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In Memoriam

Martin I. Resnick, MD
1943–2007

Dr. Martin I. Resnick, Consulting Editor for the *Urologic Clinics of North America* (2005–2007) and previously for the *Atlas of the Urologic Clinics* (1993–2004), passed away during the production of this issue. The staff members of the *Clinics* department, like many publishers who had the opportunity to work with Dr. Resnick, were saddened to learn of his death. There are no adequate words to convey how grateful we feel to have worked with such a wonderful person. Dr. Resnick's dedication to the *Clinics* and his focus on quality were unparalleled. His achievements as Consulting Editor can only be shadowed by his achievements as a kind and compassionate physician and human being. His congenial, supportive, and altruistic demeanor made every contact a pleasant one. Dr. Resnick will be dearly missed.

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Foreword

Martin I. Resnick, MD
Consulting Editor

Urolithiasis is a common disorder, and epidemiologic studies over many years have demonstrated that approximately 15% of individuals will form a stone sometime during their lifetime. Although calcium oxalate stones predominate, the cause of stone formation varies, based on differences in urinary parameters. Approximately 2 to 3 decades ago, much effort was expanded in understanding the mechanisms of stone formation, and treatment modalities were developed. These efforts have had significant in reducing the incidence of stone formation and in controlling new stone growth.

Perhaps one of the most significant changes in urologic care during the past several decades has been in the management of patients who have existing stones in the urinary tract. The development of extracorporeal shock wave lithotripsy followed by a variety of endoscopic techniques has reduced the morbidity associated with stone treatment and also has led to further developments and innovations that have had a very positive impact on our patient population.

Dr. Margaret Pearle has compiled an excellent group of articles reviewing many of the issues related to stone evaluation and treatment. Both the different types of stone and new technological developments for the management of renal and ureteral stones are addressed. The economics of stone management, which is recognized as increasingly important, is also clearly outlined in this issue.

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Preface

Margaret S. Pearle, MD, PhD
Guest Editor

Upper urinary tract stones are a significant source of morbidity and cost in Western society. With genetic, environmental, and metabolic risk factors for stone formation, the disease affects a large cross-section of the population. Consequently, strategies aimed at stone prevention are attractive. To that end, a thorough understanding of the pathogenesis and pathophysiology of stone disease is critical to target key physiologic processes that can be manipulated to prevent stone formation. Likewise, the identification of individuals at high risk of stone formation can streamline the selection, evaluation, and treatment of patients who have a history of stones.

Despite efforts to prevent stone formation, however, stones do and will continue to occur. Therefore surgical treatments with the least morbidity and highest effectiveness are sought continuously. New innovations in minimally invasive surgical modalities have increased their effectiveness and reduced the morbidity so that ureteroscopy and percutaneous nephrostolithotomy now compete with shock wave lithotripsy as first-line therapy for renal and ureteral stones. Although shock wave lithotripsy technology has remained relatively static during the last 2 decades, recent efforts to optimize treatment parameters are resulting in more efficient and efficacious shock wave treatment as well.

In this issue of *The Urologic Clinics of North America*, all aspects of stone disease, from pathogenesis to surgical treatment to prevention, are explored to provide the reader with a comprehensive understanding of stone disease and an update on the most recent innovations in surgical and medical management. The contributing authors, all leaders in the field of stone disease, have graciously lent their expertise to this special issue devoted to urolithiasis.

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Epidemiology of Stone Disease

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Epidemiology, the study of the distribution and determinants of disease, can help with the understanding and management of stone disease in several ways. First, epidemiologic studies can quantify patterns and the burden of disease. Second, large epidemiologic studies can identify risk factors that may provide insight into pathophysiologic processes related to stone formation. Third, these types of studies offer a means to examine interactions among factors, such as those related to diet or the gene environment. Because nephrolithiasis is a complex disease, an understanding of the epidemiology, particularly the interactions among different factors, may help lead to approaches that reduce the risk of stone formation.

Prevalence

Stone disease is common with the lifetime risk of stone formation in the United States exceeding 12% in men and 6% in women [1,2]. However, the prevalence of nephrolithiasis, defined as a history of stone disease, varies by age, sex, and race. The prevalence appears to have increased in the last quarter of the twentieth century for men and women, blacks and whites (Figs. 1 and 2) [2]. This apparent increase may reflect an actual increase in stone disease, or it may stem from increased detection of asymptomatic stones discovered with the greater use and higher sensitivity of imaging studies. Apparent prevalence of stone disease has also increased in other parts of the world, including Japan [3] and Germany [4].

Stone disease prevalence within the United States varies by racial background [2,5]. A history of stone disease is most common among older white males (~10%), and lowest in younger black females (~1%). The prevalence in Asians and Hispanics falls somewhere in between.

Prevalence of stone disease also varies by geographic location within the United States. A study of over 1 million individuals found a north–south and west–east gradient such that the highest prevalence of stone disease occurred in the southeastern United States [6].

Incidence

Several population-based studies have demonstrated that incidence rates, defined as the onset of an individual's first kidney stone, vary by age, sex, and race. As with prevalence, the incidence rates are highest in white males. For men, the incidence begins to rise after age 20, peaks between 40 and 60 years at about 3/1000/y and then begins to decline [1,7,8]. For women, incidence rates seem to be higher in the late 20s (2.5/1000/y) and then decreasing to 1/1000/y by age 50. This rate then appears to remain relatively constant for the next several decades [1,8–10].

Although earlier studies suggested that incidence rates were rising in the United States, a recent study from Rochester, Minnesota, suggests that this trend may be changing. Using the same methodology as a study done 30 years earlier that showed increasing incidence rates in

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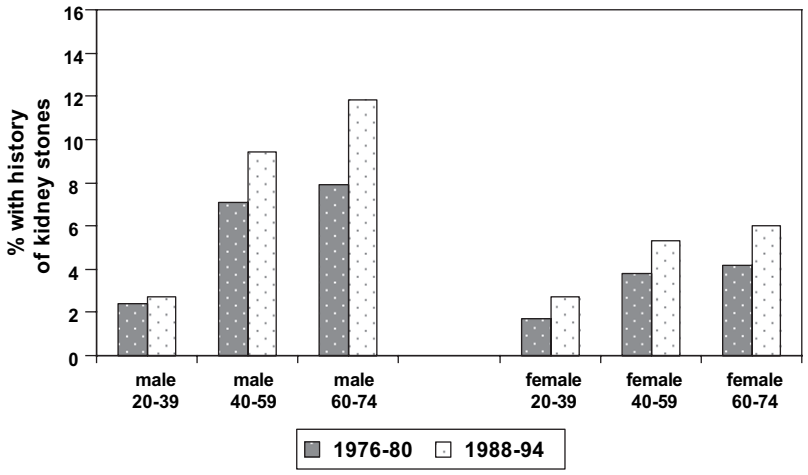

Fig. 1. Prevalence of stone disease by sex and age. (*Adapted from* Stamatelou KK, Francis ME, Jones CA, et al. Time trends in reported prevalence of kidney stones in the United States: 1976–1994. Kidney Int 2003;63(5):1817–23, with permission.)

men and women between 1950 and 1974, the recent study found that the incidence rates since 1990 may be falling in men and have reached a plateau in women [11].

Recurrence rates

Early reports suggested that if left untreated the likelihood of forming another stone after the initial episode was 30% to 40% at 5 years [1]. These figures from observational studies are similar to the recurrence rates in the control arms of recently published randomized trials [12,13]. Encouragingly, the treatment arms of many of the randomized trials have shown dramatic reductions of 50% or more in recurrence rates [12–15]. These reductions by medication or dietary interventions emphasize that recurrent stone disease is preventable.

Risk factors

Our understanding of the risk factors for stone formation has increased substantially over the

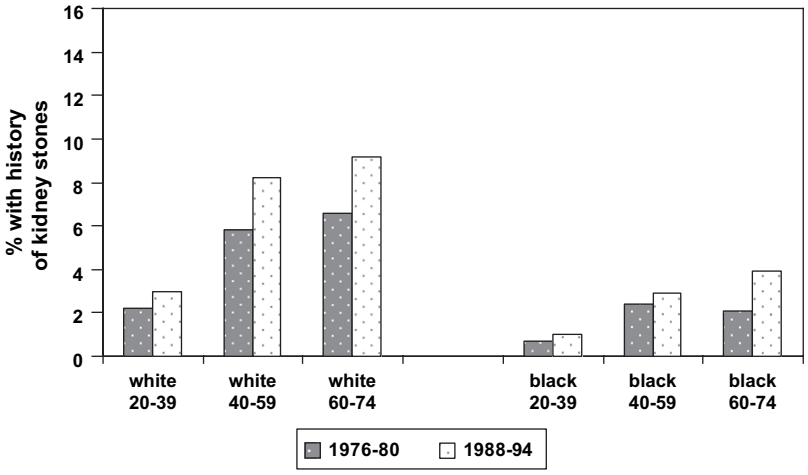

Fig. 2. Prevalence of stone disease by race and age. (*Adapted from* Stamatelou KK, Francis ME, Jones CA, et al. Time trends in reported prevalence of kidney stones in the United States: 1976–1994. Kidney Int 2003;63(5):1817–23, with permission.)

past several decades. Risk factors are generally divided into nondietary, dietary, and urinary categories.

Nondietary

Family history

The risk of becoming a stone former is more than 2.5 times greater in individuals with a family history of stone disease [16]. This higher risk is likely due to a combination of genetic predisposition as well as similar environmental exposures (eg, diet). A polygenic inheritance has been proposed to account for the tendency to calcium oxalate stone formation in families [17]. While a number of genetic factors have been clearly associated with rare forms of nephrolithiasis, information is still limited on genes that contribute to risk of the common forms of stone disease.

Systemic disorders

Although nephrolithiasis has traditionally been considered a renal disorder, overwhelming evidence suggests that it is in fact a systemic disorder. Primary hyperparathyroidism, renal tubular acidosis, and Crohn's disease are well-described conditions that increase the risk of formation of calcium-containing stones. Primary hyperparathyroidism may be found in 5% of stone formers [18].

More recently, a number of other common conditions have been convincingly linked to nephrolithiasis. Increasing body size as assessed by weight, body mass index (BMI), or waistline measurements is associated with an increasing risk of stone formation independent of other risk factors, including diet [19]. The magnitude of the increase in risk from BMI is higher in women than in men. For example, the risk of stone formation for individuals with a BMI greater than or equal to 30 compared with those with a BMI 21 to 23 was 30% higher among men but nearly twofold higher among women. Weight gain also increases the risk of stone formation. A 35-lb weight gain since early adulthood increased risk of stone formation by 40% in men and 80% in women. The mechanism or mechanisms for the increased risk associated with larger body size are unknown.

A history of gout increases the likelihood of forming kidney stones, both uric acid and calcium oxalate. In a national health survey, individuals with gout were 50% more likely to have a history of stones [20]. When examined prospectively, a history of gout was associated with a doubling of the risk of forming a stone, independent of diet, weight, and medications [21]. Although the mechanism for this relationship is unknown, possibilities include insulin resistance and acid–base defects.

More recently, diabetes mellitus was found to raise the risk of stone formation, independent of diet and body size [22]. Cross-sectionally, individuals with a history of type II diabetes mellitus were more than 30% more likely also to have a history of nephrolithiasis. Prospectively, a history of type II diabetes mellitus increased the risk of stone formation by 30% to 50% in women but not in men.

Environmental factors

Individuals working in a hot environment appear to be at higher risk for stone formation [23]. In many situations, lack of access to water or bathroom facilities may lead to lower fluid intake and thus, because of lower urine volume, a higher risk of stone formation.

Dietary factors

The composition of the urine is influenced by dietary intake and several dietary factors have been proposed to modify the risk of nephrolithiasis. Nutrients that have been implicated include calcium, animal protein [24], oxalate [25], sodium [26], sucrose [27], magnesium [28], and potassium [29]. Because patients who develop stones often change their diet, studies that retrospectively assessed diet may be hampered by recall bias. Other studies have examined the relation between diet and changes in the lithogenic composition of the urine, often using calculated relative supersaturation. However, the composition of the urine does not completely predict risk and not all the components that modify risk are included in the calculation of supersaturation (eg, urine phytate). Thus, prospective studies are best suited for examining the associations between dietary factors and risk of actual stone formation.

Calcium

The first prospective study of dietary factors and the risk of incident stone disease was performed in a cohort of more than 50,000 male health professionals aged 40 to 75 years at baseline [7]. Although dietary calcium had been strongly suspected of raising the risk of stone disease, men with a higher intake of dietary calcium actually had a lower risk of incident nephrolithiasis independent of other risk factors. This inverse association has been confirmed in two other prospective studies in women [9,10] and in an updated

analysis in men [30]. Although the mechanism of this effect is unknown, low calcium intake is known to increase oxalate absorption and urinary excretion [31], and individuals with lower calcium intake have lower 24-hour urine oxalate excretion. However, because those taking in high levels of calcium may be consuming high quantities of dairy products, the major source of dietary calcium in the United States, it is possible some other factor in dairy products, besides calcium, protects against stones. A subsequent study showed that low dietary calcium intake may increase the risk of stone formation, even among individuals with a family history of stones [16].

The above-mentioned observational data were subsequently confirmed in a randomized trial by Borghi and colleagues [12] that compared a low calcium diet (400 mg/d) to a diet containing 1200 mg/d of calcium, along with low sodium and low animal protein intake, in men with hypercalciuria and calcium oxalate stones. The rate of recurrence fell by 50% in the higher calcium intake group. While some authorities still question whether a high calcium diet reduces the risk of stone formation, overwhelming evidence shows that calcium restriction is not beneficial and may in fact be harmful, both by promoting stone formation and accelerating bone loss.

Despite similar bioavailability, the impact of supplemental calcium appears to be different from dietary calcium. In an observational study of older women, calcium supplement users were 20% more likely to form a stone than were women who did not take supplements, after adjusting for dietary factors [9]. In younger women and men, there was no association between calcium supplement use and risk of stone formation [7,10]. The discrepancy between the risks from dietary calcium and the risks from calcium supplements may be due to the timing of calcium intake. In these studies, calcium supplements were often taken between meals, which would diminish binding of dietary oxalate. The recently published Women's Health Initiative randomized trial also demonstrated a 17% increased risk of stones with calcium supplementation [32]. However, these results should be interpreted cautiously because the participants were instructed to take their supplements with meals, and the supplements contained both calcium and vitamin D.

Oxalate

The role of dietary oxalate in the pathogenesis of calcium oxalate nephrolithiasis is unclear [33]. The proportion of urinary oxalate derived from dietary oxalate is controversial; estimates range from 10% to 50% [33]. In addition to the gastrointentinal absorption of dietary oxalate, urinary oxalate is also derived from the endogenous metabolism of glycine, glycolate, hydroxyproline, and vitamin C. Due to variable and often low bioavailability, much of the oxalate in food may not be readily absorbed. The dietary contribution of urinary oxalate may be higher in stone formers. Up to one third of patients with calcium oxalate nephrolithiasis may have increased absorption of dietary oxalate. In some cases, a deficiency of oxalate degradation by the bacterium *Oxalobacter formigenes* in the gut could be the culprit [33]. The impact of dietary oxalate on risk of stone formation has not yet been studied prospectively because of the lack of sufficient and reliable information on the oxalate content of many foods. However, recent reports using modern approaches to measure the oxalate content of food [34,35] have opened the possibility of these studies being completed soon.

Other nutrients

Several other nutrients have been studied and implicated in the development of stone formation, but several of the associations with risk vary by age, sex, or BMI. High animal protein intake leads to increased calcium and uric acid excretion as well as decreased urinary citrate [36], all of which increase the risk of stone formation. An increased risk of stone formation was observed for higher animal protein intake only among men with BMI less than 25 [30]. A higher intake of sodium [26] or sucrose [27] increases calcium excretion independent of calcium intake, whereas potassium supplementation decreases calcium excretion [29] and many potassium-rich foods increase urinary citrate due to their alkali content. Prospective studies demonstrated that sucrose was associated with an increased risk in women [9,10] and higher dietary potassium intake decreased risk in men and older women [7,9,30]. Recently, phytate was also found to reduce substantially the likelihood of stone formation in younger women [10].

Magnesium complexes with oxalate, thereby potentially reducing oxalate absorption in the gastrointestinal tract and decreasing calcium oxalate supersaturation in the urine. A few randomized trials have examined the effect of magnesium supplementation on stone recurrence. However, magnesium was given in combination with other compounds (eg, thiazide diuretic or potassium

citrate) and the dropout rates were high. Currently, it is uncertain whether magnesium supplementation has an independent beneficial effect. In prospective observational studies, higher dietary magnesium was associated with a 30% lower risk of stone formation in men [30], but not in women [9,10].

Vitamin C (ascorbic acid) can be metabolized to oxalate; thus, higher vitamin C intake could increase the risk of calcium oxalate stone formation. A metabolic trial demonstrated that the consumption of 1000 mg of supplemental vitamin C twice daily increased urinary oxalate excretion by 22% [37]. An observational study in men found that those who consumed 1000 mg or more per day of vitamin C had a 40% higher risk of stone formation compared with men who consumed less than 90 mg/day (the recommended dietary allowance) [30]. This relationship was observed only after accounting for dietary potassium intake. Although restricting dietary vitamin C does not seem appropriate (as foods high in vitamin C are also high in inhibitory factors, such as potassium), a calcium oxalate stone former should be encouraged to avoid vitamin C supplements.

Vitamin B_6 is a cofactor in oxalate metabolism, and vitamin B_6 deficiency increases oxalate production and urine oxalate excretion. Although high doses of supplemental vitamin B_6 may be beneficial in selected patients with type 1 primary hyperoxaluria, the use of vitamin B_6 in other settings remains unclear. Based on observational data, high intake of vitamin B_6 may reduce the risk of kidney stone formation in women [38] but not in men [39].

Fluid intake and beverages

When the urine output is less than 1 L/d, risk of stone formation is markedly higher. Observational studies [7,9,10] and a randomized controlled trial [40] have demonstrated the importance of fluid intake in reducing the likelihood of stone formation.

Patients with stone disease often ask what they should and should not drink. Despite previous beliefs to the contrary, observational studies have found that coffee, tea, beer, and wine are associated with a reduced risk of stone formation [41,42]. Although citrus juices theoretically could reduce the risk of stone formation [43], orange juice consumption was not associated with stone formation and grapefruit juice intake was associated with a 40% higher risk [41,42]. Grapefruit juice is known to have a number of effects on intestinal enzymes, but the mechanism for the observed increased risk is unknown. Previous studies suggested an increased risk for soda consumption and unadjusted results from observational studies also suggested an increased risk. However, after controlling for other dietary components, consumption of soda (including soda with caffeine, soda without caffeine, diet soda, and conventional sweet soda) was not associated with the risk of stone formation [41,42]. Although skim and whole milk were not associated with risk in the observational studies, probably because these studies adjusted for the intake of dietary calcium, milk intake likely reduces the risk of calcium kidney stone formation.

Urinary factors

The 24-hour urine chemistries provide important prognostic information and direct therapeutic recommendations for prevention. Traditionally, urine results have been categorized as "normal" or "abnormal," but recently there has been a greater appreciation of two important points. First, the urine values are continuous so the dichotomization into "normal" or "abnormal" is arbitrary and potentially misleading. Second, stone formation is a disorder of concentration, not just the absolute amount excreted. Although such terms as hypercalciuria are often used both clinically and scientifically, the limitations of these terms should be remembered.

Hypercalciuria has been traditionally defined as urine calcium excretion greater than or equal to 300 mg/d in men and 250 mg/d in women [44] on a 1000-mg/d calcium diet. Based on these definitions, about 20% to 40% of patients with calcium stone disease have hypercalciuria. Although a higher cutoff value in males makes sense from a calcium balance perspective, it does not for stone formation, particularly given that 24-hour urine volumes are slightly higher in women [45].

Hyperoxaluria is defined as urinary oxalate excretion greater than 45 mg/d. Elevated urinary oxalate excretion may be present in up to 40% of male stone formers and in up to 10% in female stone formers [45]. Although mean urinary oxalate levels may not differ between cases and controls, oxalate does appear to be an important independent risk factor for stone formation [45].

The relation between uric acid metabolism and calcium stone disease has been intriguing. Some investigators have reported that hyperuricosuria (defined as excretion >800 mg/d in men or

>750 mg/d in women) is seen more frequently in patients who form calcium stones than in normal subjects [46], but others have found no difference [45]. Although allopurinol in a double-blind trial successfully decreased recurrence rates of calcium stones in patients with hyperuricosuria [14], the role of uric acid in calcium stone disease remains unsettled.

Hypocitraturia, typically defined as 24-hour excretion less than or equal to 320 mg/d, increases risk for stone formation [47] and is found in 5% to 11% of first-time stone formers [45]. At present, insufficient evidence is available to conclude that increasing urinary citrate into the high-normal range provides additional protection.

Low urine volume, for which a variety of definitions have been used, is a common and modifiable risk factor. When defined as 24-hour urine volume of less than 1 L/d, 12% to 25% of first-time stone formers have this abnormality [45]. Observational studies have demonstrated that the risk of stone formation decreases with increasing total urine volume [45], and a randomized trial confirmed the value of increasing urine volume [40].

Summary

Epidemiologic studies have expanded our understanding of stone disease. It is clear that a variety of risk factors contribute to the risk of stone formation and that the importance of these risk factors varies by age and sex. The individual impact of traditional risk factors (eg, calcium, animal protein) has been quantified and new factors (eg, body size, phytate) have been identified. Results from these studies have forced a reappraisal of our view of risk factors for stone disease. The results from epidemiologic studies can be applied in the clinical setting with the goal of reducing the likelihood of stone formation.

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Pathogenesis of Renal Calculi

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Kidney stones are a common entity, affecting approximately 5% of American women and 12% of American men. Recent reports have suggested that the prevalence of kidney stone disease is increasing [1]. Considerable advances have been made over the last 3 decades in the diagnosis and management of kidney stone disease, such as helical CT imaging, enhanced metabolic evaluation, and minimally invasive surgical therapies—shock wave lithotripsy (SWL), percutaneous nephrolithotomy (PNL), and ureteroscopy (URS). Advances in our understanding of the pathogenesis of renal calculi have not paralleled this progression in diagnosis and treatment, however.

Although much is understood about the physical chemistry involved in nephrolithiasis, the inciting factor and sequence of events that lead to the formation of a kidney stone remains elusive. Significant research has been performed using animal models and cell culture experiments; however, it is unclear whether these outcomes are transferable to human kidney stone formers. Recent efforts to understand the pathogenesis of nephrolithiasis in humans have led to a delineation of the human surgical anatomy, histopathology, and metabolic factors in a variety of kidney stone formers [2–5]. This work has suggested that there are distinct stone phenotypes; and the cascade of events leading to kidney stone formation may be different, depending on this phenotype. This article reviews the current theories on the pathogenesis of renal calculi.

The physical chemistry of stone formation

Supersaturation and the upper limit of metastability

Urinary supersaturation (SS) is necessary for clinical stone formation. SS is the driving force for a phase change from dissolved salt to solid; that is to say that at SS values less than 1, crystals will be dissolved in solution, and at SS values greater than 1, crystals may form (Fig. 1) [6]. The concentration at which saturation is reached and crystallization begins is called the thermodynamic solubility product (Ksp). Ksp is a constant equal to the product of the concentration of the pure chemical components of the solute at saturation. Although the SS can be estimated by the ratio of a particular dissolved salt to its solubility, computer programs exist that calculate SS based on the free ion concentration of the major ionic species in urine in light of the total concentrations of the ions, the pH, and the stability constants of the various ion pairs [7,8]. SS values, as measured by 24-hour urine tests, have been shown to correlate with stone composition, underscoring the importance of SS in stone formation [9].

Although SS is simple to calculate in water, urine is a much more complex solution, containing substances that affect the formation of calcium

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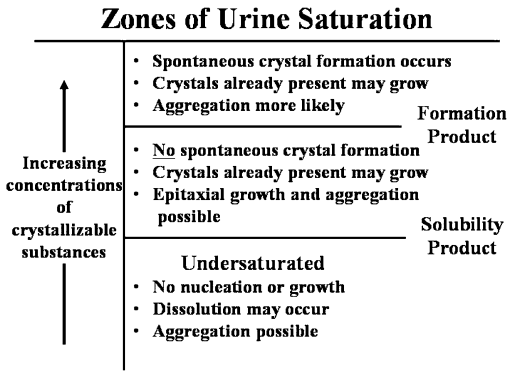

Fig. 1. Physical chemistry of stone formation.

oxalate (CaOx) and calcium phosphate (CaP). The range of SS between the solubility product and the point at which crystals form, known as the formation product (Kfp), is referred to as the metastable zone (see Fig. 1). The term metastable is used because the concentration of the salt, for example CaOx, is above its solubility, and precipitation is inevitable. The amount of calcium or oxalate required to produce a solid phase of CaOx or CaP is known as the upper limit of metastability (ULM) [6]. Asplin and colleagues [10,11] have demonstrated that ULM is lower among stone formers and varies with urinary SS.

Nucleation and crystal formation

The first step in crystal formation is nucleation. In a pure solution, nucleation will occur at a critical level of SS, which is referred to as homogeneous nucleation. In urine, however, crystal nuclei can form on existing surfaces, such as cell membranes, cellular debris, other crystals, red blood cells, and urinary casts, through a process known as heterogeneous nucleation [12,13]. Heterogeneous nucleation occurs at a lower level of SS than does homogeneous nucleation [14].

All crystals have a lattice structure that can be characterized by X-ray diffraction. If the lattice structure of one crystal is similar to that of another crystal, the second crystal may be able to nucleate and grow on the first. This is a process referred to as epitaxy [15]. The role of epitaxy in crystal growth has been debated [16–21]; however, nuclei are known to form larger crystals if the urine remains supersaturated with respect to the precipitating salt [22].

In addition to crystal growth, crystal aggregation, or agglomeration, is thought to be an important mechanism in stone formation. When crystal nuclei are present in an aqueous solution, collisions between crystals caused by chemical or electrical forces can lead to crystal aggregation. The combined process of crystal growth and aggregation has been offered as a hypothesis in the pathogenesis of stone disease through the formation of crystals large enough to occlude the lumen of the collecting duct [23].

Crystal retention

A volume of literature suggests that crystal retention is necessary for stone formation. Once a crystal is retained in the tubules of the kidney, growth can occur in the presence of SS or aggregation of crystals. Two general mechanisms have been proposed for crystal retention: the free particle hypothesis, and the fixed particle hypothesis. The free particle hypothesis suggests that nucleation followed by rapid crystal growth occurs within the tubular lumen, resulting in crystal trapping at the site of the papillary collecting duct and subsequent stone formation; however, the steps necessary to produce a clinical stone event have not been elucidated [24,25]. Finlayson argued against this hypothesis, stating that there was insufficient time for the formation of a lumen-obstructing crystal mass because of the rapid flow of ultrafiltrate through the tubule [26].

The second theory of crystal retention, the fixed particle hypothesis, postulates the adherence of crystals to some underlying surface, such as renal epithelial cells [27–29]. Based on data from cell-culture studies, some investigators have proposed an integral role for crystal binding molecules, such as phosphatidylserine [30,31], sialic acid [32,33], osteopontin [34], and hyaluronan [35,36], in crystal retention and crystal-cell interaction.

Inhibitors and promoters of crystal growth

Urinary saturation with CaOx is common in non-stone formers, indicating the role of factors other than SS in stone formation. A number of substances found in the urine have been shown to modulate crystal formation, growth, and aggregation (Box 1). Investigators have hypothesized that differences in these substances may play a role in the pathogenesis of renal calculi. For example, some individuals with supersaturated urine may be able to prevent crystallization because of the presence of urinary inhibitors.

Box 1. Modulators of crystal formation

- Pyrophosphate
- Magnesium
- Citrate
- Tamm-Horsfall protein
- Nephrocalcin
- Osteopontin
- Bikunin (Inter-α-inhibitor)
- Calgranulin
- Prothrombin F1 fragment
- Albumin
- RNA and DNA fragments
- Glycosaminoglycans
- Renal lithostathine

Urinary inhibitors of the CaOx system have been best studied. Most of the inhibitory activity resides in macromolecules such as glycoproteins and glycosaminoglycans. The molecules are anionic, with long stretches of polyanion chains that can bond with surface calcium atoms and prevent crystal growth. These inhibitors frequently contain post-translational modifications such as phosphorylation and glycosylation [37]. The following urinary inhibitors have been identified: citrate, magnesium, pyrophosphate, nephrocalcin, Tamm-Horsfall protein (THP), uropontin, crystal matrix protein (F1 prothrombin fragment), lithostathine, inter-alpha-trypsin inhibitor molecule/uronic acid-rich protein (bikunin), albumin, RNA and DNA fragments, glycosaminoglycans, and calgranulin [6]. The extent to which these inhibitors modulate stone formation remains an area of active research, and is discussed in more detail below.

Some of the same substances that inhibit one stage of crystal formation may promote another stage, such as aggregation. For example, glycosaminoglycans promote crystal nucleation, but inhibit crystal aggregation and growth [38]. THP has also been shown to act as both a promoter and an inhibitor, depending on molecular size, the state of self-aggregation, and the concentration of citrate in the urine [39–42].

Role of proteins/matrix

Kidney stones contain a variable amount of noncrystalline organic material called matrix. The matrix is believed to originate from the proximal tubule, and chemical analysis of the matrix has demonstrated the presence of 65% hexosamine and 10% bound water [43,44]. The amount of matrix present in kidney stones varies, with most solid urinary calculi having a low matrix content of 3% [45,46]; however, calculi that develop in the setting of urinary tract infection may have a matrix content as much as 65% [47].

The role of the matrix in urinary stones has been debated. Scanning electron microscopic studies of CaOx stones have revealed organic material between adjacent crystals, supporting the hypothesis that matrix acts as a ground substance [48,49]; however, another explanation for the presence of matrix in stones is via a nonspecific adsorption of organic compounds on growing crystals [50]. Boyce and King [51] isolated a muco-protein material from the matrix, and termed this matrix substance A. Substance A was described as an organic compound composed of protein and carbohydrate components that was present in the urine of recurrent stone formers. Subsequent immunologic investigation of substance A revealed three or four antigens unique to stones [52].

A more recent study by Jones and colleagues [53] used a stone-forming animal model (hyperoxaluric rat) to clarify the role of urinary proteins in kidney stone formation. All animals in the stone-forming group had pathologic evidence of early stone formation (diffuse intranephronic calculosis) that was consistently associated with a reduction in the excretion of low molecular weight urinary proteins. Alcian blue staining confirmed the presence of matrix within clumps of the intranephronic CaOx crystals, suggesting that low molecular weight urinary proteins are selectively incorporated within the crystalline structure of a stone early in its formation. The contribution of the matrix and urinary proteins in stone formation remains an active area of research. Future efforts using proteomics and molecular biology may prove critical in unraveling their specific role [54].

Theories of stone pathogenesis

Crystal-induced renal injury

One pathway by which crystal retention has been hypothesized to occur in the kidney is as a response to tissue injury. The majority of the evidence for this theory has been obtained through the use of animal models and tissue culture experiments [55]. Experimental induction of hyperoxaluria leads to crystalluria and CaOx crystal deposition in the kidney [29].

Hyperoxaluria triggers increased urinary excretion of enzymes associated with renal epithelial cell injury, such as N-acetyl-β-glucosaminidase, gamma-glutamyl transpeptidase, and alkaline phosphatase [56]. Oxalate is thought to induce injury through the production of reactive oxygen species (ROS) and subsequent lipid peroxidation [57]. These ROS are normally dealt with by endogenous antioxidant defenses in the kidney; however, excessive production can overwhelm this system, resulting in oxidative stress and renal injury [58]. In addition to the production of ROS, oxalate is thought to increase the gene expression and production of several urinary macromolecules, such as phosphatidylserine, CD44, osteopontin, and hyaluronan, which may modulate crystal adherence to renal epithelial cell surfaces [59–61].

The results of tissue culture studies have been used to provide evidence for crystal adherence to injured renal epithelial cells, but not to healthy inner medullary collecting duct (IMCD) cells. When primary cultures of IMCD cells were exposed to crystals of CaOx, the crystals preferentially adhered to cells with impaired tight junctions [62]. A subsequent study using mechanically injured MDCK-1 cells cited similar conclusions, because CaOx crystals were found to adhere specifically to the surfaces of injured or regenerating cells [63]. Again, this adherence is thought to be mediated by crystal-binding molecules that may be affected by cell injury.

Crystal adherence and deposition are thought to induce renal interstitial inflammation with migration of macrophages [57]. These macrophages release tumor necrosis factor-α (TNF-α), which results in the increased expression of several matrix metalloproteinases (MMP) [64]. MMP are the main matrix-degrading enzymes, and have been shown to play a role in the erosion of atherosclerotic plaque [65]. Therefore, it has been suggested that these MMP may play a similar role in the erosion or ulceration of subepithelial deposit at the renal papillary surface, creating a nidus for stone formation.

Despite the proposed role of oxalate in the formation of renal calculi, there have been several criticisms of the experimental models used to provide evidence for crystal-induced renal injury. In the most common model, ethylene glycol (EG), a precursor of oxalate, is given to rats to induce hyperoxaluria [61,66,67]. The animals develop crystalluria and CaOx deposition with renal tubular injury. The criticisms of this model for the study of CaOx nephrolithiasis is that EG consumption can cause injury to multiple organs as well as inducing a metabolic acidosis [68,69]. Furthermore, many other metabolites of EG have been shown to cause injury to the renal epithelium [70]. Animal models have been further questioned, in that cellular injury has been created using supraphysiologic (100×) levels of oxalate [71–73]. Holmes and colleagues [74] studied the changes in plasma and urinary oxalate following oral dietary oxalate loading in humans. They reported no evidence of acute renal injury or oxidative stress following an 8 mmol oxalate load. Cell culture studies have confirmed that oxalate is toxic to renal tubular cells only at supraphysiologic concentrations [73].

This model for studying oxalate toxicity has also been criticized in that many of these cell culture studies were performed using renal proximal tubule cells, rather than cells from the collecting duct [75–79]. Finally, and perhaps most importantly, there have been no studies of living, human, idiopathic CaOx stone formers that have supported the theory of crystal-induced renal injury. In fact, recent investigation by Evan and colleagues [4,27] of human papillary biopsies from well-characterized CaOx stone formers did not detect any evidence of stones forming as a result of tubular epithelial injury caused by oxalate toxicity. These models represent at best severe hyperoxaluria, such as that seen in primary hyperoxaluria; a condition not commonly observed in common idiopathic calcium oxalate stone formers.

Free particle formation in tubular lumen

The free particle hypothesis suggests that nucleation followed by rapid crystal growth occurs within the tubular lumen, resulting in crystal trapping at the site of the papillary collecting duct and stone formation [25]. Finlayson and Reid [26] argued against this hypothesis, stating that there was insufficient time for the formation of a lumen-obstructing crystal mass because of the rapid flow of ultrafiltrate through the tubule; however, some recent investigations using new data on nephron dimensions, SS, and crystal growth rates in urine, and incorporating the size-increasing effect of crystal agglomeration have proposed that during the normal transit time through the kidney, crystalline particles can be formed that are large enough to be retained [24].

Robertson [80] compared and contrasted three mathematical models used to describe the flow of urine through the renal tubule and the composition of tubular fluid throughout the length of the nephron. All three models agreed that, under normal conditions, the likelihood of individual crystals growing large enough to be trapped within the measured urine transit time of 3 to 4 minutes is very small. Therefore, it was concluded that either there had to be aggregation of crystals or some other factor that delays the passage of crystals. Robertson introduced three new hydrodynamic factors that may lead to delay of crystal passage: (1) fluid drag close to the tubule walls, (2) the drag effect of tubular walls on particles traveling close to the tubule walls, and (3) the effect of gravity on particles traveling in upward-draining sections of tubule. Data obtained from these mathematical models after introducing these new hydrodynamic factors have been interpreted as demonstrating that the ''free-particle'' model of calcium stone formation is still possible.

Intravascular phenomenon

Low and Stoller [28] have introduced a new hypothesis for the primary event in the formation of nephrolithiasis. They proposed that stones form as a result of an intravascular phenomenon within the vasa recta, at the innermost portion of the renal papillum. Injury to the papillary vasculature and subsequent repair is proposed to result in an atherosclerotic-like reaction with calcification. The resulting calcification could eventually erode into the renal papillary ducts of Bellini (BD), serving as a nidus for calculus formation. Furthermore, free and esterified cholesterol have been identified within kidney stones, and the study authors cite this as evidence supporting this theory of stone formation. This theory was based upon multiple epidemiological, clinical, physiological, and anatomical observations; however, although intriguing, it has not been confirmed in the studies by Evan and colleagues [27] of living human stone formers. In fact, human papillary tissue obtained from idiopathic calcium oxalate stone formers, including the vasa recta, are normal in areas where Randall's plaque is developing.

Insufficient or abnormal urinary inhibitors

The presence of a lower than normal concentration of urinary inhibitors has been proposed as a mechanism for the pathogenesis of stone disease. Robertson and colleagues [81] suggested that stone formation may depend on the balance between two opposing forces: SS and urinary inhibitors. Urinary citrate is considered an inhibitor of stone formation by binding calcium to reduce SS, and inhibiting nucleation and growth of calcium crystals. Citrate is routinely measured in the metabolic evaluation of stone formers, and when low is considered to be a risk factor for stone formation. Asplin and colleagues [10,82] have investigated the role of crystal inhibition in stone-forming men and women. When compared with normals, stone-forming men showed reduced calcium oxalate monohydrate (COM) growth inhibition and reduced ULM in relationship to SS; however, there was no difference in aggregation inhibition. Evaluation of female stone formers demonstrated reduced CaP and CaOx ULM values in relation to SS, which is a defect that could promote stones by facilitating crystal nucleation. In contrast to the male stone formers, there was no difference in growth inhibition.

In addition to the amount of urinary inhibitor present, stone formers may have qualitative defects in crystal inhibitors. For example, THP, a potent aggregation inhibitor of COM, has been shown to exist in a predominantly self-aggregated form in stone formers that reduces its effectiveness as an aggregation inhibitor [83]. The inhibitor nephrocalcin (NC) has also been shown to be abnormal in COM stone formers, in that the NC molecules lack gamma-carboxyglutamic acid and fail to inhibit COM crystallization normally [84–86]. In addition to THP and NC, Suzuki and colleagues [87] have demonstrated the presence of an aberrant form of the inhibitor bikunin in male stone formers.

Because of the number of inhibitors present in urine, it is difficult to know which are the most important in stone formers. Therefore, the measurement of urinary inhibitors or the replacement of inhibitors other than citrate as therapy is not part of the routine management of kidney stone patients at present; however, this remains an area of great interest.

Nanobacteria

Nanobacteria (NB) are cytotoxic, sterile-filterable, gram-negative, atypical bacteria detected in bovine and human blood that have been implicated in a variety of disease states, such as atherosclerotic heart disease, periodontal disease, and renal cystic disease [88–94]. Recent investigations have speculated that NB may play a role in

the formation of renal calculi by nucleating carbonate apatite on their surfaces [95–98]. In an in vitro study, Ciftcioglu and colleagues [88] demonstrated the presence of NB in 70 of 72 kidney stones analyzed by scanning electron microscopy and immunofluorescent staining. The presence of these NB was independent of stone type; however, apatite stones gave the highest immunopositivity. Further studies have revealed in vitro calcific stone formation by NB as well as stone formation following NB inoculation of rat kidneys [95,96]. Based on these findings, it has been hypothesized that NB colonization could damage renal tubular epithelial cells, resulting in biomineralization and subsequent stone formation.

Despite these reports, the role of NB in stone formation is controversial [99]. Cisar and colleagues [100] demonstrated that biomineralization previously attributed to NB may be initiated by nonliving macromolecules and transferred on ''subculture'' by self-propagating microcrystalline apatite. Chan and colleagues [101] were unable to detect the NB antigen by enzyme-linked immunosorbent assay in all of 16 renal calculi. They also failed to isolate DNA using polymerase chain reaction primers for the published sequence of 16S RNA from enzyme-linked, immunosorbent, assay-positive fetal bovine serum cultures, and thus confirmed the negative results of other investigators [102,103]. Therefore, the contribution of NB, if any, in apatite nucleation and crystal growth remains uncertain.

Stasis

Stasis of urine has been proposed as an etiologic factor in the formation of kidney stones in patients who have anatomic abnormalities of the kidney, such as ureteropelvic junction obstruction (UPJO), calyceal diverticulum (CD), horseshoe kidney, hydronephrosis, and medullary sponge kidney [104,105]. The distorted renal anatomy is thought to result in crystal retention caused by a delayed washout of crystals and risk of urinary infections; however, stasis has been questioned as the sole etiologic factor. Several investigators have demonstrated that metabolic abnormalities contribute significantly to stone development in these patients [106–108]. A recent study by Matlaga and associates [109] demonstrated that urinary risk profiles of patients who had diverticular calculi were similar to those of CaOx stone formers, suggesting a metabolic etiology of diverticular stones. The SS CaOx of urine aspirated directly from the diverticula was significantly lower than that of the renal pelves, however, supporting the role of urinary stasis in the pathogenesis of calyceal diverticular calculi. Therefore, it may be that a combination of metabolic abnormalities and stasis predispose these patients who have anatomic abnormalities of the kidney to stone formation.

Randall's plaque

Over 6 decades ago, Alexander Randall conducted a detailed examination of the papillae of more than 1000 nonselected cadaveric renal units [110]. He observed calcium salt deposits in the tip of the renal papillum in 19.6% of individuals studied. These deposits, which he termed plaque, were interstitial in location, composed of CaP, and not observed in the tubular lumen. Randall hypothesized that these areas of plaque would be an ideal site for an overgrowth of CaOx to develop into a calculus. Since Randall's observations, reported in 1940, little progress has been made in defining the role of plaque in the pathogenesis of kidney stone disease, for the most part because of a lack of appropriate in vivo data, but perhaps also aided by the fact that Randall tried to expand his hypothesis to fit all stone formers.

Kuo and associates [111], however, reported the safety of performing renal papillary and cortical biopsies at the time of PNL in a series of 19 stone formers. Subsequent data derived from the tissue of living, well-characterized human stone-formers have demonstrated a prominent role for Randall's plaque in the pathogenesis of stone disease [4,112]. Metabolic and surgical pathologic findings in four distinct groups of stone formers have clearly shown that ''the histology of the renal papilla from a stone former is particular to the clinical setting'' [2,4,5,27,112].

Evidence for the role of Randall's plaque in the pathogenesis of renal calculi

Idiopathic CaOx stone formers

The vast majority of stone formers are idiopathic CaOx stone formers, making this group critical to the understanding of the pathogenesis of nephrolithiasis [4]. Idiopathic CaOx stone formers may be defined as those patients who form CaOx stones without any systemic cause other than idiopathic familial hypercalciuria [113]. When examined with high resolution digital imaging, the renal papillae of all such patients were

noted to have sites of Randall's plaque, which were manifest as irregular, whitish lesions generally located on the papillary tip, just as Randall initially described (Fig. 2A). A cohort of non–stone-forming patients served as a control population, and when the papillary surfaces of these patients were examined, rare sites of Randall's plaque were identified (Fig. 2B). The renal papillae of both the stone-former and non–stone-former groups were carefully mapped, for the purpose of quantifying the papillary surface area covered by plaque. The fractional plaque coverage of the stone formers was significantly higher (7.6% versus 0.5%) than the control (non–stone-former) patients [113,114].

Subsequent histologic examination of the papillary tissue by Evan and colleagues [4] using a Yasue metal substitution technique demonstrated that plaque was composed of calcium salts (Fig. 3A), and originated in the basement membranes of the thin loops of Henle (Fig. 3B). These deposits were always localized to the inner medullary interstitial space, and followed the thin loops of Henle to the basal surface of the urothelium (see Fig. 3A). Higher power imaging demonstrated that crystalline deposits as small as 50 nm could be identified in the basement membrane of otherwise normal-appearing thin loops of Henle (Fig. 3C), and were closely associated with Type I collagen bundles in the interstitial space of the papillary tip (Fig. 3D). The mineral composition of the interstitial deposits was identified as hydroxyapatite, based on Fourier-transform infrared (FTIR) microspectroscopy and electron diffraction analysis. CaOx was not detected in any of the specimens. In addition to confirming Randall's initial observations, Evan and colleagues demonstrated that this process was occurring in normal tissue, with no evidence of cellular injury such as inflammation or fibrosis driving the process. Rather, the basement membrane and the large fields of Type I collagen may be an ideal matrix to attract calcium and phosphate, and the pathophysiology of crystal deposition at the thin loops of Henle may be strongly linked to the patient's hypercalciuria.

To better understand the role of Randall's plaque in stone formation, Evan and colleagues [3] characterized the apatite plaque particles in the inner medulla of the kidneys of CaOx stone formers and explored the relationship of plaque apatite to osteopontin. The deposits of hydroxyapatite ranged from single crystals in the basement membranes of the thin loops of Henle, to dense interstitial collections forming a syncytium of mineral deposit islands in a sea of organic material. Transmission electron microscopy (TEM) showed the single deposits to be generally spherical in shape, as small as 50 nm, and laminated with mineral and organic molecules

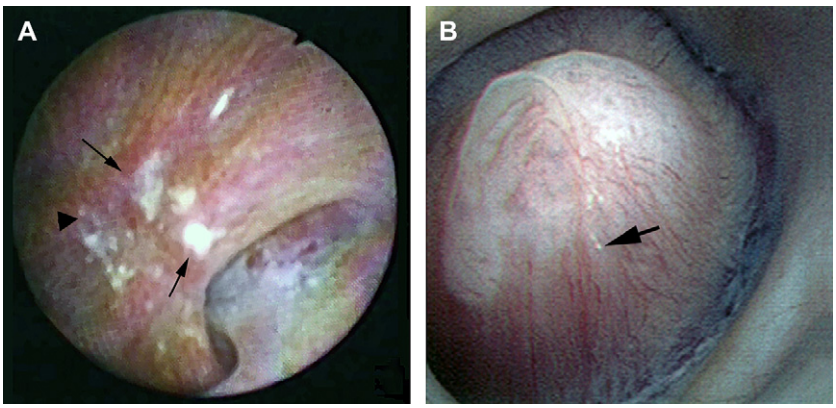

Fig. 2. Endoscopic images of Randall's plaque in CaOx stone formers versus controls. In (*A*), an example of a papilla from a CaOx stone former demonstrating several sites of Randall's plaque (*arrows*), which appear as irregular white areas beneath the urothelium. In addition, a plaque site was noted that lacked a urothelial layer and is thought to be a site where a stone had been attached to the side of the papilla (*arrowhead*). In contrast (*B*), endoscopic examination of a papilla from a non–stone-former, demonstrates no distinct sites of Randall's plaque; rather, a nodular appearing structure (*arrow*) was seen along the side of the papilla. (*From* Evan AP, Lingeman JE, Coe FL, et al. Randall's plaque of patients with nephrolithiasis begins in basement membranes of thin loops of Henle. J Clin Invest 2003;111(5):607–16; with permission.)

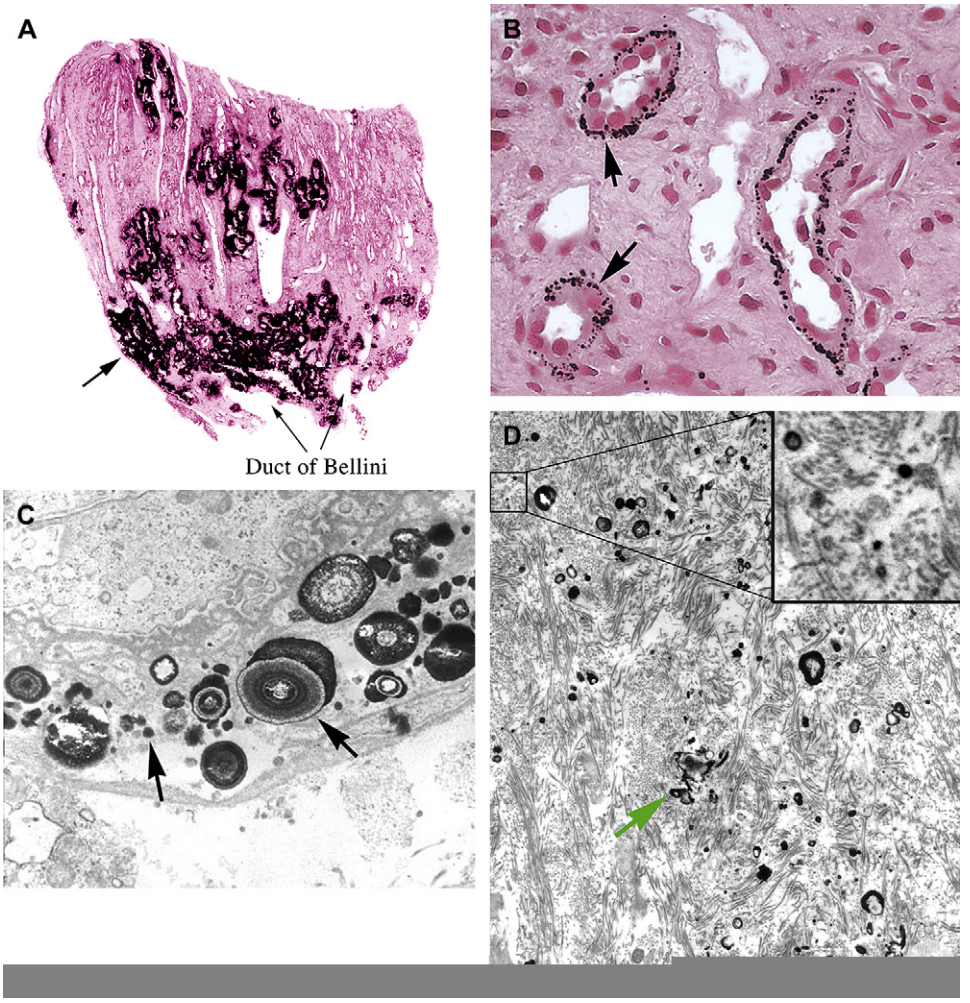

Fig. 3. Histologic examination of Randall's plaque in CaOx stone formers. (*A*) Low-magnification light microscopic image of a papillary biopsy specimen from a CaOx patient, the sites of calcium deposits (*arrow*) were stained black by the Yasue metal substitution method for calcium histochemistry (magnification ×100). (*B*) These initial sites of crystal deposition (*arrows*) originated in the basement membrane of the thin loops of Henle (magnification ×1000). (*C*) Transmission electron microscopy (TEM) demonstrates crystalline deposits (*arrows*) as small as 50 nm in the basement membrane of otherwise normal appearing thin loops of Henle (magnification ×15,600). (*D*) Numerous deposits (*green arrow*) are shown closely associated with Type I collagen bundles in the interstitial space of the papillary tip of this CaOx stone former (magnification ×4750). The inset illustrates the relationship of the initial small sites of crystal formation on individual collagen fibers at higher magnification (magnification ×16,500). (*From* Evan AP, Lingeman JE, Coe FL, et al. Randall's plaque of patients with nephrolithiasis begins in basement membranes of thin loops of Henle. J Clin Invest 2003;111(5):607–16; with permission.)

layered one over the other (Fig. 4A). Immunohistochemical studies confirmed that osteopontin was present in the organic layer, positioned on the outer surface of the crystal and the overlying organic molecular layer, suggesting that osteopontin is involved in plaque biology (Fig. 4B).

In addition to the histopathologic data, there is metabolic and clinical evidence supporting the Randall's plaque theory of stone pathogenesis. Kuo and associates [114] measured papillary plaque surface area in a cohort of idiopathic CaOx stone-formers, and then compared these data to the metabolic data derived from two 24-hour

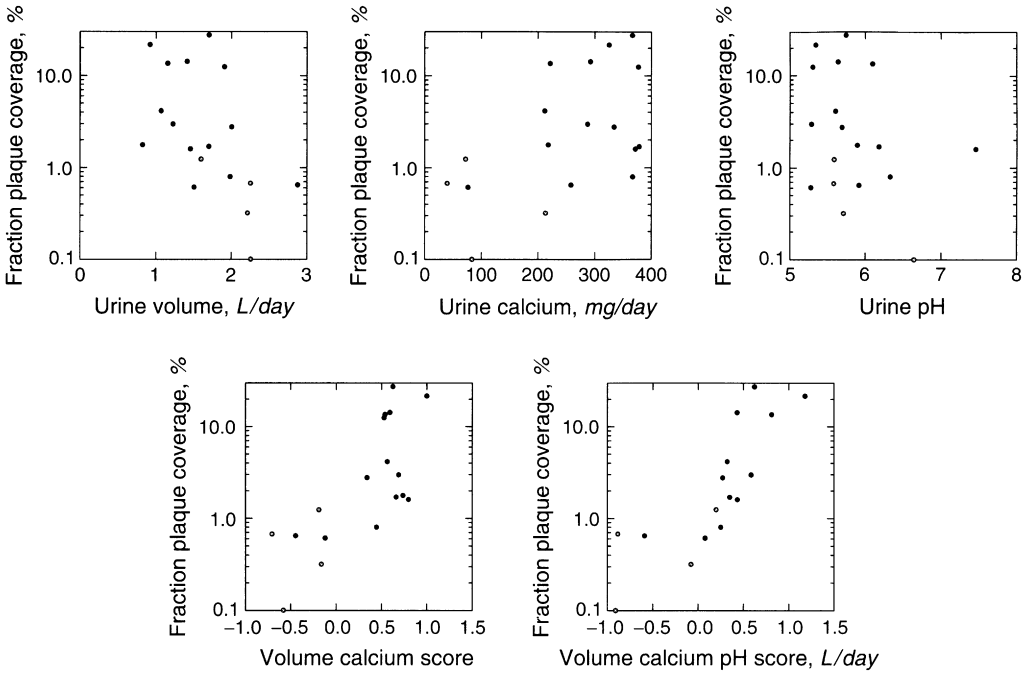

Fig. 5. Fractional plaque coverage per papillum varies inversely with urine volume (*upper left panel*) among stone formers (*closed circles*) and non stone-forming control subjects (*open circles*). Plaque coverage varies with urine calcium excretion (*upper middle panel*) and is inverse to urine pH (*upper right panel*). A composite multivariate regression score using urine volume and calcium excretion (*lower left panel*) and one that includes urine pH as well (*lower right panel*) strongly correlate with plaque coverage. (*From* Kuo RL, Lingeman JE, Evan AP, et al. Urine calcium and volume predict coverage of renal papilla by Randall's plaque. Kidney Int 2003;64(6):2150–4; with permission.)

excretions compared with the idiopathic CaOx stone formers.

Endoscopic examination of the renal papillae of the brushite stone formers demonstrated three different types of deposits. The first pattern was sites of Randall's plaque as seen in the idiopathic CaOx patients (Fig. 7A). The second pattern was large, yellow deposits projecting from the opening of the BD into the urinary collecting space (Fig. 7B). The third pattern was suburothelial

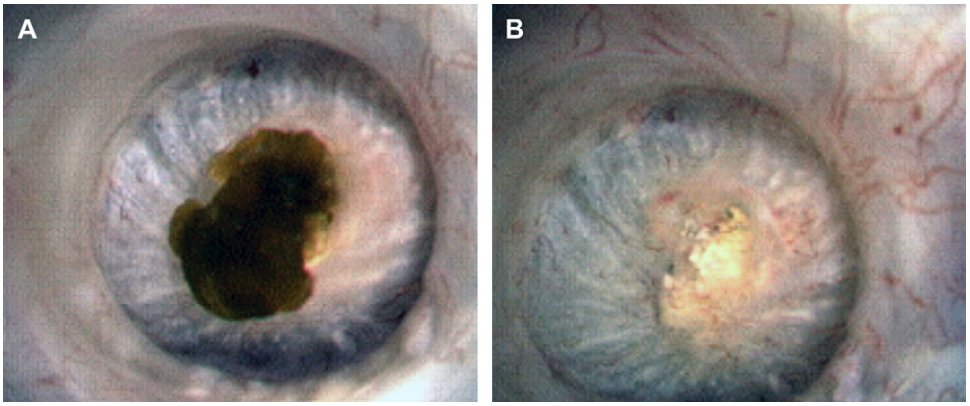

Fig. 6. (*A*) A calcium oxalate stone at the tip of a renal papilla demonstrating extensive plaque deposition. (*B*) This same renal papilla from (*A*) following stone removal exposing plaque and inner medullary collecting ducts.

