accounting for 75-80% of stones, followed by struvite with an incidence of 5-15%, uric acid 5-10%, cystine 1-2.5% and ammonium urate 0.5-1%. Mixed calculi such as calcium oxalate-phosphate (35-40%) and uric acid-calcium oxalate (5%) may form. Other highly uncommon presenting stones are made by xanthine, 8-dihyfroxyadenine, protein matrix and drugs (e.g. indinavir, triamterene, sulfasalazine, etc.). [3-5]

Besides stone size, location and shape, secondary complications and pre-existent anatomical anomalies, the knowledge of stone composition could be of major importance when considering the therapeutic options. [6-8] Stones that pass spontaneously or are captured following disintegration can be analyzed by X-ray crystallography and infrared spectroscopy. [9] Obviously, since these analysis can be performed after resolving the case, they may provide utile information only for prophylactic measures or future recurrent episodes of urolithiasis. [10] For immediate assessment of stone composition without available fragments for analysis, conclusions can be based on:

- Microscopic examination of urinary sediment for presence of crystals (struvite, cystine, urate, indinavir)
- Urine pH (low in patients with uric acid stones, high in patients with struvite)
- Urine bacteriology for urease producing bacteria (struvite)
- Serum level of uric acid
- Qualitative cystine test (e.g., sodium nitroprusside test)
- Radiological characteristics of the stone (grade of opacification, shape)

Various matters have been described as possible constituents of urinary calculi (**Table 1**). [11] Special stones are defined as either rare or those that by their composition impose particular diagnostic, therapeutic and prophylactic considerations.

1. CALCAREOUS STONES: BRUSHITE AND CALCIUM OXALATE MONOHYDRATE

Brushite (calcium hydrogen phosphate dihydrate; $CaHPO_4.2H_2O$) represents an initial phase of calcium salts, formed by spontaneous precipitation or deposition on an organic matrix, in a normal acid environment (pH 6-6.9). A prerequisite for the crystallization of brushite, is hypercalciuria. In alkaline urine, such as after meal (alkaline tide), brushite undergoes a rapid phase transformation or is hydrolyzed into stable hydroxyapatite. This mechanism explains the rare occurrence of predominantly brushite stones which ranges only 0.6-1.4%. [12,13] The mechanical properties of brushite have been evaluated by ultrasound and microidentation techniques, that scaled its hardness as related to SWL fragility as high. Higher hardness with lower SWL fragility was found for calcium oxalate monohydrate (COM) calculi ($CaC_2O_4 \bullet H_2O$). [14,15] Brushite and COM account for 30-60% of SWL failures of calcareous stones.[16,17] On KUB films these stones are characterized by dense opacity and smooth contour. Radiodensity alone, as determined by a KUB, may be an indicator of a worse SWL outcome only when the stone size exceeds 1 cm. [18] As CT has become the most common imaging modality for evaluating patients with renal colic, several studies have examined whether CT attenuation values can be used to predict stone composition and fragility. Although uric acid calculi may be differentiated from calcium stones based on their Hounsefield units, in the clinical practice, the fragility of calcium composed stones is unpredictable by CT. [19,20]

Brushite composition represents a risk factor for recurrent urolithiasis and occurrence of COM

Table 1. Constituents identified in urinary calculi

Chemical Name	Formula	Mineralogic Name
Calcium oxalate monohydrate	$CaC_2O_4 \bullet H_2O$	Whewelite
Calcium oxalate dihydrate	$CaC_2O_4 \bullet 2H_2O$ (to $2 \bullet 5H_2O$)	Weddellite
Magnesium hydrogen phosphate trihydrate	$MgHPO_4 \bullet 3H_2O$	Newberyite
Magnesium ammonium phosphate hexahydrate	$MgNH_4PO_4 \bullet 6H_2O$	Struvite
Hydroxyapatite	$Ca_{10}(PO_4)_6\,(OH)_2$	Hydroxyapatite
Carbonate-apatite	$Ca_{10}(PO_4)_{6-x}\,(OH)_{2-y}\,(CO_3)_{x+y}$	Carbonate-apatite
Calcium hydrogen phosphate dihydrate	$CaHPO_4 \bullet 2H_2O$	Brushite
Uric acid	$C_5H_4N_4O_3$	
Uric acid dihydrate	$C_5H_4N_4O_3 \bullet 2H_2O$	
Ammonium acid urate	$C_5H_3N_4O_3NH_4$	
Sodium acid urate monohydrate	$C_5H_3N_4O_3Na \bullet H_2O$	
Tricalcium orthophosphate	$Ca_3(PO_4)_2$	Whitlockite
Cystine	$[-SCH_2CHNH_2COOH]_2$	
Xanthine	$C_5H_4N_4O_2$	

stones predicts high risk of recurrence with similar composition. In addition to low SWL fragility, these stones typically fragment in large pieces which do not pass spontaneously requiring multiple ancillary treatments including endourological procedures. These facts explain a clinical trend toward preference of upfront ureteroscopic and percutaneous procedures in order to increase the treatment success with a single procedure. Brushite has been reported to be soluble in acid chemolitic agents such as hemiacidrin and Suby's solution (pH 3.5-4). [21] Although performed without anesthesia, this approach implies insertion of a loop or 2 nephrostomy tubes to allow continuous irrigation. It carries significant risks of infection and mortality (cardiac arrest) due to hypermagnesemia. With the advances of the endourologic techniques, today, irrigating chemolysis has been abandoned, remaining of historical significance only.

Although a comprehensive metabolic evaluation may not be cost effective in patients with their first occurrence of stones, patients with risk factors for stone recurrence should be evaluated. [22] Hypercalciuria in brushite stones is intestinal in origin and absorptive hypercalciuria type I was noted in 63% of patients with brushite stones compared with 17% to 30% with other stones. [13] The urinary environment of patients with hypercalciuric calcium nephrolithiasis was reported to be supersaturated with brushite. A decrease in urinary calcium and the saturation of brushite by certain medical treatments has been associated with improved prophylactic outcome. In addition to the general recommendation of increased fluid intake, pharmacological treatment should be contemplated. The most effective and best tested hypocalciuric agents are thiazide diuretics. [23] Reduction of calciuria has been attributed to enhanced reabsorption of calcium in the distal convoluted tubule and sodium depletion. In order to avoid thiazide-induced potassium loss, which causes intracellular acidosis producing hypocitraturia, thiazides should always be

prescribed with a potassium supplement, either dietary or pharmacological. Potassium citrate is the preferred choice, because it provides both potassium and citrate. [24] Indapamide is another potential hypocalciuric agent carrying fewer side-effects than thiazides. [25,26]

2. CYSTINE STONES

Cystine stones are caused by inherited defects of renal transport and carry an estimated incidence of one per 20.000. [27,28] Inactivating mutations in one of the two possible subunits (rBAT or b0+AT1) of the multisubstrate basic aminoacid transporter in the kidney leads to urinary wasting of aminoacids, such as cystine, arginine, lysine, and ornithine. [29] The phenotype is cystine because its insolubility leads to the pathological process of calculus formation. Two responsible genes have been identified: mutations in the SLC3A1 gene, located on the chromosome 2p, cause cystinuria type I, while variants in SLC7A9 have been demonstrated in non-type I cystinuria. [30] More than 50% of asymptomatic homozygotes develop kidney stones with 75% of these patients presenting with bilateral calculi. [28] Pure cystine stones are observed in 60–80% of cases. Electronic microscopic assessment revealed rough and smooth subtypes of cystine. Smooth calculi have an irregular, interlacing crystal structure, making them more resistant to SWL fragmentation than the more homogenous hexagonal crystal structure of the rough subtype. This assessment however can not be done before treatment. Cystine stones have a faint homogeneous ground-glass appearance on KUB films. Although they may reach staghorn size, small stones may not be visible. An accurate initial diagnosis is most readily made by non-contrast CT. Since cystinurics form stones early in their life and have life long recurrence risk, ultrasonography should be considered for follow-up in order to reduce accumulation of large radiation exposure by repeated use of CT.

The probability to obtain complete fragmentation of cystine stones with one or more SWL sessions is 30%. [31,32] When considering SWL as an option, an upper limit of 1.5 cm diameter for upper ureteral or renal cystine calculi is proposed. Oral thiol therapy may produce cystine calculi that are more fragile because cystine is replaced by apatite in approximately 30% of cases, rendering these stones more SWL sensitive [32]. Therefore, ureteral stones and renal stones larger than 1.5 cm should be treated more effectively by either retrograde or percutaneous endourological approach. Percutaneous chemodisolution with acetylcysteine and 0.3-0.6 molar of alkaline THAM solution was practiced in the past with limited success. [33-35] With the advent of the minimally invasive surgical techniques, direct irrigation is rarely used today.

Prevention is the corner stone approach in patients diagnosed with cystinuria. Hydration therapy to produce urine volumes of more than 3 liters per day and urine alkalinization to a pH of 7-7.5 are the main concepts of prophylaxis. The first line alkalinizing agent is now potassium citrate, at an optimal dose achieved by titration, and used with caution in patients with renal impairment. Commonly, adults achieve the optimal pH at a dose of 60–80 mEq/d divided into 3–4 doses (15–20mL/d). [30] When hydration and alkalinization fail to prevent recurrence, drug therapy with chelators or antiurolithics should be initiated in order to reduce the cystine urinary concentration below 300 mg/l. [36]. Thiol compounds combine chemically with cystine to form a soluble disulfide complex that prevents stone formation and may even dissolve existing stones. **Table 2** summarizes available drugs.

In conclusion, cystinuria is a challenging condition characterized by high recurrence and early age of presentation, necessitating long and close follow-up. Treatment should aim to reduce the number of recurrent stone events in a patient's lifetime, to preserve maximal renal function and to limit radiation exposure.

3. URIC ACID STONES

The lack of uricase in humans results in uric acid (2,6,8-trioxypurine) as the end product of purine metabolism. Uric acid is a weak acid and its solubility is influenced by concentration and pH. In urine, the solubility of uric acid is primarily determined by urinary pH, that at a level of more than 5.5 causes loss of 1 protone resulting in formation of anionic urate. Uric acid derives by endogenous production (purine synthesis, tissue catabolism; 300-400 mg/day) and by exogenous pool that varies with diet. The formation of uric acid from the purine pool involves the activity of xanthine oxidase. Two thirds of the uric acid pool is elimi-

Table 2. Drug therapy for prevention of cystine stones

Drug	Solubility increment	Dose	Adverse reactions, cautions and comments
D-Penicillamine [37] (1st generation)	X 50	1-2g/day	Rash, arthralgia, leucopenia, GI intolerance, nephritic syndrome, vit B-6 deficiency, pancytopenia; contraindicated in preganancy
Alpha-mercaptopropionylglycine [38] (2nd generation) (Tiopronin, Thiola®)	30-50% more than with D-Penicillamine	10-15 mg/kg/day	Better profile than D-penicillamine; contraindicated in preganancy
Captopril [39] (thiol 1st generation; ACE inhibitor)	X 200	75-150 mg/day	Used for concomitant treatment of hypertension in cystinuric patients
Bucillamine (Rimatil) [40] (*N*-(2-mercapto-2-methylpropionyl)-L-cysteine (3rd generation dithiol)		200 mg/day	Low toxicity profile Available in Japan and Korea

nated by renal excretion. [41] Uric acid stones can be classified based on crystalline composition as anhydrous uric acid, uric acid dihydrate, sodium acid urate monohydrate or ammonium acid urate. [42] At present, differences in crystal composition and growth have no clinical implications. Excessively acidic urine is present in gout and idiopathic uric acid stone formers and is much more common than hyperuricosuria as a cause of uric acid stones. Secondary causes of low pH can result from excessive acid load or alkali loss, such as arises with chronic diarrhea and inflammatory bowel disease. The finding of hyperuricaemia without gouty arthritis in patients with uric acid nephrolithiasis, hypertriglyceridaemia and obesity, led to the term of gouty diathesis. [43] High body-mass index, glucose intolerance, and type 2 diabetes are common in uric acid stone formers. In addition, diabetic stone formers have a 30–40% rate of uric acid stones compared with the 5–8% in the general stone forming population. These findings link uric acid stones and excessively acidic urine to obesity and type 2 diabetes.[44-48] Myeloproliferative and lymphoproliferative disorders can result in an increased rate of nucleic acid production and turnover with subsequent hyperuricosuria. During chemotherapy for myeloproliferative disorders, tumor necrosis may result in severe hyperuricosuria, crystalluria and acute urinary obstruction. The incidence of uric acid stones in these patients is approximately 40%. Benign disorders associated with uric acid calculi include sickle cell disease, hemolytic anemia, thalassemia and polycythemia. [41] Several congenital enzymatic defects may result in hyperuricosuria. One of them, hypoxanthine guanine phosphoribosyl transferase deficiency is a X-linked form and occurs only in men. In the severe form known as the Lesch-Nyhan syndrome patients present with mental retardation, self-mutilation, gout and uric acid stones. Another X-linked disorder associated with hyperuricemia and hyperuricosuria is phosphoribosyl pyrophosphate synthetase overactivity. Type 1 glycogen storage disease, an autosomal recessive disorder caused by glucose-6-phosphatase deficiency, is also Associated with increased risk of uric acid calculi.

In comparison to other stones, uric acid stones occur in an older population. [49] Uric acid stones are relatively radiolucent on KUB films. Noncontrast CT is the best modality for initial evaluation and allows differentiation from other possible radiolucent reasons for obstruction (e.g. papillary necrosis, transitional cell carcinoma and fungal bezoars). CT density assessed by Hounsfield units revealed a significant difference between uric acid (344±152) and calcium oxalate (652±490) stones. [50] Uric acid stones may reach staghorn size. When stones cause acute complications, such as obstruction, infection or renal failure, and when they are very large, an active endourological intervention is required. All lithotripsy modalities are effective. Holmium:YAG lithotripsy of uric acid calculi releases cyanide, however, without any toxicity or side effects. [51] SWL could be an effective approach for renal stones smaller than 20 mm, however, it implies either real time ultrasonography or use of contrast material for targeting. [52]

In non complicated cases, maintenance of a daily urinary volume of 1.5-2 l, urine alkalinization and reduction of uricosuria are the main measures of medical therapy and prevention. Although dissolution of large uric acid renal stones was reported, an upper limit of 20 mm stone diameter is commonly recommended. The goal of urinary alkalization is to achieve a pH of 6-6.5. Commonly, potassium citrate (30-60 mEq/day) is efficiently use for this scope. It should be titrated because pH >6.5 may result in calcium phosphate stone formation. Reduction in hyperuricosuria can be achieved by dietary restriction of purines and drugs. Urinary urea nitrogen excretion correlates with purine intake and can be used during followup to determine compliance with dietary restrictions. [53] Patients not responding to dietary modifications should receive allopurinol, a xanthine oxidase inhibitor that stop conversion of the xanthine and hypoxanthine in uric acid. Allopurinol also decreases de novo purine synthesis. Inhibition of purine synthesis does not occur in patients with myeloproliferative disorders or hypoxanthine guanine phosphoribosyl transferase deficiency. Therefore, xanthine stones may form during allopurinol therapy in these individuals. [54] In patients with myeloproliferative disorders allopurinol should be given before chemotherapy to reduce the risk of uric acid stones due to cell lysis. Allopurinol is commonly administered in a daily dose of 300 mg/day that should be adjusted in patients with renal insufficiency. Minor side effects such as skin rash and gastrointestinal irritation may occur. Increased liver enzymes have been reported requiring followup during long-term treatments. The most severe reported side effect is allergic response resulting in hemorrhagic skin lesions and potentially fatal vasculitis (the Stevens-Johnson syndrome). Pruritus precedes the development of skin lesions and patients should be instructed to stop the medication if this occurs. [41]

4. XANTHINE AND HYPOXANTHINE STONES

Xanthine and hypoxanthine calculi are rare stones that occur in patients with myeloproliferative disorders or hypoxanthine guanine phosphoribosyl transferase deficiency (Lesch-Nyhan syndrome) treated by allopurinol. Another disorder associated with formation of xanthine stones is xanthinuria type I, a rare autosomal recessive disorder of purine metabolism. It is caused by mutations of the XDH-gene on chromosome 2p22 resulting in deficiency of the enzyme xanthine oxidoreductase or dehydrogenase that catalyzes the last two steps of the purine degradation pathway. Xanthinuria type I is characterized by strongly diminished production of uric acid and by accumulation and high urinary excretion of hypoxanthine and xanthine. In about half of all patients urolithiasis will occur. The disease appears to be relatively prevalent in the Mediterranean region. [55] A lack of response to urinary alkalinization may suggest the diagnosis of xanthine and 2,8-dihydroxyadenine stones. These stones are radiotransparent and have the same imaging properties as uric acid stones. Active stone removal follows the recommendations made for uric acid stones. Preventive measures in patients with primary xanthine stones are not satisfactory. No specific therapy is available. A low-purine diet is advocated but the most important measure is to ascertain a high fluid intake. Although xanthine calculi typically develop in acidic urine and the pKa of xanthine is 7.4, urinary pH manipulation only modestly elevates the solubility of xanthine. This manipulation is a preventive measure and is unlikely to result in dissolution of existing stones. Allopurinol dose manipulation has been suggested, however, the degree and direction of dosage adjustment is controversial. Increasing allopurinol dose to further inhibit xanthine oxidase theoretically increases excretion of the more soluble hypoxanthine limiting conversion to xanthine. Conversely, since uric acid is more soluble than xanthine, reduction of allopurinol dose to maintain high normal serum and urine uric acid levels combined with appropriate hydration and urinary pH manipulation could be more effective. [56]

5. MATRIX STONES

Matrix urinary calculi are composed by 65% proteiceous material in comparison to only 2.5% in other calculi. Fibrinomas, colloid calculi or albumin calculi have been used as synonyms. [57] Matrix is an organic substance consisting of approximately one-third carbohydrate (as mucopolysaccharide) and two-thirds protein (as mucoprotein). Hexose and hexosamine are the principle carbohydrate components of matrix while threonine and leucine with serine, tyrosine, arginine and lysine in smaller quantities are the principle protein components. Matrix calculi have been reported in association with urinary tract infections, especially with proteus species and E. coli, with chronic renal failure and with hemodialysis [58]. The soft consistency of matrix may lead to staghorn formation with progressive obstruction. The radiographic appearance of matrix calculi depends on the amount of mineral content, presence of infection, size and shape. On KUB films they are radiolucent or weekly radiopaque, sometimes with gas trapped within or around the stone. On contrast studies they may appear as filling defects, arising the need for differential diagnosis with blood clots, tumors, polyps, small uric acid or cystine stones, varices, ureteritis cystica and sloughed renal papillae. The low mineral content is probably the cause of absence of marginal acoustic shadowing on ultrasonography, mimicking a space occupying lesion. Occasionally, diagnostic ureterorenoscopy may be needed to establish the diagnosis. CT assessment may show densely calcified centers or peripheral rim mineralization of variable density [59]. Matrix stones are usually large in volume and are unlikely to pass spontaneously. Extracorporeal shock wave lithotripsy is ineffective due to the gelatinous nature of the stone. Thus, ureteroscopic and percutaneous approach are the treatments of choice. Administration of perioperative specific or wide spectrum antibiotics and maintenance of low pressure irrigation during the endourological approach are essential in reducing the risk of postoperative septic complications.

6. DRUG-INDUCED STONES

a) Triamterene

Triamterene is a potassium-sparing diuretic that is often given singly or in combination with hydrochlorothiazide in the treatment of hypertension. Up to 70% of orally administered triamterene appears in urine, and patients may develop either pure or mixed triamterene stones. [60] Patients with triamterene stones almost always have a history of nephrolithiasis. Triamterene is faintly radiopaque on plain radiography. It cannot be dissolved by pH manipulation and, rather, must be treated with conventional lithotripsy techniques. With the advent of other potassium-sparing diuretics, it appears prudent to eliminate the use of triamterene in patients with a history of nephrolithiasis. [61]

b) Indinavir

Indinavir is a protease inhibitor medication that is commonly used to treat human immunodeficiency virus infection. The mechanism of indinavir stone formation is probably related to crystallization of the drug in urine. The incidence of symptomatic indinavir nephrolithiasis in patients on indinavir therapy has been estimated from 3.6% to 22%. [62] Patients at increased risk for indinavir lithiasis appear to be those with concentrated urine and those with hemophilia and hepatitis, possibly due to decreased hepatic metabolism of the drug. There are no known inhibitors of indinavir crystallization.

Indinavir calculi are radiolucent and typically not identifiable on X-ray imaging including CT. Some patients form stones that contain a calcium component, which may be radiographically visible. Urinalysis reveals the presence of typical rectangular and fan shaped or starburst crystals in about 20% of the cases.

Hydration and analgesic therapy are recommended for initial treatment of indinavir stones. Indinavir therapy may need to be temporarily or permanently discontinued, in which case another protease inhibitor may be prescribed. Drainage and endourological interventions may be necessary for patients with prolonged renal obstruction, signs of sepsis, or unremitting symptoms.

c) Guaifenesin and ephedrine

Individuals consuming large quantities of cough medicines containing ephedrine or guaifenesin are at risk of developing stones derived mainly from urinary excreted metabolites. [63] Many of these patients are prone to drug and alcohol dependency. The stones are radiolucent on conventional radiography but radiopaque on computed tomography (CT). These calculi should be treated similarly to other types of calculi and substance abuse counseling is recommended after treatment.

d) Silicate

Silicate urinary calculi are extremely rare in humans. They occur only in patients taking large amounts of antacids containing silicates (e.g., magnesium trisilicate) The urinary excretion of silicate is normally less than 10 mg/day but approaches 500 mg/day in patients taking magnesium trisilicate. Trisilicate is converted to silica or silicon dioxide by gastric acid. Silicate calculi are poorly radiopaque and easily treated with conventional lithotripsy methods. Prevention of recurrence can be assured if the patient eliminates the use of magnesium trisilicate antacids. [64]

e) Sulfa medications

The administration of sulfonamides can be complicated by the development of crystalline aggregates of these drugs. Obstructing urinary calculi has been reported with metabolites of sulfamethoxazole-trimethoprim, sulfadiazine, and sulfasalazine. The solubility of sulfonamides is greatly enhanced by increased urinary pH, and sulfonamide-induced calculi may be avoided with adequate hydration and urinary pH manipulation. Sulfa-induced calculi are radiolucent on plain radiography. [5,61]

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II. STONE SIZE AND LOCATION

INTRODUCTION

Urolithiasis has plagued mankind for many thousands of years of recorded history. Treatment options and definitions for success are predicated not so much on the skill of the surgeon, and the tools at his/her disposal, but equally as important are the characteristics of the stone under treatment. The size and location are often the most important characteristics. The following discussion will define four specific groups of stones (Staghorn, Lower pole, Proximal ureteral, and Multiple renal stones) involving the upper urinary tract (UUT). We shall define and discuss how the urological literature defines these specific stones, discuss indication for intervention, and therapeutic options for each particular scenario. This review will focus as best as it can on the highest levels of evidence available, clinical guidelines when available and consensus documents where literature is scarce.

1. PCNL MONOTHERAPY FOR THE MANAGEMENT OF STAGHORN CALCULUS

a) Introduction

Staghorn calculi are branched stones that occupy a large portion of the collecting system. Typically they fill the renal pelvis and branch in several and or all of the calices. An untreated staghorn calculus is likely to destroy the kidney and/or cause life threatening sepsis. (1,2) Complete removal of stone is crucial in order to eradicate infection relieve obstruction, and prevent further stone growth. Percutaneous nephrolithotomy (PCNL) is currently the preferred first line treatment for staghorn and large renal calculi (3). PCNL is less morbid than open surgery and offers equivalent stone clearance rates (3,4). With increasing stone size and complexity, PCNL may require a longer operative time and multiple tracts to achieve complete clearance. (5) The aim of any treatment modality for treating staghorn calculi should be cost effective, safe, complete stone clearance. Our policy of managing staghorn include multiple ultrasound guided predetermined punctures and clearance of the stone in a staged manner in a single hospital stay.

b) Management

Preoperative preparation includes adequate imaging for stone size, renal anatomy and function. Intra-Renal anatomy is assessed on anteroposterior and oblique plain x-ray KUB, in addition all underwent appropriate blood investigations and intravenous pyelogram.All patients receive appropriate perioperative antibiotics.

Percutaneous nephrostomy is placed in patients with renal insufficiency to improve drainage and renal function. If necessary, they undergo preoperative dialysis to improve the safety of the procedure. Similarly, patients with severe infection are initially managed with pre-operative PCN to improve drainage and function. We have found Double “J” stent inadequate for renal decompression. It is our policy to establish ultrasound guided percutaneous drainage under local anesthesia in a predetermined desired calyx which will facilitate stone removal later.

All PCNLs are done under general anesthesia. 5Fr ureteric catheter is placed and bladder drained with 16 Fr Foley catheter. Prone position is given with support under chest and pelvis with padded bolsters.

Renal access is predetermined after studying the stone configuration and intra-renal anatomy of collecting system. First, the numbers of calyces to be approached are determined and the number of punctures ascertained. One of the punctures will be the main one which would clear maximum stone burden. Remaining ones would be secondary, which will clear the peripheral calyceal stones. We prefer multiple peripheral tracts to clear residual calyceal stone which may not be cleared easily through the main tract. Secondary punctures are aimed at clearing the calyceal stone and appropriate pelvic part of the stone. We do maximum of three, and occasionally four punctures to appropriate calyx before dilating the main tract to the maximum. Secondary punctures are secured by passing the guide wire in either ureter or a distant calyx.

All initial punctures are done by operating urologist himself under ultrasound guidance. Subsequent punctures are done under fluoroscopy and each is stabilized by passing guide wire in either ureter or in other calyx. Except the main one, all other guide wires are secured outside. Tract dilatation is done with a screw dilator which allows a single step dilatation to 14 Fr, thereafter the tract is dilated with serial telescopic Alken dilators (upto24Fr). Main tract is dilated to facilitate placement of 26Fr or 28Fr Amplatz sheath, while secondary tracts if necessary, are dilated till they can accommodate 20 or 24 Amplatz sheath.

Since 1994 we have been using pneumatic lithotripsy with suction to disintegrate stone. Recently we have started using the combination of ultrasound and Pneumatic lithotripsy for fragmentation. This significantly reduces the nephroscopy time. We limit our lithotripsy time to one and half hour. Procedure is abandoned if the stone is not at all accessible or due to bleeding obscuring the vision .If we have not used the puncture in the first sitting and feel a need of dilating the tract in a subsequent sitting, a 14Fr Malecot catheter is placed for tract maturation.

A 20 or 22Fr Nelaton catheter is placed as a nephrostomy tube. In multiple tract procedures, the secondary tracts are drained by 12 or 14Fr tubes.

Second stage, if necessary is scheduled after 72 hours. Exact position of residual fragment is determined by a X-ray KUB taken on second post operative day.

Stone free status is decided on x-ray evaluation with an AP and Oblique plain film. Patients are followed in out patient every three months for first year, thereafter yearly clinical evaluation is done with renal ultrasound, X-ray KUB, blood and urine examinations.

A retrospective analysis was carried out at our centre of patients with Staghorn calculi who underwent PCNL as a monotherapy between 1991 and April 2007. This included 684 patients (725 renal units). The male to female ratio was 4:1 (568 males and 116 female patients) with an age range between 1 to 76 years.

Majority of the cases required one or two tracts to clear the stone bulk, though as the stone bulk increased so did the number of tracts (**Table 1**). Though the mean hemoglobin drop was not significant, the blood transfusion rates were higher in those with multiple tracts (**Table 2**).

c) Discussion

The goals in treating complete staghorn calculi are complete stone clearance with no residue, minimal morbidity, no mortality. Further the chosen treatment modality should be cost effective. Percutaneous nephrolithotomy is an important component of treatment in these stones. AUA Nephrolithiasis guidelines panel on staghorn calculi suggest that percutaneous monotherapy with multiple tracts is associated with 79% stone clearance rate, acute complication rates of 15%, transfu-

Table 1. Number of tracts versus stone clearance

No.of tracts	**PS(%) 376**	**CS(%) 220**	**CC(%) 129**	**Total = 725**
1	165(44.8)	38(17.0)	22(19.0)	225 / 31.6%
2	148(37.5)	69(31.4)	56(42.5)	273 /36.6%
3	39(11.1)	62(29.3)	33(26.5)	134 /19.5%
>3	25(7)	50(22.9)	18(13.3)	93 /12.4%
Complete clearance with PCNL			614(84.7%)	
Residual stones			111 (15.3%)	
Overall clearance after auxiliary procedures(ESWL)			654 (90.2%)	

Table 2 . Hemoglobin drop and number of tracts

Average drop in Hb :	
Single tract	1.4gm%.
Multiple tract	2.1gm%.
Overall	1.9gm%
Tract wise Transfusion rate	
No. of tracts	**No. of patients**
1 tract	18/225 (8.0%)
2 tracts	22/273 (8.1%)
3 tracts	17/134 (12.7%)
4 tracts	7/46 (15.2%)
5 tracts	17/47 (36.1%)

sion rates of 18% and is preferred to combination therapy, SWL monotherapy and open surgery. (3)

The perceived concerns regarding multiple tracts which include greater bleeding and higher complication rates have been addressed in previous studies. (7) *Hegarty et al* in their study noted a mean drop in hemoglobin in patients having multiple tracts was similar to that in patients needing a solitary tract; the use of multiple tracts did not lead to a higher incidence of complications. Complete clearance was achieved in 95% of the cases. (5) *Aron et al* in their study achieved complete clearance in 84 % of cases with multiple tracts (2 tracts in 11, 3 tracts in 68, 4 tracts in 39 and 5 tracts in 3). (8) *Liatsikos et al* have described multiple angular punctures to approach the superior, middle and lower pole of the kidney for the management of staghorn calculi with 87% stone clearance rates in single session. (9) Auge et al in their series found no significant difference in blood loss, transfusions, complications or length of surgery as the number of tracts increases. (10) Gupta et al in their series concluded that aggressive PCNL monotherapy using multiple tracts is safe and effective, and should be the first option for massive renal staghorn calculi. (11) Al Jawani NA et al evaluated the effectiveness of percutaneous nephrolithotomy (PNL) in the management of patients with complete staghorn stones and found PNL useful in the management of patients with complete staghorn stones, either as monotherapy or in combination with SWL as It was associated with little morbidity and the procedure can be instituted even in centers with limited facilities. (12)

In our series, the overall hemoglobin drop was 2.1gms and in patients with single tract 1.4gm% and multiple tracts was 2.1gm%. Although this is not statistically significant, it reflects the associated co-morbidities in patients with multiple tracts, such as anemia, renal insufficiency. In our series there were no major complications with multiple tracts.

A few surgical points which merit mention are, all Percutaneous access were achieved by urologist with ultrasound guidance, at the outset all guide wires were positioned in the desired calyces, as we believe this becomes increasingly difficult as the procedure proceeds. We restricted our Nephroscopy time to 90 minutes and staged the procedure if the vision was poor. Complete clearance was ensured intraoperatively by fluoroscopy and also with a plain X-ray KUB 48 hrs post operatively before removing the tubes

The policy of multiperc PCNL has enabled us to achieve a complete clearance in 84.1% of cases, in a single hospital stay (average 12days) with minimal morbidity (**Table 3**). The approach of multiperc is also cost effective as it does not require a cost of additional equipment.

2. CONCLUSION

Staghorn stones can be completely cleared with Multi-Perc approach. While comparing morbidity amongst single and multiple tracts, the blood transfusion and overall complication rates are higher in multiple tracts, but the major complications are similar and not significantly different in either group. More punctures are required for complete clearance and more stages are needed for the safety of the patient. Morbidity of multiperc approach is bleeding, which most of the times is managed conservatively. Complete clearance of staghorn calculi with multi-perc is safe, efficacious and cost effective.

Table 3. Straghorn calculi and clinical complications

Author	No. of renal units	Mean stone bulk	Pre-op renal insufficiency	Clearance rate	Transfusion rate	Overall Complication rate
Gupta NP et al, Urol Int. 2005;75(4)	121 renal units (103 patients)	4,800 mm^2	9.7%	84% complete clearance rate (that improved to 94% with SWL in 8 renal units)	17.4%	23.1%
Al Jawani NA et al Saudi J Kidney Dis Transpl. 2007 Mar;18(1)	119 renal units (110 patients)	Complete staghorn calculus	18.5%	78.6% (overall success rate after PNL and SWL in 108 renal units was 89.4%)		9.2%
Mammadov R, Cal C et al Urology. 2007 Apr;69(4)	193 renal units (193 patients)	843.1mm^2	none	85.4%	23.8%	35.2%
Preminger G et al J Endourol, 2001:(15) A60	67 renal units	Size NA			28%	10.4%
Claro JA et al, Urology 2005 Apr;65(4)	119 patients	6,900 mm^2		84.8%		28.5%
Mihir M Desai et al, J Endourol,vol20,oct 2006	20 patients	2157 mm^2	45%	95%	20%	10%
Al-Kohlany KM J urol,2005;173,469	43 renal units	18.7 cm^3	11.6%	74%	11.6%	16.3%
MPUH et al	725 renal units	1402mm^2	18.6%	84.1%(91.1% after auxillary procedures)	11.6%	22.8%

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III. LOWER POLE STONES

The management of symptomatic lower pole renal stones represents an area of continuing controversy. The lower pole of the kidney presents a unique anatomical challenge. Various treatment alternatives exist, including shock wave lithotripsy (SWL), percutaneous nephrolithotomy (PNL) and flexible ureteroscopy (URS).

1. INFUNDIBULOPELVIC ANATOMY

Overall stone free rates after ESWL for lower pole renal calculi range from 21% to 72% [1,2,3, 4]. The efficacy of ESWL for lower pole renal calculi is determined by a number of factors including stone size and composition, caliceal anatomy and the type of lithotriptor used [5,4,6,7]. The most studied anatomic factor has been the infundibulopelvic angle, but considerable controversy exists as to its role [3,8,5, 9, 10].

Sampaio et al first studied the role of caliceal anatomy on stone clearance rates using a 3-dimensional polyester resin endocast of the pelvicaliceal system of cadaver kidneys [5]. They proposed that patients with an infundibulopelvic angle of less than 90° would have poorer stone clearance rates after ESWL. Of their sample 74% of cadaveric resin casts of the kidneys of non-stone formers had an angle of more than 90 degrees. Other groups have subsequently confirmed these findings clinically, and have analyzed additional factors related to lower pole caliceal anatomy as predictors of shock wave lithotripsy efficacy [9,11-13,8,1]. Elbahnasy et al retrospectively analyzed the impact of lower-pole anatomy on stone-free rates after flexible ureteroscopy or ESWL for lower-pole caliceal stones less than 15 mm [3, 11]. Preoperative IVP studies were reviewed to measure lower pole infundibular length, infundibular width and the lower pole infundibulopelvic angle. Lower pole infundibular length was measured in mm. from the most distal point at the bottom of the infundibulum to a midpoint at the lower lip of the renal pelvis. Lower pole infundibular width was measured in mm. at the narrowest point along the infundibular axis. The lower pole infundibulopelvic angle was determined in degrees between 2 axes, including the ureteropelvic axis connecting the central point of the pelvis opposite the margins of the superior and inferior renal sinuses to the central point of the ureter opposite the lower kidney pole, and the central axis of the lower pole infundibulum. They demonstrated that the infundibulopelvic angle was more obtuse in stone-free ESWL patients, the infundibular length shorter and the infundibular width greater in patients with residual fragments.

Recent studies have raised questions about the impact of renal anatomy on prediction of stone clearance and reproducibility of the parameters [9, 14-16]. Madbouly et al retrospectively reviewed the impact of lower pole renal anatomy on stone clearance after SWL in 108 patients [13]. The stone free rate at 3 months was correlated with lower pole infundibular length and width in mm as well as with the lower pole infundibulopelvic angle in degrees. They concluded that differences in the intrarenal anatomy of the lower pole had no significant impact on stone clearance after SWL. The authors suggested that differences in results may be due to differences in the method of infundibulopelvic angle measurement. Similarly, other authors have reported no correlation between anatomical parameters in their SWL success rates [9, 15]. Again, the definition of the IPA has tended to vary, with at least four different methods of measurement described [3, 5, 10,8].

This lack of a standardized approach to the measurement of the infundibular pelvic angle has led to inter- and intraobserver variability in findings and an inability to reproduce similar clinical results. This arises as the definition of the infundibular pelvic angle tends to vary from one investigator to another [5, 8, 11]. It has also been argued that as the pelvicaliceal system is dynamic, measurements of any structure within the collecting system would change during persitalsis, thereby rendering any measurement from a single IVP film imprecise [17].

Tuckey et al proposed another lower pole anatomical parameter, the caliceal-pelvic height, as a predictor of ESWL treatment efficacy [1]. This distance is measured between a horizontal line from the lowest point in the stone bearing calyx to the highest point of the lower lip of the renal pelvis. They reported a 92% stone free rate in patients with a caliceal-pelvic height of less than 15 mm and only 52% stone free rates in those with a caliceal-pelvic height of greater than 15 mm. this height represents the vertical distance that the stone has to travel against gravity, but does not take into account the width of the infundibulum.

Although it seems intuitive that lower pole caliceal anatomy should influence success in patients in whom ESWL is being considered, it remains unclear what parameters will influence stone clearance and what parameters are most predictive of success. Lack of consensus of a standardized approach to the measurement of these parameters as well as poorly defined arbitrary cutoffs contribute to the continuing controversy.

2. EXTRA-CORPORAL SHOCKWAVE LITHOTRIPSY

Shock wave lithotripsy though noninvasive and simple to perform, is associated with poor clearance of fragments from the lower pole, resulting in relatively low stone-free rates [9, 18]. The persistence of stone fragments in the lower pole predisposes to future stone growth, symptomatic recurrence and infection [19]. Lingeman et al., in a meta-analysis reviewed 2927 patients and showed that the overall stone free-rate for SWL for lower pole renal stones was 60% [7] **(Evidence Level I)**. The analysis also demonstrated an inverse relationship between stone burden and stone free rates. When stratified for stone size, the results of the meta-analysis showed stone free rates of 33%, 56% and 74% for stones greater than 20mm., 11 – 20 mm and less than 10 mm. respectively [7]. Albala et al in a prospective randomized multi-center trial compared SWL and PNL as primary treatment for lower pole renal stones in 128 patients to determine optimal therapy [9] **(Evidence Level I)**. The study was further stratified according to aggregate renal stone size (1 to 10, 11 to 20 and 21 to 30 mm). The overall 3-month stone-free rates for SWL and PNL were 95% for PCNL and 37% for SWL. Morbidity was low overall and did not differ significantly between the groups. Stone-free rates for SWL and PNL groups in the 1-10, 11-20 and 21-30 mm groups were 63 versus 100%, 23 versus 93% and 14 versus 86%, respectively. An important take home message from this study was that as stone size increased greater than 10 mm, the likelihood of being stone-free with SWL decreased dramatically.

In an attempt to optimize results after SWL, different strategies have been proposed for lower pole nephrolithiasis, such as inversion therapy [20,21], direct irrigation of the lower calices during SWL [22], forced diuresis with percussion of the flank area [23] or medical adjunctive therapy [24]. Others have attempted to correlate radiographic findings on noncontrast CT in order to determine a stones likelihood to fragment [25-27,28,29]. Pareek et al evaluated 50 patients who underwent SWL for 5 to 10 mm. upper urinary tract stones [28] **(Evidence Level III)**. Chemical analyses and density calculations (Hounsfield units-HU) were performed for each stone and post-treatment radiographic assessment categorized patients into a stone-free or a residual stone group. Thirty-two patients were stone free, defined as residual stone fragments less than 3 mm, after SWL and 18 had residual stones. The study showed a statistically significant inverse relationship between stone clearance and HU. The residual stone group had an average measurement of 926.20 units and the stone-free group an average of 551.20 units. Similarly, Joseph et al prospectively evaluated the attenuation value of renal calculi on unenhanced axial computerized tomography (CT) images as a predictor of calculous fragmentation by SWL [30] **(Evidence Level II/B)**. They reviewed 30 patients with renal calculi up to 20 mm. Patients were grouped according to calculous attenuation value as groups 1—less than 500, 2—500 to 1,000 and 3—greater than 1,000 HU. Of the 30 patients 24 (80%) underwent successful treatment. The rate of stone clearance was 100% (12 of 12 cases) in group 1, 85.7% (6 of 7) in group 2 and 54.5% (6 of 11) in group 3. The success rate for stones with an attenuation value of greater than 1,000 HU was significantly lower than that for stones with a value of less than 1,000 HU (6 of 11 versus 18 of 19 cases). Patients in group 3 required a greater median number of shock waves for stone fragmentation than those in groups 1 and 2 (7,300, 2,500, and 3,390, respectively). They reported that the mean attenuation value and number of shock waves required for calculous fragmentation correlated significantly ($p < 0.001$). Although further studies are required, attenuation values on non-contrast CT scan may be a means of improving the efficacy of SWL for patients with lower pole renal stones and may have some role in patient selection.

The persistence of stone fragments despite successful communition after SWL appears to be due to the gravity-dependent location hindering spontaneous passage. To address this, various groups have suggested that adjunctive therapy consisting of manual percussion, diuresis and inversion (PDI) may improve clearance [21,20]. It is suggested that PDI therapy may assist in clearance of lower pole stones by increasing urine production by higher than normal fluid intake just before the PDI session to "flush out" the stone fragments using the force of gravity to assist passage of stone fragments by placing the patient in the prone Trendelenburg position and finally by using percussion to the flank to cause vibrations in the renal system to assist in dislodgement of fragments. In a study by Chiong et al the clearance rates for lower pole kidney stones in patients receiving SWL alone were compared with those receiving sequential SWL plus PDI therapy [21] **(Evidence Level IIA)**. In this single-blind study, 108 patients who underwent SWL treatment for lower pole renal stones with a total diameter of 2 cm or less were prospectively randomized into two groups. One group of 49 patients received SWL only and the other group of 59 patients received a median of four sessions of PDI therapy 1 to 2 weeks after each SWL session. The patients from both groups were comparable in terms of stone characteristics and infundibulopelvic anatomy. All patients underwent a maximum of four SWL treatments. For all assessable patients, the radiologically documented complete stone clearance rate at 3 months for the SWL-alone group was 35.4% and for the SWL plus PDI group was 62.5% ($P = 0.006$). In this study, PDI therapy was well tolerated by all patients, with negligible morbidity arising from its administration. The authors concluded that mechanical percussion, diuresis, and inversion therapy is effective as an adjunct when combined with SWL treatment in aiding the clearance of lower pole renal calculi.

It has been reported that appropriate medical treatment initiated after SWL, even in the presence of residual calculi, might control active stone disease by decreasing the saturation of stone-forming substances or enhancing inhibitory activity. Citrate

complexes with calcium, thereby decreasing urinary saturation, and has been shown to inhibit the aggregation of calcium oxalate crystals [31] Soygur et al prospectively evaluated the effect of potassium citrate therapy on stone recurrences and residual fragments after SWL for lower caliceal calcium oxalate urolithiasis [24] **(Evidence Level IIA)**. They evaluated 110 patients who underwent SWL for lower pole stones and who were stone free or who had residual stone 4 weeks later were enrolled in the study. All patients had documented simple calcium oxalate lithiasis without urinary tract infection and with normal renal morphology and function. Four weeks after SWL, 56 patients who were stone free and 34 patients who had residual stones were independently randomized into two subgroups that were matched for sex, age, and urinary values of citrate, calcium, and uric acid. One group was given oral potassium citrate 60 mEq per day, and the other group served as controls. In patients who were stone free after SWL and receiving medical treatment, there were no stone recurrences at 12 months whereas untreated patients showed a 28.5% stone recurrence rate ($P < 0.05$). Similarly, in the residual fragment group, the medically treated patients had a significantly greater remission rate than the untreated patients (44.5 *v* 12.5%; $P < 0.05$). The authors concluded that potassium citrate therapy significantly alleviated calcium oxalate stone activity after SWL for lower pole stones in patients who were stone free and significantly ameliorated the outcome of patients with residual fragments by decreasing growth or agglomeration. It was suggested that such therapy may be allowing spontaneous passage and thus increasing the clearance rate. These results have been supported by other investigators [32].

3. PERCUTANEOUS NEPHROLITHOTOMY - PNL

With the advances in instrument design, development of hydrophilic wires and balloon dilatation and improvements in technique, the morbidity of PNL has decreased significantly over the past decade [33,34]. Results from the Lower pole study group showed that stone size had little influence on stone free rates, achieving an overall 95% stone free rates [9] (Level 1). Hospitalization for the percutaneous group was significantly longer than for the SWL group (2.66 days v 0.55 days, $p < 0.0001$), however quality of life data were significant in that they showed no important differences between the groups. This suggests that percutaneous removal as currently practiced is well tolerated despite its greater degree of invasiveness. It is generally agreed that stones that stones larger than 1 cm should be treated by PNL as the results of SWL for these stones are poor.

4. FLEXIBLE URETERORENOSCOPY- URS

Advances in the development of endoscopic technology and have expanded the range of indications for flexible ureterorenoscopy (URS). These improvements include the development of improved ureteroscopes, the holmium:YAG laser and newly designed ureteral access sheaths. Reported stone free rates range from 52% to 87% in various recent URS series for lower pole stones [35,36,37,38]. URS has been limited by difficulty in accessing some lower calices and by the loss of defection of the ureteroscope with instrument passage. The introduction of tipless nitinol baskets and graspers has facilitated the treatment of lower pole calculi because the small size and marked flexibility cause minimal loss of ureteroscope deflection, allowing lower pole stones to be repositioned from a lower calix to a more accessible middle or upper calix [37]. Schuster et al retrospectively reviewed 95 patients with lower pole calculi. They reported in patients with radiographic follow-up greater than 1 month complete success was obtained for 77% of stones 1 cm. or less treated in situ versus 89% treated with displacement first (p = 0.43). For calculi greater than 1 cm. complete success was obtained for 2 of the 7 (29%) treated in situ versus all 7 (100%) treated with displacement (p = 0.005). Repositioning the stone had little advantage in patients with stones 1 cm or less but it markedly improved outcomes in patients with stones greater than 1 cm.

