Nephrolithiasis

Gilberto B. González and Charles Y.C. Pak

Introduction

Kidney stones, formed within the upper urinary tract, are concretions of different mineral salts mixed with an organic matrix. Nephrolithiasis has plagued humans since antiquity. The oldest urinary calculi on record actually comes from an Egyptian mummy dated about 4800 BC. A renal colic due to stone was the first renal disease described by Hippocrates. Considered a classic, this description included a differential diagnosis between renal and bladder stones [1]. Galen (AD 130) was the first to associate stones with a metabolic origin [2]. Some of the notable figures in history who suffered from stones include Pliny, Sir Walter Scott, Benjamin Franklin, Napoleon, and Lyndon B. Johnson [3].

During the past 20 years, notable advances have been made in the nephrolithiasis field. Pathophysiologic mechanisms for many causes of stones have been clarified, and specific molecular defects are beginning to be unraveled [4, 5]. It is now possible to diagnose the cause of stone disease in > 95% of patients [6], and new drugs provide improved treatment options [7 – 9]. Facilitated stone removal has become possible with the introduction of the endoscopic approach [10] and extracorporeal shock wave lithotripsy (ESWL) [11].

Despite these advances, only a few practicing physicians avail themselves of new diagnostic methods and preventive treatment modalities in the management of stone disease. Reasons for this lapse are 2 fold. First, the facility with which stones can now be removed has led to a disparagement of the need for medical diagnosis and treatment. Why bother to have tests done and take drugs for a long duration, when one feels well between stone episodes? Instead, all one has to do is to undergo lithotripsy when, once in a while, a stone is formed and causes trouble.

Second, our group advocated a selective treatment approach that necessitated a careful differentiation of various causes of stones and the selection of specific drugs for each cause. The complexity of this process may have led some physicians to forego the medical approach. However, urinary stone risk factors are not modified by urological procedures alone [12], and nephrolithiasis carries a lifetime recurrence rate as high as 80% [13]. Consequently, a medical approach, directed at prevention of recurrent stone formation, is still required. Strict adherence to the selective approach seems impractical except at a large stone research center. In this chapter, a new and simplified approach for the medical management of kidney stones is proposed, which any physician may readily adopt.

Epidemiology

More than 95% of urinary stones encountered in developed countries are localized in

the kidney or upper urinary tract. Bladder stones are found most commonly in men with prostatic diseases and children who live in less-developed countries in Southern Asia and the Middle East. These stones, related to malnutrition or infection, are a different entity from nephrolithiasis and will not be discussed in this chapter. The true incidence of nephrolithiasis is not well known. Most of the studies have underestimated the problem because they relied on data from hospital records. As many as 70% of patients will not require hospitalization [14]. In an attempt to address this issue, Johnson et al. [15], studied the incidence and prevalence rates for symptomatic, noninfected renal stones over a 25-year period in a well-defined population of Rochester, Minnesota. They found an annual age-adjusted incidence rate for males of 123.6 per 100,000 population in 1974, a 57% increase from 1950. The incidence rate for females was stable over the study period at 36.0 per 100,000. The peak incidence occurs between the ages of 15 – 44 years, during the most productive years [14]. Recurrence rates increase with follow-up: 14%, 35%, 52%, and 75% after 1, 5, 10, and 20 years from the first stone episode, respectively [16, 17]. Thus, recurrence is the rule rather the exception.

Based on this and other population studies, it has been estimated for the United States population that 5 – 15% will have symptomatic stone disease by the age of 70, with the prevalence being twice as common in men as in women. Worldwide, the lifetime stone prevalence in men > 60 years of age varies from 1.5% in China, to 5.4% in Japan, around 8% in the United Kingdom, Germany and Sweden, 12% in Canada, and 20% in Saudi Arabia [18]. Obviously, these differences can be explained in part by variations in study design, but they also reflect real changes due to genetic, nutritional, and environmental influences.

Nephrolithiasis leads to considerable morbidity – renal colic, hematuria, and infection (UTI). It accounts for 0.9% of hospital discharges, with a mean duration of hospital stay of 3 days. The total annual cost in the United States, including direct costs from hospitalization and outpatient evaluation, and indirect costs from lost wages, was estimated to be $1.83 billion in 1993 [19]. In addition, loss of kidney function may occur because of complications such as infection and obstruction, and from damage during surgery. Up to 1% of patients in a dialysis program developed end-stage renal disease (ESRD) secondary to stones [20]. Mortality from stone disease is rare and data are not available.

Stone Composition

Mineral salts, mostly in a crystalline form, account for > 95% of the weight of a kidney stone. A heterogeneous material called matrix is found in concentric layers or radial striations throughout the stone and explains the remaining weight.

The composition of the different crystalline components in stones varies from one part of the world to another, depending on specific methods of analysis and prevalence of stone risk factors. Infrared spectroscopy and X-ray diffraction crystallography offer the highest degree of certainty for the correct analysis of the stone [21]. The most recent series of stone composition based on those techniques for some industrialized countries are summarized in Table 1 [21 – 23]. The majority of stones are mixtures of 2 or more components. Calcareous stones, occurring as calcium oxalate alone or in combination with apatite, comprise approximately 75% of all stones. Cal-

Table 1. Frequency of Occurrence of Components in Renal Stones

Stone type	Mineral name	Mandel 1989 USA (10,163)	Leusmann 1990 Germany (5,035)	Daudon 1995 France (10,438)
I) Calcareous stones				
Calcium oxalate monohydrate	Whewellite	55.4	70.2	42.8
Calcium oxalate dihydrate	Weddellite	34.6	43.6	23.2
Basic calcium phosphate	Apatite	26.9	51.0	15.3
Calcium hydrogen phosphate	Brushite	1.7	2.1	1.0
II) Non-calcareous stones				
Magnesium ammonium phosphate	Struvite	12.6	10.1	2.8
Uric acid		12.6	10.0	8.8
Cystine		0.5	1.0	1.2
Miscellaneous		2.3	2.1	2.4

Numbers indicate the percentage occurrence of the most common stone type in the series. In parentheses is indicated the number of stones.

cium oxalate crystals are found in monohydrate and dihydrate forms, which have different lattice structures and microscopic appearances. Only 5% of stones are principally made of calcium phosphate salts such as apatite or brushite. Noncalcareous stones account for no more than 20% of stones. Struvite stones comprise 5 – 10% of stones; they are often called infection stones because they develop from infection of the urinary tract with urea-splitting organisms. Pure struvite stones are rare; they typically occur as mixtures with carbonate apatite or other calcium salts. Uric acid, the major end product of purine metabolism, accounts for 5 – 10% of stones in Europe and United States. However, endemic regions exist in the Mediterranean countries and in the Near East, where up to one third of all stones are composed of uric acid [24]. Cystine stones, comprising about 1%, are diagnostic of cystinuria, an inherited disorder of dibasic amino acid transport. The miscellaneous group (approximately 2%) includes rare forms of stones such as 2,8-dihydroxyadenine and xanthine (due to inborn errors of metabolism), triamterene or silica (from drug treatments), or matrix calculi (which contain mostly organic molecules and occur in association with chronic UTI) [25, 26].

Stone matrix is composed of about 64% protein, 12% organic ash, 10% bound water, 9% nonamino sugars, and 5% glucosamine. These organic materials might not only derive from substances normally present in urine, but may also be produced by epithelial cells from the trauma induced by an enlarging stone [27].

Pathogenesis

Nephrolithiasis is a heterogeneous disorder; stone composition and the underlying

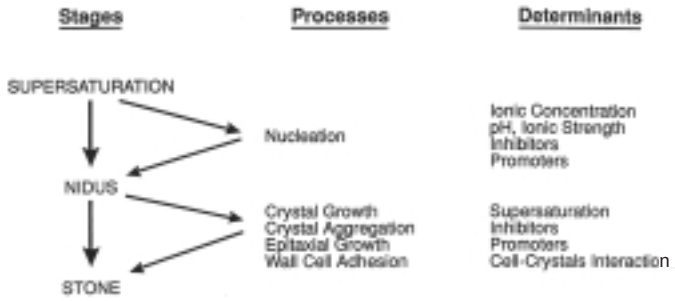

Figure 1. Pathogenesis of stone formation. (Adapted from Pak CYC 1993 Urolithiasis. In: Schrier RW, Gottschalk CW (eds): Diseases of the Kidney (Fifth Ed). Little, Brown and Company, Boston, figure 25-1, p 73, with permission).

mechanisms responsible for stone formation are diverse. Three principal theories of stone formation have been invoked. The precipitation-crystallization theory considers stone formation to be a physicochemical process of precipitation of stone-forming salts from a supersaturated urinary environment [28]. The inhibitor theory holds that a deficiency in urine of substances that physicochemically prevent crystallization leads to stone formation [29]. In the matrix theory, the stone is believed to form in an organic matrix, analogous to the mineralization of the bone [30]. While none of these theories is exclusive of the others, the precipitation-crystallization theory has the most experimental support.

A current scheme for stone formation considers the process to begin by nucleation of a crystal nidus from a supersaturated urinary environment, followed by transformation of the nidus into a stone through crystal growth, epitaxial growth, and crystal aggregation (Figure 1) [31]. This scheme is consistent with all three classic theories, because stones could form without or within an organic matrix and because lack of inhibitors could facilitate the process.

By whatever mechanism, the necessary condition that must occur for stones to form in human urine is nucleation, defined as the beginning of a crystalline solid phase. Homogeneous nucleation refers to the process of spontaneous crystal formation that occurs for any stone-forming salt when its urinary saturation exceeds the limit of metastability. However, in a complex solution such as urine, many foreign surfaces are constantly present cell debris, epithelial membranes, another crystal species (e.g.), and crystals may nucleate on such foreign surfaces in a phenomenon known as heterogeneous nucleation. Because it is not necessary to reach a critical cluster size for nucleation, it is more likely that heterogeneous nucleation occurs at lower levels of metastability [27]. This process may also be the basis for the formation of stones of mixed composition. Examples of heterogeneous nucleation are nucleation of calcium oxalate by seeds of calcium phosphate or by uric acid. The urinary environment of patients with stones is typically supersaturated with respect to stone constituents and possesses a reduced limit of metastability. Thus, the nucleation process is facilitated in the stone-forming urinary environment. This increased propensity for nucleation is reflected, for instance, by the reduced amount of soluble oxalate or calcium required to elicit spontaneous precipitation of calcium oxalate and calcium phosphate in urine of stone-forming patients [32, 33].

Once a crystal nidus has been formed, other events must occur to allow this nidus to become large enough to get lodged in the urinary tract. In principle, the retention of particles within the renal tubule can occur through several mechanisms: by the addition of new

crystals of the same chemical composition to the nucleus (crystal growth); by agglomeration of preformed crystals into large clusters (crystal aggregation); or by epitaxial growth, the process whereby material of one crystal type is precipitated upon the surface of another whose lattice dimensions are almost identical. Alternatively, the stone-forming crystals may react with components of the renal tubular cell, become attached, and grow [27, 34].

Supersaturation of crystalloids can result from the following processes:

- An increase in free ion concentrations, through too little urine output (a concentrated urine), an absolute increase in the amount of a stone-forming constituent excreted in urine (such as calcium, oxalate, uric acid or cystine), or a reduction in natural ligands (such as citrate, which forms a soluble complex with calcium).
- An alteration in the urine pH, because low urinary pH (< 5.5) increases urinary saturation of uric acid, whereas high urinary pH raises that of calcium phosphate and magnesium ammonium phosphate.
- A change in the ionic strength, which alters the ionic activity of stone-forming constituents [34].

Several methods for assessing supersaturation levels in urine have been reported [27, 35]. The urinary activity product provides the best estimate for the state of saturation with respect to stone-forming ions. It is calculated for any given salt, such as calcium oxalate, by estimating ionic activities with a computer program. When the activity product, e.g. $[Ca^{2+}] \times [Ox^{2-}]$, is divided by the corresponding thermodynamic solubility product (solubility product of calcium oxalate in artificial solutions), a relative saturation ratio is derived [35]. A value > 1 represents urinary supersaturation, whereas a value < 1 indicates undersaturation.