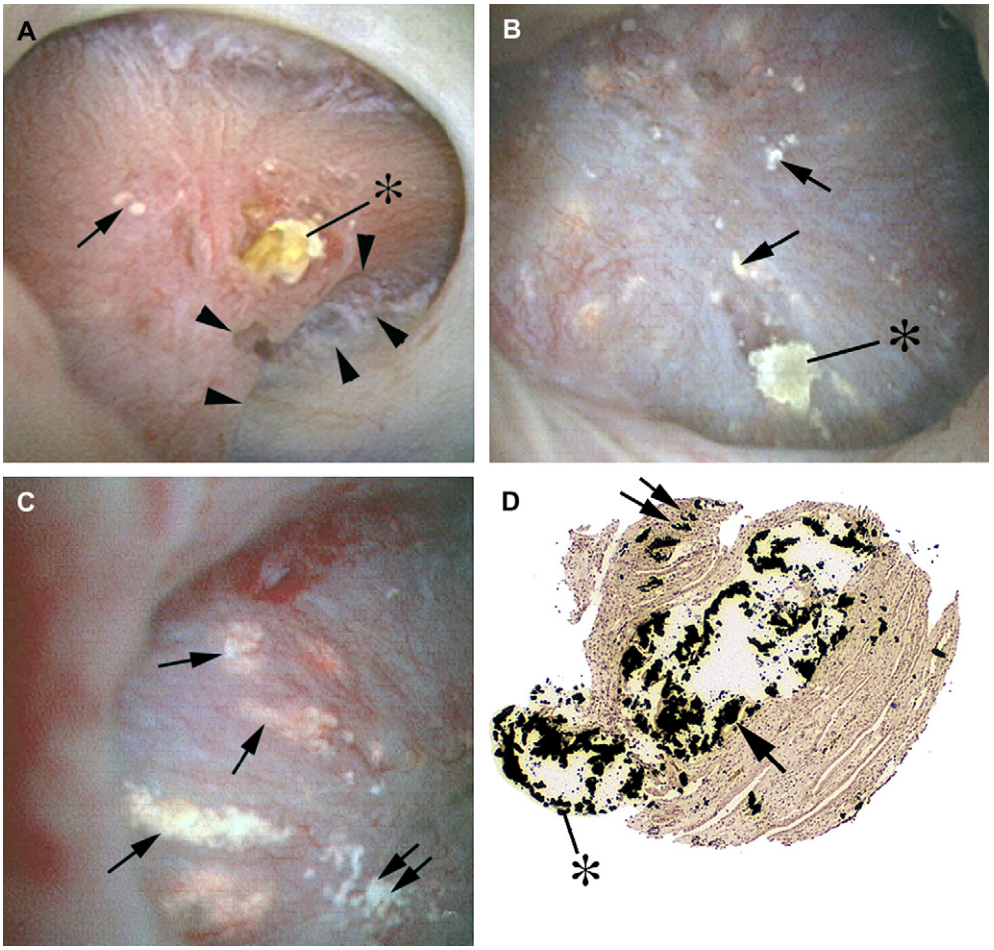

Fig. 7. Endoscopic and histologic images demonstrating three distinct patterns of crystal deposition in brushite stone formers. The first pattern (*A*) consists of irregular white areas of crystalline deposits —Randall's plaque (*arrows*)— beneath the urothelium, as described for idiopathic CaOx stone formers. In addition, the papilla from brushite patients possess sites of a yellowish crystalline deposit at the opening of the BD (*A, B*,*) and in a suburothelial location on the sides of the papilla (*C*, *double arrows*). Note the enlargement of the opening of a BD that is filled with crystalline material (*) seen as a depression or "pit" on the papilla (*A*). A large pit (*arrowheads*) is seen along the side of the papilla (*A*) and does not appear to be associated with a BD. Low power magnification light microscopic images of a papillary biopsy from a brushite stone former (*D*) confirms that these sites of crystal deposition are composed of calcium, as indicated by the Yasue metal substitution method for calcium histochemistry; and that they are located in the BD (*arrow*) and associated IMCD (*). Yasue-positive material (apatite) is also noted in the interstitium adjacent to thin loops of Henle (*double arrow*) (magnification ×100). (*From* Evan AP, Lingeman JE, Coe FL, et al. Crystal-associated nephropathy in patients with brushite nephrolithiasis. Kidney Int 2005;67(2):576–91.)

yellow deposits on the sides of the papillary tip and clearly within the lumens of inner medullary collecting ducts (Fig. 7C). Histopathologic techniques confirmed the sites of interstitial crystal deposits, as well as the IMCD and BD that were engorged with crystalline deposits (Fig. 7D). The papillae of the brushite stone formers were noted to be covered with depressions, or pits, which were most commonly associated with dilated openings of BD, but occasionally were found on the sides of a papillum.

Histologic examination of the crystal-filled medullary collecting ducts revealed extensive cell injury surrounded by interstitial fibrosis (Fig. 8A). Some tubules altogether lacked viable cells. Other tubules contained cells that were obviously dead as detected by TEM analysis. Cuffing by fibrosis of single crystalline-filled collecting ducts

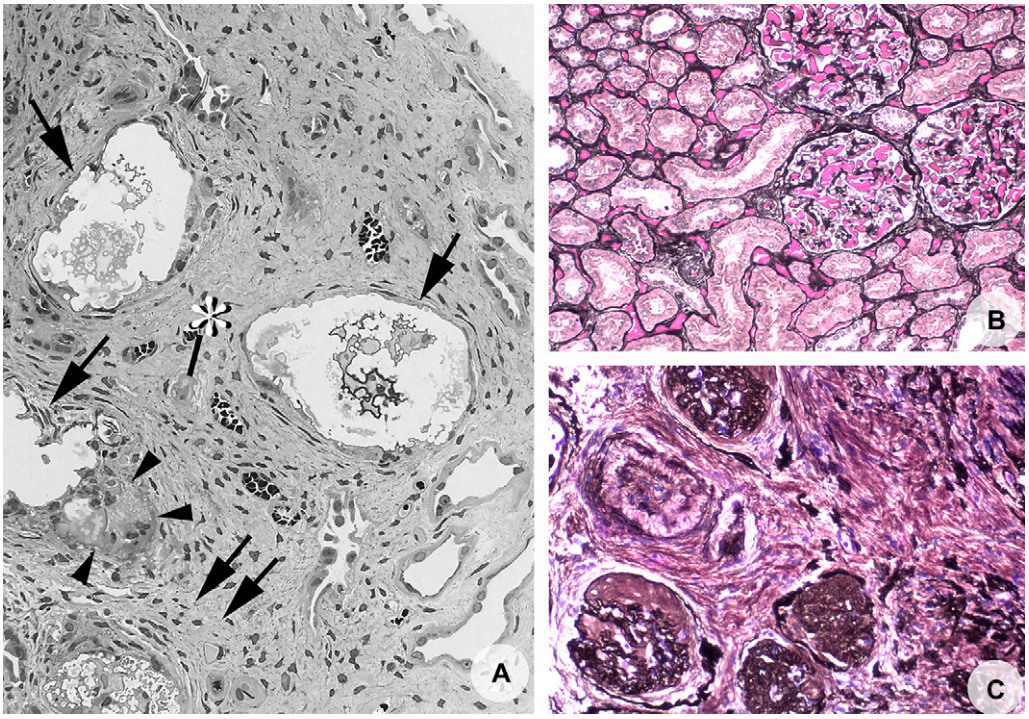

Fig. 8. Histologic findings in brushite stone formers. (*A*) Light microscopic images of papillary biopsies that were decalcified with 0.1 mol/L ethylenediaminetetraacetic acid (EDTA) reveal extensive cellular damage in several IMCD (*single arrows*) where the mineral had been chemically removed. In addition, extensive regions of interstitial fibrosis surround the injured collecting tubules (*double arrows*). Entrapped, injured thin loops of Henle and vasa recta (*) are also noted in these fields of interstitial fibrosis. An occasional giant cell (*arrowheads*) was observed near damaged collecting ducts (magnification ×1100). (*B*) A cortical sample from a normal human kidney is compared with that of a brushite stone former (magnification ×1000). (*C*) The cortical biopsy from the brushite patient demonstrates advanced glomerulosclerosis, moderate tubular atrophy, and interstitial fibrosis (magnification ×1000). (*A*) *From* Evan AP, Lingeman JE, Coe FL, et al. Crystal-associated nephropathy in patients with brushite nephrolithiasis. Kidney Int 2005;67(2):576–91, and (*B* and *C*) *From* Coe FL, Evan A, Worcester E. Kidney stone disease. J Clin Invest 2005;115(10):2598–608; with permission.)

extended well around nearby thin loops of Henle and vasa recta. The interstitial changes were also detected in the cortical biopsies, along with advanced glomerulosclerosis, tubular atrophy, and interstitial fibrosis (Fig. 8B, C); however, there was no evidence of inflammation in any of the tissue samples, confirming that this process is not the consequence of dystrophic calcification. These changes were not detected in the cortical biopsies of CaOx or intestinal bypass patients.

Intestinal bypass patients

Patients who undergo jejuno-ileal bypass (JIB) surgery for bariatric reasons have been reported to form CaOx kidney stones, likely as a consequence of metabolic derangements induced by the procedure. In a cohort of patients who had previously undergone JIB procedures and subsequently formed kidney stones, Evan and associates [4] conducted the same rigorous set of studies as performed in the idiopathic CaOx and brushite stone formers. Endoscopically, the renal papillae of these patients showed no evidence of Randall's plaque. Instead, small nodular deposits appeared to project off of the urothelium, close to the openings of the BD (Fig. 9A). Histologic examination of the papillary biopsies revealed Yasue-positive deposits only in the lumens of a few IMCD as far down as the BD (Fig. 9B).

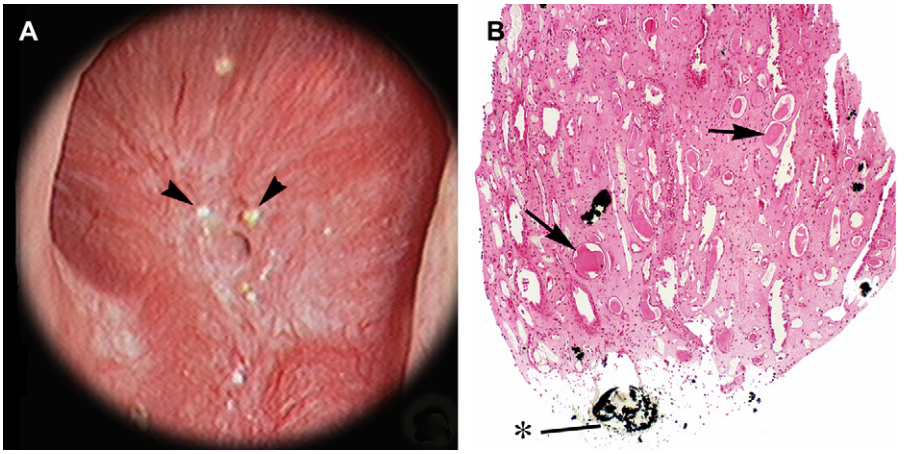

Fig. 9. Endoscopic and histologic images of Randall's plaque in intestinal bypass patients. (*A*) Endoscopic image of a papilla from an intestinal bypass stone former does not demonstrate distinct sites of Randall's plaque; rather, several nodular-appearing structures (*arrowheads*) were noted near the opening of the BD. (*B*) Low magnification (×100) light microscopic image of a papillary biopsy from an intestinal-bypass patient reveals crystal deposition only in the lumens of a few collecting ducts as far down as the BD (*). A large site of crystal material was seen in a BD. No other sites of deposits were noted. Dilated collecting ducts (*arrows*) with cast material and regions of fibrosis around crystal-filled collecting ducts were observed. (*From* Evan AP, Lingeman JE, Coe FL, et al. Randall's plaque of patients with nephrolithiasis begins in basement membranes of thin loops of Henle. J Clin Invest 2003;111(5):607–16; with permission.)

No crystalline deposits were found in the interstitium or around the thin loops of Henle. By light microscopy and TEM, crystals were found attached to the apical surfaces of the collecting duct cells or completely filling the tubular lumen, leading to extensive cell injury and death. Similar to the idiopathic CaOx stone-formers, the crystal deposits on micro FTIR and electron diffraction analysis were confirmed to be hydroxyapatite. No CaOx was detected in any of the papillary or cortical biopsies.

In summary, the histopathology of the JIB patients demonstrates a lack of plaque on the renal papillae, and instead, tubules harboring intraluminal crystal deposits. These findings suggest a pathogenesis of stone formation distinct from the idiopathic CaOx stone former. Perhaps the most remarkable finding in this subset of stone formers was that the crystals in the tissue biopsies were hydroxyapatite, an unexpected finding because all patients were hyperoxaluric (mean urine oxalate 106 mg/24 hours) and formed predominantly CaOx stones. Although the mechanism by which this process is initiated remains unclear, ductal obstruction may lead to damage of the cells of the medullary collecting duct, thereby altering pH regulation and supporting apatite crystal retention [112].

Cystine stone-formers

Cystine stone disease occurs as a result of genetic defects in the di-basic amino acid transporters that permit excessive cystine excretion [119]. These patients are notoriously difficult to treat because of rapid stone growth, and often require multiple surgical treatments. A recent study by Evan and associates [2] has delineated the surgical anatomy and gross and microscopic pathology of the renal papillae, medulla, and cortex in cystine stone formers. To determine the specific tissue changes in this stone-forming phenotype, seven cystine stone formers undergoing percutaneous nephrolithotomy were studied, using digital endoscopic mapping and imaging of the renal papillae followed by renal papillary and cortical biopsies.

The papillae of these patients revealed many dilated BD with cystine crystal plugging. Crystal plugs often projected into the urinary space. Tissue analysis revealed evidence of IMCD dilation and surrounding interstitial fibrosis (Fig. 10A). In both

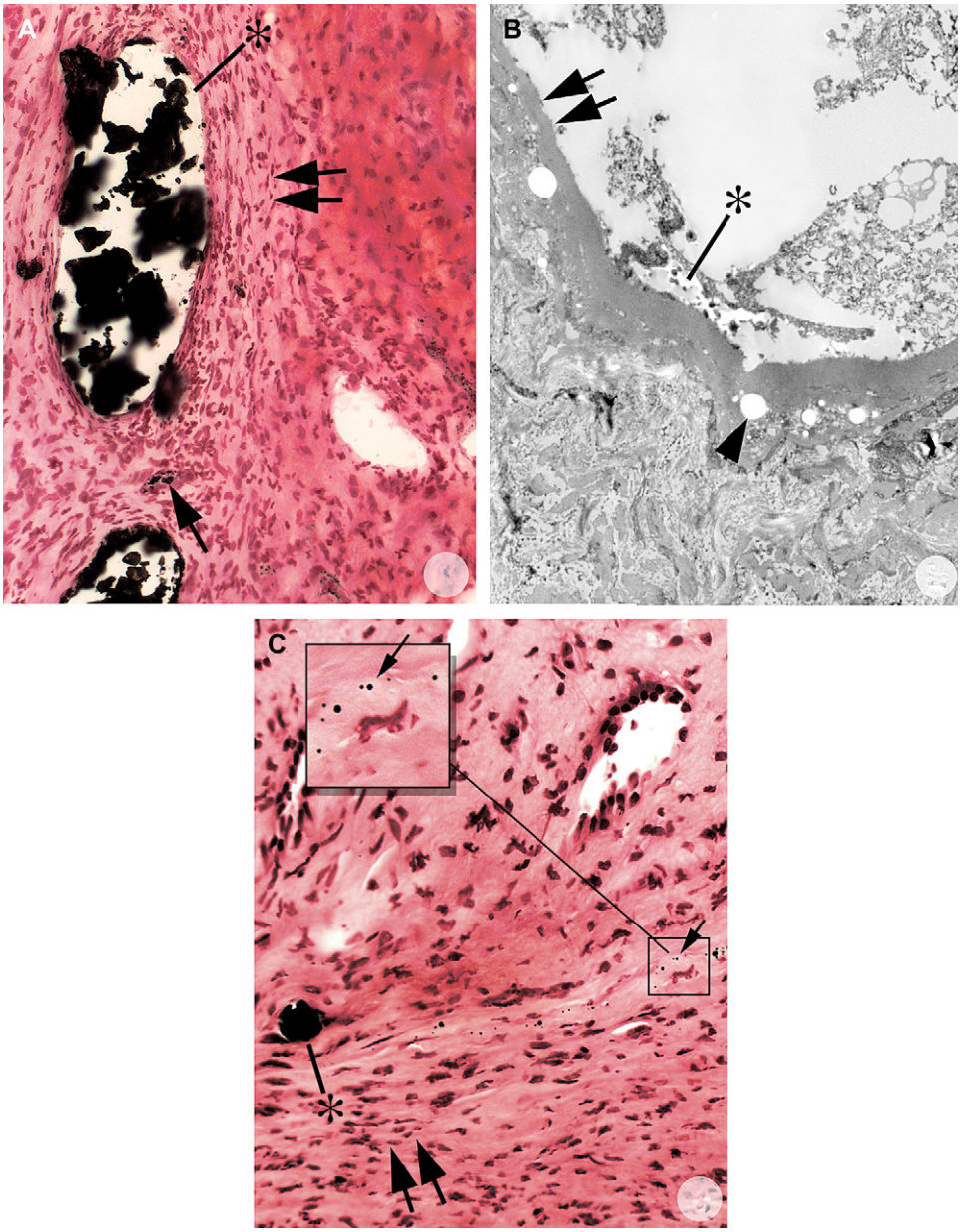

Fig. 10. Histologic findings in cystine stone formers. (*A*) Yasue staining for calcium detected tiny crystalline deposits in the basement membranes of thin loops of Henle (*single arrow*), a pattern identical to the interstitial plaque termed Randall's plaque 1. Additional interstitial changes included varying degrees of interstitial fibrosis surrounding sites of intratubular crystalline deposits (*double arrows*) in IMCD (*) (magnification ×1100). (*B*) TEM image demonstrates epithelial cell injury in the thin loop of Henle with frank necrosis exposing the tubular basement membrane (*double arrow*) as well as crystalline material admixed with cellular debris within the tubular lumen (*). Note the presence of crystalline deposits within the basement membranes (*arrowhead*) and in the interstitial space (magnification ×6000). (*C*) Interstitial fibrosis (*double arrow*) surrounds sites of intratubular crystal deposits in loops of Henle (*). The magnified inset depicts tiny deposits (*single arrows*) of interstitial plaque (magnification ×1200). (*From* Evan AP, Coe FL, Lingeman JE, et al. Renal crystal deposits and histopathology in patients with cystine stones. Kidney Int 2006;69(12):2227–35.)

the loops of Henle and IMCD, epithelial cell injury varied from flattening to complete necrosis (Fig. 10B). Many IMCDs were dilated, with or without crystal plugging. Apatite crystals were identified in the lumens of the loops of Henle and IMCD (Fig. 10C). The large plugs of crystal in BD were always cystine, whereas the IMCD and thin loop of Henle deposits were invariably apatite. The amount of interstitial Randall's plaque was equivalent to that found in non-stone formers. Cortical biopsies revealed glomerular obsolescence and interstitial fibrosis.

Evan and colleagues [2] hypothesize that cystine crystallizes in the BD, with the probable result of cell injury, interstitial reaction, and nephron obstruction. The finding of cystine crystal plugging in the BD lumen is not surprising, in that water extraction is virtually complete and cystine concentrations would resemble those in the urine, which are high enough to cause crystallization and stones. These events have the potential to induce cortical change and loss of IMCD tubular fluid pH regulation, resulting in apatite formation. The pattern of IMCD dilation and loss of medullary structures is most compatible with such obstruction, either from the BD lumen plugs or urinary tract obstruction from stones themselves.

Summary

The pathogenesis of renal calculi is not a simple process, and likely varies based on stone phenotype. Despite great research efforts and a considerable number of theories, the exact cascade of events that lead to kidney stone formation is as yet unknown; however, great progress has been made by many research groups. Although animal models and cell culture studies have been used to research the process of kidney stone formation, the correlation of the findings in these studies may only apply to a minority of stone formers who exhibit significant hyperoxaluria, such as in primary hyperoxaluria. Recent data from human papillary and renal cortical biopsies in stone formers have not only provided evidence for the role of Randall's plaque in the pathogenesis of kidney stone disease, but have also demonstrated that the histology of the renal papilla is particular to the clinical setting. These data suggest the presence of individual stone-forming phenotypes, meaning that each group of stone formers has a unique surgical anatomy, histology, and metabolic profile. The authors believe that Randall's plaque is the initiating site for subsequent stone formation in idiopathic CaOx stone formers; and that all of their stones grow on a site fixed to plaque. Future studies aimed at characterizing the role of urinary proteins at the plaque interface and in promoting or inhibiting crystal nucleation will be integral to our understanding of the mechanisms involved in kidney stone formation. Through these research efforts, we may be able to develop novel strategies for the prevention and treatment of kidney stone disease.

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Evaluation of the Recurrent Stone Former

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At one time, metabolic kidney stone disease was evaluated and treated primarily by endocrinologists and nephrologists. Until the 1980s, stone clinics were commonplace in academic settings where a team of internists and urologists would see patients together to sort out the evaluation and set up a treatment plan for the recurrent stone former. With the introduction of extracorporeal shock wave lithotripsy (SWL) about 25 years ago, a dramatic change took place in the clinical practice of kidney stone prevention. As the morbidity of SWL is low and the treatment can be performed on an outpatient basis, many urologists feel that it is more practical to treat the offending recurrent stone rather than undergo a complex metabolic evaluation and a rigorous treatment plan to prevent future stone episodes. This rationale may be applicable to the first-time or occasional recurrent stone former, such as a patient who forms new stones less frequently than once every 5 years.

However, for the more frequent stone formers, and even for some first-time stone formers interested in preventing future episodes of renal colic, a metabolic evaluation is necessary. Medical management of urolithiasis is now within the clinical domain of the urologist. The urologist, rather than members of other medical specialties, seems to have the primary responsibility of the medical management of stone disease. Thus, it is essential for the urologist to have a good working knowledge of the principles of metabolic evaluation and kidney stone prevention.

Are patients interested in the prevention of kidney stones?

Grampsas and colleagues [1] queried 199 consecutive patients undergoing SWL about their interest in the metabolic evaluation and medical management of stone disease. Tables 1 and 2 show the percentage of first-time and recurrent stone formers undergoing lithotripsy who are interested in the medical management of their stone disease [1]. Almost all patients, first-time and recurrent stone formers alike, were very interested in finding out why they form kidney stones and were eager to follow a fluid, dietary and/or drug therapy program to prevent stones in the future. Such a high level of patient interest is probably due to the severity of pain associated with renal colic and the significant time lost from work and other fruitful activities. However, only 30% of the first-time stone formers and 46% of the recurrent stone formers were ever offered a metabolic evaluation either by their internist or urologist (see Table 1).

The most captive patient for kidney stone prevention is the symptomatic recurrent stone former. Once the patient becomes symptom free, he or she is likely to lose interest in a metabolic evaluation. The patient does not have to be stone free to undergo a metabolic evaluation. The only prerequisite is the absence of gross hematuria and renal obstruction. From a practical standpoint, a 2- to 4-week wait after SWL or an endourological procedure is usually required before the collection of the 24-hour urine specimens.

Who needs a metabolic evaluation?

Any patient who has had a kidney stone and desires a metabolic evaluation should be offered one. The first-time, adult, calcium stone former

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Table 1
Patient attitude to metabolic evaluation for urolithiasis

Evaluation attitude	First-time stone former	Recurrent stone former
Interested in finding out why they form stones	95%	96%
Interested in preventing stones in the future	99%	98%
Willing to collect a 24-hour urine sample	92%	99%
Offered an evaluation by physician or urologist	30%	46%

Data from Grampsas SA, Moore M, Chandhoke PS. 10-year experience with extracorporeal shockwave lithotripsy in the state of Colorado. J Endourol, 2000;14:711.

without a family history of kidney stones and other underlying metabolic abnormalities may be the only exception. The likelihood that such a first-time calcium stone former will form another symptomatic stone is about 50% in the next 5 to 10 years. A metabolic evaluation in these patients is often normal; as such, they can be managed by fluid therapy alone.

Box 1 lists patients that should be considered for a metabolic evaluation. Patients who form either uric acid or cystine stones generally have a significant metabolic abnormality that can be treated. Besides identifying this abnormality, the evaluation also helps determine the drug choices and dosage. Among calcium stone formers, those who have recurrent stones and those who have multiple stones or bilateral stones at their first presentation should also have an evaluation. Obesity is linked to urolithiasis [2,3] and urologists are often challenged in the treatment of kidney stones in morbidly obese patients. Thus, to reduce the likelihood of future intervention in such surgically challenging patients, a metabolic evaluation may be prudent for a morbidly obese patient, even after only one stone episode. Children with a stone history should always have an evaluation as a correctable metabolic abnormality is often found in these patients. Any patient with bone, gastrointestinal, or endocrine disease that coexists with stone disease should have a metabolic evaluation. Often, treatment of the primary bone, renal, or gastrointestinal disease will also result in decreasing the recurrence of kidney stones.

Box 1. Patients who may benefit from a metabolic evaluation

All uric acid and cystine stone formers
Calcium stone formers with a history of forming stones
Calcium stone formers with multiple stones
Calcium stone formers with stones that are difficult to treat
Children who form calcium stones
Any patient with a solitary kidney forming calcium stones
Calcium stone formers with nephrocalcinosis or bone diseases
Calcium stone formers with gastrointestinal diseases

Table 2
Patient attitude to medical treatment of urolithiasis

Treatment attitude	First-time stone former	Recurrent stone former
Willing to modify diet	96%	97%
Willing to take medication	86%	87%
Willing to increase fluid intake	99%	97%
Willing to follow a life-long prevention program	92%	99%

Data from Grampsas SA, Moore M, Chandhoke PS. 10-year experience with extracorporeal shockwave lithotripsy in the state of Colorado. J Endourol, 2000;14:711.

Specific and nonspecific medical treatment of kidney stones

The aim of medical management of stone disease is to decrease the supersaturation of the crystal components in urine. The pathogenesis of the idiopathic calcium stone is complex and a variety of metabolic, anatomic, and inhibitor factors determine stone formation. However, the only parameter we are currently able to manipulate is the supersaturation of the associated crystal components in the urine. To prevent future stone episodes, this supersaturation needs to be decreased.

The argument has been made that nonspecific therapy should also be effective in calcium stone formers because it lowers urine supersaturations. For example, if a patient has hypercalciuria, treatment with potassium citrate to elevate urinary

citrate should decrease urinary calcium oxalate supersaturation even though urine calcium remains high. Alternatively, a patient who has hypocitraturia as the primary metabolic diagnosis may be treated with a thiazide to lower urinary calcium and thus calcium oxalate supersaturation.

There are several problems with this approach of not making a specific metabolic diagnosis and a rational management decision. Not only is there the risk of missing a significant associated medical diagnosis but also a risk of rendering a treatment that will not be clinically effective. For example, patients who have either renal or bone disease related to metabolic acidosis are best treated with the correction of the acidosis. Thus, treatment with potassium citrate in these patients successfully treats both the acidosis and the associated hypercalciuria. Patients who have mild hyperoxaluaria because of an intestinal hyperabsorption of oxalate are best treated with dietary oxalate restriction rather than a thiazide or other nonspecific treatment.

Without a metabolic evaluation, it is impossible to know which patients will benefit from a dietary restriction or a dietary excess of calcium. For example, recommending a calcium-restricted diet to a patient with mild hyperoxaluria will aggravate the hyperoxaluria and make stone disease worse. Increasing calcium intake in a patient with absorptive hypercalciuria will likely worsen hypercalciuria and increase the frequency of stone recurrence [4].

As reviewed by Pearle [5], clinical trials for urolithaisis show definitive clinical benefit only for specific medical therapy, as compared with nonspecific therapy. Clinical trials indicate thiazides work best in patients with hypercalciuria, potassium citrate is effective in patients with hypocitraturia, and allopurinal only works in patients with hyperuricosuric calcium urolithaisis [5]. As such, from a pathogenesis and clinical evidence standpoint, nonspecific therapy cannot be recommended for the medical management of kidney stone patients. Specific medical therapy requires a metabolic evaluation to make the correct diagnosis and to render either a fluid, dietary and/or drug therapy to achieve optimal management of the patient.

When is metabolic evaluation and medical management cost-effective?

As previously mentioned, a metabolic evaluation is generally recommended for the recurrent calcium stone former. The cost of drug therapy, medical office visits, metabolic evaluation, and treating an acute stone episode is also a consideration in determining when medical management is cost-effective. In such an analysis, the frequency of stone recurrence at which medical therapy becomes equivalent to treating a recurrent stone episode may be estimated. Such estimates will vary depending on the specific health care delivery systems.

Chandhoke [6] evaluated this frequency estimate for academic centers from 10 countries. As the cost of drug therapy and surgical therapy varied considerably among the various institutions, the frequency of stone recurrence at which the medical management and the cost of managing an acute stone episode became equivalent ranged from 0.58 in the United Kingdom to 4.4 in Germany [6]. In the United States, this stone frequency estimate was 0.69 for a fee-for-service facility. As such, it is estimated that a recurrent calcium stone former should have a recurrence at least once in 2 years in the United States for medical prophylaxis to be cost-effective. In the above estimates, the cost of suffering and time lost from work and other gainful activities was not accounted for. However, from a particular health care provider's perspective, where cost may be a significant issue, one can estimate which recurrent stone formers would be candidates for a medical prophylaxis program from a cost-effective standpoint.

Importance of stone analysis and adequacy of urine collection

The first step in a metabolic evaluation is to know the patient's stone analysis. This information will dictate the type of evaluation and the appropriate treatment plan. The metabolic evaluation of uric acid and cystine stones is very different from that of calcium-containing stones.

Often a stone is retrieved neither by the patient nor the urologist for stone analysis. Patients who pass stones spontaneously but are unable to catch them in their voided urine are somewhat of a dilemma in terms of a metabolic evaluation. With CT being the imaging choice for acutely symptomatic patients, often a corresponding plain abdominal radiograph (KUB) is unavailable. Hounsfield unit measurement of kidney or ureteral stones less than a centimeter is unreliable and the variability of this measurement in calcium-containing stones makes this an impractical

approach to determine the stone composition. Fortunately, in most recurrent stone formers and in those patients who end up having SWL or an endourological procedure, a stone analysis eventually becomes available.

The basic feature of a metabolic evaluation is the collection of a 24-hour urine sample by the patient for analysis. Despite specific instructions as to how to collect a 24-hour urine sample, patients sometimes will either miss collecting a urine void or occasionally collect too much urine. This error is best corrected by determining the amount of creatinine in the 24-hour urine sample. Men should have 20 to 25 mg/kg/d and women should have 15 to 20 mg/kg/d of creatinine in their 24-hour urine samples. As such, if there is an incorrect collection, one can recalculate the 24-hour urine chemistries by normalizing for what the appropriate amount of creatinine should be in the 24-hour urine sample. This mathematical correction avoids having the patient collect a new 24-hour urine sample and also saves the cost of repeat analysis of the urine chemistries. The volume of urine collected by the patient is not a useful determinant of the adequacy of collection.

Metabolic evaluation for noncalcium-containing stones

For uric acid stones, a serum and a 24-hour urine sample should be sent for creatinine and uric acid determination. If serum or urinary uric acid is elevated, the patient may be treated with allopurinol 300 mg/d (side effects: rash, liver enzyme abnormalities). Patients with normal serum or urinary uric acid are best managed by alkali therapy alone.

For struvite stones, patients should be followed closely for recurrent infections. Underlying anatomical abnormalities that predispose patients to recurrent kidney infections should be corrected. Metabolic evaluation should be undertaken in most patients, especially if a calcium stone coexists with the struvite stone.

The metabolic evaluation of cystine stones includes a 24-hour urine sample for quantitative cystine determination. Cystine stones are best prevented by reducing urinary cystine concentration, hydration, increasing the solubility of cystine by alkalization, and decreasing urinary cystine excretion by drugs. The metabolic evaluation helps to titrate the dose of drug therapy to achieve a urinary cystine concentration of less than 300 mg/L.

Metabolic evaluation for calcium-containing stones

There are two types of metabolic evaluations available for calcium stone formers: a limited metabolic evaluation and a comprehensive metabolic evaluation (Box 2). A limited metabolic evaluation involves the collection of one or two

Box 2. Limited and comprehensive metabolic evaluations

Limited metabolic evaluation

1. Evaluation of serum calcium, sodium, potassium, serum urea nitrogen, creatinine, carbon dioxide, chloride, uric acid.
2. Evaluation of two random 24-hour urine samples for volume, creatinine, calcium, oxalate, uric acid, citrate, sodium.

Comprehensive metabolic evaluation

1. Evaluation of two random 24-hour urine samples for volume, creatinine, calcium, oxalate, uric acid, citrate, sodium, potassium, UN, phosphate, magnesium.
2. One week of low-calcium, low-oxalate, low-sodium, and low-purine diet followed by 24-hour urine sample on the restricted diet. Evaluation of serum calcium, sodium, potassium, UN, creatinine, carbon dioxide, chloride.

Calcium load test

1. After 2-hour fasting, from 6 AM to 8 AM, measure urinary calcium/creatine ratio.
2. At 8 AM, administer 1-gm oral calcium load (45 mL NeoCalciumGluconate).
3. From 8 AM to 10 AM, collect urine and measure urinary calcium/creatine ratio.
4. From 10 AM to noon, collect urine and measure urinary calcium/creatine ratio.

random 24-hour urine samples. In a comprehensive metabolic evaluation, the patient first collects the random 24-hour urine samples and then goes on a week of a restricted calcium, oxalate, sodium, and purine diet. After the collection of a third restricted-diet 24-hour urine sample, the patient undergoes a calcium load test (see Box 2).

A limited evaluation is best suited for most urological practices whereas the comprehensive evaluation is used within the framework of metabolic stone clinics in academic settings. The major difference in the two types is the further differentiation of the hypercalciurias in the comprehensive metabolic evaluation. The major benefit from differentiating the hypercalciurias is to determine if dietary calcium restriction is a viable treatment alternative for the patient with absorptive hypercalciuria. In a limited metabolic evaluation, all patients with hypercalciuria and normal serum calcium should be treated with a thiazide.

A comprehensive metabolic evaluation also yields more useful diagnostic information and a higher number of metabolic abnormalities in stone formers compared with a limited metabolic evaluation [7]. As shown in Table 3, two 24-hour urine samples, compared to a single 24-hour urine sample, significantly improves the likelihood of finding metabolic abnormalities [7]. The likelihood of finding a metabolic abnormality in a recurrent calcium stone former is 68% for a single 24-hour urine sample, 75% for two 24-hour urine samples, and 90% for a comprehensive metabolic evaluation [7]. In the United States, hypercalciuria is also the most common metabolic cause of stone formation. In a limited metabolic evaluation with two 24-hour urine collections, hypercalciuria occurs in almost half (47%) of the patients. In a comprehensive metabolic evaluation, hypercalciuria is discovered in almost two thirds (65%) of the patients (see Table 3). In patients who prefer only dietary management of their stone disease, the comprehensive metabolic evaluation also provides the most useful information.

Table 3
Yield of metabolic abnormalities from limited and comprehensive metabolic evaluations

Metabolic abnormality	Percent in single 24-hour urine sample	Percent in two 24-hour urine samples	Percent in comprehensive evaluation
Low urine volume	56%	62%	62%
Hypercalciuria	35%	47%	65%
Hyperoxaluria	19%	28%	38%
Hyperuricosuria	18%	23%	24%
Hypocitraturia	27%	32%	41%

Data from Yagisawa T, Chandhoke PS, Fan J. Comparison of comprehensive and limited metabolic evaluations in the treatment of patients with recurrent calcium urolithiasis. J Urol 1999;161:1449–52.

A recent study by Borghi and colleagues [8] suggests that a low-protein, low-salt diet may be preferable over a low-calcium diet in hypercalciuric stone formers for preventing stone recurrences. Furthermore, based on the epidemiological studies of Curhan and colleagues [9], who have shown that the incidence of stone disease is inversely related to the magnitude of dietary calcium intake in first-time stone formers, there is trend in the urolithiasis community not to restrict dietary intake of calcium in recurrent stone formers. This is especially true for postmenopausal women in whom there is an increased concern for the development of osteoporosis. Thus, if dietary restriction of calcium is not a viable treatment option, conducting a comprehensive evaluation is unnecessary in these patients. Some advocate limiting dietary calcium intake between 800 mg to 1000 mg if the patient is hypercalciuric and treating all hypercalciurics diagnosed as such with a thiazide.

Box 3 shows the possible diagnostic outcomes for a patient undergoing a metabolic evaluation. The values shown in parenthesis are those for normal adults. These values should sometimes be adjusted based on the patient's weight. Values for children are often noted as mg/kg/d and adjustments in these values are necessary for overweight individuals. In a limited metabolic evaluation, potential diagnoses are a low urine volume, hypocitraturia, hyperoxaluria, hyperuricosuria, and/or hypercalciuria. In a comprehensive metabolic evaluation, the hypercalciurias are further subdivided into absorptive, renal leak, and resorptive hypercalciurias. Often, even a limited metabolic evaluation will reveal more than one metabolic abnormality. In such cases, a single therapeutic strategy might be used or multiple therapeutic strategies might be used simultaneously, depending upon how aggressive one wants to be in medical management. Generally, the severity of stone recurrence will dictate how aggressive one should be with medical therapy.

A urinary volume less than 2 L/d is a common finding in recurrent calcium stone formers (see Box 3). As the goal of medical management is to decrease the supersaturation of crystal components,

Box 3. Potential diagnoses from a metabolic evaluation of a recurrent calcium stone former

Low urinary volume (<2 L/d)
Hyperoxalauria (>40 mg/d)
Hyperuricosuria (>750 mg/d)
Hypocitraturia (<300 mg/d)
Hypercalciuria (>250 mg/d in women; >300 mg/d in men)
  Types I, II, and III absorptive hypercalciuria
  Renal leak hypercalciuria
  Resorptive hypercalciuria

increasing the urinary volume achieves this goal in stone formers of all types. A clinical trial of idiopathic calcium stone formers has also shown a significant benefit of increased water intake alone in the prevention of stone recurrence [10].

Hyperoxaluria is defined in adults as oxaluria exceeding 40 mg/d. Inherited primary hyperoxaluria is a rare metabolic disorder that causes renal oxalosis in childhood, when it is usually fatal. In adults, hyperoxaluria is usually secondary to increased oxalate absorption from the gastrointestinal tract. This condition is frequently found in patients with inflammatory bowel disease and in patients following small-bowel bypass surgery for the treatment of morbid obesity. Foods with high-oxalate content are spinach, soy, rhubarb, beets, nuts, chocolate, tea, wheat bran, and strawberries. In the gastrointestinal tract, oxalate binds normally with calcium, limiting its absorption. However, in malabsorption syndromes, excess fatty acids bind calcium in the intestine and leave more free oxalate for absorption. Treatment for this condition is dietary restriction of oxalate. If this fails to lower the urinary oxalate, then calcium supplementation may be given to bind oxalate in the intestine. Occasionally, pyridoxine may be helpful in patients with mild metabolic hyperoxaluria.

Hyperuricosuria, defined as uric acid excretion greater than 750 mg/d, is associated with calcium oxalate stones in 20% of patients. In hyperuricosuric calcium nephrolithaisis, uric acid may bind to stone inhibitors or promote calcium oxalate stone formation on a uric acid nidus [11]. The treatment is a low purine diet and/or allopurinol 300 mg/d.

Citrate is an important inhibitor of calcium oxalate stone formation. Hypocitraturia is defined as less than 300 mg/d of urinary citrate excretion. Citrate complexes with calcium and thus decreases the amount of ionic calcium available for stone formation. In addition, it has a direct inhibitor activity on calcium oxalate nucleation. Treatment is best accomplished with potassium citrate supplementation, 60 to 120 mEq daily in divided doses.

Hypercalciuria is defined as urinary calcium excretion greater than 300 mg/d in men and greater than 250 mg/d in women. This is the most common type of metabolic abnormality found in stone patients. Absorptive hypercalciuria is secondary to increased calcium absorption from the intestine, which results in a higher urinary excretion of calcium. With a comprehensive metabolic evaluation, absorptive hypercalciuria can be differentiated from other forms of hypercalciuria using the calcium load test (Table 4).

Table 4
Diagnosis of the various hypercalciurias

	Hypercalciuria				
		Absorptive			
Measure	Renal leak	Type I	Type II	Type III	Resorptive
Fasting calcium/creatinine ratio	>0.11	<0.11	<0.11	<0.11	>0.11
Calcium load test calcium/creatinine ratio	>0.22	>0.22	>0.22	>0.22	>0.22
Serum calcium	Normal	Normal	Normal	Normal	Increased
Parathyroid hormone	Marginal	Normal	Normal	Normal	Increased
Urine calcium on diet		No change	Normal	No change	
Serum phosphate		Normal	Normal	Decreased	

Table 5
Treatment of the various hypercalciurias

	Hypercalciuria				
		Absorptive			
	Renal leak	Type I	Type II	Type III	Resorptive
Treatment	Thiazides	Thiazides	Low-calcium diet	Ortho-phosphate	Parathyroid removal

Table 5 shows the appropriate treatment for the patient based on the diagnoses shown in Table 4.

In absorptive hypercalciuria, the fasting urinary calcium excretion is normal. In type I absorptive hypercalciuria, patients have an increased urinary calcium excretion even on a calcium-restricted diet. Treatment is hydrochlorothiazide 25 to 50 mg/d or cellulose phosphate 5g orally three times daily (see Table 5). Hydrochlorothiazide increases the renal reabsorption of calcium from both the proximal and distal tubules, causing decreased excretion of calcium. Cellulose phosphate prevents calcium absorption from the intestine.

Type II absorptive hypercalciuria is the most common type of absorptive hypercalciuria and is dependent on dietary calcium. Patients not at risk for developing osteoporosis may limit their calcium intake to 600 to 800 mg/d. In those patients in whom there is a concern for osteoporosis and in whom dietary therapy fails to lower the urinary excretion of calcium to normal, thiazides may be used. There is some concern that thiazide therapy in patients with type II absorptive hypercalciuria may lose its hypocalciuric effect when used long term.

Type III absorptive hypercalciuria is secondary to a renal phosphate leak. Low serum phosphate increases 1,25 vitamin D, increasing the absorption of phosphate as well as calcium from the intestine. Treatment is dietary phosphate supplementation with orthophosphate 250 to 2000 mg three times daily.

Resorptive hypercalciuria accounts for less than 5% of calcium stones. These patients have hypercalciuria due to increased calcium bone loss, as in hyperparathyroidism. Parathyroid hormone is elevated along with urinary phosphate. Treatment is removal of the parathyroid adenoma. Renal leak hypercalciuria is an intrinsic defect of the renal tubule to reabsorb calcium. This condition is effectively treated with a thiazide.

Summary

Patients who develop kidney stones, either for the first time or recurrently, are interested in knowing why they form stones and how to prevent them. Depending on the patient's age, lifestyle, and personal beliefs, they will choose a dietary therapy regimen, a drug therapy regimen, or both as their medical management. The urologist today seems to have the primary responsibility in not only the surgical but also in the medical management of urolithaisis. With knowledge of the patient's stone analysis and therapy preferences, an appropriate metabolic evaluation and treatment plan can be implemented.

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Pathophysiology and Management of Calcium Stones

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Nephrolithiasis is a common disorder that accounts for significant cost, morbidity, and loss of work. In the United States., the estimated annual expenditure for the diagnosis and treatment of nephrolithiasis approached $2.1 billion in 2000, almost certainly an underestimate, without taking into account lost wages and reduced work productivity [1]. Indeed, there is a one in eight lifetime chance of being diagnosed with urinary stones [2–4]. Although in most cases stones are source of discomfort and inconvenience without significant risk to health, progressive loss of renal function can occur after repeated episodes of stone disease. In a French study of over 1300 patients newly requiring hemodialysis, 3.2% of cases were directly related to stone disease [5].

With comprehensive evaluation, metabolic abnormalities can be identified in over 90% of stone formers, and the institution of preventive dietary and medical measures has resulted in substantial reduction in stone recurrence rates [6,7]. A careful medical and dietary history, serologic tests, and urinalysis constitute the initial screening tools in stone formers. Stone analysis by radiographic crystallography or infrared spectrophotometry is an important component of this initial evaluation, because comprehensive metabolic testing may be foregone in lieu of more directed evaluation in patients who have non–calcium-containing stones such as uric acid and cystine, in whom the underlying pathophysiologic abnormalities are implied by the stone composition [8]. In contrast, calcium stones (calcium oxalate [CaOx] and calcium phosphate) form as a result of a variety of environmental risk factors and metabolic derangements, and identification of these factors composes the mainstay of the evaluation and treatment plan for these patients.

Among the various stone compositions, calcium-containing stones represent approximately 75% to 80% of upper tract stones. The remaining 20% to 25% are composed of struvite, cystine, uric acid, and other stones [9]. In this article, the authors review our current understanding of the pathophysiology of calcium stone disease, and propose contemporary medical and dietary prophylactic regimens.

Pathophysiology

CaOx stones are the most common stone type (60% of all stones), followed by the calcium phosphate subtypes hydroxyapatite (20%) and brushite (2%). Mixed calcium stones containing both calcium phosphate and CaOx are common [10]. When over 30% of the stone volume is composed of calcium phosphate, it is classified as hydroxyapatite or apatite, depending on the crystal morphology.

The basis for calcium stone formation is supersaturation of urine with stone-forming calcium salts. A number of dietary factors and metabolic abnormalities can change the composition or saturation of the urine so as to enhance stone-forming propensity. Among the metabolic conditions are hypercalciuria, hypocitraturia, hyperoxaluria, hyperuricosuria, and gouty diathesis (Table 1), and these conditions are reviewed in detail. Dietary factors also play a role in stone

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Table 1
Classification of underlying conditions in calcium stone formers

Condition	Metabolic/environmental defect	Prevalence
Hypercalciuria		
Absorptive hypercalciuria	Increased GI calcium absorption	20%–40%
Renal hypercalciuria	Impaired renal calcium reabsorption	5%–8%
Resorptive hypercalciuria	Primary hyperparathyroidism	3%–5%
Hyperuricosuric calcium nephrolithiasis	Dietary purine excess, uric acid overproduction or overexcretion	10%–40%
Hypocitraturic calcium nephrolithiasis		
Chronic diarrheal syndrome	GI alkali loss	—
Distal RTA	Impaired renal tubular acid excretion	—
Thiazide-induced	Hypokalemia and intracellular acidosis	10%–50%
Hyperoxaluric calcium nephrolithiasis		
Primary hyperoxaluria	Genetic oxalate overproduction	—
Dietary hyperoxaluria	Excessive dietary intake	2%–15%
Enteric hyperoxaluria	Increased GI oxalate absorption	—
Gouty diathesis	Low urine pH	10%–30%

Abbreviations: GI, gastrointestinal; RTA, renal tubular acidosis.

occurrence, and are discussed with regard to their role in preventing stone formation.

Hypercalciuria

Hypercalciuria is arguably the most important pathophysiologic risk factor in calcium stone formation. Urinary calcium raises ionic calcium concentration and increases urinary saturation of stone-forming calcium salts (calcium phosphate and CaOx). In addition, complexation of calcium with urinary inhibitors such as citrate and glycosaminoglycans reduces urinary inhibitory activity, thereby increasing stone risk.

Several lines of evidence support a pathogenetic role for hypercalciuria in calcium stone formation. First, hypercalciuria is the most common abnormality identified in stone formers, occurring in 35% to 65% of cases. Second, pharmacologic therapies aimed at reducing urinary calcium have been shown to reduce rates of recurrent stone formation [11]. Finally, recent investigations suggesting that Randall's plaques may represent potential precursors to calcium stones have shown that plaques occur more commonly in stone formers, and that their number is directly correlated with urine calcium levels and number of stone episodes [12,13].

Hypercalciuria is defined as urinary calcium excretion of greater than 200 mg daily. Although the term "idiopathic hypercalciuria" has been used to denote elevated urinary calcium, irrespective of the underlying pathophysiologic mechanism, hypercalciuria can be more precisely classified according to the site of primary metabolic derangement, whether intestine, kidney, or bone. Accordingly, hypercalciuria can be divided into three distinct subtypes: (1) absorptive hypercalciuria (AH), characterized by intestinal hyperabsorption of calcium; (2) renal hypercalciuria (RH), resulting from impaired renal tubular calcium reabsorption; or (3) resorptive hypercalciuria, caused by bone demineralization [14].

Although hypercalciuria is classified according to the site of the primary defect in calcium transport, secondary changes can occur at other sites; that is, renal calcium leak leads to secondary hyperparathyroidism, which results in bone resorption and increased intestinal calcium absorption.

Hypercalciuria has a rich genetic predisposition. Nearly half of patients who have hypercalciuria have a family history of stone disease [15]. Although studies suggest that multiple genetic defects can lead to the hypercalciuric phenotype, in some cases a single gene defect has been implicated [16].

Absorptive hypercalciuria

AH occurs in approximately 55% of stone formers, and is characterized by increased intestinal absorption of calcium [17]. The positive calcium balance suppresses parathyroid hormone (PTH) secretion and increases the renal filtered load of calcium, leading to increased urinary calcium excretion. AH is classified as Type I or II, according to the response to dietary calcium restriction. AH Type I is diet-unresponsive,

whereas in AH Type II, urinary calcium normalizes in response to a low calcium diet.

The pathophysiologic mechanism responsible for AH has not been elucidated. Vitamin D has been postulated to play a pathogenetic role in intestinal calcium hyperabsorption; however, ketoconazole-induced inhibition of vitamin D and steroid metabolism has not produced a consistent clinical response, suggesting that vitamin D-dependent and independent processes may be involved [18]. Recently, mutations in the gene coding for a soluble form of adenylate cyclase were identified in 40% of AH patients in whom bone loss, especially of L2-4 vertebral bodies, contributed to the phenotype [19]. The mechanism of action of this protein and its role in AH has not yet been elucidated; however, together these data suggest that AH is a complex polygenetic disease that requires further study.

Renal hypercalciuria

RH is caused by impaired renal tubular reabsorption of calcium. Renal loss of calcium reduces serum calcium and secondarily stimulates PTH secretion. Consequently, increased intestinal calcium absorption caused by enhanced 1,25-$[OH]_2D$ synthesis and mobilization of calcium from bone caused by increased PTH lead to hypercalciuria. Serum calcium remains normal because the loss of calcium in the urine is offset by enhanced intestinal calcium absorption and bone resorption. The pathogenesis of renal calcium leak is unknown. Several factors have been implicated in RH, including salt abuse and excessive urinary prostaglandins [20,21]. RH is relatively uncommon, occurring in approximately 9% of stone formers.

Resorptive hypercalciuria

Resorptive hypercalciuria is a rare cause of stone disease that is most commonly associated with primary hyperparathyroidism. Excessive PTH secretion from a parathyroid adenoma leads to bone resorption, increased renal synthesis of 1,25-$[OH]_2D$ (calcitriol), and enhanced intestinal absorption of calcium. In a recent review of over 20,000 reported cases [22], a solitary parathyroid adenoma was responsible for 89% of cases of primary hyperparathyroidism; however, in 11% of cases multiple adenomas or parathyroid carcinomas were identified. Consequently, a neck ultrasound and Technetium 99 m-sestamibi scan are recommended to identify one or more abnormal glands. Post-parathyroidectomy normocalcemia was achieved in 95% to 97% of patients in this series.

Other causes

Other less common causes of hypercalciuria include hypercalcemia of malignancy, sarcoidosis, hyperthyroidism, and vitamin D toxicity. Tumor-derived PTH related peptide (PTHrP) has been shown to be the major pathogenic factor in humoral hypercalcemia of malignancy, with detection of these molecules in 80% cases [23]. To date, there have been no successful pharmacologic measures for suppressing the hypercalcemic effects of PTHrP. A number of granulomatous diseases, including sarcoidosis, tuberculosis, and histoplasmosis, have been reported to cause hypercalcemia, although sarcoidosis is the one most commonly associated with nephrolithiasis. The sarcoid granuloma produces 1,25-dihydroxyvitamin D_3, which causes increased intestinal absorption of calcium, hypercalcemia, and hypercalciuria [24,25]. Sarcoidosis is suspected by clinical history (ie, history of a persistent cough) and confirmed by measurement of serum vitamin D and calcitriol levels [26]. This condition is effectively treated with corticosteroids. Vitamin D toxicity is suspected by a history of excessive vitamin D use, and is managed by restriction of vitamin D intake or limiting sunlight exposure.

Hypocitraturia

Citrate is the most abundant organic anion in human urine, and is a well-recognized inhibitor of stone formation. Hypocitraturia is defined as urinary citrate excretion of less than 320 mg daily, although this is a somewhat arbitrary cutoff, because the acid-base status of the patient strongly determines total citrate excretion. Hypocitraturia is a well-known risk factor for calcium nephrolithiasis, and has been identified in 20% to 60% of calcium stone formers [27].

The protective effect of citrate is threefold, arising from its buffering capacity, its ability to complex with calcium in solution, and its inhibitory activity [28]. The buffering action of citrate is manifest during an alkali challenge, such that only a small rise in urinary pH occurs with an alkali load, thereby mitigating against calcium phosphate precipitation. Secondly, as an anion, citrate forms a soluble complex with calcium, reducing the ionic activity of calcium and decreasing urinary saturation of stone-forming calcium salts (CaOx and calcium phosphate). Finally, citrate directly inhibits crystallization, aggregation, and

agglomeration of CaOx and calcium phosphate, thereby further reducing stone formation.

Urinary citrate excretion is determined by acid-base status, and in particular, the intracellular pH of renal proximal tubule cells [27]. Acid load promotes proximal tubular reabsorption of citrate and reduced citrate synthesis, leading to hypocitraturia, whereas alkali load reduces tubular reabsorption and enhances citrate synthesis, thereby increasing urinary citrate excretion. Therefore, a logical and simple form of therapy for hypocitraturic calcium stone formers is alkali citrate [6].

A variety of pathologic states associated with acidosis leads to hypocitraturia. Distal renal tubular acidosis (RTA) is associated with systemic acidosis, and is characterized by high urine pH (>6.8) and low serum bicarbonate and potassium [29]. Chronic diarrheal states are also associated with systemic acidosis because of alkali loss in the stool. Excessive animal protein provides an acid load that promotes bone loss and causes hypocitraturia [30]. A recent study investigating the effects of a high protein, low carbohydrate diet, typified by the Atkins' diet [31], demonstrated a significant reduction in urine pH and citrate during both the induction and maintenance phases of the diet. Other causes of acidosis associated with hypocitraturia are thiazide-induced hypokalemia, which produces intracellular acidosis, and vigorous exercise, which produces lactic acidosis [32]. Finally, idiopathic hypocitraturia may represent an isolated abnormality, unrelated to an acidotic state.