The second phase of the lower pole stone study sought to further clarify the treatment algorithm for lower pole stones and investigated the role of URS in the treatment of lower-pole renal stones [39] (**Evidence Level I**). Pearle et al randomized 78 patients with 1 cm or less isolated lower pole stones were to SWL or URS. The primary outcome measure was stone-free rate on noncontrast computerized tomography at 3 months. Secondary outcome parameters were length of stay, complication rates, need for secondary procedures and patient derived quality of life measures. A total of 67 patients randomized to SWL (32) or URS (35) completed treatment. The 2 groups were comparable with respect to age, sex, body mass index, side treated and stone surface area. Operative time was significantly shorter for SWL than URS (66 vs 90 minutes). At 3 months of followup 26 and 32 patients who underwent SWL and URS had radiographic followup that demonstrated a stone-free rate of 35% and 50%, respectively. This was not statistically significant. Intraoperative complications occurred in 1 SWL case and in 7 URS cases (failed access in 5 and perforation in 2), while postoperative complications occurred in 7 SWL and 7 URS cases. Patient derived quality of life measures favored SWL.

The authors noted a higher SFR for URS compared with SWL, however the difference was not statistically significant. The authors suggested that their study was underpowered to ensure that the lack of a difference would hold with greater patient numbers. While SFRs were comparable between the groups, secondary outcome parameters largely favored SWL.

IV. PROXIMAL URETERAL STONES/URETEROPELVIC JUNCTION

1. CLASSIFICATION

For the purposes of this manuscript, proximal ureteral stones will be those calculi found within the lumen of the ureter of a non-duplicated, single system at the levels from ureteropelvic junction (UPJ) and the pelvic inlet. For the purposes of clarity we have combined stones at the UPJ and considered those to be the uppermost location of proximal ureter stones. We have elected to exclude situations whereby ureteral narrowings or strictures are present as these anatomical features will affect stone fragment passage and not the treatment modality per se. For this reason we will exclude patients with concomitant congenital ureteropelvic junction obstructions from the analysis and discussion.

2. INDICATIONS FOR INTERVENTION

It goes without saying that it is difficult to render an asymptomatic patient asymptomatic. Whereas many renal calculi that are not enlarging or causing obstruction can be observed, it is relatively well accepted that ureteral calculi have a high incidence of leading to renal obstruction, therefore, should usually be treated. Of all of the clinical symptoms that bring patients to our attention, pain (i.e., renal colic) is by far and away the most common. Other indications for intervention include fever, azotemia, hydroureteronephrosis, loss of renal cortical thickness, nausea and vomiting. Non-surgical treatment options include observation, hydration, and medical expulsive therapy. Surgical options will be highlighted below.

3. THERAPEUTIC OPTIONS

Essentially all modes of contemporary endourological intervention including shockwave lithotripsy (SWL), Ureterorenoscopy (URS) and percutaneous management (PCN) have gained essential roles in managing affected patients. Laparoscopic/Open surgery have limited roles, and medical expulsive therapy has not been rigorously evaluated exclusively for isolated UPJ or proximal ureteral stones.

a) Observation

It has been well accepted that spontaneous passage of symptomatic single ureteral calculi is size and time dependent. Prior to the advent of SWL and URS there was only one alternative and that was open ureterolithotomy. Observation or watchful waiting has been associated with spontaneous passage rates of 38%-85% for stones < 5mm, and 0-10% for stones larger than 10 mm [40, 41]. In fact, cumulative data from 6 case series demonstrated that spontaneous passage was related to location at presentation with calculi discovered in the distal third of the ureter having a spontaneous passage rate of 45%, compared with the mid third of 22%, and the proximal third of 12%. When stones did pass they generally did so within 4 weeks [41].

Several Authors have developed predictive guides and artificial neural networks to help predict the likelihood of spontaneous passage. These have been created with historical retrospective data or case series [42-44]. Most studies agree that variables such as sex, race, laterality do not have a profound influence on outcome, whereas duration of symptoms before seeking medical attention and degree of hydronephrosis may some influence.

b) Medical Expulsive Therapy (MET)

In an attempt to increase the spontaneous passage rate, some authors have advocated the addition of pharmacotherapeutics to assist with the stone/fragment passage. These drugs include alpha-adrenergic agonists, calcium channel blockers, and corticosteroids [45]. This topic is covered in greater detail in section B.2.

A recent article by Hollingsworth et al., evaluated 14 randomized controlled trials (RCT) assessing efficacy of MET. Nine of these trials utilized placebo control or observation (no treatment) as the control. Primary endpoint was spontaneous passage of stones, with secondary endpoints including time, analgesic use, pain episodes and need for intervention. Their conclusion was that the published evidence provides support for the use of expulsive medical therapy in the treatment of urolithiasis. Minimally invasive surgical methods have all but replaced the morbidity associated with open stone surgery, however, patients are still exposed to surgical and anesthetic risks. Based upon the review of this limited amount of data MET might provide a viable alternative to surgery for select patients with small ureteral calculi. **[Evidence Level II/B]**

c) Shockwave Lithotripsy (SWL) & Ureteroscopic (URS)

SWL and URS are both well established forms of management for ureteric calculi. There are no prospective randomized trials available to support the use of one over the other. To complicate matters even further, there has been a technological evolution leading to the availablility of several different types of ureteroscopes, intracorporeal lithotripsy devices and techniques, laparoscopic expertise as well as significant changes in SWL technology making superiority of one form of treatment over the other difficult to discern. Attempts to objectively evaluate the scant comparative literature on this subject has led to the formation of the 1997 American Urological Association (AUA) practice guideline on ureteral stone treatment and the European Association of Urology (EAU) *Guidelines on Urolithiasis* [46, 47]. The former document having been based upon meta-analysis and the latter being primarily based upon expert panel opinion. The best evidence available consists of meta-analyses of existing retrospective case series', comparative series' or matched pair analysis [48-50]. A combined review of the topic with collaboration between the EAU and the AUA is forthcoming but is not currently available as of this writing. Besides having few comparative randomized trials, studies performed to evaluate treatment outcomes are not standardized as to which model of shockwave lithotripter is being investigated, nor in the style of ureteroscope (rigid versus flexible) and intracorporeal lithotripter.

What is known currently is that SWL has become the primary treatment choice for renal calculi less than 2 cm and proximal ureteral calculi that do not pass spontaneously. SWL is considered by many to be the least invasive treatment modality and high success rates have been reported for calculi along the entire urinary tract [48, 51, 52]. SWL is considered less morbid, requires less anesthesia and less analgesia than URS and other procedures. Stone size is a known variable affecting Stone free rates (SFR) for SWL, however, little is known about size with respect to SWL and proximal ureteral stones. The available data would suggest that larger calculi fare less well with SWL, but results with URS are less dependent upon size [53, 54 55]. Sofer et al demonstrated excellent efficacy utilizing URS along with the Holmium:YAG laser for proximal ureteral stones of all sizes reporting SFR of 97% [56]. Lam et al., performed a retrospective review of 500 consecutive cases and selected patients who underwent SWL in situ versus URS with Holmium:YAG laser lithotripsy and compared SFR and Efficiency Quotient (EQ) for stones in the proximal ureter and stratified their results according to size [57]. EQ which was introduced by Denstedt et al in 1990 is a measure of treatment effectiveness when comparing lithotriptors but has been used in other studies to compare one form of treatment to another [58]. For stones >1 cm SFR was 93% for URS compared to 50% for SWL. The EQ's were 0.76 and 0.43 respectively. For the stones less than 1 cm the results were comparable (URS - SFR 100% vs 80%; URS - EQ 0.81 vs 0.72) [57]. They concluded that for proximal ureteral stones < 1cm SWL is the initial treatment of choice due to lower morbidity. **(Evidence Level III)**

Wu et al, in 2 comparative studies demonstrated superior efficacy of URS compared to SWL for proximal ureteric stones [49, 59]. Similarly, Hollenbeck et al at the University of Michigan reported in a retrospective review evaluated bivariate analyses and determined that stone size and proximal ureteral location were negative indicators for success when comparing to distal stones [60]. In a patient preference study out of Norway, Karlsen et al found that although URS made patients stone free faster [stone-free rate at 3 weeks was 58% and 78% (P = 0.061)] there was no difference at 3 months [SFR 88% and 89% (P = 1) for SWL and URS, respectively] it did so at the expense of more analgesic use, and a higher bother score (dysuria, hematuria, and flank pain) [61] **(Evidence Level III)**

A prospective randomized trial comparing SWL with URS for large upper ureteral stones has been performed [62] Lee et al evaluated 42 patients with single, radiopaque >1.5 cm proximal ureteral stones and randomized them by lots to 2 possible treatments – SWL (Sieman Lithostar 2) or URS (semi-rigid with Pneumatic impactor, electrohydraulic, or ultrasonic lithotriptors). This study which demonstrated equivalent EQ between the two and superiority of SFR for URS. The URS group also had higher incidence of complications according to the authors (5 ureteral perforations). This study had some limitations with respect to small sample size. (**Evidence Level III** due to methodology)

In an attempt to overcome the limitations of descriptive studies, Stewart et al recently published a matched pair analysis comparing SWL and URS [50]. The authors claim that the study design allows for meaningful comparisons to be made on a small number of matched patients. They evaluated close to 1500 patients and only 27 matched pairs could be found. SFR in the URS group varied from 82% to 100% when the holmium laser was introduced. There was no statistically significant difference in any of the clinical parameters evaluated in this cohort. The authors conclude that the choice of therapy depends more on availability of equipment, scheduling conflicts and patient preference rather than any significant benefit of one treatment modality over the other [50] **(Evidence Level II)**

Lastly, Kijvikai et al recently published a systematic literature review and performed outcomes analyses on 87 English language, peer reviewed articles. Their conclusion was that due to higher stone clearance rates for stones > 10mm, URS was the treatment of choice. In addition, they felt that when SWL is contraindicated (Pregnancy, or bleeding diathesis, URS is the preferred method. **(Evidence Level II)**

d) Percutaneous (PNL)

Percutaneous puncture and access to the urinary tract has a long established track record. Once thought to be reserved for treating large and complex renal calculi, pioneering surgeons at the University of Minnesota popularized and modified the technique in the 1980's [63, 64]. Antegrade access to proximal ureteral impacted calculi has many advantages. Visualization is generally great because of the ability to use large bore rigid or flexible endoscopes such as the flexible cysto-nephroscope as well as high flow irrigation. Intrarenal pyelovenous backflow of infected urine is minimized due to low pressure systems. Fragments are irrigated "Downstream" toward the bladder with minimal risk of retropulsion toward the kidney. Several case series report extremely high SFR (range from 86-100%) [65, 66]. There are no randomized controlled trials, therefore recommendations are based upon best available evidence from clinical trial and comparative study. Kumar et al noted that they were able to treat 86 impacted upper ureteral calculi in 80 patients with 86% stone free after one procedure and the remaining treated by salvage SWL and ureterolithotomy [65]. Maheshwari found that only 55% of their patients with large impacted proximal ureteral calculi were stone free when URS was performed, increasing to 85% with the addition of SWL [66]. Comparatively 100% SFR was achieved with an antegrade approach. Complications were minor in both groups. In one prospective randomized study by Karami patients with moderate hydronephrosis and impacted upper ureter stones > 1cmwere randomized to receive retrograde URS or "blind, tubeless" antegrade approach with pneumatic impaction as a means of lithotripsy. Retropulsion and secondary treatments (stent and SWL) were common in this study with an incidence of 34%. The conclusion was that due to very high need for ancillary procedures and expense for flexible URS with laser lithotripsy that antegrade approach was effective [67]. Percutaneous antegrade ureteroscopy can be considered when URS/SWL has failed, equiptment is unavailable or when URS is not able to be performed due to anatomic constraints such as urinary diversion, ureteral stricture or in renal transplant patients [68, 69].

e) Open/Laparoscopic surgery

The role of open surgery for ureteral stones has certainly diminished with the advent of SWL, retrograde URS and antegrade URS. It may be indicated for large (> 3 cm) ureteral stones where the risk of ureteral damage from URS may be felt to be so great that stricture will have a high likelihood, in failed endourological procedures, in children if endourological equiptment is not available, or in cases where an open/laparoscopic procedure is concomitantly being performed [70, 71 72]. As with other types of surgical procedures, if expertise exists in performaing laparoscopic surgery, then that would be preferred over open surgery [73].

RECOMMENDATIONS

LOWER POLE STONE

Recommendation	*Level of Evidence*
PNL is more effective than ESWL in larger stones	**I**
Passage of fragments is dependent on caliceal anatomy	**II**
Morbidty of PNL is higher	**II**
Flexible URS in cases up to 1-2 cm	**III**
PNL is an option for the treatment of calculi located in the proximal ureter. Stone free rates are very high and in experienced hands complications can be minimal.	**III**

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D. SPECIAL SITUATIONS

I. MORBID OBESITY

1. INTRODUCTION

Changes in the lifestyle and eating patterns have increased in the population the incidence and prevalence of overweight, obesity and morbid obesity not only in industrialized but also in developing countries. Morbid obesity is defined as a Body Mass Index (BMI) over 40, 100% above the ideal body weight, or more than 45. (100Lbs) overweight (1). It is estimated that the obesity epidemic affects 300 million people worldwide (2). In United States it was reported in 2005 that 31% of American population were obese (BMI $\geq$ 30 kg/m?) and 30% were overweight (BMI=25-29.9 kg/m?). The cost of obesity-related conditions has been estimated from 5.7-6.8% of total medical expenditures in US (3,4). Not only this factors are important to understand the public health problem for several countries, but also the technical, medical and associated diseases problems that these groups of patients have and specifically in the context of associated renal stones. Furthermore, according with the epidemiologic trends it is expected an increase in obese population, with the corresponding needs of training medical and surgical specialties to solve the associated co-morbidities.

2. EPIDEMIOLOGY

In 1999, Serio et al, in a randomized 89 753 interviews based study reported that the prevalence of obesity was 19.3% in female stone formers compared to 11.6% in female non-stone forming controls (P< 0.001). For males it was similar, 17.2 and 11.4% respectively (5). **[Evidence Level III]**. Association between stone disease and obesity has been reported. Negri and co-workers, reported a Relative Risk (RR) of having suffered from urolithiasis about 1.58 (95% confidence interval (CI): 1.20-2.08) in obese men and 1.67 (95% CI: 1.25-2.24) in obese women. This RR was even higher in obese men (2.54) in the 15-44 years group. The risk of urolithiasis was also significantly increased in the overweight groups (BMI=25-29.9 kg/m?) (6) [LE=3]. In another study, Ramey et al reported a risk of being obese or overweight (BMI > 25 kg/m?) 1.8 times higher (95% CI: 1.04-3.11) in stone formers than in controls.

Pearl and colleagues, reported in morbidly obese patients with upper urinary stones series, renal anomalies associated in 21% of cases and also co-morbidities of 56% in addition to obesity (7) **[Evidence Level III]**.

Obesity might predispose to urolithiasis by observing differences in electrolyte composition of urine from obese and non-obese patients. Powell et al, published that urine osmolality and mean urine concentration of uric acid was higher in obese patients that in non-obese patients. Also, they found a lower urine pH, increased total urine volume and increased 24–h excretion for most of electrolytes in obese than non-obese patients. They suggest this might predispose to acid uric stones or act as promoter for calcium stone formation (8) and several publications agree with these findings (9, 10 & 11) **[Evidence Level III]**.

Serious bone and metabolic anomalies have been diagnosed in morbidly obese population. It has been observed that patients submitted to bariatric surgery may present problems related with malabsorption, metabolic bone disease (osteoporosis, osteomalacia) and secondary hyperparathyroidism. These patients may also have increased risk to develop renal stone disease (12, 13) **[Evidence Level III-IV]**.

3. DIAGNOSIS

The diagnosis of renal stones in morbidly obese population represents not only a challenge for the X-ray equipment to support the patient's weight and body surface but also a challenge for transportation staff, radiologist staff and X-Ray technique protocol.

The conventional Kidney, Ureter & Bladder (KUB) plain is difficult to be set because x-ray protocol must be custom according to patient's body composition but minimum required quality images not always are successful. The information might be limited in morbid obese patients. Also it is for Ultrasound (US) imaging.

Intravenous Pyelography (IVP) & Helical Computed Tomography Scan (CT) (contrasted or non-contrasted) are considered very useful to approach renal stone in obese patients but they must have special custom according with patient's anatomy and radiologist's experience in case of morbid obese patients. CT table may be too narrow to support patient's corporal economy. It is necessary to keep in mind that several of the X-Ray and CT tables have weight limitations in the 300-pound range. Patient might be secured by safety belt but taking care about not to compress respiratory function and the CT study must be done fast because some patients do not easy tolerate supine position. In morbid obese patients in whom CT scan is possible to be performed and in patients having renal stone burden tributary of Extracorporeal Shock Wave Lithotripsy (ESWL) is recommended to measure the distance from the skin surfaces to center of the renal stone to figure out if ESWL would work in the each specific morbid obese patient's context. The CT Scan gantry inner diameter must be taken in count prior planning the study and compared with patient's biggest diameter and circumference (girth). There is not a consensus X-ray protocol set for radiologists for this purposes. IVP and CT scan sensibility and specificity for renal stone in morbidly obese patients population need to be determined.

4. TREATMENT

The overweighed, obese and morbidly obese patients populations with renal stones represents an amazing challenge not only for patients caregivers, physician, nurses and operating room staff but also for the most seasoned endourologist and anesthesiologist. It is expected that associated medical and mechanical co-morbidities in these patients increase the risks of medical and surgical complications. Until now there is not a consensus about which one of the available therapeutic treatments are the best option to treat obese and morbidly obese patients with renal stones.

a) ESWL

There are several limitations to perform successfully ESWL in obese and morbid obese patients with renal stones: ESWL table needs to have special reinforcement, technical difficulties either with fluoroscopy or ultrasound to get good imaging to localize the stone and focalize the shock waves, when using fluoroscopy more time may be required and overheat of the X-Ray generator with consequent automatic shout down alarm in the middle of the procedure may be observed. The most important limitation is related with is the shock wave attenuation by body fat. The distance between F1 and F2 must be not larger than 13 cm. Several ESWL devices announce F1 to F2 distance range of 13 to 17 cm.

ESWL in obese and morbidly obese patient has been considered from some authors as a contraindication because the low stone free rates reported and because technically is difficult to match F2 with renal stone and the likelihood of producing unnecessary renal or surrounding organs tissue damage (14). It is recommended to do in advance a simulation of patient size and device capacities and limits to establish if the treatment could be completed.

Thomas and Cass (15) published in 1993 their results of ESWL in morbidly obese patients using a second-generation tubeless lithotripter to treat renal (88%) and upper ureteral (12%) stones. They treated 81 patients weighing more that 300 pounds (mean 326). All patients were treated in supine position and were positioned using various aids, such as the extended shock pathway and abdominal compression. General anesthesia was used in 52% of cases and epidural and monitored intravenous sedation were used in 2% and 46% respectively. Patient's maximum radiation exposure was calculated in 62 rad in the cases of stones > 3 cm without significant hazard. Only 77% of the patients were stented. Overall retreatment rate was 11%, 9% for single stones and 17% for multiple stones. ESWL treatment time was similar for each kind of anesthesia. Only 72% of patients completed follow up at 3 months or longer after procedure, they report overall stone-free rate of 68% increasing to 78% by adding 6 extra patients (10%) with stone fragments of 4mm or less considered clinically insignificant stones in this population. They argue that this second generation litotriptor device has a wider operating table, heavier to support this kind of patients and the plus is besides the treatment deep of 15cm from skin, the distance of 24.1cm between F1 and F2 focal points was perhaps the longest of any available lithotripter (in that time). **[Evidence Level III]**

Parrek et al, reported the outcomes of 100 patients that underwent ESWL and were classified based on BMI and Hounsfield Units (HU). They selected patients with stones between 5 -10 mm located in upper, middle, lower calyx, renal pelvis or in proximal ureter (upper urinary tract) and were treated with electrohydraulic ESWL. BMI and HU were determined prior treatment. In the group of patients rendered stone free, the mean BMI was 26.9 ± 0.5 and average attenuation stone number (HU) was 577. In the group of patients with residual stones, they found a BMI of 30.8 ± 0.9 and mean attenuation stone number of 910 HU (16). **[Evidence Level III]**

In a different publication, also Pereek and associates, reported a CT scan tool applied to 64 patients with renal stone with size from 0.5 to 1.5 cm located in the lower pole in order to predict successful stone fragmentation in patients that underwent electromagnetic ESWL treatment with 220 and 140 Electromagnetic Shock Emitters (EMSE). They determined, HU density, BMI for each patient and specially measured in 0°, 45° & 90° the skin-to-stone distance (SSD) on non-contrasted CT scan prior ESWL treatment. They divided the patients in stone free group and residual stone group defined as stones of $\geq$ 2mm. They found mean stone size of 9.2 $\pm$ 1.2 mm vs. 8.0 $\pm$ 1.3 mm, mean BMI of 26.1 $\pm$ 0.5 vs. 28.5 $\pm$ 0.9, average stone HU density of 66.3 vs. 92.5, and mean SSD of 8.12 $\pm$ 1.74 cm vs. 11.53 $\pm$ 1.89 cm in stone free and residual tone groups respectively. They applied a statistical analysis by logistic regression to this data and they conclude that the limit to success according to SSD measurement was 10 cm with sensitive of (87%) and specific (85%) point of the Receiver Operating Characteristic (ROC) Curve to predict stone fragmentation. (Odds Radio 0.32, 95% Confidence Interval 0.29 to 0.35, $P < 0.01$). According with author's statistical analysis, SSD showed to be much more powerful predictor, overweighing both BMI and HU density. They proposed that SSD might be the factor linking the association of obesity and SWL failure. They also suggested that this tool might be useful to plan and treat successfully urinary stones at any level (17). **[Evidence Level III]**

Delakas and co-workers published a retrospective series with multivariate logistic regression analysis in 688 patients that underwent ESWL with second-generation electrohydraulic lithotripter. They found in the multivariate analysis that unsuccessful outcome was significantly related to: (1) pelvic ureteral stones (odds ratio [OR] 4.2; 95% CI 1.97, 8.19); (2) stone size >10mm (OR 3.46; 95% CI 2.16, 5,53); (3) obstruction (OR 1,93; 95% CI 0.99, 3.77); and (4) obesity (OR 1.87; 95% CI 0.95, 3.77). When the four features were present, the cumulative risk of treatment failure increased to 82.95%. These variables may enable identification of a subgroup of patients who will fail initial SWL and would be better candidates for endourological procedures (18). **[Evidence Level III]**

Wang and colleagues correlated SWL failure with higher number of stones (more than 2), a larger maximal stone size (>12mm), a higher stone burden (>700mm?), higher maximal stone density (>900 HU) and the shape of the stone (non-round or non-oval). It was a multivariate analysis based on clearance of fragment by unenhanced helical CT (l9). **[Evidence Level III]**

Gupta and associates reported the best ESWL outcome also based on unenhanced helical CT in those patients with a calculus diameter of <1.1 cm and mean densities of $\leq$ 750 HU. They needed three or fewer ESWL treatment sessions with stone clearance rate of 90%. The worst ESWL outcomes was in those patients with calculus diameter >1.1cm, calculus densities of >750 HU and they needed three or more complementary ESWL sessions with clearance rate about 60%. According with authors, the stronger predictor of outcome was calculus density than stone size alone (20). **[Evidence Level III]**

b) PCNL

Percutaneous Nephrolithotomy (PCNL) have lead a important role for the treatment of pelvic and complex renal stones and it is widely considered in several endourological institutions as the first treatment option.

The American Urological Association (AUA) through the AUA Guideline on Management of Staghorn Calculi 2005 (21) concluded PCNL should be the first treatment option for most patients. Further more, they defined the "Index" patient as " …an adult with staghorn stone (non-cystine, non-uric acid) who has two functional kidneys (function of both kidneys is relatively equal) or a solitary kidney with normal function, and whose overall medical condition, body habitus and anatomy permit performance of any of the four accepted active treatment modalities, including the use of anesthesia". As it can be inferred it does not apply for overweighed, obese and morbidly obese patients. **[Evidence Level I]**. They do not mention some specification or recommendation for this patient population, similarly, the 1994 AUA Nephrolithiasis Clinical Guidelines Panel does not provide any recommendation (22) **[Evidence Level IV]**. On the same manner, the European Association of Urology (EAU) 2001 and 2006 Guidelines on Urolithiasis do not mention specific recommendation for the obese patient populations (23, 24). **[Evidence Level IV]**

Recent publications about outcomes of PCNL according with body weigh or BMI are limited.

Carson et al, reported in 1988, 44 PCNL in obese patients, they were classified according with patient's percentage above ideal body weight; one group (30 patients) had 20%-50% over ideal body weight (152 to 210 pounds), another group (14 patients) had greater than 50% over ideal body weight (187 to 384 pounds), both groups were compared with non-obese patients. The stone-free rate was 83.3 and 85.7% versus 83.9%, respectively. Mean operating time was 52.8 and 55.4 versus 53.5 minutes, respectively. Hospital stay was 6.2 and 6.9 versus 6.8 days, respectively. They found no significant differences among the three groups in the above-mentioned parameters including access and complication rates (25). **[Evidence Level III]**

In 1997, Faerber and Goh (26) reported retrospectively the results of 93 morbidly obese patients treated with percutaneous nephrolithotripsy compared with a normal weight group. They found that morbidly obese group had smaller stones and if single access was required in both groups the operative time was similar, but if multiple access sites were necessary in morbidly obese patient the time was higher. The stone free rate was 89% vs. 82%, (not statistically difference) and the overall rate of complications was 16% vs. 37% in normal weight and morbidly obese groups respectively. The hospital stay was 3.5 days vs. 4.4 days in normal versus morbidly obese patients. **[Evidence Level III]**

Pearle and associates (7) published in 1998 their outcomes in patients with BMI $\geq$ 30 that underwent PCNL for renal stones in 2 combined institutions. They detected 57 patients (24.2%) with BMI > 30 (mean 38.9 $\pm$ 7.4, range from 30.1-63.9, mean weight was 112.1 $\pm$ 24.1 kg) among 236 patients. Renal anomalies were present in 21%, 56% of that patients had co-morbidities in addition to obesity. Staghorn calculi were present in 19 patients (31.7%) and mean cumulative stone size was 14.5$\pm$ 8.7 mm. They performed 96 procedures in 60 renal units (1.6 per unit). They determined the overall stone-free rate of 88.3% and the stone free rate for staghorn and non-staghorn stones of 84.2% and 90.2%respectively. Average operative time was 181.2 $\pm$ 91.4 minutes. Complications were present in 8 patients (14%). Hospital stay was 4.9 $\pm$ 3.1 days. Blood transfusion was necessary in 5 patients (8.8%) but they had initial hemoglobin < 12g/dl. **[Evidence Level III]**. They suggested technical modifications for percutaneous access (harder and longer needle) and advices to success in this kind of patients as optimization of fluoroscopy. **[Evidence Level IV]**

Burtt et al (27) in 2002 review the records of eight morbidly obese patients (BMI > 40 kg/m^2) compared with 16 consecutive patients with BMI of <40 that underwent PCNL for renal calculi. They found mean weight of 137.8 kg vs. 75.4 kg, mean BMI of 44.7 kg/m^2 vs. 25.7 kg/m^2, mean operative duration was 74 vs.74 minutes, hospital stay was 5 days vs. 4 days and stone-free rate was of 85% vs. 94% for morbidly obese and non-obese patients, respectively. Most of the comparisons were similar between both groups. They reported low complications rate. **[Evidence Level III]**

Koo and co-workers (28) reported in 2004 their percutaneous stone surgery experience in obese patient with percutaneous access and punction performed by single surgeon. They classified 181 patients in four groups according with Word Health Organization (WHO) criteria (29) for BMI: < 25 (normal) [65 patients], 25-29.9 (overweight) [79 patients], 30-39.9 (obese) [67 Patients] and > 40 kg/m^2 (morbidly obese) [12 Patients]. They performed 223 procedures in 195 renal units. They found mean BMI of 22.1, 27.5, 33.8 and 43.9 kg/m^2, respectively. The average operative time was 75.2, 68.8, 68.5 and 81.4 min, respectively. Hospital stay was 6.5, 6.6, 6.1, and 5.8 days, respectively. The stone success rate was 79, 76, 79 and 83%, respectively; minor complications were reported as 17, 18, 24 & 25%, respectively, and major complications were present only in first and second group with 1.5 and 5%, respectively. In some obese and all of the morbidly obese patients was necessary to do a slightly larger skin incision at the puncture site to reach the level of abdominal fascia. They needed to convert to open surgery three cases, 1 patient in the normal weight group due postoperative pyrexia and 2 in the overweight group due to major hemorrhage and perforation of collecting system. 15 procedures (6.7%) were unsuccessful because access failure. Another three patients had open nephrolithotomy (1.3%), 1 patient underwent nephrectomy (0.89%) and 1 patient partial nephrectomy (0.44%).**[Evidence Level III]**

Recently, in 2007, Sergeyev and colleagues published their percutaneous surgery experience according to body mass index and kidney stone size. Among 148 patients submitted to PCNL, only 85 had complete files to do the review. 37 patients (43.5%) were in the obese or morbidly obese group (BMI, >30Kg/m^2; mean 36.2), 33 patients (38.8%) were in overweight group (BMI, 25 to 29.9 Kg/m^2;

mean 27.6) and 15 patients (17.7%) were within or below their ideal weight (BMI, < 25 kg/ m^2; mean 22.65). Stone-free rate were 89.1%, 100% and 93.3% respectively. Initial data analysis according with stratified BMI revealed no statistically significant differences in terms of blood loss, stone surface area, age or postoperative fever among three groups; only the hospital stay was significantly different among groups, being surprisingly higher in the "normal" weight patients due to one patient who developed pulmonary embolism and another one who developed sepsis after initial procedure. A diameter of 20 mm corresponds to surface area of 314 mm^2. They used a surface of 300 mm? to differentiate patients with "smaller" or "larger" stone burden. Patients with stone surface area below 300 mm^2 had 100% stone-free rate after initial procedure. Patients with stone surface area of 300 mm? or more had a stone-free rate of 85.7%, 100% and 69.2% for "normal", overweighed and obese/morbidly obese groups respectively after initial procedure. It trends toward a greater need for second look nephroscopy in last group with large stone burden (>300mm^2), and may be related to the combination of the stone volume and body habitus. (30) **[Evidence Level III]**

Modifications to standard percutaneous nephrolithotripsy technique have been proposed in several publications to help the surgical approach in obese and morbid obese patients.

Segura (31) published in 1990 two options to deal with this population according with his personal experience. The first one was to dilate the tract, leaving a nephrostomy tube and allow the tract to mature for a few days (to stage the procedure). After maturation of the tract, a flexible instrument can be used, which should be adequate to reach all stones. The second option he proposed was to extend the incision in the skin from the usual 1cm to 3 to 4 cm. This will enable the urologist to push the nephroscope 1 or 2 cm deeper into the flank, which may be just enough to complete the case. He reported his biggest and heaviest patient weighed some 453 pounds. Fortunately, he was able to complete successfully the case. He proposed a third advice. A simple maneuver to determine whether access is possible [before US and CT imaging improvement developments]: a needle is inserted through the flank until the point is on the stone. Measurement of this length and comparison with the length of the available instruments will determine whether the percutaneous procedure is possible. It could be considered a basic, primitive or earlier determination of Skin-to-Stone Distance (SSD), but more invasive and ready to do on the field of operating room. He also suggested that ureterorenoscopy if possible to perform, may actually be the simplest method to deal with the problem. **[Evidence Level IV]**

Kerbl and colleagues (32) in 1994 published a percutaneous stone removal technique for morbidly obese patient with the patient in a flank position. The patient's weight was 328 pounds with complete left staghorn calculus. The patient was unable to lie in supine position because he became markedly short of breath. Anesthesiologist considered prone position would not be feasible and suggested positioning the patient in right lateral decubitus to have control of patient intubation. Urologist used a 40 cm. 18-gauge Ring biliary needle to do percutaneous puncture under fluoroscopy guidance. They use a 30F Amplatz sheath in combination with ultrasonic lithotripsy to initially approach the stone and completed the case with flexible nephroscope and dye laser. They reported in addendum on this article another case with weight of 450 pounds with multiple bilateral ureteral and renal calculi treated with rigid and flexible ureteroscopy and laser bilaterally in a single event. Due long operative time a nephrostomy tube was placed on the right side with the patient in lateral position and the lithotripsy through the matured tract was completed three weeks later successfully with flexible ureterescope and laser without complications. **[Evidence Level IV]**

Giblin and associates (33) proposed in 1995, a modification to standard percutaneous nephrolithotripsy. They measured radiographically skin-to-stone distances to determined if standard Amplatz access sheath (28F in diameter, 16 cm in length) and standard 26 F rigid nephroscope could reach the stone. If not, they used extralong Amplatz sheaths (32 F in diameter, 18-24 cm in length), a 30F gynecologic laparoscope (working length 27 cm), standard ultrasonic lithotripsy probes (38 cm in length) and bronchoscopic grasping forceps (diameter 2,5 mm, working length 50 cm). With this equipment all stones could be reached and treated. 26 or 28 F nephrostomy tubes were placed after the procedure. Also, they enlisted a series of 5 cases with weight ranging from 260 to 313 lbs and with skin-to-stone distance range from 20 to 24 cm. In most of them previous ESWL had failed. They suggested to add into the above mentioned Dr.

Segura´s second advice that it might be mandatory to secure the Amplatz sheath to the skin with a heavy suture to avoid losing it in the voluminous subcutaneous fat. They found their technique remarkably simple an effective modification to standard PCNL technique. **[Evidence Level IV]**

Curtis et al (34) published in 1997 another modification of PCNL technique for morbidly obese patient. They proposed to use CT scan to measure the depth of the subcutaneous fat in an specific case who had previously failed due to lack of a long enough Amplatz sheath. Once they determined by CT the depth of subcutaneous fat, a skin incision 12 cm long down to the muscle sheath and a new tract was then formed from there allowing a safe placement of Amplatz sheath and staghorn calculus was removed successfully with lithoclast. **[Evidence Level IV]**

c) Retrograde ureterolithotripsy

Trends to perform less invasive procedures in urology and the technological evolution with the development of smaller and more flexible endoscopes provide the possibility to access upper urinary tract without skin and kidney punction. This technique appears specially desirable in obese and morbidly obese patients, trying to avoid as much as possible to do a more invasive procedure in this risky population.

Nguyen and Belis (35) in 1998 published their experience treating urolithiasis in 48 morbidly obese patients with Ureterolithotripsy (UL) using pulsed-dye laser, PCNL and combined treatments. Mean weight of patients was 286 lbs. (range 205 to 385). Average stones size was 1.7 cm and 1.1 cm for renal and ureteral stones respectively. No stones > 2 cm were treated. They reported 73 endoscopic procedures (9.8 F flexible ureteroscope); 48 were UL, 4 were ureteroscopic bascket extraction and the remaining 21 were PCNL. 36 patients had single procedure; 8 had 2 procedures; 3 patients had 3 combined procedures of either multiple ureteroscopic treatments or PCNL+UL techniques. When single treatment were evaluated, the stone free rate was 77.8% for UL and 60% for PCNL. In repeated UL+UL, the stone-free rate increased to 97% and 89% for PCNL+UL. **[Evidence Level III]**

Grasso, Conlin and Bagley reported their experience with retrograde uretropyeloscopy of stones 2 cm and larger including minor staghorn calculi in 51 patients with previous failure or refused ESWL and PCNL procedures. Four patients were morbidly obese (7.8%). There were 66 large stones, 2 cm or larger (45 renal stones [mean stone size 24.2 mm] and 21 ureteral stones [mean stone size 23mm]). After the initial procedure using flexible ureteroscopes form 6.9 to 9.5 Fr in combination with holmium laser lithotriptor, complete fragmentation was observed in 76% and 95% of renal and ureteral stones respectively. After a second procedure the stone fragmentation was 91% for renal and 100% for ureteral stones. Six months follow up was available only in 25 patients, 15 (60%) had completely clear imaging, 6 (24%) had small lower pole debris that was decreasing on serial imaging and 4 (16%) had new stone growth related with co morbidities. They had no intra-operative complications but they reported three complications related to pyelonefritis, prostatic bleeding in patient under anticoagulant and cerebral vascular accident. (36). **[Evidence Level III]**

Andreoni et al (37), reported in 2001 results in 10 obese and super obese patients (BMI >50) treated with flexible ureteroscopic lithotripsy. The mean BMI was 54 (range 45-65.2). Average stone size 11.1 mm (range 2-25 mm). In 5 patients there was single stone, the biggest size 20 mm. the other 5 patients had stones in multiple sites (ureter, renal pelvis and calyx) with size from 2mm to 25mm. They used 7.5 F and 9.4 F flexible ureteroscopes in 70% and 30% of cases, respectively. No intra operative complications were observed, only one postoperative complication related with transient azoemia associated at the use of aminoglycoside antibiotic. Average hospital stay was 0.8 days. Stone free rate after single treatment was 70%. No patient required a blood transfusion. **[Evidence Level III]**

Monga and co-workers published a series of ureteroscopic treatments for renal calculi in morbidly obese patients (MO). Among 54 patients, 16 (29.6%) were morbidly obese patients. The remaining patients (38) were classified as non-obese patients. Stone size were stratified as < 10mm or ≥ 10mm. Overall success rate was 83% for MO group and 67% for normal weighed patients without significant difference. According with stone size, the success rate for renal calculi ≥ 10mm was 100% in MO patients and 38% in non-obese patients (P=0.09). They reported at 4 weeks follow up stone-free rates of 100% for stones up to 10mm and 75% in patients with stones 10 to 18 mm. the most difficult calculi to treat were those in the lower pole measuring 10 to 15 mm with an overall stone-free rate of 57%. Authors proposed that ureteroscopy can be considered an excellent alternative to percutaneous stone removal. (38). **[Evidence Level III]**

When combining flexible endoscopy with holmium laser lithotripsy, Grasso reported a successful calculus clearance for ureteral stones (mean stone size 10.7mm) in 97% of patients with single treatment and 99% for additional session. For renal stones (mean stone size 20.5 mm) the successful calculus clearance was 78% for initial procedure and of 95% in additional session. The major complication rates have decreased from 4.6% in 1988 to current days close to 0% (39) **[Evidence Level III]**

Chung et al (40) in 2006 published their experience of simultaneous bilateral retrograde intrarenal surgery (RIRS) for stone disease in 4 patients with significant co-morbidities. Mean age was 62 years. All patients had history of failure to several previous treatments. Average stone burden was 8.8 cm. two surgeons performed simultaneously ureterolithotripsy with 7.5 flexible ureteroscopes and holmium laser equipment without ureteral access sheath. Three patients needed to be scheduled for a second stage procedure. Average total and specific operative time of simultaneous bilateral retrograde renal surgery in initial treatment was 256 and 131 minutes respectively. For second stage procedure the treatment time was 235 and 95 minutes respectively. No mayor complications were noted. **[Evidence Level III]**.

d) Open surgery

To perform an open surgery in obese patients is avoided as mush as possible in any of the surgical specialties due to associated co-morbidities, higher risk of complications and technical problems during the surgery. To treat renal and/or ureteral stones in these patients is very challenged.

Hoffman and Stoller (41) in 1992 published a comparison of endoscopic and open stone surgery in 4 (females) morbidly obese patients. Their weight ranged from 360 to 550 lbs. Two females became stone free; one of them required initial double J stent placement, two ESWL failures and finally a successful PCNL. The other patient became stone free after a single open pyelolithotomy successfully. The 3rd patient, developed necrotizing fasciitis, treated with wound debridement but the stone was untreated because of high risk and was managed with double J stents and antibiotics. The 4th patient had stone fragmented but not stone-free status after two rigid ureterorenoscopy, unsuccessfully open pyelotomy and final flexible ureterorenoscopy with stone fragmentation. This patient developed rabdomyolysis and cerebrovascular accident. The authors detailed several recommendations to take care of these high risk patients, and propose technical suggestions that must be kept in mind when approaching this challenge. **[Evidence Level III-IV]**

Paik et al (42), in 1998 reported their experience with open stone surgery among 780 procedures during 5 years in several hospitals. There were 42 open procedures (5.4%). They found 4 morbidly obese patients that represented only 10% of open cases series. Among 15 patients that underwent open pyelolithotomy (35.7%) there were 2 morbidly obese patients (13%), one >170 kg. In the 14 patients with anatrophic nephrolithtomy (33%) there were 2 morbidly obese patients (>140 kg). Authors suggest that open surgery may have very specific accepted indications. **[Evidence Level III]**

Al-Kohlany and colleagues (43) published a prospective randomized trial comparing open versus percutaneous nephrolithotomy. 79 patients with 88 complete staghorn stones defined as filling the entire collecting system or at least 80% were included in the study. PCNL group had 43 patients and open surgery group had 45 patients. Intra-operative complications were present in 7 patients (16.3%) in the PCNL group and in 17 patients (37.8%) in Open group (p=<0.05). Major postoperative complications were observed in 8 patients (18.6%) in the PCNL group and in 14 (31.1%) in the open group without significant difference. The mean operative time was 127 $\pm$ 30 vs. 204 $\pm$ 31 min (P<0.001), mean hospital stay was 6.4 $\pm$ 4.2 vs. 10 $\pm$ 4.2 days (P <0.001) and mean return to work 2.5 $\pm$ 0.8 vs. 4.1 $\pm$ 1 weeks (P<0.001). Stone-free rate was 48.8% for PCNL and 66.7% for open groups at discharge home. Patients were evaluated at 3 months and the stone free rate increased to 74% and 82% respectively because complementary electromagnetic ESWL was indicated in residual stones in both groups. The postoperative renal function (mean 4.9 months after surgery) improved or remained stable in 91% and 86.7% for PCNL and open surgery groups. PCNL is a valuable treatment option in complete staghorn stones with a stone-free rate close to open surgery. The higher morbidity, larger operative time, longer hospital stay and return to work in the open surgery group suggest that this is not an attractive option. This amazing trial unfortunately did not classify the BMI that would be helpful to figure out possible results in selected populations. **[Evidence Level II]**

RECOMMENDATIONS

Recommendation	*Level of Evidence*
In morbidly obese population with renal stones <2 cm, ESWL may be a treatment option	**III**
ESWL is NOT recommended in the context of patients with BMI > 30, stone size bigger than 1 cm and stone density higher than 900 HU	**III**
PCNL should be considered a therapeutic option with stone-free rates and incidence of complications comparable to normal weight patients	**III**
Flexible Retrograde Ureterolithotripsy may be considered an acceptable and safe option in selected patients	**III-IV**
Open Stone Surgery should NOT be considered the first option and only in failures on special situations	**III**

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II. THE OLD AND FRAGILE PATIENT

1. INTRODUCTION

The better quality of life, advancements in science and technology have increase life expectancy for human beings. Thus, the world population grows and gets older each year. The elderly population, defined as persons over 65 years old (1) has increased recently and the trends show us that in the coming years it will be for governments a big challenge to give the appropriate services and cover their specific needs to this population.

Worldwide, the elderly population in 2007 midyear is estimated in 495,929,009. The elderly population projections for year 2050 are about 1,578,209,840. In the United States of America the numbers are 37,849,672 and 86,705,637, respectively (1). The elderly increased by a factor of 11, from 3 million in 1900 to 33 million in 1994. In comparison, the total population, as well as the population under 65 years old, tripled (2). Under the U.S. Census Bureau's middle series projections, the number of persons 65 years old and over would be more than double by the middle of the next century to 80 million. About 1 in 8 Americans were elderly in 1994, but about 1 in 5 would be elderly by the year 2030 (3).

2. STONE DISEASE IN ELDERLY POPULATION

An epidemiological analysis reported that estimated annual incidence of urinary stones in geriatric patients to be 2%. (4) **[Evidence Level III]**. In a large retrospective review, Hiatt and co-workers published from 175,000 outpatient data medical files urinary stone in 1.9/1000 between ages 60 to 69 years and 1.1/1000 after age 70 years (0.1%). (5) **[Evidence Level III]**

Gentle and associates reported in a large series of 5,942 stone formers patients, 721 geriatric stone formers patients that represented 12% of cases. Mean age was 71 years (range 65 to 89) with male predominance in 71% of the cases. 2/3 of these geriatric patients had aberrant urinary values and 29% had isolated hypocitraturia compared with 17% in the younger group. They had increased incidence of uric acid stones and underwent parathyroid surgery almost four times more than younger patients. (6) **[Evidence Level III]**

Mhiri and colleagues, published from a retrospective review, 174 geriatric patients with urolithiasis (age ranged from 65 to 88 years old) and represented 10% of all the adult urolithiasis cases of their series. (7) **[Evidence Level III]**

3. TREATMENT

a) ESWL

Delakas et al, reported in a univariate and multivariate analyses their experience with 1096 patients with ureteral stones treated with second-generation electrohydraulic ESWL. In univariate analysis they compared stone free rates according with age of patients (<60 years vs. >60 years) without significant difference (P=0.52). 8 **[Evidence Level III]**

Abe and associates, published a multivariate analysis of 3023 patients with renal and ureteral stones that underwent ESWL with three different lithotripters. Stone free rate in general for patients > 60 years was 57% significantly lower when compared with younger group populations (P=0.0001). (9) **[Evidence Level III]**

Ng, Wong and Tolley did a multivariate analysis in 2192 patients with single radio-opaque renal or ureteral stones treated with ESWL with three different lithotripters. In initial analysis, patients >60 years old had stone-free rate of 37.6% at three months of follow up. The predictive variable (OR) for stone-free rate at 3 months after ESWL for patients > 60 years, was 0.643 (0.506-0.818; CI 95%) when compared with the reference (≤ 40 years). Patients age was a significant factor for stone-free rate and those aged > 60 years had the worst results, especially for renal stones, not for ureteric stones (10). **[Evidence Level III]**

Short and long terms effects have been reported after ESWL. Janetschek and co-workers associated an increased age related incidence and prediction of new onset hypertension by intrarenal resistive index after ESWL. A group of 20 patients aged 60 to 80 years were followed 26 ± 6 months after ESWL. All the patients had no hypertension prior to treatment. They found elevated resistive index levels in 75% of patients (mean 0.74 ± 0.05, normal less than 0.7) and new onset of hypertension was present in 45% of patients ≥ 60 years within 26 months after ESWL treatment. There was a strong correlation between elevated resistive index levels and diastolic blood pressure (correlation coefficient 0.903), which suggests underlying renovascular disease after ESWL exposure (11). **[Evidence Level III]**

Krambeck et al, published long term effects of ESWL treatment with first-generation Dornier HM3 after 19 years in 578 patients with renal and proximal ureteral stones compared with matched control group. Patients undergoing ESWL were more likely to have hypertension (odds ratio [OR] 1.47, 95 confidence interval [CI] 1.03-2.10, p=0.034) and diabetes mellitus (OR 3.23, 95% CI 1.73-6.02. P<0.001) than controls. Increased risk of diabetes was maintained in a multivariate analysis and was related to number and intensity of shock waves. Hypertension was more associated in patients when ESWL was applied bilaterally (12). **[Evidence Level III]**

b) PCNL

The publications on Percutaneous Nephroli-thotomy in the specific elderly population (≥65 years old) are limited.