Despite the importance of supersaturation in stone formation, the urinary environment of normal subjects without stones is often supersaturated with respect to calcium oxalate, the most common stone salt. To explain lack of stone formation, studies during the past 40 years have sought the presence of inhibitors that retard crystallization processes, particularly of calcium oxalate. These substances have been defined as molecules that raise the metastable limit (so that nucleation would be initiated at a higher supersaturation), inhibit secondary nucleations, or reduce the growth rate and aggregation of crystal nuclei [36]. The mechanism of action appears to be the adsorption of the inhibitors to specific growth sites on the crystal surfaces, which are thought to be dislocations in the crystal lattice. This adsorption prevents the further deposition of crystal lattice ions and prevents the crystals from "sticking" together in an aggregation process [34]. A list of proposed inhibitors is shown in Table 2. Macromolecular inhibitors have been isolated from

Table 2. Urinary Crystallization Inhibitors

I) Low-molecular-weight substances
1. Citrate
2. Magnesium
3. Pyrophosphate
4. Trace metals

II) High-molecular-weight substances
1. Glycosaminoglycans
2. Nephrocalcin
3. Prothrombin F1 peptide
4. Tamm-Horsfall protein
5. Uronic acid rich protein
6. Uropontin

the soluble part of the organic matrix of kidney stones or in the urine. Small molecules (citrate and pyrophosphate) play a prominent role in the inhibition of crystal growth of calcium phosphate [37], whereas larger molecules [36] (glycopeptides and glycosaminoglycans) are believed to play a prominent role in the inhibition of calcium oxalate crystallization. Urinary excretion of some of these inhibitors, e.g. citrate [38] and glycosaminoglycans [39], has been reported to be reduced in some patients with stones. In other studies, Tamm-Horsfall protein and nephrocalcin have been reported to be structurally and functionally abnormal in recurrent calcium oxalate stone formers. However, the role of these organic macromolecules in the pathogenesis of nephrolithiasis has not been well established. Finally, epithelial cell injury and the response of renal cells to crystals might be relevant to the effective growth of renal calculi [40, 41].

Other factors, such as anatomical abnormalities, predispose to stone formation. Nephrolithiasis may be found in association with ectopic, polycystic, or horseshoe kidney, or with stenosis at all levels of the urinary tract. In these conditions, it is generally accepted that secondary urinary stasis predisposes to infection stones or exaggerates stone disease. Medullary sponge kidney is often associated with calcareous renal calculi. There is no convincing evidence that this structural abnormality causes stone formation, because patients with medullary sponge kidney and stones have the same spectrum of biochemical abnormalities as the overall population of stone formers without tubular ectasia [26].

In summary, the pathogenesis of nephrolithiasis is multifactorial and involves alteration in physicochemical and biological mechanisms that regulate the solubility of the urine. Not all aspects of stone formation are well understood, and the exact site in the kidney at which initial steps in stone formation take place is unknown. However, from a clinical point of view, abnormalities or risk factors that predispose to stone formation can be identified in most patients with stones from analysis of their urine.

Urinary Risk Factors for Nephrolithiasis

The frequency and pathogenetic significance of most important urinary risk factors for renal stones are described in Table 3. Data from 1,270 patients with recurrent nephrolithiasis studied during the last 20 years under the same ambulatory protocol were considered in estimating the relative frequency of various risk factors [6]. No abnormality was found in only 4% of patients. Several independent disturbances may, in fact, coexist in a given patient. The co-occurrence of various derangements could be explained by (1) superimposition of a dietary or environmental aberration on an underlying metabolic abnormality, (2) coexistence of separate metabolic abnormalities in the same patient (e.g. distal renal tubular acidosis (RTA) causing hypercalciuria and hypocitraturia), and (3) primary metabolic abnormality causing other derangements (e.g. increased intestinal calcium absorption, leaving less calcium remaining in the gut to bind oxalate, thus resulting in hyperoxaluria).

Hypercalciuria

Hypercalciuria is the most common underlying abnormality, encountered in approxi-

Table 3. Incidence and Pathogenetic Significance of Risk Factors for Nephrolithiasis

Risk factor	Incidence (%)*	Effect in Urine
Hypercalciuria	61	Increased saturation of calcium oxalate and calcium phosphate Reduced inhibitor activity against crystallization of calcium salts by binding negatively charged inhibitors (citrate, chondroitin sulfate) and inactivating them
Hyperuricosuria	36	Increased saturation of monosodium urate Facilitated calcium oxalate crystallization by heterogeneous nucleation or binding macromolecular inhibitor
Hypocitraturia	31	Increased saturation of calcium salts via reduced calcium binding Reduced inhibitor activity against spontaneous nucleation and agglomeration of calcium oxalate,crystal growth of calcium phosphate and heterogeneous nucleation of calcium oxalate by monosodium urate.
Low urine volume	15	Increased saturation of stone-forming salts
Low urinary pH (pH < 5.5)	10	Low uric acid solubility
Hyperoxaluria	8	Increased saturation of calcium oxalate
Hypomagnesiuria	7	Increased saturation of calcium oxalate from reduced binding of oxalate
High urinary pH (pH > 7.0) (struvite stones)	6	Increased saturation of calcium phosphate Increased saturation of struvite (if ammonium ion concentration is high)
Cystinuria	1	Increased saturation of urine

*Represents percentages of patients among 1,270 stone formers studied in Dallas who had each risk factor, either singly or concurrently.

mately 60% of patients with stones. It is usually defined in adults on an unrestricted diet (about 1 g of calcium intake) as urinary calcium excretion in 24 hours > 250 mg in women and 300 mg in men, or 4 mg/kg body weight in patients of either sex [42]. When calcium intake is restricted for one week to 400 mg/day and sodium intake to 100 mEq/day, the upper limit of normal for urinary calcium excretion is 200 mg/day [43].

The association of hypercalciuria with nephrolithiasis was first recognized by Flocks [44]. A pathogenetic role for hypercalciuria in stone formation is supported by several lines of evidence. First, the urinary saturation of calcium oxalate and calcium phosphate has been shown to correlate directly with urinary calcium concentration. Moreover, the urinary environment of patients with hypercalciuric nephrolithiasis was typically supersaturated

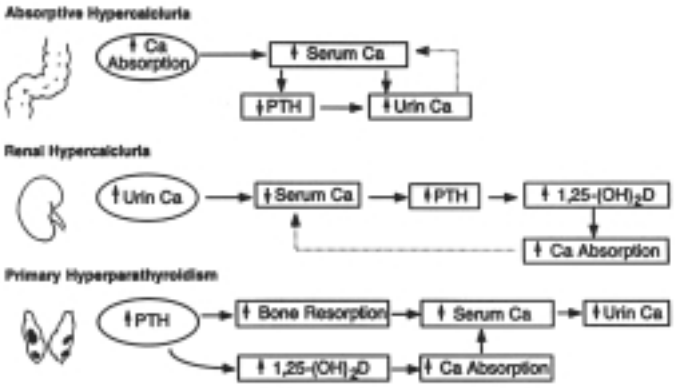

Figure 2. Schemes for the major forms of hypercalciuria. (From Pak CYC 1990 Hypercalciuric calcium nephrolithiasis. In: Resnick MI, Pak CYC. (eds): Urolithiasis.: WB Saunders, Philadelphia, figure 3-5, p 44, with permission.)

with respect to these salts [33]. It was initially suggested that hyperoxaluria was more effective than hypercalciuria in augmenting the urinary saturation of stone-forming calcium salts [45]. However, a reexamination of the problem disclosed an equivalent action of calcium and oxalate. Within the range of concentrations encountered in urine, the rise in calcium concentration was as effective as the increase in oxalate concentration in raising the urinary saturation of calcium oxalate [43]. Indeed, correction of hypercalciuria with the administration of thiazides [46] or sodium cellulose phosphate [47] has effectively reduced stone formation in hypercalciuric patients. Second, hypercalciuria may reduce the inhibitor activity in urine by binding negatively-charged inhibitors and inactivating them. Thus, Zerwekh and colleagues reported that the inhibition of spontaneous nucleation of calcium oxalate exhibited by citrate and chondroitin sulfate was reduced by calcium [48]. Lastly, failure of medical therapy in some patients with calcium nephrolithiasis has been associated with persistent hypercalciuria [49].

Most patients with hypercalciuric nephrolithiasis are normocalcemic and have no obvious cause for increased calcium excretion. The term idiopathic hypercalciuria was used by Albright et al. to denote this entity [50]. Pak, et al. broadly categorized hypercalciuria of nephrolithiasis into 3 types (Figure 2) [43].

Absorptive hypercalciuria (AH), the most common stone-forming entity [6], is characterized by a primary enhancement of intestinal calcium absorption. Following oral calcium ingestion, there is a transient hypercalcemic response which leads to hypercalciuria by enhancement of renal filtered load of calcium and suppressed secretion of parathyroid hormone (PTH), a hormone known to increase renal reabsorption of calcium. AH appears to be inherited as an autosomal dominant trait [51]. Our group in Dallas have devoted considerable effort to delineating the pathophysiology of this disturbance. Although increased circulating calcitriol concentrations have been reported for AH patients and could explain the elevated intestinal calcium absorption, we have not observed frank elevations in serum calcitriol in the majority of our patients [52]. This observation suggests that vitamin D-independent processes or increased intestinal sensitivity to the action of vitamin D might be operative in a majority of the AH patients.

When patients with AH are challenged with a short course of ketoconazole, an inhibitor of steroid synthesis, the ensuing reduction in

calcitriol synthesis produces a decline in intestinal calcium absorption and in urinary calcium in some, but not all, patients [53]. This finding suggests some dependency or sensitivity of the gut to the prevailing concentration of 1,25-$(OH)_2D_3$. Furthermore, we previously reported increased vitamin D receptor (VDR) numbers in activated lymphocytes from some patients with AH who had normal circulating 1,25-$(OH)_2D_3$ levels [54]. These observations, as well as a report of increased intestinal VDR concentration in the genetic hypercalciuric rat [55], an animal model with a phenotype similar to that of the human disease, all prompted a detailed examination of VDR expression in patients with AH. However, extensive molecular biological studies have so far failed to support a pathophysiological importance of vitamin D. Thus, no alteration was found in the VDR cDNA coding region from patients with AH [56]. The gene for VDR or 1-α-hydroxylase of vitamin D was not linked to the inheritance pattern of AH from linkage analysis [57]. Again, there was neither an increase in VDR levels in skin fibroblasts, a recognized vitamin D-responsive cell, nor increased sensitivity to upregulation of VDR numbers by 1,25-$(OH)_2D_3$ in patients with AH [58]. These studies do not preclude a role of VDR concentration in intestinal tissue from patients with AH, where prolongation of the protein's half-life may promote increases in intestinal calcium absorption, hypercalciuria, and nephrolithiasis. Moreover, there may be involvement of other vitamin D responsiveness genes.

Renal hypercalciuria and primary hyperparathyroidism each account for no more than 2% of patients with renal stone disease [6]. In renal hypercalciuria, there is a primary renal leak of calcium, with a transient hypocalcemia. This stimulates parathyroid function, and the excess of PTH leads to calcium mobilization from bone and increased intestinal calcium absorption via 1,25-$(OH)_2D_3$. The cause for the renal leak of calcium is not known. The restoration of normal serum PTH, 1,25-$(OH)_2D_3$ and intestinal calcium absorption upon correction of renal calcium leak by thiazide supports the proposed pathogenetic scheme [59]. Resorptive hypercalciuria is most commonly due to primary hyperparathyroidism. The excessive secretion of PTH stimulates bone resorption, increasing serum calcium and renal filtered load of calcium. Furthermore, PTH-induced renal synthesis of 1,25-$(OH)_2D_3$ leads to enhanced intestinal calcium absorption, leading to further increase in serum calcium and filtered renal calcium load.