Hyperoxaluria

Hyperoxaluria is defined as urinary oxalate excretion of greater than 40 mg daily. Hyperoxaluria is thought to increase the risk of stone formation by increasing urinary saturation of CaOx. Additionally, rat studies have implicated oxalate in crystal growth and retention by means of renal tubular cell injury mediated by lipid peroxidation and the generation of oxygen free radicals [33]. Human studies of normal subjects ingesting large doses of oxalate, however, have not shown increases in markers of oxidative stress or renal injury, and consequently the role of oxalate-induced cell membrane damage in CaOx stone formation has not been fully elucidated [34].

The effect of oxalate on stone formation depends on the interaction between calcium and oxalate that takes place in the intestine and urine. In the intestine, oxalate absorption is modulated by dietary oxalate and the formation of a poorly absorbed calcium-oxalate complex. In the setting of dietary calcium restriction, calcium-oxalate complex formation is reduced, thereby increasing luminal free oxalate that is absorbed from the intestine and excreted in the urine. In the urine, calcium-oxalate interaction results in formation of a soluble complex that lowers ionic oxalate concentration. Although historically urinary oxalate was considered a more important contributor to CaOx stone formation than urinary calcium, a recent study demonstrated that urinary oxalate and urinary calcium contribute equally to the urinary saturation of CaOx [35].

Hyperoxaluria can be associated with primary disorders in biosynthetic pathways (primary hyperoxaluria), malabsorptive states (enteric hyperoxaluria), excessive dietary oxalate intake (dietary hyperoxaluria), or high substrate levels (excessive vitamin C). Primary hyperoxaluria is caused by a rare inherited autosomal recessive disorder in glyoxalate metabolism by which the normal conversion of glyoxalate to glycine is prevented, leading to oxidative conversion of excess glyoxalate to oxalate, an end product of metabolism. Systemic oxalosis ensues, and leads to excretion of markedly high levels of urinary oxalate, increasing urinary saturation of CaOx and causing stone formation and nephrocalcinosis. At diagnosis, 54% of hyperoxaluric patients have had stones and 30% have nephrocalcinosis [36]. Without treatment, end-stage renal failure occurs by age 15 years in 50% of patients, with an overall mortality of 30% [37].

Two forms of primary hyperoxaluria have been identified, primary hyperoxaluria type 1 (PH1) and primary hyperoxaluria type 2 (PH2), which differ in the enzyme defect responsible for the disease (Fig. 1). In the past, liver biopsy with immunostaining for alanine-glyoxalate aminotransferase (AGT) or glyoxalate/hydroxypyruvate reductase (GRHPR) was required to diagnose the type 1 and type 2 forms, respectively [38]. Currently, a polymerase chain reaction using a serum sample can identify the three most common mutations in the involved genes. Indeed, one study reported that 66% of patients who had hyperoxaluria were diagnosed without the need for liver biopsy [39].

The diagnosis of primary hyperoxaluria should be suspected in the calcium stone-forming child, or in adults with severe hyperoxaluria (greater than 100 mg/day), because nephrolithiasis is the most common presenting symptom of the disease. Transplantation of the kidney or liver is generally

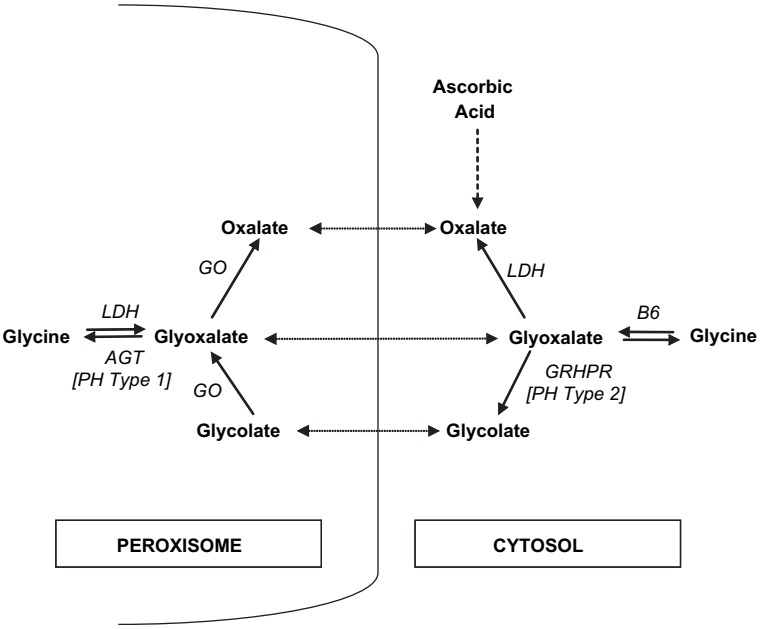

Fig. 1. Oxalate biosynthetic pathway. Type 1 primary hyperoxaluria is caused by a deficiency in peroxisomal alanine glyoxalate aminotransferase. Type 2 primary hyperoxaluria is caused by a defect in cytosolic glyoxalate reductase/hydroxypyruvate reductase. AGT, alanine-glyoxalate aminotransferase; GHPHR, glyoxalate reductase-hydroxypyruvate reductase, GO, glycolate oxidase; LDH, lactate dehydrogenase.

required in patients who have end organ failure. Although current opinion holds that simultaneous liver transplantation is required to replete the underlying hepatic enzymatic deficiency, renal transplantation alone was associated with an 84% 6-year survival, compared with a 56% survival with combined liver-kidney transplant in a study of pediatric patients [40]. This difference in survival may be confounded by higher disease severity in the combined transplant group, along with the more complicated postsurgical course in patients with two transplanted organs.

The most common cause of hyperoxaluria among stone formers is intestinal disease/resection associated with a malabsorptive state. In the setting of fat malabsorption, saponification of fatty acids with luminal calcium reduces calcium-oxalate complex formation in the gut, increasing the pool of unbound oxalate available for absorption, and ultimately leading to hyperoxaluria. In addition, the poorly absorbed fatty acids and bile salts are thought to increase colonic permeability to oxalate, further enhancing oxalate absorption and urinary excretion [41]. Other urinary stone risk factors associated with malabsorptive states include low urine volume caused by dehydration, low urinary pH as a result of bicarbonate loss in stool, hypocitraturia from metabolic acidosis, and low urinary magnesium from poor absorption. Any condition associated with malabsorption and chronic diarrhea may be associated with hyperoxaluria, including intestinal resection, inflammatory bowel disease, and celiac sprue.

A concerning and potentially increasing cause of enteric hyperoxaluria is bariatric surgical procedures. The rise in the prevalence of obesity in North America led to a sixfold increase in bariatric surgery procedures between 1990 and 2000 [42]. Jejunoileal bypass surgery, popularized in the 1970s, was associated with a 39% rate of new stone occurrence during a 16-year mean follow-up in one study [43]. Urine collections in these patients demonstrated profound hyperoxaluria (mean 111 mg/day) and hypocitraturia (148 mg/day). Consequently, this operation was abandoned because of the high risk of kidney stones, and in some cases, renal failure. Since then, many patients who had recalcitrant, frequent stones and profound hyperoxaluria or hypocitraturia have undergone jejunoileal bypass reversal. Dhar and colleagues [44] showed that after surgical reversal, hyperoxaluria resolved (with urinary oxalate dropping from 112.5 mg pre-reversal to 33.8 mg/day post-reversal), although mild

hypocitraturia persisted (22 mg/day pre-reversal and 227 mg/day post-reversal), albeit at levels amenable to oral alkali citrate therapy.

More recently, Roux-en-Y gastric bypass surgery or various forms of gastric banding have become the bariatric operations of choice. Asplin and Coe [45] collected 24-hour urine specimens from 132 gastric bypass patients, and found significantly higher urinary oxalate levels (83 ± 2 mg/day) in this group of patients compared with control groups of either unselected calcium stone formers or non-stone formers (39 mg ± 2 mg and 34 mg ± 1 mg, respectively; $P < .001$ for both comparisons); however, oxalate levels were not quite as high as those seen in jejunoileal bypass patients (102 mg ± 4 mg/day). Severe hyperoxaluria (>100 mg/day) was identified in 23% of bypass patients, compared with 0.5% of unselected stone formers. CaOx supersaturation, the driving force for kidney stone formation, was higher in gastric bypass patients (12.1 ± 0.5 mg) than in unselected stone formers (9.0 ± 0.1 mg), non-stone formers (7.4 ± 0.8 mg), and jejunoileal bypass patients (8.9 ± 1.1 mg).

In a sobering study, Nelson and associates [46] identified 23 patients who had enteric hyperoxaluria after gastric bypass surgery, manifest by either oxalate nephropathy or the formation of CaOx stones. Indeed, 2 patients ultimately required hemodialysis. With the exponential increase in bariatric surgery for the treatment of morbid obesity, we are likely to see a rise in the incidence of hyperoxaluria and CaOx stone formation. With longer follow-up of patients undergoing Roux-en-Y gastric bypass or gastric banding, a better understanding of the associated urinary derangements and their treatment will become possible.

Hyperoxaluria in the absence of intestinal disease can occur from excessive dietary intake of oxalate-rich foods such as nuts, chocolate, brewed tea, spinach, and rhubarb. Severe calcium restriction may reduce intestinal oxalate binding, thereby increasing intestinal oxalate absorption. Excessive vitamin C intake has also been shown to increase oxalate excretion by in vivo conversion of ascorbate to oxalate [47]; however, observational studies of two large cohorts did not demonstrate an increased incidence of stone disease among subjects consuming the highest amounts of vitamin C [48,49].

Oxalate-degrading bacteria such as *Oxalobacter formigenes* have been shown to colonize the intestine of normal individuals, and may reduce intestinal oxalate. Absence of these bacteria has been linked to increased urinary oxalate levels [50] and higher rates of stone formation in stone formers [51]. The contribution of oxalate-degrading bacteria to CaOx stone formation has not been fully elucidated.

Hyperuricosuria

Hyperuricosuria can lead to CaOx stone formation by heterologous nucleation on the surface of monosodium urate crystals [52]. Hyperuricosuria is defined as urinary uric acid exceeding 600 mg daily. The most common cause of hyperuricosuria is increased dietary purine intake, because uric acid is the end product of purine metabolism. Numerous other acquired and hereditary diseases can lead to hyperuricosuria, however, including gout, myelo- and lymphoproliferative disorders, multiple myeloma, hemolytic disorders, and hemoglobinopathies.

The pathophysiology of hyperuricosuric CaOx nephrolithiasis is intimately related to urinary pH. At pH less than 5.5, poorly soluble undissociated uric acid precipitates, leading to uric acid or CaOx stone formation. At pH greater than 5.5, uric acid is found predominantly in its dissociated form, increasing urinary saturation of monosodium urate and promoting CaOx stone formation through heterogeneous nucleation [53]. Furthermore, monosodium urate has been shown to bind to urinary inhibitors, thereby reducing urinary inhibitory activity and indirectly promoting CaOx crystallization [54].

Gouty diathesis

Gouty diathesis refers to uric acid stone formation associated with primary gout [55]. The invariant feature of this disorder is low urine pH, which promotes the precipitation of the sparingly soluble, undissociated form of uric acid, leading to uric acid stone formation. Gouty diathesis is also a risk factor for CaOx stone formation, however. Although uric acid, which is favored at low pH, is not as efficient as monosodium urate in promoting CaOx stone formation, it too leads to CaOx crystallization by way of heterogeneous nucleation. Although the etiology of low urine pH in these stone formers has not been fully elucidated, an association has recently been established between uric acid stone formation and non–insulin-dependent diabetes [56]. Insulin resistance, the cause of non-insulin diabetes, has been shown to impair renal ammoniagenesis, which in turn reduces urinary ammonium and lowers urine pH.

Treatment

Dietary modification

Hosking and colleagues [57] coined the term "stone clinic effect" to describe the reduction in stone formation seen with dietary measures alone. Dietary modification can reduce urinary excretion of stone constituents or increase urinary inhibitors. In low-risk stone formers, dietary measures alone may be sufficient to prevent stone recurrence without the need for drug therapy; however, dietary modification should always accompany drug therapy in patients who have more severe disease. A number of dietary factors have been shown to influence stone formation, including fluids, sodium, animal protein, calcium, and oxalate.

Fluids

A high fluid intake reduces urinary saturation of stone-forming calcium salts and dilutes promoters of CaOx crystallization. In two large observational studies, a high fluid intake was inversely related to risk of kidney stone formation [58,59]. Furthermore, a prospective, randomized trial assessing the effect of a high fluid intake [60] showed a 55% reduction in stone recurrence rates in the group adhering to a high fluid intake compared with the control group, who received no specific recommendations. In general, patients are recommended to consume enough fluid to maintain a urine output of at least 2 L daily. The fluid intake required to produce the target urine volume varies according to the activity level of the patient and the weather.

Not all beverages are comparable with regard to their beneficial effect. Alcoholic beverages, coffee, and tea were shown in observation studies to reduce the risk of stone formation [61,62]. Interestingly, grapefruit juice was shown in these same studies to be associated with a 40% higher risk of stone formation. This finding is counterintuitive, because citrus fruits have been thought to be beneficial in preventing stone formation as a result of their high citrate content. Although no randomized clinical trials have evaluated the effect of specific fruit juices on rates of incident or recurrent stone formation, a number of metabolic studies have investigated the effect of citrus fruit juices on urinary stone risk factors. The key factor in the effect of citrus juices on stone-forming risk is the cation accompanying the citrate, which determines the net alkali load delivered, and subsequently the urinary pH and citraturic response. Citrate is almost completely metabolized to bicarbonate. If the accompanying cation is hydrogen ion, the alkalinizing effect of citrate is neutralized. Potassium-rich fruit juices such as orange juice [63], but not potassium-poor juices, like cranberry juice [64], provide organic anions that are metabolized to alkali, thereby increasing urinary pH and citrate. Although lemonade, which is replete with citric acid was shown in one metabolic study of subjects on a random diet to increase urinary citrate [65], another study in which subjects were maintained on a controlled metabolic diet [66] showed no increase in urine pH or citrate with lemonade consumption. Grapefruit juice, which has a high potassium content, was shown to increase urinary citrate, but the effect on urinary saturation of CaOx was offset by a concomitant increase in urinary oxalate, such that overall there was no change in the relative saturation of CaOx between the control and grapefruit phases of study.

Sodium

A high salt intake increases stone risk by reducing renal tubular calcium reabsorption and increasing urinary calcium. In addition, high urinary sodium increases urinary saturation of monosodium urate, and reduces urinary citrate via sodium-induced bicarbonate loss. Consequently, inhibitory activity against CaOx and calcium phosphate is reduced, monosodium urate-induced CaOx crystallization is enhanced, and urinary saturation of CaOx and calcium phosphate is increased. Furthermore, high urinary sodium reduces the efficacy of thiazide treatment for hypercalciuria by blunting the hypocalciuric effect. The benefit of concomitant restriction of salt and animal protein in reducing urinary calcium was demonstrated in a randomized trial [67]. In general, salt intake should be limited to 2000 to 3000 mg daily.

Animal protein

Animal protein provides an acid load because of the high content of sulfur-containing amino acids. As such, a high protein intake reduces urine pH and citrate and enhances urinary calcium excretion via bone resorption and reduced renal calcium reabsorption [68]. Additionally, the purine load potentially increases urinary uric acid, and increases the risk of CaOx stone formation.

Observational studies have shown a positive correlation between animal protein consumption and new stone formation in men but not women [58,59]. Interestingly, a randomized trial

comparing a low animal protein, high fiber, high fluid intake with a high fluid intake alone in a group of first-time CaOx stone formers showed a higher rate of stone formation in the low protein group compared with the control group [69]. The control group instructed on a high fluid intake alone had a higher urinary volume than the study group, however, which could have confounded results. In contrast, Borghi and colleagues [67] demonstrated a lower rate of stone formation in hypercalciuric stone formers maintained on a normal calcium, low protein, low sodium diet compared with subjects maintained on a high fluid diet alone. Restriction of animal protein (red meat, fish, poultry) to no more than two servings daily is recommended.

Calcium

Traditionally, calcium restriction has been recommended to reduce urinary calcium and urinary saturation of CaOx; however, two large cohort studies [58,59] and a randomized trial [67] showed a protective effect of a high/normal calcium intake against incident/recurrent stone formation. The protective effect of a high calcium intake in both studies was attributed to the decline in urinary oxalate that results from reduced intestinal oxalate absorption in the face of increased luminal calcium-oxalate complex formation. However, urinary oxalate levels depend on dietary calcium and oxalate intake and the state of intestinal calcium absorption. By concomitantly restricting calcium and oxalate in the diet, the rise in urinary oxalate associated with dietary calcium restriction can averted [70]. Indeed, a retrospective study of a large number of calcium stone formers [71] demonstrated that a short-term program of broad dietary modification, including both calcium and oxalate restriction, resulted in a significant decline in urinary calcium in hypercalciuric patients, without a change in urinary oxalate. In a long-term retrospective study of 28 hypercalciuric calcium stone formers, dietary calcium and oxalate restriction, along with a thiazide diuretic and potassium citrate, reduced urinary calcium without raising urinary oxalate, and reduced urinary saturation of CaOx and stone formation [72]. Thus, hypercalciuric patients may be optimally treated with a program of modest calcium and oxalate restriction, along with pharmacologic therapy. Severe calcium restriction should be always be avoided so as to prevent a negative calcium balance; however, mild calcium restriction to no less than one serving of dairy daily should be part of a program of broad dietary modification in patients who have hypercalciuria.

Normocalciuric patients, on the other hand, do not benefit from dietary calcium restriction, and therefore a liberal calcium intake is recommended in this group of patients [71].

Oxalate

The relative contribution of dietary oxalate and endogenous oxalate production to urinary oxalate is controversial. Dietary oxalate has been estimated to account for 10% to 50% of urinary oxalate, depending on dietary calcium and oxalate intake and the bioavailability of oxalate in foods [34]. CaOx stone formers who have mild hyperoxaluria have been shown to have increased intestinal absorption and renal excretion of oxalate, which may account for their increased risk of stone formation [73]. In general, restriction of oxalate-rich foods, such as nuts, chocolate, tea, and dark roughage is recommended.

Vitamin C has been implicated in calcium stone formation because of in vivo conversion of ascorbic acid to oxalate. A metabolic trial demonstrated a 20% to 33% increase in urinary oxalate with the consumption of 2 g of vitamin C daily. Likewise, a large male cohort study showed a 41% increased risk of stone formation in men consuming 1 g or more of vitamin C daily compared with those consuming less than 90 mg daily [74]. As such, limitation of vitamin C supplements to 500 mg or less daily is recommended.

Drug therapy

For those patients in whom conservative dietary measures fail or those who have more aggressive stone disease or identifiable metabolic abnormalities, pharmacologic therapy, along with dietary measures, should be initiated. Drug therapies aimed at correcting underlying metabolic derangements can reduce the likelihood of recurrent stone formation. In some cases, medical therapies are initiated empirically, without regard to the metabolic background of the patient. The benefit of targeted versus empiric medical therapy has never been formally addressed; however, for the purposes of this discussion, drug therapies are reviewed with respect to the abnormalities they are targeted to correct.

Thiazide diuretics

Thiazide diuretics are reserved for patients who have severe hypercalciuria (urinary calcium >275 mg/day) or for patients who have mild

hypercalciuria and reduced bone mineral density. The hypocalciuric action of thiazides is attributed to enhanced calcium reabsorption in the distal renal tubule. In addition, thiazide-induced extracellular sodium depletion promotes sodium and calcium reabsorption in the proximal renal tubule, further reducing urinary calcium. As such, a high sodium intake can attenuate the hypocalciuric action of thiazide diuretics.

The recommended dosages of commonly used thiazide diuretics for a normal sized adult are hydrochlorothiazide 25 mg twice daily or chlorthalidone 25 to 50 mg daily. An alternative, nonthiazide diuretic, indapamide (1.25–2.5 mg daily), has a similar mechanism of action to thiazides and has been shown in a randomized trial be effective in reducing stone recurrence [7]. The use of thiazides may be limited in 30% to 50% of patients by side effects, including fatigue, dizziness, impotence, musculoskeletal symptoms, or gastrointestinal complaints. Because thiazides can deplete serum potassium, the addition of a potassium supplement is recommended. Thiazide-induced hypokalemia can also lead to intracellular acidosis and hypocitraturia, and therefore the use of potassium citrate (10–20 mEq twice daily) can prevent both hypokalemia and hypocitraturia.

A number of randomized trials have demonstrated a benefit of thiazide diuretics and indapamide in reducing the rate of stone recurrence in calcium stone formers [7,75–78]. Interestingly, in some of these trials, thiazides were successfully used unselectively, without regard to urinary calcium levels [7,75]. In a meta-analysis of randomized medical therapy trials [11], a 21% risk reduction in stone recurrence rates was demonstrated with the initiation of thiazides or indapamide.

Potassium citrate

Potassium citrate is effective in the treatment of patients who have calcium stones and normal urinary calcium. By providing an alkali load, potassium citrate increases urinary pH and citrate, thereby increasing urinary inhibitory activity, and perhaps reducing urinary calcium. In a randomized trial, potassium citrate was shown to reduce stone recurrence rates by 75% among hypocitraturic stone formers [6].

In patients who have gouty diathesis, potassium citrate raises urinary pH and reduces uric acid-induced CaOx stone formation. For patients who have hyperuricosuric CaOx nephrolithiasis and who are unable to tolerate allopurinol, potassium citrate therapy has been shown to be effective in reducing stone recurrence rates [79].

Potassium citrate is prescribed at a starting dose of 10 mEq three times daily, or 20 mEq twice daily. Potassium citrate can be used for treatment of patients who have hypocitraturia, or for normocalciuric calcium stone formers regardless of other associated abnormalities. In patients who have hypercalciuria, potassium citrate is prescribed along with a thiazide diuretic or indapamide to prevent thiazide-induced hypokalemia and hypocitraturia.

For patients who have enteric hyperoxaluria, potassium citrate therapy can raise urine pH and citrate; however, dosages higher than those used for idiopathic calcium nephrolithiasis (up to 120 mEq daily) may be required. Furthermore, because of the rapid intestinal transit associated with chronic diarrheal syndromes, a liquid form of potassium citrate may be better absorbed.

Allopurinol

In calcium stone formers who have moderate to severe hyperuricosuria and in whom dietary modification fails, allopurinol has been shown to reduce urinary uric acid levels and prevent recurrent stone formation [80]. Allopurinol is a xanthine oxidase inhibitor that prevents the conversion of hypoxanthine to xanthine, the precursor of uric acid. The medication is generally well-tolerated, and side effects are limited to irreversible liver enzyme elevation and skin rash. Because of a risk of progression to Stevens-Johnson syndrome, report of a skin rash with allopurinol should prompt immediate cessation of the drug.

Pyridoxine

Vitamin B6, or pyridoxine, promotes the conversion of glyoxalate to glycine, thereby reducing the substrate for oxalate production [81]. Pyridoxine (100 to 400 mg daily) is most often used for the treatment of primary hyperoxaluria. Because the elevated urinary oxalate levels associated with enteric hyperoxaluria are derived primarily from intestinal oxalate hyperabsorption, reduction of endogenous oxalate production by pyridoxine is likely to be of limited value. In these patients, a regimen of dietary oxalate restriction, potassium citrate therapy, and calcium supplementation is effective in reducing urinary oxalate, correcting the metabolic acidosis and hypocitraturia, and restoring normal calcium balance.

Summary

Calcium-containing stones are the most frequent stone type identified. The pathophysiology of calcium stone formation is complex and often multifactorial; however, systematic identification of underlying metabolic abnormalities and the initiation of dietary and pharmacologic prophylactic regimens can successfully correct stone risk factors and reduce the likelihood of stone recurrence.

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Uric Acid Nephrolithiasis

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Uric acid was first identified as a component of kidney stones in 1776 [1,2]. This initial report also identified a relationship between uric acid stone development and an underlying metabolic condition, gout. Since then, uric acid nephrolithiasis has been found to be associated with various metabolic conditions and additional pathophysiologic mechanisms have been elucidated. Yet many key questions remain unanswered regarding uric acid production, excretion, and the factors involved in nephrolithiasis. This article reviews recent insights into the pathophysiology of uric acid nephrolithiasis and the management of these stones.

Epidemiology of uric acid stones

Uric acid nephrolithiasis comprises approximately 10% of the total stone burden in the United States [3]. However, this value exhibits considerable geographic and racial diversity. The proportion of uric acid stones is significantly higher in Middle Eastern countries, such as Israel (40%) [4]; in Okinawa, Japan (16%) [5]; and in some European countries, including regions in Germany (25%) [6]. In the United States, a high prevalence of uric acid nephrolithiasis was reported in the Hmong population, an ethnic group with Chinese ancestry who emigrated from Laos [7]. When compared with a non-Hmong population, the Hmong patients demonstrated increased stone risk with over 50% of the stones containing uric acid. The factors related to these global and ethnic variations in uric acid stone risk have not been identified.

Recent studies have illustrated metabolic factors that affect the epidemiology of uric acid nephrolithiasis. An epidemiologic study that included over 200,000 subjects from three cohorts found that type 2 diabetes mellitus is associated with kidney stone disease [8]. Stone composition was not assessed. However, smaller studies have demonstrated increased prevalence of uric acid stones in type 2 diabetics, suggesting that uric acid stones contribute to the higher stone risk in this population [9,10]. An initial report by Pak and colleagues [9] found an association of uric acid stones with type 2 diabetes mellitus. This finding was confirmed in another study of 4718 kidney stones, of which 631 were obtained from patients with diabetes mellitus and 4087 from nondiabetic stone formers [10]. A significantly higher proportion of pure uric acid stones was found in diabetic patients than in nondiabetics (28.5% versus 13%, $P < .0001$). This difference was even greater when mixed uric acid–calcium stones were included in the proportion of uric acid–containing stones (35.4% versus 16.8%, $P < .0001$). Additionally, a comparison of diabetic and nondiabetic stone formers found that 35.7% of stones in diabetics were composed of uric acid versus 11.3% in nondiabetic stone formers [11].

Similarly, obesity is associated with a higher prevalence of uric acid nephrolithiasis. A report of 32 obese stone formers found that 63% of their stones were composed of uric acid [12]. Additionally, a French study compared the proportion of uric acid stones in lean nephrolithiasis patients (body mass index (BMI) < 25 kg/m^2) with that

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of obese patients (BMI $\geq$ 30 kg/m^2) [13]. Uric acid stones constituted 6.8% of the total stone burden in lean patients, but 24.1% in the obese subjects. The increased prevalence of uric acid stones in obese and diabetic subjects suggests that a common underlying mechanism, such as insulin resistance, may influence stone risk [14]. This mechanism may also contribute to the ethnic and geographic variations in stone prevalence.

Uric acid metabolism

Uric acid production results from the degradation of purines, derived exogenously from diet and endogenously from de novo purine biosynthesis that includes nucleic acid turnover and production from nonpurine precursors. Purine synthesis occurs in the liver and involves recycling of guanine and hypoxanthine. In states of nucleotide excess, these bases are converted to xanthine and then to uric acid via xanthine oxidase [15]. Tissue catabolism, such as with myeloproliferative conditions, hematologic disorders, or following administration of chemotherapy, may result in increased purine catabolism. Additionally, high purine consumption due to a purine-rich diet will also increase the uric acid load. A comparison of subjects given a purine-rich versus a purine-free diet demonstrated that the purine-rich diet caused a 50% or greater increase in urinary uric acid excretion with concurrent elevations in serum uric acid [16,17]. Increased purine production or consumption of purine-rich foods results in hyperuricosuria in subjects with normal renal function. Hyperuricemia may occur, depending on the extent of compensatory hyperuricosuria and intestinal uricolysis.

Uric acid physicochemical properties

Uric acid provides a means for nitrogen excretion in animals such as insects, reptiles, and birds. In contrast, mammals primarily excrete nitrogen as urea, rendering them ureotelics [18]. However, mammals produce uric acid as a product of purine metabolism. In most mammals, uric acid is metabolized to the more soluble allantoin, and is thus excreted. Because humans and apes lack the hepatic enzyme uricase, they cannot convert uric acid into allantoin and therefore exhibit serum uric acid levels up to 100-fold higher than those in other mammals [19]. Furthermore, humans and apes excrete significantly higher amounts of uric acid and, because of its poor solubility, are at increased risk for uric acid precipitation when it is excreted.

Urine pH is the primary determinant of uric acid crystallization. Uric acid is a weak organic acid with an ionization constant (pKa) of 5.5; however, in urine, at a temperature of 37°C, the pKa is 5.35 [20,21]. Uric acid is less soluble than its base, urate, such that in urine with a pH of 5.35 only 90 mg/L, uric acid remains in solution. At this pH, urine becomes supersaturated with undissociated uric acid, which subsequently precipitates to form uric acid stones (Fig. 1).

With increases in urine pH, more uric acid is converted to urate and the tendency for uric acid crystallization decreases. However, urate solubility is influenced by such urinary cations as monosodium urate, which has lower solubility compared with monopotassium urate [22,23]. Increased urinary supersaturation with monosodium urate accounts for the formation of calcium oxalate stones through heterogeneous nucleation or by binding of inhibitors of calcium oxalate crystallization [24]. In addition to monosodium urate, uric acid is also conducive to heterogeneous nucleation of calcium oxalate crystallization through the process of epitaxial crystal growth [25–27]. The different solubility of urate salts is the basis for use of potassium alkali rather than sodium alkali in the treatment of uric acid stones [28].

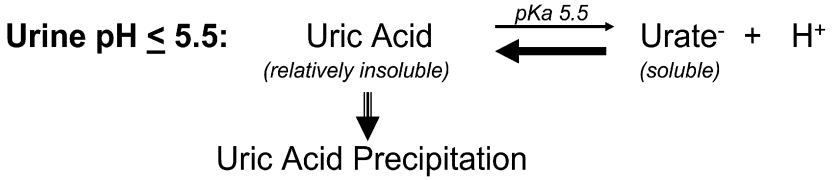

Fig. 1. Physicochemical properties of uric acid. Uric acid pKa is 5.5. Therefore, at a urine pH less than 5.5, the equilibrium shifts to the left allowing for greater uric acid concentration and less urate. Because uric acid is relatively insoluble, this shift results in greater uric acid precipitation. H^+, hydrogen ion.

Renal excretion of uric acid

Approximately one third of uric acid elimination is achieved by the gut, while the kidneys are responsible for most remaining uric acid excretion [29]. Renal uric acid transport is a complex process that involves several processes at the proximal tubule. The proposed model includes glomerular filtration followed by reabsorption, secretion, and postsecretory reabsorption (Fig. 2A). Typically 90% of filtered uric acid is reabsorbed by the renal proximal tubule, resulting in a fractional excretion of uric acid of 10%. Although the mechanisms of uric acid transport remain incompletely understood, some insight has been gained from recent investigations.

Once uric acid is freely filtered at the glomerulus, it undergoes reabsorption via a newly identified uric acid transporter, URAT1 (encoded by *SLC22A12*) [30]. This urate-anion exchanger is found in the apical membrane of renal proximal tubular cells and is considered the predominant regulator of serum uric acid levels (Fig. 2B) [31]. Organic anions, such as lactate, nicotinate,

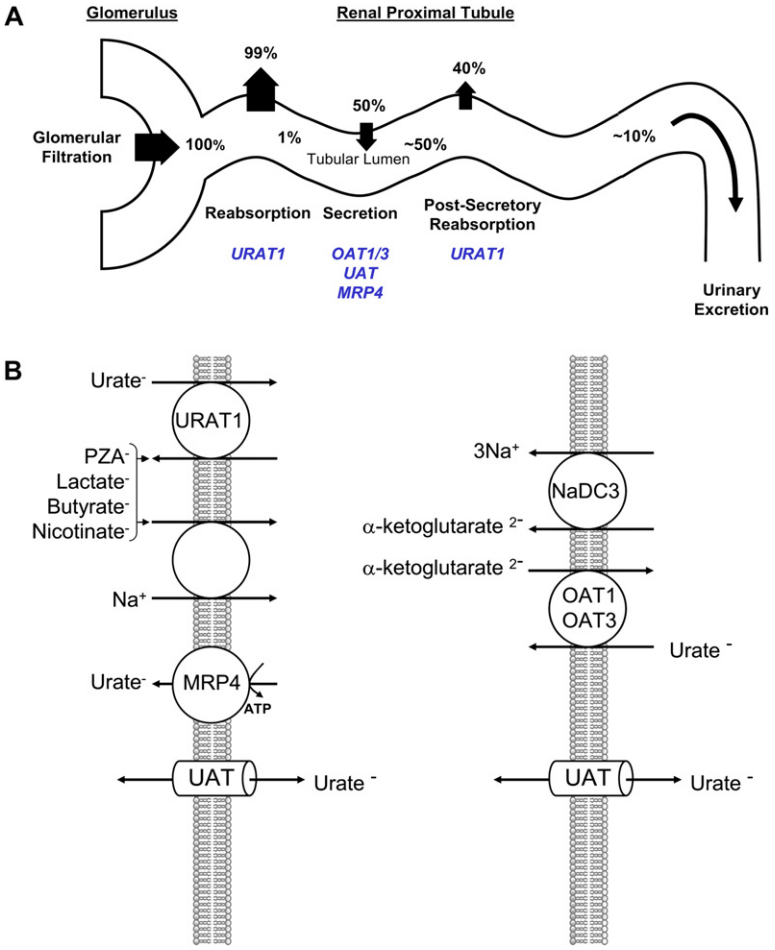

Fig. 2. (*A*) Four-component model of renal uric acid handling. Uric acid is freely filtered at the glomerulus. Ninety-nine percent of uric acid is then reabsorbed in the proximal tubule followed by 50% secretion and 40% postsecretory reabsorption. The final urinary uric acid excretion is approximately 10%. (*B*) Molecular mechanisms for urate transport in the renal proximal tubular cell. Urate is reabsorbed into the cell via uric acid transporter 1 (URAT1) after stimulation by intracellular anions. Urate may also be taken up into the cell via organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3), or urate channel (UAT). UAT is also present on the apical membrane and may be responsible for transcellular transport. Multidrug-resistance–associated protein 4 (MRP4) is found on the apical membrane, requires adenosine triphosphate, and may be responsible for apical urate secretion.

pyrazinamide, and low-dose salicylates promote URAT1-mediated urate absorption by trans-stimulation from inside renal proximal tubular cells [30]. In contrast, uricosuric agents, including probenecid, benzbromarone, nonsteroidal anti-inflammatory drugs, and the angiotensin receptor antagonist losartan, inhibit urate transport via cis-inhibition from the apical side of the transporter [30].

Some patients with URAT1 mutations demonstrate uric acid excretion in excess of their glomerular filtration rates, supporting a role for renal uric acid secretion [32]. Uric acid excretion by renal proximal tubular cells most likely involves basolateral uptake of uric acid, followed by apical secretion. Organic anion transporters (OAT), specifically OAT 1 and OAT 3, have been identified in the basolateral membrane and most likely mediate uric acid uptake into proximal tubule cells [31,33,34]. Sodium-dependent uptake of alpha-ketoglutarate has been shown to stimulate basolateral urate uptake in exchange for alpha-ketoglutarate [35,36]. Mechanisms responsible for uric acid secretion from the apical membrane have yet to be fully elucidated. A recent report identified an organic anion transporter, OATv1, in the apical membrane of porcine renal proximal tubular cells. This transporter was demonstrated to transfer urate in addition to other organic anions and has been proposed as a mechanism for urate efflux. However, its presence and relevance in humans has yet to be determined.

Another potential means for urate secretion may be mediated by the organic anion transporter multidrug-resistance–associated protein 4 (MRP4) [37]. This protein is expressed in the kidney and liver and may account for urate transport in both organs. Another protein, the urate channel (UAT), has also been proposed to be involved in uric acid transport [38,39]. UAT is expressed on apical and basolateral membranes throughout the kidney, which suggests that it may play a role in urate efflux or transport across cells [38]. However, its role and relevance in net renal uric acid handling remains unknown.

Pathophysiology of uric acid nephrolithiasis

Three primary factors contribute to the development of uric acid nephrolithiasis: low urinary volume, hyperuricosuria, and acidic urine pH (Box 1). Evaluation of a uric acid stone former should include assessment for these three factors,

Box 1. Risk factors for uric acid nephrolithiasis

- Low urinary volume
  - Chronic diarrhea
  - Excessive perspiration
  - Chronic dehydration
- Hyperuricosuria
  - Enzymatic deficiencies
    - Hypoxanthine guanine phosphoribosyl transferase deficiency: Lesch-Nyhan syndrome (if partial deficiency: Kelley-Seegmiller syndrome)
    - Phosphoribosylpyrophosphate synthetase overactivity
    - Glucose-6-phosphatase deficiency: type I glycogen storage disease (GSD), von Gierke disease
    - Debrancher deficiency: type III GSD, limit dextrinosis
    - Muscle phosphorylase deficiency: type V GSD, McArdle disease
    - Muscle phosphofructokinase deficiency: type VII GSD, Tarui disease
  - URAT1 mutations: hypouricemic hyperuricosuria
  - Urate overproduction
    - Gout
    - High dietary intake of purines
    - Myeloproliferative disorders
    - Hemolytic anemia
    - Chemotherapy-induced tumor lysis
  - Uricosuric drugs
    - Probenecid
    - High-dose salicylates
    - Radiocontrast agents
    - Losartan
- Low urinary pH
  - Increased base loss
    - Diarrhea
  - Increased acid intake
    - High consumption of animal protein
  - Increased endogenous acid production
    - Insulin resistance
    - Exercise-induced lactic acidosis
  - Decreased urinary ammonium
    - Insulin resistance
    - Gout

which should then guide treatment. The most prevalent feature in idiopathic uric acid nephrolithiasis is a low urinary pH. However, all three predisposing causes should be considered.

Low urinary volume

Low urinary volume, by increasing the relative saturation of stone-forming constituents, is pathophysiologic in the development of all kidney stones. In nephrolithiasis patients, a urinary volume less than 2 L/d is considered to be stone promoting [40]. Any form of volume depletion, such as excessive perspiration or chronic diarrheal states, may contribute to uric acid stones. Typically, a low urine volume is insufficient to singularly account for uric acid lithiasis, but in the context of low urine pH low urine volume may exacerbate stone-promoting risks.

Hyperuricosuria

Hyperuricosuria is typically defined as urinary uric acid excretion in excess of 700 mg/d [40]. Various genetic and environmental factors may augment urinary uric acid excretion. Urate overproduction and, consequently, hyperuricosuria have been proposed as mechanisms for uric acid stone formation in primary gout. However, more recent studies have demonstrated that uric acid excretion is not elevated in gout patients [41,42]. Such results suggest alternative causative mechanisms, instead of hyperuricosuria, in gouty patients.

Hyperuricosuria also occurs in rare, hereditary enzymatic disorders including (1) hypoxanthine guanine phosphoribosyl transferase (HPRT) deficiency (Lesch-Nyhan syndrome) and partial HPRT deficiency (Kelley-Seegmiller syndrome); (2) phosphoribosylpyrophosphate synthetase overactivity (PRPS superactivity); and (3) glycogen storage diseases I (glucose-6-phosphatase deficiency), III (debrancher deficiency), V (muscle phosphorylase deficiency), and VII (muscle phosphofructokinase deficiency) [18,43]. The first two conditions are X-linked disorders whereas the glycogen storage diseases are autosomal recessive disorders. These conditions are associated with hyperuricemia (>10 mg/dL) and significant hyperuricosuria (>1000 mg/d) that predisposes to gout, renal failure, and kidney stone formation. Affected subjects may present during childhood; however, plasma uric acid levels may remain normal until puberty, particularly in Lesch-Nyhan syndrome [44]. Urinary uric acid levels are elevated during childhood, allowing for recognition of the disease before puberty.

Mutations in URAT1 are responsible for the rare condition of renal hypouricemia, which is associated with low serum uric acid levels and increased urate clearance [32]. Although affected subjects are usually asymptomatic, they are at increased risk for nephrolithiasis and exercise-induced acute renal failure [45]. Kidney damage following exercise is ascribed to greater production of urate and to reactive oxygen species that may be toxic to renal epithelial cells [32,46]. It is not known whether URAT1 polymorphisms contribute to the development of uric acid kidney stones.

Acquired states of uric acid overproduction may also contribute to hyperuricosuria. Such conditions may be related to high dietary purine intake or increased purine metabolism associated with a malignancy or chemotherapy. Uricosuric drugs, such as probenecid, high-dose salicylates, radiocontrast agents, and losartan, increase uric acid excretion [47,48]. These agents may predispose to uric acid lithiasis, particularly during drug initiation or in association with hyperuricemia [15]. It is recommended to avoid their use in cases of uric acid overproduction [2].

Low urine pH

The overriding pathogenic factor in uric acid nephrolithiasis is an unduly acidic urine pH, whereas hyperuricosuria is a relatively rare cause of uric acid stones. The acidic environment promotes titration of more soluble urate to relatively insoluble uric acid, predisposing to uric acid precipitation. In most uric acid stone formers, the etiology of the acidic urine is unknown. However, secondary causes should be considered before the etiology is defined as idiopathic.

Conditions that contribute to acidic urine involve base loss and increased acid generation either endogenously or via ingestion of an acidic diet (Table 1). Diarrhea results in stool loss of bicarbonate, rendering the urine more acidic. It further contributes to lithogenic risk because of the associated volume loss and increased urinary saturation [49]. Similarly, strenuous physical activity can generate lactic acidosis, contributing to a low urine pH, which is further complicated by volume depletion from perspiration [50]. A diet rich in animal proteins provides an acidogenic load, in addition to providing a purine load that contributes to hyperuricosuria [51].

Table 1
Differential diagnosis of uric acid stones

Findings	Stone type				
	Uric acid	Xanthine	2,8-Dihyr-oxyadenine	Mixed uric acid–calcium	Hyperuricosuric calcium
Radiographic findings:					
Radioopaque?	No	No	No	Yes	Yes
Urinary findings:					
Urine pH	Low	Normal	Normal	Normal or low	Normal
Urinary uric acid	Normal	Increased or normal	Normal	Normal or increased	Increased
Fractional excretion of uric acid	Low	Normal	Normal	Normal or low	Normal
Urinary calcium	Normal	Normal	Normal	Normal or increased	Normal
Serum findings:					
Serum uric acid	Increased	Low	Normal	Normal or increased	Normal
Other:					
Responds to alkali therapy?	Yes	No	No	Yes	Yes

Acidic urine is also associated with primary gout, regardless of the presence of kidney stones. In their review of 325 gout patients, including those with and without a nephrolithiasis history, Yu and Gutman [52] found that 92% of the subjects had a urine pH less than 5.6. A recent study of 140 gout patients revealed similar findings with a mean urine pH of 5.4 in stone formers and 5.6 in non-stone formers [42]. In the absence of an identifiable cause, such as in gouty patients, an acidic urine pH is defined as idiopathic.

Pathophysiology of low urine pH

The pathophysiological mechanisms underlying low urine pH in idiopathic uric acid stone formers are complex. Recent studies have shown that two mechanisms play a key role in the acidification defect (Fig. 3). First, endogenous acid production may be increased, requiring greater acid excretion. Secondly, urinary ammonium, the primary urinary buffer, is decreased [41]. Alterations in renal ammonia production or transport result in an impaired buffering capacity and lower urine pH. Such an environment, with higher acid production and diminished ammonium content, necessitates increased dependence on other urinary buffers, collectively referred to as titratable acids, for acid excretion. Both mechanisms contribute to the overly acidic urine found in uric acid stone formers.

Impaired ammonium excretion has been demonstrated in several studies. Gout patients, with and without stones, were found to exhibit low urinary ammonium excretion when compared with controls matched for urine pH [52]. Compared to stone-free gout patients, stone-forming gout patients had an even greater decline in urinary ammonium. Further evidence of an ammonium defect was provided by studies of idiopathic uric acid stone formers, examined on a fixed, metabolic diet [9,41]. In addition to exhibiting low urinary ammonium excretion, idiopathic uric acid stone formers were unable to augment renal ammonia production, as demonstrated by the administration of an acute acid load, which amplified the ammoniagenic defect [41]. Similar findings are demonstrated in a study that evaluated uric acid stone formers on a random diet [14]. In this setting, urinary ammonium excretion failed to increase in association with greater dietary acid intake, reflected by higher urinary sulfate measurements.

In the absence of adequate ammonium buffering, idiopathic uric acid stone formers depend on urinary titratable acids and decreased urinary citrate excretion to maintain net acid excretion. Studies on both fixed and random diets indicate a greater proportion of net acid excretion exists as

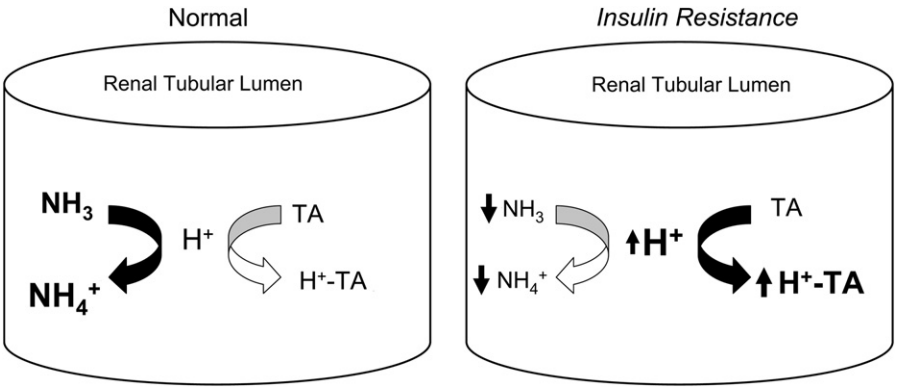

Fig. 3. Acid buffering in a normal individual compared to acid buffering in a patient with insulin resistance. Normal individuals rely primarily upon ammonia for acid buffering. Patients with insulin resistance have greater acid production. Additionally, they exhibit decreased renal ammonia (NH_3) and, subsequently, decreased ammonium (NH_4^+) production. The compensatory mechanism is increased dependence on titratable acids (TA), which allow for generation of a lower urine pH. Insulin resistance may contribute to decreased renal ammonia production, increased acid production, and increased titratable acids.

titratable acid in this population [14,41]. A low urinary citrate has been demonstrated in association with these findings, which may reflect proximal tubule cell acidification [53]. Moreover, idiopathic uric acid stone formers consistently demonstrate higher net acid excretion at any given acid load, which suggests greater endogenous acid production in these subjects [14,41,54].

Potential pathophysiological role of insulin resistance

Insulin resistance has been increasingly associated with idiopathic uric acid nephrolithiasis and may provide a pathophysiologic link (see Fig. 3). Several investigations have provided evidence supporting a relationship between uric acid nephrolithiasis and insulin resistance [9–11,41]. First, a cross-sectional study demonstrated that idiopathic uric acid stone formers manifest many features of the metabolic syndrome, including obesity, dyslipidemia, and glucose intolerance, all of which are linked to insulin resistance [41]. One report found that over 50% of uric acid stone formers exhibit glucose intolerance or type 2 diabetes mellitus [41]. Evaluations of type 2 diabetic stone formers further support this relationship. Secondly, patients with obesity or type 2 diabetes mellitus have a higher proportion of uric acid stones when compared with lean or nondiabetic subjects [10–13].

Insulin resistance may predispose to uric acid nephrolithiasis by contributing to the development of acidic urine. An inverse relationship was demonstrated between body weight and urine pH in a large population of stone-forming subjects [55]. Urine pH has been demonstrated to directly correlate with glucose disposal rate, a measure of peripheral insulin resistance determined by the hyperinsulinemic, euglycemic clamp method [54]. Insulin resistance may influence urine pH via both mechanisms previously discussed: greater endogenous acid generation and impaired ammonium production.

Studies of type 2 diabetic patients and uric acid stone formers indicate these subjects excrete more net acid at any given dietary acid intake [14]. Such findings suggest greater endogenous acid production, although the responsible acid has not been identified. To date, the role of insulin resistance in augmenting endogenous acid production has not been fully elucidated. Plausible mechanisms include greater lactic acid or ketoacid production, each related to insulin resistance [56].

The role of insulin in promoting renal ammoniagenesis in vitro was identified in canine renal proximal tubular segments incubated with glutamine, the principle substrate for renal ammonia production [57]. Secretion of ammonium is dependent on the sodium–hydrogen exchanger NHE3 [58]. Insulin has been shown to activate this exchanger in a dose-dependent manner, thus stimulating ammonium secretion [59,60]. In one study, under hyperinsulinemic euglycemic conditions, insulin caused a robust increase in urinary ammonium excretion in normal subjects [54]. However,

in a preliminary study, the renal ammoniagenic response to hyperinsulinemia was shown to be blunted in idiopathic uric acid stone formers [61]. The effects of insulin resistance on renal ammonia excretion are still under investigation.

Evaluation of uric acid nephrolithiasis

The initial evaluation of a uric acid stone former should include a complete history and physical with a focus on secondary factors, described above, that contribute to stone formation [62]. A review of medications and diet should be included. Identification of an underlying cause will guide future management.

Definitive diagnosis depends upon stone analysis to reveal complete or partial uric acid content. If the calculus is not available for evaluation, radiographic and metabolic features may suggest the presence of uric acid lithiasis. These stones appear radiolucent on evaluation by roentgenography, but are portrayed by CT. Furthermore, an acidic urine pH suggests that a uric acid component may be present. A 24-hour urine collection should be obtained on all subjects to evaluate for predisposing abnormalities, including low urine volume, hyperuricosuria, high urinary sulfate, hypocitraturia, and low urine pH.

Differential diagnosis

Stone analysis distinguishes uric acid lithiasis from other stones in the differential diagnosis (see Table 1). Both xanthine and 2,8-dihydroxyadenine (2,8-DHA) stones are radiolucent on radiographic evaluation and therefore may be mistaken for uric acid stones. Xanthine calculi typically develop in patients receiving allopurinol or in patients with congenital conditions, such as Lesch-Nyhan syndrome or hereditary xanthinuria, an autosomal recessive deficiency of xanthine oxidase [63]. 2,8-DHA stones occur in patients with the autosomal recessive disorder, adenine phosphoribosyltransferase deficiency [2,44]. Both stone types are extremely insoluble and do not respond to alkali therapy, thus providing a diagnostic clue. Serum uric acid is low in hereditary xanthinuria.

The differential diagnosis also includes calcium calculi, such as hyperuricosuric calcium stones and mixed uric acid–calcium oxalate stones. Hyperuricosuria is a risk factor common to both calcium and uric acid stones. However, calcium nephrolithiasis is more commonly associated with hyperuricosuria than is uric acid nephrolithiasis [16,64]. A report evaluating metabolic abnormalities and related kidney stones found that 78% of hyperuricosuric stone formers have calcium oxalate stones and 10% have calcium phosphate stones [65]. The hyperuricosuria usually results from dietary indiscretion and purine gluttony. Other features that distinguish these patients from uric acid stone formers include a normal serum uric acid concentration and a normal urine pH [66]. In contrast, in patients with mixed uric acid–calcium oxalate stones the main metabolic derangement is a low urine pH [65].

Treatment of uric acid nephrolithiasis

Lifestyle modifications

Fluid and dietary modifications should be recommended to all patients with uric acid stones. Fluid intake should be increased to maintain a urinary volume of approximately 2 L/d. The diet should be modified to decrease consumption of animal proteins to Recommended Dietary Allowances of 0.8 g/kg/d [67].

Pharmacological treatment

Allopurinol, a xanthine oxidase inhibitor, is frequently used in the treatment of hyperuricosuric patients with uric acid nephrolithiasis. The dose of allopurinol is 300 mg/d for urinary uric acid excretion higher than 600 mg/d in women and higher than 700 mg/d in men. Allopurinol should be used invariably in patients with primary gout and hyperuricemia and/or hyperuricosuria, and in patients with inborn errors of metabolism, myeloproliferative disorders, or hemolytic anemia; and as a prophylactic measure with chemotherapy-induced tumor lysis. The side effects of allopurinol are uncommon but may be grave and often occur in patients with renal insufficiency [68].

Febuxostat is a newly released purine analog inhibitor of xanthine oxidase. This drug has been used in the treatment of hyperuricemia in patients with gout. Febuxostat, at daily oral doses of 80 to 120 mg, was shown to be more effective than 300 mg daily allopurinol in lowering serum urate and gouty attacks [68]. However, its efficacy against uric acid nephrolithiasis has not yet been carefully examined. Febuxostat has an advantage over allopurinol as it is metabolized in the liver and may be safely used in patients with renal impairment. Rasburicase is a recombinant uricase

that converts uric acid to more soluble allantoin and lowers uric acid excretion. The use of this drug is limited to oncological clinical conditions with high urate turnover.

Alkali treatment

Typically, the prevailing abnormality in uric acid nephrolithiasis is an acidic urine pH. Both potassium citrate and sodium alkali therapy (Table 2) can effectively increase urine pH to prevent stone recurrence and, in some cases, to dissolve existing calculi [28,69,70]. Potassium citrate is preferred because it also reduces urinary calcium, thereby decreasing the propensity for calcium oxalate crystallization and reducing the risk for calcium oxalate stone formation [28,69]. It also has an advantage over sodium alkali therapy because potassium urate is more soluble than sodium urate in the urinary environment, thereby attenuating the heterogeneous nucleation of calcium oxalate salts [24]. However, sodium citrate or sodium bicarbonate is a reasonable alternative in patients intolerant to potassium salts and those with impaired renal function. The initial recommended alkali dose is 30 to 40 mEq/d. Twenty-four–hour urine pH should be monitored frequently and the alkali dose titrated to maintain urinary pH above 6.1, but less than 7.0 to avoid complications of calcium phosphate stones [71]. At this pH range, the amount of undissociated insoluble uric acid is decreased significantly to normal values ($<$150 mg/d). Sodium alkali therapy may also predispose to calcium nephrolithiasis in the presence of hyperuricosuria, high urinary sodium concentrations, and elevated calcium oxalate or calcium phosphate relative saturation ratios.

Carbonic anhydrase inhibitors (acetazolamide, topiramate) may be used as alternative alkalinizing agents [72]. This treatment is effective in significantly raising the urine pH. However, the risk of calcium phosphate stones may increase because of lower urinary citrate due to systemic metabolic acidosis. Additionally, a rise in urinary pH causes a predominance of urinary monohydrogen phosphate (pKa 6.7), causing increased complexation of calcium [73–75].

In those subjects who are intolerant to pharmacological treatment, orange and grapefruit juice may be used. These agents have been shown to exert both citraturic and alkalinizing effects [76,77]. However, juices are known to increase urinary oxalate and calcium excretion. Therefore they should be used with caution [76–78]. Furthermore, not all citrate-rich juices provide an alkaline load. In orange and grapefruit juice, the citrate is complexed with potassium, resulting in urinary effects similar to administration of potassium citrate. However, in lemon juice, a proton accompanies the citrate, thus negating the alkaline load [79].

Summary

The prevalence of nephrolithiasis in the United States is increasing [80]. This rise in stone risk is associated with increasing prevalence of the metabolic syndrome and type 2 diabetes mellitus [81]. Because uric acid nephrolithiasis is emerging as a feature of insulin resistance, the prevalence of these calculi may also increase. Recent data suggest that uric acid nephrolithiasis is not an independent disorder but is part of a spectrum of abnormalities associated with obesity and insulin resistance. A low urine pH has emerged as a renal manifestation of the metabolic syndrome, allowing for further study of how the metabolic syndrome affects the kidney. Additional studies are necessary to elucidate why only some diabetics with acidic urine develop uric acid stones. Potential mechanisms include the presence of inhibitors that prevent uric acid crystallization or diurnal variations in urine pH that allow for dissolution of uric acid crystals. Although uric acid stones are more prevalent in insulin-resistant subjects, the extent of risk does not warrant screening for

Table 2
Effects of medical therapies for uric acid nephrolithiasis

	Medication			
Measure	Potassium citrate	Sodium citrate	Sodium bicarbonate	Orange juice
Urine pH	Increases	Increases	Increases	Increases
Urine citrate	Increases	Increases	Increases	Increases
Urine calcium	No change	Increases	Increases	No change or increases
Urine oxalate	No change	No change	No change	Increases
Side effects	Nausea	Nausea	Bloating	Glucose load

stones in all subjects. However, routine screening of a 24-hour urine pH is a simple means to identify those subjects at risk for stones. In subjects with a urine pH less than 5.5, it is reasonable to pursue additional evaluation with a stone-risk profile and ultrasound.