Sahin and colleagues published their experience retrospectively with 28 PCNL in 27 patients older than 60 years and were compared with younger group. Elderly patients represented 13.5% of their percutaneous experience. Co-morbidities were present in 17 patients (62.9%). Staghorn stones represented 25% vs. 22% of elderly and younger groups respectively without statistical significance. There was a higher incidence of solitary kidney (anatomically or functionally) in elderly group

(29% vs. 7%), P= 0.003) due to kidney lost secondary to nephrolithiasis in the contralateral kidney. The success rate after PCNL was 89% for elderly population and 92% for younger group without statistical significance. Transfusion rates were higher in older patients, 21.4% vs. 18% in the younger group, but did not have statistical significance (P=0.662), neither had difference the complications rate. They also reported no renal deterioration in solitary kidney population (13). **[Evidence Level III]**

Anagnostou and co-workers reported retrospectively 135 patients over 70 years, submitted to percutaneous surgery for renal stone compared with younger adult group (17-69 years old). Complete and partial staghorn calculi incidence was similar, (15.55 vs. 16%) and (22.6% vs. 22.9%) in older and younger groups, respectively. Stone-free status achieved by surgery alone was 60.7 % in the elderly group compared with 53.4% in younger patients without statistical significance. Adverse events were present in elderly group in 11% and 9% in the younger group. There were 2 serious events in the extremely elderly population ($\geq$ 80 years. [n.16]). Authors conclude that PCNL is as safe and effective in elderly population as it is in younger adults (14). **[Evidence Level III]**

Stoller and associates, published a retrospective review of 42 PCNL performed in 33 patients aged 65 years and older, they were compared with 160 PCNL performed in younger patients over same time period. Complete staghorn calculi and average stone size were similar for elderly and younger groups (47% vs. 55%, 3.8 cm vs. 4.3 cm) respectively. Stone-free rate including residual fragments <5mm 3 months after surgery was 82% in elderly population. Higher rate transfusion was needed in elderly group (26% vs. 14%, P<0.01) despite similar preoperative hemoglobin levels. No deaths were reported and serious complications were infrequent (15). **[Evidence Level III]**

c) Retrograde ureterolithotripsy

Flexible ureteroscopy has achieved day by day a very important role as a minimally invasive treatment alternative for upper urinary tract stones, including proximal ureter and renal stones.

Several reports on successful retrograde ureterolithotripsy in combination with laser have been published since early 1980´s, most of reported series present acceptable success in stone-free status and low complications rates even in elderly population. Blute et al and Harmon et al from Mayo Clinic (16,17) reported an age range of their patients from 10-92 years (mean 43.7 years old), in Abdel-Razzak and Bagley´s series, the mean age was 52.6 years old (range 22 to 85 years) (18), Andreoni et al, found average age of 46.7 years (range 33-68 years) (19), Grasso et al published 2 series, the age range of their patients population was 10 to 77 years old (20,21), Chung et al presented a small series of simultaneous bilateral retrograde intrarenal surgery (RIRS) performed for stone disease in patients with significant co-morbidities., the mean age of their patients was 62 years (22).

Unfortunately, the concern of age was not considered as special variable in their analyses. It might be desirable to design new trials or to reanalyze these finding alone or together with current publications to determine if the age factor is a determinant variable in terms of success, complications and co-morbidities, especially if flexible retrograde ureterolithotripsy could be proposed as the desirable treatment in elderly patients.

d) Open surgery

After the development of minimally invasive options to treat renal stones in the last three decades, the role of open surgery has decreased to represent in large series from 2.5% to 5.4% of all the procedures in the end of the last century (23). During the “golden” era of open surgery (the only option available) the elderly population was very low. Thus, we can only refer to the cases of patients with serious co-morbidities in non-elderly populations (without specific elderly age criteria), assuming that some of these co-morbidities are present in the elderly patients, but the evidence is limited. Hofmann and Stoller reported a small series of open stone surgery in morbidly obese patients and co-morbidities, in which none of the patients were elderly (mean age 36.7 years; range 26 to 50 years) (24). Al-Kohlany et al, published a prospective randomized trial to compared open vs. percutaneous nephrolithotomy treatment for complete staghorn. The open group mean age was 48.7 years old (range 26 to 75 years) and for 48.6 years (range 57 to 65 years) fro PCNL (25).

RECOMMENDATIONS

Recommendation	*Level of Evidence*
ESWL is an option for small renal stones	**III**
PCNL may be considered and age is not a serious issue in outcomes in terms of stone free status and minor complications	**III**
In older patients (>80 years) there is a potential increased need of blood transfusion and incidence of more serious complications	**III**
Flexible Retrograde Ureterolithotripsy is a possible option	**III-IV**
Open surgery has very few indications	**IV**

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III. ASYMPTOMATIC RENAL CALYCEAL STONES

1. INTRODUCTION

Small and asymptomatic renal stones used to be untreated prior the introduction of Extracorporeal Sock Wave Lithotripsy (ESWL) since the only therapeutic option available during that time was open surgery. ESWL is considered an attractive option to treat the majority of small renal calculi, but recently, several series have reported its possible limitations and risks.

The natural history of asymptomatic renal stones has not been well documented nor prognostic factors have been identified for patients with asymptomatic stones who are at risk of becoming symptomatic.

2. INCIDENCE

In United States of America in 1986 a co-operative study reported that 36% of all calyceal stones treated were less than 10mm in diameter (1), a more recent report describes that in the 90´s more than a half of the stones were less than 10mm in diameter (2,3). **[Level of Evidence III]**

3. NATURAL HISTORY OF ASYMPTOMATIC RENAL CALYCEAL STONES

Hübner and Porpaczy published in 1990 a review of the evolution of 62 patients with asymptomatic calyceal stones. The observation period was during the pre-SWL era and the average follow-up was 7.4 years. They found that 83% of all patients with asymptomatic caliceal stones required intervention within 5 years of diagnosis and only 10% of patients with caliceal calculi remained symptom-free after 10 years (4). **[Level of Evidence III]**

Glowacki et al, reviewed a cohort of 107 patients (mean follow-up: 31.6 months). 68% of patients remained asymptomatic for the duration of the study. Of the symptomatic patients, 15% passed one stone and 53% required intervention. Cumulative 5-year probability to develop a symptomatic event was 48.5% (5). **[Level of Evidence III]**

Burgher and co-workers evaluated the natural history of asymptomatic calculi and the risk of progression of disease in 300 patients with average age 62.8 years (range 23.1-89.0) and average follow-up of 3.26 years (range: 0.2-10.0 years). Mean cumulative stone diameter at presentation was 10.8 mm (range 1.0-74.0 mm). 48% of patients had multiple calculi. They found that 77% of patients experienced disease progression (need of surgical intervention, development of pain or stone growth on serial images), with 26% requiring surgical intervention. They suggested under statistical analysis, intervention rates of 50% at over 7 years. Isolated stone $\geq$ 4mm on presentation were 26% more likely to fail observation than patients with smaller solitary calculi ($P=0.012$). Stone growth was more common for lower-pole stones (61% vs. 47%). Urine uric acid concentration correlated positively with the stone growth ($P=0.05$) and serum uric acid concentration predicted stone growth ($OR=3.6$). They considered that small non-uric acid calculi in the upper pole may be most amenable to observation. They suggested that stratification of risk of progression according to presenting stone size; location and composition may facilitate discussions with the patients regarding the alternatives of observation versus intervention (6). **[Level of Evidence III]**

Streem et al, reported that 43% of patients with small, non-infection-related stone fragments after ESWL, followed expectantly, would require intervention or have symptomatic episodes within an average of 2 years and that an estimated 71% would require treatment within 5 years (7). **[Level of Evidence III]**

4. OBSERVATION

The information is limited. The preliminary information suggests that patients with asymptomatic renal (calyceal) stones will become considerably symptomatic during first 5 years after initial diagnosis if observation is chosen. Jewett and co-workers reported in 154 asymptomatic patients the same risk of hypertension in a randomized trial with ESWL for treated and non-treated groups (8). **[Level of Evidence II]**

The reports of immediate (hypertension, especially in patients $\geq$ 60 years old) or long term effects (hypertension and diabetes) of ESWL after the treatment of average renal stones (symptomatic and large) and the consideration of being not always as a benign procedure limits the generalized use of this treatment alterantive for asymptomatic renal stones (9,10). **[Level of Evidence III]**.

5. INTERVENTION

Kelley and associates, reported preliminary results on a randomized controlled trial of prophylactic ESWL for small asymptomatic renal calyceal stones. They included 228 patients with small stones (< 15 mm total diameter). Mean follow-up was 2.2 years (range 1-5). 28 patients (28%) in the ESWL group were stone free, compared with 16 (17%) in the observation group (odds ratio 1.95, 95% confidence interval, CI, 0.97-3.89, P=0.06). Additional treatments and strategies were necessary in 21 (21%) patients in the observation group and 15 (15%) in the ESWL group. (odds ratio 0.66, 95% CI 0.32-1.37, P=0.27). They conclude that prophylactic ESWL for small asymptomatic renal calyceal stones does not appear to offer any advantage to patients in terms of stone-free rate, quality of life, renal function, symptoms or hospital admissions. Observation was associated with a greater risk of requiring more invasive procedures. Longer follow-up is required (11). **[Level of Evidence II]**

Bilgasem and co-workers evaluated the results of flexible ureteroscopic removal of small (<1 cm) asymptomatic renal stones associated with ipsilateral ureteral stones after performing rigid ureteroscopy (holmium lasertripsy) for ureteral stones in 29 patients. Mean stone size was 5.7 mm, 89.5% renal stones were located in lower calix. It was only added 16.7 minutes for flexible ureteroscopy after the rigid ipsilateral instrumentation. Renal stones were taken out with tipless Nitinol basket removal devices and when necessary also laser was used. They found an immediate success rate of 90%. One-month follow-up confirmed stone-free rate of 100%. Authors concluded this procedure appears to be safe and effective with acceptable prolongation of the operative time (12). **[Level of Evidence III]**

See active monitoring for the recommendations.

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IV. BLEEDING DIATHESIS

1. INTRODUCTION

The event of an unanticipated serious bleeding during elective open surgery (i.e. major vascular lesion) has been the most afraid situation for surgeons. This situations and serious bleeding during trauma surgery due to vascular and solid organ lesions for blunt or penetrating trauma are also manageable by advanced surgical technical procedures and appropriate reposition of red blood cells and several blood components among other strategies. A bigger challenge represents the patients with congenital or acquired bleeding disorders and also patients under medical anticoagulation therapy having a disease tributary of surgery.

The population with congenital or acquired bleeding disorders is extremely low, and includes Haemophilia A, B and von Willebrand´s Disease, these conditions accounts for 95 to 97% of all cases. The remaining bleeding defects are so estrange among general population including Factor VII deficiency with prevalence of 1:500,000 and prothombin (Factor II) and Factor XIII deficiency with an incidence of 1 in 2 million (1). **[Level of Evidence III]** For these problems the preventive and corrective therapy by substitution of the missing or defective coagulation factor(s) and several other strategies are used to reduce and solve in advance most of the bleeding surgical problems.

It is much more common that the surgeons face up patients with clinical bleeding problems secondary to another underlying diseases (hepatic failure, leukemia, disseminated intravascular coagulation, sepsis etc.,) or iatrogenic as medical prophylactic anti-thrombosis or anticoagulation prescription as indicated in atrial fibrillation, cardiac mechanical valves, cardiac bypass, and anti-thrombophilia treatments. It represents a major problem because in most of these situations to withdraw the anticoagulant treatment can lean the patients without the protective effect against the risk of embolism. Large experience has been developed in the fields of liver transplant, cardiac surgery and orthopedics to lead surgery and bleeding disorders.

In the urology field the experience on surgery and especially renal stones surgery in patients with bleeding disorders is limited.

Unfortunately, there is not a general or good specific blood test (cost-effective) for screening of coagulation disorders in patients without prior diagnosed bleeding disorders. For them the most valuable tool (cost-effective) is to do a very detailed interview with patient and patient's family past medical/surgical histories with focus on easy bleeding settings just trying to detect patients with potential sub-clinical bleeding patterns status prior plan any surgery (2). **[Level of Evidence IV]**

In order to minimize the risk of bleeding it is recommended the following approach to patients that will undergo surgical procedures, including minimally invasive procedures as PCNL. Complete blood counts and coagulation profiles must be assessed. Preoperative transfusion of platelets may be required immediately prior to surgery or PCNL when platelet concentration is below 50–80,000 per deciliter. International normalizing ratio (INR) is a sensitive test for coagulation factor deficiency, and values greater than 1.5 should be corrected. Outpatient anticoagulants can be withheld (if not-contraindicated) a week prior to surgery in most patients without significant sequela. For those on coumadin, Vitamin K can also be given over several days prior to surgery. In others, when INR remains persistently elevated, transfusion of fresh frozen plasma (FFP) immediately prior to PCNL may be appropriate. For patients at high risk for embolic events, such as those with mechanical valves, the use of heparin and a treatment 'window' may be useful. Patients without known coagulopathic conditions do not need additional hematological screening profiles. It is also recommended to avoid as much as possible hypothermia in the patients and to assess ionized serum calcium and replace it in cases of previous anemia that had required transfusion of more than two units (3). **[Level of Evidence IV]**

2. TREATMENT

a) ESWL

The potential for perirenal or intrarenal hemorrhage after extracorporeal shock wave lithotripsy has been well documented in non-selected population. It has been reported in up to 4.1% to 25% of treated renal units (4,5). **[Level of Evidence IV-III respectively]**. In fact, almost all significant post-shock wave lithotripsy bleeding has occurred in patients with previously unrecognized or untreated coagulopathic conditions, including haemophilia, sodium warfarin use and a prolonged partial thromboplastin time. Thus, ESWL has been considered an absolute contraindication to use shock wave lithotripsy in patients with uncorrected bleeding disorders (4,6,7). **[Level of Evidence IV]**

There are anecdotal reports of successful ESWL treatments for renal stones in patients with bleeding disorders including 3 cases (2 haemophilia A and 1 haemophilia B) with or without increased hemorrhage events. All they had administration of appropriate substitution therapy prior the ESWL session (8,9). **[Level of Evidence IV]**

b) PCNL

PCNL is a major surgery in spite of the minimal incision, therefore the procedure may be considered an absolute contraindication in patients with renal stones and uncorrected hemorrhagic diathesis (6). **[Level of Evidence IV]**

There are 2 anecdotal reports of successful 2-staged PCNL treatments for 2 patients with haemophilia A without bleeding complications. One patient received prior to ESWL appropriate F VIII substitution therapy and the other patient received recombinant factor (rFVIII) for religious reasons. Both did well during and after the procedure (10,11). **[Level of Evidence IV]**.

c) Retrograde ureterolithotripsy

Due to the low invasiveness nature, flexible retrograde ureterolithotripsy appears to be a good option to approach renal stones in several adverse scenarios with low complications rates (12-18). It could be also in the scenario of patients with bleeding disorders. It has been considered that the risk of bleeding complications during ureteroscopy is negligible (19) **[Level of Evidence I]**

Kuo et al, published a small series of 8 patients with known uncorrected bleeding diatheses with upper tract calculi and transitional cell carcinoma treated with flexible retrograde ureterolithotripsy using holmium laser. Mean age of patients was 58.2 years with a range of 42 to 74 years old. Six patients were under Coumadin medication with mean INR of 2.1; Two more patients were thrombocytopenic and one of them had also von Willebrand´s disease. None of the bleeding diatheses were corrected before surgery. Six of 7 patients (85%) who underwent laser fragmentation for calculi were stone free on follow-up at 1 month. The patient who underwent transitional cell carcinoma ablation had not tumor recurrence at 4 months of follow-up. There were 2 patients with bleeding complications; one related with to procedure, involving an episode of oliguria secondary to a small ureteral clot. It was cleared without surgical intervention. The other patient developed epistaxis after administration of ketorolac for pain (20). **[Level of Evidence III]**

Watterson and colleagues reported a series of 25 patients (29 upper tract urinary calculi) with bleeding diatheses treated with holmium:YAG laser lithotripsy in two tertiary stone centers. The mean age of patients was 61 years (range: 42 to 84). 17 patients were under oral warfarin sodium administration, liver dysfunction in 3, thrombocytopenia in 4 and von Willebrand´s Disease in 1. Only one patient with lymphoma with recent chemotherapy received 2 units of platelets before surgery to increase the platelet count to 36 X 10?/l. There were 20 ureteral stones and 9 stones were intrarenal, six of them in lower pole calyx. Stone fragmentation was completed to achieve a particle size of 2 to 3 mm. Mean stone size was 11.9mm (range 6 to 25). No effort was made to extract or remove the fragments. One patient was lost to follow-up. The overall stone free rate after a single procedure was 93% (26 of 28 cases). For renal stone it was 89% (8 of 9). 1 patient with residual calculi underwent successful staged ureteroscopic holmium laser lithotripsy and 1 was under clinical surveillance for a small asymptomatic caliceal stone. The authors reported that early in the series, 2 cases had concomitant use of electrohydraulic lithotripsy but it was ruled out after one of these patients developed retroperitoneal hemorrhage. Significant bleeding complication occurred during 1 of the 30 procedures (3%). 26 of the 30 ureters were stented postoperatively (87%). 27 of 30 cases (90%) were performed as an outpatient basis (6). **[Level of Evidence III]**.

d) Open surgery

Open surgery to remove stones located inside the kidney represents a major challenge because its high risk of bleeding for nature in normal coagulating patients. In the context of patients with hemorrhagic diatheses it represents a higher risk of bleeding complications also with high risk of life-threatening scenario. Same as some minimally invasive procedures as ESWL and PCNL are considered absolute contraindication to treat renal stones in patients with uncorrected bleeding disorder, open surgery must be considered in the highest risk. Publications of this field are limited.

RECOMMENDATIONS

Recommendation	*Level of Evidence*
ESWL, PCNL and Open stone surgery are ABSOLUTELY CONTRAINDICATED in the treatment of renal stones in patients with uncorrected bleeding diatheses	**IV**
In case withdrawal of anticoagulation therapy is precluded, flexible URS is the preferred treatment option.	**III**

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V. RENAL ABNORMALITIES

1. ECTOPIA

Renal ectopia is defined as the congenital displacement or malposition of the kidney, with an associated shortened ureter and aberrant blood supply. Ectopic kidneys may be located in the pelvis, iliac fossa, abdomen, thorax or contralateral renal fossa. Crossed fused ectopia and the transplanted pelvic kidney will be discussed in later sections. Reported incidence at autopsy varies between 1in 500 and 1 in 1200 [1,2]. The ectopic kidney is often small and malrotated with its axis lying between horizontal and vertical. Urinary drainage can be impaired by stenosis at the ureteropelvic (due to the anterior position of the renal pelvis) or ureterovesical junctions, which may cause hydronephrosis [3].

Treatment Options:

Renal location and function, stone location and size, and local expertise all influence choice of procedure and, in most cases, the familiar array of management options are available. Extracorporeal shock wave lithotripsy (ESWL) in the prone position has been used with success in patients with small calculi (sub-25mm) in a non-obstructed system [4], **Table 1** (**Evidence level III**). The presence of overlying bone or impaired urinary drainage may contraindicate ESWL or reduce the efficacy of fragment clearance [5]. Percutaneous stone extraction (PCNL) has also been reported in a retrospective case series. Renal Access may be difficult due to the abnormal anatomy of the renal pelvis. Initial stone free-rates are high, though major complications can occur (**Table 1**) (**Evidence level III**). Endoscopic treatment has progressed in recent years with the development of smaller and more flexible ureteroscopes and advances in laser technology.

Ureteroscopic treatment of accessible calculi has also been reported retrospectively (Table 1). The ureter may be short, or occasionally long and tortuous, but the site of the ureteric orifice is usually normal. Proponents of URS argue that the lower morbidity and hospital stay observed make it preferable to PCNL [6] (**Evidence level III**). Laparoscopic surgery has essentially replaced open sugery in the treatment of the most complex presentations and where less invasive treatments have failed. Published data is limited to retrospective, small number case series (**Table 1**).

2. FUSION ABNORMALITIES: HORSESHOE AND CROSS-FUSED ECTOPIA

A horseshoe kidney is defined as the presence of two renal masses that lie on either side of the midline, which are joined by midline parenchymal or fibrous tissue. Horseshoe kidney is the most common renal fusion abnormality, occurring in 0.25% of the population [7,8]. The kidneys lie vertically, and their failure to rotate causes their calyces to point posteriorly, with an anteriorly sited renal pelvis. The ureters insert high onto the renal pelvises, and descend, bending anteriorly over the kidneys, but enter the bladder at normal sites. Up to one third of patients have ureteropelvic junction obstruction (UPJO) [9,10]. Urolithiasis is the most common complication in the horseshoe kidney, reportedly occurring in approximately 20% of patients [11-13]. There have been no prospective studies comparing treatment modalities in this group of patients. The term 'cross-fused ectopia' incorporates the other anatomical abnormalities where a kidney is located contralateral to the side that its ureter enters the bladder, and is fused to the other kidney. These abnormalities also predispose to hydronephrosis, infection and urolithiasis.

Treatment Options:

a. **Conservative**: Two studies have shown that the majority of patients with urolithiasis in horseshoe kidneys have a treatable metabolic abnormality, therefore it is recommended that all patients should have a full metabolic survey [14,15] **Evidence level III**).

b. **ESWL**: There are several published case series using ESWL in the treatment of horseshoe kidney calculi (**Table 2**) (**Evidence level III**). Ureteropelvic junction obstruction should be ruled out prior to ESWL [16]. The data suggests that ESWL is a safe and efficacious treatment modality in this scenario in the treatment of stones less than 15mm (**Evidence level III**). However multiple sessions are often required. In centres where PCNL or laparoscopic surgery is unavailable, ESWL with a JJ stent in situ can be used.

c. **PCNL.** PCNL has been used and reported extensively, either as first-line treatment of large stones (often ≥20mm) or when ESWL has failed to sufficiently treat the stone burden [17-21]. Safety of percutaneous puncture (usually via the most superior calyx with the patient prone) is enhanced by the anatomical accesibilty of the

Table 1. Results of treatment of cacluli in ectopic kidneys

Author/ Reference	**Treatment**	**Number of patients**	**Stone size**	**Stone-free rate**	**Notes/ Complications**
Tunc [102] [**III**]	ESWL	14	Mean 2.3 cm.sq	57% at 3 months	
Al-Tawheed [103] [**III**]	ESWL	8	Mean 15mm	100% at 3 months	JJ stent if >15mm
Kupeli [104] [**III**]	ESWL	13	Mean 2.1 cm.sq	54%	
Desai [105] [**III**]	PCNL	9	Mean 24mm	100% at 6 months	33% required 2nd PCNL. No major complications
Gupta [106] [**III**]	PCNL	16	NA	100%	31% required 2nd PCNL. One bowel injury
Matlaga [107] [**III**]	PCNL +/- laparoscopic assisted	8	NA	100%	75% laparo-scopic assisted. 25% required 2nd PCNL. No major complications
Weizer [108] [**III**]	Uretero-scopic	4	Mean 14mm	75% at 1-2 months	No complications
Gupta [109] [**III**]	Laparoscopic	2	NA	100%	One conversion to open

Table 2. Results of ESWL in cacluli in abnormally fused kidneys

Author/ Reference	**Number of patients**	**Fusion Abnormality**	**Stone size**	**Stone-free rate**	**Notes**
Sheir [110] [**III**]	34	Horseshoe	≤15mm	79%	
Sheir [111] [**III**]	15	Horseshoe	>15mm	53%	
Tunc [112] [**III**]	45	Horseshoe	Mean 2.2 cm.sq	67%	JJ stent if >20mm
Al-Tawheed [113] [**III**]	9 (13 stones)	Horseshoe	Mean 15mm	30%	Adjuvent URS/open surgery/PCNL in 7 stones; JJ stent if >15mm
Serra [114] [**III**]	37	Horseshoe	Mean 14mm	33%	
Lampel [115] [**III**]	37	Horseshoe	Mean 14mm	76%	Adjuvent URS in two patients
Tunc [116] [**III**]	4	Cross-fused	Mean 3.0 cm.sq	25%	JJ stent if >20mm

collecting system and mediality of the major vessels [22]. However, bowel injury has been reported, leading to the use of laparoscopy-guided PCNL access by some groups [23]. Overall success with PCNL, defined as achieving a stone free state, is superior to ESWL, especially with technological advances such as flexible nephroscopes ([24],**Table 3**) (**Evidence level III**).

d. Ureteroscopic treatment. A retrograde endoscopic approach to calculi in horseshoe kidneys has been reported, though to a much lesser extent than ESWL and PCNL [25]. Weizer *et al.* published a series of URS in four patients with horseshoe kidneys [26]. Mean stone size was 14mm, holmium laser lithotripsy via a flexible ureteroscope was used. Three patients had complete stone clearance, the other had a remianing 2mm fragment (**Evidence level III**). Andreoni *et al.* published a case report using flexible URS over an access sheath in a patient with a horseshoe kidney containing 3 calculi [27]. There were no residual fragments greater than 2mm. This sparse, Level III data suggests that flexible URS may have a role in specialist centres in suitable patients.

e. Surgery. As discussed above, laparoscopic surgery has been used to facilitate PCNL access. Saggar and colleagues have reported a successful laparoscopic excision of a non-functioning moeity due to calculus disease [28]. The advent of ESWL, endoscopic and laparoscopic technologies has lead to open surgery becoming almost obsolete.

3. POLYCYSTIC KIDNEY DISEASE

Renal cystic disease is divided into acquired cystic degenerative disease (five or more cysts), congenital autosomal recessive (infantile) and autosomal dominant (adult) polycystic kidney diseases (ADPKD). The latter occurs in 0.1% of the population, causing significant renomegally and often leads to end-stage renal failure [29]. Urolithiasis occurs in 8-36% of patients with ADPKD, and is thought to be partly related to urinary stasis in the intrarenal collecting system secondary to compression from bulky cysts [30,31]. A metabolic aetiology may be present and it is reported that approximately 50% of calculi in ADPKD contain uric acid [32]. The level of cystic disease may make the interpretation of imaging more difficult if numerous cysts are present.

Treatment Options:

a. Medical treatment: Patients should have serum and urinary metabolic screening to identify and treat abnormalities such as hypocitraturia, hyperuricosuria and hyperuricemia [33] (**Evidence level III**). Caution should be used when advising patients who are in end-stage renal failure about fluid intake.

b. ESWL. There is no randomised data comparing treatment modalities in this group of patients. The largest published series in recent years is by Deliveliotis *et al.* [34] (**Evidence level III**). Mean stone diameter was 10.5mm. Five patients with ADPKD and four with multiple cysts were included. One month following a single session of ESWL, stone-free status was observed in 20% of patients with ADPKD and 75% of patients with multiple cysts. No side effects were reported. Ng *et al.* published their centre's experience of ESWL in 3 patients with ADPKD [35] (**Evidence level III**). In this small retrospective series, ESWL was used successfully and without complications as a monotherapy in two patients, and as an adjunct to PCNL in a third patient.

Table 3. Results of PCNL in cacluli in abnormally fused kidneys

Author/ Reference	Number of patients	Fusion Abnormality	Stone size	Stone-free rate	Major complications
Shokeir [117] [**III**]	34 (45 stones)	Horseshoe	Mean burden 6.64sq.cm	73.5%	13% 3 haematuria, 1 ureteric obstruction, 1 bowel injury
Raj [118] [**III**]	24	Horseshoe	Mean burden 4.48sq.cm	87.5%	12% 1 pneumothorax 1 uretero-colonic fistula 1 renal pelvis perforation
Aridogen [119] [**III**]	28 (33 stones)	Horseshoe	Mean burden 4.73sq.cm	93.9%	3.6% 1 haematuria

c. **PCNL.** There is a paucity of data using PCNL in polycystic kidneys. Ng and colleagues used PCNL prior to and after ESWL in one patient with a good outcome [36].

d. **Ureteroscopic treatment.** Again, there is a lack of data in this field. Ng *et al*. used a retrograde technique to successfully treat a proximal and a distal ureteric stone in two patients with ADPKD [37].

e. **Surgery.** Polycystic kidneys that remain symptomatic may be surgically removed, often using minimally invasive (laparoscopy or hand-assisted laparoscopy) techniques, though complication and conversion rates are high [38,39] (**Evidence level III**).

4. CALYCEAL DIVERTICULUM

A calyceal diverticulum is a urine-filled intra-renal sac (lined by transitional urothelium) of embryonic aetiology that communicates with the pelvicalyceal system by a narrow neck. The majority are asymptomatic, and the incidence is reported to be less than 0.5% [40,41]. Calculi are reported to form in 10-50% of patients with a calyceal diverticulum, and may present with pain, haematuria or infection [42]. The aetiology of lithiasis is thought to be urinary stasis, though in a series of 12 patients all were found to have at least one metabolic abnormality, the most prevalent being low urine volume (11 patients), hypocitraturia (10) and hypercalciuria (7) [43] (**Evidence level III**). Generally, treatment is indicated when the calculi are symptomatic or significantly increasing in size [44].

Treatment Options:

a. **ESWL**. Stone clearance after ESWL can be hindered by the narrow neck of the diverticulum. Historically, series have reported stone-free rates of 20-58% [45-47]. A recently published retrospective case-note review used ESWL in 38 calculi (mean size 12mm) [48]. At three month follow-up, stone-free and symptom-free rates were 21% and 61% respectively. The authors advocated ESWL as first line treatment in patients with small calculi and a diverticular neck that is seen to be patent with IVU (**Evidence level III**).

b. **PCNL** has been recommended in treating large stones (e.g. >15mm), and has been described and reported in retrospective data and literature reviews [49-53]. Technical points include demonstration of anatomy with retrograde pylography, single direct puncture into the diverticulum, stone removal, dilatation of the diverticular infundibulum, cavity fulgaration and nephrostomy placement [54]. Recent data is summarised in **Table 4.**

c. **Ureteroscopic treatment.** URS is less invasive than percutaneous and surgical methods of treating calyceal diverticular calculi. The clinical situations in which it is thought to be best utilised are small stones in upper and accessible middle pole calyces. A flexible ureteroscope is recommended. Location, cannulation and occassionally balloon dilatation of the diverticular orifice may be technically difficult. After stone treatement, holmium:YAG laser infundibulotomy or electrocautery cavity fulgaration can be performed [55-58]. Published data of this technique is limited to case series, with recent stone-free rates varying from 19% (17 patients [59]) to 58% (18 patients [60]) (**Evidence level III**).

d. **Surgery.** The laparoscopic approach has been advocated by some authors in the treatment of large calculi or where the parenchyma overlying the diverticulum is very thin, thus making a per-

Table 4. Results of PCNL in cacluli in calyceal diverticulae

Author/ Reference	Number of patients	Stone size	Stone-free rate	Major complications
Turna [120] 44 [**III**]	18	Mean 20.6mm	83% at 3 months	17% 2 haematuria 1 pneumothorax
Kim [121] 48 [**III**]	21	Mean 11.6mm	87.5% at 3 months	None
Auge [122] 51 [**III**]	18	Mean 12.0mm	80% at 3 months	11% 1 pneumothorax 1 pneumohaemothorax
Monga [123] 52 [**III**]	11	Mean 10.2mm	100% at 3 months	9% - 1 pneumothorax

cutaneous approach difficult [61,62]. Imaging such as retrograde pyolgraphy is often required to visualise the diverticulum. At the cost of the invasiveness of this procedure, stone free rates are reported as 100% [63] (**Evidence level III**).

5. TRANSPLANT KIDNEY

Urolithiasis in a transplanted kidney is uncommon, affecting 0.1-1% of grafts [64-66]. The aetiology has been described to include hypercalcaemia secondary to persistent hyperparathyroidism, recurrent infection, stone formation on a foreign body (stent, suture or staple), or distal renal tubular acidosis. Another cause is 'donor-gifted allograft lithiasis', where the donor kidney is transplanted with a pre-existing stone(s). Renal colic is masked due to the denervated kidney, thus the diagnosis is often made due to investigation of deteriorating renal function (including anuria), or the onset of sepsis. Prompt and efficacious treatment is required to avoid the potential loss of graft function.

Treatment Options:

a. **Medical.** As described above, a metabolic abnormality may be a factor in transplant calculi formation, hence patients should be screened and treated [67]. In transplanted kidneys, intervention may not be required in some situations, especially non-obstructing stones found in the early post-operative period. Spontaneous stone passage was reported in two of 21 renal calculi (4mm and 4.5mm upper pole) [68], three patients with non-obstructing stones [69], and three patients in a series of 19 patients [70] **(Evidence level III).**

b. **ESWL.** Challacombe *et al.*'s reported a series of 13 patients with transplant kidney calculi treated in the prone position with ESWL as monotherapy in 12 patients, and in combination with PCNL in the other [71]. A stent or percutaneous nephrostomy was required in nine patients, and multiple sessions were often required to achieve stone clearance. Klingler and colleagues successfully treated eight calculi up to 12mm in length with ESWL, though three required temporary nephrostomy placement [72] (**Evidence level III**).

c **Percutaneous stone extraction.** In transplanted kidneys, PCNL whilst supine is faclilitated by the pelvic location of the kidney, though tract development may be hindered by fibrous tissue encasement and bleeding [73]. In Streeter *et al.*'s series of calculi obstructing allograft ureters, four were successfully treated with PCNL [74]. Of those where PCNL failed, one required open surgery and the other had failed URS, and eventually required nephrectomy. Challacombe *et al.* used PCNL in three patients: twice successfully and once failing in a large staghorn that subsequently underwent open surgery [75] (**Evidence level III)**. Three successful PCNL procedures in calculi greater than 20mm were reported in Klinger *et al.*'s series [76] (**Evidence level III**).

d. **Ureteroscopic treatment.** URS is often technically difficult due to the angle and position of the uretero-neocystostomy. In the sparse published data, URS has been used successfully as monotherapy in two patients [77], and four patients [78] (**Evidence level III**).

e. **Surgery.** Open nephrolithotomy should be reserved only for cases where other treatment modalities have failed. Occasionally ureteric reconstruciton may be used to treat a refractory stricture.

6. INFUNDIBULOPELVIC ANGLE

The infundibulopelvic angle, i.e. the angle between the lower pole infundibulum and the renal pelvis (LIP angle), is thought to be important in stone clearance following ESWL. However, variations in measuring technique and inter- and intra-observer measurement errors make interpretation of the published literature difficult. An LIP angle greater than 90° achieves better drainage than an acute angle when the patient is lying on their contralateral side [79]. High level evidence is lacking; analysis of 74 patients who underwent ESWL for lower pole calculi showed a stone free rate of 75% in patients with an LIP greater than 90° compared to 23% with an LIP less than 90° [80] **(Evidence level III**). A retrospective study of 205 calculi treated with ESWL by Ghoneim *et al.* reported that patients with an infundibulopelvic angle greater than 90° had a stone-free rate of 84%, compared to 66% with an acute angle [81] **(Evidence level III**). Contrary to this, a recent study by Danuser and colleagues reported that infundibulopelvic angle did not have a role in treatment success of ESWL in 96 patients [82] **(Evidence level III**).

7. ORGANOMEGALLY, SCOLIOSIS, MEGACOLON

Patients with neurological or spinal deformity can sufffer secondary problems affecting the urinary tract, such as recurrent sepsis, stone formation and renal impairment which can be a significant cause of morbidity. Patients with such conditions are at risk of increased stone formation 7 - 11%. As the deformity is often associated with other issues of immobilisation, poor fluid intake together with possible bladder and bowel dysfunction, then the issues for achieving stone clearance are significant. Similarly the problems of altered anatomy in many of these patients means that traditional treatment options eg ESWL may not be possible due to shockwave localisation and as a consequence more invasive modalities may be required eg PCNL to achieve stone clearance. The literature is sparse in these fields and the overall evidence level is **III.**

8. URETEROPELVIC JUNCTION OBSTRUCTION (UPJO)

The main aetiology of lithiasis in patients with UPJO is obstructed flow of urine, though other factors such as infection and metabolic abnormalities may play a role. Renal calculi are found in up to 20% of patients treated for UPJO [83,84]. Over the past decade percutaneous, laparoscopic and robotic surgery have superseded an open surgical approach in the management of concomitant UPJO and renal calculi.

Bernado *et al.* reported a retrospective series of 90 patients with UPJO and calculi, managed with simultaneous percutaneous endopyelotomy and stone extraction [85]. All patients were stone free after surgery, 8% developed stone recurrence within the mean seven year follow up (**Evidence level III**).

Ramakurmar and co-workers have reported their experience of concomitant transperitoneal laparoscopic pyeloplasty and pyelothilotomy in 19 patients [86]. In most patients an Anderson-Hynes or Y-V pyeloplasty was performed, with an operating time of 4.6 hours. Two patients with continued hydronephrosis had failure of pyeloplasty. The two- and twelve-month stone-free rates were 90% and 80% respectively (**Evidence level III**).

A recent retrospective series of eight patients with UPJO and calculi using a robotic laparoscopic Anderson-Hynes pyeloplasty and stone extraction has been published [87]. Mean operative time was 276 minutes, no complications were encountered, and all patients were stone-free at mean one year follow up (**Evidence level III**). Although these results are promising, cost and availability limit this modality of treatment, and critics argue that outcomes with laparoscopic surgery are equivalent at a much reduced cost [88].

9. URINARY DIVERSION

Urinary tract lithiasis is a common complication of urinary diversion, affecting 10-12% of ileal and 3-4% of colonic conduits [89,90]. Aetiological factors include infection with urease-producing bacteria, hypercalciuria (secondary to chronic acidosis and vitamin D resistance), urinary stasis and stone formation on staples or non-absorbable sutures [91]. Treatment is dependant on stone factors and local expertise. First line treatment of sub-2cm, uncomplicated stones is usually ESWL, though composition and anatomical factors influence success. Case series have reported stone-free rates following ESWL alone as 81% (27 patients [92]), 82% (11 patients [93]) and 92% (25 calculi [94]) (**Evidence level III**).

A retrograde ureteroscopic approach is feasible in upper tract calculi with a refluxing ureteral anastomosis, and can be combined with an antegrade approach [95]. Published data, however, is sparse. Percutaneous management is preferred for larger calculi or in those with failed ESWL or URS. A recent case series using PCNL in 20 patients with upper tract calculi and urinary diversion reported a stone-free rate of 75% [96]. Three major complications were encountered: heavy bleeding, septicaemia and urinary leakage. Open and laparoscopic surgery are reserved for the most complex and difficult scenarios, e.g. patients with continent diversions [97]. Life-long follow up is recommended for recurrent stone-formers, and prophylactic measures such as increased fluid intake and treatment of infection and metabolic abnormalities is advised [98] (**Evidence level III**).

10. MEDULLARY SPONGE KIDNEY (MSK)

MSK is an abnormality occurring in the medullary pyramids of the kidney, characterised by cystic dilatations of the collecting ducts. Recurrent nephrolithiasis associated with MSK is thought to be due to ectatic collecting ducts and metabolic abnormalities such as hypocitraturia [99]. MSK nephrolithiasis can be treated with modalities used in normal kidneys, and the importance of metabolic analysis and prophylaxis should be recognised [100,101].

RECOMMENDATIONS

RENAL ABNORMALITIES

Recommendation	*Level of Evidence*
Treatment options depend on renal, location, stone location and size and local expertise	**III**

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E. COMPLICATIONS IN PERCUTANEOUS NEPHROLITHOTOMY

PCNL is generally a safe treatment option and associated with a low but specific complication rate [1]. Many complications develop from the initial puncture with injury of surrounding organs (e.g. colon, spleen, liver, pleura, lung). Other specific complications include postoperative bleeding and fever [2].

Based on an overview of the literature, we present PCNL as a step-by-step approach including the description of possible complications, their origin and management. A MEDLINE-search was performed reviewing the literature between 1982 and 2007. All complications were stratified into 5 grades according to the modified Clavien classification system (**Table 1**), which has proven to be significantly correlated with the complexity of the surgery and the length of the hospital stay [3,4].

I. TECHNICAL CONSIDERATIONS

1. PREPARATION OF PATIENTS

The careful selection and preparation of patients is of upmost importance to decrease the complications of PCNL. All patients should undergo the following diagnostic workup:

- Definition of stone size (KUB and ultrasound)
- anatomy of the collecting system (intravenous pyelogram)
- urine analysis and culture
- serum creatinine, clotting parameters
- isotope renogram if indicated (i.e. staghorn calculus)

In case of a staghorn calculus and/or existing urinary tract infection, the patients are treated antibiotically according to the testing at least one day prior to the procedure (**Table 2**). Patients with decreased renal function should be pre-treated with intravenous infusion of normal saline.

2. TECHNIQUE OF PERCUTANEOUS NEPHROLITHOTOMY

Principally, the procedure can be performed under epidural anaesthesia. Most centres, however, prefer general anaesthesia. Prior to the procedure, a retrograde study is performed and a ureteral catheter placed at the uretero-pelvic junction. Optional a ureteral balloon catheter can be used to minimize the risk of migration of fragments into the ureter. The collecting system is moderately filled with contrast dye (i.e. with addition of methylene blue).

a) Positioning of the patient

Precise access to the kidney during percutaneous nephrostomy is facilitated by careful positioning of the patient and reduces the possibility of subsequent intra-operative complications. The following positions are described:

- The flat prone position on a fluoroscopic table
- The deflected prone position on a cushion
- The oblique prone position on a fluoroscopic table
- The oblique supine position on a fluoroscopic table

PCNL is usually carried out with the patient placed in prone position. One may use a specially designed cushion enabling a deflected position respectively place the patient flat on the fluoroscopic table. Some authors prefer an oblique prone [5] or oblique supine position [6-8].

The deflection of the patient placed on special cushion may increase the distance between the 12th rib and iliac spine, thereby enlarging the area for adequate puncturing of the kidney [9,10]. On the other hand, this leads to a higher position of the patient on the fluoroscopic table, which may interfere with the handling of the nephroscope and probes [11]. Urologists favouring the oblique supine position claim it facilitates an easier access for the subsequent PCNL [6-8]. However, recent comparative studies could only document a reduction of the operating time (Evidence Level I/B), because the changing of the position of the patient after the retrograde study is not required [8]. It is important to note that in the oblique supine position (ie. supported by a triangulated cushion), the axis of the kidney will not be the same as in the flat prone position.

Table 1. Modified Clavien classification system of postoperative complications [3]

Complication Grade		Description
I		Deviation from the normal postoperative course without the need for intervention, ie pharmacological, radiological or surgical
II		Minor complications required pharmacological intervention, including blood transfusion and total parenteral nutrition
III		Complications required surgical, endoscopic or radiological intervention, but self-limited
	IIIa	Intervention without general anaesthesia
	IIIb	Intervention with general anaesthesia
IV		Life threatening complications requiring intensive care unit management
	IVa	Single organ dysfunction (including dialysis)
	IVb	Multi-organ dysfunction
V		Deaths resulting from complications

Table 2. Preparation of patients prior to PCNL

Stone type	Findings	Measures
Single stone (ie. lower calix)	Urine culture sterile	perioperative Antibiosis (ie. Gyrase-inhibitors)
Complex stone (ie. Staghorn)	Urine culture sterile	Antibiotic prophylaxis
One day prior to PCNL (ie. Gyrase-inhibitors)	Urine culture positive	Antibiotic treatment before PCNL (acc. to antibiogram)
	Normal creatinine Creatinine > 1.5 mg/dl)	no infusion preop.. 1500 ml Na Cl-infusion the night before PCNL

b) Puncturing of the collecting system

For the puncture of the collecting system, several techniques have been described. This can be performed by a well-trained urologist or a radiologist:

1 A combination of ultrasound (free-hand technique, fully-guided system) and fluoroscopy. Based on sonographic imaging the puncture is carried out to the desired calyx. The final placement of the needle is mostly accomplished under fluoroscopic control.

2 Puncturing of the kidney under fluoroscopic guidance.

In this technique, the collecting system is filled with contrast dye and the axis of the kidney is determined based on a fluoroscopic image with the patient in horizontal and/or oblique position.