Some hypercalciuric patients cannot be categorized into these major variants. Many of them present with fasting hypercalciuria with normal parathyroid function. This presentation may reflect abnormal renal clearance of absorbed calcium in patients with absorptive hypercalciuria. However, recent studies suggest that in some of these cases, hypercalciuria may be partly skeletal in origin because of cytokine-induced bone resorption [60].

Hyperuricosuria

The association of hyperuricosuria with uric acid stone formation is universally recognized [61]. However, it is less commonly realized that hyperuricosuria is also associated with the formation of calcium oxalate stones, even in the absence of hypercalciuria or hyperoxaluria. This association was first noted by Coe et al. who reported that these patients respond favorably to treatment with allopurinol [62].

Figure 3 explains calcium stone formation in the setting of hyperuricosuria, although this scheme has not been clearly validated [63] (Figure 3). Hyperuricosuria, in the setting of

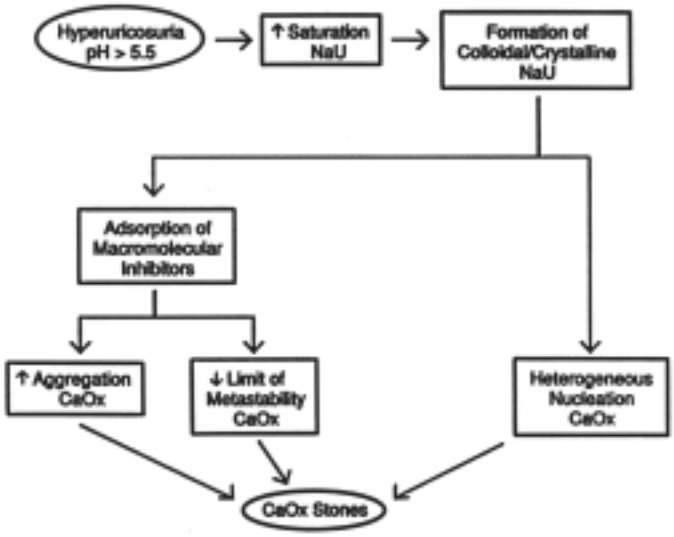

Figure 3. Scheme for calcium oxalate stone formation from hyperuricosuria. NaU = monosodium urate; CaOx = calcium oxalate. (From Pak CYC 1990 Hyperuricosuric calcium nephrolithiasis . In: Resnick MI, Pak CYC. (eds): Urolithiasis.: WB Saunders, Philadelphia, figure 5-1, p. 80, with permission.)

normal pH at which adequate dissociation of uric acid occurs, produces urinary supersaturation of monosodium urate. The resulting formation of colloidal or crystalline monosodium urate causes formation of calcium oxalate stones by heterogeneous nucleation [64, 65], or by adsorption of macromolecular inhibitors [66].

The usual upper limits for normal uric acid excretion are 750 mg/day in women and 800 mg/day in men. However, urine specimens with normal pH of 6.4 were invariably supersaturated when the content of the total dissolved urate exceeded 300 mg/L [63]. Thus, a more functional definition of 600 mg/day for normal upper limit of uric acid excretion is employed in our laboratory at Dallas, assuming a desired urine volume of 2 L/day. Depending on the definition used for hyperuricosuria, it is present in 20 – 40% of the stone-forming population.

The most frequent cause for hyperuricosuria is a purine-rich diet (red meat, poultry and fish). Recurrent stone formation can be ameliorated by dietary purine deprivation [63]. In a minority of patients, hyperuricosuria results from urate overproduction (e.g. myeloproliferative disorders) or uricosuric drugs (e.g. high doses of aspirin).

Hypocitraturia

Citric acid is a tricarboxylic acid with pKa's of 2.9, 4.3, and 5.6. Therefore, in plasma, citrate exists predominantly as a trivalent anion, citrate^{-}. Intracellular citrate is a key component of the tricarboxylic acid cycle (Krebs' cycle), in which ATP is produced from glucose and other fuels [67]. Citrate represents the most abundant of the organic anions and acids present in the urine and plays an important role as an inhibitor of the crystallization of calcium salts.

The physicochemical action of citrate is summarized in Figure 4. Citrate probably acts chiefly through the formation of a complex with calcium, causing a reduction in the ionic calcium concentration and the urinary saturation of calcium oxalate and calcium phos-

Figure 4. Scheme for the inhibitor activity of citrate. (From Pak CYC 1990 Hypocitraturic calcium nephrolithiasis In: Resnick MI, Pak CYC. (eds): Urolithiasis.: WB Saunders, Philadelphia, figure 6-1, p.91, with permission.)

Table 4. Causes of Hypocitraturia

I) Acidosis
1. Distal renal tubular acidosis
   Complete
   Incomplete
2. Chronic diarrheal syndrome
3. Hypokalemia
4. Strenuous physical exercise
5. High sodium or meat intake

II) Urinary tract infection

III) Idiopathic

phate [68]. In addition, citrate directly inhibits agglomeration of calcium oxalate [69] and spontaneous nucleation of calcium oxalate [70], and may also impair urate-induced crystallization of calcium oxalate [71]. The loss of inhibitor activity of citrate leads to increased saturation, enhanced heterogeneous nucleation, and facilitated crystal growth and aggregation of calcium oxalate (Table 3).

The principal cause for hypocitraturia in nephrolithiasis is acidosis or acid retention (Table 4). Acidosis reduces urinary citrate both by enhancing renal tubular reabsorption and by impairing peritubular uptake and synthesis of citrate. Renal citrate lyase activity is increased by chronic acidosis, leading to reduced intracellular citrate and enhanced tubular reabsorption [67].

Distal acidification defect (type I) is the only form of renal tubular acidosis (RTA) associated with nephrolithiasis. Acidosis is characteristic of distal RTA (due to an inability to excrete acid) and is characterized by systemic metabolic acidosis or defective urinary acidification following an ammonium chloride load, and urinary pH > 6.5 in the absence of UTI. The acidosis is a hypokalemic, hyperchloremic, nonanion gap metabolic acidosis. In the complete form, metabolic acidosis is present before an ammonium chloride load is given. In the incomplete form, urinary acidification following ammonium chloride load is impaired, despite normal serum electrolytes before the load. Chronic diarrheal states are associated with acidosis secondary to intestinal alkali and potassium loss. The degrees of hypocitraturia are generally proportional to the severity of intestinal fluid loss. Hypokalemia, itself a result of intracellular acidosis, may in turn cause hypocitraturia (e.g. during thiazide treatment).

Other causes of acidosis-induced hypocitraturia are strenuous physical exercise (from lactate accumulation), high sodium intake (from bicarbonaturia), and a high meat diet (from increased acid ash content). Hypocitraturia is also found in UTI, probably from the degradation of citrate in urine by bacterial enzymes and bacterial consumption of citrate. In a significant number of cases, there is no apparent cause of hypocitraturia; dietary acid excess may be responsible. Our own studies do not support existence of primary citrate malabsorption. Citrate absorption from the gastrointestinal tract was directly measured by using the intestinal washout technique. In both normal subjects and in patients with stones, citrate absorption was very efficient, with nearly 100% absorption in 3 hours [72 – 74].

Hypocitraturia has been variously reported in 19 – 63% of patients with nephrolithiasis [75]. This variation reflects different normal ranges for urinary citrate established by various laboratories. In the laboratory at Dallas, hypocitraturia is defined by citrate < 320 mg/day for adult men and women [76]. This value of 320 mg/day was derived from a large number of normal subjects in this laboratory. Among stone-forming patients, no significant difference in urinary citrate was found between men and women. In distal RTA, urinary citrate is invariably < 320 mg/day [77]. Finally, this limit provides a good empirical definition of hypocitraturia, because patients with urinary citrate below this level often show a clinical response to potassium citrate therapy that is superior to the response in patients with citrate > 320 mg/day [78]. Using this definition, hypocitraturia was found in 31% of our population of stone-forming patients [6].

Low Urine Volume

Low urine output represents one of the major risk factors, predisposing to all forms of stone disease. It may be the result of an inadequate fluid intake or elevated extrarenal loss of fluid (e.g. chronic diarrhea or excessive sweating in hot climates) [79 – 81]. Failure to increase urine volume has been identified as a predictor of relapse of calcium nephrolithiasis during treatment [49]. Low urine output increased the urinary saturation of all stone-forming salts by increasing the concentration of constituents of the stone. Conversely, urinary dilution was found to reduce the propensity for the crystallization of calcium salts in urine by lowering the urinary saturation of brushite and calcium oxalate, and by increasing the minimum supersaturation needed to elicit spontaneous nucleation of calcium oxalate [80]. With a stringent definition of 1 L/day as the low normal limit of urine volume, 15% of patients had this risk factor [6]. Had we used a higher figure of 2 L/day, indicative of desired urine volume [80], a much higher percentage of patients would have had low urine volume.

Low Urinary pH

The principal determinant of uric acid crystallization is its relative insolubility in the acidic urinary environment. Thus, the solubility of uric acid is pH dependent (Figure 5). Below a pH of 5.5 (the pKa of uric acid), most of the uric acid remains in an undissociated form, possessing a low aqueous solubility of < 100 mg/L [63]. This unusually acid environment leads to the development of uric acid stones. Once a uric acid stone is formed, it could induce formation of calcium oxalate stones by the same mechanisms already mentioned for monosodium urate (see *Hyperuri-*

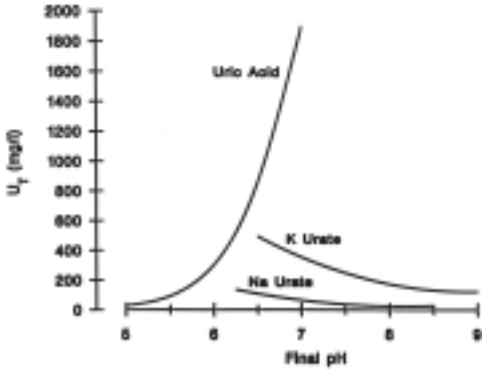

Figure 5. Uric acid solubility and transformation to urate salts. (From Pak CYC 1990 Uric acid nephrolithiasis. In: Resnick MI, Pak CYC. (eds): Urolithiasis.: WB Saunders, Philadelphia, figure 7-1, p 106, with permission.)

cosuria). Secondly, the urinary saturation of uric acid increases proportionately with the rise in total uric acid concentration. With a rise in pH, more uric acid becomes dissociated into an anionic form, approaching 100% at pH 6.5. Thus, the propensity for uric acid crystallization is low at higher urinary pH [63].

Low urinary pH could result from environmental or nutritional aberrations, such as dehydration, strenuous physical exercise, and consumption of a diet rich in animal proteins [82]. Undue urinary acidity may be due to metabolic disturbances as well, such as chronic diarrhea [83] or, most often, gouty diathesis [84, 85].

The term gouty diathesis represents the formation of uric acid and/or calcium stones in patients with primary or latent gout. Stones may precede articular manifestations of primary gout in up to 40% of those patients. The 2 types of gouty diathesis, presenting with uric acid stones or calcium stones, share similar clinical and biochemical features characteristic of primary gout. Thus, a substantial percent of gouty diathesis patients have gouty arthritis, hyperuricemia, hypertriglyceridemia, and high renal tubular reabsorption of urate, in addition to a low urinary pH (< 5.5) unaccounted for by dietary acid excess or intestinal alkali loss [84]. The underlying mechanism in gouty diathesis responsible for undue urinary acidity is still unknown. Some patients have decreased ammonium excretion even with normal glomerular filtration rate (GFR), however, the cause for this defective urinary ammonium excretion is unclear [86]. Since there is a reciprocal increase in urinary titratable acidity, no systemic acidosis occurs [87, 88]. Gouty diathesis was found in 10% of recurrent stone-formers [6].