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Management of Cystinuria

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The initial description of cystinuria is credited to Wollaston [1], who reported on bladder calculi composed of cystic oxide in 1810. Two decades later, Berzelius [2] noted that such calculi lacked oxide. At the turn of the nineteenth century, Friedman [3] defined the chemical structure of cystine, the true composition of the aforementioned stones. In 1908, Garrod [4] incorrectly characterized cystinuria as an inborn error of metabolism, but correctly noted that it was an inherited disorder. In 1955, Harris and colleagues [5,6] reported the inheritance as autosomal recessive.

Cystinuria is a monogenic disorder in which there is a transepithelial transport defect of dibasic amino acids, including cystine, ornithine, lysine, and arginine (COLA). This results in diminished reabsorption of these amino acids in both the intestine and renal proximal tubule. The defect in renal reabsorption occurs at the apical membrane of proximal tubular cells. This increases excretion of these amino acids and promotes cystine supersaturation and crystal formation in urine, which can eventuate in cystine stone formation. The other amino acids are soluble at normal urinary pH and do not become stone components. The gastrointestinal defect is not pathologic because these are not essential amino acids and their di-peptide forms are still transported [7,8].

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Epidemiology

The estimated prevalence of cystine stones varies. The overall prevalence of the disease is 1 out of 7000 in neonates, but is influenced by ethnicity. One out of 2,500 neonates among Libyan Jews versus 1 out of 100,000 Swedes have the disease [9]. Homozygous prevalence is 1 in 20,000 while heterozygous expression is 1 in 20 to 1 in 200. Some have estimated that cystine stones account for as many as 1% to 2% of all urinary stone, but other studies report that the percentage is much lower [10,11]. A study by Mandel and colleagues [12] determined the prevalence to be 0.6% among United States veterans. Cystine stones comprise 6% to 8% of the stones reported in pediatric series [13,14]. Much like patients with other monogenic disorders associated with stone formation, these patients manifest their stone-forming condition at a younger age.

The International Cystinuria Consortium (ICC) has compiled demographic data on cystinuric patients [15]. The age of onset ranges between 2 to 40 years, but the median is 12 years for males and 15 years for females. Males are more likely to be affected before the age of 3 years. Similarly, men have 0.42 stone events per year while women have 0.21. Ten of the 224 patients in the ICC data did not develop stone disease, but only 2 of these patients were over 40 years of age. The ICC found that regardless of phenotype or genotype the clinical manifestations were the same. There are gender differences amongst siblings that have same mutations [16]. These differences have been attributed to other stone risk factors, which can be influenced by environment and genetics.

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Normal COLA renal transport

A review of the mechanisms of normal COLA renal transport is subsequently provided as a platform to understanding this disease process. The transporters involved in di-basic amino acid transport are known as heteromeric amino acid transporters. They consist of an amino glycosylated heavy subunit and an unglycosylated light subunit [17–20]. Different genes encode for these two subunits. The heavy subunit is derived from the SLC3 family while the light subunit is from the SLC7 family. The two chains, linked by a disulfide bridge, course through the cell membrane as well as inside and outside of the membrane [20]. The amino group of the heavy chains is within the cell and the carboxyl moiety is outside the cell. Both such light chain components are within the cell.

The two heavy subunits cloned thus far are rBAT and 4F2hc. The rBAT that heterodimerizes with a light chain is called b0,+AT and the whole unit is referred to as B0,+. It is located on the apical surfaces of the renal proximal tubule and the intestinal mucosa, where it promotes reabsorption of COLA amino acids. The protein 4F2hc, also known as CD98 or fusion regulatory protein 1 (FRP1), heterodimerizes with a light chain called y^+LAT1, which is located on the basolateral membrane of these cells. This complex facilitates COLA amino acid transport from the cell into the blood compartment. These two complexes have low capacity and high affinity for the COLA amino acids and are sodium independent. Sodium-dependent neutral amino acid transporters are present at the apical and basolateral membranes and maintain a high intracellular level of neutral amino acids. This maintains a membrane potential that facilitates COLA amino acid transport. The intracellular metabolism of cystine to cysteine further drives this process by maintaining a favorable cystine concentration gradient for reabsorption (Fig. 1).

There is evidence that the aforementioned heavy and light chain proteins involved in COLA amino acid transport may be dimerized to other protein subunits in the renal proximal tubule [21]. For example, there is a gradient for rBAT expression along the proximal tubule (S3 straight segment > S2 lower convoluted segment > S1 upper convoluted segment) that is opposite to that for b0,+AT [22,23]. However, there is sound experimental evidence that b0,+AT and rBAT form the main transporter involved in COLA amino acid transport [24].

Phenotypic characterization

A phenotypic classification of cystinuria was established before the responsible genes were

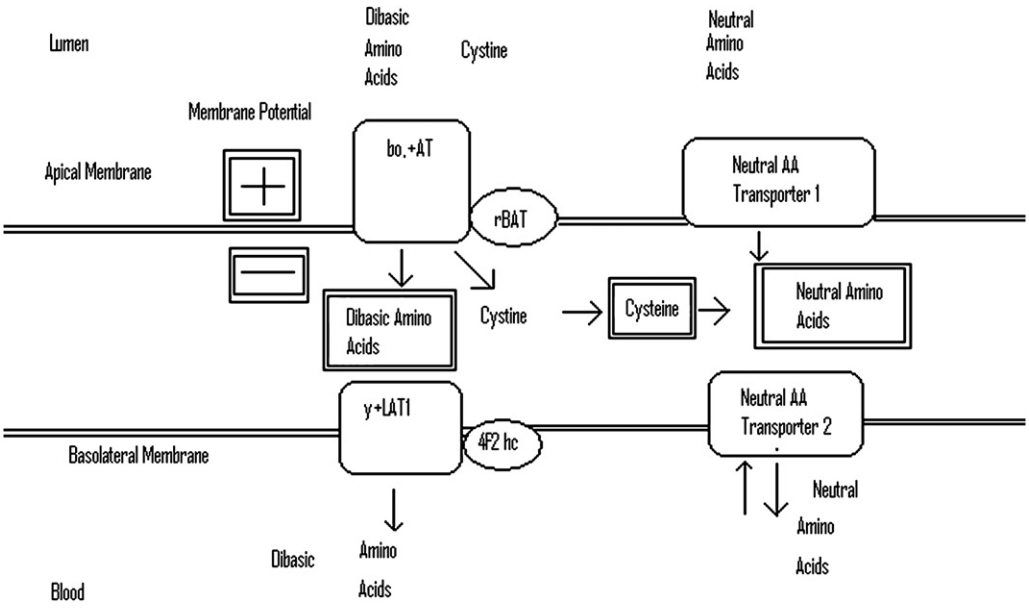

Fig. 1. Normal di-basic amino acid transport. AA, amino acid.

identified. While this system currently has no clinical utility, it will be reviewed as it is linked to the phenotype/genotype classification system currently employed, and to assist the reader with interpretation of the earlier cystinuria literature. Rosenberg and colleagues [25] initially classified cystinuric patients into three different phenotypic groups based on parental urinary cystine excretion. The type I/I group is comprised of two parents with normal cystine excretion (<100 μmol/g creatinine), indicating that they are obligate heterozygotes but silent carriers (I/N where N = normal). This is the most common form of cystinuria and has been referred to as "classic cystinuria." There is no active transport of cystine or other di-basic amino acids in the kidney or gut in type I/I. It has a recessive pattern of inheritance. The next two types are referred to as non-type I cystinurics. They display dominant transmission with incomplete penetrance [26]. In type II/II, both parents have high urinary cystine excretion (990 to 1740 μmol cystine/g creatinine) and are obligate heterozygotes (II/N). These patients have reduced gut and renal di-basic amino acid transport. The defects are usually less severe than they are for type I/I, but heterozygotes may develop nephrolithiasis. In type III/III, both parents have cystine excretion of 100 to 660 μmol/g creatinine and are also obligate heterozygotes (III/N). These patients have reduced gut and renal di-basic amino acid transport. However, type III/III patients have a greater reduction in intestinal transport than does the type II/II cohort.

The newer classification system developed by the ICC is genetically based and its generation was stimulated by studies demonstrating that two genetic mutations were found to be involved in all three phenotypes [16,27]. The new classification is based on the loci of the genetic defect in addition to the urinary cystine excretion of the obligate heterozygotes. In this system, type A occurs when there are two mutations of SLC3A1 and type B occurs when there are two mutations of SLC7A9. The type I/I patients of the initial classification system are now referred to as type A cystinurics while both type II/II and type III/III patients are classified as type B cystinurics. Type A cystinurics are completely recessive while type B cystinurics are incompletely recessive. This classification system is more appropriate because some SLC7A9 heterozygotes have been found to have a urinary excretion phenotype equivalent to SLC3A1 heterozygotes [15]. This new classification system also allows for cases where patients have defects in both genes. Such patients are classified as AB [15,28]. There is little data on the prevalence of each type of cystinuria. The ICC has reported that 38% of their subjects are type A, 47% type B, and 14% type AB. This newer classification currently has no clinical utility but may prove to be important if gene therapy is used in the future or when pharmacologic therapy becomes more targeted. The involved mutations have not been demonstrated to influence disease severity and cystine excretion may vary amongst similar genotypes of the same kindred.

Mutations and cystinuria

The SLC3A1 gene encodes for the rBAT subunit, which is associated with type A cystinuria [29]. Linkage analysis has shown that the SLC3A1 gene is located on chromosome 2 [30,31]. SCL3A1 is normally composed of 45 kilobases (kb) with 10 exons and 9 introns ranging from 500 to 13,000 base pairs (bp). The SLC7A9 gene encodes for the b0+,ATl subunit associated with type B cystinuria. Linkage analysis has shown that this gene is on chromosome 19.12-13.1 [32–35]. Much more is known about SLC3A1 gene mutations.

Over 103 rBAT mutations have been described [15]. Several mutation types have been reported, including nonsense, missense, splice-site, frameshift, chromosomal rearrangements, and deletions. The most common mutation involves the substitution of threonine for methionine 467 (M467T). It represents 26.4% of all type A mutations amongst the ICC cohort [15]. The mutation results in a trafficking defect that prevents the rBAT subunit from reaching the plasma membrane. Several other SLC3A1 mutations cause trafficking defects [36,37]. rBAT mutations may also impact the transport properties of the b0,+AT subunit. The genetic heterogeneity of SLC3A1 is reported to be greater than that of SLC7A9 [15]. A list of some of these mutations is provided in Table 1 [38–47].

Ethnicity influences the mutational profile. In Europe, cystinuria is the second most frequently inherited recessive disorder. Mutational diversity is profound [48]. For example, there are significant differences in major mutations between southeastern and western Europeans, and a complex duplication mutation is limited only to Germans. Only 66 SLC7A9 mutations have been

Table 1
Novel SLC3A1 mutations

Ethnicity	Mutation
Chinese	Missense mutations D210G and S547L, and IVS6 + 2T > C. [38]
Greek	F266S, T351I, R456C, and N516D [39]
Czech and Slovak	Three missense mutations: G140R, D179Y and R365P; one splice-site mutation: 1137-2A > G; one deletion: 1515_1516delAA; and one nonsense mutation: Q119X (novel) [40]
Spanish	I105R and 1670insAT [41]
Swedish	P261L [42]
Italian	Point mutations: S168X, 765 + 1G > T, 766-2A > G, R452Q, Y461X, S547W, L564F, and C673W [43]
Unspecified ethnicity	[P122S (364C > T) and 1601delAC] [44]
Japanese	Missense mutations: L346P, I445T, and C673R; one bp deletion: 1820delT; and two bp insertion: 1898insTA [45]
American	Missense mutations: G1934C, C1259G, T1607G, and G1373A; single-base insertion mutation: 2022insT; a single-base deletion mutation: 163delC; a 23-base deletion mutation: del782A-804A; and a complex mutation that consisted of a 36-base deletion (delC431-3 to T463) and a duplication insertion of 468 T to 474 A after nucleotide 474 [46]
Muslim Arab	Splicing mutation: 891 + 4A→ G [47]
Spanish	Point missense mutation: M467T [29]
Swedish	Two missense mutations: P261L and V330M; and one single–base-pair deletion: 1009delA [28]

described to date [15]. G105R is the most frequent such mutation in the ICC cohort. It represents 27.4% of all type B mutations in the ICC cohort [15]. Another common mutation involves V170M where methionine replaces valine. This mutation is most commonly seen in Libyan Jews and it represents one of the mutations expressing a type 1 phenotype with total or almost total loss of transport function. Several missense mutations are associated with transport function defects [26]. The five most common type B mutations account for 63.1% of all identified SLC7A9 allele mutations [15]. Most recently, Brauers and colleagues [49] demonstrated specific polymorphisms in exons 3, 4, 5, and 6 of SLC7A9 with significantly different allelic distribution between cystinuric patients and controls. Despite the difference, these variants were found not to affect splicing behavior. The distribution is probably due to an association with undetected mutations in the gene. In 2005, Schmidt and colleagues [50] were the first to correlate a splice mutation (c.605-3A) in a cystinuria gene with a proven functional consequence. Table 2 provides a list of some of these mutations.

As with SLC3A1, certain ethnic groups have been used to study the SLC7A9 mutation. Studies as early as 1974 demonstrated the high frequency of cystinuria amongst Libyan Jews [51]. Most members of this ethnic group with cystinuria have type B disease and they have been used as a genetic repository for studying SLC7A9 mutations [34,52,53].

Associated diseases

Several diseases and syndromes are associated with cystinuria. These associations were used to identify loci for the cystinuria genes. Cystinuria is linked to the hypotonia-cystinuria syndrome, which includes generalized hypotonia at birth, minor facial defects, and failure to thrive. Over time, these subjects develop cystine stones, growth

Table 2
Novel SLC7A9 mutations

Ethnicity	Mutations
Chinese	C137R, c.730delG, IVS10 + 2_3delTG, and IVS12 + 3insT [38]
Greek	479-1G > C, Y232C, D233E, and 1399 + 1G > T [39]
Czech and Slovak	One missense mutation: G319R; one insertion: 611_612insA; and one deletion: 205_206delTG [40]

hormone deficiency, hyperphagia, and obesity. This complex phenotype involves mutations at SLC3A1 and the recently discovered deletion of the oligo peptidase called PREPL [54]. Both of these genes are closely linked as SLC3A1 is on 2p16.3 and PREPL is on 2p21. A number of case reports and small case series have linked cystinuria to other diseases and conditions, including mental retardation, Fanconi syndrome, hyperuricemia, cystathioninuria, phenylketonuria, Muckle-Wells syndrome, Jeune Syndrome, Hartnup disease, and ocular–cerebro-renal dystrophy (Lowe's syndrome) [55–63].

Clinical manifestations

The clinical manifestations of cystinuria are related to stone formation and include pain (flank, abdominal, vaginal, testicular, and scrotal), hematuria, lower urinary tract symptoms, urinary tract infection, and a variety of other symptoms and occurrences, including nausea, emesis, anorexia, and failure to thrive. Fifty percent of asymptomatic individuals with cystinuria eventually develop symptomatic stones. The stones are bilateral in 75% of cases [64,65]. The reasons for unilateral occurrence have not been determined but anatomic factors are hypothesized [65].

Patients with homozygous cystinuria may develop stones composed of cystine and other components. Sakhaee and colleagues [66] reported that 9 of 27 (30%) patients with cystinuria had cystine stones mixed with calcium salts. This can be explained by other underlying metabolic abnormalities among these patients. In the Sakhaee cohort, 18.5% had hypercalciuria, 44.4% had hypocitraturia, and 22.2 % had hyperuricosuria. If patients have cystine stones mixed with other components, standard 24-hour urine testing should be considered to search for other metabolic abnormalities. If these are present, dietary modifications and medical therapy directed at their correction should be strongly considered.

Heterozygous cystinuria is thought to be a risk factor for the formation of noncystine stones. This is based on the higher prevalence of this condition in noncystine stone formers as compared with non–stone-forming subjects. Resnick and colleagues [67] reported that the prevalence of this condition was 13.5% in calcium oxalate stone formers while only 1.2% in a control cohort. Thomas and colleagues and Giugliani and colleagues also reported a higher prevalence of this trait in noncystine stone formers. Thomas and colleagues reported 7.8% and Giugliani and colleagues reported 4% [67,68]. In contrast, Carpentier and colleagues [69] reported only a 1.4% prevalence of heterozygous cystinuria in calcium oxalate stone formers but a higher prevalence, 2.8%, in those with recurrent stones. The discrepancies in the reported prevalence of heterozygous cystinuria in noncystine stone formers reflect differences in patient populations and are most likely influenced by geographic diversity and referral patterns. In vitro studies have demonstrated that cystine is a promoter of calcium oxalate crystal growth and aggregation. Martins and colleagues [70] incubated pooled undiluted urine samples with cystine and demonstrated an enhancement of calcium oxalate crystal precipitation. These crystals were examined with scanning electron microscopy and were devoid of cystine components. These findings suggest a salting out effect that induces calcium oxalate crystal formation, much like the proposed mechanism for hyperuricosuria promoting the formation of calcium oxalate stones [71]. The aforementioned evidence reviewed supports the role of heterozygous cystinuria as a risk factor for the development of noncystine stones, mainly those composed of calcium oxalate.

Diagnosis

Urinalysis may lead to the diagnosis of cystinuria because the presence of the classic hexagonal crystal should raise suspicion. It has been reported that 25% of pediatric patients with this disorder have cystine crystals on urinalysis [72]. Family history of cystinuria, particularly in a sibling, is another prompter. The diagnosis can also be established with a stone analysis demonstrating that all or part of the calculus contains cystine. Further urine testing may aid in the diagnosis. A quick screening qualitative test is the cyanide-nitroprusside test, a colorimetric test reported to be beneficial in screening for homozygous patients [64]. It detects the presence of cystine at a threshold concentration of 75 mg/L. Thus, it will be positive in some heterozygotes. The sensitivity of the test was 0.72 and specificity was 0.95 in one report [73]. The test has not gained wide popularity because of the potential sources of error, such as interference of substances (acetonuria, homocystinuria) or drugs with the colorimetric reaction of the test [72]. Quantitative 24-hour urinary cystine

excretion is used to confirm the diagnosis and to direct therapy. Chromatographic techniques are used to measure cystine excretion and the pH of the specimen is increased to greater than 7.5 to dissolve any cystine crystals present [74]. Since cystine excretion exhibits diurnal variation, some investigators advocate separate day and night urine collections for all cystinurics to identify periods of supersaturation masked by the 24-hour urine collection [75]. The normal daily excretion of cystine ranges from 0 to 100 μmol/g creatinine. Patients excreting more than 1.3 mmol/g creatinine (>300–400 mg/d) are considered homozygotes and those with intermediate excretion are heterozygotes [72,76]. The urine cystine supersaturation of heterozygotes is typically below that which would generate cystine crystals and stones [76]. While genetic testing can be used to establish the diagnosis, the results do not currently influence therapy and thus such assessments have no clinical utility. The diagnosis should also be suspected if a sulfur odor is emitted during laser lithotripsy of a stone.

Imaging characteristics

Most cystine stones are opaque on plain film imaging and may have a ground glass appearance. However, they tend to be less opaque than calcium oxalate stones because of a lower density and a lower effective atomic number [77]. Some are only faintly opaque. Small stones and stones in large patients may be difficult to visualize. Bhatta and colleagues [78] have classified the plain film radiographic appearance of cystine stones as having a rough external surface (R) or a smooth contour (S). The R-type stones have an organized crystal structure while the S-type are comprised of a smaller and irregular crystal structure. The latter were found to be more resistant to shock wave lithotripsy (SWL). The ultrasonographic appearance of cystine stones is similar to that of more common stone types. The use of stone attenuation coefficients measured by CT scanners employed in clinical practice is not discriminatory and thus does not permit the identification of cystine stones [79,80]. Kim and colleagues [81] have reported that the in vitro CT attenuation coefficients of R- and S-type cystine stones may discriminate these stone types, with R-type stones measuring 702 Hounsfield units (HU) (±206 HU) and S-type stones measuring 921 HU (±51 HU). The R-type stones had a higher percent of radiolucent internal voids, which may explain their susceptibility to SWL. These findings were also confirmed with a more sensitive type of CT imaging, micro-CT. The benefit of using such CT parameters for SWL selection in this cohort has not been established. Zarse and colleagues [82] have performed in vitro micro-CT studies on a number of stone types and reported that this technique is capable of identifying different stone types, including cystine. This suggests that future advances in CT imaging may permit accurate in vivo identification of stone type.

Dietary and medical therapy

Unfortunately, there have been few advances in the treatment of cystinuric patients in the last 15 years despite better understanding of the genetic components of this disease. These patients are prone to recurrence and, therefore, medical and dietary therapies are important components of management. Increased fluid intake decreases urine cystine concentration with the aim to reduce cystine in urine to less than 300 mg/L. The patient's total daily cystine excretion can be used to estimate the desired urinary volume. Dent and colleagues [83] found hydration could reduce stone activity in two thirds of cystinuric patients. Preferred fluids include a combination of mineral water and citrus juices. Mineral water is rich in bicarbonate and citrus juices contain citric acid. The consumption of such products promotes a diuresis and increases urinary pH, both of which are beneficial for these patients. A 3-L daily urine output is a general target goal for adults and 40 to 50 mL/kg every 24 hours in children. Typically, greater than 4 L/d of fluid intake daily is needed to maintain urine volumes of 3L/d [84]. Patients can monitor their specific gravity using nitrazine indicator paper, which may stimulate them to consume more fluid if the specific gravity is too high. A specific gravity of less than 1.01 is ideal [85]. Consumption of fluids before bedtime is recommended and nocturnal intake may be advisable in those patients with extremely active stone disease [86].

Cystine is derived from the essential amino acid methionine. At one time, a low methionine diet was recommended for cystinuric patients [87]. However, such a diet has a limited impact because most ingested methionine is used for protein synthesis. Methionine is derived from meat, a major source of animal protein in Western cultures.

Limited animal protein consumption has a number of general benefits for the generic stone former, including a reduction is calcium and uric acid excretion and an increase in urinary pH and citrate excretion. Therefore, moderate animal protein restriction may theoretically benefit the cystine stone former.

Since COLA transport is partially sodium dependent, sodium restriction may reduce cystine excretion [88]. In fact, a modest response to sodium restriction has been reported in this cohort [89]. Therefore, based on this response and the association with other generic stone risk reduction benefits associated with sodium restriction, limiting sodium intake to 100 mEq per day in adults is recommended. A limitation on sodium intake is supported by the report of other associated metabolic abnormalities in this cohort, including hypocitraturia and hypercalciuria [89].

Urinary pH manipulation therapy has a limited role in the management of this cohort because cystine solubility does not increase significantly until the urinary pH is 7.5 or higher. These patients have been reported to have higher urinary pH than non–stone-forming controls. That is, a mean of 6.79 as compared with 6.09 [90]. Therefore, given this and the theoretical risk of calcium phosphate stone formation when urinary pH is 7.5 or higher, there is a small therapeutic window for pH improvement [91]. Nevertheless, the patient's urinary pH should be kept between 6.5 and 7.0. For patients with a pH below this range, this range is best achieved with the administration of potassium citrate. A dose of 10 to 20 mEq twice daily in adults usually suffices. Sodium bicarbonate and sodium citrate can be used in potassium-intolerant patients. However, sodium load may perturb other stone risk factors, as previously discussed [89]. Patients should monitor their urinary pH with dipstick testing to assure maintenance in the proper range. pH manipulation has limited impact as monotherapy and other measures must be considered in those with active stone disease [83].

Dietary supplements have been administered to a small number of cystinuric patients to reduce cystine excretion. Birwe and colleagues [92] administered 5 g of ascorbic acid daily and reported a mild reduction in cystine excretion. Jaeger and colleagues [89] demonstrated that the administration of oral glutamine to a patient with cystinuria resulted in a mild decrease in cystine excretion. However, this effect disappeared when dietary sodium was restricted. These findings suggest that there is no current role for the use of such agents in the management of cystinuric patients.

The use of pharmacologic agents that promote a disulfide exchange reaction with cystine creating a more soluble compound is recommended for patients who are refractory to the aforementioned conservative measures. In addition, such agents may be considered in those who have cystine excretions above 500 mg per day or a urinary cystine concentration of 300 mg/L [91]. When prescribed, pH manipulation should be maintained together with the aforementioned dietary measures.

A review of cystine structure is warranted to better understand the mechanism of action of these drugs. Two cysteine molecules form a disulfide bond to create cystine (Fig. 2). All cystine binding agents contain a thiol group. This group dissociates to bind with one of the sulfide moieties of cystine. This thiol disulfide exchange allows these drugs to generate one molecule of cysteine and form a disulfide bond with the other cysteine. The resultant cysteine and the drug-cysteine products are more soluble in urine. The main achievable goal of this type of therapy is a reduction in stone activity because significant stone dissolution does not occur in this setting.

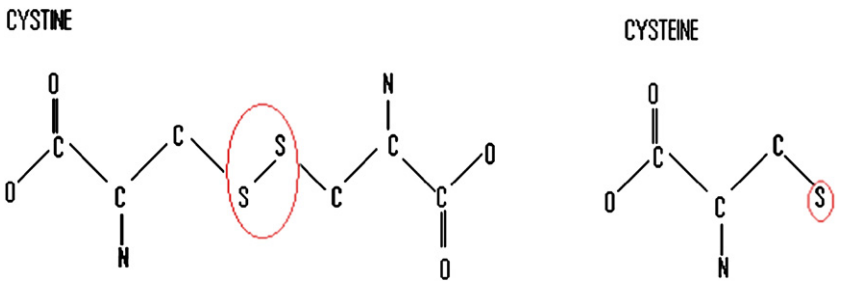

Fig. 2. Cystine and cysteine. C, carbon; N, nitrogen; O, oxygen; S, sulfur.

D-penicillamine was the first such agent used for this purpose [93]. The resultant D-penicillamine-cysteine complexes are 50 times more soluble than cystine in urine (Fig. 3) [94]. The beneficial action of this drug is dose dependent and, unfortunately, so are the associated side effects. There are numerous potential adverse effects, including rash, abnormal taste sensation, nausea, vomiting, diarrhea, anorexia, fever, arthritis, thrombocytopenia, and nephrotic range proteinuria. D-penicillamine chelates metals and heavy metal deficiencies have been reported in humans and dogs [95,96]. In addition, D-penicillamine has an antipyridoxine effect and pyridoxine supplementation (50 mg/d) is recommended during treatment [97]. The aforementioned side effects have resulted in 50% of patients discontinuing therapy [98]. This agent is not considered front-line therapy at this time but may be continued in those who are receiving and tolerating it well.

Alpha-mercapto-propionylglycine (α-MPG; tiopronin) is similar to D-penicillamine in action, but the reported toxicity is significantly less. Pak and colleagues [99] reported on a group of cystinuric patients who were treated with α-MPG or D-penicillamine and compared drug side effects. The spectrum of adverse reactions was similar in both groups. However, multiple adverse symptoms were significantly more common in those receiving D-penicillamine and a higher percentage, 69.4% versus 30.6%, discontinued therapy due to adverse side effects. This has lead to α-MPG being more commonly used. The dose ranges from 300 to 1200 mg/d in adults.

The angiotensin converting enzyme inhibitor captopril can also form a drug-cysteine complex leading to a more soluble compound. Some have reported that this agent performs as well or better than α-MPG or D-penicillamine while the opposite has been cited by others [100–105].

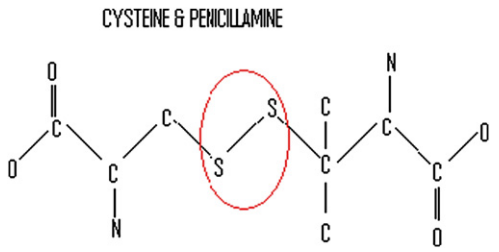

Fig. 3. Penicillamine-cysteine complex. C, carbon; N, nitrogen; O, oxygen; S, sulfur.

The use of this agent is a consideration in those who are intolerant of the other two agents or who can benefit from the blood pressure reduction induced [106]. The side effect profile is much less severe than the aforementioned thiol drugs. It should not be administered to those with hyperkalemia. The usual dose is 75 to 150 mg per day in adults.

Other drugs have been proposed for treating these patients. Bucillamine is a di-thiol drug used for treating patients with rheumatologic problems. It has been used to treat patients with cystinuria but the studies have been too limited to assess its true efficacy and tolerability in this cohort [107]. Other thiol drugs currently being evaluated for treating cystinuria include meso-2,3-dimercaptosuccinic acid [108]. Ampicillin has been shown to increase cystine solubility in vitro [109]. Ampicillin is unique in that it binds to the carboxyl group of cystine to form a soluble complex. However, the amount of ampicillin needed to produce a clinical effect may not be tolerated.

Several groups have studied the impact of thiol agents on stone activity. However, trans-study comparisons are limited because of the varying methods used to measure success. Chow and colleagues [110] compared thiol agents to hydration and urinary pH manipulation. With the latter, patients experienced 1.6 stone events per year while the addition of D-penicillamine or α-MPG reduced stones events to 0.52 per year. In patients who failed or could not tolerate the traditional thiol agents, captopril was administered, which resulted in 0.71 stone events per year. Martin and colleagues [111] noted the maintenance of a stone-free status in 44.7% of those treated with treatment consisting of hydration, urinary pH manipulation, and α-MPG. Pak and colleagues [99] reported on patients treated with α-MPG and segregated results based on whether the patients received prior treatment with D-penicillamine (group 1) or not (group 2). Stone remission occurred in 63% of group 1 and 71% of group 2 while stone formation rates were reduced 81% and 94% respectively in these cohorts. Barbey and colleagues [84] reported a 78% reduction of stone events in patients treated with α-MPG or D-penicillamine. In addition, 55% of the patients had no stone activity. The mean follow-up was 11.6 years. Worcester and colleagues [112] demonstrated that medical therapy significantly decreased the need for stone-removing procedures. However, despite this decrease, the surgical

intervention rate remained higher than that for ''routine'' stone formers.

Thiol agents should be avoided during pregnancy, especially during the first trimester, because such agents have been demonstrated to be teratogenic [113]. Gregory and colleagues [114] found that with careful medical management there was no increased risk to the cystinuric mother and her fetus during pregnancy. Pregnant patients should continue on fluid therapy and pH manipulation; the latter being accomplished with sodium bicarbonate because potassium citrate is not recommended in this setting. Some have advocated the use of thiol agents only in those pregnant patients with extremely active stone disease and only after the first trimester. However, the limited experiences with thiol use during pregnancy and the potential for teratogenic events underscore the importance of a critical risk–benefit analysis before such therapy is considered [114].

Monitoring urinary cystine excretion has been used to determine the impact of medical therapy and assess patient compliance. However, certain limitations with this approach warrant discussion. For example, in the commonly employed urinary cystine assays, no distinction is made between the thiol-drug cysteine complexes and cystine. Certain approaches have been taken to overcome this deficit. Goldfarb and colleagues [115] recently reported that a solid-phase assay could distinguish between these two substances. In this technique, a known amount of crystalline cystine is added to the patient's urine. If the urine is supersaturated, further crystals are added to the solid phase and hence more solid phase is recovered after incubation indicating that the cystine capacity is negative. A negative cystine value is thus assigned. The opposite holds true for undersaturated urine where the solid phase reduces with incubation and positive cystine capacity values are generated. The impact of thiol drugs is not obscured by this methodology.

Compliance with medical therapy and follow-up may have a profound impact on the disease course of these patients. Pareek and colleagues [116] reported that noncompliant patients were four times more likely to undergo a stone-removing procedure as compared with those who adhered to medical therapy. However, despite the potential benefits of preventive measures, a significant number of patients are noncompliant. Pietrow [117] found that over 38 months only 4 of 26 (15%) cystinuric patients on medical therapy were judged to be compliant based on a goal of maintaining urinary cystine concentration less than 300 mg/L. There are several possible reasons for this behavior pattern. A number of these patients manifest their disease during childhood and adolescence, a time when compliance may be difficult to achieve and maintain. In addition, the side effects, costs, and dosing schedules for medical therapy may also have made compliance difficult.

Renal impact

Patients with cystinuria are at risk for developing renal insufficiency and renal failure. This was initially documented by Assimos and colleagues [118] who reported that 5.8% of a cystinuric cohort had renal insufficiency. Male gender, multiple open surgical stone-removing procedures, and nephrectomy for stone-related complications were positively correlated with renal insufficiency in this series. The number of open surgical stone-removing procedures had a significant positive correlation with nephrectomy in the cystinuric population. The cystinuric cohort had a significantly higher percentage of patients who had undergone nephrectomy compared with a calcium oxalate cohort (14% versus 2.9%). Others have reported that as many as 17% of patients with cystinuria develop renal insufficiency [119]. Worcester and colleagues [112] reported that the mean creatinine clearance of cystinuric patients attending their clinic was lower than that for routine stone formers and that their creatinine clearance declined over time. Nephrolithiasis may cause renal failure in a small number of patients. Jungers and colleagues [120] reported that this was the underlying cause of end-stage renal disease (ESRD) in 2.2% of this cohort in 1998 through 2000. While struvite stone formers comprised 42.2% of these subjects, 4.4% had cystinuria. Renal transplantation is an effective treatment for those patients who develop ESRD [121]. Cystine stones do not develop in the transplant graft provided that it was not harvested from a cystinuric donor [122]. While multiple bouts of stone-related obstruction and the consequent repetitive stone-removing procedures used to treat patients with cystinuria are thought to play a major role in the development of renal dysfunction, other factors may be involved. Evan and colleagues [123] performed renal cortical and papillary biopsies in patients with cystinuria during percutaneous nephrostolithotomy and subjected this tissue to light, electron microscopy, infrared

spectroscopy, and electron diffraction. They found cystine crystals plugging the ducts of Bellini. The cells lining this area were frequently injured or absent. Many of the inner collecting ducts (IMCD) were dilated. Apatite crystals were found in the lumens of the loops of Henle and the IMCD. The papillary interstitium frequently was inflamed and there were also fibrotic changes. Glomerular obsolescence and interstitial fibrosis were detected in the cortex. This cascade of findings suggests that these patients have intranephronal obstruction, which could promote renal dysfunction.

Pediatric patients

Follow-up data on subjects who present with cystinuria during childhood are scarce. Schwartz and colleagues [124] described their experience with five cystinuric children with a mean age of 13.5 years at presentation. The children had a total of 31 stone events over a 2.4-year period. Long-term follow-up was available for only one (9.6 years) during which she had a total of six events. Her linear growth, weight, social development, and academic performance were not affected.

Stone removal

Patients with cystinuria frequently require stone-removing procedures. The type of intervention has not been demonstrated to influence recurrence at 1 and 5 years [125]. However, it is important to achieve a stone-free state because recurrent stone activity has been demonstrated to be higher in those with residual calculi [126,127].

The physio-chemical properties of cystine stones are thought to contribute to their decreased SWL fragility. This has been attributed to the organic structure of cystine, which leads to a weak acoustic interface and attenuates the impact of shock waves. However, this does not influence the effectiveness of intracorporeal lithotripsy [128,129]. There have been few reports of the treatment of cystinuric patients with SWL. The series are small, and stone stratification and outcome reporting methods differ. However, a uniform finding in these studies is that SWL appears to work best in those with smaller stones (typically $\leq$1.5 cm in largest dimension). Harada and colleagues [130] reported that 3 of 4 patients with ureteral stones less than 2 cm were rendered stone free with a mean of 1.5 treatment sessions. The other patient was lost to follow-up. Chow and Streem [125] reported that 8 of 9 such patients with upper-tract cystine stones with a mean stone surface area of 1.4 cm^2 were rendered stone free, 1 requiring another SWL treatment and another an auxiliary ureteroscopic procedure. Katz and associates [131] reported on treating 13 cystine-stone–containing renal/ureteral units with SWL (mean number of treatments: 2.3). Eight of 9 subjects with a stone less than 1.5 cm in the largest dimension were rendered stone free as compared with only 2 of 4 with larger stones. Kachel and colleagues [127] reported that SWL of 5 patients with cystine stones greater than 1.5 cm in the largest dimension resulted in all having stone fragments greater than 5 mm in the largest dimension at the end of the treatment, as compared with 1 of 10 with smaller stones. These investigators did not provide stone-free data. Slavkovic and associates [132] reported on treating 6 cystinuric children. Three had a stone volume greater than 1 cm^3 and only 1 became stone free as compared with 2 of 3 with smaller stones. Some of the previously reviewed imaging characteristics may be used to help predict SWL results in this cohort. However, they have not yet been validated. Careful patient selection for SWL is important for a variety of reasons. Patients tend to start having stone events at a young age. They are prone to recurrence and are subject to repetitive stone-removing procedures. Finally, the cumulative effect of multiple SWL procedures in such patients is unknown.

Retrograde ureteroscopic stone removal can be effective in patients harboring cystine stones less than 3 cm in the largest dimension. These stones are readily fragmented with the holmium: yttrium-aluminum-garnet (holmium:YAG) laser and with pneumatic and electrohydraulic lithotripsy devices. The development of better grasping devices, stone baskets, and flexible ureteroscopes, and the employment of a ureteral access sheath have facilitated this approach. Rudnick and colleagues [133] reported on using this approach in six cystinuric patients with renal stones 1.5 to 3.0 cm in their largest dimension. Five of six were either rendered stone free or had residual stone fragments less than 3 mm in the largest dimension. The other patient refused further therapy. Kourambas and colleagues [134] reported on this approach in three patients with cystine renal calculi (mean size: 2.2 cm in the largest dimension) and two were rendered stone free. Retrograde ureteroscopy may be the best

approach for treating cystinuric patients with stones of this size.

Percutaneous nephrostolithotomy (PCNL) is the preferred approach for treating cystinuric patients with larger renal calculi. Results achieved are similar to those with other stone types. Chow and Streem [125] reported on using PCNL to remove cystine stones from 41 renal units with a mean stone surface area of 7.97 cm^2. Thirty-five (85.4%) were rendered stone free and only 4 (9.8%) required repeat or auxiliary interventions.

Contact chemolysis via percutaneous nephrostomy was once commonly used for treating patients with cystine renal calculi. However, the many advances in endourologic surgery and the many days needed to achieve successful chemolysis have relegated this approach to a historical bin. Acetylcysteine, D-penicillamine, tromethamine E, and sodium bicarbonate have been used for chemolysis. Burns and colleagues [135] used in vitro studies to conclude that acetylcysteine was the optimal agent because it could increase urinary pH to 10. In contrast, Dretler and colleagues [129] found tromethamine E to be the superior agent. Saltzman and Gittes [136] found that acetylcysteine and tromethamine E had similar efficacy. Some have reported that initially treating these patients with SWL increases the stone surface area and facilitates chemolysis [137,138].

Open stone surgery is not required in most cystinuric patients and is only a consideration in those who have extremely large and complex staghorn calculi. The reported association with open surgery and risk of renal functional and anatomic loss in these patients is another reason to avoid this approach [118]. Bilateral ileal ureter replacement is also rarely indicated and is an option for patients who have extremely active cystine stone formation, who are refractory or intolerant of medical therapy, and who need frequent stone-removing procedures [139]. Open or laparoscopic nephrectomy may be required in those who have nonfunctioning kidneys.

Patient follow-up

The high risk of recurrence and the potential for renal dysfunction over time make close follow-up of cystinuric patients mandatory. Radiographic determination of stone activity is necessary. Renal ultrasonography is an ideal modality because the patients are not subject to repetitive radiation exposure. It is reasonably sensitive for detecting renal stones and very accurate for detecting renal atrophy and hydronephrosis. Other imaging modalities can be used when indicated. The follow-up interval is indexed according to stone activity and is usually every 6 months in those with inactive or minimally active stone disease but an interval of 3 months or less may be required in those with accelerated stone formation.

Patients on medical therapy require periodic blood testing. Serum electrolytes, serum urea nitrogen, and creatinine should be checked at least every 6 to 12 months in those treated with urinary pH manipulation. A complete blood count, serum comprehensive metabolic profile, and urinary dipstick test for protein should be assessed at least every 6 months in those being treated with thiol agents. Urinary pH should also be checked at these intervals, especially in those on pH manipulation regimens. Urinary cystine capacity testing may be used in those with significant stone activity because it may help identify those who are noncompliant and also facilitate dose changes in those receiving thiol agents.

The authors have embraced a proactive approach regarding the surgical removal of cystine stones identified during follow-up. If the patients have an aggregate stone size of 1 to 3 cm in the largest dimension, the authors advocate ureteroscopic stone removal, even if asymptomatic. PCNL is reserved for those with larger stone burden. The authors feel that this helps maintain patients in a minimally invasive treatment domain.

Summary

Patients with cystinuria should be considered as having complex stone disease. Treatment success is based on close follow-up, effective preventive and stone-removing strategies, and patient compliance. Compliance with medical therapy and follow-up needs to be improved and better strategies to promote this are required. The genetic defects causing this disorder have been well characterized and this should facilitate development of better and, the authors hope, more tolerable medications for this cohort. Cystinuria is considered an "orphan disease." As a consequence, the pharmaceutical industry has not been enthusiastic about taking on efforts to attack it. Perhaps the recent establishment of an advocacy group, the International Cystinuria Foundation, will help in this regard. This disease

is potentially curable with gene therapy. The development of techniques for gene delivery to proximal tubular cells is encouraging and is an important initial step in achieving this goal [140].

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Pathophysiology and Management of Infectious Staghorn Calculi

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Staghorn calculi are large, branched stones that fill all or part of the renal pelvis and extend into the majority of the renal calices. While "staghorn" describes configuration rather than composition, most staghorn stones consist of pure magnesium ammonium phosphate (struvite) or a mixture of struvite and calcium carbonate apatite. These stones are also referred to as infection stones because of their strong association with urinary tract infection caused by urea-splitting organisms. Stones composed of uric acid or cystine may also grow in a staghorn configuration, but this only rarely occurs with calcium oxalate or phosphate stones. If left untreated, staghorn calculi may lead to deterioration of renal function, end-stage renal disease, and life-threatening urosepsis [1]. Recently, the American Urological Association (AUA) Nephrolithiasis Guidelines Panel conducted a critical meta-analysis of the existing literature to determine the optimal management for staghorn calculi. This article briefly discusses the pathophysiology of staghorn calculi and, based on the panel's recommendations, examines the alternative medical treatments (eg, chemolysis) and surgical treatments (eg, shock wave lithotripsy (SWL), open surgery, ureteroscopy, and percutaneous nephrolithotomy (PCNL)) available for staghorn patients.

Pathogenesis

Struvite calculi have plagued man since the beginning of civilization, dating back approximately 7000 years ago to the era of the ancient Egyptians [2]. In 387 BC Hippocrates first documented an association between urinary tract infections and urinary stones [3]. Over 2000 years later in 1845, a Swedish geologist named Ulex discovered magnesium ammonium phosphate in bat guano and named the substance "struvite" after his mentor, the Russian diplomat Baron H.C.G. von Struve. Struvite calculi are typically referred to as infection stones because of their strong association with urinary tract infections with urease-producing bacteria. The most important urease producers include *Proteus*, *Klebsiella*, *Pseudomonas*, and *Staphylococcus* species [4]. However, the most ubiquitous uropathogen, *Escherichia coli*, only rarely produces urease and thus is an infrequent cause of staghorn calculi [3]. Infection stones are characterized by their large size and exceptionally rapid growth. In fact, 4 to 6 weeks may be sufficient time for an infection stone to form and subsequently develop into a staghorn stone that involves the entire renal pelvis and calices [5]. Most commonly, staghorn stones are composed of a mixture of struvite (magnesium ammonium phosphate) and calcium carbonate apatite. Normal urine is undersaturated with ammonium phosphate, and struvite stones only form when ammonia production is elevated and urine pH is increased, thereby decreasing the solubility of phosphate [6]. This occurs when urinary tract infection with a urease-producing organism is present (Fig. 1 (*A*)) [3,5]. First, bacteria-produced urease breaks down urinary urea into ammonia plus carbon dioxide, which then hydrolyzes to ammonium ions and bicarbonate. Binding to available cations then produces carbonate apatite and magnesium ammonium phosphate. Carbonate apatite begins to crystallize at a urine pH greater than or equal

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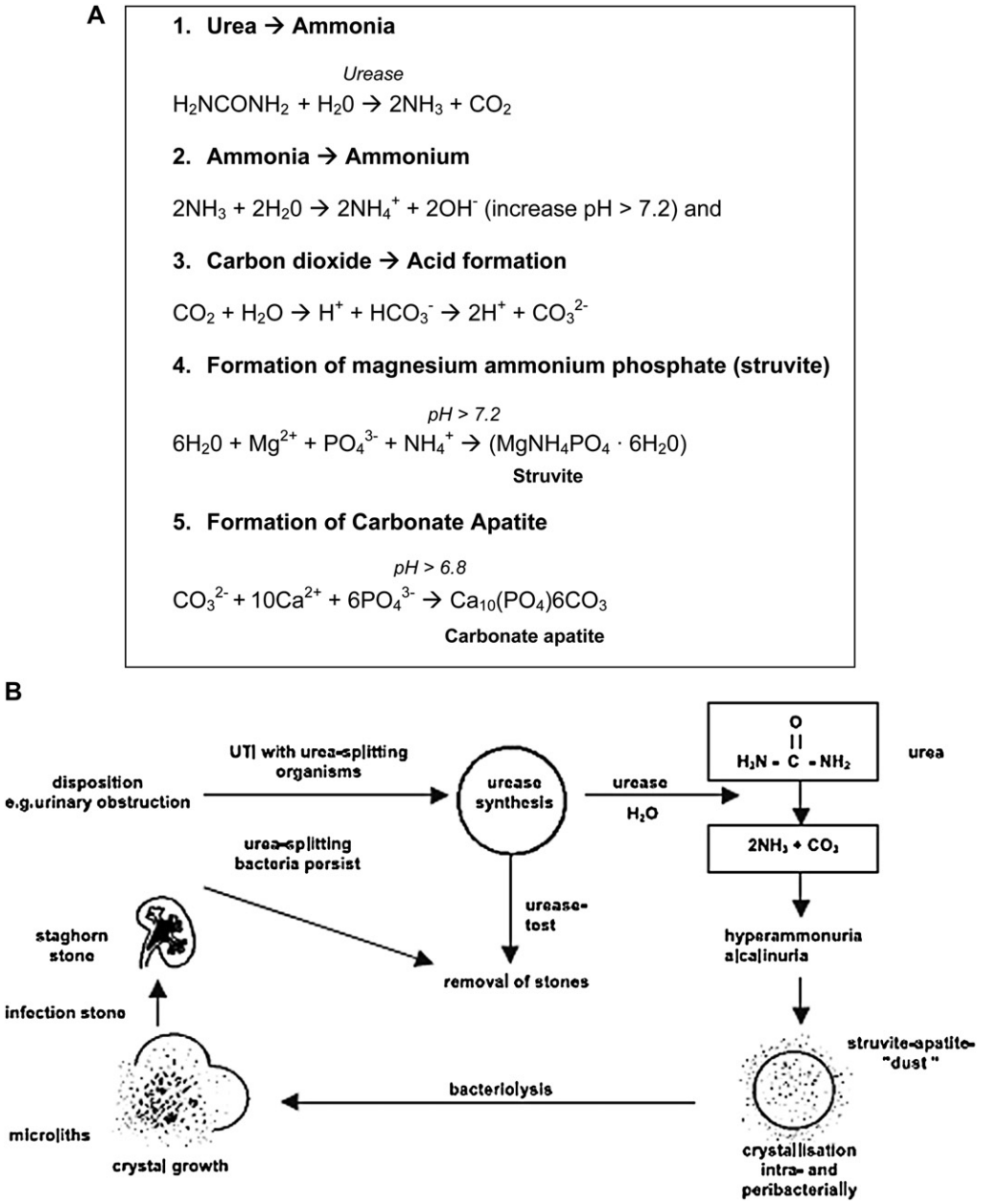

Fig. 1. (*A*) Pathogenesis of struvite–carbonate-apatite stone formation. (*B*) Pathogenesis of infection stone. UTI, urinary tract infection. (*B adapted from* Bichler KH, Eipper E, Nabor K, et al. Urinary infection stones. Int J Antimicrob Agents 2002;19(6):491; with permission from the American Chemical Society.)

to 6.8 while struvite precipitates only at a pH greater than or equal to 7.2 [5]. Citrate normally forms complexes with calcium (Ca^{2+}) and magnesium (Mg^{2+}), but this protective effect is lost in infective conditions because the high concentrations of bacteria metabolize the citrate [6].

The pathogenesis of struvite stone formation is illustrated in Fig 1 (*B*) [5]. ''Struvite–apatite dust'' is formed around the bacteria and facilitates crystal growth. Crystallization may occur both intra- and peribacterially. Apatite crystals grow inside the bacteria and, after bacteriolysis, microliths

formed may serve as a nidus for stone formation. Crystals growing peribacterially may settle on the bacteria and form a phosphate cover, and bacteria enclosed within the stone serve as a source of recurrent infections. Stone propagation occurs extremely quickly because of the constant supply of reactants and the alkaline milieu, in which struvite and apatite are poorly soluble. Additional pathogenic factors include the formation of an exopolysaccharide biofilm [7]. Inflammation also leads to increased mucus secretion, which in turn acts as a matrix for crystal aggregation. Finally, ammonia induces damage to the surrounding protective urothelial glycosaminoglycan layer and thus increases bacterial adherence to the transitional epithelium [3].

Struvite stone formation typically occurs in patients with recurrent urinary tract infection and retained urine. Predisposing factors include urinary tract obstruction, chronic indwelling catheter, urinary diversion, and neurogenic voiding dysfunction [5]. Most women with struvite stones have a normal urinary calcium excretion and likely form pure struvite stones de novo after a urinary tract infection. Pure struvite stones also form in other patients prone to infection, such as those with a ureteral diversion or neurogenic bladder. Meanwhile, mixed stones made up of struvite and calcium carbonate apatite occur in some women and most men. Presumably these hypercalciuric patients begin with calcium-oxalate stone formation and develop superimposed infection with struvite deposition [8–10].

Clinical manifestations, diagnosis, and natural history

As previously mentioned, struvite stones may grow rapidly over a period of weeks to months and, if left untreated or inadequately treated, may progress into staghorn calculi. Unlike patients with small calcium stones, infection calculi tend to be insidious and chronic in formation and typically do not present with the acute renal colic frequently seen with an obstructing ureteral stone. Instead, staghorn calculi usually develop in the renal collecting system and remain there until a diagnosis is made. While many patients are asymptomatic, others may present with recurrent urinary tract infection, gross hematuria, vague abdominal pain, fever, and urosepsis [2]. Urinalysis reveals an alkaline urine pH (>7.0) and frequently magnesium ammonium phosphate crystals. Staghorn calculi are usually readily detectable on abdominal plain films as faintly radiopaque stones. However, CT has emerged as the imaging study of choice for renal calculi in general and is particularly useful in preoperative planning for staghorn calculi. Renal scintigraphy may be indicated to assess differential renal function in those patients with chronic pyelonephritis and/or obstruction.

The natural history of staghorn calculus disease is one of progressive morbidity and mortality. The rationale for an aggressive therapeutic approach has long been recognized. In 1976, Blandy and Singh [11] reported an alarmingly high 10-year mortality rate of 28% with conservative treatment while the corresponding rate associated with surgical management was 7.2%. Subsequently, Koga and colleagues [12] reviewed outcomes in 167 staghorn stone patients with a mean follow-up of 7.8 years. Compared with surgical treatment, conservative treatment was associated with a significantly higher risk of chronic renal failure (36%), higher morbidity, and higher mortality rates. Most recently, Teichman and colleagues [13] (1995) conducted a retrospective review of 177 consecutive staghorn patients with an average follow-up of 7.7 years. Overall rate of renal deterioration was 28%. No patient with complete stone clearance died of renal-related causes versus 67% of those who declined treatment. Therefore, untreated staghorn calculi almost certainly destroy the kidney and ultimately pose a significant mortality risk secondary to end-stage renal disease as well as septic complications [9].

Treatment

Staghorn calculi are primarily managed surgically with complete stone clearance as the goal of treatment. In selected patients who are otherwise poor surgical candidates, dissolution therapy remains an alternative. Dissolution therapy may also be useful following surgical therapy for treatment of residual fragments. Currently, several surgical treatment options exist for staghorn calculi, including SWL, ureteroscopy, PCNL, open surgery, and combination therapy. Herein the authors describe these options with an emphasis on PCNL, the first-line treatment for most patients with staghorn calculi.

Dissolution therapy

Chemolysis, or dissolution therapy, of struvite stones has been around for over 70 years. In 1932

Keyser attempted dissolution of stones by retrograde infusion [14], and in 1938 Hellstrom dissolved a renal stone using boric acid and permanganate [5]. Subsequently in 1943 Suby and Albright developed Suby's solution, which was later modified to Suby's solution G, consisting of citric acid, magnesium oxide, and sodium carbonate [15]. The addition of magnesium decreased mucosal irritability and enhanced stone dissolution by undergoing ion exchange with calcium. Using a nephrostomy tube or ureteral catheter, Suby's G may be instilled to dissolve renal stones composed of calcium carbonate apatite and struvite. Additional chemolytic agents include hemiacidrin. Hemiacidrin is similar in composition to Suby's G but also contains D-gluconic acid [5]. Acids provide hydrogen ions and citrate to form soluble complexes with the calcium (calcium citrate) and phosphate (phosphoric acid) components of the calculus [14]. The acidic pH of these solutions is also responsible for their clinical effectiveness because the solubility of struvite calculi is significantly increased at pH below 5.5. Mulvaney [16] published the first reports using hemiacidrin to dissolve infection stones in 9 of 13 patients, either partially or completely. Due to early reports of complications, namely sepsis and electrolyte abnormalities, the Food and Drug Administration (FDA) withdrew approval for the use of hemiacidrin for renal irrigation in 1962 [15]. Nemoy and Stamey [17] investigated reports of side effects and deaths due to hemiacidrin therapy and concluded that treatment is contraindicated in the presence of urinary tract infection. Moreover, the investigators noted that therapy should not be performed if renal colic exists and serum magnesium levels should be closely monitored to prevent hypermagnesemia, a potentially fatal complication. While modifications in techniques have improved safety, chemolysis is risky. Low intrarenal pressures must be maintained ($<$25 cm water), serum magnesium and phosphate must be monitored closely, and the urine must be sterile [15]. Accordingly, broad-spectrum antibiotics are given before, during, and for approximately 10 days after completion of treatment.

In a contemporary series by Tiselius and colleagues [18], 118 patients with staghorn stones underwent combined SWL and percutaneous chemolysis with hemiacidrin and achieved an overall stone-free rate of 60%. All treatments were performed without general or regional anesthesia. Although the investigators reported a very low complication rate, most patients required a long hospital stay, with a mean of 32 days. The investigators concluded that minimally invasive treatment of staghorn stones with SWL and chemolysis is a feasible alternative in high-risk patients and when other procedures are impossible. Other researchers have investigated the effectiveness of initial chemolytic dissolution before surgical treatment. Using an in vitro model, Heimbach and colleagues [4] showed that stone comminution with SWL can be improved by varying the physical properties of infectious stones through initial chemolytic treatment with Suby G solution. Although promising in vitro, clinical trials have not yet been performed.

Due to associated costs, prolonged hospital stay, and risk of complications, chemolysis has a limited role in the treatment of staghorn stones. Furthermore, advances in endourological techniques have yielded well-proven, superior outcomes compared with chemolysis. Though largely ineffective as monotherapy for staghorn calculi, chemolysis may be an attractive adjunct following surgical management to treat residual fragments and decrease stone recurrence.