Regardless of the technique, a peripheral puncture to transverse a minimum of cortical tissue has to be aimed at, to avoid injury to major intrarenal vessel, to avoid fistula injury, to establish the shortest tract between the skin and calyx, and to minimize radiation exposure, as verified in a similar study [11].

Afterwards, a 0.97mm floppy-tipped guide-wire is passed through the needle into the collecting system. A working channel is then established using telescope dilators, under x-ray control or balloon dilatation [12]. Then, a standard 26 F nephroscope was placed directly into the kidney over the established tract.

The number and type of access depends on the treated stone size (i.e. staghorn stone) and localization (upper pole, lower pole) as well as on the treatment strategy (single session PCNL versus combination with ESWL). Whereas some authors prefer a standardized access through the lower calyx with additional treatment of stones not reachable via this access by subsequent extracorporeal shock wave lithotripsy [2,13], other authors advocate multiple tracts (i.e. upper pole) to clear the collecting system in a single session [14-16]. Advantages of upper pole access include optimal manipulation in case of stone burden in the upper and lower calices, however with a slightly increased complication rate (i.e. pleural injury) [14,17].

c) Stone manipulation

For stone disintegration several technologies can be used:

1 an ultrasound lithotripsy probe.

Except in case of very hard stones (i.e. calcium oxalate monohydrate) it enables fragmentation with simultaneous evacuation of the gravel.

2 ballistic devices (ie. Lithoclast)

This provides efficient and cost-effective disintegration of the stones. However, the fragments have to be extracted via the nephroscope sheath or the Amplatz access sheath. The latter has the advantage, that due to its flexibility larger fragments can be extracted.

3 Holmium-YAG-laser.

The Holimium-laser is mainly used via flexible nephroscopes or in case of a "mini-perc" via F17-pyeloscope. Flexible instruments are used when stone fragments migrate into other calyces or in case of additional stone burden in other calyces not accessible by the rigid nephroscope.

d) Postoperative care

At the end of the procedure, a 22 F Foley catheter is used as a nephrostomy tube and blocked with 1-2 ml in renal pelvis. Alternatively a red rubber catheter or a detachable silicone balloon catheter can be placed. An antegrade nephrogram is taken 24 to 28 hours after the procedure (depending on the clarity of urine). The tube is removed if there was no extravasation or retained calculi.

II. COMPLICATION RATES IN THE LITERATURE

In the current literature (**Table 3**), the total complication rate is up to 83% [10-12, 14-32]. These complications are mostly clinical insignificant bleeding or fever. The number of significant bleedings is reported below 8 % [12,14-17,19-22].

Conservative treatment is successful in most of these cases (Clavien Grade I) and blood transfusion (Clavien Grade II) was required in 5-18% [12,14-17,19-23]. The frequency of major complications ranged from 0.9 to 4.7% for septicemia (Clavien Grade IV), 0.6 to 1,4% for renal hemorrhage requiring intervention (Clavien Grade III) [12,14-17,19-26]. Access related complications included 2.3 to 3.1% for pleural and 0.2 to 0.8% for colonic injury (Clavien Grade III).

III. SPECIFIC COMPLICATIONS AND THEIR PREVENTION

Significant complications in PCNL can be divided into complications related to the access, and complications, which are related to the stone removal.

The sources of intra-operative complications are generally attributable to:

- Incorrect patient selection

- The lack of adequate equipment

- Technical errors

1. PATIENT SELECTION

Correct patient selection is important for all percutaneous endourological procedures, but particular when selecting patients for percutaneous nephrolithotomy. Surprisingly, reports suggest that PCNL in pre-treated kidneys is not associated with a higher morbidity but may take longer and usually leads to a higher percentage of auxiliary procedures [2,32].

PCNL is contraindicated if the patient has an untreated coagulopathy, *untreated* urinary tract infection (UTI) or pyonephrosis.

The presence of concomitant disease such as diabetes, or pulmonary disease, or cardiovascular disease enhances the risk of a sub-optimal outcome for PCNL; similarly, in malfunctioning kidneys, or infected stones.

If the patient is grossly obese, has a spinal deformity, a branched collecting system, a horseshoe or malrotated kidney, the procedural difficulty is increased. The might be a controversy about obesity, however at least the authors experienced that

Table 3. Complications in PCNL. An overview of the literature.

COMPLICATION	CLAVIEN CLASSIFICATION	INCIDENCE (REFERENCES)
Extravasation	Grade I	7,2% (n=582, [20])
Renal hemorrhage	Grade I / II	0,6% (n=318, [21]) 1,4% (n=1854, [23]) 0.3% (n=315, [2]
Transfusion	Grade II	11,2% (n=582, [20]) 17,5% (n=103, [26]* 0.0% (n=315, [2]
Acute pancreatitis	Grade II	0.3% (n=315, [2]
Fever	Grade II	21,0% (n=81, [25]) 21,4% (n=103, [26]* 22,4% (n=582, [20]) 32.1% (n=315, [2]
Sepsis	Grade IV	0,8% (n=582, [20]) 0,97% (n=103, [26]* 2,2% (n=318, [21]) 4,7% (n=128, [27]) 0.3% (n=315, [2]
Colonic injury	Grade III a/b	0,2% (n=1000, [18]) 0,2% (n=582, [20]) 0,29% (n=5039, [28]) 0,8% (n=250, [30]) 0.0% (n=315, [2]
Pleura injury	Grade III	2,3% (n=128, [27]) 3,1% (n=582, [20]) 0.0% (n=315, [2]
Perioperative mortality	Grade V	0,3% (n=318, [20]) 0,3%, (n=582, [21]) 0,78% (n=128, [27]) 0.3% (n=315, [2]

*multitract PCNL due to large staghorn stones gross obesity increased the risk of complications: It is technically more demanding (i.e. length of nephroscope sheath) and the patients usually suffer from associated diseases (i.e. diabetes mellitus).

Large stone size will increase rate of complications.

2. ADEQUATE EQUIPMENT

a) Instruments for PCNL

Urologists have to check all instruments (i.e. dilators, graspers, nephroscope) properly prior to the procedure; in particular, the functionality of the lithotriptor devices (i.e. ultrasonic, ballistic, laser). Moreover, it is advisable to have at least two different devices for stone disintegration available.

b) The type of needle and sheath

Needles with a facette-cut tip are preferable because of improved visibility during ultrasound scanning [33]. The use of a flexible silicone sheath enables easier manipulation when inserting the guide-wire.

c)Technical aspects

1. Puncturing of the collecting system

While in the United States and United Kingdom, renal access is established by radiologists, in some European centers, urologists puncture by themselves, using combined ultrasound/fluoroscopic guidance systems such as a sector scanner or semicurved scanner [47] . This technique allows a more sophisticated approach, as it is possible to determine the axis of the kidney exactly and, by injecting a contrast dye, ensures that the needle is correctly positioned (**Figure 1**).

It is also possible to perform an ultrasound guided free-hand puncture using a sector scanner and with the patient in an oblique supine position, but this free-hand technique, and its use particularly in the oblique supine position, requires a greater degree of experience than when using a fully-guided ultrasound system.

All ultrasound-based techniques do not require any additional diagnostic imaging techniques, such as CT urogram. However, these might be useful to determine the choice of the calyx for optimal stone manipulation.

Usually, a subcostal approach is used, although a supracostal approach is preferred for certain indications like superior calyx stones, staghorn stones or stones of the proximal ureter. A significant chest complication rate of around 5% has to be taken in mind when choosing the supracostal approach [17].

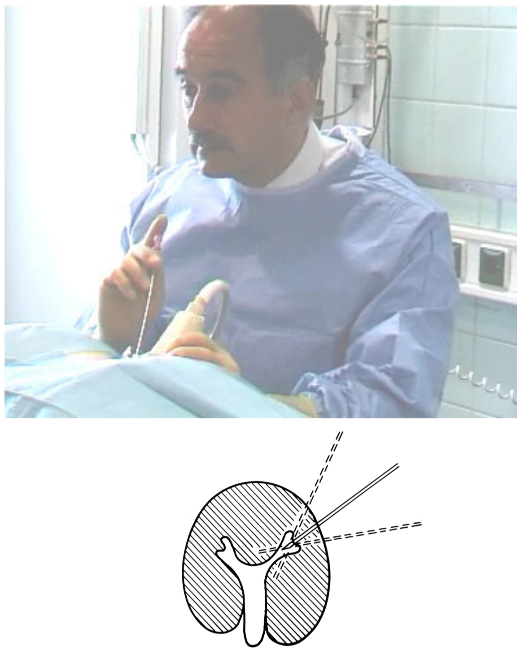


Figure 1. Puncturing of the collecting system
a) Free-hand technique of ultrasonic guided puncture
b) Ideal renal puncture through calyx shown by the medial needle. Even though puncturing through the papilla, a wrong angle of the needle can result in repuncturing the parenchyma after entering the collecting system (dotted needles).

2. Placement of the guide wire

It is important to avoid perforation of the renal pelvis when introducing the guide wire after puncturing the calyx. In the literature perforation rates up to 7,2% (Clavien I/II) are reported [15]. This potential problem can be avoided by using a J guide wire, which has a soft tip. We prefer guide-wires with an inner core. It is also vital to incise the fascia parallel to the needle in order to avoid problems with the dilatation process. In some problematic cases (i.e. previous renal surgery) it may be preferable to use a more rigid guide wire such as the Lunderquist wire.

d) Complications related to the access

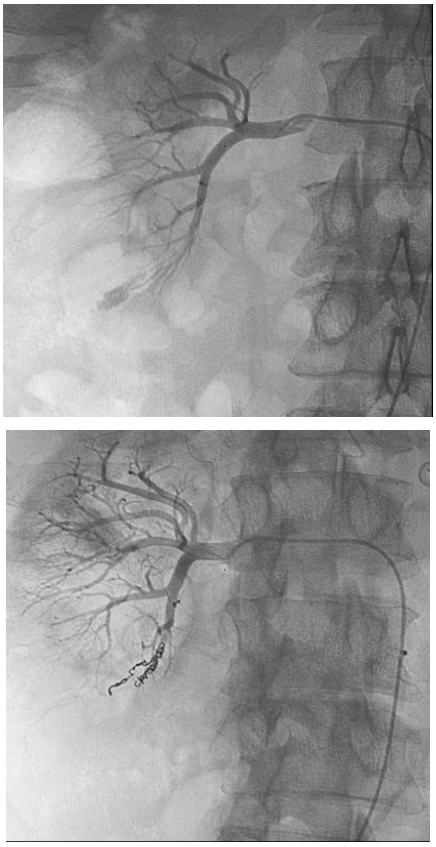
1. Parenchymal bleeding

Common source for a bleeding during PCNL is the nephrostomy tract itself. These bleedings can be prevented if the kidney is strictly punctured through a calyx and a minimal angulation of the dilation system and the nephroscope shaft (Fig. 2). To avoid extensive angulation, a flexible nephroscope should be used for stone parts in other calyces. If bleeding significantly impaires endoscopic view, the procedure should be terminated; a nephrostomy should be placed [21] and clamped for 40-60 minutes to provide a tamponade within the collecting system to provide haemostasis (Clavien I). The second procedure can be carried out after 24 or 48 hours if macrohematuria has cleared in order to provide optimal precondition for the re-intervention. In a case of persistent relevant bleeding (Clavien III), a renal angiography should be carried out with the possibility of a superselective embolisation (**Figure 2a, b**).

Lacerations (Clavien I/II) can occur during the dilation of the tract and during definitive surgery in terms of stone removal. Fluoroscopic monitoring of the dilation process (metal dilator, balloon) can minimize the risk of laceration. If lacerations occur, intraoperative bleeding can be induced and is likely to hamper the further procedure. If significant bleeding in terms of decreased visibility or haemoglobin-relevant bleeding occurs, a nephrostomy tube should be placed and a re-intervention planed 48 hours later. The nephrostomy may tamponade further bleeding.

Lesions of the vascular system can also lead to *late bleeding complications* arising from pseudoaneurysm or arteriovenous fistulas (Clavien III) and usually need therapeutic intervention like embolization [23] (**Figure 3 a/b**). These complications are rare but can occur up to three weeks after PNL. Sasrivastava et al. identified stone size as a risk factor for these complications. Urologists have to keep them in mind, they are present in around 1% of patients [23].

Figure 2. Renal vascular anatomy. Puncture of renal pelvis or through caliceal infundibulum leads to an increased risk of vascular injury.



Figures 3 a/b. Arterial bleeding after PCNL from a lower pole artery (A) and occlusion of the lower pole artery by super selective coiling.

2. Organ injuries

PLEURAL INJURY

The risk for an injury of the pleura and the lung increases if the puncture is above the 12th rib (ie. by 10%). Puncture using ultrasound control and/or a puncture after exhalation may prevent pleural injury. If the puncture is through the pleura, extravasation of irrigation fluid or the entry of air into the pleural space should be prevented. If a hydro- or hematothorax (Clavien III) occurred, a chest tube has to be inserted. Thoracoscopy or thoracotomy is only very rarely necessary. Of course, the preference of lower calyx access in combination with flexible nephroscopy and / or extracorporeal shock wave lithotripsy practically avoids this complication [2,7,9,14,16,17].

INJURY OF DUODENUM, COLON AND OTHER ABDOMINAL ORGANS

More than thirty published papers are reporting on colonic injury (Clavien III) during PCNL. The largest, recently published series of 5039 procedures [28] identified several risk factors including left side procedure, horseshoe kidney and advanced patient age. The risk of perforation can increase up to 1%. Further risk factors represent an inflated colon and a very thin patient. Additionally, the urologist should be cautious if the patient has had previous bowel surgery, which increases the potential risk for injury of the duodenum or the colon. If an extraperitoneal perforation occurres, the gastrointestinal tract has to be separated from the urinary tract (**Figure 4**). Therefore a catheter has to be placed into the colon and conservative treatment with antibiotics can be performed. Minimally invasive treatment of colonic injury is successful in most cases [28-31]. In case of an intraperitoneal perforation (Clavien IIIa), open surgery has to be performed immediately. The risk of puncturing of the colon can be minimized by the use of sonographic control (visualization of the bowels) and correct patient selection (as the risk factors have been identified).

An injury of the spleen is very unlikely if the puncture is below the 12th rib, however splenomegaly increases the risk. The injury of the spleen can be prevented by puncture under ultrasound control. Spleen injuries (Clavien IIIa) are in most cases associated with relevant bleeding and therefore emergency exploration and splenectomy have to be performed.

Figure 4. Colonic injury after failed renal puncture for PCNL. Clearly, filling of the intestine by contrast agent is detected after filling of the nephrostomy.

e) Complications related to the stone removal

1. Septicemia

Septicaemia (Clavien IV) can occur as a result of infection introduced via the access to the kidney, or if the stones are infected. Following PCNL, fever is significantly higher and more frequent in the cases with infected urinary stones than in those with sterile stones [31]. Renal insufficiency increases the risk. Prophylactic antibiotics and draining of a pyonephrotic kidney before performing PCNL is mandatory [9]. Antibiotics can be applied by single-dose or short-course antibiotic prophylaxis protocols with no significant differences between both in case of sterile urine [22]. The duration of surgery and the amount of irrigation fluid are significant risk factors for postoperative fever [25].

It is also important to prevent a high pressure in the collecting system [31] and to keep the duration of operating time to a minimum (i.e. <90 minutes).

The literature reveals sepsis rates between 0,97% [22] and 4,7% [23]. In the Mannheim series, one patient (0,3%) died from urosepsis (Clavien V) despite adequate antibiotic treatment [2]. In cases where septicemia has occurred, the patient should receive intensive care therapy including forced diuresis, antibiotic treatment, optimal renal drainage and electrolyte control [2,9]. The observed pathophysiological origin of an observed acute pancreatitis (Clavien II) remains unclear.

2. Extravasation and fluid absorption

The common source for extravasation and fluid absorption (Clavien II) is a perforation of the collected system. Methods of prevention include to manipulate only under x-ray or endoscopic control, to use an open or continuous flow system, and to use normal saline as irrigant. However, even with these precautions a high-fluid volume syndrom may develop. Therefore, if the fluid discrepancy (inflow / outflow) exceeds 500ml, the procedure should be stopped and a nephrostomy be placed. Monitoring of the serum electrolytes mandatory.

Urine extravasation following PCNL (Clavien II/III) may occur in case of severe perforation of the collecting system or the nephrostomy tract (extraperitoneal). Problems are flank pain or signs of infections under antibiotic treatment. Percutaneous drainage of the urinoma and the collecting system (i.e. additional double- or mono-J-stent) may become necessary.

IV. CONCLUSIONS

To avoid the complications associated with percutaneous endourological procedures and to ensure optimum outcomes for patients urologists need to consider a number of factors when planning or performing PCNL. Therefore, training and experience of the urologist are critical, as it is careful patient selection, accurate positioning, and the use of the best available instruments. Evidentally, there is a lack of randomized studies concerning the management of complications after PCNL.

RECOMMENDATIONS

IN PREVENTING COMPLICATIONS

Recommendation	*Level of Evidence*
Single dose antibiotic treatment is equivalent to short-term prophylaxis in case of sterile urine culture	**Ia/B**
In case of staghorn stones, despite sterile urine culture one may find purulent puncture during PCNL (3-10%). Surgery has to be delayed	**IIa/B**
Ultrasound guided punctures minimizes the risk of colonic injury	**IV/B**
The risk of hydrothorax and overall risk is higher with supracostal punctures (ie. 2-4 %)	**IIa/B**
Most bleedings after PCNL can be managed conservatively	**IV/B**
Multiple tracts are associated with a significantly higher rate	**IIa/B**
Most of delayed bleedings following PCNL are due to AV-creation	**III/B**

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F. TRAINING

I. PERCUTANEOUS NEPHROLITHOTOMY

1. INTRODUCTION

In an active Urological department, 30% of the surgical working load was caused by renal and ureteral stones [1]. Percutaneous nephrolithotomy (PCNL) has a defined role in the treatment of renal stones, specifically for large stones [1] **(Evidence Level 2/B)**. PCNL is performed worldwide in 5% of renal stone surgery [1]. The last European survey has shown that PCNL is widely performed with a mean of 16.8 percutaneous procedures a year for the respondents [3] **(Evidence Level 3b/C)**. Thus over more 25 years of worldwide practice, PCNL remains a milestone technique with very low major complication rate and a very high success rate. All these data bring the motivation to learn this procedure.

However there is a well known steep learning curve for PCNL and Urologists remain reluctant to this surgery, regarding the postoperative hemorrhage (1%) or organ perforation (0.3-3%) risks [3-6] **(Evidence Level 3a/B)**. Indeed the major and difficult step of PCNL is the ability to obtain an appropriate access to the renal cavities which reduces the risk of vascular injury and leads to a better stone free rate [7] **(Evidence Level 3a/B)**. Therefore the most important issue among surgeons concerning PCNL is its learning curve [8] **(Evidence Level 3b/C)**.

There is very few data on the teaching of renal percutaneous access and PCNL. In addition to the apprenticeship, inanimate simulators, virtual reality simulators and robotics provide new perspectives to the 21st century.

We have reviewed the literature regarding the training for PCNL and the number of procedures per year required to maintain a surgical proficiency. We have matched keywords, throughout Medline, MeSH and Cochrane databases: renal or urinary stone/ percutaneous / nephrostomy/ endourology/ educational/ training / learning curve / expertise/ skill / residency/ practice/ survey/ simulator/ robotics. For this topic we have defined, if possible, levels of evidence based on ICUD and WHO recommendations.

2. PCNL: SPECIAL CLINICAL FEATURES

a) Anatomical features:

The renal cavities have a huge variability in their three dimensional (3D) presentation. Despite main calices are more or less in the same area in orthotopic kidney, two identical caliceal 3D positions are not likely to be found. Thus it is not easy to standardize a very precise and reliable technique without the help of an expert in order to adapt the procedure to the patient anatomy.

Percutaneous access to the kidney requires a true expert system, using or not additional tool as computer. Currently the routine 3D computer tomography (CT), performed before most of PCNL procedures, provides excellent representations of this anatomy and allows a preplanning step [9] [**(Evidence Level 3b/B)**.

However the 3D rendering shape of the cavities is obtained by the maximum intensity projection (MIP) which does not show the relationship between the calices and the different organs, as colon in particular, and the kidney motion. Limitation with robot-assisted percutaneous renal access (PAKY) is related to the mobile kidney within the retroperitoneum during respiratory variation and to the various tissue interfaces that the needle must traverse before reaching the collecting system (6 [3a/C]).

Additional real time control, as ultrasound actually, should be the safest technique in an expert system [10-11] **(Evidence Level 3b/C)**. Montanari et al reported a 98% success rate in their experience of 330 percutaneous renal access procedures under ultrasound fluoroscopic guidance[10]**(Evidence Level 3b/C)**. Urologist has to be the expert, feeling the different interfaces from the skin to the cavities and the resistance during the motion of the nephroscope and tools.

b) Complex cases

PCNL is mostly performed for large or complex stones in the departments of Urology where it has to be taught. Failures of ESWL in the moderate stone cases (10-20 mm) are currently proposed to flexible ureteroscopy in the academic stone centers. Thus PCNL is more and more indicated to complex cases. Even if cases of increased complexity should be faced during the learning process in order to measure progress in training [12], the number of simple cases may be insufficient at the initial phase.

3. MOTIVATIONS TO LEARN

Percutaneous renal access is an integral step in percutaneous renal drainage and percutaneous nephrolithotomy [13]. Obtaining renal access in the operating room remains a challenging task for many urologists. Inaccurate placement of the needle can risk injuring the kidney and adjacent organs, thus compromising the planned percutaneous procedure, as well as the clinical outcome of the patient ([6] **(Evidence Level 3a/C,** [7] **(Evidence Level 3a/B)**.

A recent survey revealed that only 11% of urologists performing percutaneous nephrolithotomy routinely obtained percutaneous access themselves [8] **(Evidence Level 3a/B)**. Reasons for this trend may include lack of training, comfort level and other parameters as better equipment in Radiology or extra time to obtain access [14]**(Evidence Level 3b/C)**. But the development of techniques to establish a safe and reliable percutaneous access has provided significant progress in percutaneous intrarenal procedures [8] [**(Evidence Level 3b/C)**. Urologists are increasingly obtaining access themselves, as this eliminates reliance on a second «surgeon» and increases flexibility with respect to procedure timing and the location of the access tract [13].

Today Urologists still have to learn how to perform safely and effectively the percutaneous access by themselves [14] **(Evidence Level 3b/C)**. Training in the more technically challenging aspects of endoscopic lithotripsy must be encouraged, but the training on open surgery should be at the same time on the endoscopic, laparoscopic or extracorporeal training [15-17].

4. DIFFERENT FORMS OF TRAINING

a) Book, video and apprenticeship

The traditional method of acquiring surgical skills is by apprenticeship and involves an extensive period of training with patients.

The learning process of surgical skills begins with the theoretical approach written in books and journals. The next step is mentored practice on patients until the moment that the trainees were considered mature enough to perform the surgical procedure by themselves. Nevertheless, an enormous gap exists between what can be read in books or taught by experts and the reality encountered when operating on patients. Since the introduction of audiovisual technology, after theoretical learning the apprentice has had the opportunity of watching recorded real procedures before switching to real practice.

Surprisingly few models have been developed to train urologists in percutaneous renal access [13]. Animal models allow surgical training in an environment more akin to reality. Porcine model has been used but training on animals is difficult to organize, not so close to human reality and very high cost.

Thus surgical simulation is increasingly being considered for training and testing. Laguna et al have recently published an exhaustive review on this topic. Two types of surgical simulators exist: inanimate and virtual reality simulators [12].

b) Inanimate simulators

Hands-on intraoperative training continues to be the primary method for learning percutaneous renal access. However, bench model and simulator-based education offer a useful adjunct [13-18].

Hacker et al have used an ex-vivo perfused porcine kidney, a chicken carcass, artificial stone and all the equipment required for a PCNL procedure [19] **(Evidence Level 3b/C)**. The model is low cost. But introducing animal organs in an operating room (OR) and the lack of kidney motion will limit application of this bench model.

Very few articles have assessed whether the laboratory proficiency acquired in inanimate models correlates with improved performance in humans [12].

c) Virtual reality simulators

Virtual reality (VR) is a computer-generated environment that reproduces detail to mimic reality. Model-based and virtual reality simulation is gaining interest as alternative training, allowing repetitive practice in a stress-free environment where mistakes do not adversely affect patients.

Most of the literature is related to GI endoscopy, laparoscopic surgery and ureteroscopy, rigid and flexible [18, 20-21] **(Evidence Level 2/B)**.

Felsher et al have recruited 75 surgical attendings, fellows, and residents in order to compare experienced GI endoscopists and beginners [20] **(Evidence Level 2/B)**. Showing that experienced attendings are better than residents, the simulator appeared to be valid. But these results did not show any evidence of an educational impact.

In a randomized study, Chou et al have reported that incorporating simulators, inanimate or virtual reality, into the preliminary training of urology residents may improve their initial clinical performance to practice rigid ureteroscopy [18] **(Evidence Level 2/B)**.

In a comparative study on 16 residents and 16 students, despite VR training, medical students were unable to perform cadaver ureteroscopy comparably to resident. Ogan et al concluded that VR training is unable to override the impact of clinical training, although it may help shorten the learning curve early in training [22] (Evidence Level 2/B).

To our knowledge there is no data regarding the evaluation of virtual reality simulators for PCNL as it was done for ureteroscopy [23]. A virtual reality simulator which may aid in training for PCNL procedures is currently being developed. The PERC Mentor is still in evaluation [13].

Virtual reality simulators have a real future in this field. Simulation must provide tactile feedback in order to provide an optimal surgical environment. In spite of current limitations, there is no doubt that improvements in computer will provide the right tactile information ([12][R]). New kinds of force and visual feelings should be incorporated into the simulators which allow for an objective assessment of the trainee's skills [12]. On the other hand, the fact that real instruments can be incorporated into the endoscopic simulation makes it easier to generate a realistic sensation of pressure and force [12].

In the future they will probably be an important preoperative tool simulating the pathology to be treated as well as the results of the planned procedure to be performed [12].

Before being included as a routine procedure, expensive new technologies should bear the burden of proof of their effectiveness and reliability. The translation of virtual reality (VR) skills into clinical endoscopic proficiency has not been demonstrated. We do not know the transfer efficiency rate or the ratio of how much time spent training in the simulator is equivalent to time learning on the real task [12].

d) Robotics

Robots may help Urologist to get the calix of choice, quicker and safer.

The utilization of robots in surgery was first explored in the 1980s in neurosurgery and orthopedic surgery. The earliest application of robotics to urologic surgery began in 1989 applied for transurethral resection of the prostate.

Su et al have tested on patients the percutaneous access to the kidney (PAKY), associated to a remote control module (RCM) which allows a urologist to remotely align the percutaneous needle along a selected trajectory path under fluoroscopic guidance using the superimposed registration principle, while minimizing radiation exposure to the hands. In this open study, PAKY-RCM seemed to be a reliable and safe robot with a drop of 50% in the time to access the cavities compared to the manual procedure[6] **(Evidence Level 3a/C)**. The study did not evaluate the training impact of this robot.

Another way to proceed is to use a real time ultrasound probe in projection on registered fluoroscopic image recorded at the time of the puncture. This technique improves the caliceal access which takes account of the renal environment while minimizing the radiation exposure to less than few seconds. It is also an excellent educational tool, teaching to novice and young surgeons the spatial anatomy while feeling of the needle progression [11] **(Evidence Level 3b/C)**.

The ideal system could be a computer-based tracking system to automatically adjust and account for changes in the position of the target calix caused by tissue deformation during needle advancement as well as by respiratory movement [6] (Evidence **Level 3a/C)**.

In conclusion numerous devices have evolved as educational tools in a variety of fields. Whether these tools can be used for validation of physicians' skills has yet to be determined.

Urologists have to embrace the new training technologies and remain active participants in their applications to the care of the urologic patient [6] **(Evidence Level 3a/C)**.

5. LEARNING CURVE

The surgical learning curve remains primarily a theoretical concept; actual curves based on surgical outcome data, mostly in the field of radical prostatectomy, are rarely presented[24]. PCNL procedure has a steep learning curve leading to higher complication rate in the beginning of the experience [25] **(Evidence Level 3/C)**.

The first aim is to determine surrogate markers in order to evaluate the surgical expertise and the number of procedures needed to gain the surgical competence in the PCNL procedures. In urology, studies defining the learning curve are mostly focused on cancer surgery and specifically on laparoscopic procedures [8]. There are very few publications on this topic.

To define the learning curve for percutaneous nephrolithotomy there are some potential surrogate markers. Although the most relevant clinical end points for PCNL are the stone clearance and the complication rate, they may not be the best tools for assessing the learning curve in the PCNL procedure [8]. Allen et al used operation and fluoroscopic screening times and also radiation dose. With these markers the learning curve of a single surgeon suggests that competence at performing PCNL is reached after 60 cases and excellence is obtain after 115 [26] **(Evidence Level 3b/C)**. Taniverdi et al have studied prospectively, using many parameters, including stone free rate and complications rate, the learning curve of one surgeon. The two markers showing an improvement were the operation and fluoroscopic screening times. No further decrease in the operation time was observed after case 60. A drop in the mean fluoroscopy screening time was observed from a peak of 17.5 ± 3.2 min in the first 15 cases to 8.9 ± 4.3 min for cases 46 through 60. This decline continued in cases 61 to 104, but the decline was not significant. Authors suggested that competence in PCNL is obtained after 60 cases [8] **(Evidence Level 3b/C)**.

However the number of PCNL required to gain the surgical proficiency in treatment of renal stone disease is uncertain [8]. Residents are comfortable with percutaneous access after an average of 21.2 ± 4.5 access procedures during residency [14] **(Evidence Level 3b/C)**. Urologists who were comfortable performing percutaneous access after residency performed significantly more percutaneous access procedures during residency than those who were uncomfortable (24.4 ± 5.6 procedures and 10.6 ± 3.1 procedures respectively, p = 0.046) [14] **(Evidence Level 3b/C)**. Therefore, authors suggest that performing 24 or more percutaneous access procedures during residency may increase resident proficiency immediately after residency.

Another objective is to determine if the practice after residency is related to the training. Bird et al reported an interesting survey of 1102 urologists regarding the treatment of large renal stones: from the 564 responders, 73% of the urologists were comfortable performing percutaneous nephrolithotomy and those trained to perform PCNL during residency were more often comfortable with this procedure [27] **(Evidence Level 3b/C)**.

It seems quite clear that new forms of training have to be incorporated into surgical skills learning. Cases of increased complexity should be faced during this process in order to measure progress in training [6].

6. EVALUATION AND GRADING

With colonoscopic simulators significant differences in performance were shown between the experienced and beginner groups. Further validation studies are needed to determine whether it may be used in the future for qualification and certification purposes [20] **(Evidence Level 2/B)**.

An Endoscopic Surgical Skill Qualification System in urological laparoscopy has started in Japan [28]. This qualification system is based on assessment by 2 referees who view videotapes on the entire laparoscopic procedures. The aim of this process is to promote safer surgical procedures.

As soon as simulators, integrating complex cases, will be available, endourological qualification system could be applied for PCNL in the future.

7. CONTINUING EDUCATION

The maintenance of sufficient skills in percutaneous access may require continuing education to refresh the urologist's technique after residency [14]. Emphasis should be placed on providing continuing education opportunities to maintain competency in this important technique.

Urologists trained in percutaneous access were significantly more likely to perform percutaneous surgical procedures than those not trained in percutaneous access (88% and 38%, respectively, p = 0.04) [14] **(Evidence Level 3b/C)**. But only 27% of urologists trained in percutaneous access continue to perform percutaneous renal access compared to 11% of those untrained (p = 0.33) [14] **(Evidence Level 3b/C)**.

The survey conducted by Lee et al has shown that urologists trained in access perform a mean of 14 ± 4 percutaneous renal procedures annually while those untrained perform 3.3 ± 1.7 procedures (p = 0.02) [14] **(Evidence Level 3b/C)**. These results are similar to those of the European survey published by Michel et al, showing a mean of 16 PCNL performed per year after the training phase. Thus it is suggested that a minimum of 14-16 PCNL per year could be required to maintain urologist's competence. There is a relationship between training in percutaneous access, and a significant increase in the number and complexity of PCNL being performed by the urologist [14] **(Evidence Level 3b/C)**.

However, as there are no validated surrogate markers to define the learning curve, there are no data on continuing education markers. Cases of increased complexity could be the second line of the training, performed with experts in academic urological centers. In the future simulators and robots will probably be an important tool simulating the pathology to be treated and useful to the continuing education [12].

II. TRAINING IN A STONE CENTER

Training in the more technically challenging aspects of endoscopic lithotripsy must be encouraged [17].

The number of simple PCNL procedures has a trend to decrease in the era of flexible ureteroscopy and represents about 5 – 10 % of all the treatment for urinary stones. PCNL is mostly performed for large or complex stones in the departments of Urology where it has to be taught. Regardless the percutaneous access, PCNL has become more and difficult to learn.

A resident has to perform about 24 PCNL to obtain a good proficiency during his residency. Taking account of the complex cases, procedures performed by the seniors, an Academic Department of Urology, with one new resident per year, has to recruit about 500 cases of renal stone cases per year in order to ensure a training program.

The maintenance of sufficient skills in the treatment of renal stones may require continuing education to refresh the urologist's technique after residency and regular practice, with about 15 PCNL performed each year [14].

These data lead to conclude that performance is directly related to the volume of activity of each surgeon per year. Stone Centers providing all the endoscopic treatment options seems to provide the best conditions to ensure a sufficient volume of patients recruited.

Currently there is a lack of data on how many procedures needed to be performed to gain and to maintain the surgical competence in the PCNL procedures.

Continuing education in percutaneous access may benefit from the incorporation of teleproctoring, teleconferencing or virtual reality simulation [14,29] **(Evidence Level 2/C)**.

Regardless PCNL which is currently the most complicated technique to teach, flexible or rigid ureteroscopy has the advantage of a larger recruitment and a simpler technique. Ureteroscopic virtual simulators are validated.

In conclusion safety and efficacy is likely related to the recruitment of the center, allowing the best equipments, but is also related to the training during residency and the continuing educational program followed by the attending.

III. CONCLUSIONS

Literature on the topic of training and the recruitment required for each center as well, has a very low level of evidence. Some original publications above-mentioned, based on randomized studies, have a level of evidence 2 in the ICUD/WHO system, but there are limited to the evaluation of new techniques or tools in the field of training. Their results have to be confirmed by larger scale studies.

However training is obviously recommended. Learning curves published for PCNL and ureteroscopy are coherent with a plateau gained after 40 to 60 procedures performed solo.

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Management of Ureteral Calculi

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CONTENTS

Management of Ureteral Calculi

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A. INTRODUCTION

H-G TISELIUS

The medical care of patients with ureteral stones is an important part of everyday urology. An acute stone colic caused by an obstructing stone in the ureter is probably the most common way in which stone disease presents. As a result of the usually very intense pain, these patients almost always will require medical attention and hospital admittance is common. A major fraction of ureteral stones pass spontaneously with or without pharmacological treatment. Whether a ureteral stone will pass spontaneously or not is to a large extent determined by the size of the stone and it is generally considered that stones with a diameter of not more than 5 mm have a very good chance of spontaneous passage, but other factors also play a role and the stone passage might take as long as 40 days [1]. For small stones that do not pass spontaneously or cause severe symptoms or for stones that have a size that makes spontaneous passage unlikely several treatment options are available for their active removal. We have the traditional open/incisional surgical procedures, percutaneous surgery (PCNL), ureteroscopic surgery (URS), extracorporeal shock wave lithotripsy (SWL) and laparoscopic surgery, just to mention the procedures in the order they have been introduced clinically.

Epidemiological data that show the real incidence, prevalence and need of active stone removal are difficult to find in the literature. The explanation for that is that these patients are taken care of at several levels of the health care system, many in an out-patient setting beyond statistical control and without standardised recordings for a defined population.

At the time of diagnosis/treatment a large proportion of urinary tract concrements are present in the ureter, but there are obvious geographical variations. Thus Schneider and coworkers [2] found ureteral stones in 48-60 % of their 47 000 patients in Germany. In contrast only 29 % of patients in Saudi Arabia had stones in the ureter [3].

There are, however, several reports that indicate an increased incidence of stone disease [4]. Moreover, it is likely that stones previously left for spontaneous passage, today more frequently are removed actively because of the ease by means of which such a step can be carried out. In an Australian population the conservative treatment of patients remained at a fairly constant level around 59 % during the period 1980-1997 [5]. This level of conservative treatment is much lower than that reported from a Swedish population 1969-1970 whereby spontaneous passage of stones was recorded in 87.5 % of the men and 81.5 % of the women [6]. In another Swedish study from 1981 the annual incidence of stone colic was estimated to approximaly 1400 for population of one million. At that time active stone removal with surgery was applied in only 9 %, which is a level that apparently is lower than that usually recorded today.

According to recent statistics from the catchment area (Stockholm, Sweden) of one of the authors, patients with urinary tract stones fulfilling the indications for active stone removal during 2000-2007, 2305 had their stones in the kidney and 1729 in the ureter. Accordingly 43 % of the patients had their stones in the ureter. There was a small annual variation with a range between 38 and 47 %. At the time of treatment 46 % of the ureteral stones were found in the proximal ureter, 16 % in the mid and 38 % in the distal ureter.

In a defined population of 1.92 million in the Stockholm area, the number of patients in whom active stone removal was carried out during 2006 was 469; this means a total of 244 for a population of one million. The recordings in this particular population are of interest inasmuch as all patients subjected to active stone removal were accounted for, the number of patients is in good agreement with recordings and assumptions made previously [7, 8], whereby approximately 200-250 patients with ureteral stones would fulfill the indications for active stone removal of ureteral stones. In addition it needs to be emphasized that obstructing ureteral stones are not uncommon following SWL of stones primarily located in the kidney. Although geographical variations might be considerable these figures nevertheless give an idea of the impact that removal of ureteral stones has in urological practice.

The general recommendation usually is to proceed to active stone removal when the stones have a diameter exceeding 5 mm.

B. ANATOMIC CONSIDERATIONS AND IMAGING PROCEDURES

S. Nakada

The ureter is a luminal organ with a protective and functional urothelium, an underlying mucosal layer that contains sensory and motor nerves and capillaries, a smooth muscle layer, and an outer layer of adventitia. Contraction of the smooth muscle results from electrical activity altering the membrane potential [9]. While these layers are consistent along the course of the ureter, the proximal ureter has a thinner layer of muscularis and may be more susceptible to damage during ureteroscopy.

The urothelium plays a critical role in ureteral function by forming a protective barrier and participating in cell-to-cell communication with ureteral smooth muscle, neurons and capillaries in response to changes in the luminal environment through release of mediators [10]. Vascular and neuronal tissues in the mucosa integrate the ureter with other organ systems. Interruption of the luminal barrier due to edema, stretch or inflammation can expose the mucosal layer to chemical stimuli which are then interpreted centrally [11]. The smooth muscle cells provide contractile function (inner, helical layer) as well as structural support (outer, mesh-like layer).

Ureteral blood supply and extrinsic anatomy also contribute to ureteral stone passage. Blood supply for the ureter above the pelvic brim arises medially from multiple sources, including the renal artery, gonadal artery, abdominal aorta and common iliac artery. Below the pelvic brim, arterial inflow arises laterally from the internal iliac arteries and its branches. From an extrinsic standpoint, the iliac vessels and ureterovesical junction provide relatively narrowed locales for ureteral stone passage. Moreover, the presense of any ureteral stricture disease pose significant obstacles to stone passage. Downstream ureteral obstruction can significantly alter ureteral stone passage and subsequent medical and surgical management.

The ureter may be anatomically divided into 3 segments, the proximal ureter (the ureter above the sacral bone), the middle ureter (the ureter aligned with the sacral bone) and the distal ureter (the ureter below the sacral bone). The exact delineation of the various segments varies slightly between reports (**Figure 1**). A section from 2 cm above to 2 cm below the sacroiliac joint was used to define the mid ureter in one study [12]. Other authors have suggested an extension of the mid ureter from the

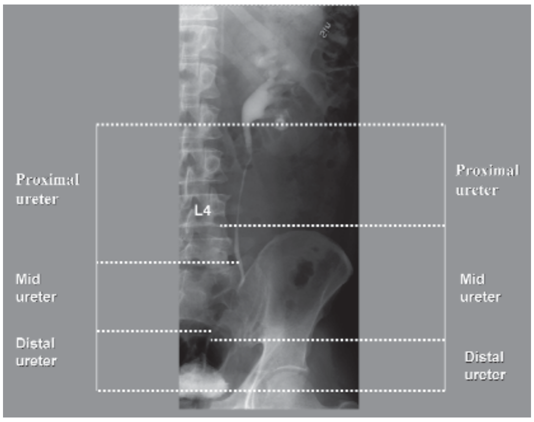

Figure 1. Anatomical sections of the ureter.

level of the fourth lumbar vertebra (which roughly corresponds to the pelvic brim) to 1 cm below the sacroiliac joint [13].

Proximal ureteral stones are often best treated with shock wave lithotripsy due to ease of targeting, however new generation flexible ureteroscopes have made this technique safe and effective. The iliac vessels may prove problematic in mid-ureteral stones, due to the fact that ureteroscopic manipulations may be more complicated. Difficulty imaging mid-ureteral stones and the necessity of prone positioning for shock wave lithotripsy further confound stones lodged in the middle ureter [14]. Although many ureteral stones obstruct at the ureterovesical junction, distal ureteral stones are most amenable to ureteroscopy or shock wave lithotripsy.

Various imaging techniques are available to diagnose and manage ureteral stones. Renal ultrasound can be used to detect hydronephrosis; however the risk of non-dilated obstructive uropathy as well as the possibility of nonobstructive congenital hydronephrosis can be confounding [15].

Abdominal plain films are useful in circumstances in which there is a known radioopaque stone in the process of passing. Generally, renal ultrasound and plain abdominal radiographs represent a low yield, low risk assessment tool.

Intravenous urography provides anatomic data regarding the collecting system and discriminating data for surgical planning, as well as providing evidence of quantifiable obstruction. Unfortunately, intravenous contrast is required for this procedure. Noncontrast CT is highly sensitive for urolithiasis, and may provide more data regarding stone density and subsequent stone composition for the practicing urologist without requiring intravenous contrast [16]. Noncontrast CT is therefore a most suitable study in the emergency room setting for diagnosis and initial management, and in the future may become the definitive imaging study for all stone disease [17].

Diuretic renography is a quantitative, sensitive measure of ipsilateral renal function and ureteral obstruction. However, renography offers little anatomic information and thus is a limited tool for surgical planning [18]. Finally, retrograde pyelography can be useful, either prior to ureteroscopy or to verify the presence of radiolucent stones. Notably, with the increasing availability of helical CT, retrograde pyelography has become less and less desirable.

C. ACUTE STONE COLIC

M. Gallucci

Renal stone colic is a common and complex clinical problem. Ureterolithiasis appears to be the most frequent cause of this condition and affects 3-5% of the entire population in industrialized countries. Renal colic is defined as acute flank pain which might radiate to the groin, lower abdomen or external genitals due to the passage of a ureteral stone. The major pain component in renal stone colic is caused by dilatation of the renal pelvis and calices and the condition might be associated with nausea, vomiting, dysuria and hematuria [19-24].

The best imaging study to confirm the diagnosis of a ureteral stone in a patient with acute flank pain is unenhanced, helical CT of the abdomen and pelvis. The sensitivity of CT was 96%, as compared with 87% for urography [24-28].

Urgent intervention for renal colic is indicated in a patient with an obstructed, infected upper urinary tract, impending renal deterioration, intractable pain or voimiting, anuria, or high-grade obstruction of a solitary or transplanted kidney. When urgent interventation is unnecessary, the clinician must decide whether to follow a patient expectantly for spontaneous stone passage or to perform an elective interventation [29-37]. The relief of pain is usually the most urgent step in patients with acute renal colic. EAU Guidelines [38] suggest that pain relief can be accomplished by administration of the following agents: diclofenac, ketorolac, ibuprophen, hydromorphone, methamizol, pentazocine, and tramadol. When diclofenac was compared with ketoprofen in a randomized study, no differences were recorded between the two substances. In addition to a direct effect on pain, nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors provide effective analgesia by blocking afferent arterioral vasodilatation, thereby reducing diuresis, edema and ureteral smooth-muscle stimulation. When NSAID agents are used for renal colic, pain relief is achieved most rapidly by intravenous administration [39], but intramuscular injections are also effective and sometimes a more convenient form of treatment for a patient with an intensive colicky pain. If NSAID agents, COX-2 inhibitors or desmopressin is used, overhydration should be avoided, since the objective of treatment is to reduce the pressure in the collecting system and ureteral spasm. Hydromorphone and other opiates without simultaneous administration of atropine should be avoided because of the increased risk of vomiting. The role of diuretics and high volume fluid therapy in acute ureteric colic should be examined to determine their safety and efficacy in facilitating stone passage.

According to the EAU guidelines the recommendation is to start with diclofenac whenever possible and change to an alternative drug if the pain persists [38].

D. SPONTANEOUS AND PHARMACOLOGICALLY FACILITATED PASSAGE OF URETERAL STONES

S. Nakada and M. Gallucci

Ideally, patients with ureteral stones will pass them spontaneously while enduring minimal pain and complications. The majority of stones which pass spontaneously do so within 4-6 weeks. Miller and Kane reported that of stones ≤ 2mm, 2-4mm and 4-6mm, 95% of those which passed did so by 31, 40 and 39 days, respectively [1, 40]. Studies have shown spontaneous passage rates of 71%-98% for small (<5mm) distal ureteral stones, with urinary-stone size and location being the two important predictors of stone passage. There is prospective evidence that larger calculi (>7mm) typically do not pass [41]. Stones located more distally typically pass more readily than those located in the middle or proximal ureter. Regardless, the majority of ureteral stones pass spontaneously, and conservative measures are frequently recommended depending on the clinical circumstance [42].