Hyperoxaluria

Oxalate is a useless end product of metabolism and is excreted primarily in the urine. It is clinically relevant to renal stone formation because of the low solubility of its calcium salt (calcium oxalate) [89]. Both in patients with recurrent calcium nephrolithiasis and in normal subjects, urinary saturation of calcium oxalate is directly correlated with urinary oxalate concentration. As mentioned previously, a rise in oxalate concentration is equally effective as a rise in calcium concentration in augmenting the saturation of calcium oxalate [68].

Normally, about 10% of urinary oxalate is derived from diet, 25 – 30% comes from direct metabolic conversion of ascorbic acid and tryptophan, and 60% is attributable to oxidation of glyoxalate. Two major pathways for glyoxalate degradation are its transamination to alanine and glycine. This last step requires pyridoxine (vitamin B_6) as a cofactor (Figure 6) [90].

Hyperoxaluria, defined as a daily urinary oxalate excretion > 44 mg, is found in around 10% of recurrent stone formers [6]. It results from 2 main mechanisms: either intestinal

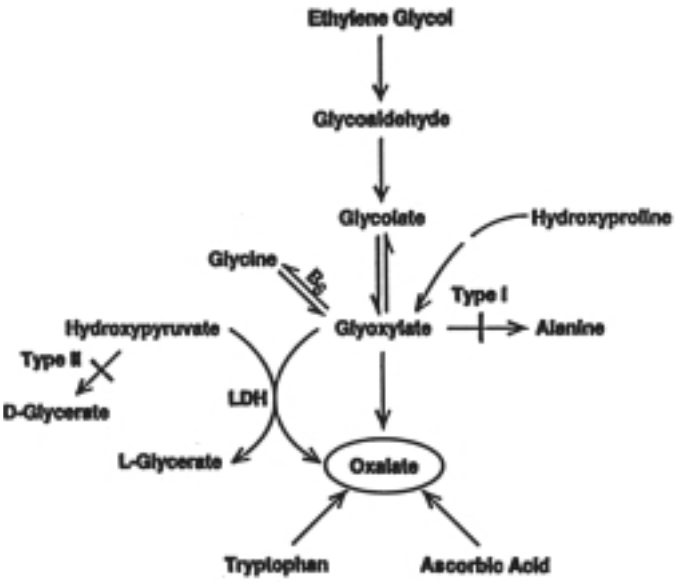

Figure 6. Biosynthetic pathway for oxalate. (From Pak CYC 1990 Hyperoxaluric calcium nephrolithiasis. In: Resnick MI, Pak CYC. (eds): Urolithiasis.: WB Saunders, Philadelphia, figure 4-2, p 68, with permission.)

Table 5. Causes of Hyperoxaluria

I) *Increased intestinal oxalate absorption*
1. High-oxalate diet
2. Enteric hyperoxaluria
3. Low intraluminal calcium concentration

II) *Increased oxalate synthesis*
A) Enzymatic disturbances
1. Primary hyperoxaluria, type 1 and type 2
2. Pyridoxine deficiency

B) Increased availability of precursors
1. Ascorbic acid
2. Ethylene glycol and methoxyflurane

hyperabsorption of oxalate or, less frequently, from increased synthesis of oxalate (Table 5).

In general, only 2 – 5% of oxalate from food is normally absorbed. Foods of high oxalate content are leafy green vegetables, nuts and peanut butter, brewed tea, and chocolate. Slight to moderate hyperoxaluria could develop from an excessive intake of oxalate-rich foods. In such cases, urinary oxalate is normal after one week on a diet poor in oxalate [6, 89]. Enteric hyperoxaluria is defined as hyperoxaluria occurring in patients with ileal disease (Crohn's disease, ulcerative colitis, jejunoileal bypass or intestinal resection) or fat malabsorption (pancreatic insufficiency, celiac sprue or bacterial overgrowth) [83, 90]. Two mechanisms have been implicated. First, the intestinal mucosa may become more permeable to oxalate from the direct action of nonabsorbed bile salts and fatty acids. Second, the nonabsorbed bile salts and fatty acids may complex divalent cations, reducing the amount of free calcium and magnesium in the intestinal lumen. Fewer divalent cations would be available to bind oxalate, leaving an enlarged pool of absorbable oxalate. An intact colon is essential for the development of hyperoxaluria, because it is the principal site of oxalate absorption. The occasional mild hyperoxaluria found in patients with absorptive

hypercalciuria or low calcium intake may occur in a similar fashion from the reduced complexation of oxalate by calcium.

Hyperoxaluria due to increased oxalate synthesis occurs less frequently. Primary hyperoxaluria is an inherited abnormality of oxalate metabolism. Patients with this condition excrete more than 80 mg/day of urinary oxalate. Two types have been well characterized (Figure 5). In type 1, the more common, there is a deficiency of the enzyme alanine:glyoxylate aminotransferase, whereas in type 2 the enzyme D-glyceric dehydrogenase is deficient. The typical sequelae of primary hyperoxaluria are early nephrolithiasis, nephrocalcinosis, systemic oxalosis, and renal failure leading to death [91]. Preliminary data suggest that pyridoxine deficiency may induce hyperoxaluria in some patients; thus, pyridoxine supplementation might be useful in some cases.

Vitamin C in doses > 500 – 1000 mg/day may induce a rise in urinary oxalate by serving as a substrate for oxalate synthesis. A similar mechanism is seen in those rare cases of severe hyperoxaluria (often associated with renal failure) induced by ethylene glycol or methoxyflurane [89].

Hypomagnesiuria

Magnesium inhibits stone formation by binding oxalate, thus reducing the saturation of calcium oxalate. Moreover, it has a modest inhibitory effect on the crystal growth of calcium oxalate [92, 93]. Thus, calcium oxalate crystallization could be enhanced in the setting of hypomagnesiuria. Hypomagnesiuria occurs in chronic diarrheal syndrome from malabsorption of magnesium, thus increasing the risk for nephrolithiasis in patients with bowel disease [94]. In the absence of intestinal disease, hypomagnesiuria, defined as urinary magnesium excretion < 50 mg/day, was present in 7% of patients with stones in the series at Dallas [6]. This entity (termed hypomagnesiuric calcium nephrolithiasis) is probably dietary in origin. Most patients give a history of avoidance of magnesium-rich food [95], and magnesium metabolism has been reported to be normal in patients with calcium nephrolithiasis [96]. Most of the hypomagnesiuric patients also have hypocitraturia.

High Urinary pH

– *Calcium phosphate stones*. Urinary pH has a pronounced effect on the supersaturation of calcium phosphate salts by influencing the dissociation of phosphate to form HPO_4^{2-} (a component of brushite stones) and PO_4^{3-} (a component of apatite) [97]. Thus, at pH < 6.9, brushite ($CaHPO_4 \cdot 2H_2O$) is the predominant phase of calcium phosphate salts, whereas a higher pH favors the formation of apatite ($Ca_5(PO_4)_3(OH)$) [98]. This relationship explains at least some of the mechanisms for the occurrence of calcium phosphate stones in patients with distal RTA [99, 100] or infection.

– *Infection stones*. These stones occur in urine infected with urea-splitting organisms and are composed of a combination of struvite ($MgNH_4PO4 \cdot 6H_2O$) and carbonate-apatite ($Ca_{10}(PO_4)_6CO_3$). Figure 7 illustrates the pathogenesis of infection stones. The action of urease within the urinary tract produces high levels of ammonium, carbonate, and urinary pH > 7.2. The resulting alkalinity of urine increases the amount of trivalent phosphate, as already mentioned. Thus, the urinary environment becomes supersaturated with struvite and carbonate apatite, leading to the crystallization of

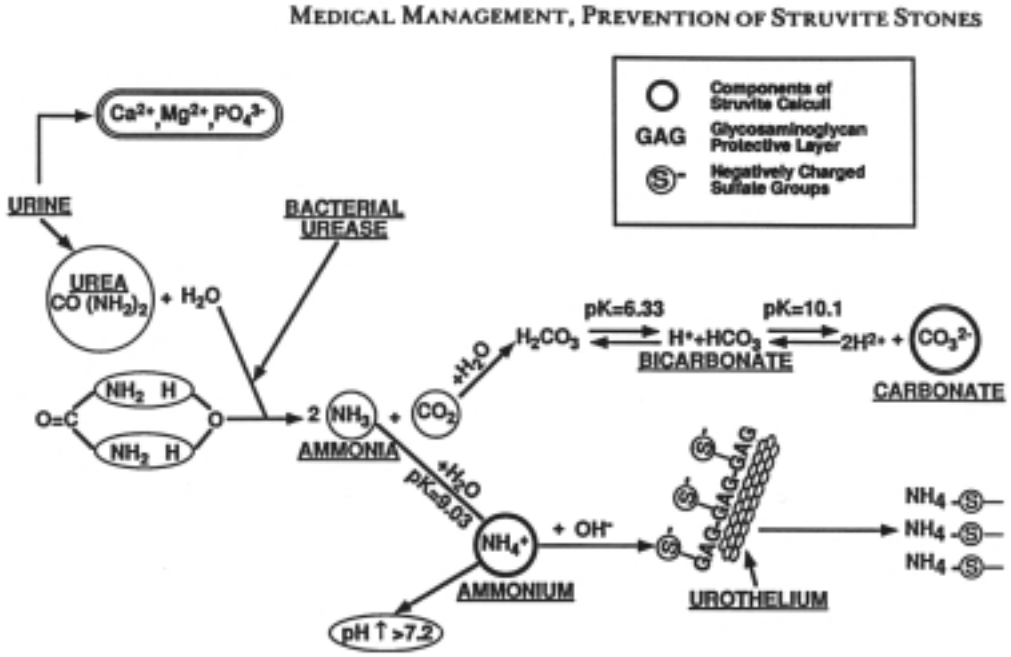

Figure 7. Pathogenesis of stone infection. (From Wong HY, Riedl CR, Griffith DP 1996 Medical management and prevention of struvite stones. (In: Coe FL, Favus MJ, Pak CYC, Parks JH, Preminger GL (eds.): Kidney Stones: Medical and Surgical Management, Lippincott-Raven Publishers, Philadelphia, figure 1, p 943, with permission).

these stone constituents. Moreover, propagation of struvite crystals is enhanced by its adhesion to the sulfate groups of the glycosaminoglycan layer protecting the urothelium. Both factors combined can lead to rapid development of large stones [101]. The experimental evidence suggests that infection stones can be formed only in the presence of urea and urea-splitting organisms. Thus, a high urinary pH alone in the absence of other factors would promote the crystallization of calcium phosphate, but not struvite [102]. Infection stones account for 6% in the series at Dallas [6]. *Proteus* species are responsible for the majority of infection that cause these stones in all age ranges. Other common organisms that produce urease are *Haemophilus influenzae, Staphylococcus aureus, Yersinia enterocolitica,* and *Ureaplasma urealyticum* (this last requires special culture techniques for its detection). *Escherichia coli* does not produce urease and therefore is not responsible for the formation of infection stones [103].

Cystinuria

Cystinuria is an autosomal recessive disease characterized by increased urinary excretion of the dibasic amino acids cystine, arginine, lysine, and ornithine. Only cystine is insoluble enough to precipitate in physiological settings. Thus, the most important pheno-

Table 6. Role of Urinary Risk Factors in the Different Types of Renal Stones

Urinary risk factor	Calcium Oxalate	Calcium Phosphate	Uric Acid	Infection Stones	Cystine
Hypercalciuria	√	√			
Hyperuricosuria	√		√		
Hypocitraturia	√	√			
Low urine volume	√	√	√	√	√
Low urinary pH			√		
Hyperoxaluria	√				
Hypomagnesiuria	√				
High urinary pH		√		√	
Cystinuria					√

√ = risk factor

typic expression of cystinuria is the predisposition toward cystine stones (1% of renal stones) [104].