Surgical therapy

Shock wave lithotripsy

While SWL is the most common treatment for renal calculi, it is not usually used as monotherapy in the treatment of staghorn calculi because of low stone-free rates, which range from 18% to 67% [19–23]. Additionally, SWL for staghorn calculi may be associated with significant potential morbidity, including steinstrasse, renal colic, sepsis, and perinephric hematoma. However, SWL is the least invasive of the stone treatments and should be considered in combination with other treatments and in select cases as monotherapy. The section on PCNL and "sandwich therapy" discusses combination therapy incorporating SWL.

El-Assmy and colleagues [24] retrospectively reviewed 92 patients who underwent SWL monotherapy for partial staghorn calculi to determine predictors of treatment success and long-term clinical outcome. Using a Dornier MFL 500 lithotripter, they achieved complete stone fragmentation in 95.7% of patients, with 86% of patients requiring multiple SWL treatments (mean: 2; range: 1–6). At 3 months, overall stone-free rate was 60% (55/92), with only increasing stone

surface area significantly affecting complete clearance of fragments. Significant complications occurred in 12 patients (13%): 2 developed high-grade fever and 10 (10.8%) had renal obstruction caused by steinstrasse. Unplanned secondary procedures were required in 18.4% of patients. Long-term follow-up (mean: 7.5 years; range: 2–16 years) in 49 patients demonstrated a stone-free rate of 59% (29/49). These long-term results are similar to those found by Mattelaer and colleagues [25], who reported a stone-free rate of 60% after a mean follow-up of 72.4 months in 58 patients with staghorn calculi. In terms of stone surface area and SWL success, El-Assmy's findings are also consistent with those previously reported by Lam and colleagues [22]. Among a subgroup of 12 patients with a nondilated collecting system and a stone surface area less than 380 mm^2, SWL monotherapy yielded a 91.7% stone-free rate.

The pediatric population seems to be particularly well suited for SWL monotherapy for staghorn calculi. This is thought to be related to a relatively limited stone burden, better shock wave transmission, and a more compliant ureter for the passage of stone fragments. Orsola and colleagues [26] performed SWL monotherapy for staghorn calculi in 14 children (age 14 months to 13 years) and reported a 73.3% stone-free rate after an average of two SWL sessions. Lottmann and colleagues [27] demonstrated similarly high stone-free rates of 85.7% in pediatric patients 5.5 months to 2 years of age. No major complications occurred and follow-up dimercaptosuccinic acid scintigraphy revealed no decrease in differential renal function in this pediatric population.

Thus, final guideline recommendations concerning SWL and staghorn calculi are that it should be reserved for selected patients. In summary, adult patients with low-volume staghorn calculi in a nondilated collecting system and pediatric patients may represent good candidates for SWL monotherapy.

Ureteroscopy

Flexible ureteroscopy has not traditionally been used in the treatment of staghorn calculi. However, with improvements in ureteroscope technology (eg, greater deflectibility, more suitable working channel sizes, and greater durability) and the introduction of the holmium:yttrium-aluminum-garnet (holmium:YAG) laser and nitinol baskets, this approach has gained popularity in selected patients as a primary or adjunctive treatment.

Complex branched staghorn calculi can be difficult to treat percutaneously in one sitting through one access tract even with the combination of rigid and flexible instruments. Therefore, multiple access tracts are sometimes necessary, which increase the risks of potential operative morbidity and postoperative discomfort. As such, flexible ureteroscopy can be used in combination with PCNL to gain access to the entire stone and avoid multiple access tracts. In treating seven patients who had multiple or branched renal calculi and who would otherwise have been treated with PCNL, Marguet and colleagues [28] used multiple tracts with the combined approach. Patients in this series were initially treated with flexible ureteroscopy in the supine position, followed by holmium laser lithotripsy or basket extraction of peripheral caliceal calculi. Patients were then repositioned prone for standard PCNL. When comparing these patients to a group of similar patients undergoing multiple-access PNCL, there was little difference in operative time (142 versus 166 minutes, $P = .36$) and there was less blood loss among patients treated with the combined approach (79 versus 345 mL, $P < .05$). Five of seven patients were stone-free 3 months postoperatively, with two patients demonstrating asymptomatic residual fragments measuring less than 3 mm in their longest dimension. Similarly, Landman and colleagues [29] treated nine staghorn calculi (six complete, six partial) with combined flexible ureteroscopy and PCNL via a single lower-pole access. In contrast to the technique used by Marguet, patients were prone for the entire procedure and retrograde flexible ureteroscopy and antegrade PCNL were performed simultaneously. No major and four (44%) minor complications occurred. Complete stone clearance was achieved in seven of nine patients (78%) using a single nephrostomy tract. Ureteral access sheaths were used in both the Marguet and Landman series to aid in the retrograde removal of small fragments.

To date, there have been no published series of flexible ureteroscopy as monotherapy for staghorn calculi. At the authors' institution, a number of patients with multiple comorbidities that precluded more invasive interventions have been successfully treated with staged flexible ureteroscopy for partial staghorn calculi.

Anatrophic nephrolithotomy

Anatrophic nephrolithotomy (AN) was first popularized by Smith and Boyce in 1968 [30]. In

their classic description, the boundary of the segmental renal blood supply was identified by clamping the posterior arterial branch and injecting methylene blue. The kidney was then incised along the demarcated avascular plane between the anterior and posterior blood supply. Following stone removal, infundibular reconstruction and formal closure of the entire collecting system was performed.

The indications for AN have continuously narrowed over the past several decades with the emergence of PCNL and SWL. Nevertheless, this procedure still has a place in the urologist's armamentarium for certain patients. Paik and colleagues [31] reviewed 780 procedures performed for stone removal or fragmentation during a 5-year (1991–1995) period and found 42 (5.4%) were performed open. Fourteen of these patients underwent AN for large complete or near-complete staghorn calculi filling a majority or all of the renal collecting system. AN operative time averaged 216 minutes, estimated blood loss was 750 mL, and hospital stay was 5.8 days. There were three minor complications and the postoperative stone-free rate was 93%.

Multiple series have demonstrated AN to be superior to less invasive therapies in select cases of staghorn calculi. Assimos and colleagues [32] demonstrated that in patients with staghorn calculi and any degree of caliceal dilatation, AN resulted in a stone-free rate of 89% to 100%, compared with 12% to 25% with PCNL with or without SWL. Additionally, AN patients had shorter hospital stays and lower costs. Similarly, in a series of patients with partial or complete staghorn calculi, Esen and colleagues [23] reported a stone-free rate of 80% for AN versus 50% for PCNL plus SWL.

Morey and colleagues [33] described a modified AN in 15 patients with 16 full staghorn calculi deemed too complex for endoscopic treatment. Their technique differed from the classic description by Smith and Boyce in that the parenchymal incision was made 1 to 2 cm posterior to the lateral kidney surface without segmental vascular dissection, the collecting system was not reconstructed, and closure was accomplished only with a posterior renal capsular flap. Stone-free status was obtained in 13 of 16 cases (81%) and no patient suffered major morbidity. Notably, nuclear renography in 13 cases with dimercaptosuccinic acid revealed minimal change in postoperative ipsilateral renal function (38% versus 42% preoperatively). In a slightly larger series of 24 patients (33 procedures), Melissourgos and colleagues [34] reported similar outcomes also using a modified AN for complete staghorn calculi with a stone-free rate of 83.3%. Mean hospital stay was 8.2 days (range: 7–12 days). Renal function remained unchanged or slightly improved in 15 patients, while a slight worsening of renal function was noted in 9 patients, from an average 39% before to 35% after AN.

The AUA guidelines panel reports on the indications for open stone surgery as follows: ''Open surgery (AN) is an appropriate treatment alternative in unusual situations when a struvite staghorn calculus is not expected to be removable by a reasonable number of percutaneous lithotripsy and/or SWL procedures'' [1]. Treatment with PCNL with or without SWL has been shown to be increasingly less successful when the stone surface area is greater than 2500 mm^2 and there is worsening collecting system dilatation [22]. Furthermore, anatomic abnormalities, infundibular stenosis, poorly compliant patients, and morbid obesity may be indications favoring AN as the treatment of choice [35].

Percutaneous nephrolithotomy

First described by Fernstrom and Johannson in 1976, PCNL was initially used for the treatment of small renal calculi. However, with the advent of electrohydraulic and ultrasonic lithotripsy, PCNL was extended to include staghorn calculi [36,37]. Based on its superior efficacy and low morbidity, PCNL has now emerged as the treatment of choice for the management of staghorn calculi.

Early studies comparing PCNL and AN showed that PCNL is less expensive, is associated with a decreased need for blood transfusion, requires a shorter hospital stay, and allows a more rapid return to work [38]. Around the time of its introduction, retrospective series reported stone-free rates between 63% and 90% using PCNL monotherapy. This wide variability was likely secondary to differences in stone burden and in percutaneous techniques. In a large retrospective review of 878 renal units containing staghorn calculi treated with PCNL over a 9-year period, Chibber [39] found an overall complete clearance rate of 93%, with 98.5% for partial calculi and 71% for complete staghorn calculi. Stone load was greater than 3 cm in all cases. Although the morbidity was slightly higher than SWL monotherapy, the complication rate was still acceptably low at 4%.

While PCNL has become increasingly popular as the primary treatment for stone removal over

the past 20 years, only two prospective, randomized trials have been conducted to critically evaluate outcomes with PCNL-based techniques. In the first reported study, Meretyk and colleagues [19] (1997) included 50 kidneys containing staghorn calculi. Twenty-seven renal units were treated with SWL monotherapy and 23 were treated with PCNL (with or without SWL). Stone-free rates were more than three times greater in the PCNL group compared with the SWL group (74% versus 22%, $P = .0005$). Furthermore, significantly more complications and unplanned ancillary procedures were noted in the SWL group than in the PCNL group. The investigators concluded that PCNL-based therapy was superior to SWL monotherapy in the treatment of staghorn calculi.

Based on findings of the Meretyk trial and an extensive meta-analysis by the AUA guidelines panel, the 2004 clinical practice guideline report was developed and parallels the findings and recommendations of the 1994 report. According to the 2004 review by the panel, PCNL should be the first-line treatment for most patients [1]. The panel reported a stone-free rate of 78% (74%–83%) using PCNL monotherapy for the treatment of complete staghorn calculi, which was equivalent to open surgery (71%) and superior to both SWL monotherapy (54%) and SWL plus PCNL (66%). Despite differences in stone-free rates, complications were similar for all treatment modalities: open (13%), PCNL monotherapy (18%), SWL (19%), and PCNL plus SWL (17%). PCNL-related transfusion rates ranged from 14% to 24%. The need for further PCNL procedures varied from 10% for simpler stones to up to 50% for more complex stones. On average, patients required 1.3 PCNL procedures.

Since publication of the 2004 panel review, Al-Kohlany and colleagues [40] published the second prospective, randomized trial examining PCNL for the management of staghorn calculi. A total of 79 patients with 88 complete staghorn stones were randomized to PCNL (43) or open surgery (45). Both treatment groups were equivalent in regard to stone-free rates at the time of discharge (49% versus 66%) and at longer than 3 months follow-up (74% versus 82%). With stone-free rates approaching those of open surgery, PCNL offers several advantages, including a lower transfusion rate (14% versus 33%), a lower intraoperative complication rate (16% versus 38%), a shorter operative time (127 versus 204 minutes), a shorter hospital stay (10.0 versus 6.4 days), and an earlier return to work (2.5 versus 4.1 weeks).

To further improve outcomes with PCNL, several technical refinements have been advocated for staghorn stones, including multiple percutaneous accesses and the use of flexible nephroscopy. Flexible nephroscopy is commonly used to facilitate stone clearance because the sharp angles of the pelvicaliceal system are difficult to maneuver with rigid nephroscopy. Wong and Leveillee [41] described a series of patients who underwent PCNL for complex staghorn calculi, including 45 complete and 7 partial staghorn calculi, with a mean stone burden of 6.7 cm (range 5.0–10.0 cm). The investigators reported that use of flexible nephroscopy with holmium:YAG laser lithotripsy and nitinol basket stone extraction rendered staghorn-containing renal units stone-free in a mean of 1.6 procedures. Of the 45 renal units treated through a single percutaneous access, 43 (95%) were rendered stone-free. No complications occurred secondary to use of the holmium:YAG laser. Based on these favorable results, the authors support a staged procedure via a single upper-pole percutaneous access using flexible nephroscopy and the holmium:YAG laser.

Given the complex branching nature of staghorn calculi, some investigators prefer multitract PCNL to achieve complete stone clearance. Aron and colleagues [42] reviewed their experience in 121 renal units (103 patients) with large complete staghorn renal calculi and with the majority of patients requiring three or four tracts. All 121 units had one upper polar access tract, of which 92 (76%) were supracostal. Complications included blood transfusion (18), pseudoaneurysm (2), fever (22), septic shock (1), and hydrothorax (3). Using this aggressive approach, multitract PCNL monotherapy achieved an 84% complete clearance rate that improved to 94% with SWL in 8 renal units with small residual fragments. However, multiple tracts with multiple nephrostomy tubes may add to increased postoperative patient discomfort, increased hospital stay, multiple scar formation, and, ultimately, increased morbidity and cost.

As an alternative to multitract PCNL, other investigators have described angular percutaneous access, a novel triangulation technique that involves a single subcostal skin incision with multiple angular punctures to approach the superior, middle, and lower poles of the kidney. Liatsikos and colleagues [43] reviewed 100 patients with staghorn calculi (90 complete, 10 partial)

managed using the triangulation technique and achieved a high stone clearance rate of 87% in a single session by PCNL alone. Overall complications occurred in 7% of patients, with one excessive hemorrhage requiring embolization and one hydrothorax. Considering the acceptable complicate rate, high stone clearance (87%), short hospital stay (4.6 days), and single-session treatment, the authors endorse angular access as the treatment of choice for staghorn calculi.

Residual stone burden following PCNL is particularly problematic because fragments may propagate and serve as a source for recurrent urinary tract infection. Though commonly used for the management of residual fragments, ''second-look'' PCNL has not been well studied. In a recently published retrospective review by Davol and colleagues [44], PCNL was effective for single-stage treatment of large renal calculi. Aggressive stone clearance obviated the need for routine second-look nephroscopy. Factors associated with an increased risk of residual or recurrent calculi included younger patient age and the presence of a staghorn calculus. According to the investigators, the excellent stone-free rates achieved suggest that routine second-look nephroscopy may not be necessary for most patients undergoing PCNL.

In summary, PCNL is a safe, effective, and minimally invasive approach for the management of staghorn calculi. PCNL remains the treatment of choice for staghorn calculi based on its higher stone-free rates and lower complication rates.

Combination therapy

Combination therapy refers to the use of multiple endourological techniques for the treatment of staghorn calculi. The rationale behind combination therapy is that exploiting the advantages of multiple techniques will facilitate stone clearance. PCNL allows for the rapid removal of a high volume of easily accessible stone as well as accurate assessment of stone-free status. Oftentimes, however, small residual fragments adjacent to the nephrostomy tract cannot be accessed or safely approached. SWL is particularly helpful in such cases. The most commonly used regimen of combination therapy is ''sandwich'' therapy. Classically described by Streem and colleagues [45] in 1987, sandwich therapy, or PCNL–SWL–PCNL, consists of primary percutaneous debulking followed by SWL of residual inaccessible infundibulo-calcyceal stone extensions or fragments. Finally, a secondary percutaneous extraction is performed. Streem and colleagues [46] (1997) subsequently reviewed their series of 100 patients treated with sandwich therapy and reported a stone-free rate of only 63%, with a hospital stay of 12.2 days and transfusion rate of 14%. Though well popularized in the 1990s, combination therapy is less commonly used today due to its inferior results compared with PCNL monotherapy. For example, Schulze and colleagues [47] found that 76.7% patients were stone-free after combination therapy and this decreased to 61.1% at the end of follow-up due to recurrence. In a larger series of 343 cases of staghorn calculi by Lam and colleagues [48], PCNL alone achieved a stone-free rate of 91% compared with 78.1% to 79.1% with the combination approach. More recently, a review by Merhej and colleagues [49] of 101 patients with staghorn calculi showed that a combination regimen produced a stone-free rate of 67%, consistent with prior findings. According to the AUA guidelines panel, percutaneous nephroscopy should be the last procedure for most patients undergoing combination therapy. In their report, the panel emphasizes that residual fragments are unlikely to be completely removed following SWL unless repeat PCNL is then performed [1]. In fact, Segura and colleagues [50] reported a remarkably low stone-free rate of 23% when SWL was the last combination procedure.

If combination sandwich therapy is undertaken, it must essentially be considered as a percutaneous-based therapy. That is, SWL should be used only as an adjunct to minimize the number of access tracts. With liberal use of flexible nephroscopy and ureteroscopy, improved PCNL techniques have provided near-complete stone removal at the time of the initial procedure, diminishing or eliminating the need for SWL [1,9].

Prevention

Following primary surgical treatment of staghorn calculi, medical management may be useful in preventing stone recurrence. Strategies include dietary modification and oral therapies that acidify the urine (pH $<$ 7.19), inhibit ammonia production (urease inhibitor), and sterilize the urine.

Dietary modification

Dietary manipulations for preventing struvite calculi have not gained widespread use. However, the goals would include the reduction in urinary

phosphate, magnesium, and ammonia. In 1945, Shorr [51] proposed a regimen of a low-phosphorous, low-calcium diet in conjunction with oral estrogens and aluminum hydroxide gel. The oral estrogens act to decrease calcium excretion by their effects on bone mineralization. Aluminum hydroxide gel binds phosphate in the gut and is excreted entirely in the stool as aluminum phosphate. The net result of these manipulations is less substrate excretion in the urine to bind surrounding lithogenic molecules. Subsequent clinical studies using this approach demonstrated partial or complete stone dissolution in 23% of patients and stone growth in only 10% [52]. In a long-term follow-up study by Lavengood and Marshall [53], patients maintained on the Shorr regimen following nephrolithotomy had a 10% recurrence rate compared with 30% in patients who did not follow the regimen. Lotz and colleagues [54] reported several metabolic abnormalities associated with the use of aluminum hydroxide, including constipation, anorexia, lethargy, bone pain, and hypercalciuria. In summary, with limited evidence and significant side effects associated with substrate depletion, this treatment regimen cannot be recommended. However, avoidance of foods and vitamin supplements high in phosphorus and magnesium would be reasonable.

Urinary acidification

The solubility of struvite stones is highly dependent on urinary pH and crystallization occurs only between 7.2 and 8.4. In vitro studies have demonstrated that acidification of struvite stones to pH less than 6.5 increases the solubility of stones and can be used to dissolve stones. Such agents as ascorbic acid and ammonium chloride have been unsuccessful in producing long-term urinary acidification. Moreover, ascorbic acid may actually promote urinary alkalinization through increased citrate production [2]. However, acidification of urine has been demonstrated with an oral dose of the amino acid L-methionine, which is metabolized to sulfate and hydrogen ions via L-cysteine. A single dose of 1500 mg of L-methionine caused a reduction of the urinary pH values to 6.0 to 6.2 [6]. Jacobs and colleagues [55] demonstrated in vitro that the dissolution rates of struvite stones in artificial urine rose with a decreasing pH value. Specifically, the diminution of the pH value by 0.75 units from 6.5 to 5.75 increased the dissolution rate by greater than 35%. The authors hypothesize that oral L-methionine may be used to assist in the dissolution of struvite stones in vivo. Though in vitro studies are encouraging, additional studies are needed to examine the utility and safety of oral L-methionine in humans.

Urease inhibitors

Urease inhibitors are oral agents that inhibit stone growth by blocking the cascade of events that lead to supersaturation of struvite precursors. First identified in 1964, acetohydroxamic acid (AHA) is the only FDA-approved urease inhibitor today [15]. In addition to causing an irreversible inhibition of the enzyme urease, AHA works synergistically with several antibiotics and thereby facilitates the sterilization of urine. This agent is particularly effective because of its high renal clearance and ability to penetrate the bacterial cell wall. Well-designed studies have confirmed its clinical value and shown that AHA decreases the urinary alkalinity and ammonia levels, even in the presence of infection. Three randomized, placebo-controlled studies demonstrated significant reduction in stone growth with AHA compared with placebo [56–58]. Unfortunately, in all three studies, over 20% of patients discontinued the drug secondary to serious neurologic, hematologic, and dermatologic side effects. Moreover, many patients with struvite stones have concomitant renal impairment, which increases the risk of toxicity and decreases the effectiveness of AHA. AHA is contraindicated in patients with serum creatinine greater than 2.5 mg/dL^2. AHA may inhibit further stone growth but does not clear existing stones. In summary, the clinical utility of urease inhibitors remains limited until newer agents with fewer side effects are developed.

Antibiotics

The presence of persistent infection has been demonstrated to increase the risk of stone recurrence. Thus, eradication of the infection and elimination of the source of urease with antibiotics is a critical step in stone prevention. Martinez-Pineiro and colleagues [59] reported on 99 consecutive patients surgically treated for staghorn calculi. Of those patients stone-free following the operation, 31.5% had a recurrence, and 56.5% had resistant urinary tract infection. Progressive growth occurred in 61.5% of the infected cases, while 87.5% of the recurrences in patients with sterile urine remained stabilized. Additionally, in the group of nonrecurring lithiasis, only

16% had urinary infection. Beck and Riehle [60] treated a cohort of patients with 3 months of culture-specific antibiotics following SWL monotherapy. Of patients stone-free after treatment, 80% remained free of stones. Of patients with stone fragments measuring 5 mm or greater in any dimension, 78% showed progressive stone growth despite antibiotic therapy. Antibiotics may suppress bacteriuria, but in the presence of remnant fragments their effectiveness in eliminating infection is compromised.

In summary, medical management has a minimal role in the initial treatment but may be used for prevention after definitive surgical treatment. Attempts to treat chronically infected urine in combination with elimination of stone fragments provide the best defense against stone recurrence.

Cost-effectiveness

In the modern era of health care cost containment, urologists must examine the various treatment options for staghorn calculi from a cost-effectiveness standpoint. Chandhoke [61] developed a cost-effectiveness index to estimate the average cost of rendering one patient stone-free and found that PCNL monotherapy and combination sandwich therapy were each more cost-effective than SWL monotherapy. Taking stone surface area into account, this study suggests more specifically that combination sandwich therapy and SWL monotherapy are equivalent if the stone surface area is less that 500 mm^2. However, when stone surface area exceeds 1000 mm^2, combination sandwich therapy is much more cost-effective than SWL monotherapy. This study failed to examine the cost-effectiveness of PCNL monotherapy based on stone surface area. Overall, this study highlights the economy of percutaneous-based procedures for the management of staghorn calculi. As refinements in techniques are ongoing, future studies will be needed to comprehensively evaluate the cost-effectiveness of treatments for staghorn calculi.

Summary

Staghorn calculi are large stones that fill the renal pelvis and extend into the majority of the calices. These stones are usually composed of pure struvite or struvite in combination with calcium carbonate apatite. Staghorn stones are strongly associated with urinary tract infection caused by urease-producing bacteria. Untreated staghorn calculi are likely to destroy the kidney and thus an aggressive therapeutic approach is clearly warranted. According to the AUA Nephrolithiasis Guidelines Panel, complete stone removal should remain the therapeutic goal to "eradicate any causative organisms, relieve obstruction, prevent further stone growth and any associated infection, and preserve kidney function" [1]. This is best accomplished with definitive surgical treatment. Considering the various modalities for staghorn disease, PCNL should be the first-line treatment for most patients based on its superior efficacy and low morbidity. Nephrectomy is a reasonable option for staghorn patients with a nonfunctioning or poorly functioning kidney. Finally, following stone removal, periodic surveillance with imaging and urinalysis is important to evaluate for stone recurrence.

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New Concepts in Shock Wave Lithotripsy

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Shock wave lithotripsy (SWL) technology has advanced rapidly in terms of shock wave generation, focusing, patient coupling, and stone localization, making it the most widely used treatment for renal calculi [1]. Subsequent modifications to the original lithotripters have focused their efforts on operator convenience and optimizing the compressive wave component of the shock wave, neglecting the contribution of the tensile component of the waveform. As a consequence, current lithotripters have suffered from inferior fragmentation rates compared with the original HM3 lithotripter [2].

In contrast, recent progress in SWL research has improved our understanding of the primary mechanisms for stone comminution and tissue injury in SWL. It is now recognized that the disintegration of renal calculi in a lithotripter field is the consequence of dynamic and synergistic interaction of two fundamental mechanisms: stress wave–induced dynamic fracture in the form of nucleation, growth, and coalescence of preexisting microcracks inside the stone [3] and cavitation erosion caused by the violent collapse of bubbles near the stone surface [4]. Similarly, two different mechanisms have been proposed for SWL-induced tissue injury: shear stress due to shock front distortion [5] and cavitation induced inside blood vessels, especially the expansion of intraluminal bubbles [6].

This monograph reviews the basic principles of SWL. However, the focus is on new research on stone fragmentation and tissue injury and how this improved understanding of shock-wave technology is leading to modifications in lithotripsy that will allow this therapy to be a safer, more effective treatment for nephrolithiasis.

SWL principles

Despite the large number of lithotripters available, all of these devices rely on the same laws of acoustic physics. Shock waves (ie, a special form of sound waves) consisting of a sharp peak in positive pressure followed by a trailing negative wave are generated extracorporeally and passed through the body to fragment stones. The change in density and acoustic impedance from water to calculus results in stone fragmentation [7]. All lithotripters share four main features: (1) an energy source to generate the shock wave, (2) a device to focus the shock wave at a focal point, (3) a coupling medium, and (4) a stone localization system.

Shock wave generation and focusing

The two basic types of energy sources for generating shock waves are point sources and extended sources. The electrohydraulic generator produces shock waves by an electric spark-gap of 15,000 to 25,000 V of 1-μs duration (point source). This high-voltage spark discharge produces the rapid evaporation of water that generates a shock wave by expanding the surrounding fluid. The generator is located in an ellipsoidal reflector that concentrates the reflected shock waves at a second focal point, F2, with F1 being the origin of the primary shock waves.

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Piezoelectric shock waves are generated by the sudden expansion of ceramic elements excited by a high-frequency, high-voltage pulse. While each of these elements moves only slightly in response to a pulse of electrical energy, the summation of the simultaneous expansion of multiple elements results in a high-energy shock wave directed to the focal point at the center of the sphere. The shock wave is propagated through either a small water basin or a water-filled bag to the focal point, F2. The spherical focusing mechanism of the piezoelectric lithotripters provides a wide area of shock wave entry at the skin surface, which causes minimal patient discomfort but a very narrow focal point with the smallest amount of energy at F2 compared with other energy sources [8].

In electromagnetic devices, shock waves are generated when an electrical impulse moves a thin, circular metallic membrane, which is housed within a cylindrical "shock tube" (extended source). The resulting shock wave passes through an acoustic lens and is directed to the focal point, F2. The shock wave is coupled to the body surface with a moveable water cushion and coupling gel [9]. Alternatively, when energy is passed through a cylindrical coil, the resulting magnetic field pushes away the surrounding cylindrical membrane producing a shock wave that can be focused by a parabolic reflector. While these devices produce reliable shock waves with consistent pressures and focus on F2, they also produce a small focal region that may result in higher renal-tissue injury [2].

Coupling medium

While the original Dornier HM3 machine used a 1000-L water bath to transmit the shock waves into the patient, current lithotripters were designed to alleviate the physiologic, functional, and economic problems of the large water bath. Current models use an enclosed water cushion, or a totally contained shock tube, to allow simplified positioning and "dry" lithotripsy [10].

Stone localization

Stone localization during lithotripsy is accomplished with either fluoroscopy or ultrasonography. While fluoroscopy provides the urologist with a familiar modality and has the added benefits of effective ureteral stone localization [11], it requires more space, carries the inherent risk of ionizing radiation to both the patient and medical staff, and is not useful in localizing radiolucent calculi. Sonography-based lithotripters offer the advantages of stone localization with continuous monitoring and effective identification of radiolucent stones, without radiation exposure [8]. Combined systems allow for localization with fluoroscopy and real-time monitoring with ultrasound reducing the ionizing radiation exposure. Many commercially available lithotripters now use a modular design in which the fluoroscopy unit is not attached to the lithotripter reducing storage space as well as allowing use of the fluoroscopy unit for other procedures [9].

Mechanisms of stone fragmentation

The mechanisms described for stone comminution include compressive and shear-induced fracture, spallation, and cavitation. As the calculus develops in vivo, it is formed by both crystallization of minerals as well as organic matrix material. This combination forms an inhomogeneous and imperfect material that has natural "defects." When the shock wave encounters a stone, the force generated in the plane of the shock wave places stress on these imperfections, resulting in compression-induced tensile cracking [2].

However, several early investigators observed cracks in in vitro stone fragmentation studies that were perpendicular as well as parallel to the shock wave. Eisenmenger [12] proposed that the shock wave propagates faster in the stone than in the surrounding urine and that this difference in pressure results in a positive pressure front. As long as F2 is larger than the stone, the front generated results in circumferential compression resulting in perpendicular and parallel cracks in the stone.

As the sound wave travels out of the posterior surface of the stone, it encounters a change in density at the stone-urine interface. This effect results in reflection and inversion of part of the wave back onto the stone. If the negative pressure reflected back onto the stone exceeds the tensile strength of the stone, nucleation and formation of microcracks occur that can coalesce to result in fragmentation. This process, known as spallation, can also occur internally where there are fluid-filled cracks or cavities within the calculus [2].

These first two mechanisms result from the positive-pressure component of the shock wave. However, when shock waves pass through fluid, the tensile or trailing negative pressure wave creates bubbles at the interface between the stone and the fluid (nucleation site), which can be on the

surface of the stone or in internal fluid-filled cracks. The change in pressure is what causes these bubbles to form and grow. As the pressure drops further, the bubbles expand. However, as the shock wave passes, the pressure rises causing the bubble to violently collapse, releasing its energy. These bubbles release their energy as a powerful jet releasing compressive forces on the stone. The formation and behavior of bubbles is known as cavitation and we now realize that this mechanism plays a major role in stone fragmentation as well as in tissue injury. This mechanism will be described later in this review [13,14].

These forces act in conjunction to ultimately fragment a stone in vivo [15]. Cleveland and van Cauwelaert [16] demonstrated in an in vitro study that stone orientation, size, geometry, and internal structure all play a role in which mechanisms result in stone fragmentation. However, several studies have demonstrated that suppression of cavitation results in decreased efficiency of stone fragmentation. Auge and colleagues [17] showed decreased comminution of stones in castor oil compared with degassed water due to suppression of cavitation bubble formation. While the positive component of the wave did result in fragmentation of the stone into large pieces, cavitation is likely necessary to produce fine passable fragments.

Mechanisms of tissue injury

Clinical experience treating patients with SWL has demonstrated that while SWL is generally safe, shock waves have well-recognized acute renal complications. Although clinicians have long recognized the acute effects of SWL, most have believed that there was no long-term sequela to shock wave treatment. Several series with short follow-up have demonstrated conflicting information on the medical complications of SWL [2]. However, a recent study of 630 patients treated in 1985 with the HM3 lithotripter demonstrated an increased risk of hypertension (odds ratio 1.47, 95% confidence interval 1.03–2.10, $P = .034$) compared with nonsurgically treated stone patients. In addition, after controlling for body mass index, this group also found an increased risk of diabetes mellitus (odds ratio 3.75, confidence interval 1.56–9.02, $P = .003$) for the SWL-treated group [18]. Although this report was a case-controlled study, its findings again raise concerns regarding SWL and emphasize the importance of understanding the mechanisms of SWL-induced tissue injury.

The mechanism of tissue injury was initially believed to be mechanical trauma to small vessels and renal tubules caused by cavitation forces or shear stress [5,6]. However, basic science research has demonstrated that cavitation-induced injury to small vessels and renal parenchyma, as well as SWL-induced renal vasoconstriction are the driving forces behind SWL-induced injury. In addition, these initial injuries appear to further potentiate renal injury via tissue free radical formation. The resulting scar, as previously mentioned, is believed to be the cause of the chronic effects of SWL.

Cavitation-induced renal injury

Although cavitation bubbles are a desired effect in the region of the stone, their formation in other locations (tissue, blood vessel lumen) is an unwanted end product that results in tissue injury. Investigators have demonstrated in vitro that cavitation bubble expansion can rupture artificial blood vessels [6]. Other investigators have shown in animal models that cavitation takes place in kidneys exposed to shock waves. Presumably, reducing unwanted cavitation inside blood vessels should decrease kidney injury during SWL. When modifications to an electrohydraulic lithotripter designed to reduce tissue injury were applied to an animal model, there was a smaller area of tissue injury compared with the unmodified lithotripter. While more studies are needed, it appears that cavitation bubbles inside small blood vessels induced by shock waves play a major role in tissue injury during stone treatment [19].

Renal vasoconstriction and SWL-induced renal injury

Recent investigations have elucidated yet another potential mechanism of renal injury secondary to high-energy shock waves. Evidence suggests that SWL exerts an acute change in renal hemodynamics (ie, vasoconstriction) that occurs away from the volume targeted at F2, as measured by a transient reduction in both glomerular filtration rate (GFR) and renal plasma flow (RPF). These studies have demonstrated not only a decrease on GFR and RPF of kidneys exposed to SWL, but also a decreased RPF (but not GFR) in contralateral, untreated renal units of minipigs [20,21]. Prolonged vasoconstriction

may result in tissue ischemia and permanent renal damage.

Free radical–induced renal injury

Several investigators have hypothesized that oxygen free radicals may be an integral element in shock wave–induced renal injury through an indirect mechanism. Vascular injury causes areas of tissue ischemia, which become susceptible to free radical production as reperfusion occurs. This insult can create abnormally high levels of free radicals, oxidants produced by the normal processes of cellular metabolism and cellular injury [22]. The toxicity of free radicals is attributed to their ability to initiate lipid peroxidation of cellular membranes [23]. Intrarenal hemorrhage from damaged vessels may compound the problem since the iron content of red blood cells can also catalyze the formation of free radicals [24].

It appears that the entire treated kidney is at risk of renal damage from SWL-induced direct vascular and distant vasoconstrictive injury, both resulting in free radical formation. Although previous studies have suggested that the hemodynamic effects are transient in nature in normally functioning kidneys, patients with baseline renal dysfunction may be at significant risk for permanent renal damage [20,21]. Patients of concern may be pediatric patients, patients undergoing multiple SWL treatments to the same kidney, patients with solitary kidneys, vascular insufficiency, glomerulosclerosis, glomerulonephritis, or renal tubular insult from other causes.

Table 1
Advances in lithotripsy

Lithotripsy advances	Examples
Changes to lithotripter	Attenuating cavitation-induced injury • Modified reflector insert • Acoustic diode • Direct wave suppression Enhancing cavitation-induced stone fragmentation • PEAA generator • Dual-pulse lithotripsy
Modification to treatment strategy	Slowing SWL delivery rate Voltage stepping Low-voltage pretreatment Prefocal alignment
Adjuncts to improve SWL safety and efficacy	Medications • Antioxidants • Altering the chemical environment surrounding the stone • Improving stone expulsion Patient selection • Determining SWL success by stone density on imaging • Stone to skin distance • Body mass index • Pelvicalyceal angle • Infundibular length

Abbreviations: PEAA, piezoelectric annular array; SWL, shock wave lithotripsy.

Lithotripsy advances

Based on our current understanding of cavitation in stone fragmentation as well as the role of cavitation, vasoconstriction, and free radical formation in SWL-induced tissue injury, several groups are investigating ways in which SWL can be clinically effective and safe. This insight has resulted in research focusing on changes to the lithotripter design, changes in treatment strategy, and the addition of medical adjuncts (Table 1). In addition, recent clinical research has focused on improving patient selection.

Changes to the lithotripter

Attenuating cavitation-induced injury

A reflector insert has been designed that can be integrated with the original Dornier HM-3 reflector to create a second shock wave that is approximately 4 μs behind the original shockwave. As a result, the second shock wave partially cancels the negative tensile component of the original wave, preventing cavitation bubbles from overexpanding in blood vessels and reducing their chance of rupture.

In comparison with cavitation in tissue, SWL-induced bubbles in the aqueous medium surrounding a stone are usually larger because of strong wave reflection and bubble aggregation, and the enlarged bubbles on the stone surface usually collapse within several hundred microseconds after the passage of the shock front. Therefore, this modification controls cavitation, reducing tissue injury while preserving its utility

for stone fragmentation [25]. Others have described similar modifications with similar findings [26].

In addition to the focused wave, there is a second direct wave that is generated at the shock wave source. A device has been constructed to suppress this direct wave. This direct wave induces cavitation before the arrival of the focused wave, which might interfere with the cavitational activity of the focused wave. Studies have demonstrated suppression of cavitational activity by installing a direct wave suppressor close to the spark source [27].

Enhancing cavitation-induced stone fragmentation

Because the reflector insert does weaken the cavitation bubble expansion at the surface of the stone, a second modification has been suggested to the original electrohydraulic lithotripter. A piezoelectric annular array (PEAA) generator consisting of six spherically concaved segment transducers made of piezocomposite material were mounted axis-symmetrically on a carrier surrounding the outer surface of the HM-3 reflector. The PEAA generator produces a forced and intensified collapse of cavitation bubbles near a target stone while avoiding potential tissue injury in the interposing tissues because of the small overlap in acoustic fields [28].

In vitro studies demonstrated improved stone comminution of the combined modified reflector with the PEAA generator on artificial stones as well as decreased phantom blood vessel rupture compared with the unmodified HM3 [29]. These modifications were recently tested in an animal model. The combined modified reflector and PEAA generator resulted in improved stone comminution of stones implanted in swine kidneys and decreased renal parenchymal injury compared with the unmodified HM3. Importantly, these modifications can be applied to other lithotripters, to reduce tissue injury while preserving the impact of cavitation on stone comminution.

Dual pulses have been shown to localize and intensify cavitation damage in vitro. Pressure doubling as a result of synchronous arrival of the two pulses at the focus created increased bubble growth and increased foil pit depth while asynchronous timing between the two pulses resulted in disruption of radial dynamics and negligible pitting to foils [30]. Also, the volume and rate of stone disintegration increased with the use of the two reflectors, with production of fine ($<$2-mm) fragments. Sheir and colleagues also demonstrated that placing the shock sources at a 90-degree angle might improve comminution [31].

Studies have also investigated the impact of dual shock heads on tissue injury in an in vitro model. In animal experiments, dual pulses increased comminution at the focus without increasing injury in surrounding regions [32]. Further studies have evaluated both the tissue effects and clinical outcomes of dual-pulse lithotripsy in clinical trials. Patients treated with the dual-head device showed minimal morphological changes to the renal parenchyma despite delivering twice as many shocks. These results appear to confirm the relative safety of dual-pulse lithotripsy in a patient population, although the long-term effects have not been assessed. These clinical studies support the concept that improving cavitation can significantly impact stone comminution without increasing tissue injury [33].

Modifications to treatment strategy

Rate of shock wave delivery

While there has been a trend to deliver more shock waves in a shorter period of time, in the belief that "more is better," several recent randomized controlled trials have demonstrated that a shock rate of 60 shocks per minute resulted in greater stone-free rates over patients receiving 120 shocks per minute for renal calculi smaller than 2 cm. While treatment time was increased, there was no increase in complications [34]. Other investigators have demonstrated that even a rate of 90 shocks per minute may result in greater stone comminution than 120 shocks per minute without the greater treatment time requirement [35].

Altering shock wave delivery

Voltage stepping involves initiating treatments at a low kV and then gradually increasing the power output. While this treatment strategy has not been tested clinically, the simple alteration of voltage stepping might be able to improve clinical stone comminution while decreasing renal parenchymal injury [36].

In the same vein as voltage stepping, animal studies have shown that treating a remote location of a kidney with a low-voltage dose of shock waves (12 kV) before treating the stone-bearing portion of the kidney with a normal dosage of shock waves causes global vasoconstriction. Investigators believe that the low-voltage shock waves caused vasoconstriction of the entire kidney, which protected the treated segment of the

kidney from hemorrhagic injury. This same vasoconstrictive effect may be the reason for reduced renal injury seen in animals exposed to increasing energy doses (voltage stepping) [37].

Cavitation activity appears to occur 1 to 3 cm proximal to F2. Animal studies have documented that stone comminution could be improved, with no increase in renal tissue injury if the F2 of the shock wave was moved 2 cm beyond the stone (pre–focal alignment). This strategy may improve stone fragmentation by targeting cavitation to the stone surface [38].

Adjuncts to improve SWL safety and efficacy

Antioxidants

A large body of evidence suggests that free radicals play a role in SWL-mediated tissue injury. Several studies have investigated the role of antioxidants in protecting the renal parenchyma against free radical injury. Allopurinol, verapamil, mannitol, vitamin E, and even citrate, all known free radical scavengers, have been shown to reduce tissue injury or decrease the results of parenchymal injury (renal tubular enzymes) in animal and clinical studies, respectively. Further in vitro and animal studies are currently under way to elucidate the intriguing role of antioxidants in protecting against SWL-mediated renal injury. It is believed that pretreatment of patients at high risk for acute and/or chronic SWL-mediated renal injury might protect against the deleterious effects of shock waves [39].

Improving stone fragmentation

The acoustic and mechanical properties of various stone compositions are significantly different and thus result in varying degrees of fragility. Consequently, results of SWL may be influenced accordingly. The fragility of various stone compositions when exposed to various chemolytic solutions has been studied. The suggestion that chemolytic pretreatment increases stone fragility has been verified by the finding of increased stone comminution after SWL testing. These data suggest that by altering the chemical environment of the fluid surrounding the stones it is possible to increase the fragility of renal calculi in vitro. Further investigations must be performed to identify ways to alter the surrounding urine of stones treated with SWL and whether this concept can be clinically accomplished to improve stone fragmentation [40].

Improving stone expulsion

Several reports have demonstrated that calcium channel blockers, steroids, and alpha blockers all may improve spontaneous passage of ureteral stones. In fact, similar studies have demonstrated improved stone clearance and shorter time to becoming stone free in patients treated with nifedipine or tamsulosin following SWL, as compared with a control group. Additionally, retreatment rates were lower for the medical treatment group compared with control subjects. A recent randomized 12-week study of tamsulosin versus placebo for 130 patients treated with SWL for renal calculi demonstrated a statistically significant improvement in stone-free rates for the tamsulosin-treated group ($P = .04$) [41].

Improving stone/patient selection for SWL

Another way to enhance the efficacy of SWL is improve patient selection. Advances in CT have allowed better determination of internal stone architecture. As a consequence, a few studies have demonstrated that determining the Hounsefield units (ie, density unit of material on CT) of renal stones on pretreatment noncontrasted CT could predict stone free-rates of patients treated with SWL. Current micro-CT and newer multidetector CT scanners have the potential to identify stone composition based on CT attenuation [42,43]. Therefore, stone compositions that are ''SWL resistant,'' such as calcium oxalate monohydrate or cystine stones, may be identified and those patients subsequently treated with endoscopic modalities, thereby limiting the need for multiple procedures. Clinical trials using this concept will need to be performed.

Other factors such as the distance of the stone from the skin, weight of the patient, and other imaging modalities are being investigated to help determine who is likely to benefit the most from SWL and which patients should be treated initially with endoscopic modalities [43–45].

Summary

SWL has revolutionized the way in which urologists manage urinary calculi; however, growing evidence suggests that this procedure is not benign and may increase the risk of long-term side effects. Recent research has provided insight into how SWL results in stone comminution, as well as tissue injury. The positive-pressure component of a shock wave causes a stone to crack, while cavitation results in finely passable fragments.

However, cavitation in addition to SWL-induced vasoconstriction is a major culprit in SWL-induced tissue injury. Cavitation bubble expansion appears to cause small-vessel rupture in the shock wave field. Cellular injury is likely mediated through free radical species formation. This knowledge is resulting in several novel modifications to improve both stone-free rates and SWL safety.

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Advances in Percutaneous Nephrostolithotomy

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A percutaneous approach to the kidney was first described in 1955 by Goodwin and colleagues [1]. This approach, with the insertion of a nephrostomy tube, was used to provide drainage for an obstructed renal unit. This example led to the recognition that the same access could also be used as a working channel, resulting in the percutaneous removal of a kidney stone, as first reported by Fernström and Johansson [2] in 1976. Shortly thereafter, dilation of the percutaneous tract became routine, and soon practitioners performed rigid and flexible nephroscopy and intrarenal manipulation and fragmentation of calculi. Thus began the era of percutaneous renal surgery, as familiar to all urologists.

Over the past 30 years, percutaneous nephrostolithotomy (PCNL) has largely replaced open renal surgery for the management of large upper-tract calculi. In a nationwide study using the International Classification of Disease, Ninth Revision (ICD-9), procedure and diagnostic codes, Morris and colleagues [3,4] found that between 1988 and 2002, the annual use of PCNL in the United States increased from 1.2 per 100,000 to 2.5 per 100,000 residents while open surgery declined from a total of 1980 cases in 1992 to only 332 cases in 1998 when Medicare beneficiaries with nephrolithiasis were assessed [3,4].

As with all new treatments and especially minimally invasive treatments available in 2006, a pertinent question is: How many procedures does one have to perform before competence is achieved? Allen and colleagues [5] evaluated the cases of an endourologist with no solo PCNL experience and reviewed such parameters as operating time, fluoroscopy time, and radiation dose. This data was then compared with those of an expert endourologist with over 1600 cases. They found that after 115 cases these parameters reached a plateau for the novice surgeon and were equivalent to those of the expert surgeon.

General indications for PCNL in the age of extracorporeal lithotripsy and advanced ureteroscopic techniques

Multiple factors are involved in the decision whether to treat renal calculi with extracorporeal shock wave lithotripsy (SWL), ureteroscopy, or PCNL. The factors are the size, number, and composition of the stones, as defined by Hounsfield units (HU); the location of the stones; and the presence or absence of hydronephrosis, calyceal diverticulum, ureteropelvic junction obstruction with calculus, and renal anomalies (eg, horseshoe or pelvic kidney).

Stone size

Stone-free rates after extracorporeal SWL decrease markedly based on stone size. Lingeman and colleagues [6] in 1987 showed that for stones less than or equal to10 mm, the stone-free rate is 77% and this decreases to a mere 29% for stones greater than 30 mm. As a corollary to the latter, the auxiliary procedure rate increases from 12% to 46%. Clearly, the larger the stone, the more efficient percutaneous removal becomes. In the early 1990s, sandwich therapy became an attractive option for these large calculi that were typically treated percutaneously followed by lithotripsy and a second percutaneous procedure to clear any significant residual fragments following lithotripsy [7,8].

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However, a more recent study by Denstedt and colleagues [9] showed that primary PCNL resulted in better stone-free rates than sandwich therapy (84% versus 63%) with shorter hospital stay (6 days versus 12.2 days) and decreased need for blood transfusion (1.6% versus 14%) when compared with the sandwich approach advocated by Streem and colleagues [8]. Accordingly, many centers have abandoned the sandwich approach in favor of primary percutaneous treatment because primary percutaneous treatment seems to promise higher stone-free rates and fewer complications. Regarding complete staghorn calculi, a meta-analysis by the Guidelines Committee of the American Urologic Association has led to the recommendation that these complex cases be approached percutaneously to achieve an average stone-free rate of 65%, compared with 62%, 36%, and 42% for open surgery, sandwich therapy, and lithotripsy alone, respectively [10].

Stone composition

CT is now routinely used to diagnose renal lithiasis and to plan treatment. The CT stone density has been found to correlate with clearance rates following lithotripsy. In general, stones less than 500 HU can be expected to have clearance rates of 80% to 100%. This decreases to 70% to 72% for stones measuring 500 to 1000 HU, 26% for stones greater than 1000 HU, and 0% for stones measuring greater than 1200 HU [11]. Armed with this knowledge, a prudent practitioner should use stone size and CT stone density as a guide in recommending to patients either primary ureteroscopic or percutaneous treatment in favor of SWL.

Collecting-system anatomy

Determining the best treatment for the lower-pole stone continues to be an especially difficult challenge. Many calyceal and renal pelvic parameters correlate with the ability of lithotripsy to clear lower-pole calculi and thus may be used as a guide to select the best treatment modality. These include calyceal pelvic height, infundibular length, infundibular width, and lower-pole infudibulopelvic angle, and may be used to determine whether PCNL is the ideal approach or whether ureteroscopy or SWL are suitable first-line management alternatives. Typically, intravenous pyelogram (IVP) determines these parameters [12]. However, with the use of noncontrast axial CT, these parameters are less often determined, but three-dimensional reconstruction may allow these calculations to be made even more precisely. To date, no articles have compared IVP-based findings with CT-based findings with regard to these various parameters.

Poulakis and colleagues [13], using an artificial neural network based on results in 701 patients, determined that an infundibular width of 5 mm or more, an infundibulopelvic angle of greater than 45°, a normal body mass index, and normal urine transport (absence of hydronephrosis) were the only factors that predicted stone clearance following extracorporeal lithotripsy. This group did not find that stone size or chemical composition of the stone were significant factors affecting the stone-free rate; Hounsfield units were not considered in this analysis. An equal number of groups have confirmed or refuted these findings [12–17]. In those studies showing that calyceal anatomy did not affect clearance rates, low patient numbers and multiple different lithotriptors, along with concomitant inversion therapy, may have contributed to the lack of correlation [16,17]. Therefore, for lower-pole stones with unfavorable calyceal anatomy, and measured Hounsfield units greater than 500, the authors believe the best approach is either ureteroscopic (stones up to 10–15 mm) or percutaneous (stone >15 mm).

With regard to three-dimensional reconstructed CT, Al-Qahtani and colleagues [18] in 2003 studied the calyceal anatomy in 36 normal kidneys and characterized the three-dimensional CT anatomy. They found that the upper pole was drained by a single infundibulum in 100% of cases; the middle calyces were drained by two infundibuli in 89% of cases; and the lower pole was drained by a single infundibulum in only 36% of cases and by two infundibuli in 64% of cases.

Subsequently, Thiruchelvam and colleagues [19] performed a modified sequence CT urogram involving placement of an abdominal compression band, rocking the patient side-to-side to mix administered contrast with the urine in the pelvicalyceal system, and administration of furosemide to induce a diuresis. Multiplanar reconstruction and three-dimensional reformatting permitted all stones to be identified despite the presence of contrast within the collecting system. Posterior calyces in 9 of 10 patients were accurately identified and filled with contrast, thus enabling the preoperative selection of the most appropriate calyx for puncture.

Another important finding has been the significance of the skin-to-stone distance determined on

CT, specifically related to the lower-pole stone. Pareek and colleagues [20] evaluated 64 patients treated with a Doli-S lithotriptor, 30 of whom were stone free and 34 of whom had residual stones. The focal length of this lithotripter is 15 cm. This group showed that in patients rendered stone free, the mean skin-to-stone distance was 8.12 cm (± 1.74 cm) versus 11.53 cm (± 1.89 cm) in those with residual fragments. It is therefore recommended that if the skin-to-stone distance is greater than 10 cm with any measurement (specifically measured on CT at 0°, 45°, and 90° to the stone) lithotripsy is likely to fail. The caveat here is obviously the focal length of the lithotriptor used. However, the focal length on the three most common machines in use is as follows: Storz Modulith: 16.5 cm; Siemens Lithostar: 15.5 cm; Medstone STS: 15.3 cm [21].

Hydronephrosis

Another key consideration in the evaluation and selection of the treatment ideally suited to a given patient and stone is the presence or absence of hydronephrosis. Winfield and colleagues [22] in 1988 found that in normal undilated systems the stone-free rate following extracorporeal lithotripsy was 70% with an auxiliary procedure rate of 12%. By contrast, in hydronephrotic systems, the stone-free rate was only 53% with an auxiliary procedure rate of 27%. These findings are also supported by the artificial neural network of Poulakis and colleagues [13].

Special circumstances

Unique circumstances mandating modifications to the standard approach include stones in pediatric kidneys, the transplanted kidney, stones within calyceal diverticula, horseshoe kidneys, and other malrotated or malpositioned kidneys. These will not be further discussed here as they are addressed elsewhere in this issue.

Endoscopic energy source

The most common percutaneous endoscopic lithotripsy energy sources in use today are the holmium yttrium, aluminum, and garnet (holmium:YAG) laser; the ultrasonic lithotriptor; the pneumatic lithotriptor; and a combination ultrasonic–pneumatic device. Electrohydraulic lithotripsy is not commonly employed in present-day practice because the previously mentioned devices are safer and perceived to be more efficient. The holmium:YAG laser is the only commonly used intracorporeal energy device that can be combined with either the flexible nephroscope or flexible ureteroscope. Attempts so far at making flexible ultrasound or pneumatic probes have not been wholly successful because the resulting probes have been much stiffer than the laser fiber and too stiff to be practical.

Devices combining ultrasound and pneumatic lithotripsy are most efficient for stone fragmentation. Such a device was first tested clinically by Haupt and colleagues [23] in 2001. Fifteen patients, 14 with renal stones and 1 with a bladder stone were treated. Ten of the 14 patients with renal stones were rendered stone free and the device was noted to significantly reduce the time needed to treat large staghorn calculi. Subsequent to this, Auge and colleagues [24] in 2002 compared this device with the standard Lithoclast and ultrasonic devices. They found that in an in vitro stone phantom model, the combination device was capable of fragmenting stones into small pieces much more efficiently than either device individually (7.0 minutes versus 25.3 minutes versus 19.9 minutes, respectively).

The holmium:YAG laser is generally less efficient than the combined device described above. Cuellar and Averch [25] used the holmium:YAG laser for PCNL in 71 consecutive patients undergoing 90 procedures. A unique manually controlled suction device was used in combination with a 365-μm laser fiber. The mean stone burden was 3.25 cm and a stone-free rate of 83% was obtained with the laser versus 73% without, as determined by postoperative noncontrast CT. The mean operative time was 167 minutes with the holmium:YAG laser and 104 minutes without the holmium:YAG laser. A combination of ultrasonic lithotripsy with the rigid nephroscope and holmium:YAG laser lithotripsy with the flexible nephroscope seems to work most efficiently. Having a laser system available facilitates flexible endoscopy and lithotripsy of those stone-bearing calyces that cannot be reached with rigid instrumentation.

Access

Traditionally, access to the renal collecting system has been achieved either by fluoroscopic guidance after retrograde (contrast and/or air) pyelogram or by ultrasound-guided puncture. Typically, a posterior calyx is entered using a nephrostomy needle. After one guide wire (ie, safety guide wire) is passed into the system, the

tract is dilated with serial dilators up to 10 F catheter, at which time either a dual lumen catheter or an 8/10–F-catheter coaxial system is introduced so that a second guide wire (ie, working guide wire) can be passed into the system. Dilation of the tract is then performed either with serial flexible dilators (eg, Amplatz dilators) or a high-pressure balloon dilator to a 30–F-catheter size, after which a nephrostomy sheath is placed [26].

At the University of California, Irvine, the authors have adopted an endoscopic-guided approach to facilitate direct visualization during the creation of the access tract. Such endoscopic guidance was initially reported by Grasso in 1995 [27] and again in 2003 by Kidd and Conlin [28], but only as applied to cases in which fluoroscopic guidance failed to allow successful puncture. However, due to the advent of the ureteral access sheath, which provides for easy ureteroscopic access to the renal pelvis, the authors are now routinely gaining access endoscopically with the following technique.