There is growing evidence that medical expulsive therapy, the administration of medications to facilitate stone passage, is efficacious. Recent studies have demonstrated that this approach may accelerate the spontaneous passage of ureteral stones as well as stone fragments following successful SWL [43-47]. Use of α-adrenergic receptor antagonists and calcium channel blockers for expulsive medical therapy has been proposed as a way to enhance stone passage. Interest in these drug classes stems from our understanding of ureteral smooth-muscle physiology and urinary obstruction [40, 48-50]. Hollingsworth and associates [51] performed a meta-analyis of published literature in which calcium channel blockers or α-receptor antagonists were prescribed to patients with ureteral stones. These patients had a 65% greater likelihood of stone passage than those not receiving medical expulsive therapy. The pooled risk ratios and 95% confidence intervals for α-blockers and calcium channel blockers were 1.54 (1.29-1.85) and 1.90 (1.51-2.40), respectively.

Notably, tamsulosin has been the most common α-blocker utilized in recent studies. Despite this, Yilmaz and colleagues demonstrated that tamsulosin, terazosin and doxazosin were equally effective in this setting. [52]. Collectively, these studies demonstrate that medical expulsive therapy not only increases the rate of stone passage, but reduces the time to stone passage and minimizes ureteral colic. The beneficial effects of these agents may be attributed to ureteral smooth muscle relaxation mediated via relevant cellular interactions, depending on the agent utilized.

Medical expulsive therapy should be considered for ureteral stone size < 1cm [8, 40, 53-55].

Evidence suggests that relaxing the ureter in the region of the stone and increasing hydrostatic pressure proximal to the stone help to facilitate ureteral stone passage [56, 57]. Such a relaxation can be accomplished by giving calcium-channel blockers and α-receptor antagonists. The effects are mediated through the active calcium-channel pumps and adrenergic α-1 receptors present in ureteral smooth muscle. In addition several studies have reported that patients given such treatment have a significantly reduced time to stone passage, fewer pain episodes, and lower analogue pain scores and they needed significantly smaller doses of analgesics. Side effects were not reported for all studies, and the occurrence of therapy-related transient hypotension and palpitations was low at 3.5%.

In some studies, corticosteroids were used in the treatment of stone passage but incremental benefit of steroid use was small and the use of steroids in concordance with other agents remains controversial [51].

Medical expulsive therapy is rapidly gaining clinical interest, however since many stones pass spontaneously and surgery for smaller stones is well tolerated, widespread acceptance has not been achieved at the time of this publication. Moreover, many of the current studies emanate from the urologic literature, and it is the emergency physician and primary physicians who often see the patients initially [58, 59].

In summary, spontaneous passage of ureteral stones with or without medical expulsive therapy continues to evolve in parallel with medical prevention and surgical therapy. As a general rule, ureteral stone patients who elect this approach should have well controlled pain without clinical evidence of sepsis. Patients also should be subjected to periodic imaging studies to monitor stone position and to assess for associated obstruction using the imaging techniques as noted in this chapter. Surgical therapy and ongoing prevention should be applied to select individuals.

E. URETERIC STONE REMOVAL WITH EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY (SWL)

D. Bolton and B Newell

After the first successful treatment of urinary calculi by extracorporeal shock wave lithotripsy described in 1980 [58], SWL revolutionised the treatment of renal and ureteral calculi worldwide. Prior to 1980 the centrepiece of management of obstructing ureteral stones larger than 5 mm in diameter was open surgery [59]. When Chaussy reported his first series of 72 patients in 1982 SWL was established as a safe and effective procedure for the treatment of renal and ureteric calculi [60].

I. EVOLUTION OF SWL TECHNOLOGY

The laws of acoustic physics govern the ability of lithotripsy machines to fragment calculi. In order for SWL to work, a lithotripter must have an energy source for shock wave generation, a device to focus the shock wave at the stone, a shock wave coupling medium and a method for localising the stone.

Three main types of shock wave generation exist for use by urologists: electrohydraulic, piezoelectric and electromagnetic. First generation electrohydraulic lithotripters (Dornier HM3) use an electric spark gap to generate the shock wave which is focussed with an ellipsoid reflector. This system utilises a water bath as the coupling medium through which the shock wave propagates. The shock wave however, is painful and patients usually require general or spinal anaesthesia. Piezoelectric and electromagnetic generators appeared on 2nd and 3rd generation lithotripters, as did gel-filled cushions to act as a coupling medium. Piezoelectric generators involve multiple small ceramic elements being excited by a high frequency, high voltage input. The small outputs from these ceramic elements summate at the focal point of the machine to produce a high energy shock wave. Because each shockwave travels along an independent pathway through the body, patients require less anaesthesia and analgesics. Finally, electromagnetic generators work in a similar way to an audio speaker cone: output is focussed with an acoustic lens creating an intense shock wave at the focal point. These generators may be associated with greater pain often requiring more anaesthetic or analgesic cover.

Stone localisation is achieved through either fluoroscopic or ultrasonic modalities. Ultrasound, whilst efficacious for renal calculi, is not as useful as fluoroscopy in the location of ureteral stones due to the lack of a clear acoustic interface. Radiolucent stones within the ureter can be most effectively seen with the use of contrast instilled in either a retrograde or antegrade fashion or via intravenous administration [61].

With a generated shock wave focussed on a localised calculus, the stone may be fragmented through a combination of 4 mechanisms: compressive fracture, spallation, cavitation and dynamic fatigue.

1. COMPRESSIVE FRACTURE

As the shock wave from the lithotripter reaches the stone, a force is imparted placing stress on stone imperfections and defects which results in tensile cracking. Additionally circumferential compression of the calculus may occur when the focal point of the lithotripter is larger than the stone because the shock wave travels faster through the calculus than the surrounding urine and hence a circumferential "squeezing" force exists [62].

2. SPALLATION

As the shock wave exits the posterior surface of the stone, there is a change in impedance (stone-fluid interface). This reflects the positive compressive wave as a negative tensile wave which, if large enough, leads to comminution of the stone at sites of weakness

3. CAVITATION

Cavitation is the formation and subsequent dynamic behaviour of bubbles. As the shock wave passes through liquid, its trailing negative pressure wave creates bubbles at the interface between stone and fluid. As the pressure falls, the bubbles expand. The subsequent rise in pressure results in bubble collapse and release of energy which also contributes to the fragmentation.

4. DYNAMIC FATIGUE

During the course of SWL treatment, the stone is subjected to multiple forces leading to cracks and changes to its surface. This accumulation of damage leads to dynamic fatigue and ultimate fragmentation of the stone [63].

II. FACTORS INFLUENCING SUCCESS OF SWL IN TREATING URETERIC CALCULI

1. LITHOTRIPSY MACHINE COMPARISON

Whilst the principles of SWL remain unchanged, lithotripter technology has undergone rapid transformation, largely due to clinical influence guiding developers to engineer smaller machines with less focal point pressure and thus a reduced requirement for general anaesthesia. Consequently some 2nd, 3rd and 4th generation lithotripters have generally shown inferior fragmentation rates compared to the original 1st generation HM3 lithotripter. Third generation machines introduced computer monitoring of the treatment as well as a dual localising system. The latest generation of machines includes the advances of previous generations but added portability, together with the ongoing potential to avoid regional or general anaesthesia.

Remarkably, the first lithotripter, the Dornier HM3, remains the gold standard for SWL treatments in ureteric and renal calculi. Many studies demonstrate its superior efficacy as compared to later generation machines [64-66]. Stone free rates at 3 months have been reported to be as high as 96%. Comparisons of second and third generation machines have produced variable and often conflicting results [66-69]. More recent advances such as dual pulse lithotripsy, tandem shock waves, and voltage stepping have been suggested to improve outcomes with SWL, however data to justify such adjustments is not yet available from substantial randomised studies [70, 71].

2. STONE AND LOCATION

In a review of approximately 20,000 patients treated for ureteral calculi with SWL the European Association of Urology Guidelines identified that stone-free status was achieved in 81%, with only a 12% re-treatment rate [72]. These combined results represent a benchmark against which the outcomes of controlled trials and individual centre studies may be compared.

Salman et al [73] looked at factors involved in achieving a stone free result in the treatment of ureteric stones with SWL (Storz SL 20). In this group of 468 patients, overall success rate of SWL was 84% with a re-treatment rate of 51%. After correlation of patient and stone characteristics with outcome, only 3 significant factors were identified; stone location, stone size and stenting. Stones > 8 mm in diameter and stones < 8 mm had stone free rates after SWL of 67% and 90% respectively.

In a similar study in 2003, Abdel-Khalek et al [74] analysed 938 patients with ureteric stones treated with SWL (Dornier MFL 5000). Multivariate analysis revealed the same three factors as significant predictors of SWL stone free rate. This group had a similar overall stone free rate at 3 months (89%) but with a re-treatment rate of 50%. They found that patients with stones > 10 mm in diameter had a stone-free rate of 83% compared to 90% in patients with stones < 10 mm in diameter. Stone location was also a significant predictor with lumbar ureter stones providing the highest success with SWL. Non stented patients had a higher stone free rate than those who were stented (90% compared to 81% respectively). This group went on to develop a multivariate analysis model to estimate the probability of stone-free status after SWL. The sensitivity of the model was 83%, the specificity 91% and the overall accuracy 87% [75]. While this analysis is generally relevant it is worthy of note that variant outcomes could be expected between institutions, and individual treatment centres need to develop their own such algorithm based on local experience to optimize outcomes.

Mid ureteric calculi have traditionally been less successfully treated via SWL due to pelvic bone attenuation [76]. Initial attempts resulted in less than 10% of the shock waves reaching the stone. Subsequent alterations to 1st generation machines including permitting prone treatment allowed sufficient energy levels to reach the stone for effective fragmentation to be demonstrated in select series. Halachmi's study looked at large ureteral stones treated with the HM3 and showed a stone-free rate of 80 % for mid ureteric calculi with a re-treatment rate of 20 % [64]. These figures have not been reproduced with newer generation machines, and SWL is not the preferred option in the management of calculi in this location.

Distal ureteric calculi have repeatedly been shown to be adequately treated by SWL, with multiple machines being used [77-79]. Exceptions to this generalisation include instances of infection, complete ureteric obstruction and failure to adequately visualise a stone prior to the time of planned SWL therapy. Two prospective randomised control trials by Pearle and Peschel produced slightly conflicting opinions as to the efficacy of SWL for distal ureteral stones. Peschel [77] recommended ureteroscopy as a first line therapy over SWL especially for small stones, whereas Pearle found that both modalities were highly efficacious with a 91% success rate at 21 and 24 days respectively [79]. The recommendation of Pearle et al related to reduced operating time, outpatient nature of SWL and the lower morbidity post procedure. This study utilised the HM3 whereas Peschel's research utilised the later generation Dornier MFL 5000, and it may be the machine difference that conferred poorer stone clearance of distal ureteric calculi in the treatment group.

Although many authors, including the above, list SWL as the first choice in management of distal ureteric calculi, newer generation ureteroscopes and stone lasers have shown an equivalent or better success rate, with stone free status being definitively ascertained at the time of surgery.

3. STENT OR NON-STENTED URETER

The use of stents in SWL for ureteric stones is debatable in a non-infected system. The rationale for such intervention is to provide an expanding fluid chamber at the location of the calculus being treated. In some recent series, non-stented patients have faired better than stented patients with a stone-free rate of 89% compared to 75% respectively at 3 months [73]. Stenting of patients, however, was not undertaken as a randomised study in this series, and thus there may have been some case selection bias influencing the results in the stented and non-stented cohorts.

In an additional recent study by Musa [80], 120 patients with renal stones were assigned to having either a double-J stent or no stent prior to SWL. SWL was then performed and patients were followed up at 1 and 3 months. At three months, 88% of stented and 91% of unstented patients were stone free leading to the conclusion that there is no benefit of internal stenting prior to SWL therapy. Multiple studies have shown high patient satisfaction rates after treatment of ureteric calculi even with the use of ureteric stents.

Ureteric stenting is regarded as mandatory in the management of ureteric stones in a solitary functioning renal system.

Where stents are used, the double-J design has been standard. Newer helically ridged ureteric stents aim to facilitate distal migration of stone fragments post SWL. In-vivo studies have reported facilitated expulsion of ureteric stone fragments using helically ridged stents [81, 82], but no randomised controlled trials have since been reported to confirm their efficacy.

4. PROXIMAL URETERIC STONES : PUSH BACK VERSUS IN-SITU TREATMENT

Stones in the proximal ureter were traditionally pushed back into the renal pelvis in association with treatment via SWL. Multiple studies have indicated a higher success rate for stones that were manipulated proximally compared to stones left in-situ before SWL [83-85]. Additionally, it was noted by Lingeman that significantly less energy was needed for complete disintegration of the stone floating in the kidney and that the number of subsequent procedures was less for stones pushed back [86]. Conversely, a study by Rassweiler demonstrated both the in-situ group and the push-back group to have an 87% stone free rate [87]. This was later confirmed by Cass who demonstrated a 73% stone free rate in upper ureteric stones at 3 months with push back, as compared to a 79% clearance in the group with in-situ SWL treatment [88]. Further studies since have demonstrated that for uncomplicated ureteral calculi, ureteral stone manipulation is not mandated, though it may result in a potentially higher treatment success rate and in fewer repeat emergency room attendances after SWL [69, 85, 89, 90].

5. STONE COMPOSITION

The composition of ureteral stones also influences the success of SWL. It was reported by Ramakumar in 1999 that plain x-ray KUB can accurately predict stone composition in up to 39% of cases [91]. Recent studies have looked at attenuation values of calculi as a means of predicting those stones more likely to fragment and thus those stones more amenable to SWL therapy. The results suggest Hounsfield units may be a useful indicator, however further studies are required to confirm the validity [92-94]. Most stones will respond well to treatment by SWL, although those stones with a higher mineral density may result in a higher re-treatment rate. Cystine stones respond poorly to SWL, and earlier recommendations have suggested such calculi and those stones of >750 Hounsfield units (usually calcium oxalate monohydrate) might best be primarily treated with ureteroscopy in view of the anticipated higher re-treatment rate after SWL [93].

6. ULTRASOUND VERSUS X-RAY LOCALISATION

Many latest generation lithotripters have the ability to provide ultrasound and fluoroscopic imaging. Whilst combined imaging may be useful for pyelocalyceal calculi, evidence suggests fluoroscopy remains the gold standard of imaging ureteric stones. In the setting of radio-lucent ureteric stones, the use of radiographic contrast via antegrade or retrograde instillation or intravenously is accepted as a method to facilitate fluoroscopic imaging of the stone. With modern lithotripters having smaller focal areas and lower shockwave energy, the importance of accurate stone targeting cannot be understated.

7. FEMALE PATIENTS

The use of SWL in women of childbearing age has been questioned, due to radiation dosages incurred and potential effects of shock wave impulses on ovaries, although no fetotoxic effect has been confirmed [95].

III. CLINICAL OUTCOMES AND RECOMMENDATIONS FOR SWL TREATMENT OF URETERAL STONES

There is a paucity of level 1 evidence in the literature that specifically address SWL efficacy in ureteral stone disease. A recent Cochrane Collaboration review of management of urinary calculi [96] concentrated on only six such studies [77, 79, 97-100]. With reports that adjuvant medical therapies (α-receptor antagonists, calcium-channel blockers, steroids) may also improve stone free rates, future studies will need to be controlled in this respect also. Blinding of patients and investigators in such studies remains problematic.

The low number of randomised controlled trials for management of such calculi has resulted in meta-analyses of single arm studies being used to estimate probability of an outcome from a given intervention using the Confidence Profile Method in several reviews. Using this method the American Urological Association’s Ureteral Stones Clinical Guidelines Panel of 1997 concluded that whilst most ureteral stones pass spontaneously, those that fail to can be treated with either SWL or ureteroscopy. Their meta-analysis of 327 articles produced a recommendation that SWL should be first line therapy for most patients with stones <1 cm diameter in the proximal ureter. For larger stones PCNL and ureteroscopy were also acceptable options. It was concluded distal stones could be treated with either SWL or ureteroscopy regardless of size [101]. The additional randomised trials comparing SWL and ureteroscopy which have reported since these guidelines were published (referenced above), provide data which does not conflict with such recommendations.

Matched Pair analysis also has been utilised as a method of obtaining justifiable data in the management of calculi using SWL, both as a comparison to ureteroscopy and in the evaluation of alternate lithotripters [66, 102, 103]. Similarly Kanao et al [104] have used multivariate analysis and logistic regression to produce nomograms to predict 3 month stone free probability after a single SWL treatment.

Based on the available level 1, 2 and 3 evidence presented above it appears possible to make the following recommendations on the management of ureteral calculi using extracorporeal shock wave lithotripsy:

- SWL remains as first line therapy for most proximal ureteric stones (Grade B recommendation).
- Stone push-back for upper ureteric calculi is not mandatory in the absence of infection, and noted benefits may be outweighed by the morbidity and cost associated with stent insertion (Grade B recommendation).
- Lower ureteric calculi may be treated equally successfully by either SWL or ureteroscopic stone extraction based on the experience of the operator and facilities available (Grade B Recommendation)
- Mid ureteric stones are less amenable to SWL treatment. Whilst lithotripters can target stones whilst the patient is in the prone position, re-treatment rates remain high. With the advent of improved ureteroscopic and laser technology, SWL is not usually first line therapy for calculi in this region (Grade B Recommendation).
- Results of SWL are institution dependant and as such clinicians should be guided by their institution's experience and choice of equipment as to whether mid & lower ureteric calculi are subjected to SWL as a first line treatment (Grade B Recommendation).

F. URETERORENOSCOPIC STONE REMOVAL (URS)

T. Knoll

Extracorporeal shockwave lithotripsy (SWL), introduced to clinical practice more than two decades ago [60], is the standard treatment of most upper urinary stones. However, SWL regularly requires repeated treatments and does not disintegrate all calculi successfully. Meanwhile, technical progress made small-calibre scopes with good optical quality widely available and the holmium laser offers effective and safe intracorporal lithotripsy. These developments may have supported a tendency to perform today more and more ureteroscopies (URS) for ureteral calculi. This section will give an overview of current indications for URS, technical standards, recommendations for doing the procedure, results and complications.

I. INDICATIONS

1. PROXIMAL URETERAL CALCULI

Most guidelines still recommend SWL as a proven effective first line treatment for proximal ureter stones [105, 106]. In the pre-laser era, ballistic lithotripsy was mainly used for ureteroscopic stone disintegration. Fragment expulsion was a well-known problem that often prevented successful stone treatment. With the improvement of flexible scopes and the introduction of the Ho:YAG laser, success rates of URS have largely improved even for proximal stones [107]. Considering the actual literature URS with Ho:YAG laser lithotripsy seems to reach higher stone free rate than SWL for larger stones >10 mm [99, 108, 109] . Both procedures reach good SFR for stones <10 mm why SWL should be preferred as the least invasive approach.

2. DISTAL URETERAL CALCULI

The optimal active therapy for distal ureter stones, SWL or URS, remains controversial. Both procedures are associated with high success and low complication rates. Available studies report comparable success rates from 86% to 100%. For distal ureter stones, Peschel et al. reported comparable success rates for URS and SWL (100% and 90% resp.) from a prospective randomised trial in 80 patients, but ureteroscopy had advantages in terms of operation time, time to stone free status and x-ray application [77]. Evaluation of patient satisfaction showed as well a favourable result for URS because of the earlier stone clearance. Therefore, the authors recommended URS as a first line treatment for distal ureteric stones. Honeck et al. demonstrated excellent results for both groups and concluded that treatment decision should be drawn individually together with the patient [110].

For the same stone localisation, Pearle et al. evaluated 64 patients with a maximal stone size of 15 mm in a prospective randomised study [111]. Minor complications occurred in 9% of SWL and 25% of URS groups but did not reach statistical significant difference. In contrast to Peschel et al., operation time was shorter in the SWL group. This finding was explained by the use of a first generation lithotripter. Patient's satisfaction was high and did not differ between both procedures. Shorter operation time failed to translate into lower operating costs in the study of Pearle. Higher costs of

SWL, mainly because of high lithotripter costs, were as well reported by others authors [112].

In a recent Cochrane Database review including six randomized clinical trials, Nabi et al. concluded that ureteroscopy achieves a better SFR but has more complications than SWL [113, 114]. Overall, SWL and URS seem to have comparable stone free rates for distal ureter stones. While the advantage of SWL is its non-invasiveness, the advantage of URS is the immediate stone removal.

II. TECHNIQUE

1. ENDOSCOPES

Semirigid URS: The semirigid ureterorenoscope consists of a stainless steel shaft and fibre optic bundles as well as a working channel for irrigation and insertion of working instruments. Because of the use of glass fibre, a limited flexion of the "semirigid" endoscope of approximately 20° is possible. Modern semirigid ureteroscopes with external diameters of 6-10.5 Fr. allow access to the upper urinary tract, mostly without separate dilatation of the ureter [114, 115]. Instruments with larger diameter are accompanied with a higher risk for ureter injury due to the stronger dilatation.

Flexible URS: Flexible ureterorenoscopes with shaft diameters of 6.5-9 Fr. also allow easy access to the upper urinary tract in most cases without previous dilatation [116]. Flexible ureterorenoscopes should not be used in the distal ureter, where semirigid instruments are a lot easier to handle.

While some authors advice to use flexible URS for all stones proximal from the iliacal vessel crossing [117], others prefer the use of semirigid scopes even for proximal stones because of better endoscopic view and a wider range of stone extraction or stone disintegration tools. However, flexible URS facilitates passage of strictures or ureter kinking. To our knowledge, no data have been published describing higher a complication rate of semirigid compared to flexible ureteroscopy. At least in the hands of experienced surgeons, complications are rare for both procedures.

2. INTRACORPORAL LITHOTRIPSY

Endoscopic intracorporeal lithotripsy is usually necessary before extraction of larger fragments. Electrohydraulic, pneumatic, ultrasound and laser probes are available:

Electrohydraulic: Flexible electrohydraulic lithotripsy probes (EHL) are available in different sizes for semirigid and flexible ureterorenoscopes. Technical principle: An electric spark is generated at the tip by electric current. The resulting heat creates a cavitation bubble, which generates a shock wave. Generally, EHL can be used to disintegrate all stones (even cystine or hard stones like calcium oxalate monohydrate). However, the heat spreading in all directions often causes damage to surrounding tissues why EHL is not recommended for intracorporeal lithotripsy anymore [118].

Pneumatic: Pneumatic or ballistic lithotripters are often used with 2.4 Fr. probes for semirigid ureterorenoscopy. The achieved disintegration rates reach > 90%. The main advantages are high cost efficiency through low purchase costs and safe application [119-122]. The problem though is frequently seen proximal stone migration [123]. By inserting a Dormia basket or special tools preventing proximal stone migration this side-effect can be inhibited [124]. Flexible probes are available but cause a significant restriction of flexion [125].

Ultrasound: Ultrasound-based lithotripsy probes induce a high frequent swinging of the handle through a piezoceramic element which transformes electric energy into ultrasound (23,000-27,000 Hz). This ultrasound is passed along the metal probe to the tip and induces a vibration. Contact with the stone causes disintegration. Recently, probes are available that combine ultrasound and pneumatic lithtripsy and can be used for semirigid URS as well as for PNL [126].

Laser-based systems: Today *Neodymium:Yttrium-Aluminium-Garnet (Nd:YAG;* frequency-doubled (FREDDY, 532 and 1064 nm)) and *Holmium:YAG (Ho:YAG; 2100 nm) laser* are established systems for intracorporeal lithotripsy. For both lasers, fibres with different diameters are available (mostly 365 µm for semirigid ureterorenoscopy and 220 µm fibres for flexible URS) [127]. The FREDDY laser has limited efficacy for hard stones (i.e. calcium oxalate monohydrate) and cannot disintegrate cystine stones, but is less expensive than the Ho:YAG laser, which disintegrates stones of all compositions [128-130].

Although many methods for stone disintegration are available, including ultrasonic, mechanical, electrohydraulic systems, the Ho:YAG laser seems to be the first choice [130, 131]. The holmium laser energy is completely absorbed by water after 0.5

mm, hence accidental injuries of the ureter occur rarely. Compared to the Nd:YAG laser, the minimal tissue penetration of <0.5 mm reduces thermal damage. Therefore contact to the stone is mandatory for disintegration. While perforation of the ureter or renal pelvis may occur accidentally, an increased incidence for strictures could not be verified so far [132]. Compared to electrohydraulic lithotripsy, the holmium laser led to significantly higher stone free rates.

3. STONE EXTRACTION

Small fragments can often be extracted primarily or after disintegration using a forceps. Baskets can also be used to extract fragments quickly, although there is a higher risk of getting stuck within the ureter [133, 134]. Larger fragments are disintegrated before extraction. The aim of *stone disintegration* should be to achieve fragment sizes that can be extracted easily. When using a holmium laser, very small fragments ("dust") may occur. Such fragments have a high probability of passing spontaneously and can be left in place

III. TREATMENT

The following preoperative *examinations* are required:

- Patient's history, physical examination
- Anatomic variants may complicate or prevent retrograde stone manipulation (prostate adenoma, ureter re-implantation, ureterocele, ureter strictures, urinary diversion (conduit, neobladder, pouch, ureterointestinal implantation))
- Discontinuation of thrombocyte aggregation inhibitors/anticoagulation treatment should be aspired, but is not obligatory. Normal coagulation status (Quick/INR, PTT) reduces the rate of complications after URS. In case of limited coagulation ability, URS shows a minor probability for complications compared to SWL and should therefore be preferred [135]
- Plain x-ray and intravenous urography or retrograde pyelography resp. non-contrast helical CT scan
- Ultrasound
- Serum creatinine, coagulation (Quick/INR, PTT, thrombocytes)
- Urinary dip stick analysis, if necessary urine culture and antibiotic treatment according to antibiogram
- Informed consent: Infection, haematuria, colic, fever, sepsis, DJ catheter, PCN, injury of urethra/ureter and stenosis, perforation of bladder or ureter, open surgical revision, loss of kidney (very rare), application of contrast medium, hypersensitivity to contrast medium

Most interventions are performed with *general anaesthesia*. Due to the miniaturisation of the instruments a comparable outcome can be achieved by intravenous sedation [136]. This approach is especially suitable for female patients with distal ureter stones.

Many centres perform ureteroscopy as an outpatient procedure. Several groups have demonstrated that outpatient treatment is safe if patients were selected properly.

Patients are placed in lithotomy position. Abduction of the contralateral leg allows more space for the surgeon. The procedure starts with a cystoscopy, a retrograde pyelography and the insertion of a safety wire/ guide wire. The *insertion of a safety wire* should always be performed as it allows insertion of a ureter stent even after ureter perforation.

The use of a thin ureteroscope allows intubation of the orifice without previous dilatation in most cases. If primary intubation is not possible, DJ-catheter insertion and delayed URS after 7-14 days offers an appropriate alternative to dilatation. If dilatation is necessary, balloon and plastic dilators are available. If insertion of a flexible ureteroscope is difficult, prior semirigid ureteroscopy can be helpful in sense of optical dilatation.

Semirigid endoscopes are usually inserted without using a guide wire, bare passing the placed safety wire. If direct intubation of the orifice is difficult, the insertion of a second wire through the working channel can be supportive.

Flexible endoscopes are most easily inserted via a guide wire in most cases. New generation ureterorenoscopes are equipped with enhanced shafts which principally allows a direct (= free) intubation of the orifice [137, 138].

1. ACCESS SHEATHS

Access sheaths are frequently used for renal calculi if multiple ureter entries are necessary (e.g. large stone mass). They potentially facilitate stone treatment, decrease operation time, improve irrigation flow and minimize intrarenal pressure [139-141]. Vanlangendonck et al. or recommend routine use of ureteral access sheaths at least for flexible URS in the kidney. The risk of ureteral ischemia seems to be low, since access sheaths have been used now for thousands of procedures without any evidence of increased stricture formation. However, others believe access sheaths being unnecessary in most cases. For distal ureter stones, De Sio et al. demonstrated that access sheaths are more prejudicial than helpful for stone treatment [142]. This is in accordance to our experience that access sheaths are seldom needed for ureteric stones, but may be helpful for the treatment of kidney stones. In general, access sheaths are of limited benefit when treating ureteral stones.

2. STENTING AFTER URS

In many centres, postoperative indwelling ureteral stents were placed routinely. However, patients with stents seem to have significantly more symptoms like pain and irritative voiding symptoms. Additionally, routine placement of stents adds significant costs to the procedure. Recently, several randomised prospective studies reported stenting not being necessary after uncomplicated URS without significant residual stones or ureter lesions [143, 144]. Jeong et al. [143] demonstrated recently, that hematuria is more frequent after stenting. All other parameters, like pain and urinary symptoms did not show any statistical difference.

Nabi et al. recently published a systematical meta analysis on stenting after URS [145]. They summarized that patients with stents after URS have significantly higher morbidity in the form of irritative lower urinary symptoms with no influence on SFR, rate of urinary tract infections, requirement for analgesia, or long term ureteric stricture formation. However, because of the marked heterogeneity and poor quality of reporting of the included trials, the place of stenting in the management of patients after uncomplicated ureteroscopy remained unclear. Until future RCTs will solve this open question, the identification of patients being suitable for stentless ureteroscopy is the major goal. As the decision to place a ureteric stent after a difficult ureteroscopy, will never be questioned, we still advice insertion of a stent in all cases where the URS was NOT uncomplicated. It should be kept in mind that leaving a ureter in questionable condition unstented may lead to serious morbidity. Risk factors for complications after stentless URS are summarised in **Table 1.**

Table 1. Risk factors for complications after stentless ureteroscopy [143, 144, 155].

- Lithotripsy
- Bilateral procedure
- Urinary tract infection
- History of urolithiasis
- Mucosa trauma/ ureter perforation
- Operation time >45 minutes with lithotripsy
- Dilatation of ureteral orifice?
- Diabetes mellitus?

IV. COMPLICATIONS

The rate of significant complications after URS is stated with 5-9% in literature, clinically significant complications are rare with less than 1% [124, 143]. Today, ureter strictures in terms of long time complications are rare (< 1%,), previous perforations are the most important risk factor. Most frequent complications include macrohematuria from mucosa lesions and urinary tract infections that can be treated conservatively in almost all cases. Operation time was identified being a main risk factor of ureteral perforation [146]. Sofer et al. evaluated a large group of patients after laser lithotripsy and demonstrated a very low 0.35% risk of new onset ureteral strictures [107]. The most serious complication after URS is an avulsion trauma of the ureter [147].

1. SPECIAL SITUATIONS

URS may be possible in cases were SWL has low outcome or is contraindicated. Typical examples are:

Obesity: Good results have been demonstrated even in severely obese patients for the URS. Andreoni et al. treated patients with a mean body mass index of 54 and stone size <15 mm, they reached an initial stone free rate of 70% [148].

Pregnancy: In our opinion, all interventions should be avoided during pregnancy. However, URS seems to be a safe technique if treatment is absolutely necessary. While shockwave application is contraindicated during pregnancy, Lifshitz et al. successfully treated 10 pregnant women by URS and intracorporeal lithotripsy and did not note obstetric or urological complications [149].

Children: Several groups have demonstrated URS being safe and efficient in children [150-152]. Dogan et al. performed URS using scopes of maximal 10F for ureteric stones in 35 children with a mean age of 6.2 years [151]. Ho:YAG laser or pneumatic lithotripsy probes were used for stone disintegration. One-stage stone free rate was 82%, no late complications occurred within 12 months follow-up. However, comparable stone clearances are reported for SWL, which display its extraordinary efficacy in children even for large stones and difficult stone composition [153, 154]. In our opinion, ureteroscopy has comparable efficacy but higher invasiveness compared to SWL; shockwave lithotripsy is best justified as a routine measure in children.

IV. SUMMARY

When active ureteral stone treatment is necessary, the best procedure to choose is dependent on several factors, including local experience, patient's preference, available equipment and associated costs. Based on the literature, SWL is still the principal choice for most ureteral stones because of its minimally invasive nature, lack of serious complications and the avoidance of general anaesthesia. However, recent developments in ureteroscopy (small calibre scopes, laser probes) have changed the balance between SWL and URS. High success rates, low complication rate and immediate complete stone removal in most cases have made URS more than an attractive alternative in endourological stone treatment and have widened the indications. Antegrade or laparoscopic approaches are reasonable alternatives only in rare cases, where SWL and URS have failed.

G. INCISIONAL (OPEN) SURGERY, LAPAROSCOPIC SURGERY AND PERCUTANEOUS SURGERY FOR REMOVAL OF STONES LOCATED IN THE URETER

H-G Tiselius

Until approximately 20 years ago ureterolithotomy was the standard procedure for removal of stones located at all levels of the ureter. That technique, with which the stone is extracted following incision of the ureter, always has been associated with a high stone-free rate and a recent review of literature data has shown a successful outcome in more than 98 % of the treated patients. The clinical use of incisional surgery for ureteral stones has, however, been reduced dramatically due to its high degree of invasiveness in comparison with newly developed methods. The complications, the process of wound healing and the scarring are obvious drawbacks of open surgery. Today this method is an uncommon tool for removal of ureteral stones because of the successful results obtained with SWL and URS. The major indication for incisional surgery is when the stone removal has to be combined with reconstructive surgery for correction of anatomical abnormalities or when all other therapeutic possibilities have failed [156, 157].

Before proceeding to incisional surgery the laparoscopic approach constitutes a reasonably low invasive alternative [158]. The first laparoscopic procedure described by Wickham in 1979 [159] subsequently has been followed by numerous reports on a successful application of the method. Laparoscopic stone removal has been carried out retroperitoneally [160-169] or transperitoneally [170-174]. From a comparison between retroperitoneoscopic and open surgery it was concluded that the treatment results were comparable, but that the laparoscopic approach resulted in a shorter hospital stay, less need of analgesics and superior cosmesis [175]. It also was shown that the CRP-levels were lower after laparoscopic than after open surgery [176]. The major disadvantage of the laparoscopic methods is the usually long duration of the procedure. Most authors report a successful removal of ureteral stones, but such an outcome is obviously not always the case [169] and it is reasonable to consider a laparoscopic approach only when other low-invasive procedures have failed and before proceeding to open surgery[158]. The major indication thereby would be impacted stones in the mid or upper ureter [177].

Impacted or particularly hard stones in the ureter that have resisted SWL and that cannot successfully be treated ureteroscopically might be eliminated by a percutaneous approach with or without antegrade URS [178-180]. This method is particularly suitable for ureteral stones encountered in patients with urinary diversion [179]. The percutaneous technique, always should be considered before proceeding to laparoscopic or incisional surgery.

The previously rather common use of a stone basket for blind removal of stones in the distal ureter [181] has to be abandoned because of the risk of injury to the ureter and with modern technology, baskets should be used only together with ureteroscopes so that stone grasping can be made under direct vision.

In conclusion it stands to reason that the vast majority of stones in the ureter successfully can be removed with SWL or/and URS and that the more invasive procedures discussed above have a limited use for a selected group of patients with particularly problematic stones or anatomy.

H. TREATMENT OF URETERAL STONES DURING PREGNANCY

O. Traxer

Diagnosis and management of ureteral stones during pregnancy are challenging because of the concerns over the risk to the foetus. The best method to diagnose ureteral stones involve ionizing radiation, which is harmful to the development of the foetus, and shock wave lithotripsy (SWL) is contraindicated during pregnancy. Thus, the clinical management of ureteral stones in pregnancy necessarily involves limited diagnostic and therapeutic options.

I. INCIDENCE AND PRESENTATION

Urinary stone disease complicates approximately 1 in 1500 pregnancies [182] and is the most common non-obstetric reason for hospital admission during pregnancy [182]. First trimester presentation of an acute stone is decidedly rare, and most episodes of renal colic occur during the second or third trimester (80 to 90%). While most symptomatic stones are located in the ureter, renal pelvis, or ureteropelvic junction, stones may cause intermittent symptoms and obstruction. Although some series have shown a predisposition to the right side over the left, generally, calculi occur with equal frequency on both sides. The majority of patients are multiparous and a previous history of stone disease is a risk factor. Pregnancy-induced hydronephrosis, which begins in the first trimester, is the most common cause of dilation of the urinary tract in pregnancy and may cause flank discomfort or even mimic renal colic and allow preformed calculi more room for movement, resulting in renal colic and hematuria.. Upper tract dilation is seen in up to 90% of pregnant women by the third trimester and may persist for as long as 12 weeks post partum. The right ureter tends to be more dilated than the left and dilation usually does not appear below the pelvic brim.

Most pregnant women have absorptive hypercalciuria and hyperuricosuria. Hypercalciuria is the result of an elevation of 1,25-dihydroxyvitamin D_3 manufactured in placenta and consequent suppression of PTH secretion. Dietary supplementation with calcium further augments urinary calcium excretion. Increased quantities of inhibitors present in urine during gestation and increased urine output, however, may counter the risk imposed by hypercalciuria.

The diagnosis of urolithiasis during pregnancy can be challenging because many of the presenting signs and symptoms may be masked by the patient's physiologic status. As gestation progresses, the perception and localization of pain may be altered. The majority of pregnant women present with flank pain (84-100%) and gross or microscopic hematuria (75-100%). In a large series of 57 pregnant women diagnosed with renal colic and confirmed stone, 37% presented with gross hematuria, whereas 79% had microscopic hematuria. Urinary tract infection was present in 31% of the patients [183] Presenting signs can be misleading, especially if flank pain is accompanied by abdominal pain. Misdiagnoses, such as appendicitis, diverticulitis, and placental abruption, have been reported in patients subsequently confirmed to have stones. Associated signs of a urinary tract infection, especially if accompanied by fever, may be a sign of pyelonephritis, which requires aggressive treatment [182, 183].

II. IMAGING STUDIES

Ultrasound is the primary diagnostic study in pregnancy, yet it is known to be a poor test for ureteral stones. Because of the presence of hydronephrosis of pregnancy, the documentation of urolithiasis during pregnancy may not always be straightforward. The reported sensitivity of ultrasound ranges from 34% to 95%, while most authors report a sensitivity of roughly 60% [183, 184]. Hendricks et al have reported that ultrasound alone confirmed the diagnosis of urinary stones in 47 % of their patients [185]. Vaginal sonography is now being utilized to diagnose distal ureteral stones In addition, Doppler ultrasound can be utilized to measure the intrarenal resistive indices to differentiate physiologic hydronephrosis from obstruction. The presence of ureteral jets can be seen on ultrasound and interpreted as evidence of obstruction.

Intravenous pyelography (IVP) is much more sensitive, but involves ionizing radiation, which poses risks to the developing foetus. In symptomatic patients, where ultrasound has not been diagnostic, Hendricks et al have advocated a limited excretory urogram, which would normally expose the foetus to only 0.4 to 1.0 rads [185]. Computed tomography (CT) is relatively contraindicated in pregnancy because of its high radiation dose, which is considerably higher than that of a limited IVU. Nuclear medicine studies involve radiation exposure to the foetus and are unlikely to be helpful in establishing a firm diagnosis of calculi. Sobering data are available that would suggest that, as urologists, we should make every effort to avoid foetal exposure to even low doses of radiation. The risks to the foetus vary depending on gestational age. The risk of a congenital malformation is greatest during the time of organ development, which is complete by the end of the first trimester. Fortunately, stones are rare in the first trimester. The radiation dose that constitutes a safe level in pregnancy is unknown, but a 3-film IVU is considered well below the level thought to induce a doubling of the risk for congenital malformations.

Harvey and al reported a case control study investigating the relationship between prenatal X-ray exposure and subsequent childhood cancer [186]. This was a retrospective study of twins born in Connecticut during a forty year period. Twins were chosen because a limited abdominal plain film was used to diagnose the presence of a twin gestation. It was estimated that the radiation dose to the foetus ranged from 0.16 to 4 rads, with an average dose of 1 rad which is similar to the exposure of a limited intravenous pyelogram. Statistical analysis revealed a 1.6 relative risk of leukemia, a 3.2 relative risk of solid childhood cancers and an overall relative risk of 2.4 for all childhood malignancies [186]. It would therefore seem most prudent for the urologist to avoid any radiation to the foetus during gestation, unless the radiographic study is going to have a major impact on the management of the mother.

Magnetic resonance imaging (MRI) involves no radiation, but is a poor study for demonstrating calculi. No large series has looked at the application of MRI to the management of urolithiasis during pregnancy [187].

III. TREATMENT

Since most symptomatic stones presenting during pregnancy will pass spontaneously (50 to 67 % of stones), a trial of conservative management with hydration, narcotic analgesia, and prophylactic antimicrobial agents is indicated for small stones (<6 mm) [183, 188-190]. Urinary stones, however, can jeopardize the pregnancy by causing significant fever or pain and stones have also been reported as causing initiation of premature labor [191, 192]. The decision to intervene is based on stone size, persistence of symptoms and the presence of infection. Pyelonephritis is associated with a high risk of premature labor and spontaneous abortion; as such, urine should be screened periodically for the presence of bacteria. Furthermore, obstructive pyelonephritis constitutes an emergency that mandates prompt upper tract drainage. Other indications include failure of conservative management, obstruction of a solitary kidney or bilateral ureteral obstruction. For management of persistent symptoms and/or obstruction, upper tract drainage with a ureteral stent or percutaneous nephrostomy tube is indicated [193-197]. Delay of definitive stone treatment until after delivery has been advocated to avoid the potential risks to the foetus associated with general anesthesia. Ureteral stents can be placed under local anesthesia using ultrasound guidance, resulting in relief of pain and obstruction. However, disadvantages of an indwelling stent include encrustation, bladder irritability, and infection. Because of the risk of rapid encrustation during pregnancy, stent changes at least every six weeks have been recommended [198, 199]. Percutaneous nephrostomy provides an alternative to stent drainage in the obstructed, pregnant patient [197, 200, 201]. Like ureteral stent placement, nephrostomy drainage can be performed under ultrasound guidance, and the external drainage tube permits catheter irrigation in the event of tube occlusion and allows for easy catheter exchange. For patients presenting early in pregnancy, nephrostomy drainage obviates the need for frequent, operative, stent changes throughout gestation, although the nephrostomy tube should be changed approximately every six weeks as well. As delivery nears, the nephrostomy can be converted to an internal ureteral stent for comfort [202].

Definitive stone management during pregnancy has been performed with few complications. Both flexible and rigid ureteroscopy and stone fragmentation or retrieval have been reported. [203-206]. Ureteroscopy has emerged as an optional treatment of urolithiasis during pregnancy. Fifty-eight cases have been reported in the literature and the data suggest that ureteroscopy can be performed safely. Scarpa et a1 reported on the successful use of rigid ureteroscopy (7F or 9.5F) in 15 patients. In 5 patients, no anesthesia was required, and 10 patients had neuroleptic analgesia [203].

With 7F ureteroscopes, procedures can be performed with minimal anesthesia. Dilation of the ureteral orifice is rarely required. Ureteroscopy can be performed even during the last weeks of gestation. Although the use of rigid ureteroscopes at late gestation has been reported, the flexible ureteroscope is easier to manipulate in a tortuous ureter, thus reducing the risk of perforation. Most stones can be removed with stone forceps. Lithotripsy, if required, can be done safely with laser or pneumatic devices, though the latter require use of a rigid ureteroscope [204-209]. Today, if intracorporeal lithotripsy is necessary, Holmium:YAG laser lithotripsy is the modality of choice because of its shallow depth of penetration [203-207]. Ulvik and colleagues advised avoiding ultrasonic lithotripsy until further data have proved its safety to the fetus because of the possibility that high-pitched audible sound produced by the sonotrode may cause hearing injury to the fetus [208].

Although those investigators have advocated ureteroscopy during pregnancy, this may unnecessarily expose both the mother and foetus to all the potential risks of ureteroscopy. Care should be taken to minimize radiation exposure during the procedure with judicious use of pulsed fluoroscopy and shielding of the foetus.

The choice of stent insertion versus ureteroscopy should take into consideration several factors and is still on controversies: gestational age; presence of urinary tract infection; availability of ureteroscopic instruments and expertise and patient preferences. Stent insertion alone should be considered if the delivery of a full-term infant is imminent or there are signs of infection. Ureteroscopy may be indicated in cases in the first or second trimester, given the risk of infection and encrustation of a stent over a longer period of time.

Although insertion of a ureteral stent or nephrostomy tube is considered a minor procedure, repeated exchanges may have potential risk comparable to ureteroscopy performed as a single procedure. Therefore, Kavoussi and associates suggested that in selected patients, definitive ureteroscopic treatment may be preferable to stenting, especially early in gestation [210, 211].

SWL is contraindicated during pregnancy because of a theoretical risk to the foetus and/or ovaries [201, 212]. Although a retrospective series of six patients who inadvertently underwent SWL while pregnant demonstrated no adverse effects on the six healthy children who were born to these women [213], an alternative treatment option should be selected or SWL should be deferred until after delivery. For patients who are not pregnant but are contemplating becoming pregnant and are diagnosed with asymptomatic renal calculi, prophylactic treatment should be considered to avoid the difficulties of treating urolithiasis during pregnancy [198].

In summary**,** conservative management for most small to moderate non-obstructing renal calculi should suffice in most instances. For small intermittently obstructing renal pelvic or UPJ calculi, a trial of conservative therapy with hydration, analgesics, and prophylactic antibiotics may be indicated. For larger stones or persistent symptoms, upper tract drainage with a ureteral stent or nephrostomy tube is recommended. Early in pregnancy, nephrostomy drainage may be preferable to stent placement to avoid the need for repeated stent changes throughout the course of the pregnancy; during the third trimester, placement of a final internal stent can be performed. Definite stone treatment with ureteroscopy should be reserved for patients early in pregnancy who are unable to tolerate nephrostomy or stent drainage. Finally, pregnancy remains the only absolute contraindication for shock-wave lithotripsy.