The main determinant of cystine crystallization is urinary supersaturation. It has also been recognized that the solubility of cystine is pH dependent, with the lowest solubility at the low range of urinary pH, gradually increasing with a rise in pH to 7.5, and rapidly increasing above a pH of 7.5 [105]. There is no inhibitor of cystine crystallization. In the homozygous state (cystine excretion greater than 250 mg/g creatinine in a 24-hour urine collection), cystine stones invariably develop because the solubility limit for cystine is often exceeded [104].

The solute carrier family 3, member 1 (SLC3A1) gene, located on chromosome 2, codes for a protein involved in renal cystine transport. In a recent review, 9 polymorphisms and 21 different mutations were reported in the SLC3A1 gene. Most of them were base substitutions, while others were deletions. Some mutations have been found in a single individual patient, while others have been found in more than individual. Transfection studies indicate that these mutations are responsible for cystinuria. However, some cases of cystinuria are not related to defects in SLC3A1; thus, other genes might also be involved [4].

Table 6 summarizes the role of urinary risk factors in the different types of renal stones.

Medical Management

The primary objective of medical management is the prevention of recurrent stone formation. The medical approach may be fully justified because of the high rate of recurrence characterizing most forms of stone disease. Moreover, medical evaluation may disclose underlying diseases with extrarenal manifestations, such as bone disease in primary hyperparathyroidism or intestinal malabsorption syndrome in enteric hyperoxaluria.

In the past, a selective treatment approach was advocated by Pak and colleagues [51].

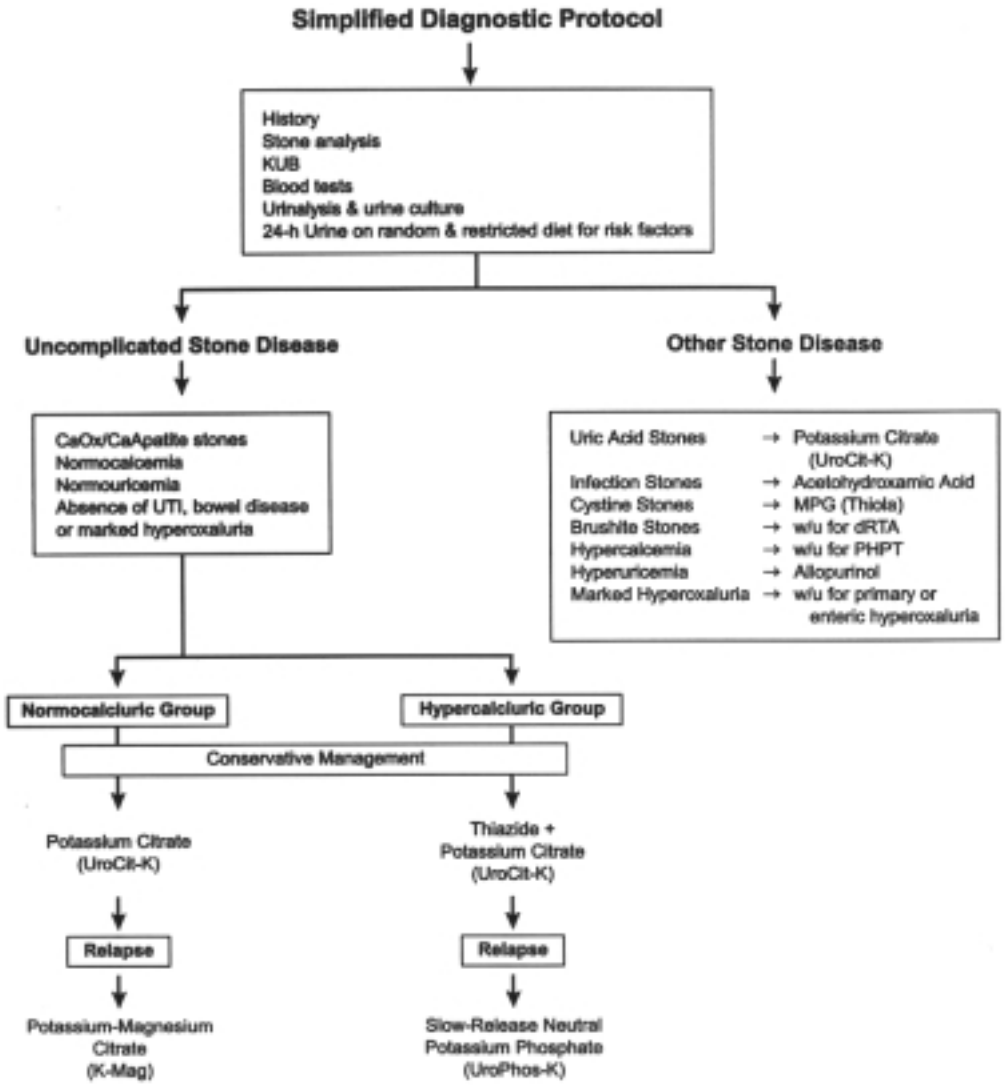

Figure 8. Algorithm for simplified approach to the medical management of nephrolithiasis.

This approach recognized heterogeneity in the pathophysiology of stone disease. After a detailed diagnostic protocol, a specific drug was selected for each cause, based on its ability to correct underlying metabolic derangements. Unfortunately, this approach seems to be too cumbersome for ready adoption for some practicing physicians. In a recent survey of 10 stone research centers from different parts of world, medical drug treatment was used sparingly and nonselectively [106]. Thus, a simplified program for the management of stones which any physician anywhere may readily adopt is described here, in lieu of a selective approach which could be used in large stone research centers.

Table 7. Stone-provoking Medications

Medications	Stone Type	Mechanism
Acetazolamide	CaP, CaOx	Hypercalciuria, Hypocitraturia, High urinary pH
Allopurinol	Xanthine	Enhanced excretion of xanthine
Ca supplements	CaOx, CaP	Hypercalciuria
Ca channel blockers	CaOx, CaP	Hypercalciuria
Loop diuretics	CaOx, CaP	Hypercalciuria
P-binding antacids	CaOx	Hypercalciuria
Silica (Antacids)	Silica	Urinary excretion of silica
Theophylline	CaOx, CaP	Hypercalciuria
Triamterene	Triamterene	Urinary excretion of triamterene
Uricosuric agents	CaOx, UA	Hyperuricosuria
Vitamin C	CaOx	Hyperoxaluria
Vitamin D	CaOx	Hypercalciuria

CaOx: calcium oxalate; CaP: calcium phosphate; UA: Uric Acid

A summary of the simplified program for medical management of nephrolithiasis is shown in Figure 8. This approach was designed to achieve 3 important purposes in medical management of nephrolithiasis.

Separation of Uncomplicated Stone Disease from Other Stone Disease

History

A careful history should be taken during the evaluation of the stone-forming patient, because it may provide clues about the severity, underlying causes and extrarenal manifestations of stone disease. It should focus on: (1) chronology of stone events, such as age of first stone passage and dates of further episodes, number and type of stones passed, spontaneous passage vs. need for surgical intervention; (2) family history of stones or personal history for bone or gastrointestinal disease, gout, chronic urinary tract infection (UTI), or nephrocalcinosis; (3) stone-provoking medications; and (4) nutritional habits [107, 108].

Patients with early onset of nephrolithiasis may suffer from inherited metabolic disorders (e. g. primary hyperoxalurias, xanthinuria, cystinuria) or have a higher risk for calcium stone recurrence. Patients with multiple stones or a family history of stones are also at increased risk of recurrence. A list of the most common medications that could cause or exacerbate stone disease is shown in Table 7. A careful history should also be taken for past medical treatments of stone disease. Their failure may indicate inaccuracy of the original diagnosis or a need for more specific therapy. Nutritional history should be taken, directing particular attention to dietary aberrations implicated in stone formation, such as low fluid intake, high calcium intake, high oxalate diet, sodium excess, animal protein excess, and low citrus fruit intake. The pathogenetic role of some of these factors will be briefly reviewed.

A recent epidemiological study disclosed that, among healthy subjects without stones, high calcium intake may reduce the risk of stone formation [109], attributed to the binding of oxalate by calcium in the intestinal tract. Unfortunately, the concurrent higher intake of potassium (citrus fruits), magnesium, phosphate, and fluids by the high calcium intake group could have clouded interpretation of the results. Moreover, these results may not be extrapolated to stone formers or hypercalciurics, since these two groups were not studied. Physiologically, high calcium intake or calcium supplementation may not confer an increased risk of stone formation in healthy subjects because of the operation of the intestinal adaptation process [110]. During high calcium intake, the fraction of calcium absorbed is decreased because of parathyroid suppression and reduced calcitriol synthesis. In healthy subjects, urinary calcium rose substantially after one month of calcium supplementation, but it decreased toward the pretreatment range during continued treatment for 2 more months [111]. In patients with absorptive hypercalciuria, the intestinal adaptation process may not operate because of the primary enhancement of intestinal calcium absorption [43]. Thus, a high calcium intake provoked a marked increase in urinary calcium that was considerably above the normal range and was apparently sustained. In contrast to healthy subjects, patients with absorptive hypercalciuria may be at increased risk of stone formation from high calcium intake.

The metabolic effect of sodium load has been examined by providing 250 mEq of sodium daily over a basal metabolic diet. As reported previously, urinary calcium increased significantly. In addition, urinary pH increased modestly and urinary citrate decreased significantly. These effects have been ascribed to bicarbonaturia from sodium-induced volume expansion. Commensurate with these changes, sodium load increased the propensity for the crystallization of stone-forming calcium salts [112].

Animal proteins are rich in sulfur-containing amino acids. When they are metabolized, sulfate is released. Thus, a high consumption of animal protein represents an acid load, which could reduce urinary citrate and pH. In addition, urinary calcium may increase because of higher bone resorption and renal calcium leak induced by the transient metabolic acidosis. Uric acid also will increase with an ingestion of all meat products (beef, poultry and fish) since they are rich in purines [113, 114].

Citrus fruits are rich in citric acid and potassium, particularly the former. Their intake is associated with a rise in urinary pH and citrate and occasionally by a fall in urinary calcium. Citrus fruits contain a modest amount of calcium (100 mg/L), vitamin C (< 500 mg/L) and oxalate (0 – 21 mg/L). The amount of these nutrients in fruit juices is probably insufficient to affect stone disease adversely. Thus, the net effect of citrus fruits is beneficial. Conversely, a low intake of citrus fruits may contribute to hypocitraturia, and may enhance the risk for stone formation [108, 115].

The role of a low fluid intake and high oxalate diet was already discussed in the section on urinary risk factors.

Stone Analysis

The diagnosis of different causes of nephrolithiasis is no longer made solely on the basis of stone composition. There is increasing reliance on underlying physiological derangements. However, stone analysis is still important and should be obtained in every stone-forming patient if a sample is available.

The disclosure of cystine, or struvite or carbonate apatite, is diagnostic of cystinuria or infection with urea-splitting organisms, respectively. The presence of 2,8-dihydroxyadenine, triamterene, silica, or xanthine indicates 2,8-dihydroxyadeninuria, treatment with triamterene or magnesium trisilicate, or xanthinuria. In these conditions, the crystallographic identification is critical for the diagnosis; laboratory and clinical data provide supporting evidence. For the remaining stones (80 – 85% of all stones), which are associated with or formed from a variety of metabolic or environmental disturbances, stone composition is helpful but not conclusive for diagnosis of the underlying disease.