The patient is first positioned prone on spreader bars and flexible cystoscopy is performed. A 0.035-in Bentson guide wire is inserted up to the renal pelvis. Over this, an 8/10–F-catheter dilator–introducer catheter is placed, through which a 0.035-in Amplatz super-stiff guide wire is passed. Over this guide wire, a 10/12–F-catheter or 12/14–F-catheter ureteral access sheath is placed up to the ureteropelvic junction; a 35-cm sheath is used in females and a 55-cm sheath is used in males. Flexible ureterorenoscopy is then performed and an upper-pole posterior calyx is selected for puncture. If there is stone in the desired calyx, it is cleared using the holmium:YAG laser. Then under fluoroscopic and endoscopic guidance an 18-gauge nephrostomy needle is passed until it is just seen in the calyx. A safety guide wire is passed through the needle and guided down the ureter. Over the safety guide wire, an 8/10–F-catheter dilator–introducer is passed, again until its tip is just seen in the calyx. The 8–F-catheter inner catheter is removed and a 0.035-in Amplatz super stiff guide wire is passed into the collecting system. Over this stiff guide wire a 4.5-mm fascial incising needle is advanced, being sure that the blade is parallel to the rib (Fig. 1). The authors then pass a balloon dilator until its tip is just within the calyx and inflate the balloon to 20 atm. The working sheath is then advanced over the balloon and into the calyx, being sure to not advance it across the infundibulum or damage the anterior wall of the calyx. Throughout the percutaneous procedure, the authors leave the ureteral access sheath in place because this allows drainage of small fragments, prevents their migration into the ureter, and results in a decreased intrarenal pressure compared with drainage via a ureteral catheter or ureteropelvic junction occlusion balloon [29–30] .

Hoenig and colleagues in 2006 (D.M. Hoenig, personal communication, August 2006) employed a variation on this theme. This group inserted a basket through the ureteroscope, captured the initial percutaneously placed wire, and pulled out the basket via the access sheath. This approach provides the benefit of an immediate through-and-through wire and eliminates need for a second guide wire. One caveat is, however, that the guide wire takes up drainage and scope space in both sheaths. This would be problematic if a 9.5/11–F-catheter sheath is used because a 7.5–F-catheter flexible ureteroscope will not pass with an 0.035-in wire within the sheath. The use of a 12/14–F-catheter sheath would not inhibit the passage of a 7.5–F-catheter ureteroscope. If the patient's ureter will only accommodate the smaller sheath, then an alternative is to remove the sheath and pass an 8/10–F-catheter dilator–introducer catheter over the through-and-through wire, followed by insertion of an 0.035-in Amplatz super-stiff wire, over which the

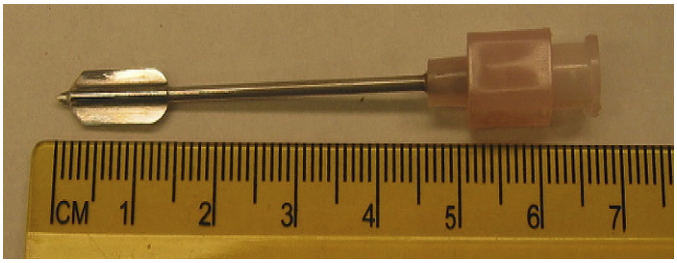

Fig. 1. Fascial incising needle, 18 gauge, 5 cm long, and 10 mm wide. Needle 4.4 mm wide is also available.

access sheath is now passed. The through-and-through wire will now be outside the sheath and will not limit the size of the stone fragments that will pass via the sheath.

Pathak, and Bellman in 2005 [31] described their experience with a single-step dilation system using the Pathway Access System. This novel access device is made of a polyester balloon and a Teflon sheath. This sheath is less rigid than a standard Amplatz sheath. The advantage of this system is that it allows for simultaneous balloon tract dilation and sheath placement in one step. This group prospectively evaluated the system in 21 patients with 11 patients randomized to a single-step technique versus 10 patients with the standard two-step procedure. The single-step device offered quicker insertion time (3 minutes versus 5 minutes 42 seconds, $P < .01$) and less blood loss.

Each of the previously described approaches requires that the patient be positioned prone. However, a few groups are performing PCNL in the supine position. This approach was first described by Valdivia and colleagues [32–34] in 1987 and they subsequently reported their extensive experience with this technique over the 11 years. The purported advantages of the supine position are the ability to complete the procedure using a local anesthetic while maintaining easy access to the urethra and ureteral orifice. In over 500 cases reported by this group, no colon perforations, no pneumothoraces, and no hydrothoraces occurred, and major hemorrhage occurred in only 3 patients. The anterior calyces are the preferred sites of puncture for this group because anterior calyces usually lie more lateral than posterior calyces.

The supine technique of gaining access has yet to gain wide acceptance. However, Shoma and colleagues [35] in 2002 reported their experience in a prospective nonrandomized study from Mansoura University, Egypt. They treated 53 patients supine and 77 prone and found 89% and 84% success rates, respectively. The overall complication rate in this study was 12% and 17% ($P = .4$) for prone and supine positions, respectively, and included bleeding (4% versus 9%, $P = .2$), urinary leakage (3% versus 4%, $P = 1$) and fever greater than 38°C (5% versus 4%, $P = 1$). There were no colon injuries. However, procedure times and length of hospital stay were not reported.

Ng and colleagues [36] also employed the supine positioning extensively at their institution in Tai Po, Hong Kong. They treated 62 patients, with the initial access gained by ultrasound to confirm the absence of interposed organs, and achieved a primary stone-free rate of 76%. One patient with multiple tracts required an emergent nephrectomy for hemorrhage 1 week following the procedure. This was reported as not being directly related to the procedure but rather due to inadvertent traction on one of the nephrostomy tubes. Again, there were no colon injuries in this series.

The supine position is an alternative approach to gaining collecting-system access. It appears to be associated with low complication rates and comparable stone-free rates. To date, there have been no series on this positioning from the United States. However, a supine position may be worth considering, especially for patients with comorbidities likely to increase anesthetic-related risks in a prone position.

Su and Kavoussi and colleagues [37] in 2002 reported their experience with a percutaneous-access-to-the-kidney robotic system and compared the robotic access to standard manual access. They compared the outcomes of 23 patients involving robotic access with 23 contemporary cases undergoing standard manual percutaneous access. The two groups were comparable when analyzed for number of attempts made to gain access, time to obtain access, estimated blood loss, and color of effluent urine following access. With the robotic system, access was obtained in 87% of cases. In 13% of cases, failure to gain access resulted in conversion to a manual technique. With further refinement of this robotic technology, the fully automated access system is likely well within sight, and the accuracy and safety of such a system, combined with image guidance, may mean the shift of practitioners, for this part of the procedure, from the tableside to the console.

Is a single tract enough?

Intuitively, the fewer punctures of the renal parenchyma necessary, the better the overall renal functional outcome should be. Pertinent questions remain: Can one achieve an equivalent stone-free rate with a single access and do multiple accesses increase the complication rate?

Kukreja and colleagues [38] in 2004 analyzed the factors affecting blood loss during PCNL. They found that in 301 procedures in 236 patients analyzed prospectively, the factors associated with significant blood loss were diabetes, multiple

tracts, prolonged operative times, and the occurrence of intraoperative complications. Higher blood loss was associated with telescoping metal dilators versus Amplatz or balloon dilation.

Wong and Leveillee [39] in 2002 reported on the use of a single upper-pole access to treat large complex staghorn calculi. They treated 45 complete and 7 partial staghorn calculi and required a mean of 1.6 procedures to render patients stone free with 18 of 35 (51%) upper-pole accesses and 4 of 10 (40%) middle and lower-pole accesses after a single procedure. The estimated mean blood loss was 238 mL and only 1 patient needed a blood transfusion.

In keeping with the single-access theme, Davol and colleagues [40] also treated 43 patients all with a single tract (calyx punctured was not specified) and obtained an immediate stone-free rate of 85%. However, this study was retrospective and the mean stone size was 2.1 cm as compared with 6.7 cm in the Wong study. Also, stone free status was determined by KUB in 82% as opposed to the more sensitive thin slice CT scan [40].

In a concerted effort to reduce the number of accesses required, Marguet and Preminger and colleagues [41] recommended the simultaneous use of retrograde flexible ureteroscopy to clear stones in calyces that would be otherwise inaccessible via a single percutaneous access. These stones were either treated with the holmium:YAG laser and fragmented or were repositioned so that they could be extracted percutaneously. Of seven patients reported, all but two were stone free, having asymptomatic residual fragments less than 3 mm. The blood loss in this group was 79 mL versus 345 mL when multiple nephrostomy tracts were used. This combined percutaneous and ureteroscopic approach using an access sheath was described by Landman and colleagues [30] in 2003. They treated nine patients, six with staghorns and three with partial staghorn calculi. The mean operative time was 3.1 hours and the mean estimated blood loss was 290 mL. No major complications occurred, but there were four (44%) minor complications. Seven patients achieved a stone-free status.

Meanwhile, some groups perform multiple accesses to clear stones in calyces that would be difficult to enter via a single tract. To this end, Aron and colleagues [42] in 2005 published their experience with 121 renal units undergoing PCNL for a mean stone size of 4800 mm^2. This patient group required a total of 397 tracts, with 121 in the upper calyx, 178 in the middle calyx, and 98 in the lower calyx. The stone-free rate was 85% and increased to 94% with extracorporeal lithotripsy in 8 kidneys with residual fragments. This is remarkably similar to the stone-free rate observed in the Davol series [40]. However, 18 patients required a blood transfusion, which represents a transfusion rate significantly higher than that in the Wong single-access series (2%) [39].

Liatsikos and Smith and colleagues [43] in 2005 reported the technique of ''angular percutaneous renal access'' employed at the Long Jewish Hospital, New York. In this technique, the needle is advanced to the desired calyx through the original skin incision. Then the guide wire is advanced into the collecting system. Dilation is then performed, followed by nephroscopy and stone removal. The mean blood loss in these patients was 450 mL with a transfusion rate of 45%. The stone-free rate was 87%. Again, it is evident that the more renal parenchymal punctures there are, especially transverse parenchymal punctures, the higher the likelihood of significant bleeding necessitating transfusion.

To tube or not to tube? That is the question

Selection of the appropriate drainage most suitable for a given patient undergoing PCNL can be challenging. Many factors, including presence of gross residual stone, anticipated likelihood of bleeding, difficulty of access, advantages and disadvantages of site selected for access, and patient factors can guide the decision. Kim and Lingeman and colleagues [44] in 2005 retrospectively reviewed 84 patients with 134 accesses to treat renal calculi greater than 2 cm. In this study, three types of nephrostomy tubes were employed, namely the Cope loop (8.5 or 10 F catheter), Malecot reentry catheter (20 F catheter) or circle loop catheters (20 F catheter). They found that patients with infection stones were more likely to require a reentry Malecot or circle loop than patients with other stone types. They recommended that if there is pyonephrosis, gross residual stone, or difficult anatomy, a reentry Malecot should be selected. If there is a single uncomplicated access, a Cope loop is suggested. However, if there are multiple accesses, a circle loop may be best.

Pietrow and Preminger and colleagues [45] randomized 30 consecutive patients to either a 10–F-catheter pigtail catheter versus a 22–F-catheter Councill-tip catheter following PCNL. The self-assessed analog pain score was statistically

significantly less 6 hours postoperatively for those randomized to the smaller catheter ($P = .03$). Also, the pain scores were less on postoperative day 1 and 2 for the 10–F-catheter pigtail catheter, as was the narcotic requirement, although these were not statistically significant.

Kader and colleagues [46] conducted a matched cohort study of 30 consecutive patients undergoing standard PCNL drained with an 8.5/6–F-catheter nephroureterostomy catheter and compared them to 60 patients drained with a 24–F-catheter Malecot catheter. There was no difference in the mean hemoglobin decrease. There was also shorter median length of hospital stay (1 day versus 4 days, $P < .001$) and less analgesic requirement on the first postoperative day (16.5 mg versus 47.8 mg of morphine equivalents, $P < .001$), in favor of the smaller nephroureterostomy catheter.

Limb and Bellman [47] in 2002 reported their series of tubeless percutaneous renal procedures, which included 86 PCNL and 26 percutaneous antegrade endopyelotomies (Table 1). A 6–F-catheter double-J stent was placed in all cases. Only 5 patients required postoperative transfusions and 1 patient developed a renal pseudoaneurysm needing selective embolization. The mean stone burden was 3.3 cm^2 ($\pm$ 2.79 cm^2; 0.25–12 cm^2) and a stone-free rate of 93% was achieved in this series. The mean length of hospital stay was 1.25 days.

Lojanapiwat and colleagues [48] in 2001 treated 37 patients with tubeless PCNL. The mean stone size treated was 3.06 cm $\pm$ 1.0 cm (Range 1.5–6 cm). This group left in place a 6–F-catheter external ureteral catheter, which was secured to the Foley catheter and removed at 48 hours. The mean length of hospital stay was 3.63 days and no patient required a blood transfusion.

Yew and Bellman [49] reported their initial experience with the 7/3–F-catheter indwelling ''tail stent'' in four patients. They found that placement of the stent was successful in all patients. No hemostatic agent was used to seal the tract in these four patients. There was also less pain and lower symptom scores associated with the ''tail stent'' when compared with a historical cohort of patients who had undergone tubeless PCNL with insertion of a standard double-J stent. In addition, the string on the distal tail of the stent was left intact so it exited the urethral meatus, thus avoiding a cystoscopy for stent removal (Fig. 2).

With the advent of the newer hemostatic agents, several groups are advocating their use for sealing the nephrostomy tract and thus omitting the need to place a nephrostomy tube for hemostatic reasons.

To this end, Mikhail and Bellman and colleagues [50] in 2003 first described the clinical use of fibrin glue to seal the nephrostomy tract following PCNL. They injected 2 to 3 mL of fibrin glue into each of 20 nephrostomy tracts, just after the sheath had been removed from the collecting system, to avoid inadvertent injection into the collecting system. This group of patients was compared with 23 consecutive patients undergoing PCNL without fibrin glue (tubeless). Although the total analgesic requirement tended to be less in the fibrin-glue patients, it did not reach statistical significance; the hematocrit decrease was also not significantly different.

Shah and colleagues [51] in 2006 reported a statistically significant ($P = .05$) decrease in the mean analgesic requirement for 17 consecutive patients undergoing tubeless PCNL with fibrin-glue injection, via a similar technique to that of Mikhail and Bellman, when compared retrospectively to a control group of 25 consecutive patients undergoing tubeless PCNL without fibrin glue.

Uribe and colleagues [52] in 2005 assessed the interaction of these hemostatic agents with urine in an in vitro model, followed by direct injection into the collecting system in an in vivo porcine model. The only agent remaining in fine suspension was gelatin matrix in the in vitro model, whereas 50% of the animals with gelatin matrix or fibrin glue directly injected into the collecting system showed evidence of obstruction on intravenous pyelogram at day 5. At the University of California, Irvine, the authors therefore prefer to use gelatin matrix to seal PCNL tracts based on the in vitro studies in the laboratory. However, the authors make every effort to prevent the gelatin matrix from entering the collecting system by routinely deploying a retrograde ureteropelvic junction 7–F-catheter, 11.5-mm balloon occlusion catheter which, after nephroscopy, is inflated at the torn calyceal edge before gelatin matrix injection [29].

The mini-perc

Jackman and colleagues [53] in 1997 first described the so-called ''mini-perc'' technique. This approach was applied to the pediatric population, with body weight ranging from 5 to 24 kg, using an 11–F-catheter peel-away vascular access sheath. Seven patients were treated and the stone-free rate at 12 weeks was 85%. There were

Table 1
Tubeless percutaneous nephrostomy

Investigator, year	Method	Comparison group	Number of patients treated	Transfusion requirement	Mean change in hematocrit (%) or hemoglobin (g/dL).	Mean analgesic requirement	Stone-free rate	Complication rate
Limb and Bellman [47], 2002	6–F-catheter double-J stent only	Not available	86	6%	Not available	Not available	93%	1.1% (renal pseudo aneurysm)
Lojanapiwat et al [48], 2001	6–F-catheter external ureteric catheter.	Not available	37	0%	Not available	Not available	92%	5.4% (minor bleeding not requiring transfusion)
Yew and Bellman [49], 2003	7/3–F-catheter tail stent	Not available	4	0%	1.7	Not available	100%	0%
Mikhail et al [50], 2003	Double-J stent; fibrin glue	23 patients with no fibrin glue (retrospective cohort)	43	Not available	6.8 (study) vs. 5.6 (control); $P = .57$	13.2 mg (study) vs. 22.9 mg (control) morphine equivalents; $P = .2$	Not available	15% (study group: fever (2), seroma (1)) vs. 13% (control group: ureteral stone (1), recurrent ureteropelvic junction obstruction (2))
Shah et al [51], 2006	6–F-catheter double J stent; fibrin glue	25 patients with no fibrin glue (retrospective cohort)	17	5.9% (study) vs. 4% (control)	1.18 g/dL (study) vs. 1.43 g/dL (control)	114.71 mg (study) vs. 159 mg (control) diclofenac sodium; $P = .05$	91.3% (study) vs. 93.1% (control)	17.6% (study) vs. 4% (control)

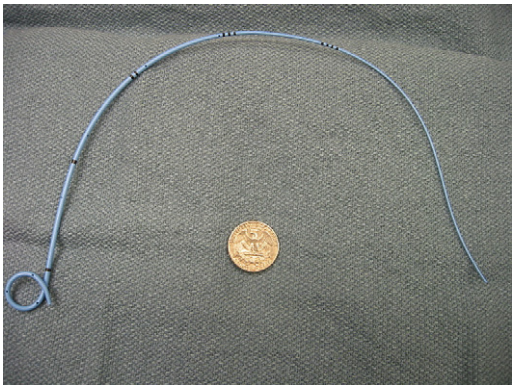

Fig. 2. A 7–F-catheter "tail stent."

no procedure-related complications. Jackman and colleagues [54] subsequently employed this technique, albeit with a 13–F-catheter ureteral access sheath, in the adult population. They treated nine patients aged 40 to 73 years with stone burdens greater than or equal to 2 cm^2. The mean operating room time was 176 minutes, mean hospital stay 1.7 days, and the stone-free rate was 89%.

Feng and colleagues [55] in 2001 conducted a prospective randomized trial of standard PCNL, mini-PCNL and tubeless PCNL. They found no advantage to mini-PCNL versus standard PCNL. Indeed, the mini-PCNL was disadvantageous with regard to visibility and optics during the percutaneous procedure. This group's version of the mini-PCNL involved dilation of the tract to 22 F catheter to facilitate placement of a 26–F-catheter sheath. Thus, the size of the access tract was much larger than in the Jackman series and this may have accounted for the increased analgesic requirement (24 mg versus 14 mg). Also, despite a larger stone burden of 4.9 cm versus 1.5 cm in the Jackman series, there was a significantly shorter mean procedure time in the Feng series, again likely related to the tract and instrument sizes (130 versus 176 minutes).

Sung and colleagues [56] in 2006 conducted a retrospective review of 72 consecutive patients who underwent a mini-perc using a 14–F-catheter peel-away sheath similar to that used in the initial description of the technique by Jackman and colleagues. The cumulative stone burden ranged from 0.24 to 39.5 cm^2. Although no total operative time was reported, the stone-free rates for stones less than 6 cm^2 was 95.7% ($n = 47$) and, for those greater than 6 cm^2, it dropped to 52% ($n = 25$). They also noted that if the longest stone measurement was less than 2.5 cm, the stone-free rate was 97.8% versus 51.9% if the longest length was greater than 2.5 cm.

Overall, the mini-perc, except in children, appears to be of little value. It does not necessarily result in a shorter hospital stay or in a quicker operation. While the mini-perc may cause less discomfort in some series, the same reduction in discomfort can be achieved today through the use of a large percutaneous tract, which facilitates the procedure, and then, through the use of a hemostatic agent, no tube needs to be left. Thus, the only potential advantage of a mini-perc approach is to create less renal damage; however, this is such a minimal difference that it is clinically insignificant.

Modes of fascial dilation

Many products are available for dilation of the nephrostomy tract. These range from mechanical dilators (eg, Amplatz and Alken dilators), to the more widely used balloon fascial dilators. It has been shown that there is potentially less renal parenchymal damage and less blood loss with balloon dilation as compared with the shear injury caused by sequential mechanical dilation [57,58]. Indeed, in one study, the transfusion rate among 50 balloon-dilated patients was only 10% versus 50% in 100 patients undergoing PCNL with the use of Amplatz dilators [59].

Important considerations in the selection of the balloon are its length, diameter, and pressure rating. Table 2 shows these parameters for several commercially available balloon catheters. When treating stones in patients who have undergone prior open or percutaneous stone removal, selection of a balloon with a higher pressure rating is suggested and the authors recommend using a fascial incising needle in these cases as it provides a 4.5-mm–diameter fascial opening that may facilitate subsequent inflation of the balloon.

Results

The method of determining stone-free status is important in assessing the true outcome of the percutaneous procedure. Numerous investigators have described various approaches. The simplest methods involve plain abdominal radiograph with or without tomograms if the original stone was radio-opaque. Denstedt and colleagues [60] in 1991 compared the sensitivity of plain abdominal radiograph alone versus plain abdominal radiograph and tomograms with flexible endoscopy, the latter being the gold standard.

Table 2
Currently available fascial dilating balloons

Type of balloon	Balloon length	Balloon pressure	Balloon outer diameter	Sheath inner diameter
NephroMax (Boston Scientific, Natick, Massachusetts)	12 cm	17 atm	10 mm	10 mm
Ultrax (Cook Urological, Spencer, Indiana)	15 cm	20 atm	6, 8, or 10 mm	6, 8, or 10 mm
Omega NV (Cook Urological, Spencer, Indiana)	12 cm	12 atm	8 or 10 mm	8 or 10 mm
X-Force (Bard Urological, Covington, Georgia)	15 cm	30 atm	8 or 10 mm	10 mm

They found that plain abdominal radiograph was largely unreliable and that even when combined with tomograms the false-negative rate was 17%.

Today, the gold standard for imaging is no longer tomograms but instead the noncontrast CT scan with 1- to 2-mm axial sections. Pearle and colleagues [61] in 1999 compared plain abdominal radiograph, noncontrast CT, and flexible nephroscopy for detection of clinically significant residual stone fragments. CT was 100% sensitive and 62% specific compared with plain abdominal radiograph, which had a sensitivity of only 46% and specificity of 82%.

Portis and colleagues [62] recently reported that high-magnification rotational fluoroscopy combined with aggressive flexible nephroscopy can identify residual fragments, which can then be removed at the same time.

As a result of the previous studies, the authors recommend meticulous, thorough flexible endoscopy before concluding a percutaneous procedure; this is combined with fluoroscopic images that are compared with the initial fluoroscopic scout image taken at the outset of the procedure. Because the authors employ a dual endoscopic approach—both antegrade nephroscopic and retrograde

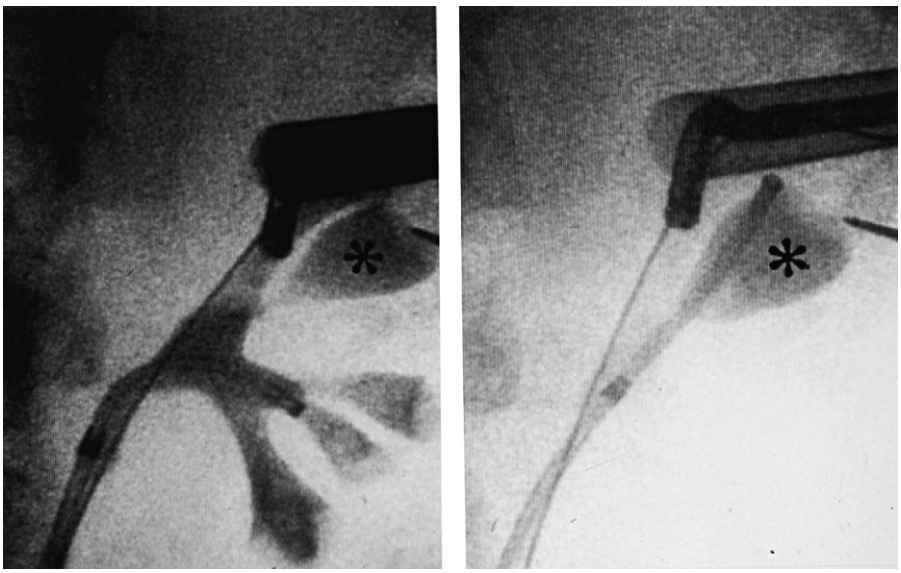

Fig. 3. Calyx (*asterisk*) that could not be accessed through a single percutaneous tract is easily entered with a retrograde flexible ureteroscope.

ureteroscopic—calyces inaccessible through the percutaneous tract can be accessed ureteroscopically (Fig. 3). If the patient appears to be stone free both endoscopically and ureteroscopically, then a tubeless technique is used. On postoperative day 1, all patients have a noncontrast CT to further assess for any residual fragments and plan further treatment if necessary. If the follow-up CT scan shows no or only a few small flecks (ie, $\leq$3 mm), then the stent is pulled in a week in the office. If the follow-up CT on postoperative day 1 shows any fragments larger than 3 mm, then the next step is outpatient flexible ureteroscopy and holmium:YAG laser lithotripsy. Such outpatient procedures are very much facilitated by the indwelling stent, which dilates the ureter so that placement of an access sheath is easier, thereby facilitating the procedure.

Future directions

Since 2006, single-access PCNL, compared with multi-access PCNL, has been associated with equivalent stone-free rates and lower complication rates . Balloon-tract dilation is preferred. An endoscopic-guided approach to puncture appears to be highly accurate and easily accomplished. The combination of the ureteral access sheath, holmium:YAG laser lithotripsy, and antegrade and retrograde ureteroscopy eliminates the need for nephrostomy tube placement after the procedure. With the use of CT scanning, stone status is more accurately ascertained and the need for further auxiliary procedures can be determined; most of these can be achieved ureteroscopically, thereby making it possible for most PCNL patients, regardless of the size of the stone, to leave the hospital on the first postoperative day.

However, the age of imaging is rapidly giving way to the age of robotics in surgery. The day is fast approaching when all percutaneous access and conceivably all ureteroscopic access will be gained via a robotic interface, thus limiting the technical expertise required to obtain accurate puncture and controlled destruction of renal and ureteric calculi. A console capable of operating a variety of endoscopic and lithotripsy equipment within the patient will likely soon arrive, so that the stone surgeon, like the prostate cancer surgeon, will be able to sit comfortably while remotely performing even the most complex percutaneous procedures.

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Advances in Ureterorenoscopy

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Ureteroscopy was initially developed in the late 1970s to diagnose and treat conditions in the distal ureter [1,2]. The technique has improved dramatically over the past 2 decades, and has evolved into a minimally invasive procedure for the diagnosis and treatment of pathology within the upper urinary tract. Today, the vast majority of intrarenal calculi are accessible and treatable using a retrograde ureterorenoscopic approach. In this article, the authors highlight recent advances in semirigid ureteroscopy and flexible ureterorenoscopy, including improvements in ureteroscope design, video/imaging equipment, intracorporeal lithotripsy devices, accessory instruments, ureteral access, ureteral stents, ureterorenoscopy training, techniques in ureteroscopy, and expanding clinical indications for ureterorenoscopy.

Ureteroscopes

Semirigid (Table 1) and flexible ureteroscopes (Table 2) have undergone modifications that have improved procedural success rates while keeping morbidity relatively low [3,4]. Durable rigid and semirigid ureteroscopes have been developed that weigh less and have new features (Fig. 1). Some small caliber, semirigid ureteroscopes have been developed with a continuous irrigation feature that optimizes the view and prevents proximal migration of stone fragments. Digital video semirigid ureteroscopes have been recently introduced. These instruments provide the current gold standard image for semirigid ureteroscopy, and involve the incorporation of a charged coupled device (CCD) chip into the distal tip of the semirigid endoscope, the so-called "chip on a stick" technology (Fig. 2A, B). This development is relatively new, however, and as such, the caliber of the video ureteroscope is slightly greater than the equivalent standard nonvideo ureteroscope. The video endoscope design obviates the need to attach a camera to the eyepiece of the ureteroscope, resulting in an easier setup in the operating room and a lighter endoscope to hold for longer cases. Springhart and colleagues [5] compared a new video semirigid ureteroscope to a standard ureteroscope and found there was no moiré (honeycomb) effect for the video ureteroscope, and the image size was 2.5 times greater on a 19″ monitor than the standard ureteroscope. Gupta [6] reported on initial clinical experience with a prototype ureteroscope with the smallest tip and shaft diameter to date, in a study in which no patient required ureteral dilation to pass the ureteroscope.

Flexible uretero(reno)scopes continue to evolve and improve rapidly, with new models being introduced each year, some by companies not previously known to manufacture endoscopes. Despite new designs with increased deflection and smaller calibers, durability has not been compromised [7,8]. Deflection has improved in

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Table 1
Contemporary semirigid ureteroscope models

Manufacturing company	Model	Working length (cm)	Tip diameter (F)	Proximal diameter (F)	Channel diameter (F)	Special features
Gyrus ACMI	Bagley MR-6/ MR-6LA	33/43	6.9	10.2	3.4/2.3	Self-dilating; super elastic triangular-shaped shaft; autoclavable
Gyrus ACMI	SlimLine MR0-742A	42	7.0	11.2	5.4	Large working channel permits two working instruments
Olympus	EndoEYE	43	8.5	9.9	4.2	Video ureteroscope; 3X better image resolution than fiber optics; no image deterioration over time
Storz	27001K/L	34/43	7.0	8.0	5.0	Unique "soft step" 1 cm tapered tip
Storz	27002K/L	34/43	8.0	—	5.5	Unique "soft step" 1 cm tapered tip; large working channel
Stryker	SRU-6	33/43	6.9	—	3.4/2.5	High density fused quartz bundle provides high resolution image
Wolf	"DOC"	33/43	6.5	8.5	4.0/2.4	Two sizable operating channels; oval-shaped
Wolf	Ultrathin	33/43	6.0	7.5	4.0	Combines small ureteroscope with large working channel

three ways: (1) the development of primary and secondary deflection mechanisms in the same ureteroscope, (2) increased primary active deflection, and (3) the understanding and application of passive deflection against the intrarenal collecting system. The increased deflection allows the experienced endourologist to access virtually any area of the intrarenal collecting system (Fig. 3). Other significant and new improvements in the design of flexible ureteroscopes include: addition of a new design distal tip composed of a proprietary Laserite (Karl Storz Endoscopy-America, Culver City, California) material that is laser resistant (Fig. 4A, B), development of a flexible digital video ureteroscope (Fig. 5), miniaturization of the distal tip to 6F or less (Fig. 6A, B), and tapered distal tip to facilitate passage past the ureteral orifice. Clayman's group has recently reported superior in vitro resolution of the DUR-D (Gyrus ACMI, Southborough, Massachusetts) flexible video ureteroscope over contemporary standard fiberoptic flexible ureteroscopes [9]. In vivo, they found that DUR-D image had no pixilation, glare, or moiré effect.

Video equipment

Video imaging technology, including digital imaging, is rapidly improving, and this has translated to better video images in the operating room for the urologist who performs ureteroscopic procedures. Significant advances include the introduction of digital imaging, increased resolution of video monitors, including high definition television (HDTV), improved endoscope fiberoptics, and miniaturization of charged coupled device (CCD) chips that are now incorporated into the distal tip of the ureteroscope. Furthermore, digital video ureteroscopes are coupled to digital control boxes that perform the equivalent functions of the camera and light source for older systems. Consequently, there is no need for a separate camera, camera cord, light source, or light cord, and white balancing is not necessary (Fig. 7). This results in improved images that are much more user-friendly to attain. These advances have resulted in drastic improvements in the quality and resolution of the images the urologist experiences in the operating room, and the process of setting up and performing ureteroscopy is much more user-friendly. The honeycomb effect that is characteristic of fiberoptic bundles is absent when a digital system is used. The recently discovered ability of companies to incorporate a tiny video chip into the distal tip of the ureteroscope could obviate the need for fiberoptic bundles.

Table 2
Contemporary flexible ureteroscope models

Manufacturing company	Model	Working length (cm)	Deflection up/down (degrees)	Tip diameter (F)	Proximal diameter (F)	Channel diameter (F)	Special features
Gyrus ACMI	DUR-D	65	250/250	8.7	9.3	3.6	Digital video ureteroscope; lightweight (1.18 lbs)
Gyrus ACMI	DUR-8E	64	170/180	6.75	10.1	3.6	Active secondary deflection of 130° gives total downward deflection of 310°
Olympus	URF-P5	70	275/275	5.4F	8.4	3.6	Beveled "Evolution tip"; built-in moiré-effect reduction filter
Storz	Flex-X2	67.5	270/270	7.0	8.5	3.6	Laser resistant tip (Laserite)
Stryker	FlexVision U-500	64	275/275	6.9	—	3.6	Locking mechanism during secondary deflection; high density fiber optic bundles for enhanced image resolution
Wolf	Viper	68	270/270	6.0	8.8	3.6	Slightly beveled, atraumatic small tip

Intracorporeal lithotripsy devices

In recent years, much of the clinical and basic science research pertaining to intracorporeal lithotriptors has focused on lasers. This is, in part, because the holmium:yttrium-aluminum-garnet (Ho:YAG) laser (Trimedyne, Irvine, California) has surfaced as the gold standard for intracorporeal lithotripsy (Fig. 8). Jeon and colleagues [10] recently confirmed earlier findings from various authors, demonstrating the superiority of ureteroscopic lithotripsy using the Ho:YAG laser over a pneumatic probe with regard to stone-free rates and complications. Consequently, there have been few clinically significant technologic improvements in intracorporeal lithotripsy devices using pneumatic, ultrasound, or electrohydraulic mechanisms.

Several new holmium laser fibers, including the InnovaQuartz (Phoenix, Arizona) and Sharplan fibers (ESC Medical Systems, Norwood, Massachusetts), have been recently manufactured, and have already undergone in vitro benchtop testing. Knudsen and colleagues [11] assessed the transmission of laser energy along each fiber, and the ability of each fiber to resist thermal breakdown in deflected states.

Several different new lasers have been developed and tested in vitro, in animal studies, and in human clinical trials. In vitro testing of the erbium:YAG laser by Kang and colleagues [12] found the erbium:YAG laser to ablate human kidney stones two to five times more efficiently than the Ho:YAG laser. Because of a 20% to 30% loss of ablation per five pulses with the erbium laser fiber, however, the study authors concluded that improvements in

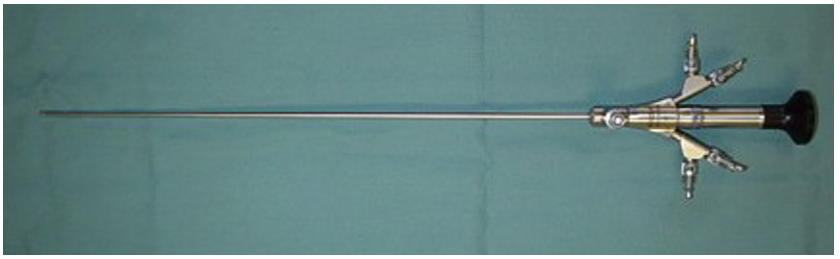

Fig. 1. Wolf dual operating channels (DOC) semirigid ureteroscope. (*Courtesy of* Richard Wolf Medical Instruments Co., Vernon Hills, IL; with permission.)

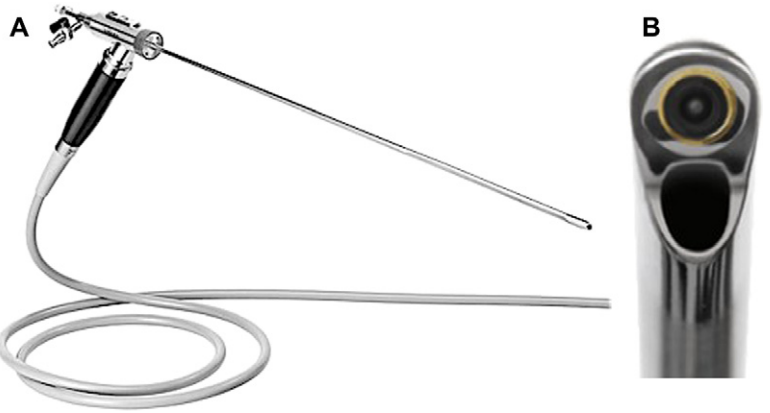

Fig. 2. (*A, B*) Olympus EndoEYE semirigid video ureteroscope. (*Courtesy of* Olympus America, Inc., Center Valley, PA; with permission.)

erbium fiber technology are required to bring erbium to the clinical world. Another new laser, the 40 W thulium laser, has demonstrated some potential advantages over the Ho:YAG laser, but its efficiency needs to be improved before it becomes clinically useful [13]. The frequency-doubled, double-pulse neodymium:YAG (FREDDY) laser is a compact, high power, user-friendly laser, which potentially makes it attractive as a laser for ureteroscopic procedures. One preliminary study for ureteroscopic lithotripsy in humans found that 72% of stones were treated completely, but the FREDDY laser was not very effective in fragmenting hard stones [14]. Furthermore, it is not useful for soft tissue ablation or incision, and thus it is less versatile than the Ho:YAG laser.

Other advances in holmium laser research involve the development of new laser fiber sheaths. A study investigating a novel temperature-activated nitinol ureteroscopic laser fiber sheath found that it improved the amount of active deflection by up to 60° compared with not using the novel sheath [15]. In another study, Razvi and colleagues [16] assessed a novel polyamide laser fiber sheath for the flexible ureteroscope, and found the polyamide sheath to have no significant effect on ureteroscope deflection with various sized laser fibers in place. Again, there was a statistically significant decrease in irrigation flow when the polyamide sheath was in place.

Accessory instruments

In addition to the standard floppy-tipped polytetrafluoroethylene (PTFE), hydrophilic, and super stiff guide wires that are commonly employed by many endourologists, various new specialty guide wires have been developed to address limitations in standard guide wires. The Sensor Glidewire (Microvasive Urology, Boston Scientific, Natick, Massachusetts) combines the benefits of a hydrophilic tip with a nitinol (NIckel

Fig. 3. Deflection of flexible ureteroscope for lower pole access. (*Courtesy of* Olympus America, Inc., Center Valley, PA; with permission.)

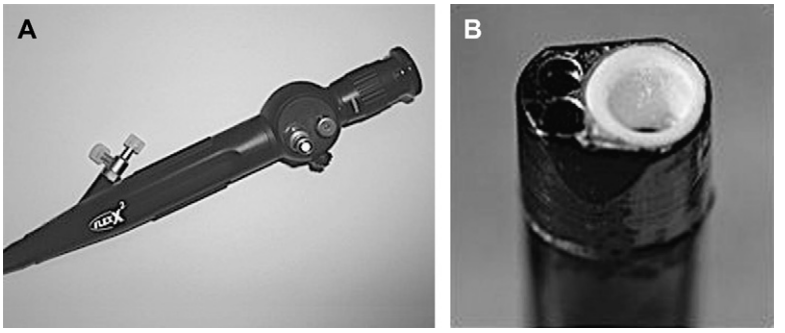

Fig. 4. Storz Flex-X2 flexible ureteroscope (*A*), with laser resistant tip (*B*). (*Courtesy of* Karl Storz Endoscopy-America, Culver City, CA; with permission. Copyright © 2006, Karl Storz Endoscopy-America.)

TItanium Naval Ordnance Laboratory) core for stiffness and "purchase" during cases, and has been shown to be superior to a standard polytetraflourethylene (PTFE) guide wire in gaining access past ureteral stones [17]. The BiWire (Cook Urological, Spencer, Indiana) is a hydrophilic nitinol wire that has a straight tip at one end and an angled tip at the other end, making it more versatile and potentially reducing inventory (Fig. 9).

There are several new stone retrieval and ureteral occlusion devices that have become commercially available over the past few years (Figs. 10A, B; 11). Bagley and colleagues [18] have outlined how ureteroscopy has evolved from 1996 to 2004. Their study showed that, during that time, nitinol baskets supplanted the three-prong grasper for removal of stones and stone fragments. Nitinol stone baskets have become the predominant device for stone retrieval, and new designs are constantly emerging. The Dimension stone basket (Bard Urological, Covington, Georgia) is an articulating tipless basket whose teardrop shape allows stone fragments of various sizes to be efficiently retrieved (see Fig. 10A). The Escape (Boston Scientific/Microvasive Urology) stone retrieval device was specifically developed for use with a small laser fiber, trapping the stone as it is ablated (see Fig. 10B). Another novel stone basket is the Halo (Sacred Heart Medical, Minnetonka, Minnesota) nitinol stone basket. It is a 1.5F tipless basket that spins using a rotary wheel at the basket handle's base, allowing the stone to spin to a different area to complete fragmentation of an entrapped calculus [19]. This avoids the typical problem of standard laser baskets, which leads to the "hole in the stone" phenomenon, while at the same time maintaining adequate irrigation because of its small caliber. The NTrap (Cook Urological) is a relatively new ureteral occlusion device that is composed of a tightly woven mesh of nitinol wires that prevents migration of stone fragments during ureteroscopic lithotripsy (see Fig. 11).

A new irrigation system for ureteroscopy, Peditrol (EMS Medical., Gloucester, United Kingdom), is a hands-free device that is activated by foot pedal. Blew and colleagues [20] tested this novel device against gravity irrigation, bag irrigation pressurized to 300 cm H_2O, and handheld 60 mL syringe irrigation, and the Peditrol irrigation device was found to be superior.

Ureteral access

Several new ureteral access sheaths have become commercially available over the past few years (Fig. 12A, B). The AquaGuide access sheath (Bard Urological) is a hydrophilic sheath with an

Fig. 5. Gyrus ACMI DUR-D flexible video ureteroscope.

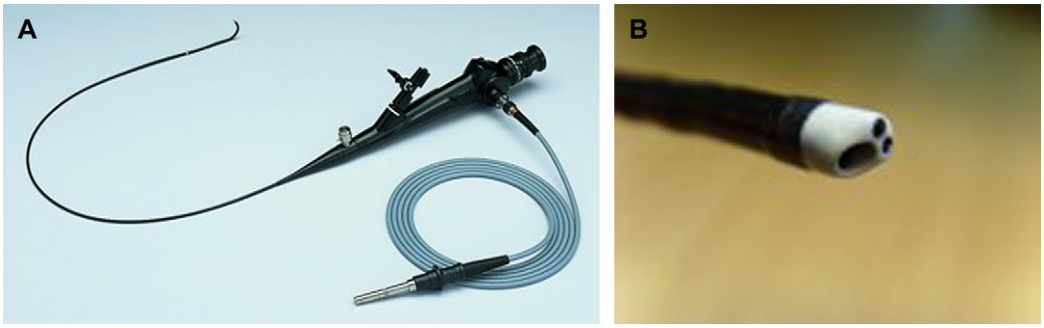

Fig. 6. Olympus URF-P5 flexible ureteroscope (*A*) with 5.4F "Evolution tip" (*B*). (*Courtesy of* Olympus America, Inc., Center Valley, PA; with permission.)

additional channel for safety wire or retrograde ureteropyelogram. The Flexor DL (dual lumen) (Cook Urological) has a secondary 3F channel at its tip for a safety wire, basket, laser fiber, or other device (see Fig. 12A). The UroPass (Gyrus ACMI, Southborough, Massachusetts) is a hydrophilic sheath with suture holes on the end for securing the sheath in place (see Fig. 12B). In a recent study, it was found to have the highest lubricity and the most resistance to buckling and kinking; however, the AquaGuide was not tested in the study [21]. A novel type of ureteral access sheath, employing a radially dilating balloon mechanism for dilation as opposed to the tapered dilating of a conventional access sheath, was tested in an animal model [22]. The study found that the novel balloon access sheath was easy to insert, and irrigation was superior to the standard access sheath. Furthermore, there was no urothelial damage or inflammation on pathologic examination. Although ureteral access sheaths were initially developed for use in adults, a recent study showed that ureteral access sheaths up to 14F were safe and effective when used in children as young as 4 years of age [23].

New designs for ureteral balloon dilators have emerged. The X-Force (Bard Urological) ureteral balloon dilator uses a patented multilayer fiber

Fig. 7. Gyrus ACMI Invisio Digital Controller. (*Courtesy of* Gyrus ACMI, Southborough, MA; with permission.)

Fig. 8. Coherent Lumenis VersaPulse PowerSuite Holmium:YAG laser.

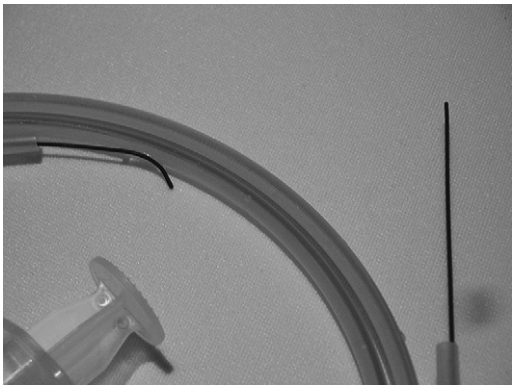

Fig. 9. Cook Urological BiWire.

technology to deliver more radial dilation force than other balloon dilators (Fig. 13).

Ureteral stents

New ureteral stents have been designed to address unresolved problems with stents, including pain, infection/encrustation, obstruction, and reflux. Over 75% of patients who have ureteral stents will have some form of morbidity associated with the stent [24]. El-Nahas and colleagues [25] analyzed the factors responsible for patient discomfort, and determined that incorrect positioning of the stent coils, infection, and longer duration of stenting all contributed to patient discomfort. A new potential strategy to deal with stent-related pain is the use of oral alpha-blockers, and in a prospective randomized clinical trial, alfuzosin 10 mg was found to result in a statistically significant decrease in urinary symptoms and pain [26]. Stent design modifications have also attempted to address the negative aspects of indwelling ureteral stents. The Polaris Loop stent (Boston Scientific/Microvasive Urology) is a novel stent with a unique design of its intravesical portion (Fig. 14). The conventional bladder coil is replaced with two thin loops, which amount to 70% less material in the bladder.

Drug-loaded, drug-eluting, and drug-coated ureteral stents have been developed to address some of the problems associated with ureteral stents [27–29]. In a recent promising study, Liatsikos and colleagues [30] demonstrated that paclitaxel-eluting ureteral stents are safe in a porcine model and did not occlude. In another promising study, Cadieux and colleagues [31] tested triclosan-loaded ureteral stents in a rabbit urinary tract infection model. The authors noted that the triclosan stents were found to have a statistically significant decrease in the number of viable *Proteus mirabilis* organisms.

A limited number of drug-incorporated ureteral stents have reached commercial realization. The Triumph stent (Boston Scientific/Microvasive Urology) is loaded with triclosan for prevention of infection and infection-related encrustation. The Radiance stent (Cook Urological) is coated with synthetic heparin for prevention of biofilm formation and encrustation. The InLay Optima (Bard Urological) is a polymer-blended stent with uniquely formulated ''pHreeCOAT'' coating to help reduce the incidence of encrustation, and is reportedly able to resist encrustation for up to 1 year in situ [32].

Metal ureteral stents were originally developed for use in patients who have malignant ureteral obstruction [33]. The Resonance stent (Cook Urological) was recently introduced for this purpose, and the first such reported stent placement in

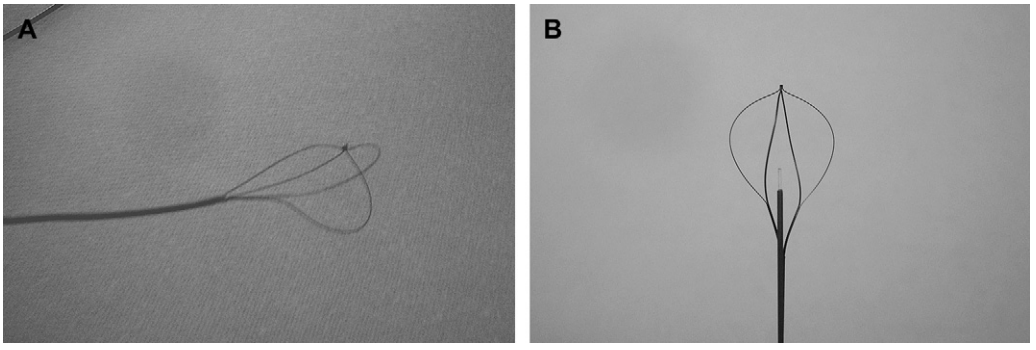

Fig. 10. New stone baskets: (*A*) Bard Dimension; (*B*) Microvasive Urology/Boston Scientific Escape.

Fig. 11. Cook NTrap ureteral occlusion device.

North America was successful in relieving ureteral obstruction that was refractory to ureteral stenting with a single 7F double-J stent and then two 6F double-J stents [34].

Ureteroscopy training

Surgical education is undergoing a revolution in terms of models and technologies for efficient and effective training such as the development of advanced computer based surgical simulators such as the URO Mentor (Simbionix, Lod, Israel) virtual reality (VR) simulator (Fig. 15). Today, training in ureteroscopy is possible with either low-fidelity bench top models or high-fidelity computer-based models. A recently published study showed that ureteroscopy training in medical students was effective using both a low-fidelity bench top model and an interactive VR computer-based simulator [35]. The validation process of the URO Mentor simulator started a few years ago [36] and continues today [37,38].

Technique of ureteroscopy

Several modifications of the original technique of ureteroscopy have been published over the past few years. An example includes the role of repositioning a lower pole calculus before performing intracorporeal lithotripsy [39–41]. Displacing a lower pole stone into a more favorable location for fragmentation has been shown to result in higher stone-free rates [42]. Another new technique that has been described is the use of lower abdominal hand pressure for semirigid ureteroscopy of the proximal ureter. Dagnone and colleagues [43] showed that this technique facilitated passage of a semirigid ureteroscope into the proximal ureter in over 50% of their patients. Yet another new ureteroscopic technique that has been recently published is ''wireless'' ureteroscopy, which involves passing a flexible ureteroscope into the ureter without the use of a guide wire. In the largest study on ''wireless'' ureteroscopy, 227 patients were successfully ureteroscoped using this technique [44]. A final advance that may have an impact on ureteroscopy outcomes, although not surgical per se, is the use of postoperative alpha blockers to try to improve stone-free rates. A recent prospective, randomized controlled trial showed that the tamsulosin group had a higher stone-free rate and a statistically

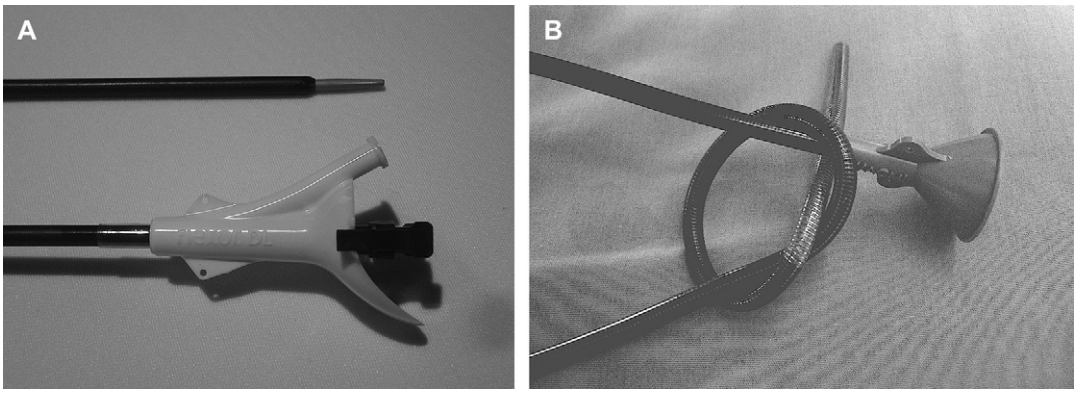

Fig. 12. Ureteral access sheaths: (*A*) Cook Flexor DL; (*B*) Gyrus ACMI UroPass.

Fig. 13. Bard X-Force ureteral balloon dilator. (*Courtesy of* Bard Urological Division, Covington, GA; with permission.)

significantly lower incidence of ureteric colic episodes [45].

Ureteroscopy for stones: expanding indications

All of the above advances have resulted in evolving indications for ureteroscopy. Ureteroscopy is emerging as a first-line procedure for

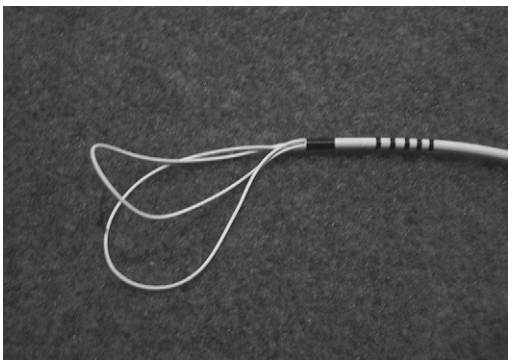

Fig. 14. Microvasive Urology, Boston Scientific Polaris Loop ureteral stent.

Fig. 15. Simbionix URO Mentor computer-based VR ureteroscopy simulator.

increasingly challenging stone cases [46]. For children, including prepubertal children, who have urolithiasis, ureteroscopy is becoming more widely accepted as first-line therapy [47–50]. This is undoubtedly because of miniaturization of ureteroscopes and ancillary devices, and the introduction of the holmium laser. Advances in ureteroscopic instrumentation have resulted in stone-free rates and complication rates similar to those for adults. Tan and colleagues [51] reported a 95% stone-free rate with no surgical complications; however, most urologists still feel that ureteroscopy in children is best done by expert endourologists or pediatric urologists skilled at endoscopy.

Ureteroscopy and holmium laser lithotripsy during pregnancy continues to become a more widely accepted treatment alternative. A recent study added further support to original reports [52,53] that demonstrated the feasibility of doing ureteroscopy and holmium laser lithotripsy during pregnancy, and the study authors added that ureteral stents should be used in this patient population to reduce early postoperative pain and analgesia [54].

Ureteroscopy in patients who have urinary diversions poses obvious challenges. Nonetheless,

there is support in recent literature for ureteroscopy as the procedure of choice [55,56]. Kieran and colleagues [56] reported a 78% success rate in accessing the renal unit via a retrograde approach in patients who have orthotopic ileal neobladder urinary diversion.

Morbidly obese patients who have urolithiasis have limited treatment options. Extracorporeal shock wave lithotripsy (SWL) and percutaneous nephrolithotripsy (PCNL) may be rendered very difficult, if not impossible, in this patient population, and ureteroscopy is often the procedure of choice [57]. Dash and colleagues [58] showed no significant difference in outcomes between morbidly obese and normal weight patients undergoing ureteroscopy. Similarly, Preminger's group [59] reported that ureteroscopy should be considered a primary treatment option for stones in pelvic kidneys.

Although ureteroscopy may have a limited role in the treatment of intrarenal calculi larger than 1.5 cm, an important transition is occurring in the treatment of proximal ureteral and selected intrarenal calculi. Larger stones are being addressed with a retrograde ureteroscopic approach. Recently, Mugiya and colleagues [60] reported their experience with retrograde ureteroscopic holmium laser lithotripsy in patients who have calculi greater than 2 cm in size. The mean stone size was 2.4 cm, and 87% of patients were successfully treated with a single procedure. Another group assessed the feasibility of performing semirigid ureteroscopy for impacted proximal ureteral stones, and had an 84% stone-free rate after one procedure [61]. All 16% of patients who underwent an auxiliary procedure were rendered stone free for a total stone-free rate of 100%. Some groups are routinely performing ureterorenoscopy for staghorn calculi, especially in patients who have significant comorbidities. Diner and colleagues [62] demonstrated that a stone-free rate of 82% was reached after an average of 1.87 necessary procedures on stones with a mean size of 3.75 cm, with no perioperative complications in this challenging patient population.

A relatively new concept is the so-called "above and below" procedure, which involves performing ureteroscopy at the same time as PCNL. This procedure appears to be gaining some popularity in the treatment of complex renal stones, because the retrograde passing of a flexible ureteroscope allows any inaccessible stones to be repositioned in line with the percutaneous access tract, facilitating removal without the added morbidity of an additional access tract. Drs. Preminger [63] and Bagley [64] have both reported their experience using this approach, and view it as being particularly useful and effective if there are one or more of the following present: synchronous ureteral calculi, bifid collecting system, stones in a parallel calyx, stenotic upper pole infundibulum, branched staghorn calculus, or multiple stones in separate locations within the collecting system.