I. TREATMENT OF URETERAL STONES IN CHILDREN

O. TRAXER

The incidence of urolithiasis in children is significantly lower than in the adult population and occurs because of a variety of factors, including defined metabolic and genetic disorders, geographic and socioeconomic boundaries, and exposure to medication and other environmental influences. In many instances, the cause of the stone is analogous to etiologies noted in adults, and treatment recommendations are frequently similar. In other instances, the formation of the stone is unique to the pediatric population, and, when these disorders are encountered, both treatment and preventive measures tend to be more specific and complex.

Although open stone removal remains in the armamentarium of many pediatric urologists, extracorporeal shock wave lithotripsy is still the gold standard for the management of renal calculi. On the other hand, due to the small size of the urinary tract in young children, some forms of intervention that are routinely used in adults, such as ureteroscopy and percutaneous procedures, must be used more judiciously. However, with the evolution of ureteroscopes and by understanding the differences in the endoscopic management of these patients, a primary endoscopic approach to the upper urinary tract of pediatric patients is now possible on a routine basis to treat urolithiasis.

I. INCIDENCE AND PRESENTATION

Children with renal stones seldom present with typical ureteric colic. In most series, about 70% of patients are diagnosed during work-up of urinary tract infection. Hematuria and abdominal pain are other presenting symptoms, with typical ureteric colic occurring in less than 15% of patients. The average age at presentation of children with renal stones is between 8 and 10 years. The male-to-female ratio is around 1.5:1, lower than the 3:1 ratio seen in adults [214].

The distribution of metabolic stone disease in children parallels that in adults, with calcium oxalate and phosphate stones being predominant. Hypercalciuria is the most common metabolic abnormality seen in patients with noninfected, nonanatomic renal stones. Uric acid stones accounting for between 5% and 10% of all stones. Cystinuria and primary hyperoxaluria are seen in 1% to 2% of patients. Distal RTA, sometimes associated with type 1 glycogen storage disease, is a rare cause of pediatric nephrolithiasis [215]. Because children with stone disease are at risk for a longer period than adults, the cumulative likelihood of stone recurrences may be higher in children. Thus, most authorities agree that a thorough metabolic evaluation is mandatory in children with nephrolithiasis. In most series, about two thirds of patients require procedural therapy to remove the stone. This rate is much higher than in the adult population.

The radiologic diagnosis of calculi in children is similar to that in adults. One significant radiologic difference between children and adults with stones was reported by Breatnach and Smith [216]. In a group of 50 children who had IVU for calculi, increased nephrographic density, or the adult intravenous urogram pattern of acute ureteric obstruction, was not seen. Because 80% of these children had associated urinary infections, generalized ureteral dilation and calicectasis were quite common and may have masked the typical radiologic signs of stone obstruction. The occurrence of lucent calculi (uric acid and, to some degree, cystine) requires urography. About 3% to 10% of calculi are radiolucent [217]. Some physicians avoid IVU in younger children because of excessive radiation exposure. Certainly, genitalia and gonads should be shielded whenever possible. Higher degrees of radiation can be avoided by the performance of a tailored urogram. Imaging by ultrasound methods can illustrate stone effectively. Often, a kidney-ureter-bladder radiograph accompanied by ultrasound of the kidneys, ureters, and bladder is sufficient.

II. TREATMENT AND RESULTS

There are few data to indicate the likelihood of stone passage relative to size and location in children. It is clear that children tend to pass stones more readily than adults, and a stone that would appear proportionately to require intervention may actually pass spontaneously in a child. The same indications for urgent intervention are applicable to children, including infection, intractable pain or nausea, and renal impairment. The potential for an associated or causative congenital impairment to urine flow should also be considered in treatment choice.

With the advent of less invasive forms of therapy, the role of open stone surgery in the treatment of children with urolithiasis has significantly declined [218].

Electrohydraulic lithotripsy and other forms of stone fragmentation have been effective in the management of children with urolithiasis. Kidney function is preserved, and any changes in the kidney, such as subcapsular hematomas, resolve with time [219]. This modality, particularly with the development of new instrumentation, has proved very effective in rendering the pediatric patient stone free [220]. Ureteroscopy tends to be more difficult, but in older children, newly developed small ureteroscopes can be passed safely with a low complication rate, thus allowing effective stone therapy [221].

III. EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY (SWL)

The majority of calculi in children are currently treated with SWL. Initially, treatment modifications were necessary on the HM3 to accommodate the small patient: flattening the gantry, lowering water levels, and shielding the lungs with polystyrene padding to prevent lung contusion. The newer generation lithotripters with a smaller focal zone require little or no lung shielding, and patient positioning on the table is technically simple even for the small infant. With over 1000 children world-wide treated with SWL, stone free rates of 64 to 96 % have been reported. Unfortunately, few series stratify outcomes by stone size or location and consequently stone free rates specifically for upper or lower ureteral stone are difficult to extract from published series.

The pediatric ureter seems to accommodate stone passage well, even with large stone burdens, and the need for post-SWL auxiliary procedures to facilitate stone passage remains under 10 % in most series. The need for preplacement of a ureteral stent in children undergoing SWL has not been specifically addressed. Specific guidelines regarding numbers of shock waves and recommended power for treatment of pediatric stone patients have not been established, however, most authors used the lowest power settings and fewest numbers of shock waves that resulted in stone fragmentation. In many HM3 series, power was maintained below 19 kV. Until further studies clarify the long-term risks of SWL, the procedure should be used with caution at the lowest power settings and with the fewest numbers of shock waves possible [222-228].

IV. URETEROSCOPY

Pediatric endourology has expanded rapidly from diagnostic cystoscopy and transurethral valve ablation to varied applications comparable to all adult endourologic techniques. This expansion has offered pediatric patients the advantages of less invasive means by which various urologic conditions may be treated, including urolithiasis that is the most common indication for ureteroscopy in the pediatric population. However, the choice of ureteroscopic stone removal in a child is a complex one that should balance the relative need for a single-intervention treatment (in contrast to the risk of needing multiple procedures, as with SWL) with the location and size of the stone and anatomic conditions who may affect the utility of ureteroscopy.

The earliest document report of an uretroscopic procedure in a pediatric patient was done by Young in 1929 on a 2-week old infant with posterior urethral valves [229]. After, the respective publications of Shepherd and Ritchey in 1988, the technique gained widespread acceptance by pediatric urologists [230, 231]. More recently, the introduction of the latest generation of flexible ureteroscopes with secondary deflection has permitted good outcomes of endoscopic management of urolithiasis [232]. Accessory instrumentation is similar to that used in adult ureteroscopic applications. Wire sizes need to be smaller to accommodate the generally smaller ureteroscopes, and they must include 0.28-inch and 0.18-inch wires. The rigidity of these wires must be sufficient to permit manipulations of the ureteroscope and passage of stents. Stone baskets and grasping devices are available as small as 1.5 Fr, but they are much less sturdy and may be frustrating to use. Balloon dilation of the ureteral orifice is occasionally needed, but there are few if any dilation balloons that are sufficiently small for young children. Use of a smaller ureteroscope is preferable [233]. An appropriate means of stone fragmentation is essential for any pediatric stone manipulation and should be integrated with the ureteroscopic instruments available. The electrohydraulic lithotripter (EHL) is a useful, all-purpose lithotripter, although it must be used carefully to avoid injury to the ureteral wall. Some surgeons do not use the EHL because of concern about ureteral wall injury; with low power settings and careful application, this is a limited risk. The new holmium:yttrium-aluminum-garnet (YAG) laser system will probably supplant the EHL for most ureteroscopic applications, and it offers the potential for retrograde upper tract stone management in younger children. The principal benefit with the holmium laser is that stone fragments do not need to be extracted because they are small enough to pass spontaneously. Furthermore, the laser fiber is only 200 µm in diameter, which does not restrict irrigant flow or flexibility in smaller endoscopes [234, 235].

There are few reports of ureteroscopic stone manipulation in children (**Table 2**), but all have demonstrated good efficacy and a minimal complication rate. Stone-free rates are about 93%, although this depends on the selection of patients for ureteroscopic intervention. If distal stones alone are approached, a very high stone-free rate may be expected, while proximal and renal stones are more challenging [235-249].

Table 2. Results of ureteroscopy in children: stone free rates and complications

AUTHOR/Year	Nb Patients (age range)	Location of stone	Nb Stone Free	Complications
Caione et al, 1990[250]	7 (3-8 yo)	Ureter	7	None
Scarpa et al, 1995	7 (< 10 yo)	Ureter	7	None
Shroff and Watson, 1995	13	Renal pelvis ad Ureter	10 (single procedure)	4/13 pneumonia, ureteral stricture, urinary retention
Smith et al 1996	11	Distal ureter	9 (single procedure)	None
Fraser et al, 1999	16 (18mo-15yo)		14	
Jayanthi et al, 1999	12	Distal ureter	11	None
Wollin et al, 1999	15 (4-17yo)	Renal pelvis and Ureter	12 (single procedure)	1, Urosepsis
Van Savage et al, 2000	17 (6mo-17yo)	Ureter	17	2/17 inability to access the ureter, ureteral perforation
Kurzrock et al 1996	17	Renal pelvis and Ureter	100%	2/17 Post-op urinary infection
Minevich et al 1997	7	Distal ureter	87%	None
Thomas et al 1993	16	Ureter	100%	1/16 transient vesicoureteric reflux
Schuster et al 2002	25	Renal Pelvis and Ureter	100%	2/25 pyelonephritis
Bassiri et al 2002	66	Ureter	88%	3/66 pyelonephritis
Russell et al	32	Renal Pelvis and Ureter	100%	1/32 pyelonephritis 1/32 proximal stonemigration
Total	**261**		**243 (93%)**	

In their series of 32 pediatric patients undergoing ureteroscopy for treatment of upper tract calculi, Russell and associates included four children with renal calculi [219]. A 6.9F or 9.5F flexible ureteroscope or a 6.9F or 8.5F semi-rigid ureteroscope was used in the series. Overall, a stone free rate of 100 % was achieved, including a second session in four patients. No ureteral perforations or strictures were reported, and the only complications were a case of pyelonephritis and proximal migration of a ureteral stone [243]. With small caliber ureteroscopes and working instruments, most pediatric ureters and kidneys can be easily accessed, in many cases without the need for dilation of the intramural ureter.

CONCLUSIONS

The majority of calculi in children are currently treated with SWL who represents the treatment of choice for a vast majority of stones in the pediatric population. However, over the past 15 years, endoscopic lithotripsy has gained international acceptance as an alternative to SWL in the management of upper urinary tract pediatric urolithiasis. A review of the literature suggest that ureteroscopic lithotripsy is a safe and effective treatment modality for the management of pediatric urolithiasis and this modality should be considered an essential part of the armamentarium of urologists. Future technological advances, knowledge of available equipment and anatomic and physiologic differences of pediatric patients, will allow the indications for pediatric ureteroscopy to evolve and will ensure a successful outcome with minimal morbidity.

J. TO CHOOSE THE MOST APPROPRIATE TREATMENT FOR REMOVAL OF URETERAL STONES

H. G Tiselius

Several decisive factors need to be considered for the active removal of one or several stones from the ureter. In this regard the available equipment as well as the expertise of the urologist are two issues that are of fundamental importance for a successful treatment. From the patient's perspective it is essential that the treatment is carried out with a method that is both effective and safe. During the past two to three decades we have seen a dramatic technical development that has given us low-invasive and non-invasive methods for the purpose of gentle active removal of stones from the ureter.

As a result of this progress there is, undoubtedly, a consensus that open/incisional surgery has lost its role as a method for dealing with stones in the ureter. There might, however, be exceptional problems for which such an approach still might be necessary [250, 251], but in most of these situations the low-invasive requirement is probably better fulfilled with the laparoscopic technique for which excellent results have been reported [252-255]. There are certainly also some patients for whom a percutaneous approach might be useful [178-180]. For the vast majority of patients with ureteral stones, however, the choice stands between SWL and URS and which of these two alternatives that is preferable, has been a matter of debate during the past years. Both methods are effective in terms of clearing the ureter, but each of them has advantages as well as disadvantages.

SWL, as discussed in detail above, is a non-invasive method that usually can be carried out in an outpatient setting with only analgesics and sedation or even without any analgesic treatment. For large, hard and impacted stones repeated shockwave sessions might be necessary. The occurrence of complications following SWL of ureteral stones is low [256], but adjunctive procedures such as stenting and use of contrast medium might be necessary for a better stone disintegration and/or stone localisation in selected patients. It is of note, however, that many lithotripters that succeeded the initial model - the unmodified Dornier HM3 - had insufficient capacity to disintegrate stones. These shortcomings are one of the major explanations of the variable results obtained and reported in the literature. Recently developed lithotripters, fortunately, seem to have been improved and they usually provide a disintegrating capacity at a level similar to that seen with the original lithotripters [257].

The literature on results of SWL for ureteral stones is very extensive and impossible to cover completely, but a reasonably representative selection of reports, comprising more than 8000 treated patients [250, 258-284], disclosed stone-free rates between 42 and almost 99 %. The average stone-free rate in these reports was 72 %. This result was obtained with a mean (SD) number of sessions of 1.28 (1.25). According to a previous review of literature [285] data the result for distal ureteral stones were best with a stone-free rate between 77 and 100 %, for middle ureteral stones 65-100 % and for proximal stones 62- 96 %. Calculated average values for distal, mid and proximal ureteral stones were 92, 79 and 81 %, respectively. This great variation might reflect differences in terms of lithotripter capacity, ambition and experience of the operator [286], use of adjunctive procedures as well as selection of patients.

The great advantage of URS is that the need of repeated treatment sessions is low and that stone removal in most patients accordingly can be completed in one session. On the other hand URS is an invasive technique that usually requires some form of anaesthesia (either general or regional). There also is a higher risk of complications with URS than with SWL and some of these complications are also definitely of severe character [287, 288]. When antegrade URS is carried out and a percutaneous nephrostomy or an internal stent is inserted after stone removal, these auxiliary steps have to be considered as well.

Results in the literature [250, 258-273, 289-296] have shown stone-free rates following URS between 69 and 100 %, with the majority of reports above 85 % with an average of 92 %. In a review by Pearle and Clayman [285] an average stone-free rate of 92 % was recorded following URS for distal ureteral stones, but for mid ureteral stones the corresponding number was only 72 % and for proximal stones 68 %.

In order to give further directions on the best method for removal of stones from the ureter we need to focus on studies of which the purpose has been to compare SWL and URS. In two randomized trials, distal ureteral stones were treated with either SWL or URS. In one of these studies [271] comprising 98 patients treated with SWL and 119 with URS, the stone-free rates after one session were 66 and 69 %, respectively. In the other randomized comparison [266], stone-free rates of 51 and 91 % were recorded despite 1.45 SWL sessions. These authors had used 1.09 sessions of URS in order to get the reported stone free rate.

In 17 clinical reports on comparison between the two treatment methods [250, 258-273, 289-296] the average stone free rates of 92 % following URS was apparently superior to that of 67 % obtained with SWL. It needs to be emphasized that in all these comparisons the number of patients treated with SWL was larger than that of the URS group and whereas 4965 patients were found in the SWL group, only 2891 had been treated with URS. Different criteria obviously had been used for referring the patients to one or the other form of treatment. Although results of SWL in several studies came up to a stone-free rate similar to that obtained with URS, it stands to reason that the ureters in general can be cleared from stone material faster and with fewer treatment sessions when URS is used as the primary procedure. This is also the basis on which many urologists make the decision in preference of URS. Others consider the non-invasive nature of SWL together with the low risk of complications and the possibility to treat the patients without general or regional anaesthesia to outweigh the disadvantage of repeated treatment sessions in a fraction of patients [258, 297] and such a view has also been favoured by patients who have been asked about their choice [260, 271]. When the need of anaesthesia was included in a treatment index the advantage of URS over SWL also disappeared [298].

It is understood that URS has an advantage over SWL for treating large stones. Kanano and coworkers [299] found that one session of SWL for stones with a largest diameter of 6-10 mm resulted in a stone-free rate of 84-86 % in comparison with only 37-42 % for stones with a diameter exceeding 20 mm. In another report in which 153 patients had been treated with SWL, using the lithotripter Dornier MFL5000 [300], the authors suggested a cut-off at 7 mm for successful SWL. Successful SWL of large stones has, however, also been reported [301], but if the re-treatment rate has to be restricted, SWL should not be chosen for large stones.

Each one of the two treatment methods - URS and SWL - has to be judged on its own merits. There is no definite winner of this competition, because there are several aspects that need to be considered. The various steps in the stone removing procedure are summarised in **Figure 2** from which conclusions can be drawn, once a decision has been made on which factor that is more important than the other. It needs to be emphasized, however, that whichever method that is selected it is essential to have the appropriate equipment, expertise and organisation. For SWL access to a lithotripter of high quality and with optimal disintegrating capacity is necessary. Precise focusing of the stone is an absolute prerequisite as is an operator with sufficient experience of selecting the proper energy level and number of shock waves. Moreover, repeated sessions have to be an accepted part of the procedure. For URS high quality ureteroscopes (semirigid as well as flexible) together with an efficient intracorporeal stone disintegrating device is necessary. So is the expertise and care exerted by the operator. The latter aspect is particularly important in order to keep the complications at a low level.

Economic aspects might have a major influence on the selection of the stone removing procedure. The re-imbursement from the health care system can be decisive for whether SWL or URS is chosen. The intention of this consideration is not to make a thorough economic analysis because there are too large variations from one country to another with different financial principles. This is also the reason why in some reports URS is a more economic alternative than SWL, whereas in others the opposite is the case. It is important to realise, however, that flexible ureteroscopes that are more and more commonly in use are both expensive and have a limited durability [302], a factor that also needs to be taken into account.

The conclusions drawn from evaluation of treatment results and recent experience of SWL and URS are that both methods are acceptable as primary treatment of stones at all levels of the ureter. URS can be used to solve problems not managed by SWL and vice versa. There are, however, certain conditions in which URS might be superior. To this group we can refer obese patients, patients with radiolucent stones, patients on continuous treatment with anticoagulation agents, such as salicylates and warfarin, and possibly selected pregnant women with ureteral stones. These aspects are discussed obove and elsewhere in this book as is the choice of stone removing method for children.

SUMMARY

The appropriate management of patients with stones in the ureter is an important part of urology. Obviously the chance for spontanaoue passage is great and the the majority of patients present with stones that can be followed conservatively. The recent experience with α-receptor antagonists and calium-channel blockers is a promising tool to facilitate passage of stones and fragments from the ureter. Both SWL and URS have proved to be excellent methods for active removal of ureteral stones. The variability in results probably is explained by differences both in experience, expertice and equipment. The more invasive procedures discussed above have a limited use for a selected small group of patients with particularly problematic stones in the ureter and in the case reconstructive surgery is necessary. Otherwise incisional (open) or laparoscopic surgery should be considered only when the less invasive therapeutic approaches have failed to clear the ureter.

Analysis of the composition of the retrieved stone material should be carried out in order to get a correct explanation for the stone formation and recurrence prevention considered in case of repeated stone formation, but this problem is discussed elsewhere in this book.

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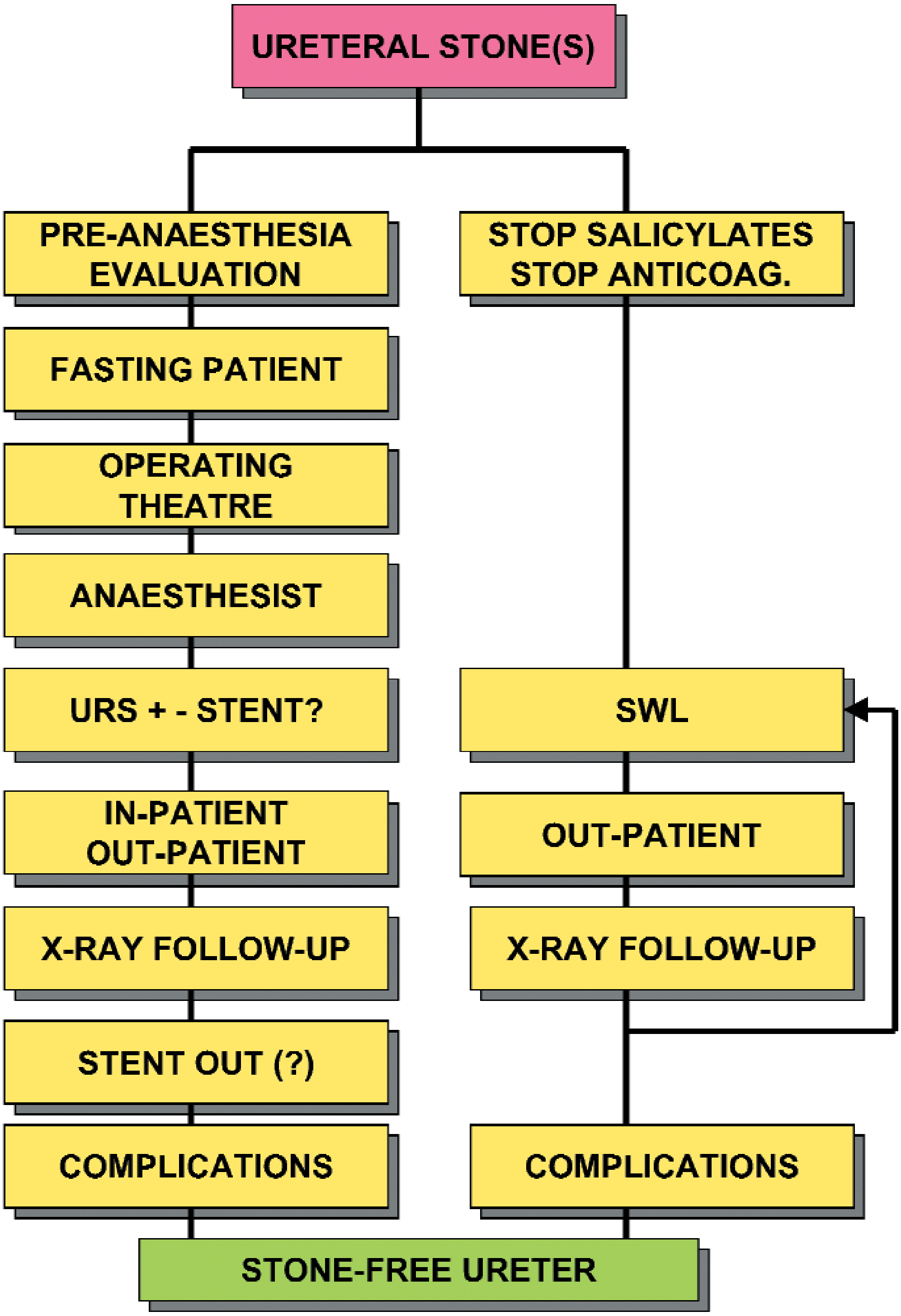
Figure 2. Different treatment procedures for removal of ureteral stones with URS (left) and SWL (right)



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Committee 7 A

Pediatric Stone Disease

Chairman

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CHRISTIAN TÜRK

CONTENTS

Pediatric Stone Disease

HASSAN RAZVI,

MICHAEL CONLIN, ENRIQUE MUES, CHRISTIAN TÜRK

A. INCIDENCE

CHRISTIAN TUERK

In developed countries, two major reasons for the increasing incidence of urinary stones among children have been identified:

1. Global increase in the incidence of urolithiasis [1]. For instance a representative survey in Germany showed an increase from 0.54% to 1.47% between 1979 and 2000. The prevalence among patients below the age of 20 years was approximately 0.6% [2].
2. The age at which the first stone episode occurs seems to have shifted in favor of younger individuals [3,4]. The reasons for this phenomenon are controversial. Lifestyles changes especially dietary, and the obesity epidemic have been suggested as potential causes. Changes in the use of diagnostic and therapeutic tools may also result in a statistical bias when comparing data over the decades.

A recent, yet unpublished multicenter meta-analysis of 140,000 cases in Germany and Austria revealed that approximately 1.35% of stones develop in patients younger than 20 years of age (personal communication, M.Straub et al.). A study in the USA showed the growing prevalence of urolithiasis as well as an association between race/ethnicity and the region of residence [1].

Developing countries however appear to be different in this regard. While a similar trend was registered in North Africa as that in industrialized countries [5], pediatric urolithiasis still is an endemic disease in certain parts of the world such as Turkey and the Far East [6]. The location of stones as well as their composition differ from those in developed countries. For example, bladder stones in children are rare in developed countries but were present in 60% of cases among pediatric patients with urolithiasis in Pakistan in the mid 1980s; this figure decreased to 15% of all cases of urolithiasis in the mid 1990s [7]. In Laos the most common cause of surgery in children was the presence of bladder stones. Nearly all of these children suffered from severe malnutrition [8]. Malnutrition is associated with a high incidence of ammonium urate stones. As many as 25% of stones in pediatric patients in developing countries are of ammonium urate while this is true of far less than 5% of cases in developed countries [7].

In summary, the prevalence of urolithiasis in children depends on socioeconomic conditions as well as ethnicity. The incidence of urolithiasis rises in developed countries, independent of age. In underdeveloped countries, malnutrition is a major reason for the prevalence of bladder stones and ammonium urate stones in children.

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B. INVESTIGATIONS

Christian Tuerk

I. INTRODUCTION

Infants and children may present with a wide range of uncharacteristic symptoms in the presence of urinary stones. Diagnostic imaging in particular, assumes an important role in the investigation of the child with an upper tract stone. Coupled with the potentially higher rates of carcinogenesis from the effects of ionizing radiation in the pediatric population, the investigation of patients with pediatric stones is a subject of great interest.

The investigations may be divided into the following categories:

- those related to the diagnosis of stones including anatomic and functional information of the urinary tract ("imaging"), and
- those related to the metabolic situation.

All investigations start with an evaluation of the patient's personal and family history, including nutritional habits and fluid intake, physical investigation and laboratory tests of blood and urine. A urine culture is mandatory [1] (Level 2 evidence, Grade A recommendation).

II. IMAGING

Following these crucial steps, several optional procedures may be used to establish the diagnosis: ultrasound (US), plain film (KUB) with or without intravenous urography (IVU), helical CT, magnetic resonance urography (MRU), or nuclear imaging.

1. ULTRASOUND (US)

US is the most popular imaging study. Its major advantages in pediatric patients are the absence of irradiation and anesthesia. US evaluation should include the kidney, the bladder, [2](level 4 evidence, Grade B recommendation) and adjoining portions of the ureter.

Stones in the visible portion of the urinary tract are easily identified by this procedure. Besides, the degree of hydronephrosis, dilatation of the ureter, renal length and width, anatomy of the parenchyma, scars, renal masses and cysts can also be established. US with a full bladder demonstrates stones in the bladder and the prevesical part of the ureter, ureteroceles, bladder masses or other anatomic abnormalities as well as the residual post-voiding volume. With the addition of color-doppler US it is also possible to show differences in the ureteric jet [3] (level 4 evidence, Grade C recommendation).

The resistive index (RI) of the arciform arteries of both kidneys is indicative of the grade of obstruction [4] (Level 4 evidence, Grade C recommendation). Twinkling artifacts might help to identify stones [5] (Level 4 evidence, Grade D recommendation).

US is able to provide information about the presence, size and location of a stone, the grade of dilatation, obstruction, as well as indicate signs of abnormalities that facilitate the formation of stones. Nevertheless, US fails to identify stones in more than 40% of pediatric patients [6,7] (Level 4 evidence) and provides no information about renal function.

2. PLAIN FILM (KUB)

In combination with ultrasound or MRU, KUB may serve as a useful aid to identify stones and their radiopacity.

3. INTRAVENOUS UROGRAPHY (IVU)

IVU is an important diagnostic tool. It is able to demonstrate nearly all stones in the collecting system and also provides anatomic and functional information. Post-interventional KUB can be easily compared with previous IVPs in cases of radiopaque stones. However, it requires the injection of contrast dye. The radiation dose for IVU is comparable to that used for a voiding cystourethrogram (dose range: 49.06 to 83.33 cGy/cm^2). Despite the need for ionizing radiation, conventional contrast imaging is indispensable in some cases [8,9] (Level 4 evidence, Grade C recommendation).

4. HELICAL COMPUTED TOMOGRAM (CT)

Non-enhanced helical CT is a well established procedure to diagnose urolithiasis in adults. Its sensitivity and specificity are the highest among all diagnostic procedures. In pediatric patients, only 5% of stones escape detection by non-enhanced helical CT [6,7] (Level 4 evidence). Sedation or anesthesia is rarely needed when a modern high-speed CT apparatus is used [2] (expert opinion). Recently developed CT protocols may further reduce the radiation exposure [10] (Level 4 evidence, Grade C recommendation). The radiation dose and the lack of information about renal function must be considered when using non-enhanced helical CT.

5. MAGNETIC RESONANCE UROGRAPHY (MRU)

The sensitivity of MRU to demonstrate urinary stones is limited, however detailed information about the anatomy of the urinary collecting system, location of an obstruction or stenosis in the ureter, and the morphology of renal parenchyma maybe provided [11] (Level 4 evidence). The absence of any radiation must be weighed against the long duration of the investigation, and the need for anesthesia in young children.

6. NUCLEAR IMAGING

The DMSA scan (^{99m}Tc-dimercaptosuccinyl acid) provides information about cortical abnormalities such as scarring but is of no help in the primary diagnosis of urolithiasis. Diuretic renogram with injection of a radiotracer (MAG_3 or DPTA) and furosemide are able to demonstrate renal function, identify obstruction in the kidney (after injection of furosemide), as well as indicate the anatomical level of the obstruction. Standardized procedures facilitate the reproducibility of these examinations. The benefit of limited ionizing rays compared to conventional X-ray and CT must be weighed against its limited value for the purpose of diagnosing urolithiasis [2,12] (Level 4 evidence, Grade C and B recommendation).

Diagnostic procedures to identify urolithiasis in pediatric patients must consider the fact that the patients may be uncooperative, require anesthesia for some modalities, and may be sensitive to ionizing rays. Therefore, ultrasound is of great significance in this setting. More than one imaging study or combinations of various procedures will be required in most cases [13].

III. METABOLIC INVESTIGATIONS

Pediatric urinary stone patients belong to the high-risk group for recurrent urinary stones [1] (Level 2 evidence, Grade B recommendation). As such, these patients and their families need specific therapeutic directions for effective stone prevention, adjusted to their metabolic risk. The risk may be based on anatomic or functional disorders of the urinary collecting system and/or metabolic abnormalities including genetic disorders. Any investigation will have to take these risks into account.

The most common anatomical or functional disorders are vesicoureteral reflux, ureteropelvic junction obstruction, neurogenic bladder dysfunction or other voiding difficulties [13] (Level 4 evidence). The majority of anatomical or functional disorders become evident when the above mentioned studies are performed. An additional voiding cystourethrogram might be necessary.

A stone is a symptom of an underlying disorder and may serve as the primary guide for further metabolic investigations. A stone analysis is essential part of the metabolic investigation of the pediatric stone former. Approximately 60% of all stones have more than one component. According to the current standard, infrared spectroscopy or X-ray diffractionmetry are mandatory. These procedures are known for their high sensitivity and specificity. A wet chemistry analysis is insufficient. A urine filtration will be required to collect a minimum of 1-5 mg of stone material. Genetic disorders such as cystinuria or xanthinuria are easily discovered by stone analysis.

In addition, 24-hour urine collections must be examined for daily excretion of calcium, oxalate, citrate, uric acid, creatinine and cysteine, if required. Serum chemistry studies should include the same parameters (excluding cystine) and additionally PTH (parathyroid hormone) in case of calcium oxalate stones [1] (Level 2 evidence, Grade A recommendation).

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C. PREVENTION AND MEDICAL MANAGEMENT

MICHAEL COLIN

Conventional wisdom has suggested that all patients under the age of 16 years of age with a history of urinary stone disease should undergo metabolic analysis. The evidence to support this recommendation is presented in the table below.

First Author	Year	Type of Study	Level of Evidence	% of Patients with Metabolic Abnormalities	Evidence Favoring Metabolic Evaluation?
DeFoor	2006 [1]	Prospective	2		Yes
Schwarz	2005 [2]	Retro review	3	27%	No
Edvardsson	2005 [3]	Retro review	3	96%	Yes
Lande	2005 [4]	Retro review	3	56%	Yes
Coward	2003 [5]	Retro review	3		Yes
Pietrow	2002 [6]	Retro review	3	38 - 50%	Yes
Battino	2002 [7]	Retro review	3	100%	Yes
Rizvi	2002 [8]	Retro review	3	25%	Yes
Sarkissian	2001 [9]	Retro review	3	31%	Yes
Noe	2000 [10]	Retro review	3		Yes
Ozokutan	2000 [11]	Retro review	3		Yes
Milliner	1993 [12]	Retro review	3		Yes
Stapleton	1987 [13]	Retro review	3		Yes
Sarica	2006 [14]	Review	4		Yes
Cameron	2005 [15]	Review	4		Yes
Straub	2005 [16]	Review	4		Yes
Faerber	2001 [17]	Review	4		Yes

RECOMMENDATION

All pediatric patients with urolithiasis should undergo metabolic evaluation. Grade B recommendation level.

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D. INTERVENTIONAL THERAPIES

ENRIQUE MUES

I. INTRODUCTION

Pediatric urolithiasis is relatively uncommon but poses a specific technical challenge to the urologist. Aims of management should be complete clearance of stones, preservation of renal function and prevention of recurrence [1]. Extracorporeal shock-wave lithotripsy continues to be the most commonly performed procedure for stone disease. Technologic advances and miniaturization of instruments in endoscopy have led to more minimally invasive treatment options for children with urinary stones requiring intervention.

The indications for operative intervention in children are similar to those in adults: infection, obstructive uropathy, persistent flank pain, as well as the failure to pass a ureteral stone after an appropriate trial of observation [2]. Fortunately most ureteral stones pass without intervention. Van Savage et al performed a retrospective analysis of 33 children who presented with a symptomatic distal ureteral calculus. Most stones < 3 mm in diameter in the distal ureter passed spontaneously. No stone > 4 mm in diameter passed spontaneously [3].

Several factors must be considered before the decision to proceed with surgical treatment is made: size of the stone, localization, anatomic abnormalities, available equipment and the surgeon´s experience. Quite clearly the management of pediatric urolithiasis is very different throughout the world-most notably due to limited access to technology in the developing world.

II. SHOCK WAVE LITHOTRIPSY (SWL)

SWL remains the most common treatment used in the treatment of pediatric stones. The efficacy, need for ancillary procedures and treatment related complications however, are not as clearly defined as in the adult population.

Lottmann et al examined the efficacy and renal parenchymal effects of SWL in 19 infants. Follow up with renal scintigraphy, over 36 months detected no acquired renal parenchymal damage [4,5].

Fortunately, nephrolithiasis among low birth weight infants rarely requires surgical management. When necessary however, Shukla et al demonstrated in a retrospective study of 8 infants (mean age 13 months and weight 7,700 gm) that SWL is effective and safe for small infants [6] (Level 3 evidence, Grade C recommendation).

Numerous studies, mostly retrospective in nature have now reported results citing acceptable stone free rates and a low rate of treatment related complications. Stone-free rates defined in different ways vary between 50 - 90%, and are influenced by factors similar to adults including stone burden and stone composition. These studies support the use of SWL as first line therapy for most children with renal or upper ureteral stones requiring intervention [7-12] (Level 3 evidence, Grade B recommendation).

Interestingly lower pole stone location in children may have less influence on stone-free rate post-SWL as it does in adults. Demirkesen et al compared stone-free rates between lower, middle and upper caliceal groups, and showed that for stones <10 mm, the results are similar [11].

The success of SWL in adults has been defined as stone-free rate status or if residual fragments are < 4 mm and presumed to be clinically insignificant. Whether this definition holds true for pediatric patients, has been questioned. Afshar et al reported a retrospective study of children with residual fragments from 4 to 5 mm post SWL. They noted in 69% of these children had adverse clinical outcomes including recurrent colic and increase in stone growth in comparison with patients rendered stone free [12]. In view of the higher risk of underlying metabolic or anatomical abnormalities, every attempt should be made to achieve a stone free state or to maintain close follow up of these patients (Level 3 evidence, Grade B recommendation).

The role of stent insertion in children undergoing SWL is a controversial subject. It has been suggested that the pediatric ureter maybe more efficient in clearing stones than adults after SWL. Gofrit et al in a prospective non-randomized study compared the outcomes after SWL of renal stones greater than 10 mm between young children and adults. The stone-free rate for children was superior to that in adults (95% versus 79%; p=0.008). Children achieved a stone-free state quicker than adults and steinstrasse was not observed in any child. The authors have therefore suggested stent or nephrostomy insertion should be used primarily for treatment of the child who is septic or with an obstructed kidney, rather than basing that decision on stone size criteria [13](Level 2 evidence, Grade B recommendation).

III. URETEROSCOPY

Advances in the design of ureteroscopes and ancillary instruments have resulted in miniaturization of the scopes required for pediatric patients. Ureteroscopic has now become part of the standard armamentarium of the pediatric urologist, with semi-rigid and flexible ureteroscopes with sizes from 4.5 - 8.7 Fr now available. Despite the improved instrumentation, the surgeon’s skill and experience remain equally important when considering ureteroscopy as a treatment option [14].

The role of ureteroscopy in the pediatric population continues to evolve. Various authors have reported retrospective case series experience, with stone-free rates in excess of 90% and with minimal complications [16-18] (Level 3 evidence, Grade B and C recommendations).

Tan et al reported a retrospective study of 23 patients with 27 renal and/or ureteral stones. The stone free rate was 95.2%. Ureteral stents were placed post-operatively in 21 patients for stone burdens of more than 6 mm, when balloon dilation was required, if significant ureteral edema or stone impaction was noted or if patients had a long travel distance to return home [15]. Satar et al assessed the safety of rigid ureteroscopy for the treatment of pediatric ureterolithiasis in 33 children with stone located in the upper, middle and lower ureter. No incidence of vesicoureteral reflux was detected with postoperative cystography [16].

Recently De Dominics et al reported a prospective randomized study comparing SWL vs ureteroscopy for distal ureteric stones, and demonstrated a statistically significant higher success rate for ureteroscopy with intracorporeal lithotripsy (94%), compared with SWL (42% after one session and 64% after two sessions) [17] (Level 2 evidence, Grade B recommendation).

The holmium:YAG laser is a safe and effective intracorporeal lithotripter for treating stones in children. Reddy et al and Wollin et al performed ureteroscopy with holmium-YAG laser without intraoperative injury [18,19]. In fact, many authors consider ureteroscopic with laser lithotripsy an excellent first line treatment for children with stones in whom conservative therapy fails, especially those with distal and mid ureteral stones [20-23] (Level 3 evidence, Grade B recommendation).

IV. PERCUTANEOUS NEPHROLITHOTOMY (PCNL)

In patients with complex or large stone burdens such as a staghorn calculi or when anatomic derangements make stone clearance using other modalities less likely, PCNL has become the procedure of first choice in the hands of the experienced endourologist possessing the proper instrumentation [24-27] (Level 3 evidence, Grade C recommendation).

The concept of the mini-perc was devised to reduce potential complications of PCNL in children [24]. Zeren et al reported a retrospective analysis of 67 PCNL procedures with a stone-free rate of 86.9%, although 23.9% of patients required blood transfusion [25].

Aron et al report a retrospective study of 19 PCNL procedures in patients with mean stone burden of 972 mm; the stone-free rate was 89% with PCNL monotherapy, which increased to 94.7% with adjunctive SWL. They used a tract dilation to 24 F, with 19 Fr sheathless nephroscope passed through an Amplatz sheath. PCNL was considered a safe option and effective for maximal stone clearance for complete staghorn stones [26].

Even among children less than 5 years of age, PCNL has been shown to be safe and effective. Staging of the procedure was preferred in children with renal insufficiency, urinary tract infection, fragmentation time > 60 minutes. The stone-free rate was 86%. There was statistically significant increase in the blood loss in patients requiring multiple tracts (p=0.008) [27] (Level 3 evidence, Grade B recommendation).

Tubeless PCNL is a well described procedure in adults, although the number of published reports, particularly in pre-school children, is extremely limited. Salem et al reported their results of a prospective study comparing outcomes between patients left tubeless versus those who had a nephrostomy tube post-operatively. Less post-operative pain and a shortened hospital stays were noted in the tubeless group. The decision on whether to use this option is best made intraoperatively and depends on the experience of the surgeon [28] (Level 2 evidence, Grade B recommendation).

V. OPEN SURGERY

Open surgery in developed countries is now usually reserved for patients with upper tract stones in association with anatomical abnormalities or for failed endourological attempts.

In developing countries on the other hand, open approaches remain important options due to the lack of endourological equipment and training. Jallouli et al report a retrospective study of 525 procedures in children in Tunisia. Stones were treated by open surgery in 80% of the cases [29].

Rizvi et al reported a retrospective study of 1,440 children in Pakistan. Open surgery was used in 70% of children with renal stones and 38% of those with ureteral stones [30].

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Committee 7 B

Stones in Pregnancy

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CONTENTS

Stones in Pregnancy

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A. EPIDEMIOLOGY & INVESTIGATIONS

Francis Keeley, Ondina Harryman

I. INTRODUCTION

Renal calculi in pregnancy pose diagnostic and management difficulties due to concerns over risks to the fetus. The customary investigations for a patient with urinary calculi involve ionizing radiation; however, during pregnancy, these investigations must be considered in the context of risks to the fetus and balanced against risks of not establishing a diagnosis. Investigations consequently may be inadequate, making management problematic. Once a definite diagnosis of a ureteric stone is made, management is typically conservative, given that procedures may endanger the health of the fetus. Fortunately, most stones occur late in pregnancy after organogenesis.

II. EPIDEMIOLOGY

The majority of literature on stones in pregnancy is based on case series involving small numbers of patients. It is an infrequent but serious problem. The incidence of renal calculi in pregnancy is estimated between 1 in 244 to 1 in 3300 [1,2,8,10] (Level 3 evidence). The incidence is similar to that in non-pregnant women of the same age. The majority (80-99%) [1,2,3] (Level 3 evidence) of patients present during the second and third trimesters, which is important as the risks to the fetus are lower. Multiparas are more commonly affected than primiparous women. Both sides are reported to be equally affected [2,3] (Level 3 evidence).

The presenting complaint in 80% is flank pain, and 99% have microscopic or visible hematuria [1,2,3] Level 3 evidence). However, this may necessitate repeated testing. The localization of pain during pregnancy can lead to misdiagnoses such as appendicitis, cholecystitis and pyelonephritis. Roughly one-quarter have a history of urinary calculi [1] (Level 3 evidence). The majority (64-85%) of patients pass the stone spontaneously, without any surgical intervention [1,2,3] (Level 3 evidence).

III. INVESTIGATIONS

The risk posed to the fetus from exposure to ionizing radiation is a critical factor in decision-making for imaging. The critical threshold for radiation exposure to the fetus is not known exactly, but it is thought that 25-80 rad doubles the risk of congenital malformation [2]. An intravenous urogram delivers a mean of 170 mrad and a maximum of 1 rad to the fetus [19]. The risks of teratogenicity and mental retardation are highest in the first trimester. However, the majority of patients present during the second and third trimesters, when the radiation risk is relatively low. The risk to the fetus must be weighed against the danger of a delayed diagnosis of an obstructed kidney. An important factor to consider is the risk of inducing premature labor through either prolonged renal colic with medical management or an invasive procedure.

Ultrasound has an excellent safety record and appears to pose no risk to the fetus; however, physiological dilatation of the ureters can be difficult to differentiate from pathological dilatation.

Conversely there may be little or no upper tract dilatation in acute obstruction. Ultrasound has been found to have an 34% sensitivity and an 86% specificity rate for detection of an abnormality in the presence of a stone in a symptomatic patient [2] (Level 3 evidence). The finding of ureteral jets in the bladder using Doppler ultrasound may be helpful to exclude complete obstruction, but its accuracy in diagnosing stones has not been established and it is unlikely to be a definitive test.

Physiological hydronephrosis occurs during pregnancy. The onset is during the first trimester, with resolution within a month of delivery. The ureters are dilated bilaterally down to the level of the pelvic brim. Progesterone is thought to affect the urinary smooth muscle in early pregnancy, causing dilatation and reducing peristalsis of the ureter. In later pregnancy, compression of the ureter from the enlarging uterus may contribute to hydronephrosis [16]. McNeily et al found that in physiological hydronephrosis the dilated ureter extends down only to the level of the common iliac artery [4] (Level 3 evidence).

Ureteric obstruction leads to vasoconstriction in the kidney. The resistive index (RI) of the infrarenal vessels can be calculated using Doppler ultrasonography. (RI= peak systolic velocity-peak diastolic velocity/peak systolic velocity). The RI is significantly higher in obstructed kidneys. A case-control study found that physiological dilatation during pregnancy did not increase the RI even though obstruction is likely to contribute to the physiologic dilatation of pregnancy. The average RI for each kidney was calculated in this study (from the upper, middle and lower RI's). The RI for moderate pelvicaliecasis was 61.7 ± 4.5 in the right kidney and 63.4 ± 6.5 in the left kidney. Hertzberg et al concluded that a high average RI (>0.7) for a kidney cannot be explained on the basis of pregnancy alone and may therefore be a useful study [6] (Level 3 evidence). Shokeir et al found the mean RI of 22 pregnant women with unilateral ureteral obstruction due to a stone was 0.69 ± 0.03 [5] (Level 3 evidence).

Limited intravenous urography (IVU) has been used as second line, and found to pick up the majority of missed stones. In order to minimise the radiation exposure, protocols of a plain film then one after 30-60 minutes are used in most studies. Computed tomography (CT) is relatively contraindicated due to the high radiation dose.