Radiologic Appearance (Kidneys, Ureter and Bladder)

Most stones can be detected by radiograph of the kidneys, ureter, and bladder (KUB) alone. Radiopaque stones include those containing calcium oxalate, calcium phosphate, and infection stones (due to their component of carbonate apatite). Cystine stones are also radiopaque, though less dense. Radiolucent stones include those composed solely of uric acid, 2,8-dihydroxyadenine, triamterene, xanthine and silica. Uric acid may have a faint radiopacity because of the incorporation of calcium salts. The morphologic appearance of radiopaque stones may provide clues to their mineral composition or to the underlying process. Cystine stones are moderately dense and have a homogeneous appearance. Struvite stones are more dense but also tend to have a rounded appearance. Cystine and infection stones may reach staghorn size. Calcium oxalate stones often have a dense, spiculated appearance.

Cortical nephrocalcinosis suggests the diagnosis of primary hyperoxaluria. Medullary nephrocalcinosis is encountered in distal RTA and primary hyperparathyroidism.

Other imaging modalities such as intravenous urography (IVP) or ultrasonography are useful in detecting radiolucent stones, anatomic abnormalities (e.g. medullary sponge kidney), or complications produced by a stone (e.g. obstruction) [116].

Blood Tests

A multichannel screen of venous blood should be performed to identify primary hyperparathyroidism (high serum calcium concentration), gouty diathesis (hyperuricemia), complete distal RTA (hypokalemia, low CO_2, and hyperchloridemia), or hypophosphatemic absorptive hypercalciuria (hypophosphatemia due to phosphate renal leak). In addition, serum creatinine and BUN are helpful to assess renal function.

Urinalysis and Urine Culture

A fresh spot urine sample should be cultured for urea-splitting organisms (suggestive of infection stones) and examined for pH (with an electrode pH). Low urinary pH (< 5.5) suggests gouty diathesis and high pH (> 7.5) is compatible with infection stones. A qualitative cystine test should be performed on the urine sample, using the cyanide-nitroprusside test, in which a purple-red color after addition of sodium cyanide and sodium nitroprusside suggests that cystine excretion exceeds 75 mg/L [117]. A false-positive test may be obtained in patients with homocystinuria and acetonuria. Follow-up quantitative analysis showing 24-hour urinary cystine > 250 mg/g creatinine confirms diagnosis. Identification of a particular crystal type in the urinary sediment is compatible with, but not

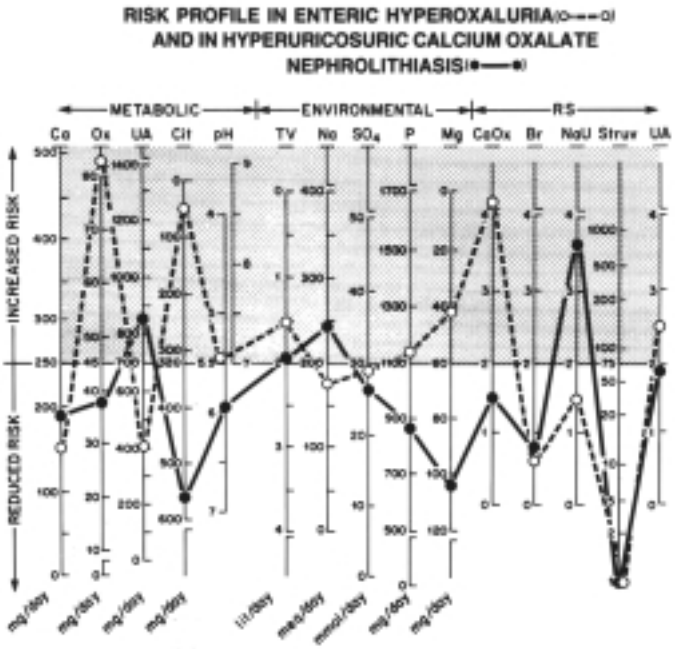

Figure 9. Graphic display of urinary risk factors in patients with enteric hyperoxaluria and with hyperuricosuric calcium oxalate nephrolithiasis. From [Pak CYC, Skurla C, Harvey J 1985 Graphic display of urinary risk factors for renal stone formation. J Urol *134:* 869], figure 3).

diagnostic of, that type of nephrolithiasis. Thus, crystalluria itself is not a pathologic finding.

24-hour Urine for Urinary Risk Factors

This simplified approach takes advantage of commercially-available stone risk analysis. The technique was first developed in our laboratory at Dallas [118]. A 24-hour urine collection kit, containing a volume marker and appropriate preservatives, is provided by the physician to the patient. After obtaining a 24-hour urine sample while the patient is kept on random diet and fluid intake, 2 30 mL aliquots are sent via regular mail to a central laboratory. The laboratory then calculates the total volume from the dilution of the volume marker and analyzes urinary constituents. Risk factors are categorized into 3 groups: metabolic risk factors (calcium, oxalate, uric acid, citrate, and pH), environmental risk factors (total volume, sodium, sulfate, phosphorus, and magnesium), and physicochemical risk factors (saturation of urine with respect to stone-forming constituents calculated from metabolic and environmental factors). Results are displayed graphically or in a tabular format.

A sample stone risk profile as originally reported in 1985 is shown in Figure 9. To provide a visual display of all available data in a single report, each risk factor is assigned a vertical line with linear or logarithmic scales. A horizontal line intersecting each vertical scale at the approximate midpoint represents the upper or lower normal limit. The direction of increasing values is appropriately adjusted, so that values below the horizontal line represent normal values (reduced risk)

Table 8. Dietary Modifications for Diagnostic Assessment

Finding in 24-h urine (on random diet)		*Modification (1 week)*
Total volume	< 2 L/day	Increase fluid ingestion
Sodium	> 200 mEq/day	Sodium restriction
Oxalate	> 45 mg/day	Oxalate restriction
Calcium	> 250 mg/day	Calcium restriction (moderate)
Sulfate	> 30 mg/day	Restriction of animal proteins
Uric acid	> 600 mg/day	Restriction of animal proteins

and those above the line represent abnormal values (increased risk). In this case, samples of two patients are displayed. A patient with small bowel disease (dotted line) had hyperoxaluria (from increased oxalate absorption), hypocitraturia and low urinary pH (from acquired metabolic acidosis), low urine volume (from diarrhea), and low urinary magnesium (from malabsorption). As a consequence, urinary saturation of calcium oxalate and uric acid was higher than normal, accounting for the susceptibility of patients with ileal disease to form stones of calcium oxalate and uric acid. The other patient (continuous line) had hyperuricosuria as the sole metabolic abnormality. Urinary sodium was high from dietary salt abuse. There was relative supersaturation of monosodium urate. The first case is a typical patient with enteric hyperoxaluria, whereas the latter is a patient with hyperuricosuric calcium oxalate nephrolithiasis.

The accuracy of urine collection could be assessed from urinary creatinine values and body weight. In a carefully studied population on a metabolic dietary regimen in whom the accuracy of urine collection was ensured, the mean urinary creatinine in men was 22.1 ± 4.7 mg/kg, whereas it was 17.2 ± 3.8 mg/kg in women. Thus, a value substantially below these figures would indicate undercollection, and a value far exceeding these numbers would suggest overcollection [108].

After obtaining a full stone risk analysis in a urine sample collected on random diet, the next step is to impose a short-term dietary modification (minimum one week) (Table 8) [119]. Fluid intake should be increased at least to ten 10-ounces glasses per day if urine volume is < 2 liters on the stone risk analysis. Salty foods and table salt should be avoided if urinary sodium > 200 mEq/day. Oxalate restriction should be imposed (avoidance of nuts, spinach, chocolate, tea, and vitamin C). Calcium intake should be restricted (avoidance of dairy products and spinach, for diagnostic purpose only) if there is hypercalciuria. Servings of meat products should be limited when there is hyperuricosuria, or if urine sulfate is high.

The last step in this simplified diagnostic protocol for nephrolithiasis is to obtain a 24-hour urine collection while the patient is on a temporary dietary modification. A limited analysis could be performed, involving 7 constituents: calcium, oxalate, uric acid, citrate, pH, total volume, and sodium. The differences in values between the full and the abbreviated analysis (random and modified diet) represent changes imposed by dietary influences.

The work-up described above should allow differentiation of most causes of stones (absorptive hypercalciuria, renal hypercalciuria, hyperuricosuric calcium oxalate nephrolithiasis, hypocitraturic calcium oxalate nephrolithiasis). However, for the simplified ap-

proach to the medical management of nephrolithiasis to be described, only the following differentiations are necessary. First, separate uncomplicated stone disease from other stone disease (Figure 8). The former, constituting the majority of patients with stones, is characterized by calcium oxalate or calcium apatite stones, normal serum calcium and uric acid, and the absence of chronic UTI, bowel disease, or marked hyperoxaluria. Other stone disease would comprise patients with primary gout with hyperuricemia, infection stones, cystinuria, distal RTA, primary hyperparathyroidism, and primary or enteric hyperoxaluria.

Categorization of Uncomplicated Stone Disease

Once patients with uncomplicated stone disease have been identified, an additional diagnostic separation is necessary in this group for purposes of medical treatment. From the 24-hour urine calcium obtained previously, uncomplicated calcium stone disease is separated into normocalciuric and hypercalciuric subgroups (Figure 8). The normocalciuric subgroup would be composed of hyperuricosuric calcium oxalate nephrolithiasis, hypocitraturic calcium oxalate nephrolithiasis, gouty diathesis, and hypomagnesiuric calcium oxalate nephrolithiasis, all presenting with normal urinary calcium. The hypercalciuric subgroup comprises absorptive and renal hypercalciuria, and dietary hypercalciuria.

Most practicing physicians should be able to identify the groups without difficulty.

A Simple Approach to Medical Treatment

Conservative Management

All patients with nephrolithiasis should be offered a conservative treatment program, similar to dietary modifications imposed for diagnostic purposes (Table 8).

Fluid intake should be sufficient to assure a urine level ≥ 2 L/day [80]. Adequate hydration in the absence of any other treatment has been recently proved to decrease stone formation by as much as 55% during a 5-year follow-up [79]. The type of liquid is generally of less concern than the volume; exceptions include the avoidance of tea in hyperoxaluria and excessive milk in absorptive hypercalciuria. Fluids are most valuable if they are distributed throughout the day. Patients also should be encouraged to measure the urine volume regularly (once every 2 – 3 months) to ensure its adequacy.

Traditionally, calcium restriction has been the mainstay of stone prevention. However, this measure may be ineffective in normocalciuric patients and may cause negative calcium balance and bone loss. Our practice is to recommend a moderate restriction of dietary calcium (limit dairy products to one serving/day) only in hypercalciuric patients with normal bone density, and not to restrict calcium in others.

Other dietary modifications have already been explained. Conservative management alone may be necessary in patients with mild disease, those with a single episode, or those without metabolic disturbance. Conservative management should always accompany specific drug therapies in patients with more severe recurrent disease, since it will improve the control of stone risk factors and may allow the use of a lower dose of recommended drugs. In severe stone disease or recurrences

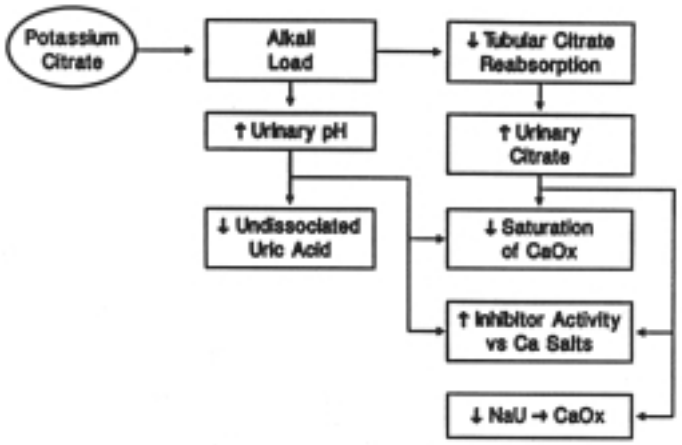

Figure 10. Physicochemical action of potassium citrate. (From Pak CYC 1990 Hypocitraturic calcium nephrolithiasis. In: Resnick MI, Pak CYC. (eds): Urolithiasis, WB Saunders, Philadelphia, figure 6 – 4, p 98, with permission).

despite conservative management, drug treatment is indicated.