Taub and colleagues [65] have recently reported two novel ureteroscopic procedures for symptomatic patients who have no other plausible explanation for their pain. The first procedure, laser papillotomy, was performed in patients who had chronic renal pain and papillary calcifications without free collecting system stones. Median follow-up was over 1 year, and 59% of the patients had durable pain relief, with no elevation in serum creatinine [65]. In another study, Kieran and colleagues [66] performed infundibulum dilation or laser infundibulotomy for symptomatic hydrocalyces. Technical success was achieved in most patients, but pain relief was achieved in only half of the patients [66].

Margulis and colleagues [67] recently published another novel application for ureteroscopy, namely retrograde renal cooling during cryoablation. They found that this method of cooling helped protect against collecting system injury.

Summary

Ureteroscopy continues to evolve rapidly as a first-line treatment modality for upper urinary tract calculi. Technologic advances have been made in several areas, especially in the areas of ureteroscope design, video and imaging, intracorporeal lithotriptors, and accessory devices, including ureteral stents. Collectively, these advances have resulted in higher stone-free rates, lower morbidity, and the ability to access virtually any area of the intrarenal collecting system in most patients, including those who have anomalous or reconstructed urinary tract anatomy.

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Treatment Selection and Outcomes: Renal Calculi

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Although the documentation of renal stones dates back over 2400 years to Hippocrates, it was not until 1550, when Cardan of Milan removed renal stones while draining a renal abscess, that the first documented renal stone surgery was performed [1]. By the late 1800s, surgeons were removing stones without concomitant renal abscesses, and nephrectomies and partial nephrectomies were performed for stone disease with the belief that stones were due to intrinsic renal defects. By 1880, Henry Morris performed the first open nephrolithotomy by entering the collecting system through the parenchyma and not the renal pelvis for fear of fistula formation [1]. By the early 1900s, the renal pelvis was the preferred route for nephrolithotomy after Oppenheimer reported decreased stone recurrence rates after pyelolithotomies [2]. The limitations of the pyelotomy approach, namely limited access to the calyces and infundibula, were overcome by the landmark introduction of the anatrophic nephrolithotomy by Smith and Boyce in 1967 [3]. This technique decreased renal parenchymal damage by incising along the avascular plane of Brodel. Using the anatrophic approach, Boyce achieved a stone-free rate of 95%, establishing a new standard for the treatment of staghorn calculi.

As the evolution of open stone surgery began to reach its peak, progress continued in the development of less invasive techniques for accessing renal stones. While the first percutaneous nephrostomy was performed by Thomas Hillier in 1865, it was not until 1955, when Willard Goodwin published his work on percutaneous nephrostomy for hydronephrosis, that it gained acceptance [3,4]. More that 20 years later, Fernstrom and Johansson [5] reported on the first planned percutaneous pyelolithotomy. While the procedure was recommended for stones less than 1.5 cm because of the limitations in the instruments available for stone retrieval, it was the beginning of minimally invasive renal stone surgery. By 1977, Kurth and colleagues [6] described the use of an ultrasonic lithotrite during percutaneous nephrolithotomy (PCNL) to fragment stones, providing a means for removing large stones through the smaller nephrostomy tract. This technique continues to be one of the most efficient methods for staghorn stone removal today.

The development of extracorporeal shock wave lithotripsy (SWL) soon followed. In 1980, Chaussy and colleagues [7] published their series of 21 patients treated with this noninvasive technology. Since then, SWL has become the first-line treatment for most renal stones. Although a great deal of work has been done developing new technology for SWL, the overall success rates have not met expectations. While second- and third-generation lithotripters have decreased both expense and analgesic requirements, the treatment success rates have not improved significantly since 1984. In fact, select studies have shown lower stone-free rates with more recent lithotripters [8]. This fall in rates may be a result of the trend toward smaller focal zones and higher peak pressures in the newer lithotripter designs.

More recently, flexible ureteroscopy has been added to the urologist's armamentarium for the treatment of renal stones. Less invasive than PCNL and more versatile than SWL, ureteroscopy has widespread indications, in part because

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of the limitations and shortcomings of PCNL and SWL. The indications for performing ureteroscopy can be found in Box 1. In 1912, Hugh Hampton Young performed the first ureteroscopy, which was on a 2-month-old child with dilated ureters secondary to posterior ureteral valves [9]. Fifty years later, the introduction of fiber-optic technology enabled Marshall [10] to perform the first flexible ureteroscopy. While flexible ureteroscopes preceded rigid ones, they were rudimentary, lacking irrigation, working channels, and active deflection. By the late 1970s rigid ureteroscopes were used to treat ureteral tumors and, by the late 1980s, ureteroscopes were being used to treat renal stones [11,12]. With the introduction of smaller ureteroscopes and the development of lithotrites small enough to be passed through a working channel, ureteroscopy has become an important technique for renal calculi.

Although not commonly performed, laparoscopic pyelolithotomy and laparoscopic-assisted PCNL warrant some discussion. In 1992, Lee and Smith [13] first described using laparoscopy as an adjunct to renal stone removal and as a means for guiding placement of percutaneous access. Subsequent to that, renal stones with concomitant ureteropelvic junction (UPJ) obstructions were treated laparoscopically [14]. This has led to laparoscopic pyelolithotomy as the sole treatment of renal stones, which has been shown to be safe, with success rates ranging from 62.5% to 100% [15–17]. This approach is particularly useful for concomitant management of renal stones and UPJ obstruction.

Treatment: preoperative planning

Appropriate preoperative evaluation for renal stones is critical and can be divided into two categories. The first category includes factors related to renal stone imaging, such as stone burden, location, level of obstruction, and renal anatomical defects. The second category involves patient clinical factors, which are variables answered through a proper history, physical examination, and laboratory results.

Box 1. Indication for performing ureteroscopy

SWL failure
Lower pole stone
Cystine stones
High CT attenuation level
Morbid obesity
Musculoskeletal deformities
Bleeding diathesis
Infundibular stenosis
Patient preference

Stone imaging factors

Four modalities are commonly used to image renal stones. These are CT, intravenous pyelogram, ultrasound, and plain radiograph of the kidneys, ureters and bladder (KUB). Of these four, CT provides the highest sensitivity and specificity for identifying urinary calculi and is commonly the primary modality for diagnosing flank pain and suspected urolithiasis [18,19]. Beyond the identification of stones, CT provides useful information for selecting an appropriate treatment, including the size, number, attenuation levels, and location of stones within the kidney, as well as the presence of hydronephrosis, skin-to-stone distance, and anatomic variations. Of these characteristics, stone burden still remains the primary determinant when selecting treatment.

Stone burden (size)

When measuring stone burden on CT, axial images provide precise measurements for stone length and width but consistently overestimate craniocaudal length [20,21]. Coronal reconstruction of CT images or KUB can be used to provide a more accurate means for assessing craniocaudal length, which is often greater than the greatest axial length [21]. Improvements in stone volume prediction, either via CT renderings or more accurate volume assessments, would likely improve treatment decisions for many borderline renal stone cases.

In general, when stone burden increases, stone-free rates decrease. It is generally accepted that for stones greater than 2 cm and for staghorn stones, PCNL is the recommended treatment. PCNL attains stone-free rates of 71% to 95% and is the best modality for large stone burdens because stone fragments are removed directly through the nephrostomy tract [22–24]. SWL leaves fragmented stones to be passed by the patient and some series have identified stone-free rates as low as 41% to 54% for large stones [25,26]. However, Grasso and colleagues [27], using ureteroscopy, achieved similar success rates to PCNL for select renal stones greater than 2 cm, although

these results have not been duplicated. The authors also recommend PCNL when treating struvite stones. For stones less than 2 cm, the treatment algorithm becomes more complicated as more variables are introduced.

Stone location

Despite recent reports of lower stone-free rates with more recent extracorporeal lithotripters, SWL remains the primary treatment for most renal stones less than 2 cm. Treatment success for SWL can be further differentiated by stone location. While stones in the renal pelvis are the most amenable to SWL, with stone-free rates of 56% to 80%, the same cannot be said for lower pole stones [28]. In a multi-institutional, prospective, randomized study comparing PNL to SWL for lower pole stones, stones greater than 1 cm treated with SWL achieved only a 21% stone-free rate compared with a 67% stone-free rate for stones less than 1 cm. Notably, this study used tomograms to assess treatment success [24]. Pearle and colleagues evaluated lower pole stones 1 cm and less and found no significant difference in stone-free rates between ureteroscopy and SWL. In this randomized trial, the stone-free rate was low in both groups: 35% for SWL and 50% for ureteroscopy. In this series, treatment success was defined by CT, an especially sensitive modality for identifying retained fragments. This study showed that patients who underwent SWL had improved convalescence, used less pain medication on average, and would be more likely to choose the same procedure again compared with patients who underwent ureteroscopy [29]. For stones less than 2 cm in the upper and middle calyces, SWL stone-free rates range from 57.4% to 76.5%, supporting this approach in most ordinary upper-tract stone cases [28].

Stone composition

Stone composition is rapidly becoming a measurable and influential factor in determining SWL success. While cystine stones are often refractory to SWL because of their ductile nature, calcium oxalate monohydrate and brushite stones resist fragmentation because of their density and hardness [30]. While it is often difficult to confirm stone composition without a sample for analysis or a history of a metabolic syndrome, imaging can be helpful in predicting composition and, possibly, stone fragility. Pure uric acid stones, which are considered amenable to SWL, are suspected when a stone seen on CT is radiolucent on plain radiographs. Meanwhile, a ground glass appearance on a KUB may suggest a cystine stone. More recently, CT attenuation levels have been used to differentiate stone compositions. In vitro studies show attenuation levels for uric acid and struvite stones to be consistently below 1000 Hounsfield units (HU), whereas calcium oxalate and hydroxyapatite usually exceed 1000 HU [31,32]. More recent studies have extended this idea one step further by directly correlating SWL success rates with CT attenuation levels. Joseph and colleagues [33] reported stone clearance rates following SWL of 54.5% for attenuation levels in excess of 1000 HU, compared with 85.7% for attenuation levels between 500 and 1000 HU and 100% for attenuation levels less than 500 HU. Gupta and colleagues [34], using 750 HU as a cutoff, found stone clearance rates of 65% for stones with attenuation levels greater than 750 HU and 90% for those with attenuation levels less than 750 HU.

Although stone composition may give insight into treatment selection, the range of fragility within a single composition can vary dramatically [35]. For example, cystine stones with rough surfaces are significantly more fragile than cystine stones with smooth surfaces [36]. No consensus data exist on the use of HU data and stone fragility, although evidence points to higher HU stones being SWL resistant. In addition, one study found skin-to-stone distance measured by CT more predictive than HU density, emphasizing the importance of a lithotriptor's maximum focal distance on stone-free rates [37]. Regardless, with the availability of noncontrast CT, urologists have access to more data than ever before. Stricter criteria for surgical decision-making are certain to emerge in the coming years.

Lower pole anatomy

Although multiple studies have evaluated the lower pole anatomy in attempts to define favorable characteristics for SWL, conflicting results have made clear guidelines impossible to develop. In addition, imaging used to measure anatomical findings requires contrast enhancement, which subject patients to an additional study and risks. Sampaio and colleagues [38] introduced the concept of an acute lower-pole–to–infundibulopelvic angle causing lower stone-free rates. Since then, it has also been suggested that lower pole infundibular width greater than 4 mm and a lower

pole infundibular length greater than 3 cm may also contribute to lower stone-free rates [39,40]. More recently, Sorenson and Chandhoke [41] reviewed excretory urography for 190 patients who underwent SWL. The investigators were unable to correlate calyceal anatomy to SWL success.

Hydronephrosis

The diagnosis of renal stones in the setting of hydronephrosis raises concerns regarding treatment selection. In the presence of renal stones, the etiology of the hydronephrosis is unclear. Hydronephrosis may stem from a physiologic obstruction, such as a UPJ, in which case fragmentation of the stone without treating the obstruction would most certainly result in retained fragments; or the hydronephrosis may be caused by the stone itself, in which case treatment of the stone would likely relieve the obstruction. The use of SWL in the setting of staghorn stones in hydronephrotic systems has resulted in stone-free rates of 26% to 56%, compared with 70% to 80% for PCNL [42,43]. The high failure rates for SWL supports the principle that SWL is contraindicated in the setting of hydronephrosis. Treatment selection in these cases should involve PCNL or ureteroscopy, either of which can diagnose and treat an underlying abnormality causing the obstruction.

Outcomes: anatomical variants

Horseshoe kidney

Horseshoe kidney is the most common renal fusion anomaly of the kidney and the risk for stones is greater than 20% [44,45]. Although stone fragmentation with SWL can be performed, the high insertion of the ureter, its anterior course over the isthmus, and the variation in the arterial and venous vasculature may prevent the passage of fragments and contribute to lower stone-free rates. Additionally, the more anterior position of horseshoe kidneys results in a longer skin-to-stone distance. For small stones in horseshoe kidneys, SWL can achieve acceptable stone-free rates of 50% to 79% [46–48]. However, large stones within horseshoe kidneys, especially stones greater than 2 cm, are better approached using PCNL with stone-free rates of 72% to 87% [49–51].

Calyceal diverticulum

Calyceal diverticula are nonsecretory urothelial-lined compartments in communication with the renal collecting system. The incidence of stones forming in calyceal diverticula range from 10% to 50% [52]. While asymptomatic diverticular stones can be observed, stones causing infection, hematuria, or pain are indications for treatment. Both stone characteristics and diverticular characteristics influence treatment selection for calyceal diverticular stones. Although SWL has been used to treat diverticular stones, the stone-free rates of 4% to 58% are not comparable to that of PCNL, which are 85% to 93%. In addition, PCNL provides excellent access for obliterating the diverticular sac with obliteration rates in excess of 80% [53–56]. Ureteroscopy is capable of achieving stone-free rates of up to 50% to 70%, but diverticular obliteration rates are low (18%). More often balloon dilation or holmium laser incision is used to open the diverticular os to allow drainage [57–59]. Finally, laparoscopic approaches to calyceal diverticular stones have been reported with good success. However, essential to success is proper patient selection. This means the selection of patients with symptomatic diverticula, thin overlying renal parenchyma, and anterior lesions inaccessible by endoscopic techniques [60].

Outcomes: patient clinical factors

Obesity

Morbidly obese patients with renal stones present a therapeutic challenge because they frequently exceed the weight limits for SWL machines, leaving ureteroscopy or PCNL as available options. For obese patients who do not exceed the weight limit, Pareek and colleagues [37] found in a series of lower pole stone patients that a skin-to-stone distance greater than 10 cm as determined on axial CT images is predictive of failure. Additionally, even though body mass index (BMI) has been shown to be an independent predictor of SWL success, this study showed skin-to-stone distance to be a more reliable predictor than either BMI or HU measurements alone [37,61]. For patients who are not SWL candidates, ureteroscopy is an excellent option for stones less than 2 cm. Stone-free rates of 70% to 78% have been reported [62,63]. Dash and colleagues [64] performed a case-matched comparison of morbidly obese and normal-weight patients with renal stones treated with ureteroscopy and found no significant difference in success or complication rates. For obese patients with large stone burdens,

PCNL may require longer instrumentation but can provide stone-free rates of up to 83% to 88% without any significant differences in morbidity compared with nonobese patients [65,66].

Bleeding diathesis

Renal lithiasis patients with a bleeding diathesis also present a therapeutic dilemma for urologists. Uncorrected coagulopathy is an absolute contraindication for both SWL and PCNL, making it necessary to correct any coagulopathies before surgery [67]. Alternatively, ureteroscopy with holmium laser lithotripsy has been shown to be both effective and safe, even in the setting of uncorrected bleeding diathesis [68].

Transplant kidneys

The incidence of transplant kidney stones is relatively low, from 0.3% to 3% [69,70]. Initial treatment should be directed at relieving obstruction before definitive stone management. The superficial location of transplant kidneys facilitates a percutaneous approach for stone removal, which is the most common method of treatment [71,72]. Ureteroscopic access on the other hand is often difficult and the variability of the length and course of the ureter can make this approach especially challenging. Nevertheless, treatment success rates have been reported to be as high as 92% [73]. Although the pelvic location of transplant kidneys can preclude localization of the stone, SWL on the prone position has been used to treat transplant kidneys. Although the data is limited, the reported success rates for SWL for stones less than 2 cm is high, with two series reporting 100% success [72,74].

Pilots

Renal lithiasis, both symptomatic and asymptomatic, presents a unique problem for aviation pilots. Due to Federal Aviation Administration guidelines, pilots with urinary lithiasis must provide documentation that there is no residual stone or significant likelihood of recurrence to prevent sudden in-flight incapacitation. For pilots wanting an expeditious treatment, the selection of treatment goes beyond success rates but includes time to becoming stone free. In a retrospective review of aviation pilots with urinary stones, Zheng and colleagues [75] found that patients treated endoscopically were much more likely to be rendered stone free after one procedure compared with those treated with SWL (100% versus 35%). They also showed that the average number of work weeks lost for SWL, PCNL, and ureteroscopy were 4.7, 2.6, and 1.6, respectively. Based on these findings, the recommendation is to allow a 1- to 2-week trial for stones that are likely to pass, and otherwise to proceed with endoscopic treatment.

Outcomes: morbidity of key procedures

Percutaneous nephrolithotomy

Compared with ureteroscopy and SWL, PCNL has the highest rate of major complications with the longest convalescence. The overall major complication rate for PCNL is between 4% and 8% [76,77]. With advancements in radiographic technology, percutaneous access techniques, and urologic instrumentation, transfusion rates have significantly declined since the earlier days of PCNL. Contemporary rates for transfusion range from 2% to 23% [76,78], while major vascular injuries requiring further intervention occurs in only 2% to 3% of cases [22,77]. Contraindications to PCNL can be found in Box 2.

Pulmonary complications, such as hydrothorax and pneumothorax, are usually related to the percutaneous access. An infracostal approach should be used when possible because complication rates of a supracostal approach are threefold greater, ranging from 23% to 100% for supra eleventh rib and 1% to 13% for supra twelfth rib [79,80].

Injury to other internal organs is rare, with colonic injury being the most common [81]. Colonic perforation is usually due to transcolonic percutaneous renal access. Patients most at risk include those with prior abdominal surgery where colonic adhesions are more likely, those with retrorenal colons (more common on the left), and those with a history of constipation or other

Box 2. Contraindications to PCNL

Absolute
- Uncorrected bleeding diathesis
- Hydatid cyst

Relative
- Urinary tract infection
- Comorbidity precluding appropriate anesthesia
- Body habitus

causes of colonic distension. Colonic injury is also more likely with lower pole and lateral renal access.

The most common medical complication associated with PCNL is postoperative fever (23–25%) [76,77]. Only a fraction of these febrile patients develop urosepsis, which has an overall incidence of 1% to 2% after PCNL [82]. Patients with infected urine from the renal pelvis or infected renal stones are at a fourfold greater risk for developing urosepsis. Preoperative urinalysis and culture are necessary to rule out infection before PCNL.

Extracorporeal shock wave lithotripsy

The convalescence and morbidity for SWL has been shown to be less than those for both ureteroscopy and PCNL, making SWL the preferred treatment for most renal stones [83–85]. The most common complication following SWL is postoperative pain, occurring in 2% to 4% of cases followed by urinary tract infection or sepsis in 1% to 2% of cases [86,87]. Contraindications to performing SWL are found in Box 3.

The incidence of subcapsular or perinephric hematoma is less than 1% for symptomatic hematomas but up to 4.1% to 19% for hematomas overall [88–90]. Knapp reviewed 3,620 patients treated with the HM3 Dornier lithotriptor and found 24 hematomas (0.66%). The only risk factor was preexisting hypertension, with the incidence of hematoma at 2.5% for hypertensive patients and 3.8% for those with poorly controlled hypertension [91]. Serra and colleagues [92] reviewed 21,699 SWL procedures, finding 31 (0.28%) cases of renal hematoma. Of the hematoma formers, 46% were being treated for hypertension, 25% had corrected coagulopathies, and 42% had prior SWL on the affected kidney. Only 10 (31%) of these patients required transfusions. The rest were managed conservatively. Dhar and colleagues [89] evaluated 415 SWL treatments to determine risk factors associated with hematoma and found age to be the only significant factor. Rubin and colleagues [90] performed CT scans on 50 patients before and after SWL. They demonstrated that 15% of patients experienced asymptomatic subcapsular hematomas while 4% of patients had asymptomatic intrarenal hematomas. This evidence suggests that the true incidence of hematoma for SWL is underreported.

Box 3. Contraindications to SWL

Bleeding diathesis
Active urinary tract infection
Weight exceeding gantry limit
Pregnancy

The natural course for patients with SWL-induced renal hematomas was evaluated by Krishnamurthi and Streem [93], who followed 19 patients with post-SWL hematomas for an average of 19.6 months. They found radiographic resolution of the hematoma within 2 years was expected without adverse effects on blood pressure or renal function.

Steinstrasse, another SWL complication, is a column of stones within a ureter that may cause partial or complete obstruction. It can occur with all small fragments, a large leading fragment, or all large fragments. Although placement of a ureteral stent before SWL can reduce the incidence of steinstrasse, it cannot prevent it from occurring, nor does it change the mode of presentation [94]. The incidence of steinstrasse is between 3% and 6% [90,95]. The major risk factor is stone size, with stones greater than 2.0 cm having a 3.7-fold increased risk when compared with smaller stones [94,95]. Presentation of steinstrasse can vary. Madbouly and colleagues [95] reviewed 4,634 patient treated with SWL and found that 72% of patients forming steinstrasse presented with obstruction and fever while 23% had silent obstruction and 5% with solitary renal units had anuria. They also found that steinstrasse was significantly more common in patients with stones treated with shock wave energy more than 22 kV. Sayed and colleagues [96] reviewed 52 patients who developed steinstrasse and found that 25 patients passed their stones with conservative measures, while repeat SWL was successful for 12 of 15, and percutaneous nephrostomy placement was effective in 10 of 12 patient. For those who failed SWL or percutaneous nephrostomy, ureteroscopy was successful in 3 of 5 patients, the remaining 2 requiring open ureterolithotomy. Finally, the use of expulsion therapies, such as tamsulosin, has been shown to reduce the number of colic episodes and the severity of pain for steinstrasse, but has not been shown to reduce the incidence of steinstrasse or the time to resolution [97].

The association between SWL and hypertension is not clear. Lingeman and colleagues [98]

evaluated 731 patients who underwent SWL with approximately 2-year follow-up and found no significant difference in the annual incidence of hypertension between SWL patients (2.4%) and non-SWL patients (4.0%). They did find, however, an average increase in diastolic blood pressure (0.78 mm Hg) that was significantly greater than that for the general population. Krambeck and colleagues [99] compared 288 patients treated with an HM3 lithotripter with urolithiasis patients managed nonoperatively. They found that SWL patients were more likely to have not only hypertension but diabetes mellitus as well. Their data showed that new-onset diabetes was related to the total number of shocks and the average intensity, while bilateral SWL was associated with hypertension.

Ureteroscopy

With smaller scopes and the almost uniform replacement of electrohydraulic lithotripters with holmium lasers as the primary energy source for lithotripsy, major ureteroscopic complications over the past decade have decreased from just under 10% to less than 1% [100]. Although complication and success rates for intrarenal ureteroscopy has improved significantly, the longer convalescence continues to preclude it from being routinely chosen over SWL as a first-line treatment [83]. A major downside of ureteroscopy for renal stones is the typical requirement of a stent. Because many urologists perform all upper-tract ureteroscopy with a sheath, postoperative stent placement is common. Because many straightforward, small-volume stones may be treated with SWL without a stent, patients often prefer SWL in cases that may be ''borderline.'' Certainly, the issue of stent discomfort may play into the decision-making for smaller (<2 cm, high HU (>1000 HU)) stones.

Because renal stones often have coexisting ureteral calculi, ureteroscopic complications for renal stones are difficult to distinguish from complications of ureteral stones. Most studies report the combined complication rates of all upper-tract ureteroscopy, which is higher than complication rates for intrarenal ureteroscopy alone. Recently, Fabrizio and colleagues [101] reported on 100 patients treated ureteroscopically for renal stones. The complication rate was 6% and those complications, which included fever and urinary tract infection, were all minor. Schuster and colleagues [102] reported on 95 patients with lower pole stones treated with ureteroscopy. Their complications included one aborted ureteroscopy due to bleeding obstructing the visual field and 10 minor postoperative complications, including urinary retention, fever, and pain. Pearle and colleagues [83] found a 20% intraoperative complication rate including two ureteral perforations and five failed access. They also reported a 20% postoperative complication rate with 6 patients experiencing pain, and one ureteral obstruction. Stav and colleagues [29] evaluated 81 patients who underwent intrarenal ureteroscopy for SWL failures. They found an overall complication rate of 16% with 2 major complications (one myocardial infarct, one cerebrovascular accident) and 11 minor complications (six urinary tract infections and five cases aborted for extravasation or bleeding that obstructed the view).

Outcomes: clinical recommendations by location

To ''tie things together,'' the authors present final recommendations on the treatment of renal stones by stone location (Fig. 1). These recommendations assume that no specific comorbidities or complex anatomic situations exist. Upper- and mid-caliceal stones are grouped together, as the authors believe these locations are clinically indistinguishable. Stones greater than 2 cm should be treated with PCNL. For stones between 1 cm and 2cm, those with unfavorable characteristics (eg, attenuation level >1000 HU, skin-to-stone distance >10 cm, or history of cystine stones), the authors recommend ureteroscopy. For the remaining upper-caliceal stones, SWL is the authors' choice as primary treatment.

While renal pelvis stones are the most amenable to SWL, they still follow the general rules of upper- and mid-caliceal stones. Stones greater than 2 cm should be approached with PCNL while noncystine stones less than 2 cm are excellent candidates for SWL. If SWL is attempted for larger stones (>1.5–2.0 cm), a ureteral stent is generally recommended to reduce the likelihood of steinstrasse [96,103].

Lower caliceal stones greater than 1 cm should be approached with PCNL as a first-line treatment. Stones less than 1 cm with unfavorable characteristics (eg, attenuation level >1000 HU, skin-to-stone distance >10 cm, or history of cystine stones) should be treated with ureteroscopy. The remaining stones are managed with SWL.

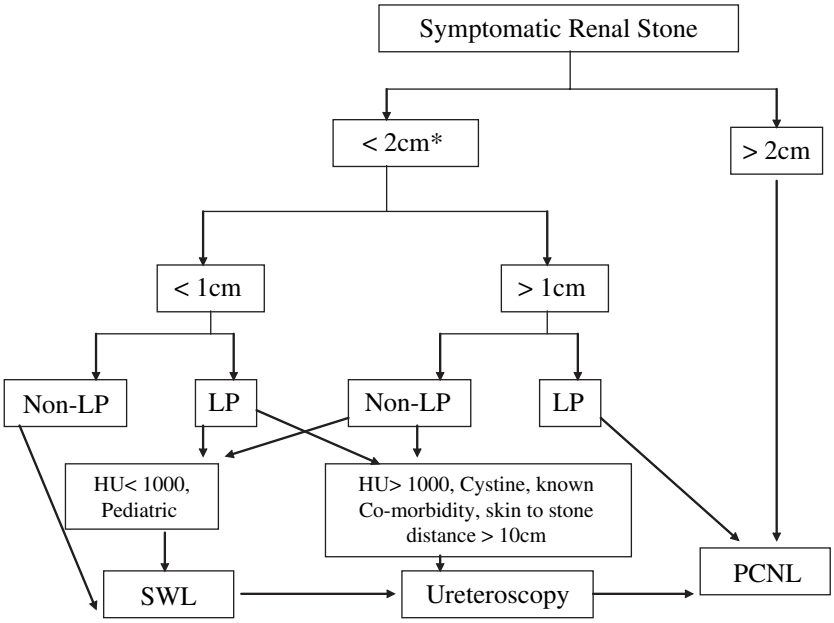

Fig. 1. Recommendations on the treatment of renal stones by stone location. LP, lower pole; URS, ureteroscopy.

Treatment and outcomes: summary

In this review of treatments and outcomes for renal stones, the authors provide an algorithm based on available outcome data for SWL, ureteroscopy, and PCNL. This algorithm, while it may help to guide the practicing urologist, is not static. New technology and research will continue to evolve, producing a wider choice of treatments, including more effective treatments, leading to higher success rates. While most symptomatic renal stones have been considered a surgical disease, medical management will come to have a greater role.

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Treatment Selection and Outcomes: Ureteral Calculi

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In 1997, the American Urological Association (AUA) published guidelines for the management of ureteral stones [1]. In the decade since then, there have been major changes in the management of ureteral calculi. Most notably, medical therapy to facilitate passage of ureteral stones has been popularized, and there have been tremendous advances in ureteroscopic technology (see the article by Beiko and Denstedt elsewhere in this issue). These developments have improved the outcomes of ureteral stone management for large numbers of patients.

This article focuses on the two main procedural treatments for ureteral calculi, shock wave lithotripsy (SWL) and retrograde ureteroscopy (URS). Additional procedural alternatives used at present include percutaneous/antegrade ureteroscopy (Perc-URS), and laparoscopic ureterolithotomy. The current status of medical expulsive therapy for ureteral stones is also reviewed.

Although randomized clinical trials comparing treatments are available for only a few specific situations, knowledge gleaned from nonrandomized comparative series, single-treatment case series and clinical experience allows us to define a number of preoperative factors that are associated with variation in clinical outcomes. Inasmuch as some of these outcome variations relate to specific treatments, these preoperative factors can be used to assist in treatment selection for a given patient. After reviewing these factors, and then discussing the efficacy and morbidity of the various treatments in general, this article concludes with specific recommendations for treatment of patients who have ureteral stones.

Stone factors

Size

The burden of calculi within the ureter can be determined exactly from mutlidimensional imaging such as CT, but in clinical practice, the greatest linear dimension of a stone as visible on CT or plain abdominal radiograph is the parameter typically used to determine stone size.

Stone size is the major objective parameter determining the likelihood of spontaneous stone passage. In summarizing the literature, the authors of the 1997 AUA Ureteral Stone Guidelines reported that distal stones less than 5 mm in size passed spontaneously with a rate of 71% to 100%, whereas distal ureteral stones from 5 to 10 mm in size passed with a rate of 25% to 46% [1]. There is a roughly linear relationship between stone size and likelihood of spontaneous passage, with one study reporting passage rates of 87%, 72%, 47%, and 27% for stones measuring 1, 4, 7 and 10 mm, respectively, on CT scan [2].

As yet, there are few data on the association of stone size with the effectiveness of medical expulsive therapy (see below for description of medical expulsive therapy). Given that smaller stones are more likely to pass than larger ones without any therapy, it is reasonable to conjecture that the impact of medical explusive therapy will be relatively greater for larger stones. In the author's experience this appears to be the case, but a systematic study has not been undertaken.

Stone burden is a major determinant of the success of procedural interventions for ureteral calculi. The 1997 AUA Ureteral Stone Guidelines

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reported that the stone-free rates of SWL and URS for proximal ureteral stones less than 1 cm in size were 84% and 56%, respectively, compared with 72% and 44%, respectively, for proximal ureteral stones greater than 1 cm [1]. Current literature (Table 1) suggests that the impact of stone size on the outcome of URS is lessening (95% versus 90% stone free, for stones less than 1 cm and greater than 1 cm, respectively), whereas it remains important for SWL (75%–80% versus 44%–60% stone free, for stones less than 1 cm and greater than 1 cm, respectively) [3–11].

For Perc-URS, open surgical ureterolithotomy, or laparoscopic ureterolithotomy, stone size appears to have a negligible effect on the success of stone removal, given that most of the reported procedures have been in selected patients who have large stone burden.

Location

The 1997 AUA Ureteral Stone Guidelines reported that spontaneous passage rates of distal and proximal ureteral stones less than 5 mm in size were 71% to 100% and 22% to 81%, respectively [1]. Location in the ureter also appears to be a determinant of stone removal efficacy with URS, whereas it does not appear to impact the results of SWL substantially. Literature available for the 1997 AUA Ureteral Stone Guidelines indicated that for ureteral stones less than 1 cm in size, URS provided a median stone-free rate of 89% in the distal ureter, but only 56% in the proximal ureter. SWL effectiveness did not vary with location; the median stone-free rates of 85% and 84% for stones less than 1 cm in the distal and proximal ureters, respectively, were similar [1]. More recent literature (Table 2) suggests that the gap between stone-free rates for URS comparing the proximal and distal ureter has closed somewhat [4,6–8,10–14]. There is a continued high success rate for URS in the distal ureter (98%), and an improvement in stone-free rate for proximal ureter stones to 80%. SWL success rates remain approximately equivalent by location (77%–89% distal, 70%–82% proximal). A decade ago, a proximal ureteral stone portended a poor success rate for URS, and therefore SWL was favored in most cases. Although a proximal location still diminishes its success somewhat, URS efficacy has now improved to the point that it is a good option for calculi in the proximal ureter.

There have been two randomized clinical trials published of URS and SWL for distal ureteral stones. Peschel and associates [15] in 1999 reported on 80 patients randomized to URS with 6.9 or 9.5 Fr rigid ureteroscopes, or SWL with

Table 1
Selected recent series comparing results of SWL and URS, by size

	SWL		URS	
	<1 cm (stone-free/treated, %)	>1 cm (stone-free/treated, %)	<1 cm (stone-free/treated, %)	>1 cm (stone-free/treated, %)
Stone-free rate, initial treatment	290/347, 84% [4] 958/1294, 74% [6] 72/110, 65% [9]	40/95, 42% [4] 77/178, 43% [6] 19/34, 56% [9]	315/319, 99% [3] 56/63, 89% [4] 240/261, 92% [8] 190/207, 92% [10] 396/408, 97% [11]	161/164, 98% [3] 45/52, 87% [4] 52/59, 88% [8] 134/155, 86% [10] 77/92, 84% [11]
Overall stone-free rate, initial treatment	1320/1751, 75%	136/307, 44%	1197/1258, 95%	469/522, 90%
Stone-free rate, including retreatment	322/347, 93% [4] 193/388, 50% [5] 475/552, 86% [7] 1069/1294, 83% [6]	77/95, 81% [4] 93/274, 34% [5] 199/243, 82% [7] 104/178, 58% [6]		
Overall stone-free rate, including retreatment	2059/2581, 80%	473/790, 60%		

All series contain data for stones <1 cm and >1 cm.

Table 2
Selected recent series comparing results of SWL and URS, by location

	SWL		URS	
	Distal (stone-free/ treated, %)	Proximal (stone-free/ treated, %)	Distal (stone-free/ treated, %)	Proximal (stone-free/ treated, %)
Stone-free rate, initial treatment	105/131, 80% [4] 529/639, 83% [7] 98/182, 54% [6]	218/301, 72% [4] 274/397, 69% [7] 750/1071, 70% [6]	79/79, 100% [12] 152/161, 94% [8] 179/184, 97% [10] 405/417, 97% [11] 331/334, 99% [14]	44/48, 92% [12] 102/120, 85% [8] 86/115, 75% [10] 30/36, 83% [11] 91/128, 71% [14]
Overall stone-free rate, initial treatment	732/952, 77%	1242/1769, 70%	1146/1175, 98%	353/447, 80%
Stone-free rate, including re-treatment	120/131, 92% [4] 213/223, 95% [13] 406/446, 91% [7] 138/182, 76% [6]	270/301, 90% [4] 227/244, 93% [13] 226/268, 84% [7] 817/1071, 76% [6]		
Overall stone-free rate, including re-treatment	877/982, 89%	1540/1884, 82%		

All series contain data for distal and proximal stones.

a Dornier MFL 5000 lithotriptor. The success rates were high in both groups—100% and 90%, respectively. The study authors concluded that URS was superior, based on shorter operative time (23 versus 58 minutes) and days to stone clearance (2.0 versus 9.9 days). The opposite conclusion was reached by Pearle and colleagues [16] in evaluating 64 patients randomized to URS with a 6.9 Fr rigid ureteroscope, or SWL with a Dornier HM-3 lithotriptor. Success rate was 100% in both groups, but operative time was shorter in the SWL group (34 versus 65 minutes), and this group had fewer complications (9% versus 25%). Discrepancies between the two studies, especially with regard to operative time, cannot easily be explained. There appears to be no clear first choice derived from these two studies.

Three recent comparisons of treatments of proximal ureteral stones, nonrandomized but with contemporaneous treatment and similar techniques, are enlightening. As presented in Table 3 [17–19], the overall initial stone-free rate of SWL for proximal ureteral stones less than 1 cm was 74%, compared with 92% for URS. For stones larger than 1 cm, the corresponding rates were 41% for SWL and 84% for URS. Complication rates were similar between the two treatments. It is clear that the initial stone-free rate for proximal ureteral calculi is greater with URS than for SWL, at any size. When one considers the possibility of retreatment, however, the results of which were not reported in these three papers, it would be expected that the success rate of SWL for proximal ureteral calculi would approach that of URS.

Composition

Stone composition is undoubtedly important in determining efficacy of stone treatment, especially SWL. Two practical issues arise, however, that render stone composition of relatively little clinical importance for the majority of patients undergoing SWL. First, the most dramatic differences are found with radiolucent uric acid calculi (easily fragmented with SWL) and relatively radiolucent cystine calculi (often refractory to SWL) [20]. This is useful information in selecting stone treatment, but only for the small minority of patients who have uric acid or cystine stones. For the majority of patients, who have calcium-based ureteral stones, the exact composition of the stone is rarely known. Moreover, the responsiveness to SWL varies considerably even among patients who have chemically similar stones [20]. To some extent, density of the stone on CT (measured in Hounsfield units [HU]) predicts stone composition, but only very roughly [21,22]. Uric acid stones in vitro have CT density below 1000 HU, and calcium oxalate and calcium phosphate typically have densities

Table 3
Three series comparing SWL and URS for proximal ureteral calculi

	SWL		URS	
	<1 cm (stone-free/ treated, %)	>1 cm (stone-free/ treated, %)	<1 cm (stone-free/ treated, %)	>1 cm (stone-free/ treated, %)
Stone-free rate, initial treatment	28/35, 80% [17] 44/73, 60% [18] 58/68, 85% [19]	10/20, 50% [17] 17/38, 45% [18] 18/51, 35% [19]	17/17, 100% [17] 73/81, 90% [18] 41/45, 91% [19]	13/14, 93% [17] 26/28, 93% [18] 43/56, 77% [19]
Overall stone-free rate, initial treatment	130/176, 74%	45/109, 41%	131/143, 92%	82/98, 84%

greater than 1000 HU [21]. Beyond this gross division, however, the overlap of values precludes any more exact determination of stone composition by CT density. Recent studies suggest that variations in CT density and composition at the microscopic level may account for the lack of association of CT density of the whole stone with overall stone composition [23].

Imaging characteristics

CT is the state of the art for detecting stones, and additionally provides important anatomical information about associated conditions. Although the correlation of CT density and composition is inexact, as explained above, there does appear to be good correlation between a stone's CT density and its fragmentation by SWL [24]. Most studies have evaluated renal stones (see the article by Wen and Nakada elsewhere in this issue), but a few have assessed ureteral calculi. Gupta and colleagues [25] reported on 112 patients who had renal and proximal ureteral calculi undergoing SWL, and found that when the calculus had a CT density 750 HU or less, the stone-free rate was 88%, but when the CT density was greater than 750 HU, the stone-free rate fell to 65%. Pareek and colleagues [26] evaluated 30 ureteral stones treated with SWL. The mean CT stone density in the 21 stone-free patients was 505 HU, compared with 889 HU in stones in the 9 patients who had residual stones.

Patient factors

Obesity

Several studies have demonstrated that obesity, whether distinguished by body mass index [27,28] or anatomical measurements such as skin-to-stone distance [29], negatively impacts the effectiveness of SWL. The proximal ureter is farther from the skin of the flank than the kidney, so the ability to get the stone within the focal zone of the lithotriptor is even more limited in ureteral compared with renal stone patients. ''Blast path'' focusing, placing the stone within the long axis of the SWL focal zone, is an option, but delivers less energy to the stone.

URS is an excellent alternative to SWL in the obese patients. Although distortion of the lower tract anatomy can occasionally make accessing the ureter challenging, once the endoscope is in the ureter, the technical aspects of the procedure are no different than in a patient of normal weight. Nguyen and Belis [30] described 48 URS for stones in obese patients averaging a weight of 288 lbs. The stone-free rate after one procedure was 78%, and 97% after a second URS. Andreoni and associates [31] reported on URS treatment for proximal ureteral or renal calculi in 10 patients who had a mean body mass index of 54. The stone-free rate was 70%.

Medical condition

Although ureteroscopy under intravenous sedation or local anesthesia has been reported [32,33], most urologists prefer regional or general anesthesia. SWL can often be performed under intravenous or oral sedation, although some data suggests that when using a lithotripter with a small focal zone, the immobility of general anesthesia may be associated with improved results [34]. Thus if the medical condition of the patient precludes or increases the risk of certain types of anesthesia, this may impact treatment decisions. In addition, untreated coagulopathy is a contraindication to SWL. Although medical coagulopathies such as von Willebrand's disease and hemophilia can be managed during SWL to allow safe

treatment [35,36], and many patients on therapeutic antiplatelet agents or warfarin can temporarily stop their medications, the coagulopathy in some patients either cannot or should not be corrected. In such cases, URS has been shown to be safe [37].

Patient preference

Because ureteral stones are rarely life- or organ-threatening, considerations derived from overwhelmingly important efficacy outcomes (eg, survival in advanced bladder cancer) are not necessarily paramount in decision-making about ureteral stones. Rather, decisions about treatment predominantly involve quality-of-life considerations that take into account not only efficacy (which is relatively straightforward), but also invasiveness and spectrum of complications. These latter considerations are very difficult to define. Patients' opinions about stone treatment efficacy are usually clear—the patient prefers a stone-free state to a stone-bearing one! Opinions about potential complications are not so clear, with tremendous variation in patients' opinions about complications. Properties of a complication such as its severity, degree of unpredictability, and overall incidence all play a role, with differing weight for different patients. Compare, for example, a complication that is common but relatively minor (eg, renal colic requiring additional oral narcotic medication) with a one that is rare but potentially very significant (eg, ureteral stricture). Reasonable, thoughtful patients can differ widely in their assessment of the relative importance of these complications, with some being swayed by the relatively high incidence in one case, and others by the severity of the complication in another. Finally, the intensity of the measure required to reduce the risk of a complication must be considered by the patient; a stent may reduce the incidence of ureteral obstruction in some circumstances, but at a price of irritative voiding symptoms. As treating urologists, the best we can do for our patients when counseling them about treatment choices is provide the best information possible, provide clear answers to questions, and assist the patient with determining the pertinent considerations to be made in the decision.

Other modalities

Medical expulsive therapy

In 1994, Borghi and associates [38] published the initial report of nifedipine combined with corticosteroids to facilitate stone passage. For the next few years there was little work on this topic, but in 2000, two studies by Cooper and colleagues [39] and Porpiglia and coworkers [40], consecutively published in the same journal issue, renewed interest in medical expulsive therapy.

A recent meta-analysis considered all randomized controlled trials in which calcium channel blockers or alpha blockers were used to treat ureteral stones, including 691 patients in nine clinical trials in the final meta-analysis [41]. Mean stone sizes ranged from 3.9 to 7.8 mm, and in all but one study calculi were in the distal ureter. The treatment regimen included an alpha blocker alone in five studies (including tamsulosin in four), tamsulosin with corticosteroids in one, nifedipine alone in one, and nifedipine with corticosteroids in three (some studies had more than one treatment arm). Typical doses included: tamsulosin 0.4 mg daily, terazosin 5 mg daily, doxazosin 4 mg daily, and nifedipine slow-release 30 mg daily.

Overall, there is a 65% greater likelihood of stone passage in the treated patients. In two published comparisons of tamsulosin and nifedipine, tamsulosin trended toward superiority over nifedipine in terms of rate of stone passage, time to stone passage, and less narcotic use in one study, and was significantly better in these same measures in the other [42,43]. Steroids do provide a slight added benefit, but do not appear to be as important as the alpha or calcium channel blockers [44]. At the author's institution, we generally use tamsulosin as the first choice for medical expulsive therapy. Because tamsulosin is available only as a name-brand formulation, if pharmaceutical costs are a consideration, then we use a generic alpha blocker (terazosin, doxazosin) or nifedipine.

Percutaneous/antegrade ureteroscopy

Placement of a ureteroscope through a percutaneous trans-renal route is an attractive way to address large or impacted ureteral stones, especially in the proximal ureter. Advantages of Perc-URS over retrograde URS include: reliable access to the kidney (initial guidewire passage is sometimes not possible from a retrograde approach in severely impacted stones); ability to use larger caliber instruments (a flexible cystoscope often can be used when there is hydroureteronephrosis above the stone); and the opportunity to flush any fragment down into the bladder rather than

having to remove bits of stone ureteroscopically or wait for them to pass. A stone-free state is readily attained. The added invasiveness of Perc-URS accounts for its use primary use in cases of very large or impacted ureteral stones. Kumar and colleagues [45] achieved an 86% initial success rate in 86 patients who had impacted proximal ureteral stones. Despite the high-risk nature of this group, the perforation rate was only 9%. Maheshwari and colleagues [46] addressed 23 proximal ureteral stones, all impacted and greater than 1.5 cm. They reported 100% success and no complications. Goel and associates [47] described complete stone eradication in 65 of 66 patients who had impacted proximal ureteral stones greater than 1.5 cm.

Laparoscopic ureterolithotomy

The 1997 AUA Ureteral Stone Guidelines stated that, for all stones in all ureteral locations, ''Open surgery should not be the first-line treatment.'' [1] That certainly has not changed, but since that document was published, there have been a number of small case series published about laparoscopic ureterolithotomy. The few comparative series suggest that laparoscopic ureterolithotomy should replace open surgical ureterolithotomy in most situations [48,49]. The steps of a laparoscopic are identical to those of an open ureterolithomy, except for the access to the ureter and the tools used. From 1997 through 2005, 15 case series of laparoscopic ureterolithotomy published in the English language literature detailed the results in 458 patients; most procedures were for large or impacted calculi [48–62]. The overall success rate is 96%. Size of the stone does not appear to be associated with outcome, but laparoscopic ureterolithotomy in the distal ureter is somewhat less successful than in the middle and proximal ureter.

Morbidity of treatments

Morbidity of stone treatment is harder to measure than efficacy. The latter can be calculated using objective endpoints, which facilitates determining the impact on treatment selection. Degrees of invasiveness are hard to quantify (extracorporeal versus transurethral versus percutaneous versus laparoscopic or open surgical). Additionally, the definition and reporting of complications varies tremendously from one article to the next. Despite this uncertainty, consideration of the invasiveness and potential complications of ureteral stone treatment are sometimes the most important factors that differentiate one treatment from another, especially in situations in which the efficacies of the treatments are similar.

Although not a complication, a very important consideration in assessing the burden placed on the patient by stone treatment is the need for retreatment. Current series of SWL for ureteral stones suggest a retreatment rate of approximately 30%. In other words, almost one in three patients will require two (or more) treatments to attain the stated stone-free rate for the group as a whole. In comparison, most URS series are reported on the basis of a single treatment. This distinction is often overlooked when comparing the efficacy of SWL and URS.

Medical expulsive therapy

In the meta-analysis of Hollingsworth colleagues [41], the authors found that transient hypotension and palpitations occurred in 3.3% to 4.2% of patients treated with nifedipine or tamsulosin. Among the 691 subjects in the nine trials, only 12 subjects dropped out—7 in the treatment arms and 5 in the control arms.

Shock wave lithotripsy

As the least invasive of the procedural options, SWL has the least severe profile of complications. To provide an estimate of the incidence of complications, the data from the series included in Tables 1, 2, and 3 have been combined and tabulated into a single estimate for each of the complications listed in Table 4. The overall rate of significant complications is 7%. Ureteral injury and stricture do not result from ureteral SWL. The single most common complication is acute ureteral obstruction, in 4% of patients. Obstruction is usually secondary to a stone fragment, but may occur from edema at the site of the treated stone or from gross hematuria with clots. Infectious complications occur with low but predictable regularity: fever in 3%, urinary tract infection in 3%, and sepsis in 2%.

Retrograde ureteroscopy

Table 4 also lists complications for URS, estimated in the same manner as for SWL. The overall significant complication rate is similar to that of SWL, at 7%. Whereas infections complications are generally at the same level (5% fever, 3%

Table 4
Selected complications of SWL and URS

	SWL	URS
Fever	16/585 (3%)	7/141 (5%)
Urinary tract infection	5/151 (3%)	28/836 (3%)
Sepsis	24/1488 (2%)	45/1855 (2%)
Acute ureteral obstruction	42/1081 (4%)	1/738 (<1%)
Ureteral injury	0/1327 (0%)	63/2994 (2%)
Ureteral stricture	0/593 (0%)	7/1109 (1%)
Overall significant complications	54/794 (7%)	90/1273 (7%)

Raw tabulation of patients included in the articles referenced in Tables 1–3.

urinary tract infections, 2% sepsis), ureteral complications differ. Acute ureteral obstruction following URS is rare, occurring in fewer than 1% of cases in the series included in this summary. It should be noted, however, that most patients in these series had a stent placed after URS. Although the literature on stentless ureteroscopy is very favorable (see article by Beiko and Denstedt elsewhere in this issue), some increase in the incidence of acute ureteral obstruction following URS would be expected without routine stent placement. Unlike SWL, the ureter is at risk of direct harm during URS, with a 2% risk of injury and 1% risk of stricture. It is the consideration of ureteral injury, albeit infrequent, that is a major reason cited when SWL is elected over URS for ureteral stones.

Percutaneous/antegrade ureteroscopy

The spectrum of complications of Perc-URS differs from that of retrograde URS in ways that would be expected, given the percutaneous access through the kidney. Of the 175 Perc-URS cases in the three series summarized above [45–47], hemorrhage requiring transfusion has been reported in five patients (3%). Additionally, the increased invasiveness of Perc-URS is accompanied by a greater risk of fever (15%) and overall significant complications (14%). Finally, in the highly selected patients with large or impacted stones undergoing this procedure, it is not unexpected that the ureteral injury rate (5%) and ureteral stricture rate (3%) of Perc-URS exceed those of retrograde URS.

Laparoscopic ureterolithotomy

Even more invasive that Perc-URS, laparoscopic ureterolithomy carries a correspondingly greater overall significant complication rate of 21% (raw tabulation of patients included in the 15 laparoscopic ureterolithomy series referenced above) [48–62]. The most common complication is prolonged urinary drainage from the operative site, in 12% of cases. Urinary extravasation has been variably described as urinoma formation or persistence of urine in the peri-ureteral drain for longer than 2 to 4 days. Most series reported the use of peri-ureteral drains, but in some cases either drains or stents or both were omitted. Given a one in eight incidence of prolonged urinary leakage, stents and drains are recommended in most cases. Surgical site and urinary infections are also more commonly reported in laparoscopic ureterolithotomy, compared with other procedures outlined in this article, at 7%. Of the series with adequate follow-up, ureteral stricture has been reported in 3% of cases.

Treatment selection

Before presenting specific recommendations for ureteral stone management, some general trends underlying the recommendations can be determined. In general, as the size of stone increases, the intensity of treatment needs to increase as well, because less intense treatments are less effective with larger stones. As such, as stone size increases, SWL becomes less attractive and URS becomes more attractive, with Perc-URS becoming most useful for the very large (greater than 2 cm) ureteral stones. Similar trends are apparent with regards to location, although here the differences are driven more by risk of complications than by efficacy. As location of a ureteral stone becomes more proximal, complications of URS increase, but those of SWL are relatively stable. For a given stone then, the tendency would be to use URS in the distal ureter and SWL in the proximal ureter. Other general trends are more obvious; as stones get harder (as indicated by known composition or CT density measurements) or patients get larger (to the point of morbid obesity), they are better treated with endoscopy rather than SWL. Treatment recommendations for ureteral calculi are summarized below:

- Calculi less than 10 mm: observation (if very small) or medical expulsive therapy (if a reasonable success rate can be expected). If medical expulsive therapy is not appropriate or fails, then URS or SWL are recommended

in most cases. All other factors being equal, URS is preferred in the distal ureter and SWL in the proximal ureter.
- Calculi 10 to 20 mm: URS or SWL are recommended in most cases. All other factors being equal, URS is favored. Perc-URS may be best in cases of stones approaching 2 cm, or in cases of severe impaction.
- Calculi greater than 20 mm: URS, or in some cases Perc-URS, is recommended for most patients. Laparoscopic ureterolithotomy is indicated as initial therapy only if URS and Perc-URS are thought unlikely to be successful.
- Stone density, body habitus, patient medical condition, and other factors will impact these general recommendations.

Note that the above recommendations address only initial surgical therapy. Choice of salvage therapy is more complicated, because the reason for failure of primary therapy may play a role in the selection of the salvage treatment.

Summary

The two most important advances in the management of ureteral calculi over the past few years have been the development of medical expulsive therapy to facilitate passage of ureteral stones, such that many calculi that would have required procedural treatment in the past now exit the ureter with only pharmacologic treatment; and the improvements in ureteroscopic technology that have enabled retrograde ureteroscopy to become a first-line option for most ureteral stones. Shock wave lithotripsy still plays an important role for many ureteral calculi, particularly smaller ones, and the addition of percutaneous/antegrade ureteroscopy and laparoscopic ureterolithotomy rounds out the treatment options for large or impacted stones. Selection of treatment based upon factors such as size, location, and others will optimize outcome for patients who have ureteral calculi.

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Treatment of Stones Associated with Complex or Anomalous Renal Anatomy

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Calculi in kidneys with complex or anomalous anatomy pose a particular challenge for the urologist. In many situations, the principles that guide treatment in normal renal anatomy also pertain to these abnormal kidneys. Because of aberrant anatomy, however, abnormal kidneys may not be amenable to the same approaches currently employed for stone disintegration or extraction in normal renal units. In general, all attempts should be made to manage uric acid calculi medically with dissolution therapy. This is especially true in these patients because of the increased difficulty of surgical intervention. The chemical composition of stones in anomalous kidneys has not been found to be different from those in normal kidneys, however. The vast majority of stones are calcium oxalate. Calculi unlikely to ever pose a medical threat should be medically managed to prevent growth and obstruction. These include small asymptomatic stones, especially those in lower-pole calyces. Because of the dilation of the collecting system associated with these abnormal renal units, the likelihood that small lower-pole calculi will cause ureteral obstruction is even less in these kidneys than it is in normal kidneys. Moreover, the treatment modalities traditionally employed for treating small lower-pole calculi (eg, shock wave lithotripsy (SWL) and ureteroscopy with laser lithotripsy) are unlikely to result in complete stone clearance in these dilated collecting systems. It has been demonstrated that residual fragments after lithotripsy procedures are likely to eventually result in clinically significant recurrent stone disease. A thorough medical evaluation, including serum chemistries, stone analysis, and 24-hour metabolic risk profiles, are mandatory in this population to minimize recurrences and prevent growth of residual fragments following therapy. This article describes methods that have been employed in managing calculus disease in aberrant renal anatomy and the criteria for judging which approach is likely to be successful without undue morbidity in this challenging patient population.