MRI is poor at specifying the nature of the intrinsic obstruction. However, a prospective case control study (11 patients) found that MR excretory urography is more accurate than Doppler ultrasound in the assessment of ureteric obstruction in pregnancy [7] (Level 2 evidence). It gives equivalent functional and additional anatomical information to isotope renography.

Retrograde pyelography has been used as a diagnostic test in cases where stones have not been diagnosed by ultrasound or KUB. Ureteral stent insertion under local anaesthetic can be achieved at the same time. Stothers et al found the presence and location of the stone in 12 of 13 patients who underwent retrograde pyelograms after an abnormal IVU. One patient had a dilated collecting system, but a stone could not be found and was presumed to have passed [2] (Level 3 evidence). Therefore, it is a useful diagnostic test, but lead shielding should be used whenever possible, and fluoroscopy time can be minimised by using short bursts.

B. MANAGEMENT OF ASYMPTOMATIC STONE IN WOMEN OF CHILDBEARING AGE

FRANCIS KEELEY, ONDINA HARRYMAN

There are no reports specifically looking at the management of asymptomatic stones in women of childbearing age. The natural history of stone disease has been studied in both sexes and across all ages. Therefore, we will consider the natural history of asymptomatic calculi in the context of whether treatment of asymptomatic stones causes fertility problems and the risks caused to mother and fetus should the stone become symptomatic during pregnancy.

The incidence of stone disease in women is increasing. A recent study looked at hospital discharges for stone disease between 1997 and 2002, and found that the prevalence of stone disease in a North American sample changed from a 1.7:1 to 1.3:1 male:female ratio. In females hospital discharges for renal calculi increased by 21.0% and hospital discharges for ureteral calculi increased by 19.2% (each $p<0.001$) [12] (Level 3 evidence).

Glowacki et al reported an inception cohort of 107 patients (male and female) with asymptomatic urinary calculi followed up for a mean of 31.6 months. 34 (31.8% became symptomatic, with spontaneous passage in 47%. The cumulative five year probability of a symptomatic event developing was 48.5%. Reviewing the outcomes of the females only (34 patients), revealed 24% became symptomatic in the follow up period [14] (Level 3 evidence).

Marshall et al found that 30.1% of the women they followed up developed a second stone (mean length of follow up 7.4 years) [11] (Level 3 evidence).

Since the introduction of extracorporeal shock wave lithotripsy (SWL), there has been an increase in the treatment of asymptomatic renal calculi. A prospective randomised study found that prophylactic SWL for small asymptomatic renal calyceal stones did not offer any advantage to patients in terms of stone-free rate, quality of life, renal function, symptoms or hospital admissions. However, a policy of observation is associated with a greater risk of requiring more invasive procedures. The study required a longer follow up to assess the validity of the preliminary findings [13] (Level 1 evidence).

A small study observed that women of childbearing age undergoing SWL did not subsequently experience fertility problems when attempting to become pregnant [15] (Level 3 evidence). A retrospective survey of women of reproductive age (mean 30 years) who had undergone SWL for distal ureteric calculi found that 10 of the 67 women had attempted to become pregnant. Overall 7 children with no malformations were born to 6 patients. Three patients had spontaneous abortions, which occurred at least one year after SWL [18] (Level 3 evidence). Animal studies found that no gross teratogenic effects and no statistical difference in the litter size or fetal weights were caused in the offspring following SWL to the ovaries [23] (Level 3 evidence). Morphological changes were observed in the short term, however, there was no morphological lesion in the long term groups [24] (Level 3 evidence).

The effect of shock waves on the embryo and fetus is not known. A study with a small number of patients found that inadvertent SWL (using ultrasound location) during the first month of pregnancy in 6 women, who gave birth to 6 children, did not cause any detectable malformations or chromosomal anomalies [17] (Level 3 evidence). Pregnancy should be considered a contraindication to SWL, given the high pressure shock waves it induces.

The options for treatment of distal ureteral stones which fail conservative management in young women include ureteroscopy and SWL. The reported success rates for both options are high. Ureteroscopy typically involves general anesthesia and manipulation of the ureter, while SWL necessitates exposing surrounding structures to a high-pressure shock wave. SWL was once felt to be contraindicated for distal ureteral stones in women of childbearing age. The shock waves produced by the original lithotriptor, the Dornier HM-3, had a large focal zone and consequently were thought to have the potential to cause permanent damage to surrounding structures. Modern lithotriptors have a much smaller focal zone, making the possibility of long-term injuries to the ovary and fallopian tube less likely. While there is evidence of short-term effects on male fertility measures [20,21,22], there is no evidence to suggest a long-term effect on female fertility. SWL may have a temporary effect on the ovary. On the balance of the limited evidence available, we feel that SWL is no longer contraindicated in women of childbearing age, although patients should be warned of the potential dangers and offered ureteroscopic removal as an option (Level 3 evidence).

In women of childbearing age we must consider the risks of urinary calculi during pregnancy, and any adverse outcomes for the mother and fetus. A retrospective cohort study found that the odds of preterm delivery (<37 weeks) among women admitted for kidney stones during pregnancy compared with those who did not have kidney stones was 1.7 (95% CI 1.51, 2.13). They were not at higher risk for other outcomes investigated (extreme prematurity, low birth weight and infant death) [8] (Level 3 evidence).

A retrospective case-control study found that there was no higher risk for congenital abnormalities in the newborns of mothers with kidney stones [9] (Level 3 evidence). A retrospective case control study found that there was a higher number of preterm premature rupture of membranes in women with kidney stones [10] (Level 3 evidence).

Due to the young age of women of childbearing age, and hence their long life expectancy, combined with the fact that the stone may become symptomatic during pregnancy, which may have adverse consequences on the fetus, we would recommend that women of childbearing age should be treated for asymptomatic stones (Level 4 evidence, Grade C recommendation).

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B. INTERVENTIONAL THERAPIES

Hassan Razvi

I. INTRODUCTION

Symptomatic urinary calculi have been reported in 1 of every 1500 pregnancies [1]. Fortunately, spontaneous stone passage occurs in up to 50-80% of patients and operative intervention can be avoided in the majority of women [2,3]. In the remaining cases however, intervention is necessary, albeit with considerable angst among the patient, family and care-givers.

Due to this cohort of patients, randomized clinical trials are not available, nor are they appropriate methods to assess alternative treatment options. Clinicians must therefore rely on information based on Level 3 evidence, which encompasses case-control and retrospective case series and Level 4 evidence or expert opinion. This report summarizes the currently available literature and the strength of the evidence.

II. INDICATIONS FOR INTERVENTION

Indications for intervention in the pregnant patient with an upper tract urinary calculous are similar to those followed for the non-pregnant patient. The pregnant patient presenting with an obstructing stone and urinary tract sepsis or a solitary kidney requires emergent urinary tract drainage, either by percutaneous nephrostomy tube insertion or stent placement. Nephrostomy tube insertion as a temporizing measure is an appealing option particularly in the first trimester as it can be accomplished employing local anesthesia and ultrasound guidance. Accelerated stent encrustation has been observed with internal stents requiring more frequent changes in the pregnant patient [4]. In general, fluoroscopy is required for insertion. For these reasons stent placement maybe more appropriate in the last trimester where the number of stent changes can be minimized and the radiation risk to the fetus is less.

The more common scenario facing urologists however, is the patient with renal or ureteral colic requiring hospitalization for pain control. Fortunately, conservative management with hydration, adequate analgesia and depending on the stage of pregnancy, fetal monitoring maybe all that is required in the majority of patients. Failure of expectant management is an indication to consider surgical intervention, but should be performed in centres with experienced endourologists and high-risk perinatal support staff available.

III. DEFINITIVE INTERVENTION : OPTIONS

In general terms, non-emergent surgical intervention is best avoided in the first trimester due to the increased risk of miscarriage [5], and in the third trimester [6] because of the heightened risk of premature labor. The second trimester has been considered the most optimal time should intervention be deemed necessary [5]. Although classic teaching had been to defer definitive treatment of the symptomatic stone and simply provide renal drainage until after delivery, the advent and availability within the past decade of small caliber endoscopes, better basket devices and new intracorporeal lithotriptors, has forced a rethinking of that philosophy. If considered clinically appropriate, definitive management is being offered with excellent maternal and fetal outcomes when performed by experienced urologists.

Rigid and flexible ureteroscope insertion can usually be performed without dilation in pregnant women, perhaps due to the smooth muscle-relaxation effects of the hormonal mileau of pregnancy [7].

Various intracorporeal lithotripsy devices have been described with ureteroscopy during pregnancy. Although there is a paucity of clinical evidence to suggest any of the modalities is harmful to the fetus, there are theoretical concerns at least that certain devices may generate energies that may pose potential danger. Electrohydraulic lithotripsy (EHL) creates an electrical discharge that has been considered a potential cause of labor induction [8]. Concerns have been raised regarding the high frequency energy produced by ultrasonic lithotripsy on fetal hearing development [9]. The use of devices with more focal energy delivery characteristics such as the pulsed dye laser, pneumatic lithotriptors or the holmium:YAG laser have therefore been reported most commonly in the literature. Several expert opinion reviews have concluded that ureteroscopy is a safe and effective management option when clinically indicated [8,10,11].

The following table summarizes the evidence from the English literature within the past 10 years on the use of ureteroscopy and basket extraction and/or pneumatic or laser lithotripsy. Only reports with more than 1 patient are included.

RECOMMENDATIONS

When considered clinically appropriate, ureteroscopy in conjunction with the holmium: YAG laser, pneumatic lithotripsy or stone extraction in the hands of a surgeon accomplished with their use is associated with excellent maternal and fetal outcomes (Level 3 evidence, Grade B recommendation).

Although case reports exists of shock wave lithotripsy (SWL) being performed on women unaware that they were pregnant [25,26,27,28,29], without fetal loss or malformation, SWL remains contraindicated due to the uncertainty of effect on the developing fetus (Level 3 and 4 evidence, Grade C recommendation).

Case reports of percutaneous nephrolithotomy have been described without fetal or maternal complications, but concerns regarding radiation exposure and prone positioning relegate this approach to the patient with unique circumstances in which other options are unsuitable [30,31] (Level 3 and 4 evidence, Grade C recommendation).

Contemporary data is lacking on the role of open stone surgery during pregnancy. In the era of minimally-invasive endourological techniques however, open surgery can not be recommended unless exceptional circumstances exist (Level 4 evidence, Grade C recommendation).

First Author	Publication and Year	Type of Study	Level of Evidence	N with stones	Lithotriptor	Stone Free Rate	Maternal or Fetal Complications
Shokeir [12]	BJU 1998	Retrospective	3	8	Ultrasound, Basket/Grasper	5/8 (63%)	Maternal UTI (2)
Tekerlekis [13]	J Endourol 1999	Retrospective	3	16	Basket/Grasper	12/16 (75%)	*Fever (2) *Premature uterine contractions (1)
Banon [14]	Clinica e Invest en Ginecologia y Obstetricia 2000	Retrospective	3	8	Basket/Grasper	8/8 (100%)	None
Butler [15]	Obstet Gynecol 2000	Retrospective	3	2	Holmium:YAG Laser	2/2 (100%)	None
Sharifi [16]	J Endourol 2001	Retrospective	3	4	Pneumatic Basket	4/4 (100%)	N/A
Lemos [17]	Int Braz J Urol 2002	Retrospective	3	14	Basket/Grasper Ultrasound	13/14 (93%)	None
Lifshitz [18]	J Endourol 2002	Retrospective	3	4	Basket/Grasper retrieval	4/4 (100%)	None
Watterson [19]	Urology 2002	Retrospective	3	8	Holmium:YAG Laser	7/8 (89%)	None
Yang [20]	J Chin Med Assoc 2004	Retrospective	3	3	Basket/Grasper	3/3 (100%)	None
Ulvik [21]	J Endourol 2005	Retrospective	3	27	Basket/Grasper	23/27 (71%)	*Ureteral perforation (1) *Premature uterine contractions (2) *Preterm delivery (1)
Usai [22]	J Endourol 2006	Retrospective	3	3	Pneumatic, Basket/Grasper	3/3 (100%)	None
Akpinar [23]	J Endourol 2006	Retrospective	3	7	Holmium:YAG Laser	6/7 86%	None
Geavlete[24]	J Endourol 2006	Retrospective	3	15	Basket/Grasper Laser (wavelength not specified)	14/15 (93%)	None

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Bladder Calculi – An Evidence-based review

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CONTENTS

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INTRODUCTION

Urinary stones in the bladder have plagued those afflicted and their appointed healers since the beginnings of medical practice. Methods of cutting for the stone in the bladder are among the most notorious operating techniques that have been described and date as far back as ancient Greece, Egypt and India. Part of the Hippocratic Oath states that "I will not cut persons labouring under the stone, but will leave this to be done by men who are practitioners of this work". Hippocrates advocated against this practice, clearly indicating that lithotomy was generally performed by people trained in this procedure but not belonging to the recognized medical profession. At the time, the procedure was unrefined, barely successful and frequently fatal.

These early techniques of lithotomy described by the medical doctor Mariano Santo (around 1488-1564), the barber-surgeons Frere Jacques de Beaulieu (1651-1719) and Frere Come (1703-1781) and Johann Jakob Rau M.D.(1668-1719) came to pass at the end of the 16^{th} century with the introduction of the so-called path-finders or probes. Medico-historical development led to constant changes in the technique as well as instrumentation for stone removal. This steady development has continued to the present day where the invention of endoscopic lithotripsy devices have led to increasingly safe and efficient surgical solutions to bladder stone disease.

I. EPIDEMIOLOGY

Interestingly, with the change in the socioeconomic state and modernity of the population, lower tract stones are now far less common than upper tract stones. In developed countries, bladder stones account for around 5 to 10% of urinary calculi. Today, children in underdeveloped nations remain at risk for ammonium urate bladder stones where a low-protein, high-carbohydrate diet and chronic dehydration predispose to endemic stones. In the developed world, bladder calculi usually occur in men older than 50 years and are often associated with bladder outlet obstruction. In the slightly younger age group, most of bladder stones are usually secondary stones, having migrated down from the upper tracts.

II. PATHOPHYSIOLOGY

1. MIGRANT CALCULI

Migrant calculi are formed in the upper urinary tract, pass into the bladder and are sequestered there. This is especially so if there is a small bladder outlet e.g. pediatric population, or bladder outlet obstruction. Retained bladder stones may grow to a large size in the bladder.

2. ENDEMIC CALCULI

Primary idiopathic (endemic) calculi are common in children of lower socio-economic background in

North Africa and Middle and Far East [1]. Similar nutritional deficiencies are seen in these children. The children are dependent on a cereal-based diet, deficient in animal proteins especially cow's milk [2]. Chronic dehydration, excessive protein or oxalate consumption, high endogenous oxalate production, and deficiencies in vitamin A, B1 and B6 and magnesium have been associated with stone formation. Children younger than 10 years are usually affected, with the peak incidence around 3 years. The male to female ratio is 10:1 [3].

Primary bladder calculi are most commonly composed of ammonium acid urate alone or in combination with calcium oxalate, but many also contain calcium phosphate [4].

3. SECONDARY BLADDER CALCULI

This is predominantly a disease of adults and accounts for approximately 5% of urinary calculi in developed countries [5].

Bladder outlet obstruction may be a etiologic factor in more than 75% of bladder calculi cases [6]. Men older than 50 years are affected and it is often related to benign prostatic hyperplasia. Incomplete bladder emptying was identified as the single most important factor in vesical stone formation [7]. Other causes of outlet obstruction are urethral stricture, bladder neck contracture, neurogenic bladder dysfunction, bladder diverticula and urogenital prolapse.

Between 22-34% of bladder calculi are associated with urinary tract infections, most commonly Proteus [6]. Bacterial urease hydrolyses urea, forming ammonium which increases urine ph, and promotes supersaturation.

Long-term catheterisation increases the risk of calculus formation. Patients with neurogenic bladder from trauma or stroke frequently required catheterisation. Patients managed with an indwelling urethral or suprapubic catheter had a ninefold increased risk and those using intermittent catheterisation or a condom catheter had a fourfold increased risk compared to patients who were catheter free and had continent bladder control within first year of injury [8]. Another study also found a 16% annual risk for patients managed with indwelling catheters who had already developed one bladder stone [9].

The incidence of calculi in augmented bladders has been reported in up to 50% of cases [10]. The problems encountered with ileal and colocystoplasty have led to the use of the stomach for bladder augmentation (gastrocystoplasty), which is associated with extremely low incidence of stones [11]

Any foreign body in the bladder has calculus potential, and the best treatment is prevention. These foreign bodies can be self-induced, iatrogenic or migrant (complications of urologic or non-urologic surgical procedures). For example, retained urethral stents, sutures or staples may have calculi formed around them. Another cause may be represented by the forgotten double J or pigtail stents, that may be complicated by calcification of the retaining loops.

There appears to be a significant association between bladder calculi and the formation of malignant bladder tumours [12].

III. MANAGEMENT OF BLADDER CALCULI

1. MEDICAL

Suby solution G or M solutions, and renacidin (10% hemiacidrin) have been used to dissolve magnesium ammonium phosphate stones [13, 14]. Hemiacidrin can also be combined with surgery or extracorporeal shockwave lithotripsy [15, 16]. It can be used to prophylactically prevent encrustations of indwelling catheters. Irrigations with acetic acid solutions (0.25% or 0.5%) or use of medications that inhibit urease can prevent recurrent magnesium ammonium phosphate calculi on chronic indwelling catheters [17].

Uric acid calculi may be dissolved with oral sodium or potassium citrate. Direct irrigation with sodium bicarbonate is reserved for refractory cases [18].

2. SURGICAL (Table 1)

ESWL is a reasonably effective option for treatment of bladder calculi with stone free rates ranging 66-100%, depending on stone volume [19, 27] and associated bladder/ bladder outlet pathology [24]. In the absence of associated pathology, the results for ESWL of small bladder stones are consistently high (87-100%) with low morbidity. Adjunctive procedures include transurethral irrigation with stone extraction [21], and TURP [23]for concomitant BPH. One prospective study with level 2 evidence [19] showed that bladder stones are not an absolute indication for TURP, if the

Table 1. Extracorporeal shock wave lithotripsy (ESWL) for bladder calculi.

author	year	study	patient	primary int	outcome	e
Millan Rodriguez F [19]	2005	NRCS	n=45 BS <4cm^2	ESWL +/- TURP	SFR 93%; adj TURP (8%)	2
Al-Ansari A [20]	2005	CS	n=64 BS+ urethral stones	ESWL	SFR 94%	3
Kilciler M [21]	2002	CS	n=20 BS	ESWL+TU (neurogenic)	SFR 100% irrigation	3
Delakas D [22]	1998	CS	n=52 BS	ESWL	SFR 94.2%, adj (19%)	3
Kojima Y [23]	1998	CS	n=17 BS+/- BPH	ESWL +/- TURP	SFR 76%, adj TURP (24%)	3
Frabboni R [24]	1998	CS	n=61 BS	ESWL	SFR 66% obstr, 96% unobstr	3
Kostakopoulos A [25]	1996	CS	n=36 BS	ESWL	SFR 72%	3
Vandeursen H [26]	1990	CS	n=10 BS	ESWL	SFR 100%	3

CS: case series; NRCS: non randomized cohort study; BS: bladder stone; TURP: transurethral resection of prostate; BPH: benign prostatic hyperplasia; primary Int: intervention; SFR: stone free rate; adj: adjunctive treatment; e: level of evidence

stones are <4cm^2. The advantages of ESWL include outpatient treatment under intravenous analgesia, and options for repeated treatments. This would be useful for patients unwilling/ unfit for general anaesthesia.

3. TRANSURETHRAL TREATMENT OPTIONS FOR BLADDER CALCULI (Table 2)

Transurethral approaches for bladder calculi or cystolitholapaxy, is a common standard of treatment, and is especially appropriate if there are associated bladder outlet pathologies. Lithotripsy can be safely combined with TURP, with one study showing slightly higher complication rate from hematuria when compared with TURP alone [28]. Various modalities of lithotripsy have been employed including mechanical, pneumatic, electrohydraulic, ultrasonic and Holmium laser energy. Bulow et al reported that EHL was an effective method of lithotripsy, but accompanied by a 1.9% risk of a bladder perforation [34]. Only one retrospective study by Razvi et al directly compared mechanical, EHL and ultrasonic lithotripsys [29], and found the pneumatic lithotripsy was more efficient than ultrasonic or electrohydraulic lithotripsy particularly for larger and harder calculi. More recently, the holmium:YAG laser has been successfully employed for lithotripsy of even large calculi with minimal morbidity [32]. The 550um side-firing fibre was found to be twice as fast at stone vaporization than the end-firing 365um fibre, with minimal fragment migration. Anecdotally, the use of the 1000um end-firing fibre has likewise has been found to be effective. Contraindications to cystolitholapaxy include small capacity bladders, multiple or large stones with small caliber urethras [35].

4. PERCUTANEOUS PROCEDURES FOR BLADDER CALCULI (Table 3)

Percutaneous approaches to bladder calculi have been advocated to reduce injury and complications to the urethra, with excellent stone free rates (89-100%), especially in patients with large or multiple stone burdens. One study directly compared percutaneous vs transurethral lithotripsy combined with TURP in a prospective non-randomised study, and found a higher stone free rate (100% vs 84%) with percutaneous cystolithotripsy [36]. There was a 5% incidence of urethral complications in the transurethral approach. Another study showed the possibility of percutaneous cystolithotripsy under local anaesthesia, a useful technique where patients are unfit or unwilling for general anaesthesia [37]. Contraindications to this technique include a history of bladder malignancy, previous abdominal/ pelvic surgery, radiation or prosthetic devices.

5. VESICOLITHOTOMY FOR BLADDER CALCULI (Table 4)

Vesicolithotomy is an effective treatment modality for all bladder stones, especially with concomitant

Table 2. Transurethral treatment options for bladder calculi

author	year	study	patient	primary int	outcome	complication	e
Asci R [28]	1999	CCS	n=93 BS +/- BPH	OMC v OMC/ TURP v TURP	SFR 94% v 93%	13% v 21% v 5%	3
Razvi HA [29]	1996	CCS	n=106	Mech, EHL,u/s, lithoclast	SFR 90v63 v88v85%	6.3 v 11.9% (+TURP)	3
Shah HN [30]	2006	CS	n=32 BS+BPH	HoLEP+ HLC	SFR 100%	12.5-15.6%	3
Chtourou M [31]	2001	CS	n=120 BS +BPH	Ballistic+TURP	SFR 97.5%	4% hematuria	3
Teichman JM [32]	1999	CS	n=14 BS > 40 mm	H: YAG	SFR 100%	Nil	3
Sinik Z [33]	1998	CS	n=52 BS+BPH	Pneumatic + TURP	SFR 100%	13%	3

NRCS: non-randomised cohort study; CCS: case control study; CS: case series; BS: bladder stone; BPH: benign prostatic hyperplasia; HoLEP: Holmium laser enucleation of prostate; HLC: Holmium laser cystolithotripsy; H:YAG : Holmium YAG laser lithotripsy; OMC: optical mechanical cystolithotripsy; TURP: transurethral resection of prostate; EHL: electrohydraulic lithotripsy; u/s: ultrasonic lithotripsy; SFR: stone free rate; SUI: stress urinary incontinence; e: level of evidence

Table 3. Percutaneous procedures for bladder calculi

author	year	study	patient	primary int	outcome	complication	e
Aron M [36]	2007	NRCS	n=54 BS+BPH	TURP+PCCL v TUCL	SFR 100 v 85%. OT time	TUCL (5%)	2
Tzortzis V [37]	2006	CS	n=31 BS	Lithoclast PCCL. (LA)	SFR 96%	19%	3
Sofer M [38]	2004	CS	n=12 BS>4cm	simultaneous PC/TUCL	SFR 100%	0%	3
Maheshwari [39]	1999	CS	n=23 BS (adults)	pneumatic, u/s PCCL	SFR 100%	0%	3
Demirel F [40]	2006	CS	n=42 BS+ neurogenic	pneumatic PCCL	SFR 100%	4.1%	3
Wollin TA [41]	1999	CS	n=15 BS	Lithoclast PCCL	SFR 100%	0%	3
Ikari O [42]	1993	CS	n=36 BS	u/s PCCL	SFR 89%	0%	3

CS: case series; NRCS: non-randomised cohort study; BS: bladder stone; BPH: benign prostatic hyperplasia; SFR: stone free rate; TURP: transurethral resection of prostate; PCCL: percutaneous cystolithotripsy; TUCL: transurethral cystolithotripsy; u/s: ultrasonic lithotripsy; LA: local anaesthesia ; e: level of evidence

Table 3. Vesicolithotomy for bladder calculi

author	year	study	patient	primary int	outcome	complication	e
Richter S [43]	2002	CCS	n=40 BPH +/- BPH	VL+TURP v TURP	SFR 100%	5% v 5%	3

CCS: case control study; BS: bladder stone; BPH: benign prostatic hyperplasia; VL: vesicolithotomy; TURP: transurethral resection of prostate; SFR: stone free rate abnormal anatomy requiring surgical correction [35]. Vesicolithotomy is the standard option for managing bladder calculi where a concomitant suprapubic prostatectomy is performed for BPH. One study has demonstrated the possibility of combining vesicolithotomy and TURP with 100% stone free rate and equivalent complications [43]. This technique is especially useful where there is a large bladder stone burden and a moderate/ minimally enlarged prostate that can be addressed transurethrally.

6. CALCULI IN AUGMENTATIONS AND URINARY DIVERSIONS (Table 5)

The principles of management of calculi in bladder augmentations and urinary diversions are similar to that for the native bladder, and depend on anatomical and stone related factors. There are no level 1/ 2 evidences to support specific recommendations for management of such calculi. ESWL has been employed for small calculi [46]. However, the resultant multiple residual stone fragments could lead to stone recurrences especially in the face of impaired emptying [47]. Endoscopic lithotripsy and stone removal via the bladder outlet is possible without affecting the continence mechanism [48], including Koch pouches [49]. Percutaneous approaches may be more suited to bladder with impassable outlets or larger stone burdens. In such cases, percutaneous access with track dilation for working ports is feasible with minimal morbidity [44, 45]. To minimize residual fragments, stone may be placed in a laparoscopic pouch and lithotripsy performed in situ before extraction of the entire sac [50-52]. Open surgery can be employed in situations of abnormal anatomy or excessive stone burdens.

IV. RECOMMENDATIONS

In summary, the evidence for surgical therapy of bladder calculi is of level 2-3; all studies being retrospective case series, case control studies or prospective cohort studies with (non-randomised) or without controls. There are no randomized trials directly comparing the different techniques. The recommendations here are therefore all of Grade C.

For bladder calculi under 4cm in diameter without associated outlet pathology, ESWL is a reasonable option without the need for general anaesthesia. One study demonstrated that a percutaneous approach is possible under local anaesthetic [37]. Larger stone burdens require some surgical intervention, without any strong recommendations for any one technique (cystolitholapaxy, percutaneous cystolithotripsy or vesicolithotomy). There is a low risk of urethral/ meatal strictures associated with the transurethral approaches [28, 30]. In the setting of associated outlet pathology commonly from BPH, the options are TURP combined with any of the above techniques without any strong recommendations for any particular one. Possible energy sources for lithotripsy include mechanical, pneumatic, electrohydraulic, ultrasonic or Holmium laser energy.

The management principles for calculi associated with bladder augmentations or diversions are similar to normal bladders, insofar as stone burdens and associated bladder pathologies. Percutaneous approaches are particularly suited for impassable urethras or tightly stenotic stomas with large stone burdens. Recurrences are a major problem since many of these calculi are associated with infection by urea-splitting organisms. Therefore adequate oral hydration with regular irrigation of the bladder or pouch to remove debris and bacteria, are of paramount importance.

Table 5. Calculi in augmentations and urinary diversions

author	year	study	patient	primary int	outcome	complication	e
Docimo SG [44]	1998	CCS	n=13 Aug bldr	p/c v open surgery	SFR 100%	hosp 1.1v 3.7days	3
Paez E [45]	2007	CS	n=12 Aug	p/c + pneumatic/ + neobldr	SFR 100% u/s	8% UTI	3

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SUMMARY IN SLIDES

Epidemiology and Economics of Stone Disease

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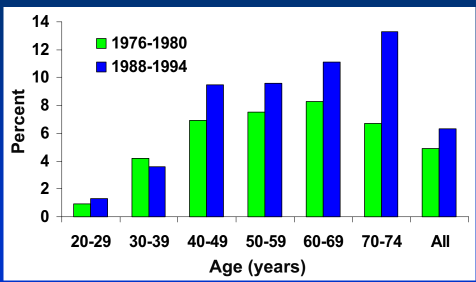
Epidemiology

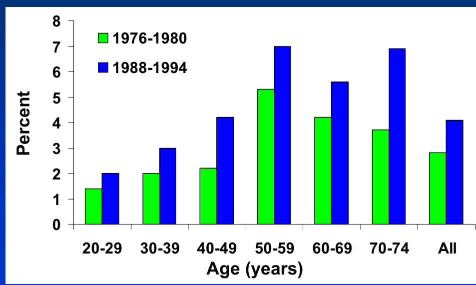
- Prevalence
- Incidence
- Risk factors
  - Dietary
  - Non-dietary
  - Urinary

Prevalence of History of Kidney Stones by Age (Males)

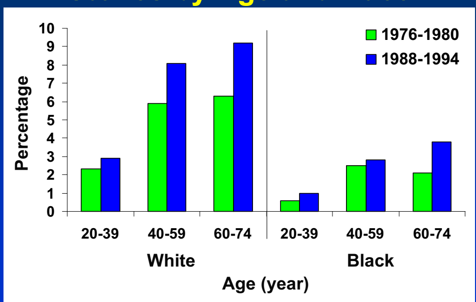


Stamatelou, Kidney Int, 2003

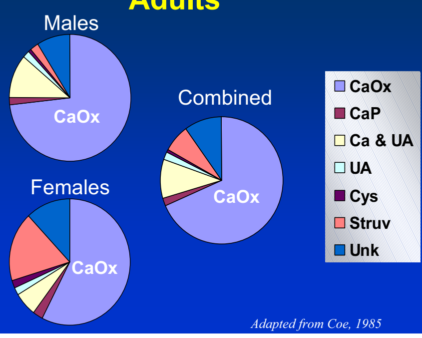
Prevalence of History of Kidney Stones by Age (Females)



Prevalence of History of Kidney Stones by Age and Race



Type of Stones & Frequency in Adults



Adapted from Coe, 1985

Risk Factors

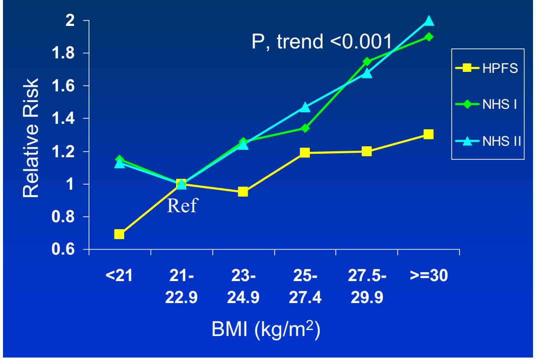
- Age
- Gender
- Geography
- Family history
- Genetics*
- Diet
  - Beverages
- Urine

- Systemic conditions
  - –Crohn's
  - –Hyperparathyroidism
  - –Obesity
  - –Gout
  - –Hypertension
  - –Diabetes
  - –Menopause
  - –Bacteria

Dietary Risk Factors

Increased risk	Decreased risk
Oxalate	Calcium, dietary
Animal protein	Potassium
Sodium	Phytate
Sucrose	Fluid
Fructose	
Calcium supplements	
Vitamin C	

Body Mass Index



Gout Increases Risk of Nephrolithiasis

- Cross-sectionally
  Males: 46%
  Females: 65%
- Prospectively
  Males 112%
  Females No data

Mattix Kramer, AJKD, 2002; Kidney Int 2003

Diabetes Increases Risk of Nephrolithiasis

	X-S	Prospectively
Males:	29%	NS
Females (older):	37%	27%
Females (younger):	67%	58%

Taylor, KI, 2005

Conclusions: Epidemiology

- Nephrolithiasis is common and likely increasing in frequency
- Dietary factors play an important role
- Nephrolithiasis is a systemic disorder
- Traditional definitions of urinary abnormalities need to be reassessed
- International studies are needed

Economics

- Medical expenditures (direct costs)
- Loss of productivity and wages (indirect costs)
- Costs vary by type of health care system

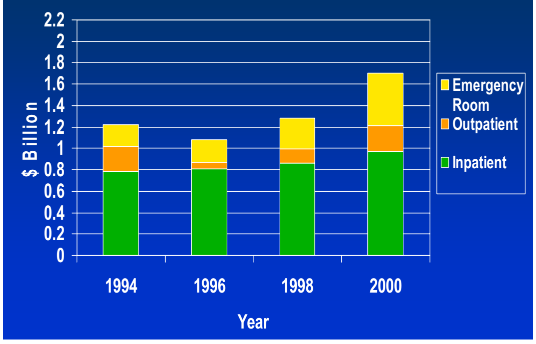
Direct Costs

- Treatment related
  - Acute episode
  - Follow-up activities including procedures
- Prevention related
  - Evaluation
  - medication

International Perspective

- Assumed that costs would be homogeneous across countries
- Majority of costs are procedure related
  - Few companies produce devices used
- But 20-fold differences in costs of ESWL, ureteroscopy and medications between countries
- Regional differences within countries seen

US Costs for Urolithiasis



Cost Assessment

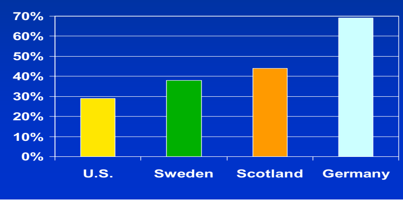
A significant impediment to understanding the financial burden associated with nephrolithiasis is the wide disparity in the cost of stone treatment among health care systems.

- Need a standardized approach for cost assessment in different countries

Acute Management Issues

NHAMCS: 226 visits/100,000 pop/year

- Costs influenced by:
  - Inpatient vs outpatient acute management
- Admission rates for acute management

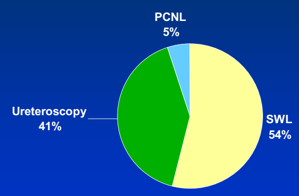


Approaches to Cost Reduction

- Reduce admissions for acute management
- Cost-effectiveness study by Lotan
  - Observation most cost-effective for ureteral stones
  - Even for proximal ureteral stones, but indirect costs likely to be higher for proximal stones
- Medication to increase likelihood of stone passage
  - Will decrease need for urologic intervention

Surgical Therapy—US

Surgery for stone disease: 400/100,000 pop



Costs vary by size, location, composition, anatomy and technology available

Models—Ureteral Stones

- Costs for SWL 21% higher than URS (Wolf)
- URS better choice than SWL (Lotan)
  - Cheaper by at least $1400
  - Higher success rate

Medical Evaluation and Management

- Costs of evaluation and medications greatly impact the recommendations
- Who pays also influences findings
  - Insurance
  - Individuals
  - Governmental subsidization
- Medical prevention appears cost effective
  - But studies biased against conservative Rx

Model—Medical Management

- First stone—conservative Rx
- Recurrence
  - Dietary most CE
  - Empiric medical Rx second
  - Directed medical RX third
- Despite higher costs, medications were associated with lower recurrence rates

Indirect Costs--US

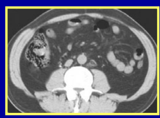
- 30% of individuals with urolithiasis missed work due to the condition
  - Mean loss of 19 hours/year

Conclusions: Economics of Uroloithiasis

- Complex
- Important due to prevalent and recurrent nature of this condition
- International comparisons difficult
  - Cost information
  - Health care delivery systems
- Standardized approaches including modeling may be useful

COMMITTEE 2

Evaluation of the Stone former



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History and Physical Examination

- Stone issue
  - Acute or chronic
- Medical and surgical history
  - Bowel disease, immobilization, diabetes, gout, RTA, obesity, 1° HPT, UTI
  - Diversion, Bariatric Surgery, Stone Removal
- Medications and supplements

History and Physical Examination

- Dietary Habits
  - Epidemiologic studies of Curhan
  - Dietary Studies of Borghi
  - Methodology
    - Dietary Recall
    - Food Frequency Questionnaire
    - Dietary Records
- Family history
  - Monogenic and Polygenic
- Focused Physical Exam

Policy Statements History and Physical Examination

- A focused history and physical examination should be done in all cases.
  Level 4 Evidence, Grade C Recommendation
- Dietary history should be elicited.
  Level 1 Evidence, Grade A Recommendation
- Family history should be elicited.
  Level 2 Evidence, Grade B Recommendation
- A query for stone inducing drugs should be made.
  Level 2 Evidence, Grade B Recommendation

Policy Statements Initial Blood Tests

- Initial blood studies should include a basic metabolic profile (BUN, serum creatinine, electrolytes, calcium, glucose) serum uric acid and phosphorus.
  Level 3 Evidence, Grade C Recommendation
- Complete Blood Count with differential and blood cultures should be obtained if the patient has signs of sepsis.
  Level 3 Evidence, Grade C Recommendation

Stone Analysis

- Most important component as it directs further testing.
- Most common techniques Fourier transform infrared spectroscopy and x-ray powder diffraction crystallography
- Uric acid, cystine and calcium phosphate are predictive of associated medical conditions.
- Trend of conversion of calcium oxalate to calcium phosphate in recurrent stone formers.

Mandel et al. Journal of Urology, 169:2026, 2003.

Policy Statement Stone Analysis

- Stone analysis should be obtained for first time and recurrent stone formers.
  Level 2 Evidence, Grade B Recommendation

Policy Statements Imaging Studies

- Non-contrast l CT is the imaging modality of choice for evaluating the majority of patients with suspected renal colic.
  Level 1 Evidence, Grade A Recommendation
- Non-contrast CT may help predict results of shock wave lithotripsy.
  Level 2 Evidence, Grade B Recommendation
- Non-contrast CT may identify those with uric acid stones.
  Level 2 Evidence, Grade B Recommendation

Policy Statements
Imaging Studies

- Non-contrast CT identifies relationships with surrounding structures which is important for certain surgical planning (PCNL).
  Level 4 Evidence, Grade C Recommendation
- Non-contrast CT provides accurately defines stone volume and orientation of the stone within the kidney.
  Level 4 Evidence, Grade C Recommendation
- Contrast CT defines collecting system anatomy and provides some index of renal function.
  Level 4 Evidence, Grade C Recommendation

Policy Statements
Imaging Studies

- Plain abdominal radiography is superior to scout NCCT for detecting urinary calculi.
  Level 2 Evidence, Grade A Recommendation
- Plain abdominal radiography and NCCT vary slightly in their estimate of the transverse and antero-posterior dimensions of urinary calculi, but there are no consistent positive or negative trends and the differences usually are not clinically significant. The cranio-caudal dimension of urinary calculi is overestimated by NCCT.
  Level 3 Evidence, Grade B Recommendation
- Plain abdominal radiography may be useful for predicting efficacy of shock wave lithotripsy for some renal calculi.
  Level 3 Evidence, Grade C Recommendation

Policy Statements
Imaging Studies

- IVP and retrograde pyelography are useful in some cases for treatment planning.
  Level 3/4 Evidence, Grade C Recommendation
- The addition of color Doppler to ultrasonography, in order to determine resistive indices, improves the ultrasound detection of obstruction by urinary calculi.
  Level 2/3 Evidence, Grade B Recommendation
- Ultrasonography plus KUB is the second choice, after NCCT, for detecting urinary calculi.
  Level 2/4 Evidence, Grade C Recommendation
- Trans-rectal or vaginal ultrasonography is superior to all other modalities except NCCT for the detection of distal ureteral calculi.
  Level 2/3 Evidence, Grade B Recommendation

Policy Statements
Imaging Studies

- Dynamic renal scintigraphy may be a useful adjunct to NCCT in determining obstruction by urinary calculi, but comparative data to other modalities are limited.
  Level 2 Evidence, Grade C Recommendation
- MRU can detect obstruction by urinary calculi, but comparative data to other modalities are limited.
  Level 2 Evidence, Grade C Recommendation
- In pregnant women, ultrasonography with color Doppler is the preferred modality for evaluation of suspected urinary calculi. "Single shot" IVP or MRU are recommended if the initial test is negative and urinary calculi are still suspected.
  Level 3/4 Evidence, Grade C Recommendation

Policy Statements
Imaging Studies

- Follow-up imaging is not recommended for a first time calcium oxalate or calcium phosphate stone former who is rendered stone free and does not have a systemic disease increasing stone risk.
  Level 4 Evidence, Grade C Recommendation
- Annual plain KUB is recommended for surveillance of the majority of adult first time stone formers with asymptomatic, radio-opaque stones.
  Level 4 Evidence, Grade C Recommendation
- Annual plain abdominal radiography is recommended for the surveillance of adults who are recurrent formers with radio-opaque stones.
  Level 4 Evidence, Grade C Recommendation

Policy Statements
Imaging Studies

- Ultrasonography is preferred for follow-up imaging of children, and those with uric acid or cystine stones. When anatomy or body habitus precludes accurate ultrasonography, NCCT is the preferred alternative.
  Level 4 Evidence, Grade C Recommendation
- More frequent or different imaging may be required for those who develop symptoms or increasing metabolic activity during follow-up.
  Level 4 Evidence, Grade C Recommendation
- Bone density testing is a consideration for select patients including those women who are post-menopausal and those with profound hypercalciuria.
  Level 3 Evidence, Grade C recommendation

Policy Statements
Urine Evaluation

- Urinalysis should be performed on all patients.
  Level 4 Evidence, Grade C Recommendation
- Urine culture should be obtained if infection is suspected.
  Level 4 Evidence, Grade C Recommendation

Policy Statements
Urine Evaluation

- 24 hour urine testing is recommended for recurrent stone formers, cystinurics, children, those with solitary kidneys or renal insufficiency, patients with multiple remaining stones, commercial air-line pilots and individuals with bowel disease.
  Level 1-4 Evidence, Grade A-C Recommendation
- Urine is collected while the patient is consuming a random diet.
  Level 2 Evidence, Grade B Recommendation
- The choice of analytes tested is based on stone analysis.
  Level 2 Evidence, Grade B Recommendation

Policy Statements
Urine Evaluation

- The collection of two 24 hour urine specimens is recommended.
  Level 2 Evidence, Grade B Recommendation

- Defining the cause of hypercalciuria with fasting calcium and calcium load testing is not indicated for the majority of patients.
  Level 2 Evidence, Grade B Recommendation

Urine Evaluation

Volume	Phosphorus
pH	Sodium
Creatinine	Potassium
Calcium	Ammonia
Uric acid	Urea Nitrogen
Citrate	Sulfate
Magnesium	Supersaturation
	Cystine*

Policy Statements
Hyperoxaluria

- Patients with extremely high levels of hyperoxaluria who do not have bowel disease should be evaluated for primary hyperoxaluria.
  Level 2 Evidence, Grade B Recommendation

- Urinary glycolate and L-glycerate are measured in those suspected of having primary hyperoxaluria.
  Level 2 Evidence, Grade B Recommendation

- Testing of DNA extracted from whole blood is used to confirm the diagnosis of primary hyperoxaluria.
  Level 2 Evidence, Grade B Recommendation

- Liver biopsy and measurement of AGRT and GR activity are used if genetic testing is not confirmatory.
  Level 2 Evidence, Grade B Recommendation

Policy Statements
Evaluation for Primary Hyperparathyroidism

- Screening for hyperparathyroidism with serum calcium testing is recommended for patients with calcium oxalate or calcium phosphate containing stones.
  Level 2 evidence, Grade B recommendation

- Measurement of serum parathyroid hormone is recommended in patients with hypercalcemia, and for those with high normal serum calcium who are recurrent stone formers or have calcium phosphate containing calculi.
  Level 1-2 evidence, Grade B recommendation

- Parathyroidectomy is recommended for patients with stones and primary hyperparathyroidism.
  Level 1 evidence, Grade A recommendation

Conclusions

- Evaluation of the stone former is an important multi-faceted task which directs subsequent patient management.
- Many steps in the evaluation process are based on consensus opinion.
- A more critical, evidenced based analysis of this process is warranted.

MEDICAL MANAGEMENT

Margaret S. Pearle--Chair

John Asplin
Marshall Stoller
Fredric Coe
Philippe Jaeger
Allen Rodgers

MEDICAL MANAGEMENT

- Drug therapy should be initiated in all SFs
- When dietary therapy fails or in setting of severe metabolic derangements, drug tx may be necessary
- Level I evidence limited for dietary measures
  - Most evidence based on metabolic studies
- Level I evidence good for drug therapy
  - Non-uniformity among trials

EFFECT OF DIET

Kočvara et al, BJU Int 84, 1999

207 Idiopathic stone formers

Group 1 N=113 — randomized — Group 2 N=94

Group 1: Specific dietary measures based on comprehensive metabolic eval; F/U at 6, 18, 36 mo

Group 2: General dietary measures; Limited screening; F/U 36 mo

new stone formation: 7% (Group 1), 23% (Group 2)

EFFECT OF FLUIDS

Borghi et al, J Urol 155, 1996

199 CaOx stone formers

High fluid intake (2L urine/d) — No specific recommendations

5 yrs w/ annual xrays and urine

12% recurrence — 27% recurrence

2621 ml/d yr 5 — 1014 ml/d yr 5

EFFECT OF FLUIDS

Does the Beverage Matter?

- No randomized trials comparing risk/benefit of specific beverages
- 3 Cohort studies based on food frequency questionnaires and rate of kidney stone occurrence evaluated risk/benefit of specific beverages

EFFECT OF FLUIDS

Does the Beverage Matter?