Treatment of Uncomplicated Stone Disease

The simplified approach advocates the use of only 2 drugs as initial options in uncomplicated calcium stone disease (Figure 8). The normocalciuric subgroup would be prescribed potassium citrate (Urocit-K) alone. The hypercalciuric subgroup would be given thiazide and potassium citrate.

The rationale for potassium citrate in uncomplicated normocalciuric stone disease is shown in Figure 10. Potassium citrate increases citrate excretion by providing an alkali load [74, 75]. The induced rise in urinary citrate should inhibit the crystallization of calcium oxalate and calcium phosphate, not only in hypocitraturia, but also in the presence of other derangements such as hyperuricosuria. In addition, potassium citrate raises urinary pH, reducing the propensity for uric acid stone formation. The complication of calcium stone should be inhibited as well from the impaired urate-induced calcium oxalate crystallization. A placebo-controlled randomized trial has validated the efficacy of potassium citrate in uncomplicated stone disease with normocalciuria [120]. Among patients treated with potassium citrate, 72% had no further stone formation during a follow-up of 3 years, compared with 20% in the placebo group. Moreover, for those in the treatment group who still formed stones, the stones developed at a lower rate than before treatment.

Potassium citrate (Urocit-K) is available as wax matrix tablets, containing 5 or 10 mEq of citrate per tablet. It is also available as a liquid, powder or syrup combining potassium citrate and citric acid (PolyCitra-K); the powder and syrup are mixed with water before ingestion. The wax matrix tablet formulation has been shown to produce less variability in the level of urinary citrate throughout the day [121]. The customary dose of potassium citrate is 20 mEq twice daily; the dose should be adjusted based on urinary citrate [74, 75]. Contraindications for its use are hyperkalemia or predisposing conditions to hyperkalemia (type IV RTA, concomitant use of potassium-sparing diuretics, adrenal insufficiency), renal failure

(GFR < 40 mL/min), active peptic ulcer disease, UTI or obstruction.

The rationale for the combined use of thiazide with potassium citrate in hypercalciuric patients with uncomplicated stone disease is based on following considerations. Thiazides are unique among diuretics in reducing urinary calcium excretion. Thiazides act directly on the distal convoluted tubule to augment calcium reabsorption, and indirectly at the proximal convoluted tubule secondary to volume depletion [122]. They are widely used in the management of hypercalciuric nephrolithiasis [123]. However, thiazide-induced hypokalemia may lead to intracellular acidosis, which provokes hypocitraturia and may thereby attenuate the beneficial hypocalciuric effect of therapy on renal stone formation [123, 124]. Potassium chloride supplementation may prevent hypokalemia and hypocitraturia. In the management of stone disease, potassium citrate is preferable because it can not only avert hypokalemia, but also raise urinary citrate, an important inhibitor of stone formation [124, 125]. Amiloride has been shown to potentiate the hypocalciuric effect of thiazides while reducing the associated hypokalemia; however, amiloride has no effect on urinary citrate [126]. Therefore, the combination of a thiazide and potassium citrate is preferred.

The recommended doses of thiazides in an average adult patient are trichlormethiazide 4 mg daily, chlorthalidone 50 mg daily, hydrochlorothiazide 25 mg twice daily, or bendroflumethiazide 2.5 mg twice daily. Long-acting agents are preferable, since compliance may be better. Potassium citrate should be added in doses of 15 – 20 mEq twice daily to prevent thiazide-induced hypokalemia and hypocitraturia. A modest sodium restriction is advisable in conjunction with thiazide therapy because excessive sodium intake attenuates the hypocalciuric effect of the drug [127].

Future Treatment of Uncomplicated Stone Disease After Relapse

Some patients may be intolerant of, or may not respond to potassium citrate therapy. Moreover, potassium citrate does not correct magnesium loss in long-term thiazide therapy or hypomagnesiuria that is encountered in 7% of patients with recurrent calcium nephrolithiasis [6]. Potassium-magnesium citrate (K_4MgCit_2 or K-Mag), a new drug under development by the Dallas group, may overcome these problems. Compared to Urocit-K at the same dose of potassium, K-Mag causes a more prominent rise in urinary citrate and pH [128] and a greater inhibition of the propensity for the crystallization of uric acid and calcium oxalate [129]. A recent placebo-controlled, randomized trial indicated that K-Mag is highly efficacious in inhibiting calcium stone formation during a 3-year follow-up. The relative risk of stone-free rate (K-Mag/placebo) was 0.15 (95% confidence interval, 0.05 to 0.44) [7]. Finally, in a randomized, controlled comparison of gastrointestinal tolerance of K-Magvs.Urocit-K, the former drug appeared to be better tolerated [130].

Thiazide may not be effective in all patients with hypercalciuric nephrolithiasis. There may be an attenuation or loss of hypocalciuric action after ≥ 2 years of thiazide treatment because of its inability to correct the underlying intestinal hyperabsorption of calcium [131]. Thiazide may cause hypokalemia, volume depletion, impotence, hyperuricosuria, and hyperuricemia.

Slow-release neutral potassium phosphate (UroPhos-K), a new drug being developed by our group at Dallas, may obviate the problem of thiazide therapy in the future. Its slow release minimizes gastrointestinal side effects, unlike conventional phosphate preparations. It causes a small sustained rise in serum phosphate and a slight parathyroid stimula-

tion within the normal range. Thus, there is suppression of calcitriol synthesis. Calcium absorption is reduced about 50% by inhibition of calcitriol synthesis as well as from the binding of calcium by phosphate in the intestinal tract. Moreover, UroPhos-K increases urinary citrate (from the alkali load) and pyrophosphate (from the rise in orthophosphate excretion), 2 important inhibitors of calcium stone formation, and inhibits crystal agglomeration of calcium oxalate [132].

UroPhos-K treatment in patients with absorptive hypercalciuria produced a substantial decline in the urinary saturation of calcium oxalate at 3-month follow-up [132]. The saturation for calcium phosphate did not change, because the rise in urinary phosphorus was compensated for by a decline in urinary calcium. Unlike thiazide, the hypocalciuric effect remained over 4 years of treatment. This effect is probably a combination of reduced intestinal calcium absorption, reduced skeletal calcium mobilization, and a possible augmented renal calcium reabsorption [133].

Thus, K-Mag and UroPhos-K promise to be useful alternatives or potentially superior agents to be used in lieu of thiazide and potassium citrate, especially in relapse.

Treatment of Other Stone Disease

Treatment of conditions other than uncomplicated calcium stone disease is well established (Figure 8).

If uric acid stones are found, gouty diathesis or conditions causing undue urinary acidity should be suspected. Potassium citrate is the treatment of choice for gouty diathesis. A dosage of 30 – 60 mEq/day in divided doses raises the low urinary pH (< 5.5) to the desired range of 6.0 – 7.0 [134]. Although sodium alkali is as effective as potassium citrate for prevention of uric acid stone formation by increasing urinary pH, it may induce the formation of calcium stones by its hypercalciuric action [135].

The mainstay of managing infection stones is surgical removal of the stone and eradication of urea-splitting organisms. Antibiotics are given before and after surgery to reduce recurrence. Acetohydroxamic acid, a urease inhibitor, reduces urinary saturation of struvite by preventing the formation of ammonium and hydroxyl ions. It may prevent stone growth and sometimes cause dissolution of existing stones. Unfortunately, its use is associated with significant side effects (hemolytic anemia, thrombophlebitis, and neurological disorders) [101].

In patients with cystine calculi and moderate cystinuria (250 – 500 mg/day), high fluid intake and potassium citrate (30 – 60 mEq/day in divided doses) is recommended to maintain urinary pH at a high normal range of 6.5 – 7.0. When further therapy is necessary, the addition of sulfur-chelating agents such as alpha-mercaptopropionylglycine (MPG or Thiola) or penicillamine will reduce cystine excretion. These agents act by complexing cysteine, the monomeric form of cystine. Both drugs are associated with frequent and sometimes severe side effects, including nephrotic syndrome, dermatitis, and pancytopenia. Penicillamine is administered in a daily dose of 1 – 2 g in 3 or 4 divided doses. Thiola (800 – 2000 mg/day in 3 or 4 divided doses) is preferred, because it has a lower toxicity profile than penicillamine [104].

Patients with brushite stone have a high recurrence rate. Distal RTA or primary hyperparathyroidism, the most frequent secondary causes, should be ruled out [100, 136]. If there is no evident secondary causes, these patients may be treated according to the guidelines for uncomplicated stone disease.

If hypercalcemia is found, work-up for primary hyperparathyroidism should be under-

taken. Parathyroidectomy is the optimal treatment for the nephrolithiasis associated with primary hyperparathyroidism. A medical approach with phosphates or estrogens (in postmenopausal women) should be used only when parathyroid surgery cannot be undertaken [137].

Allopurinol treatment should be considered for anyone with hyperuricemia because of the risk of gouty arthritis. It is administered at a dosage of 300 mg/day. Side effects are rare and include a skin rash and a reversible elevation of liver enzymes. In the event of a rash, the drug should be discontinued immediately because it may progress to Stevens-Johnson syndrome.

Finally, the finding of marked hyperoxaluria mandates a search for primary or enteric hyperoxaluria. The established treatment regimen for primary hyperoxaluria is orthophosphate, 1.5 – 2.5 g of phosphorus per day in 3 or 4 divided doses, and pyridoxine 100 mg twice a day. Orthophosphate reduces urinary calcium and augments urinary pyrophosphate. If given in a neutral form, it increases citrate excretion. Thus, the urinary saturation of calcium oxalate is reduced, and the inhibitor activity against calcium oxalate crystallization may be augmented. Pyridoxine may reduce urinary oxalate excretion by reduction of endogenous oxalate synthesis in some patients. Potassium citrate may be a useful therapeutic option in lieu of orthophosphate. Patients should be maintained on these programs as long as complications are controlled and renal function remains stable. If this is not the case, then planning for renal and/or liver transplant is necessary [89, 91].

Specific therapies to correct fat malabsorption such as a gluten-free diet (celiac sprue), pancreatic enzyme replacement (pancreatic insufficiency), or the use of antibiotics (bacterial overgrowth) may be required in some cases of enteric hyperoxaluria. In patients with significant fat malabsorption, a low-fat diet with medium-chain fatty acid supplementation should be instituted to minimize steatorrhea. Medical therapy to prevent stones in this condition is directed at decreasing oxalate absorption and correcting associated metabolic complications. Calcium citrate (400 mg of calcium with meals) may be useful to decrease urinary oxalate by binding oxalate in the intestinal tract. It may raise urinary citrate and pH by providing an alkali load. Careful monitoring of urinary calcium and oxalate should be routine. Magnesium supplements act via an identical mechanism: binding free oxalate in urine. Cholestiramine does not cause a sustained reduction in oxalate excretion. Low urinary pH and hypocitraturia can be treated with potassium citrate 40 – 60 mEq/day in divided doses. Severe cases may require larger doses up to 120 mEq/day. K-Mag, which provides citrate as well as magnesium, should be the logical therapeutic option in enteric hyperoxaluria to correct associated metabolic disturbances [89, 138].

Conclusion

This chapter presents a simplified approach to stone disease. First, obtain a full analysis of urine for stone risk factors to identify environmental or metabolic disturbances. Second, obtain an abbreviated stone risk profile after a dietary modification. Differentiate between patients with uncomplicated calcium stone disease and patients with other stone disease. In the former group, separate patients into hypercalciuric and normocalciuric subgroups. In those with normal urinary calcium, apply potassium citrate therapy. In those with hypercalciuria, treat with thiazide and potassium citrate. For those with multiple relapses, new drugs are under development, particularly potassium-magnesium citrate and slow-release neutral potassium phosphate.