Horseshoe kidneys

The horseshoe kidney, with a prevalence of 0.25%, is the most common renal fusion abnormality [1]. This congenital anomaly results from an abnormal medial fusion of the metanephric blastema originally destined to result in anatomically normal right and left kidneys. This abnormal fusion causes failure of ascent and rotation. Ascent is arrested by the inferior mesenteric artery, which arises anteriorly from the aorta just before its bifurcation. The fused kidney therefore lies more caudad in position compared with normal kidneys and, because of incomplete rotation, the renal pelvis is anterior to all of the calyces [2]. The calyces point posteriorly with the lower-pole calyces pointing caudally and medially. This is in contradistinction to normal kidneys, in which all calyces are located lateral to the renal pelvis and point laterally as well. The malrotation of the fused kidney causes insertion of the ureters to be superior and lateral (high insertion) (Fig. 1). In addition, the ureter is draped over the renal isthmus, resulting in an anterior deviation in its

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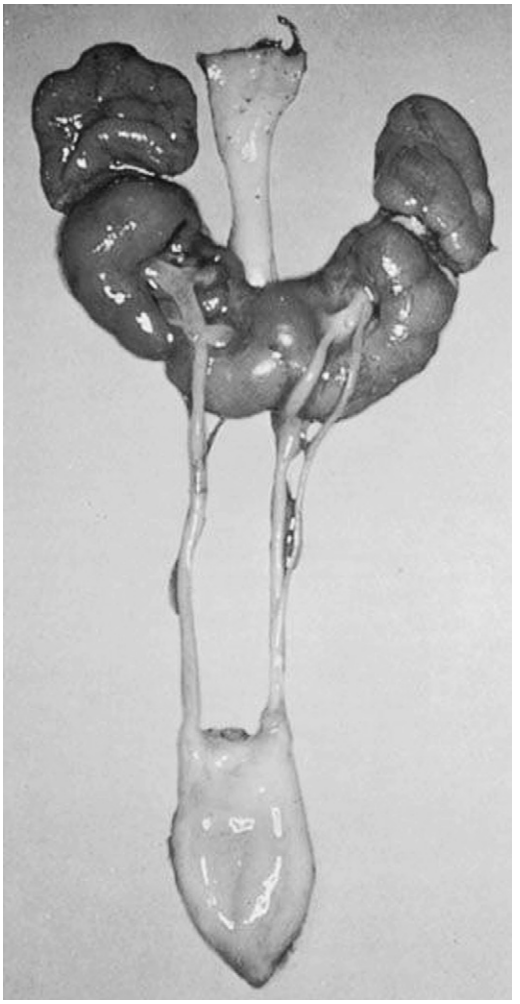

Fig. 1. Horseshoe kidney. Note the malrotation of the kidneys and high insertion of the ureters. (*From* Bauer SB. Anomalies of the upper urinary tract. In: Walsh PC, editor. Campbell's urology, 8th edition. Philadelphia: W.B Saunders; 2002. p. 1904; with permission.)

course several centimeters below the ureteropelvic junction (UPJ).

These aberrations often result in impaired urinary drainage and stasis, which can ultimately predispose to urinary stone formation. The incidence of stone formation in horseshoe kidneys is as high as 20%. The vast majority of these calculi are composed of calcium oxalate. The most common location of stones is the medial, posterior lower-pole calyx, closely followed by the renal pelvis. With the advent of noninvasive radiographic imaging, these stones are increasingly diagnosed incidentally on CT and ultrasonography performed for unrelated indications. When patients are symptomatic, they typically present with flank pain and renal colic similar to that experienced with stones in anatomically normal kidneys because the innervation of horseshoe kidneys is not anomalous. Because the surrounding structures of the kidneys are different, however, an atypical presentation, such as gross hematuria or abdominal pain with or without nausea or emesis, is not unusual.

Anatomical considerations, such as aberrant vasculature, adjacent bowel, medial location, and distorted pelvicalyceal architecture must be carefully considered in choosing a treatment modality. Extracorporeal shock wave lithotripsy (ESWL), ureteroscopy, and percutaneous nephrolithotomy (PCNL) have all been successfully performed in these kidneys with varying degrees of success.

Shock wave lithotripsy

SWL is the least invasive modality used for calculi in horseshoe kidneys. However, SWL poses particular challenges for stone localization and patient positioning. Ultrasonic localization is often not feasible because the medial location of these kidneys makes them more difficult to visualize and because intervening bowel may cast shadows that obscure the stones. Fluoroscopic targeting may be problematic because superimposed spinous process, spinal segment, or pelvic bone may obscure stone visualization.

Positioning can be challenging because the iliac crest may preclude coupling of the treatment head in the traditional supine position. Prone positioning can be used with the caveat that shock waves will most likely traverse intervening bowel segments leading to a potential for bowel injury. The authors have found it useful to place a wedge under the patient's contralateral side while the patient lies in supine position. This has two beneficial effects. The first is that medially located stones become fluoroscopically separated from the spine and are easier to identify. The second is that the shock head couples to the body surface more anteriorly, avoiding the iliac crest and creating a shorter path for the shock waves to travel, thereby facilitating placement of the stone in the F2 focal zone and enhancing fragmentation.

The factors that account for the failure of SWL in normal kidneys are compounded in horseshoe kidneys (Fig. 2). The shock wave path is longer for these kidneys with resultant attenuation of energy at the F2 focal point. Most importantly,

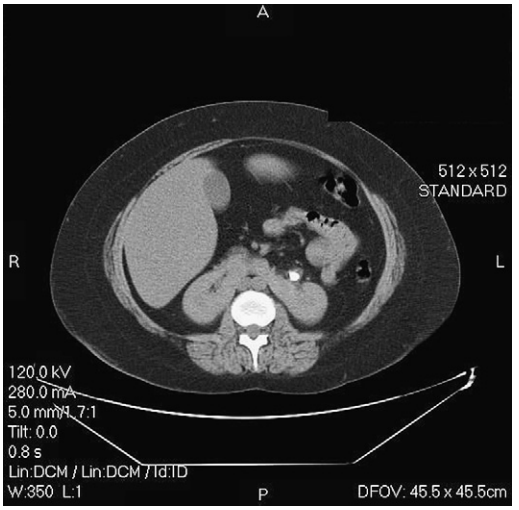

Fig. 2. Patient with a horseshoe kidney. Note the anterior displacement of the kidney and long shock wave path.

urinary stasis, dilation of the collecting system, and high insertion of the ureter hamper fragment passage (Fig. 3). Despite these obstacles, SWL has been successfully employed in horseshoe kidneys with fragmentation rates of up to 80% in selected patients [2–4]. Published stone-free rates have varied significantly from 20% to 80% (Table 1) [2–7]. In addition to stone location, stone burden has a significant influence on stone-free rates, with dismal results for stones over 3 cm [6,8,9]. Due to all of these considerations, SWL lithotripsy in horseshoe kidneys should be reserved for small stones (<20 mm) located in nondependent calyces or in the renal pelvis of minimally dilated collecting systems. Should the patient not be rendered stone free, consideration should be given for ancillary ureteroscopy and/or PCNL.

Ureteroscopy

There are few published reports on the use of ureteroscopy for calculi associated with horseshoe kidneys. The tortuous tract of the ureter, especially as it traverses the isthmus, makes semirigid ureteroscopy for proximal ureteral or renal calculi exceedingly difficult and fraught with danger. Ureteroscopy for midureteral or distal ureteral calculi, however, can be used in a manner similar to that for normal kidneys. The advent of lasers, flexible fiber-optic ureterorenoscopes, and tipless nitinol baskets has allowed access to stones in difficult calyceal locations [10]. Unlike normal kidneys, where it may be advantageous to reposition stones into the posterior lower-pole calyx, stones in lower-pole calyces of horseshoe kidneys should instead be repositioned into the renal pelvis due to the altered calyceal anatomy. In

Fig. 3. Patient with horseshoe kidney and residual fragments after SWL.

Table 1
Results of SWL in patients with horseshoe kidneys

Investigator, year	Stone diameter	Number of patients	Fragmentation rate	Stone-free rate	Re-treatment rate
Esuvaranathan, 1991 [2]	12 mm	7	Not reported	50%	50%
Kirkali, 1996 [3]	24 mm	18	78%	28%	57%
Smith, 1989 [4]	NR	14	Not reported	79%	29%
Bhatia, 1994 [5]	28 mm	27	Not reported	70%	48%
Sheir, 2003 [6]	13.5 mm	49	Not reported	71%	71%
Tunc, 2004 [7]	22 mm	46	Not reported	66%	Not reported

addition, ureteral access sheaths have improved stone clearance rates and irrigation [11]. Wizer and colleagues [10] reported complete stone clearance in three of four patients with horseshoe kidneys treated with ureteroscopic laser lithotripsy. Despite this report of success, stone-free rates can be expected to be lower than for normal kidneys because of the anterior location of the renal pelvis, high insertion of the ureter, stasis of urine, and settling of fragments in dependent portions of the dilated collecting system. Ureteroscopy is a viable alternative for patients unable to undergo PCNL or SWL, such as patients with pulmonary problems who are not able to tolerate the prone position for long periods or patients who have a coagulopathy or who are on anticoagulants and are at significant risk of hemorrhage [10]. With continued improvements in instrumentation, ureteroscopy may become the procedure of choice for calculi measuring less than 20 mm in horseshoe kidneys.

Percutaneous nephrostolithotomy

The percutaneous approach to the horseshoe kidney is predicated upon a thorough knowledge of the anatomy and vascular supply of these kidneys. The patient is placed in prone position. A more medial and posterior course is advisable given the malrotation of the calyces. Often the posterior calyces point directly posterior. Because these kidneys are more anteriorly located, the tract may be very long, especially in obese patients. Unless the patient is thin, longer sheaths and nephroscopes may be necessary. The optimal calyx to access is generally the upper-pole posterior calyx because the posterior lower-pole calyx is very medial and anterior [1,12,13]. An upper-pole posterior access allows direct access to the renal pelvis and other calyces, although the distance to reach the UPJ or lower-pole calyces may be too far for the rigid nephroscope and, therefore, flexible nephroscopy may be required. The more inferior location of these kidneys usually obviates the need for intercostal access even if an upper-pole calyx is chosen.

Fluoroscopy or ultrasound can be used to guide the percutaneous puncture, and dilation can be performed in a standard manner. Accessories, such as baskets and graspers, should be used liberally to achieve a stone-free status. Because these kidneys are less mobile than normally positioned kidneys, multiple punctures and access sites may be necessary for complete stone clearance [1,13]. The UPJ should be evaluated for obstruction, but this is best done preoperatively when crossing vessels can be assessed and functional studies, such as diuretic renography, can be performed to distinguish clinically significant obstruction versus stasis. PCNL should be considered for stones greater than 2 cm or for SWL failures. Stone-free rates of more than 75% can be attained using PCNL [1,12–14].

A preoperative CT scan is advisable to optimize planning and minimize the chance of vascular or adjacent organ injury. Because of the anterior location of the horseshoe kidney, there is an increased likelihood of a retrorenal colon, and thus, increased risk of colonic injury [12,13]. The retrorenal colon is a result of a defect in the normal development of the laterocoronal fascia combined with the absence of the kidney in the normal position [15]. In three recent series consisting of a total of 50 patients, only one colonic injury was reported [1,12,13]. Although the risk of such an injury is low, a preoperative CT with contrast before planned PCNL is recommended to eliminate any chance of this potential major complication. The management of colonic perforation should consist of withdrawal of the nephrostomy tube, placement of ureteral stent, and administration of parenteral antibiotics [15].

With horseshoe kidneys, the kidneys are displaced inferiorly and a supracostal access tract is

less likely even when the upper pole is chosen for access [1]. The risks, therefore, of pneumothorax, hemothorax, or hydrothorax are minimal. Shokeir and colleagues [12] and Raj and colleagues [1] each reported one pneumothorax in their series of 45 and 37 patients (6%), respectively. Thus, the risk of pulmonary injury is considered to be low and less than that of patients with normally placed kidneys.

Laparoscopy

The laparoscopic approach to horseshoe kidneys is feasible because of the anteriorly located renal pelvis. Care must be taken to avoid anomalous vessels. More case reports are emerging on the use of laparoscopy in horseshoe kidneys. In two reports, pyelolithotomy was used to extract calculi [16,17]. Operative time was approximately 2.5 hours and no complications were noted. Laparoscopy has also been used to assist placement of transperitoneal trocars for PCNL in difficult-to-access kidneys, much like the use of laparoscopic-assisted PCNL in pelvic kidneys [18]. Laparoscopy for calculus disease is an attractive alternative in patients who have simultaneous UPJ obstruction due to a crossing vessel [19,20]. Although the outcomes for laparoscopy to treat stones in horseshoe kidneys are encouraging, more series are needed to fully define the role of laparoscopy in horseshoe kidneys.

Pelvic kidneys

The pelvic kidney results from failure of renal ascent and is associated with an incidence of approximately 1 in 2000 to 3000 in autopsy series [21]. The left side is more commonly affected [22]. The notion that pelvic kidneys are susceptible to increased calculus formation due to the malrotation and high insertion of ureter is controversial. Gleason and colleagues [23] noted an increased incidence of hydronephrosis and calculi formation in patients with pelvic kidneys, whereas Dretler and colleagues [24] found no such association. Most patients with pelvic kidneys are asymptomatic. The diagnosis is most commonly made when a patient presents with vague abdominal complaints, which prompts imaging studies that incidentally show the ectopic kidney [25]. The low position, malrotation, and close proximity of the pelvic kidney to surrounding bony structures make treatment of calculi challenging [26]; however, surgical modalities employed in horseshoe kidneys can usually be successfully applied to pelvic kidneys.

Shock wave lithotripsy

There are few reports on the use of SWL to treat stones in pelvic kidneys. SWL can be used to treat calculi in pelvic kidneys provided there is not concomitant UPJ obstruction or significant hydronephrosis. The challenge in treating these patients is accurate localization and targeting of the calculus. Ultrasound localization is not useful in this setting and is often the reason for poor results [27]. The bony pelvis may obscure the collecting system, making calculi difficult to locate. Placing the patient prone helps alleviate this problem, but occasionally the patient can still be treated in the supine position if the bony pelvis does not block the shock wave path (Fig. 4) [26]. CT is helpful in identifying loops of bowel that can interfere with the shock wave path.

In the largest series of SWL for patients with horseshoe kidneys, 14 patients were treated, resulting in an 82% stone-free rate [26]. Others have reported stone-free rates from 25% to 92% [7,8,26–30], rates that are nearly comparable to normally positioned kidneys. Patients with large calculi have lower stone-free rates [31]. Like horseshoe kidneys, unobstructed passage of fragments is critical to a successful outcome with SWL. Despite some high reported stone-free rates, a significant number of patients require further treatment with repeat SWL, ureteroscopy, or stent insertion [26]. If a stent is used, a shorter length is required due to shorter ureteral length (Fig. 5). In

Fig. 4. Patient with pelvic kidney and staghorn calculus. Note intervening bowel loops and bony pelvis, precluding safe SWL.

Fig. 5. Patient with pelvic kidney with ureteral stent in place.

summary, in the absence of obstruction, SWL can be safely used to treat calculi in pelvic kidneys.

Ureteroscopy

There are few reports on the use of ureteroscopy in patients with stones in pelvic kidneys [10,11]. With the introduction of newer, better deflecting ureteroscopes and smaller instruments, ureteroscopy is an attractive alternative to SWL [10]. The use of an access sheath helps "straighten" the ureter in cases where the ureter is tortuous [10]. Stone-free rates of up to 80% [10,32] have been achieved. These results are similar but more consistent than SWL stone-free rates. The advantage of a ureteroscopic approach is that the good results can be achieved in most cases with a single procedure, while SWL often requires multiple procedures to achieve comparable stone-free rates. Consequently, ureteroscopy is a useful alternative to SWL or is recommended as primary therapy in cases in which the patient is not a good candidate for SWL or PCNL. The use of ureteroscopy is limited due to the pelvicalyceal anatomy, which places the renal pelvis anteriorly, thereby impairing drainage of urine and, therefore, fragments. The use of a ureteral access sheath mitigates some of these pitfalls because multiple passes of the ureteroscope may be used to manually remove all fragments. Because residual fragments pose a high risk for stone recurrence in a static system, stone-free status should be ensured through the liberal use of nitinol baskets.

Percutaneous nephrolithotomy

The use of primary PCNL in pelvic kidneys is not recommended because of the risk of injury to overlying abdominal viscera and vessels. Desai and Jasani [33] reported on the use of ultrasound guidance for direct access and was able to render all patients stone free with only minor complications. This technique involves displacing the kidney close to the abdominal wall and then using ultrasound to guide needle puncture. None of the patients in this series sustained a bowel injury. A few case reports using the traditional posterior puncture have been published. However, Monga and colleagues [34] reported a postoperative femoral neuropathy following a traditional posterior approach for accessing a pelvic kidney. An approach through the buttock similar to the standard flank approach via the greater sciatic foramen has also been reported. CT guidance is used for optimal tract placement and long instruments may be required, especially in obese patients [35]. Overall, with the significant risk of serious complications, the use of primary PCNL is not recommended for most patients with pelvic kidneys.

Laparoscopic-guided percutaneous nephrolithotomy

With the introduction of laparoscopic surgery, a minimally invasive approach can be applied to most situations in which open surgery is considered [36]. This is especially true with pelvic kidneys, where an anterior percutaneous approach can potentially injure abdominal viscera, and in situations when ureteroscopy or SWL fails. Under direct endoscopic vision, anomalous vasculature and iatrogenic injuries can be avoided [31]. Initial reports of a laparoscopic approach to stone removal in pelvic kidneys involved a three- or four-port transperitoneal approach to clear overlying bowel from the path to the kidney [22,37–41]. Typically, a ureteral catheter is placed and the calyces are imaged fluoroscopically using retrograde injection of contrast. The kidney can be accessed via an anterior percutaneous approach under direct and fluoroscopic vision. Likewise, dilation is performed under vision with placement of a nephrostomy sheath, and a standard PCNL is subsequently performed. All patients in the reported series were rendered stone free with this approach.

Subsequent reports have described various modifications of the laparoscopic approach. Zafar and Lingeman [22] reported the use of intracorporeal suturing of the nephrotomy with placement of a ureteral catheter, thereby eliminating the need for a nephrostomy tube. Hemostasis is also maintained with suturing. An extraperitoneal approach has been reported using a balloon dissector to open the extraperitoneal space [42]. A standard PCNL is performed using laparoscopic vision and fluoroscopic guidance. One benefit to this approach is that postoperative drainage is limited to the extraperitoneal space, which can be easily drained.

Laparoscopic pyelolithotomy

Laparoscopic pyelolithotomy obviates the need for PCNL [22,43–46]. Ports are placed transperitoneally and the bowel is safely displaced away from the renal pelvis. A pyelotomy is made with scissors, and the calculi are extracted under direct vision via the laparoscope using graspers via a separate port [45]. Alternatively, or additionally, a flexible cystoscope or ureteroscope can be used to perform renoscopy to clear additional fragments from the pelvis and calyces. The pyelotomy should be closed, and a double J stent is advisable if a dismembered pyeloplasty or Fenger-plasty is performed or if there is evidence of stasis on preoperative imaging. Closure can be especially challenging if the patient has dense adhesions from prior surgery or aberrant vessels are seen crossing the renal pelvis [17]. If the pyelotomy cannot be sutured closed, prolonged catheter drainage may be required until the pyelotomy seals [46]. A series of patients who underwent retroperitoneoscopy for calculi in pelvic kidneys has also been reported [47]. Occasionally, balloon-dilation of the etroperitoneum was difficult; however, when access to the pelvis was obtained, the calculi were removed 83% of the time.

Laparoscopic and robotic approaches to stone removal are emerging as ideal treatments in patients with a concomitant UPJ obstruction (Fig. 6). The authors and others have found it useful to first make a pyelotomy near the UPJ to remove all stones [16,48–50]. A flexible cystoscope or ureteroscope facilitates localization and removal of calyceal calculi. The pyeloplasty can be performed after complete stone removal simply by extending the incision into the ureter (Fenger-plasty) or by circumferentially excising the UPJ segment and reanastamosing the proximal ureter to the tapered pelvis (dismembered pyeloplasty). Operating times average 4.5 hours for both laparoscopic- and robotic-assisted pyeloplasty, and stone-free rates as high as 80% to 100% at 12 months have been achieved [48,50].

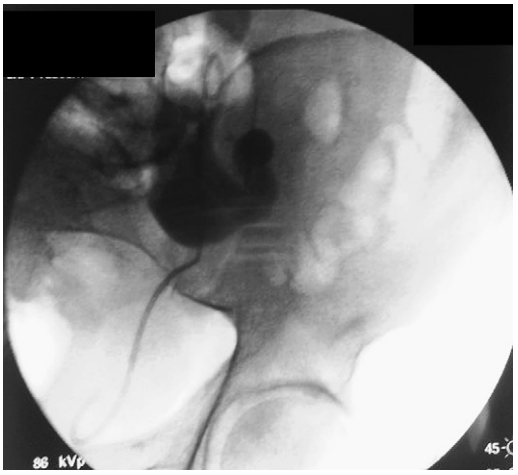

Fig. 6. Retrograde pyelogram in patient with pelvic kidney associated with renal stones and UPJ obstruction.

Crossed fused renal ectopia

The incidence of crossed fused ectopia is 1 to 1000 [51]. Six different forms of renal ectopia exist, with the incidence of each varying, depending on the type of fusion. The orthotopic unit is usually normal while the ectopic unit has been associated with cystic dysplasia [52] and hydronephrosis with or without calculus formation [53]. Treatment of patients with crossed renal ectopia is generally individualized using principles similar to patients with normal kidneys. Most articles on the treatment of nephrolithiasis and crossed fused renal ectopia are case reports. One report described SWL treatment in two patients, with only one patient rendered stone free after three sessions. The other patient underwent successful ureteroscopy [54]. Another report described laparoscopic pyeloplasty and pyelolithotomy in a pediatric patient, who was stone free at 6 months without complications [55].

Experience has led the authors to use a laparoscopic-guided approach in most situations. In a rare case, a completely percutaneous approach was made feasible by distending the renal pelvis with contrast in a patient where the preoperative

CT scan demonstrated that the renal pelvis was close to the anterior abdominal wall without intervening loops of bowel. To use this percutaneous approach, the C-arm is placed fully lateral (cross-table lateral position) to allow visualization of the renal pelvis and the anterior abdominal wall. If the pelvis is close to the surface of the skin, a puncture can be safely performed under fluoroscopic monitoring; if not close to the skin surface, a laparoscopic-guided approach is recommended.

Transplant kidney

Nephrolithiasis is a rare complication of renal transplant, with an incidence of 0.4% to 1% [56–58]. Calculi can occur de novo after transplantation or be preexistant in the donor kidney [59]. Risk factors include secondary hyperparathyroidism (commonly present in renal failure patients) and use of nonabsorbable sutures [60]. Other factors, such as hypercalcemia, recurrent urinary tract infection [56], or production of more concentrated alkaline urine [61], are identified only after further work-up for stone disease. Most calculi are composed of calcium oxalate. In half the patients, Immunosupression with cyclosporine A can produce hyperuricosuria, which is thought to contribute to stone formation. However, the data is conflicting on the role of hyperuricosuria and uric acid stone formation. Klinger and colleagues reported an incidence of uric acid calculi of 0.2%, while Harper and colleagues reported an incidence of 10% [61,62], still much lower than the incidence of calcium calculi.

The most common presenting signs are unexplained fever, increasing creatinine levels, decreased urine output, and hematuria [63]. Most transplant patients with stones do not have pain because of denervation during transplantation, although some patients report discomfort due to distension of the kidney, which stretches the overlying fascia [59]. The diagnosis of a renal calculus can sometimes be difficult. A calculus may be difficult to identify by plain abdominal radiograph or ultrasound due to the position of the kidney in the bony pelvis or due to overlying bowel gas [58]. CT is the best modality to detect a calculus. Because transplant patients depend on one kidney for renal function, calculi should be treated aggressively to minimize the possibility of obstruction and loss of function [56,59]. There are no reports of laparoscopy for treatment of stone disease in transplant kidneys.

Observation

Observation has been recommended for a very select group of patients with stones less than 4 mm in diameter and no impairment of function [62]. These patients need rigorous follow-up with serial creatinine measurements. Since the kidney is denervated, colic or pain is not present. Thus the patients need close follow-up and must be carefully counseled.

Shock wave lithotripsy

SWL is the recommended treatment for calculi less than 1.5 to 2 cm in diameter in patients with transplant kidneys [56,60]. Patients are treated in the prone position. The overlying bony pelvis may preclude adequate localization of the transplant kidney. Challacombe and colleagues [56] reported using SWL in 13 patients; 8 patients required either additional procedures, such as stent placement, percutaneous nephrostomy tube placement, or multiple SWL sessions to become stone free. Klinger and colleagues [62] reported success in 7 patients who underwent SWL; however, 2 patients were treated with a percutaneous nephrostomy tube before SWL and 1 patient required a nephrostomy tube after treatment. Despite the risk of requiring multiple procedures, SWL can be performed safely in transplant patients with calculi less than 1.5 cm. Patients should be monitored for the development of steinstrasse and oliguria. Should there be a high potential for obstruction, placement of a stent or percutaneous nephrostomy tube is recommended.

Ureteroscopy

Ureteroscopy, although technically challenging, is a feasible alternative after failed SWL. The difficulty often lies in identifying the transplant ureteral orifice, which is iatrogenically ectopic and anterior. Guide-wire access may require the use of flexible cystoscopy and specialized angled catheters, such as a Kumpe or cobra catheter. The authors have found angled hydrophilic-coated guide wires with an adjunctive torque device indispensable in negotiating the acutely angled transplant ureteral orifice. The ureter is often tortuous and redundant, and the hydrophilic guide wire is helpful in advancing to the renal pelvis and guiding ureteroscope placement. Newer ureteroscopes with an active secondary deflection or a larger turning radius are also useful in gaining access to the calices [56]. Del Pizzo and colleagues [63] reported success in six of seven

transplant patients treated ureteroscopically and Basiri and colleagues [64] reported a 67% success rate in his series. Complications included infection and a minor urine leak that was managed with a chronic indwelling catheter.

Percutaneous nephrolithotomy

PCNL is generally recommended for calculi greater than 2 cm diameter [56,60], although most reports of PCNL in transplant kidneys are case reports. The transplant kidney is often more easily accessed than pelvic kidneys due to the close proximity of the transplanted kidney to the skin [60]. Ultrasound guidance can reduce the risk of puncturing interposed intestinal bowel loops [59,65]. Once access is obtained, the tract may be difficult to dilate due to the dense scarring surrounding the kidney. Balloon dilators have been used, but coaxial metal dilators may be better for dilating the tract [60,65]. Antegrade flexible ureteroscopy may also be required due to the orientation of the transplant kidney [58]. No series are large enough to determine an average stone-free rate [66]. Because of immunosuppression in these patients, the potential complications with this approach are delayed wound healing and sepsis.

Summary

The treatment of calculi in anomalous kidneys must be individualized. These kidneys vary significantly in terms of position, hydronephrosis, calyceal anatomy, and ureteral insertion, and these factors must be considered before making a treatment decision. The principles guiding treatment remain the same as those for normal kidneys:

- Give stone-free status paramount importance.
- Minimize the number of procedures required to achieve a stone-free state.
- Treat concomitant obstruction to prevent stone recurrence.
- Use minimally invasive techniques whenever feasible to minimize patient morbidity.

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Economics of Stone Management

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The issue of cost in stone disease is complex and often relegated, perhaps rightly so, to a secondary or tertiary endpoint in patient management. One may question the need for a urologist to be concerned with economic considerations when facing a patient with a kidney or ureteral stone. Should one decide on treatment management (surgery, medication, need for more imaging or laboratory studies) based on cost considerations? Certainly for an individual patient, the clinician is bound by the specific medical needs of the patient. However, economic issues cannot be ignored. This article identifies ways in which the economics of stone management have an impact on global health care, individual patient management, and physician income. The article also addresses the financial issues related to management of the acute stone event, surgical intervention, and medical management.

The importance of perspective

The financial implications of stone management are addressed from the perspective of the payer. In the United States health care system, there are three "payer" perspectives: that of society, the hospital, and the patient.

The perspective of the patient is the most difficult and subjective perspective to evaluate because it depends on the individual's type and level of insurance, his or her deductible level, and his or her employment status. Because the incidence of stone disease is highest between the ages of 20 and 60, most stone formers are employed [1] and, in the United States, many employers are the primary source of health insurance. An insured individual is probably more likely than an uninsured individual to seek medical care. Furthermore, given the high cost of drugs, insurance with drug benefits may have an impact on the willingness of an individual to agree to and comply with medical management. By the same token, uninsured individuals may delay their care and might be less likely to take costly medications for stone prevention. In countries where medical care is available free of charge to all citizens, the issue of medical costs may have less of an impact on decisions that patients make.

When considering the hospital as payer, direct and indirect costs to the hospital are taken into account, although direct costs are easier to measure. Hospital costs include the resources required to perform a procedure and to deliver immediate and early postoperative care. Most stone procedures, including shock wave lithotripsy (SWL) and ureteroscopy, are performed on an outpatient basis, although many patients are admitted to the hospital for stone-related problems (pain, fever, obstruction). An important consideration, however, is that within each hospital system, the overall budget is compartmentalized into different cost centers. While managing stones may be profitable to a hospital as a whole, the cost of a new shock wave lithotripter, ureteroscope, or laser may be viewed as detrimental to the operating room cost center. Securing new technologies or upgrading current ones must be viewed in terms of the overall impact of stone disease on the hospital and not individualized to a specific cost center.

The perspective of society also involves both direct and indirect costs. As Medicare plays a large role in financing health care in the United States,

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a significant portion of direct costs affect the overall national health care budget. Likewise, costs borne by private insurance companies are passed on to employers and participants through higher premiums. Society is also affected by loss of work productivity that occurs during an acute stone episode or with surgical treatment. Although these indirect costs may be difficult to measure, they likely represent a significant loss of gross national revenue.

Cost versus charge

Evaluating the literature regarding the economics of stone disease is often confusing because of the interchangeable use of the terms cost and charge. The charge for a service, procedure, or medication incorporates the actual cost to produce or deliver an item, indirect costs, and profit margins. Because different components of patient care have specific and differing cost-to-charge ratios, a comparison of charges does not accurately reflect either true or relative use of resources. Furthermore, in the case of surgery or outpatient care, the cost can be readily discerned from the charge, while the "cost" of medication and equipment often incorporates profit margins for manufacturers rather than reflecting the actual cost to manufacture the product. Unfortunately, this information is not readily available.

Overall financial burden of urolithiasis

The lifetime prevalence of stone disease has been estimated at 13% for adult men and 7% for adult women in the United States [2]. The incidence of nephrolithiasis peaks between ages 20 and 60 and more than 1% of working-age adults were treated for nephrolithiasis in the year 2000 [1,3]. Using a variety of national datasets, the total annual medical expenditures for urolithiasis in the United States was estimated at $2.1 billion in 2000, including $971 million for inpatient services, $607 million for physician office and hospital outpatient services, and $490 million for emergency room services [4]. These figures represent a significant increase from 1994 when the total annual cost for urolithiasis in the United States was estimated to be $1.83 billion, including $1.23 billion in charges for evaluation, hospitalization, and treatment [5]. An increase in the population may account for a portion of the increased expenditures, but an increase in the prevalence of stone disease is likely a contributor as well.

Between 1994 and 2000, outpatient services (including physician office visits, emergency room visits, and hospital outpatient services) assumed an increasing proportion of total annual expenditures, comprising 43% of total expenditures in 1994 and 53% in 2000 [4]. Using a dataset of medical and pharmacy claims from 25 large United States employers covering over 300,000 beneficiaries, workers with claims for nephrolithiasis had approximately $3500 more in medical expenses compared with matched workers without stones ($6532 versus $3038). Of the $6532 average expenditure for workers with nephrolithiasis, prescription drug expenses accounted for approximately 18% [3]. Overall, 30% of individuals missed work as a result of nephrolithiasis, with a mean loss of 19 hours per year. Although the care of individuals with urolithiasis has shifted from the inpatient to the outpatient setting and the hospital length of stay has decreased because of more efficient and less invasive treatment modalities, costs nevertheless continue to rise. From a physician and hospital perspective, unless the overall Medicare budget allocated for stone disease increases to account for the increasing stone prevalence, then only a decrease in reimbursement for services will allow for care of a larger number of patients at the same budgetary levels.

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.

The need for inpatient versus outpatient treatment for stone disease affects the overall cost of the disease. Most patients with stones in the United States are managed on an outpatient basis. Worldwide, admission rates are more variable. In Germany, approximately 69% of patients with urolithiasis receive inpatient hospital care [6] compared with only 29% in the United States [7] and 38% in Sweden [8]. Many patients admitted to the hospital are treated conservatively. Using data from the Agency for Health Care Policy and

Research from 1980 to 1987, Clark and colleagues [5] found that among 6406 United States patients discharged from the hospital with a primary diagnosis of calculus of the kidney or ureter, only 24% (1511 patients) underwent a definitive surgical procedure for their stone during that admission. Among the 4895 patients who were not treated surgically, the average hospital length of stay was 2.65 days and the mean charge was $2153. In their study, Clark and colleagues found that only 30% of patients with stone disease required hospitalization and thus the majority of stone patients were treated on an outpatient basis. Similarly, Saigal and colleagues [3], in conjunction with the Urologic Diseases of America Project, found that only 25% of individuals with a diagnosis of nephrolithiasis submitted a claim for surgical treatment.

Radiographic imaging serves as the basis for diagnosing stones, and intravenous urography (IVU) or unenhanced helical CT are the preferred modalities. A number of studies have demonstrated the superiority of CT over IVU for the diagnosis of ureteral calculi in the setting of acute flank pain [9,10]. A randomized prospective trial comparing IVU versus CT for the diagnosis of stones in patients with acute flank pain showed that CT was more sensitive (85% versus 75%) and specific (98% versus 92%) than IVU for detecting stones [11]. Although the direct costs for CT and IVU are nearly identical (310 versus 309 euros, respectively), average in-room time was significantly shorter for CT than IVU (23 minutes versus 81 minutes, respectively) resulting in lower indirect costs for CT. Several other investigators have noted that CT has similar or lower cost compared with IVU for the evaluation of acute flank pain [12–14]. At the authors' institution, the costs of CT and IVU are comparable ($126 and $123, respectively). One benefit of IVU is that it provides a rough estimate of ipsilateral renal function and degree of obstruction, which may impact management decisions, but its role in the acute setting is limited. Data derived from the Centers for Medicare and Medicaid Services showed a 31% decrease in the use of IVU and a threefold increase in the use of CT from 1992 to 1998 [4].

While the emergency room physician often makes the initial decision regarding imaging modality, urologists are confronted with the decision of whether to observe a stone in hopes of spontaneous passage or to intervene surgically. The financial impact of this choice has not been extensively evaluated, although both alternatives can have significant financial implications in terms of direct costs (surgery, hospitalization, emergency room visits) and indirect costs (loss of work). To compare the cost associated with observation versus surgical intervention, the likelihood of spontaneous passage for stones must be estimated relative to their location. A meta-analysis of six studies comprising 2704 patients evaluated the spontaneous passage rate of ureteral stones [15]. When comparing passage rates based on stone size, regardless of location in the ureter, stones less than 4 mm and greater than 6 mm in any dimension had spontaneous passage rates of 38% and 1.2%, respectively. Spontaneous passage rates were higher for distal ureteral stones (45%) compared with middle (22%) and proximal ureteral stones (12%). Moreover, two thirds of stones passed spontaneously within 4 weeks of the onset of symptoms.

Cost-effectiveness of strategies using observation versus those using surgery depends on likelihood of spontaneous passage, stone location, stone size, and success rates for SWL or ureteroscopy. Lotan and colleagues [16] used a cost-effectiveness model taking these factors 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. The model assumed outpatient treatment in all cases and did not take into account additional visits to the emergency room (at an average cost of $625) or loss of work secondary to pain. According to the 2001 Census of Population and Housing from the United States Census Bureau, the average American worker earned approximately $141 per day in 2000 dollars. As such, although observation for patients with small distal ureteral calculi may be a cost-effective strategy, for patients with proximal ureteral stones that are unlikely to pass, observation can result in rapid accrual of additional costs owing to loss of work, emergency room visits, and follow-up radiographs. These additional costs may ultimately make this approach cost-ineffective. However, the cost-effectiveness of observational strategies increases with improvements in the likelihood of spontaneous stone passage. 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 [17–20].

Surgical therapy

The choice of surgical approach depends on a number of factors, including stone characteristics (size, location, and composition), the anatomy of the kidney and ureter, patient preference, and available technologies (ureteroscopes, holmium laser). From a financial standpoint, the overall cost of each primary treatment modality takes into account not only the efficacy of the procedure but also the cost of re-treating failures, the need for ancillary procedures or hospitalization, and indirect costs. Ureteroscopy, SWL, and percutaneous nephrostolithotomy (PCNL) are each associated with different success rates, morbidities, and costs.

While it is tempting to try to reach conclusions that are meaningful to readers worldwide, this is rarely possible when analyzing economic issues related to medicine. The lack of uniformity in the published literature related to the cost-impact of stone disease stems in part from the significant variation in treatment costs worldwide. An international economic survey of 10 countries by Chandhoke [21] found that charges for SWL varied from $373 to $9924 and those for ureteroscopy from $491 to $8108. SWL was determined to be more costly than ureteroscopy in 5 countries, equivalent in 3 countries, and less costly in 2 countries. In fact, the ratio of SWL-to-ureteroscopy charges ranged from 4:1 in Australia to 1:3 in Switzerland. As such, comparing costs among countries may be impractical and inaccurate. However, conclusions can be drawn from evaluations of costs within a single country or health care system where reimbursement rates and costs are relatively uniform. For example, in the United States, ureteroscopy is less costly than SWL when both are performed on an outpatient basis [16,21–24]. Furthermore, decision modeling may allow conclusions to be drawn using individual data derived from a particular health care system.

Renal calculi

Few studies have evaluated 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 [25]. 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 because re-treatment of some SWL patients was required.

Because of the paucity of prospective studies, several models have been used to estimate projected costs of particular treatment strategies based on treatment efficacy and procedure cost. Chandhoke [26] compared the cost-effectiveness of SWL and PCNL for the treatment of staghorn calculi using a decision analysis model in which they inputted average procedure charges from their own institution of $8213 for SWL and $26,622 for PCNL and included re-treatment and complication rates. The charges used in the model, however, did not reflect treatment of stones of uniform size; rather, they used average charges for a group of patients with varying stone burdens and numbers of procedures during the same hospitalization. Based on their model, the cost of combined SWL- and PCNL-based therapy was comparable to the cost of SWL alone for stones less than 500 mm^2, but combined SWL- and PCNL-based therapy was more cost-effective than SWL alone when the stone burden exceeded 500 mm^2.

May and Chandhoke [27] performed a similar cost analysis for SWL and PCNL treatment of solitary lower pole renal calculi using charge data from their institution and success rates for SWL and PCNL derived from a published meta-analysis [28]. In their model, all treatment failures were salvaged with secondary PCNL. For lower pole stones less than 1 cm in the largest dimension and for lower pole stones 1 to 2 cm in the largest dimension, SWL was less costly than PCNL when PCNL charges exceeded $11,099 and $12,258, respectively. For stones greater than 2 cm in the largest dimension, PCNL was less costly than SWL, provided PCNL charges remained under $21,059. Because the charge for uncomplicated PCNL was less than $15,000 at their institution, the investigators concluded that, for a solitary lower pole stone greater than 2 cm in the largest dimension, PCNL is the most cost-effective approach, while SWL is more cost-effective for lower pole stones less than 2 cm in the largest dimension despite lower initial stone-free rates.

The cost at one institution may not be generalizable to other institutions and countries. This is why decision models that take into account specific costs and success rates are best for predicting the cost-effectiveness of different treatment strategies. Recent studies suggest that success rates for SWL treatment of renal stones and, in particular, lower pole stones may be lower

than assumed in previous models [29,30]. A multi-institutional study randomizing patients with lower pole stones measuring less than 1 cm in the largest dimension to ureteroscopy or SWL revealed stone-free rates of 35% and 50%, respectively [29]. Likewise, in a randomized trial comparing SWL and PCNL for the treatment of symptomatic lower pole stones less than or equal to 30 mm in the largest dimension, PCNL stone-free rates were far superior to SWL (95% versus 37%, respectively, $P < .001$) [30]. Cost related to re-treatment plays an important role in determining cost-effectiveness, particularly when there is substantial difference in success rates between different treatment modalities. An important caveat is that cost analyses do not take into account patient preference, an important factor in decision-making. Furthermore, success rates published in the literature may not be realized by individual practitioners and consequently may not be uniformly applicable.

Ureteral calculi

Cost analyses for the treatment of ureteral stones must take into account stone location and size because these factors influence treatment outcomes. Most studies in the United States have shown that ureteroscopy is more cost effective than SWL for the treatment of ureteral stones primarily because the stone-free rates of ureteroscopy are much higher than those for SWL, which means that SWL is associated with high re-treatment costs [22,23,31]. Grasso and colleagues [31] treated 112 patients with ureteral stones (not stratified by location) using a Lithostar-Plus lithotripter or ureteroscopy and found that although initial treatment costs for the two modalities were similar, re-treatment and auxiliary procedure rates were significantly higher for SWL than for ureteroscopy (31% versus 3%, respectively) contributing to a higher global cost for SWL. Kapoor and colleagues [22] also compared the cost of SWL with a Dornier HM3 lithotripter (n = 20) and ureteroscopy (n = 32) and found ureteroscopy to be 60% less costly than SWL because ureteroscopy resulted in significantly higher success rates (97% versus 75%). In contrast, Anderson and colleagues [23] found a small cost advantage for ureteroscopy over SWL if patients with distal ureteral stones were treated on an outpatient basis, but no cost advantage if ureteroscopy treatment necessitated a short inpatient stay.

Because of different cost differentials between ureteroscopy and SWL in other countries, the cost-effectiveness of treatment modalities varies. Pardalidis and colleagues [32] from Greece found no difference in cost between SWL and ureteroscopy for distal ureteral stones despite a mean hospital stay of 2.5 days for ureteroscopy patients and outpatient treatment for all SWL patients. In contrast, Bierkens and colleagues [33] reported that SWL was less costly than ureteroscopy for treatment of middle and distal ureteral stones in the Netherlands. The average length of stay for ureteroscopy patients in their series was more than 3 days; however, if ureteroscopy was performed on an outpatient basis, the cost of SWL would exceed the cost of ureteroscopy.

In one of the few studies comparing the costs associated with treatment of proximal ureteral stones, Parker and colleagues [34] found that ureteroscopy was less costly than SWL by $6205 because of an initial treatment success of 91% for ureteroscopy and 55% for SWL.

Several decision analysis models have been used 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. Decision analysis models are also useful because they can be used to input costs and success rates unique to any institution or within any health care system to determine the most cost-effective treatment option for a given patient or stone. Wolf and colleagues [24] used decision-tree modeling to compare the cost of treating distal ureteral stones with SWL or ureteroscopy, taking into account success rates, cost, and patient preference. They estimated mean success rates for ureteroscopy and SWL using published series between 1988 and 1994, yielding stone-free rates of 92% for ureteroscopy and 74% for SWL. Their model took into account the cost of complications and also assumed a standard re-treatment arm for patients who failed initial therapy, which consisted of SWL followed if necessary by ureteroscopy and then open surgery. The average cost of SWL was 21% higher than that of ureteroscopy. By this analysis, the cost of SWL would have to drop by $1107 to reach cost equivalence with ureteroscopy.

Lotan and colleagues [16] also constructed a decision analysis model to determine the most cost-effective treatment for stones located in the proximal, middle, or distal ureter, taking into account

procedure costs and success rates. Mean success rates for each of three treatment strategies (observation, SWL, and ureteroscopy) were calculated from published series, and procedure costs were derived from their institution. Observation was determined to be the least costly pathway, provided no cost (eg, emergency room visits) was incurred when observation failed. However, ureteroscopy was less costly than SWL for the treatment of stones at all locations in the ureter. The investigators found cost differences between the two surgical modalities of approximately $1440, $1670, and $1750 for proximal, middle, and distal ureteral calculi, respectively (Table 1). The cost advantages for ureteroscopy, however, would not be present in countries where SWL is less costly or equivalent to ureteroscopy .

Table 1
Stone-free rates, treatment cost, and total cost (stratified by stone location and treatment modality) for management of ureteral stones

Treatment location	Modality	Stone-free percent[a] (range)	Total cost[b]
Distal	OBS	45 (36–71)	$1,532
	URS[c]	95 (86–100)	$2,785
	SWL HM3[c]	89 (78–97)	$4,533
	SWL other[c]	82 (59–97)	$4,729
Middle	OBS	22 (0–46)	$2,245
	URS[c]	92 (75–100)	$2,878
	SWL HM3[c]	89 (53–97)	$4,545
	SWL other[c]	78 (51–92)	$4,865
Proximal	OBS	12 (6–22)	$2,943
	URS[c]	80 (66–99)	$3,344
	SWL HM3[c]	83 (73–96)	$4,819
	SWL other[c]	84 (59–96)	$4,784

Abbreviations: OBS, observation; SWL HM3, shock wave lithotripsy using Dornier HM3; SWL other, shock wave lithotripsy with newer-generation lithotriptors; URS, ureteroscopy.

[a] Mean stone-free rates based on literature review.

[b] Total cost of treatment per decision tree.

[c] Treatment costs based on average treatment cost at a large metropolitan county hospital: URS ($2665), SWL ($4310).

Data from Lotan Y, Gettman MT, Roehrborn CG, et al. Management of ureteral calculi: a cost comparison and decision making analysis. J Urol 2002;167 (4):1624.

Medical evaluation and management

The merits of medical evaluation and dietary and drug therapy have been discussed thoroughly and will not be readdressed in this article. From a cost perspective, the financial benefits of preventing stones (avoidance of surgery and need for outpatient care) must be balanced against the cost of evaluation and medication. According to data from the Medical Expenditure Panel Survey, estimated total annual expenditures for outpatient prescription drugs for the treatment of urolithiasis between 1996 and 1998 ranged from $4 million to $14 million [4]. 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 [35]. Unfortunately, the cost, inconvenience, and morbidity of medication remain significant impediments to patient compliance with medical therapy.

Several studies have evaluated the cost-effectiveness of medical evaluation and prophylaxis. However, there is little uniformity in study design or treatment in published trials. Studies that have concluded that medical therapy is cost-effective based their conclusions on key assumptions regarding stone recurrence rates and medication risk reduction [6,36–38]. Parks and Coe [37] calculated a cost savings for the United States health care system of $1162 to $3162 per patient, per year based on an 83% remission rate after initiation of medical therapy. Although this study used actual stone recurrence rates for determining cost savings, it failed to take into account the benefit derived from conservative measures alone, which are considerably less costly than any drug treatment.

Medical management for stone disease has also been found to be cost-effective in European countries with national health care systems. Strohmaier and Hörmann [6] calculated an annual cost savings of 333.1 million DM to the German health care system, assuming an annual stone recurrence rate of 50% and risk reduction by medical treatment of 40%. In the Swedish health care system, Tiselius [36] found that assuming a baseline stone recurrence rate of 0.3 stones per year, medication costs of 220 euros per year and a cost per stone episode of 2500 euros, initiation of a medication known to produce a 50% reduction in stone recurrence rates would save 375 euros per patient per year. In the United Kingdom, Robertson [38] found that assuming a stone recurrence rate of 20% per

year, medical prophylaxis associated with a 50% risk reduction and medical evaluation at a cost of £180 per year would result in cost savings of £38 per patient per year.

More recently, Chandhoke [21] used a cost model based on an international survey looking at costs associated with stone management to determine the stone recurrence rate at which medical prophylaxis becomes cost-effective. He determined that a wide range of stone recurrence rates (0.3–4.0 stones per year) would make the cost of medical evaluation and treatment to be equivalent to that of conservative therapy (no drug). This broad range of recurrence rates is attributed to the variation in treatment costs among the countries surveyed.

While stone recurrence rates and the cost associated with medication, medical evaluation, and surgical therapy for stone recurrence are important factors in determining the cost-effectiveness of medical evaluation and therapy, several key points have not been adequately considered in many studies. First, dietary modification alone is effective in reducing stone recurrence rates, and most medical prophylaxis programs include dietary measures in addition to medications [39]. Consequently, the stone recurrence rates for conservative therapy should reflect the benefit of dietary measures. Second, only a fraction of patients (10%–20%) actually become symptomatic from a new stone and only approximately half the symptomatic patients ultimately require surgical intervention [40–42]. As such, the impact of stone recurrences is less than if all patients with recurrent stones are assumed to undergo surgery. Lastly, 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 [43]. Thus, many analyses have suffered from inherent biases against conservative therapy and in favor of metabolic evaluation and medical treatment.

Taking these factors into consideration, Lotan and colleagues [44] created a decision-tree model to compare the costs of six medical treatment strategies: dietary measures alone; empiric drug treatment; directed drug therapy based on simple metabolic evaluation with all patients treated with drugs; directed drug therapy based on simple metabolic evaluation with only those patients with demonstrable metabolic defects treated with drugs; directed drug therapy based on comprehensive metabolic evaluation with all patients treated with drugs; and directed drug therapy based on comprehensive metabolic evaluation with only those patients with demonstrable metabolic defects treated with drugs. The model assumed cost accrual for evaluation, medications, and emergency treatment and surgery for stone recurrence. For first-time stone formers, conservative therapy was the least costly strategy and yielded a stone recurrence rate of 0.07 stones per patient per year (Table 2). For recurrent stone formers, conservative treatment was less costly than drug treatments, but was associated with a higher stone recurrence rate (0.3 stones per patient per year). The remaining drug treatments were more costly than conservative treatment ($885–$1,187 per

Table 2
Outcomes of decision analysis model based on different treatment strategies

Patient	Strategy	Stone formation rate: stones per patient per year	Model cost per year
First-time stone formers	Conservative[a]	0.070	$133
	Empiric[b]	0.013	$966
	Modified SMEM[c]	0.011	$1085
	SMEM[d]	0.028	$835
	Modified CMEM[c]	0.009	$1170
	CMEM[d]	0.015	$1087
Recurrent stone formers	Conservative[a]	0.300	$258
	Empiric[b]	0.057	$990
	Modified SMEM[c]	0.048	$1104
	SMEM[d]	0.120	$885
	Modified CMEM[c]	0.041	$1187
	CMEM[d]	0.065	$1,114

Abbreviations: CMEM, comprehensive metabolic evaluation and management; SMEM, simple metabolic evaluation and management.

[a] Dietary measures alone.

[b] With potassium citrate.

[c] With potassium citrate with or without thiazide; patients with negative evaluation treated with potassium citrate.

[d] With potassium citrate with or without thiazide; patients with negative evaluation receive no medication.

Data from Lotan Y, Cadeddu JA, Roerhborn CG, et al. Cost-effectiveness of medical management strategies for nephrolithiasis. J Urol 2004;172(6 Pt 1):2278.

year versus $258 per year), but further reduced recurrence rates by 60% to 86%. Modified simple medical evaluation and management, in which drug treatment was provided to all patients after simple evaluation, was slightly more costly than empiric treatment and only minimally more effective. Comprehensive evaluation and directed medical therapy offered no advantage in cost or efficacy over empiric treatment or modified simple medical evaluation and management (see Table 2). Using this decision-tree model, it is also possible to determine the cost and risk reduction that would be required to make a particular medication cost-effective in patients with recurrent kidney stones if used empirically or based on simple metabolic evaluation (Table 3).

The cost of most drug treatments commonly used for the prevention of renal calculi (potassium citrate alone or in combination with thiazide diuretics) is high enough that even for recurrent stone formers, conservative measures are more cost-effective than current drug treatments, although at the high price of more frequent stone events. However, with a limited metabolic evaluation and directed drug therapy or empiric drug treatment only, stone recurrences can be prevented at a modest incremental cost in patients at high risk of developing recurrent stones.

International perspective

As has become apparent from the above cost analyses, 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. 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 international boundaries. In an International Economic Survey by Chandhoke [21], costs for SWL and ureteroscopy were widely disparate in different countries. Indeed, a nearly 20-fold difference was demonstrated in the costs of SWL, ureteroscopy with laser lithotripsy, and medication among different countries.

To evaluate the cost-effectiveness of medical evaluation and management strategies in different health care systems, the authors used the previously described decision-tree model [44] and applied the same baseline assumptions and costs used in Chandhoke's [21] international cost survey [45]. Converting to United States dollars per patient per year in the model, 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 all countries except the United Kingdom where empiric therapy was the most cost-effective strategy for recurrent stone formers as a result of the low cost of drug therapy (estimated at $29 per patient per year). The infrequent need for surgical intervention, as well as the low cost of surgery compared with medication contributed to the higher cost of empiric and comprehensive medical evaluation strategies. Despite their higher cost, drug treatment strategies were associated with significantly lower stone recurrence rates.

Subsidization plays a significant role in determining costs of the various strategies for managing nephrolithiasis. In countries where surgery and physician reimbursement are heavily regulated, such as the United States, strategies involving drug therapy are rarely cost-effective. Indeed, in the United States, medication costs are unregulated and, therefore, costly medications involve a large out-of-pocket expense for the patients themselves. In contrast, insurers and government-run and subsidized health care agencies like the Centers for Medicare and Medicaid dictate reimbursement rates for services associated with hospitalization and surgical procedures and for physician fees, leading to

Table 3
Medication cost threshold for empiric and modified simple metabolic evaluation and management strategies at varying levels of risk reduction

Risk reduction	Medication cost threshold for empiric therapy ($/y)	Medication cost threshold for modified SMEM ($/y)
50%	$81	–
60%	$98	$12
70%	$114	$28
80%	$130	$44
90%	$147	$61
100%	$163	$77

Abbreviation: SMEM, simplified metabolic evaluation and management.

Data from Lotan Y, Cadeddu JA, Roerhborn CG, et al. Cost-effectiveness of medical management strategies for nephrolithiasis. J Urol 2004;172(6 Pt 1):2278.

a disproportionately higher cost for medication than for surgery, particularly when taking into account the frequency of medication use (daily) compared with the infrequent need for surgery. The differential resource allocation to different components of a health care system (ie, subsidized medication versus regulated surgical costs) in different countries determines the cost-effectiveness of various treatment strategies.

Physician perspective

While many financial aspects of stone disease are important to the physician, two areas affect the physician to an especially significant degree: (1) equipment and medications and (2) Medicare reimbursement.

The ability to treat stone patients depends on the availability of quality equipment and effective medications. However, there is a conflict between the health care industry, whose goal is to provide care but limit cost, and the manufacturers of new technology and drugs, who seek to profit from their inventions. Hospitals seek to limit capital investment and, therefore, they have limited interest in continued upgrading of costly equipment. Indeed, although newer ureteroscopes have improved deflection and optics, their cost has increased to upwards of $20,000 each, despite a durability estimated at only 11 to 14 cases and repair costs of over $5000 per repair [46–48]. With regard to medical management, companies have little incentive to develop new drugs if few physicians prescribe these medications.

Meanwhile, regarding reimbursement, urologists have realized a greater than 25% to 32% decrease in reimbursement for surgical procedures over the last decade [49]. Medicare reimbursement for SWL has decreased from $803 in 1995 to $567 in 2004. In the last 5 years, reimbursement for ureteroscopy with laser lithotripsy has decreased by $55 and PCNL by $174, without taking into account inflation. Consequently, urologists are seeking to supplement their income in other areas. SWL has a separate ''facility fee'' and, as a consequence, more urologists are investing in lithotripters (36% in 1993 versus 54% in 2001) [50,51]. Likewise, physician financial interests in ambulatory surgical centers have increased from 12% in 1993 to 21% in 2001 [50,51].

While reimbursement rates may not change how physicians treat patients, they do influence the number of patients they see. In 1995, urologists saw an average of 75 patients per week, which rose to 84.6 patients per week in 2001 [50,51]. As the population ages, the demands on urologists will increase. As such, it will be important for urologists to remain vigilant to changes in reimbursement both to protect their personal income and to salvage the desirability of the practice of urology.

Summary

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 among 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 strategies for their own particular situation.

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