Author	N	RISK REDUCTION				
		Coffee	Tea	Beer	Wine	Grapefruit Juice
Curhan 1996	46,289	-10%	-14%	-21%	-39%	+37%
Curhan 1998	121,7000	-10%	-8%	-	-59%	+44%
Hirvonen 1999	27,001	-	-	-40%	-	-

EFFECT OF CITRUS FRUIT

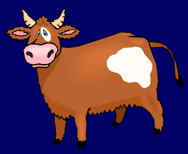
Are all juices the same?

- Fruits/juices w/ high citrate content are good source of dietary citrate
- Most citrate metabolized to bicarbonate
- Some renal excretion of unmetabolized citrate
- Beneficial effect of citrus attributed to alkali load which ↑'s Ucit excretion

CITRUS JUICE AND STONE RISK

- Among citrus juices, OJ shows most consistent benefit and cranberry juice the least
- None evaluated in prospective clinical trial!

EFFECT OF ANIMAL PROTEIN



Animal protein: Red meat, fish, poultry

- ↑ urinary uric acid due to purine load
- ↓ urine pH due to acid load
- ↑urinary calcium due to reduced pH

EFFECT OF SODIUM LOAD

Prevents renal Ca reabsorption
Every 100 mEq ↑ in UNa → 50 mg ↑ UCa

↓'s Ucitrate via Na-induced CO_2 loss

↑'s monosodium urate → CaOx crystallization

Effect of Dietary Calcium on Stone Formation

- Historically, Ca restriction recommended for stone prevention
- Wisdom of dietary Ca restriction questioned
  - Ineffective in preventing stones?
  - Accelerates bone loss?
- No RCT has assessed dietary Ca as an independent variable

EFFECT OF DIETARY CALCIUM

Curhan et al, NEJM 1993, Ann Int Med 1997

2 prospective cohort studies showed a protective effect of high calcium intake against incident stone formation

Quintiles of Ca Intake ⟶

1.0	0.74	0.68	0.68	0.66	Male
1.0	0.83	0.72	0.79	0.65	Female

RR of stone formation compared w/ lowest quintile Ca intake

DIETARY CALCIUM

Borghi et al, NEJM 346:77, 2002

120 men w/ recurrent CaOx stones and hypercalciuria

Randomized

Low Ca diet (n=60)	NL Ca, low protein, low Na diet (n=60)
5 years	
38% stone recurrence	20% recurrence
UCa decreased by 4.8 mmol/d	UCa decreased by 5.6 mmol/d
UOx increased by 44 umol/d	UOx decreased by 78 umol/d

RR=0.49

EFFECT OF DIETARY CALCIUM

- Ineffectiveness of low Ca diet in preventing stone occurrence/recurrence attributed to interaction b/w calcium and oxalate in intestinal tract

EFFECT OF DIETARY CALCIUM

- Mild calcium restriction, in the setting of oxalate restriction, lowers urinary saturation of CaOx w/o an ↑Uox
- Calcium restriction in the setting of liberal oxalate intake ↑'s urine ox but still lowers urinary saturation of CaOx
- The findings of reduced stone risk w/ high Ca intake in epidemiologic studies may be due to concurrent ingestion of stone protective factors along with a high calcium diet

DIETARY MODIFICATION

- High fluid intake
- Modest or no Ca restriction in hypercaliuria
- Normal calcium intake in normocalciuria
- Limitation of oxalate-rich foods
- Meat intake ≤ 2 servings/day
- Sodium restriction

SIMPLIFIED APPROACH TO TREATMENT

- Step 1
  - 24 hr urine for stone risk factors, stone analysis, SMA
- Step 2
  - Exclude non-calcium stones and 2° causes of stone disease (PHPT, dRTA, 1° or enteric hyperoxaluria, gout)
  - Stratify uncomplicated Ca stone formers by UCa: <200 or >200 mg/day
- Step 3
  - Dietary and pharmacologic tx

METABOLIC CAUSES OF STONE DISEASE

- Calcium-containing
  - Hypercalciuria
  - Hypocitraturia
  - Hyperuricosuria
  - Hyperoxaluria
  - Gouty Diathesis
- Other
  - Uric acid stones (low urine pH)
  - Cystinuria
  - Infection stones

SIMPLIFIED APPROACH TO TREATMENT OF CA STONES

Mod-Severe Hypercalciuria

- Indapamide + K-citrate
- Modest or no Ca restriction, other dietary measures

Normocalciuria

- K-citrate
- Liberal Ca intake, other dietary measures

RATIONALE FOR TREATMENT

Uncomplicated Calcium Stones

THIAZIDE

- Lowers urine Ca
- Causes ↓K+

K-CITRATE

- Prevents hypokalemia
- ↑'s urine citrate
- Provides alkali load

THIAZIDES

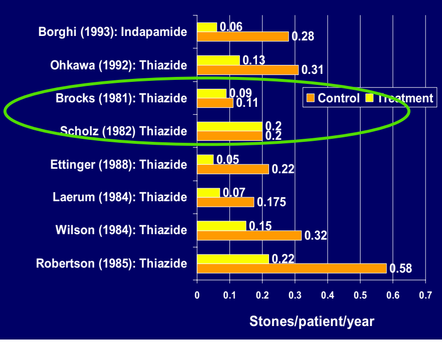
- Mechanism of action
  - Inhibits Na resorption and enhances Ca reabsorption in distal tubule
  - Indirectly enhances Na and Ca rebsorption in proximal tubule via volume depletion
- Indications
  - Absorptive or idiopathic hypercalciura
  - Renal hypercalciuria (RH)

THIAZIDES

- Side Effects
  - Hypokalemia: prescribe K supplement
  - Hyperuricemia
  - Hyperglycemia
  - Erectile dysfunction
  - Fatigue
  - Hyocitraturia

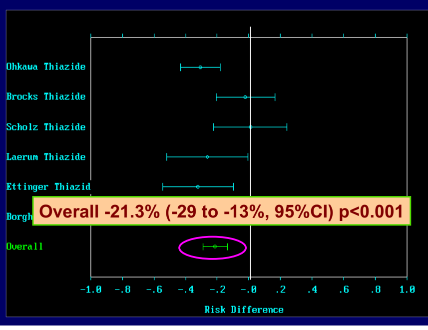
Follow serum K+, uric acid, glucose, Ca

THIAZIDE RCTS



META-ANALYSIS OF THIAZIDE RCTs

Pearle, Roehrborn and Pak, J Endourol 13, 1999



POTASSIUM CITRATE

- Indications
  - Hypocitraturia
  - Normocalciuric idiopathic calcium oxalate stones
  - Gouty Diathesis
  - Hyperuricosuria and intolerance to allopurinol
  - In conjunction with thiazide in IH
- Dosage
  - 10 meq TID to 20 meq BID
- Side Effects
  - Diarrhea
  - GI intolerance

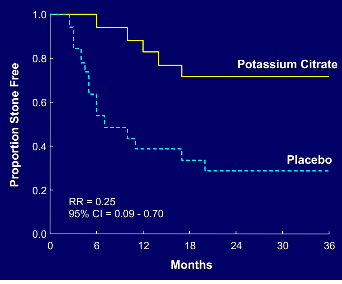
Follow serum K+, creatinine

CITRATE: RCTS

Author	RX	Selection	Duration of study	N	Stnes/pt/yr	Remission (%)	P-val
Barcelo	K Cit	Hypocit	3 yrs	18	0.1	7202	<0.05
	Placebo			20	1.1	20	
Hofbauer	Na-K-cit	Non-select	3 yrs	16	0.9	31.3	NS
	Placebo			22	0.7	27.3	
Ettinger	K-mag-cit	Non-select	3 yr	16	-	87.1	rr=0.16
	Placebo			25	-	36.4	

EFFECT OF K-CITRATE ON NORMOCALCIURIC STONE FORMERS

Barcelo et al, *J Urol* 150: 1761, 1993



TREATMENT OF OTHER CAUSES OF STONE FORMATION

Hypercalcemia	W/U for 1° HPT
Hyperuricemia	Allopurinol
Severe hyperoxaluria	W/U for 1° or enteric hyperoxaluria
Enteric hyperox	Ca supp; liquid K cit; B6
Uric acid stones	K citrate
Cystine stones	K citrate; thiola
Struvite stones	Surgery; Abx; AHA

RATIONALE FOR TREATMENT

Allopurinol

- Indications
  - Hyperuricosuria (CaOx or uric stones)
  - Gout
- Dosage
  - 100-300 mg daily
- Side Effects
  - Rash: may progress to Stevens-Johnson
  - GI intolerance
  - Hepatic toxicity

Follow serum LFTs

ALLOPURINOL: RCTS

Author	RX	Selection	Duration of study	N	Stnes/pt/yr	Remission (%)	P-val
Ettinger	Allopurinol	HUCU nl sCa	2 yrs	29	0.12	69	<0.05
	Placebo			31	0.26	41.9	
Wilson	Allopurinol	Non-select	3 yrs	17	0.48	-	NS
	No Rx			21	0.32	-	
Robertson	Allopurinol	Non-select	3 yrs	12	0.54	-	NS
	No Rx			9	0.58	-	
Miano	Allopurinol	Non-select	3 yrs	8	0.96	-	NS
	Placebo			7	0.66	-	

URIC ACID STONES

Stone Prevention and Dissolution

- Diet: Reduce uric acid concentration
  - Reduce animal protein intake
  - Increase fluid intake
- Medication
  - Increase uric acid solubility
    - Sodium bicarbonate: 1.3-2.6 gm/day
    - Potassium citrate: 20-40 meq/day
    - Potassium citrate/citric acid: 15-30 meq/day
  - Reduce uric acid concentration
    - Allopurinol 300 mg/day
    - Only necessary if urinary uric acid is elevated after urine alkalinized

CYSTINE STONES

Treatment: Dietary Modification

- Fluids: 3-4 L/day to achieve urine volume 3 L/day
  - Distribute throughout day
  - Citrus juices provide alkali load to ↑urine pH
- Low methionine diet
  - Substrate for cystine production
  - Reduced red meat, poultry, fish and diary
  - Poor compliance
- Low salt
  - Sodium ↑'s cystine excretion
  - Also ↑'s cystine solubility

CYSTINE STONES
Treatment: Alkalinization

- Goal: Urine pH 6.5-7.0
  - Solubility not significantly ↑'d until pH>7.5
  - Regardless of dose of alkali, pH rarely >7.5
  - Mean pH of cystinurics: 6.8
  - Limited role of alkalinization
- Potassium alkali preferred to avoid sodium load
- Potassium citrate 10-20 meq in divided doses

CYSTINE STONES
Treatment: Chelating Agents

- For severe cystinuria (>500 mg/d) or moderate cystinuria that fails conservative management
- Cystine concentration is reduced by complexing cysteine (monomeric form of cystine)
- Thiol-disulfide exchange forms cysteine-chelating agent disulfide complex that is more soluble than cystine

CYSTINE STONES
Treatment: Chelating Agents

- α-Mercaptopropionlyglycine (Tiopronin)
  - 2nd generation chelating agent
  - Dosage: each 250 mg/day reduces cystine by 75-100 mg/day
  - Side effects: skin rash, emesis, oral ulcers, change in stool pattern, myopathy, nephrotic syndrome
  - Lower toxicity profile than D-penicillamine
  - Can use when D-pen not tolerated

Monitor urine protein of pts on Thiola or D-Pen for nephrotic syndrome!

INFECTION STONES
Treatment

- Mainstay of treatment is surgical!
  - Removal of stones essential for eradication of organisms
- Long-term antimicrobial therapy rarely successful
  - Stone dissolution rare
  - Reserved for pts in whom surgery contraindicated
  - Use in association w/ incomplete stone clearance
  - Primary role is after stone removal

INFECTION STONES
Urease Inhibitors

- Acetohydroxamic acid (AHA): potent, irreversible inhibitor of urease
- Reliably reduces urinary pH and ammonia
- Dose: 250 mg TID
- Use in conjunction w/ Abx
- Unable to reach therapeutic conc. w/ CRI (Cr>2 mg/dl) and urine acetamide may reach carcinogenic levels
- Shown in 3 RCTs to be effective in stone prevention
- Side effect profile often prohibitive (22-68%):

FUTURE DIRECTIONS

- Pyridoxamine (derivative of B6)
  - reduces oxalate substrate in liver
  - Reduced urinary oxalate excretion in nl and hyperoxaluric rats
  - NIH trial in progress
- *Oxalobacter formigines* utilizes oxalate as substrate in intestine and may be lacking in SFs
  - Adminstration of bacteria or enzymes to SF
  - Probiotics of lactic acid bacteria show mixed results
- Bisphonates may lower U Ca and preserve bone
- Sodium thiosulfate: may reduce stone formation by unknown mxn

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CONCLUSIONS

- High fluid intake among dietary measures has been shown with Level Ib evidence to have benefit
- Restriction of sodium and animal protein is advised but direct level I evidence is lacking
- The role of dietary calcium is controversial; severe calcium restriction should be avoided

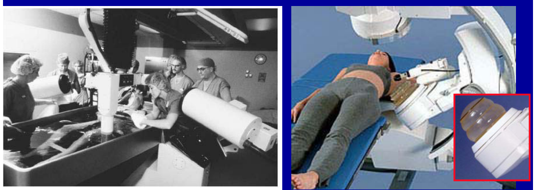
- Drug therapy, along w/ dietary measures, should be considered for high risk stone formers
- Thiazides have been shown via Level Ia evidence to have benefit, but IH may not be required
- Allopurinol has benefit (Level Ib) in Ca stone formers with HUCU
- Alkali citrate has benefit (Level IB) in hypocitraturia and perhaps in normocalciuric Ca stone formers

Stone Technology -- ESWL and Intracorporeal Lithotripsy

James E. Lingeman, M.D.

Darren Beiko, M.D., Robin Cleveland, PhD, Matthew Gettman, M.D., Kai Uwe Koehrmann, M.D., Evangelos Liatsikos, M.D., Brian Matlaga, M.D., James McAteer, PhD, Manoj Monga, M.D., Geert Tailly, M.D., and Anthony Timoney, M.D.

Evolution of the Lithotriptor



Water-bath style lithotriptors
- best record of treatment success
- fairly broad focal zone
- excellent acoustic coupling

Dry treatment head lithotriptors
- higher re-treatment rates
- most have a narrow focal zone
- SW coupled to the patient using g

Our Main Goal . . . . . .

- Reduce or prevent collateral damage without sacrificing efficacy in SW therapy
- New lithotriptors may eventually be the answer, but can we learn to do better with what we have…..
- Can the way that lithotripsy is performed be improved using the technology at hand?

SWL: Techniques

- Coupling
- Rate
- Anesthesia
- "Protection" protocol

Issues with Current Lithotriptors

- High pressure and tight focus likely work against achieving good stone breakage
  - Decreased efficacy
  - Increased retreatment sessions
- Stones are moving targets
- Higher energy levels cause greater renal trauma
- Lithotriptors may be too powerful for their own good

SWL 2007: Getting the Best Results

- Do not use highest power levels in the kidney
- "pre-treat" at lower energy levels before going up to higher levels to minimize tissue effects
- "ramping up" SW power settings during lithotripsy may be useful
- Pay attention to coupling!

SWL 2007: Getting the Best Results

- Cavitation is a critical feature of SW effects on both stones and tissue
- Consider general anesthesia to minimize patient/renal/stone movement during treatment
- Slowing the rate of SW administration enhances stone fragmentation

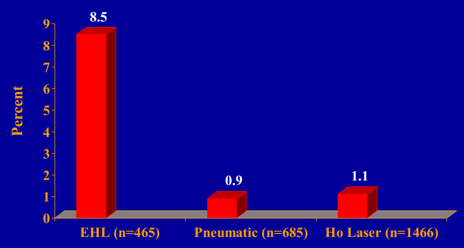
SWL 2007: Summary

- Lithotriptors less efficient but still effective for majority of stones
- The technique of SW administration may be more important than the type of lithotriptor utilized

Power Lithotripsy

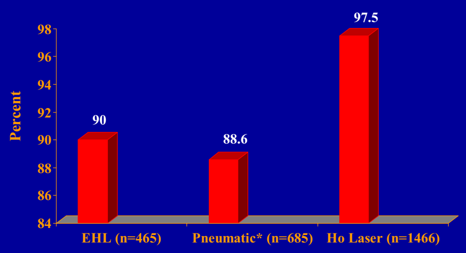
Rigid	Flexible
Ultrasound	Electrohydraulic
Lithoclast	Laser
Lithoclast/Ultrasound (Ultra)	
Cyberwand	

Intracorporeal Lithotripsy Technologies: Risk of Perforation*



*Source: Campbell's Urology 2007

Intracorporeal Lithotripsy Technologies: Successful Fragmentation*



*Stone migration in 9%

*Source: Campbell's Urology 2007

Cost Comparison of Intracorporeal Lithotripsy Devices

Device	Fiber/Probe Size	Cost	Disposables
Ultrasound	1.5 – 4mm	$13,600*	Reusable probes
Pneumatic	2.4 – 9.6 F	$26,000*	Reusable probes
Electrokinetic	2.4 – 6 F	$24,500*	Reusable probes
Electrohydraulic	1.6 – 9 F	$12,300*	Disposable probes - $180
Holmium laser (100W)	200-1000 µm	$125,000	Resuable fibers with a limited life span;
Holmium laser (20W)	200-1000 µm	$62,000	365 µm - $355 200 µm - $1095

*Average cost for major manufacturers.

Holmium:YAG Laser

Urologic Applications

- Intracorporeal lithotripsy
- Incision of ureteral and urethral strictures
- Ablation of superficial TCC
- Bladder neck incision/ prostate resection

Treatment of Renal Stones
WHO consensus meeting

Adrian Joyce
Ali Riza Kural
Pierre Conort
Mahesh Desai
Jorge Guttierez
Jens Rassweiler
Raymond Leveillee
Andreas Skolarikos
Jean de la Rosette (chair)

Treatment of Renal Stones
Treatment Options

- Active monitoring
- Medical Treatment
- ESWL
- PCNL
- URS
- Laparoscopy

Treatment of Renal Stones
Active Monitoring

• Any asymptomatic renal pelvic stones or staghorn calculi in a good functioning kidney should be treated to prevent the loss of renal function and occurance of UTI. Observation without any treatment should be reserved for unfit patients for intervention	• III
• Asymptomatic small renal stones should be followed for possibility of disease progression and UTI	• II
• Invasive treatment is not recommended for CIRF because some of those will pass spontaneously or will not require treatment	• II
• Fragments larger than 4-5 mm have greater risk to become symptomatic	• III
• Prophylactic ESWL treatment of asymptomatic renal stones or CIRFs is not superior to observation. However, ESWL is the first choice of treatment for those patients when required	• II
• Targeted medical treatment may prevent stone growth but does not improve the fate of any asymptomatic stone	• III
• The use of CT is more sensitive for detecting and measuring post procedural fragments	• III

Treatment of Renal Stones
ESWL recommendation

• ESWL in situ is considered the first-line treatment for all radio-opaque stones up to 1 cm, with the addition of antibiotics for infectious stones	• I
• Ureteral stenting for stones < 2 cm does not increase the stone free rate or reduce complications.	• I
• Ureteral stenting should be considered for renal stones > 2 cm and in patients with risk factors, including solitary kidneys, advanced age, immobility, and poor medical condition (DM, COPD,steroids)	• III

Treatment of Renal Stones
Recommendation on PCNL indications

• The term 'larger stone' is applicable to > 2 cm	• IV
• In the treatment of staghorn stones, compared to ESWL or open surgery, PCNL alone or in combination with ESWL, results in higher stone free rates, lower rate of ancillary procedures, lower morbidity, shorter operative time, shorter hospital stay and earlier recovery	• I-II
• Large stones of the lower pole (>1cm) are best managed by PCNL as a first treatment option, irrespective of the anatomy	• I
• PCNL is considered the gold standard for managing caliceal diverticula	• III
• PCNL in the horseshoe kidney, malrotated, pelvic, and Tx kidney is safe and effective	• III
• PCNL, ESWL and URS are all valuable treatment options for pediatric calculi	• II
• Previous surgery does not contraindicate subsequent PCNL	• III
• Simultaneous bilateral PCNL is a safe and efficacious procedure	• II

Treatment of Renal Stones
Recommendations on PCNL technique

• PCNL is usually performed in the prone position	• III
• PCNL in the supine position is safe and an effective alternative	• II
• Fluoroscopy is associated with an increased blood loss compared to US	• II
• CT may be useful in a selected group of patients	• III
• Robotic percutaneous access seems more accurate and safe	• II
• A supracostal approach is preferable in patients with staghorn, complex renal and proximal ureteral calculi	• III
• There is no association between the calyx of puncture and blood loss	• II
• Multiple accesses are considered when the calyx contains stones larger than 2 cm and cannot be reached with (flexible) instruments	• III
• Multiple accesses are related with an increased blood loss	• II
• The balloon dilator is regarded the 'gold' standard	• II
• Mini PCNL shows no advantages over standard PCNL	• I
• The size of ND makes no difference to patients in outcome	• I
• Tubeless surgery may be safe and effective in selected patients	• I
• Some hemostatic agents are of benefit to patients during tubeless PCNL	• I

Treatment of Renal Stones
Retrograde Intrarenal surgery (RIRS)

• Higher success rate in stones <1 cm	• III
• RIRS is the preferred treatment of choice in cases of morbid obesity, bleeding diathesis, and anomalous kidneys.	• III
• Holmium YAG 200 micron probe or 1.6-1.9 EHL probe are preferred for intracorporeal lithotripsy with flexible URS	• III
• Use of an access sheath depends on the surgeon's preferences and the use of nitinol baskets or graspers is advised.	• III
• Relocation is recommended if the stone is located in a difficult position for fragmentation	• III

Treatment of Renal Stones
residual stone fragment

• 'Clinical Insignificant Residual Fragment' (CIRF) definition is based on arbitrarily criteria	• III
• As the burden and number of CIRF increase the risk of becoming clinically significant increases	• II
• As the duration of follow-up increases, the rate of complications and the need for intervention for symptomatic episodes due to CIRF increases	• II
• ESWL re-treatment of completely fragmented but persistent stone debris appears to be justified to render the kidney stone-free	• I
• Medical therapy can control active stone formation, reduces growth or agglomeration and increases the clearance rate of residual fragments after ESWL	• I
• Medical therapy may control active stone formation and growth in patients with residual stone fragments after PCNL	• III

Treatment of Renal Stones
Lower Pole Stones

- PNL is more effective than ESWL in larger stones - I
- Passage of fragments is dependent on caliceal anatomy - II
- Morbidity of PNL is higher - II
- Flexible URS in cases up to 1-2 cm - III

Treatment of Renal Stones
Renal abnormalities

- Most Level III evidence
- Treatment options depending on renal location, stone location and size, local expertise
- SWL, URS, PCNL, laparoscopy, open

Complicated Renal Stones

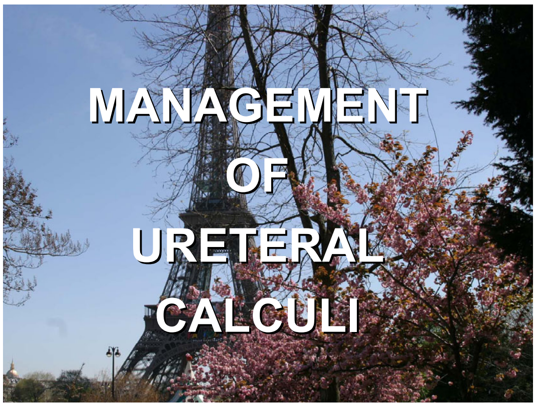
	Stone Size (cm)	Stone free rate (%)	Ancillary procedures	Hospital stay (days)	Complication rate (%)
Lower pole stone	0.5 - 1.0	70 - 100	4.0 - 63	3 - 6	3 - 38
Calyceal Diverticula	0.2 - 3.0	76 - 100	0.5 - 18	2 - 15	0 - 30
Horseshoe Kidneys	All sizes	72 - 88	8.0 - 33	3 - 10	8 - 29
Children	All sizes	67 - 100	0.0 - 32	1 - 11	0 - 28
Bilateral PCNL	All sizes	76 - 100	3.0 - 81	11 - 21	3 - 25
Obesity	All sizes	60 - 100	14 - 45	2 - 10	0 - 37
Previous surgery	Up to 3.0	51 - 92	27 - 78	3 - 7	14 - 24

Treatment of Renal Stones
Recommendations in preventing complications

- Single dose antibiotic treatment is equivalent to short term prophylaxis in case of sterile urine culture
- In case of staghorn stones, despite sterile urine culture, one may find a purulent puncture during PCNL (3-10%). Surgery has to be delayed
- Ultrasound guided puncture minimizes the risk of colonic injury.
- The risk of hydrothorax and overall risk is higher with supracostal punctures (2-4%)
- Most bleedings after PCNL can be managed conservatively
- Multiple tracts are associated with a significant higher complication rate
- Most delayed bleedings following PCNL are due to AV creation

- I
- II
- IV
- II
- IV
- II
- III

COMMITTEE 6



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NATURAL COURSE

Most ureteral stones pass spontaneously !

Good chance for stones < = 5 mm

ACTIVE STONE REMOVAL

METHODS

Incisional / open surgery

Percutaneous surgery

Ureterorenoscopic surgery (URS)

Extracorporeal shock wave lithotripsy (SWL)

Laparoscopic surgery

ACUTE STONE COLIC

URGENT INTERVENTION

Obstructed and infected upper urinary tract
Impending renal deterioration
Intractable pain
Vomiting
Anuria
High grade obstruction of:
- solitary kidney
- transplanted kidney

ACUTE STONE COLIC

PAIN RELIEF

Suggested first line treatment:

DICLOFENAC

Other alternatives:

Ketorolac	Methamizol
Ibuprophen	Pentazocine
Hydromorphone	Tramadol

SPONTANEOUS STONE PASSAGE

71 -98 % of distal stones up to 5 mm pass spontaneously

TIME TO PASSAGE

<= 2 mm	39 days
2-4 mm	40 days
4-6 mm	39 days

MEDICAL EXPULSIVE TREATMENT

Alpha-adrenergic receptor antagonists

Calcium channel blocking agents

META-ANALYSIS

Hollingsworth et al:

65 % greater likelihood for spontaneous passage with than without such treatment

MEDICAL EXPULSIVE TREATMENT

EFFECTS

Increased chance for stone passage

Reduced time to passage

Decreased ureteral colic

Most studies were made with tamsulosin, but similar effects have been shown with
terazocin
dokazocin

MEDICAL EXPULSIVE TREATMENT

PREREQUISITES

1. Well controlled pain
2. No evidence of sepsis
3. Periodic imaging

EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY

Recommendations

SWL remains as first line treatment for most proximal ureteral stones.

In the absence of infection there is no benefit of stenting before SWL.

Distal ureteral stones can be equally successfully treated with SWL and URS.

Mid ureteral stones might pose problems for SWL, because of need to treat in prone position and the usually high re-treatment rate.

URETERORENOSCOPIC STONE REMOVAL

URS has gained increased interest during recent years because of:

- Small calibre scopes
- Flexible scopes
- Holmium:YAG-laser

URETERORENOSCOPIC STONE REMOVAL

OBSERVATIONS

In six randomized studies (Nabi et al, 2007):

URS gave better stone free rates than SWL

URS had a lower need of re-treatments

but..

URS had more complications

URS was more invasive

URETERORENOSCOPIC STONE REMOVAL

STONE DISINTEGRATION

Electrohydraulic	Not recommended due to heat spreading
Pneumatic	Risk for stone migration
Ultrasound	OK
Laser	
Nd:YAG	Poor effect on hard stones: COM, cystine
Ho:YAG	Disintegrates all stones. Tissue penetration < 5 mm

SELECTION OF STONE REMOVING PROCEDURE

FACTORS OF IMPORTANCE

Local experience

Patient's preference

Available equipment

Associated costs

WHEN SWL AND URS HAVE FAILED

- Percutaneous approach
- Laparoscopic surgery
- Incisional /open surgery

2ND INTERNATIONAL CONSULTATION ON STONE DISEASE

Pediatric Stone Disease & Stones in Pregnancy

Hassan Razvi MD FRCSC
London, Canada

Pediatric Stone Disease
Epidemiology

- Relatively uncommon in developed countries (1-2% of that observed in adults)
- Increasing occurrence observed globally
  - Germany - increase from 0.54% to 1.47% between 1979 and 2000 Hess et al Eur Urol 2003
  - Improved detection?
    - Lifestyle/dietary changes?
      - Obesity, excess salt intake especially in processed foods, low water consumption

Pediatric Stone Disease
Epidemiology

- Among developing countries pediatric stone disease remains endemic
  - Reported prevalence rates 5-15% Shah et al Indian J Pediatr
  - Higher prevalence of bladder stones
    - Related to malnutrition,
    - Ammonium urate composition
  - Changing trend emerging with a predominance of upper tract stones (Level 3 evidence) Rizvi et al J Urol 2002

Pediatric Stone Disease
Investigations

- Assessment of the acute event similar to adults
  - History/Physical exam
  - Urine culture mandatory (Level 2 evidence, Grade A recommendation) Straub et al World J Urol 2005
  - Ultrasound most common initial investigation
    - Despite failing to identify stones in 40% of pediatric patients (Level 4 evidence) Palmer et al J Urol 2005

Pediatric Stone Disease
Investigations

- Non-contrast helical CT
  - Has a 95% sensitivity for detecting stones in children (Level 4 evidence) Oner et al JBR-BTR 2004
  - With current high speed machines, sedation rarely required, reduction in radiation exposure

Pediatric Stone Disease
Investigations

- Metabolic work up
  - Should be carried out in all pediatric stone formers (Level 2-4 evidence, Grade B recommendation) DeFoor et al J Urol 2006; Edvardsson et al Pediatr Nephrol 2005; Sarica Urol Res 2006
  - Higher likelihood of metabolic abnormalities
    - Cystinuria, primary oxalosis…

Pediatric Stone Disease
Interventional Therapies

- International consensus on the management of pediatric stone disease is lacking
- Given the population, a paucity of randomized trials
- Most ureteral stones <4 mm in size pass spontaneously (Level 3 evidence) Van Savage et al J Urol 2000
- Indications for intervention and aims are similar to those in adults
- Greater incidence of anatomical abnormalities may impact on choice of therapy e.g. UPJ obstruction

Pediatric Stone Disease
Interventional Therapies

- Other factors influencing treatment decisions
  - Child's age/body size
  - Stone burden, location, composition if known e.g. cystine, struvite
  - Surgeon experience
  - Access to technology

Pediatric Stone Disease
Interventional Therapies - SWL

- SWL considered the treatment of first choice due to perception it is least invasive and has reasonable efficacy
  - Despite the fact not US FDA approved!
- A number of retrospective case series have reported stone free rates of 50 - 90% with minimal morbidity (Level 3 evidence) Gupta et al J Endourol 2007; Tan et al J Endourol 2004; Soygur et al J Ped Urol 2006; Afshar et al J Urol 2004
  - Authors supported SWL as first line therapy for renal or upper ureteral stones (Level 3 evidence, Grade B recommendation)

Pediatric Stone Disease
Interventional Therapies - SWL

- Is there such a thing as "insignificant fragments" in children post SWL?
  - Fate of residuals fragments < 5 mm assessed Afshar et al J Urol 2004
    - 69% of patients had adverse outcomes (colic requiring intervention, incremental growth in stone size)
    - Every attempt should be made to achieve a stone free state (Level 3 evidence, Grade C recommendation)

Pediatric Stone Disease
Interventional Therapies - SWL

- Role of stents in children?
  - Pediatric ureter maybe more compliant and more efficient in clearing fragments?
  - Prospective comparison of children and adults with stones >10mm treated by SWL Gofrit et al J Urol 2001
    - SFR in children 95% vs 79% in adults (p=0.008) (Level 2 evidence)
  - Authors suggest stent or nephrostomy placement only in the child with sepsis or obstruction, and not to based on stone size (Level 2 evidence, Grade C recommendation)

Pediatric Stone Disease
Interventional Therapies - Ureteroscopy

- Technologic improvements permit ureteroscopy in most pediatric patients
  - Miniaturization of semirigid 'scopes
  - Ho:YAG laser
- Role continues to evolve
  - Surgeon experience
  - Access to technology

Pediatric Stone Disease
Interventional Therapies - Ureteroscopy

- Retrospective case series report SFR > 90% and with minimal morbidity for children of all ages (Level 3 evidence) Reddy J Urol 1999; Wollin et al J Urol 1999; Satar et al J Urol 2004; Tan et al Urol 2005
- Prospective randomized trial comparing SWL vs URS for distal ureteral stones De Dominics BJU Int'l 2005
  - 94% SFR for URS vs 42% (p=0.004) after single SWL session and 64% after retreatment
  - No significant difference in complication rates
  - Authors recommend URS as the treatment of choice for distal ureteral stones by a skilled endourologist (Level 3 evidence, Grade B recommendation)

Pediatric Stone Disease
Interventional Therapies - PCNL

- Initial concern about greater risk of complications, lead to suggestions that PCNL should only be performed on children > 8 years of age (Level 4 evidence, Grade C recommendation) however, with…
  - Instrumentation miniaturization
  - Improved surgical skills
  - "Mini-perc" concept Jackman et al Urol 1998
- PCNL has now been shown to be safe and effective for children < 5 (Level 3 evidence) Arun et al J Endourol 2005; Boormans et al BJU Int'l 2005; Manohar et al J Endourol 2006; Erdenetsesteg et al J Endourol 2006

Pediatric Stone Disease
Interventional Therapies - PCNL

- Current Indications (Level 3 evidence, Grade C recommendation) Farhat AUA Update 26: 2007
  - Large stone burden in association with congenital/structural anomaly
    - UPJO, calyceal 'tic
  - Stone burden > 2 cm/staghorn
  - Failed SWL/URS
  - Known cystine or struvite?

Pediatric Stone Disease
Interventional Therapies - PCNL

- Caveats
  - Requires skilled endourologist
  - Full range of endourologic instruments
  - Hypothermia, blood loss are significant concerns
  - Mini-perc (smaller tract and nephroscope < 24 Fr) although less invasive, may lead to longer OR times for clearance of larger stone burdens)
    - Requires smaller ancillary tools, if bleeding encountered visibility impaired)

Pediatric Stone Disease
Interventional Therapies - Open Surgery

- In developed countries, reserved for patients with large volume upper tract stones with
  - Congenital/structural anomaly
  - After failed endourologic procedure(s)
- In developing countries, this remains an important treatment alternative, with acceptable success rates and complication risks (Level 3 evidence)

Rizvi et al J Urol 2003; Jallouli et al J Ped Urol 2006

Stones in Pregnancy
Epidemiology

- Incidence estimates vary between 1 in 244 to 1 in 3300 pregnancies (Level 3 evidence) Butler et al Obstet Gynecol 2000; Lewis et al J Reprod Med 2003; Swartz et al Obstet Gynecol 2007
- Equal incidence to non-pregnant women of same age
- > 80% of patients present in the 2nd or 3rd trimester
- The majority of patients (64 - 85%) pass their stones spontaneously (Level 3 evidence)

Stones in Pregnancy
Investigations

- Ultrasound has historically been the preferred imaging modality because of the absence of ionizing radiation
  - 34% Sensitivity and 86% specificity in pregnancy (Level 3 evidence) Stothers J Urol 1992
    - Hydronephrosis of pregnancy R > L
    - Position of the fetus may effect imaging quality, ability to diagnose ureteral stone
  - Elevation of the Resistive Index (RI) may help to distinguish physiologic dilation of pregnancy from obstruction (Level 3 evidence) Shokeir et al Urol 2000; Hertzberg et al Radiol 1993

Stones in Pregnancy
Investigations

- Limited IVP, 2nd line investigation (Level 4 evidence)
- CT - contraindicated due to the high radiation exposure (Level 4 evidence)

Stones in Pregnancy
Interventional Therapies

- Randomized trials are not available given the patient population
- Indications for intervention are similar to the non-pregnant patient
  - Trimester of pregnancy at presentation may influence management
    - Avoidance of intervention during 1st trimester due to risk of miscarriage and 3rd trimester due to induction of pre-term labor
- Role of perinatologist/high risk obstetrical unit important in treatment decisions

Stones in Pregnancy
Interventional Therapies - Acute Event

- Absolute indications for intervention
  - Sepsis, obstruction in a solitary kidney, pre-term labor
- First trimester
  - Percutaneous nephrostomy insertion under ultrasound guidance and without need for general anesthesia is effective option (Level 4 evidence)
- Latter stages of pregnancy
  - Stent insertion maybe preferred, although risk of accelerated stent encrustation has been observed (Level 4 evidence)

Stones in Pregnancy
Interventional Therapies - Definitive Therapy

- Classic teaching had suggested definitive stone therapy should be deferred until after delivery (Level 4 evidence, Grade C recommendation)
- With the advent of small calibre semi-rigid and flexible ureteroscopes, the Ho:YAG laser and better basket devices, ureteroscopy is now considered a valid therapeutic option (Level 3 and 4 evidence, Grade B recommendation)

Stones in Pregnancy
Interventional Therapies - Ureteroscopy

Author	Type of Study, Level of Evidence	Stone Free Rate N (%)	Lithotripsy Device	Major Adverse Event
Shokeir BJU 1998	Retrospective Level 3	5/8 (63%)	Grasper, ultrasound	None
Tekerlekis J Endourol 1999	Retrospective Level 3	12/16 (75%)	Basket/grasper	None
Lemos Int Br J Urol 2002	Retrospective Level 3	13/14 (93%)	Ultrasound Basket/grasper	None
Watterson Urol 2002	Retrospective Level 3	7/8 (89%)	Ho:YAG Laser	None
Ulvik J Endourol 2005	Retrospective Level 3	23/27 (71%)	Basket/grasper	*Ureteral perforation *Preterm delivery
Geavlete J Endourol 2006	Retrospective Level 3	14/14 (93%)	Laser Basket/grasper	None

Stones in Pregnancy
Interventional Therapies - Ureteroscopy

- Although there is a paucity of clinical evidence to suggest any of the intracorporeal lithotripsy devices are harmful to the fetus, theoretical concerns exist
  - Ultrasound - effect on fetal hearing development?
  - Electrohydraulic lithotripsy (EHL) - stimulates uterine contractility?
- Devices with more focal energy delivery, such as pneumatic devices, pulsed dye laser or Ho:YAG are considered safer (Level 4 evidence, Grade C recommendation)

Stones in Pregnancy
Asymptomatic Stone Among Women of Childbearing Age

- Should a woman planning a pregnancy have her asymptomatic stone treated to avoid the need for invasive intervention and the potential risks should she become pregnant?
- Prevalence of stone disease in women in North America has increased
  - Between 1997 & 2002 male:female ratio has changed from 1.7:1 to 1.3:1 (Level 3 evidence) Scales et al J Urol 2007
- Cumulative 5 year probability of symptomatic stone event in a cohort of adults (males and females) was assessed
  - Female cohort - 24% became symptomatic (Level 3 evidence) Glowacki et al J Urol 1992

Summary

- The management of upper tract stones in children and pregnant women continues to challenge our profession
  - Ureteroscopy, as a result of technological advances, is playing a more prominent role
- Absence of randomized trials in many facets of the condition, force us to rely on "first principles"
  - Decisions based on physiological or anatomical knowledge
  - "Primum non nocere"

Stones in Pregnancy
Asymptomatic Stone Among Women of Childbearing Age

- No published trials specifically addressing the management of asymptomatic stone in women of childbearing age
- A prospective randomized trial comparing observation vs prophylactic SWL for asymptomatic calyceal stones (Level 1 evidence) Keeley et al BJU Int'l 20001
  - Although no differences in SFR, QOL, renal function or hospital admission between groups
  - Observation arm had a greater need for invasive procedures in short term follow-up

Stones in Pregnancy
Asymptomatic Stone Among Women of Childbearing Age

- Odds of pre-term labor are increased among women with symptomatic stones during pregnancy (1.7% relative risk) (Level 3 evidence) Swartz et al Obstet Gynecol 2007
  - No heightened risk of low birth weight or fetal death
- No observed effect on female fertility from SWL (Level 3 evidence)
- Women of childbearing age should be treated prior to attempting conception (Level 4 evidence, Grade C recommendation

Bladder Stones consensus group 2nd International Consultation, Paris 2007

Singapore*
Dr Michael Wong (Chair)
Dr Chong Tsung Wen

Saudi Arabia
Dr Mohammed Al Omar

Romania
Dr Petrisor Geavelete

Germany
Dr Gerald Haupt

China
Dr Zhou Liqun

South Korea
Dr Gyung Tak Sung

Japan
Dr Seiji Naito

*(assistance from Dr Nor Azhari, Dr Tricia Kuo – Singapore)

Bladder Stones - ESWL

One non-randomised cohort study (level 2)

Milan Rodriguez. Urology 2005, 66 (3) : 505-509

- N = 45
- Bladder stones < 4cm sq. Primary ESWL +/- adjunctive TURP
- End points: SFR, IPSS, TURP
- Overall SFR 93% (77% single session); 4% recurrence (mean f/u 22 months)
- Adjunctive TURP 8% (IPSS pre-treatment > 30 predictive)

Bladder Stones - ESWL

Other studies (level 3):

- Stone free rates 66-100%
- Results better in absence of associated pathology >80%
- Adjunctive procedures :
  - transurethral irrigation (neurogenic bladders)
  - TURP
- Indications:
  - in unfit/ unwilling for GA.
  - Transurethral route impassable. Stricture, penile prosthesis, AUS
  - pediatric patients
- Stone size, associated pathology (BPH) predictive of success

Bladder Stones – Transurethral approach

Two case control studies (level 3):

Asci R. BJU Int 1999, 84(1): 32-6

- N = 93
- Optical mechanical cystolithotripsy (n=32) vs OMC+TURP (n=61) vs historical control TURP (n=97)
- SFR OMC 94% and OMC+TURP 93%
- Complications 13% vs 21% vs 5%
- Conclusions:
  - 66% bladder stones with associated BPH/ adjunctive TURP
  - comparable SFR and complications : OMC vs OMC + TURP

Bladder Stones – Transurethral approach

Razvi HA. J Endourol 1996, 10 (6): 559-63

- N = 106
- Mechanical (n=53) vs ultrasonic (n=17) vs electrohydraulic lithotripsy EHL (n=16) vs lithoclast (n=20)
- SFR 90% vs 88% vs 63% vs 85%
- Complications higher when combined with TURP (6.3% vs 11.9%)
- EHL:
  - poorer SFR (especially harder calculi)
  - greater use of salvage procedures

Bladder Stones – Transurethral approach

- Indications: bladder stones with outlet obstruction
- Higher complications (8%) when combined with TURP
- Highest SFR with HLC (100%); mechanical, ultrasonic and lithoclast 85-90%
- Transurethral route contraindications:
  - small capacity bladder
  - multiple/ large stones
  - small calibre urethra

Bladder Stones – Percutaneous approach

One non-randomised cohort study (level 2)

Aron M. Int Urol Nephrol 2007, 39 (1): 173-7

- N = 54. Prostate vol>50 mls, stone size > 3cm
- TURP + transurethral pneumatic lithotripsy (n=19) vs TURP + percutaneous cystolithotripsy PCL(n=35)
- SFR 85% vs 100%
- 10% more urethral complications with only transurethral route
- shorter OR time for PCL + TURP
- conclusion: PCL + TURP more efficacious/ safer for large stones/ prostate

Bladder Stones – Percutaneous approach

- Maheshwari 1999, N= 38 (23 adults). Pneumatic, u/s lithotripsy. Minimal urethal instrumentation. SFR 100%. Complication 0%
- Tzortis 2006, N=31. Lithoclast. Local anaesthesia. SFR 96%, Complication 19% (hematuria, fever)
- Demirel 2006, N=72 (42 adults). Neurogenic bladders. Pneumatic. SFR 100%, Complication hematuria (5.6%), fever (4.1%)
- Wollin 1999, N=15. Pneumatic. SFR 100%, Complication 0%
- Ikari 1993, N=36. u/s lithotripsy. SFR 89%, Complication 0%

Bladder Stones – Percutaneous approach

- effective treatment. Good SFR, minimal complications
- larger stones/ multiple stones/ large prostate
- combined with simultaneous transurethral route (reduce OR time)
- Local anaesthetic possible:
  - Unfit patients
  - Patients who do not need TURP

Bladder Stones – Cystolithotomy

One case control study (level 3) :

Richter S. Urology 2002, 59:688-91

N=40. BPH (n=20) +/- bladder stone (n=20). Cystolithotomy+TURP vs historical TURP

SFR 100%. Complications 5% vs 5% (post opt fever).

OR time 65.7 min vs 47.3 min; hosp stay 3.8 days vs 3.4 days

- Effective treatment for all bladder stones
- minimally prolonged OR time and hospital stay vs TURP alone
- can simultaneously address large BPH requiring open surgery

Bladder Stones – Summary of therapeutic options

No strong recommendations for any particular option in view of paucity of level 1/2 evidence

- In unfit patients, ESWL is an option (better SFR < 4cm stone size, no concommittant outlet obstruction). (C)
- Larger stone burdens require invasive options. Percutaneous, open surgery less morbidity than transurethral routes. Available equipment and expertise dictates.

Bladder Stones – Summary of therapeutic options

- Transurethral route can address bladder outlet obstruction/ BPH. Higher complications with TURP. (C)
- SFR 85-100%. Holmium laser (550um), pneumatic, u/s lithotripsy, mechanical. Poorer SFR with EHL.
- Percutaneous route can be combined with transurethral approaches. (C)
- More efficacy with larger/ multiple stones. Less urethral complications.
- Percutaneous approach under local anaesthesia is possible.

Bladder Stones – Summary of therapeutic options

- Open cystolithotomy is an option with effective treatment of all bladder stones. Minimal additional OR time/ hosp stay. (C)
- Percutaneous approaches effective for the reconstructed bladder. Reduced analgesic requirements/ hosp stay vs open surgery. (C)
- Use of laparoscopic entrapment sac to increase percutaneous efficiency
- High stone recurrence rates. Treat UTI