References

[1] *Dardioti V, Angelopoulos N, Hadjiconstantinou V* 1997 Renal diseases in the Hippocratic era. Am J Nephrol *17:*214-216

[2] *Bammerlin EM* 1988 An illustrated history of the surgical removal of kidney stones. Dissertations, Academic-Texas, pp 11-19

[3] *Resnick MI, Pak CYC* 1990 Introduction. In: Resnick MI, Pak CYC (eds.): Urolithiasis. WB Saunders, Philadelphia, pp 1-9

[4] *Gitomer WL, Pak CYC* 1996 Recent advances in the biochemical and molecular biological basis of cystinuria (review). J Urol *156:* 1907-1912

[5] *Pak CYC* 1991 Etiology and treatment of urolithiasis. Am J Kid Dis *18:* 624-637

[6] *Levy F, Adams-Huet B, Pak CYC* 1995 Ambulatory evaluation of nephrolithiasis: an update of a 1980 protocol. Am J Med *98:* 50-59

[7] *Ettinger B, Pak CYC, Citron JT, VanGessel A* 1997 Randomized trial of potassium magnesium citrate in the prevention of recurrent calcium oxalate nephrolithiasis. 8th International Symposium on Urolithiasis. In: Urolithiasis 1996. Millet the Printer, Dallas (Abstract Book) 437-439. J Urol 158: 2069-2073

[8] *Pak CYC, Fuller C, Sakhaee K, Preminger G, Britton F* 1985 Long-term treatment of calcium nephrolithiasis with potassium citrate. J Urol *134:* 11-19

[9] *Pak CYC, Fuller C, Sakhaee K, Zerwekh JE, Adams BV* 1986 Management of cystine nephrolithiasis with alpha-mercaptopropionyoglycine (Thiola). J Urol *136:* 1003-1008

[10] *Bushinsky DA, Grynpas MD, Nilsson EL, Nakagawa Y, Coe FL* 1995 Stone formation in genetic hypercalciuric rats. Kidney Int *48:* 1705-1713

[11] *Chaussy C, Schmiedt E, Brendel W* 1980 Extracorporeally induced destruction of kidney stones by shock waves. Lancet *II:* 1265-1268

[12] *Fine JK, Pak CYC, Preminger GM* 1995 Effect of medical management and residual fragments on recurrent stone formation following shock wave lithotripsy. J Urol *153:* 27-33

[13] *Coe FL, Keck J, Norton R* 1977 The natural history of calcium nephrolithiasis. JAMA *238:* 1519-1523

[14] *Resnick MI, Persky L* 1995 Summary of the National Institutes of Arthritis, Diabetes, Digestive and Kidney Diseases Conference on Urolithiasis: state of the art and future research needs. J Urol *153:* 4-9

[15] *Johnson CM, Wilson DM, O'Fallon WM, Malek RS, Kurland LT* 1979 Renal stone epidemiology: A 25-year study in Rochester, Minnesota. Kidney Int *16:* 624-631

[16] *Sutherland JW, Parks JH, Coe FL* 1985 Recurrence after a single renal stone in a community practice. Miner Electrolyte Metab *11:* 267-269

[17] *Uribarri J, Oh MS, Carrol HJ* 1989 The first kidney stone. Ann Intern Med *111:* 1006-1009

[18] *Robertson WG* 1993 Urinary tract calculi. In: Nordin BEC, Nedd AG, Morris HA: Metabolic Bone and Stone Disease. Churchill-Livingstone, New York, NY, pp 249-311

[19] *Clark JY, Thompson IM, Optenberg SA* 1995 Economic impact of urolithiasis in the United States. J Urol *154:* 2020-2024

[20] *Smith CL* 1984 When should the stone patient be evaluated? Med Clin North Am *68:* 455-459

[21] *Mandel G, Mandel N* 1996 Analysis of stones. In: Coe FL, Favus MJ, Pak CYC, Parks JH, Preminger GM: Kidney Stones: Medical and Surgical Management. Lippincott-Raven, Philadelphia, pp 323-335

[22] *Daudon M, Dosimoni R, Hennequin C, Fellahi S, Le Moel G, Paris M, Troupel S, Lacour B* 1995 Sex- and age-related composition of 10617 calculi analyzed by infrared spectroscopy. Urol Res *23:* 319-326

[23] *Mandel NS, Mandel GS* 1989 Urinary tract stone disease in the United States veteran population. II. Geographic analysis of variations in composition. J Urol *142:* 1516-1521

[24] *Zaidman JL, Pinto N* 1976 Studies on urolithiasis in Israel. J Urol *115:* 626-627

[25] *Allen TD, Spence HM* 1966 Matrix stone. J Urol *95:* 284-290

[26] *Pak CYC* 1990 Miscellaneous stones. In: Resnick MI, Pak CYC (eds): Urolithiasis. WB Saunders, Philadelphia, pp 145-151

[27] *Hess B, Kok DJ* 1996 Nucleation, growth, and aggregation of stone-forming crystals. In: Coe FL, Favus MJ, Pak CYC, Parks JH, Preminger GM: Kidney Stones: Medical and Surgical Management. Lippincott-Raven, Philadelphia, pp 3-32

[28] *Vermeulen CW, Lyon ES, Fried FA* 1965 On the nature of the stone-forming process. J Urol *94:* 176-186

[29] *Howard JE, Thomas SW, Smith LH, Barker LM, Wadkins CL* 1966 A urinary peptide with extraordinary inhibitory powers against biological "calcification" (deposition of hydroxyapatite crystals). Trans Assoc Am Physicians *79:* 137-145

[30] *Boyce WH* 1968 Organic matrix of human urinary concretions. Am J Med *45:* 673-683

[31] *Nancollas G* 1976 The kinetic of crystal growth and renal stone formation. In: Fleisch H, Robertson WG, Smith LH et al: Urolithiasis Research. Plenum Press, New York, pp 5-23

[32] *Nicar MJ, Hill K, Pak CYC* 1983 A simple technique for the assessment of the propensity for the crystallization of calcium oxalate and brushite in urine from the increment in oxalate or calcium necessary to elicit precipitation. Metabolism *32:* 906-910

[33] *Pak CYC, Holt K* 1976 Nucleation and growth of brushite and calcium in urine of stone-formers. Metabolism *25:* 665-673

[34] *Meyer JL* 1990 Physicochemistry of stone formation. In: Resnick MI, Pak CYC (eds): Urolithiasis. WB Saunders, Philadelphia, pp 11-34

[35] *Pak CYC, Hayashi Y, Finlayson B, Chu S* 1977 Estimation of the state of saturation of brushite and calcium oxalate in urine: A comparison of three methods. J Lab Clin Med *89:* 891-901

[36] *Lieske JC, Coe FL* 1996 Urinary inhibitors and renal stone formation. In: Coe FL, Favus MJ, Pak CYC, Parks JH, Preminger GM: Kidney Stones: Medical and Surgical Management. Lippincott-Raven, Philadelphia, pp 65-113

[37] *Fleisch H* 1978 Inhibitors and promoters of stone formation (review). Kidney Int *13:* 361-371

[38] *Nicar MJ, Skurla C, Sakhaee K, Pak CYC* 1983 Low urinary citrate excretion in nephrolithiasis. Urology *21:* 8

[39] *Michelacci YM, Glashan RQ, Schor N* 1989 Urinary excretion of glycosaminoglycans in normal and stone-forming subjects. Kidney Int *36:* 1022-28

[40] *Coe FL, Parks JH* 1997 New insights into the pathophysiology and treatment of nephrolithiasis-new research venues (review). J Bone Min Res 12:522-533

[41] *Lieske JC, Toback FG* 1996 Interaction of urinary crystals with renal epithelial cells in the pathogenesis of nephrolithiasis. Sem Nephrol *16:* 458-473

[42] *Peacock M, Hodgkinson A, Nordin BEC* 1967 Importance of dietary calcium in the definition of hypercalciuria. Br Med J *3:* 469-471

[43] *Pak CYC, Ohata M, Lawrence EC, Snyder W* 1974 The hypercalciurias. Cause, parathyroid functions and diagnostic criteria. J Clin Invest *54:* 387-400

[44] *Flocks RH* 1939 Calcium and phosphorus excretion in the urine of patients with renal or ureteral calculi. JAMA *113:* 1466-1471

[45] *Nordin BEC, Peacock M, Wilkinson R* 1972 Hypercalciuria and calcium stone disease. Clin Endocrinol Metab *1:* 169-183

[46] *Yendt ER, Guay GF, Garcia DA* 1970 The use of thiazides in the prevention of renal calculi. Can Med Assoc J *102:* 614-620

[47] *Pak CYC, Delea CS, Bartter FC* 1974 Successful treatment of recurrent nephrolithiasis (calcium stones) with cellulose phosphate. N Engl J Med *290:* 175-180

[48] *Zerwekh JE, Hwang TIS, Poindexter J, Hill K, Wendell G, Pak CYC* 1988 Modulation by calcium of inhibitor activity of citrate, chondroitin sulfate and urinary glycoprotein against calcium oxalate crystallization. Kidney Int *33:* 1005-1008

[49] *Strauss AL, Coe FL, Deutsch L, Parks JH* 1982 Factors that predict relapse of calcium nephrolithiasis during treatment: a prospective study. Am J Med *72:* 17-24

[50] *Albright F, Henneman P, Benedict PH, Forbes AP* 1953 Idiopathic hypercalciuria: A preliminary report. Proc R Soc Med *46:*1077-1081

[51] *Pak CYC, McGuire J, Peterson R, Britton F, Harrod MJ* 1981 Familial absorptive hypercalciuria in a large kindred. J Urol *126:* 717-719

[52] *Kaplan RA, Haussler MR, Deftos LJ, Bone H, Pak CYC* 1977 The role of 1,25-dihydroxyvitamin D in the mediation of intestinal hyperabsorption of calcium in primary hyperparathyroidism and absorptive hypercalciuria. J Clin Invest *59:* 756-760

[53] *Breslau NA, Preminger GM, Adams BV, Otey J, Pak CYC* 1992 Use of ketoconazole to probe the pathogenetic importance of 1,25-$(OH)_2$D in absorptive hypercalciuria. J Clin Endocrinol Metab *75:* 1446-1452

[54] *Zerwekh JE, Yu S-P, Breslau NA, Manolagas S, Pak CYC* 1993 Vitamin D receptor quantitation in human blood mononuclear cells in health and disease. Mol Cell Endocrinol *96:* 1-6

[55] *Li XQ, Tembe V, Horowitz GM, Bushinsky DA, Favus MJ* 1993 Increased intestinal vitamin D receptor in genetic hypercalciuric rats: a cause of intestinal hyperabsorption. J Clin Invest *91:* 661-667

[56] *Zerwekh JE, Hughes MR, Reed BY, Breslau NA, Heller HJ, Lemke M, Nasonkin I, Pak CYC* 1995 Evidence for normal vitamin D receptor messenger ribonucleic acid and genotype in absorptive hypercalciuria. J Clin Endocrinol Metab *80:* 2960-2965

[57] *Reed BY, Heller HJ, Lemke M, Lane H, Reza Albarrán A, Zerwekh JE, Breslau NA, Pak CYC* 1996 Linkage analysis in absorptive hypercalciuria: Lack of linkage to the vitamin D receptor or

1,25-$(OH)_2D_3$.1-αHydroxylase loci. VIII International Symposium on Urolithiasis (Abstract Book) pp 540-542

[58] *Zerwekh JE, Reed BY, Heller HJ, González GB, Haussler MR, Pak CYC.* Normal vitamin D receptor concentration and responsiveness to 1,25-dihydroxyvitamin D_3 in skin fibroblasts from patients with absorptive hypercalciuria. Miner Electrolyte Metab (in press)

[59] *Zerwekh JE, Pak CYC* 1980 Selective effects of thiazide therapy on serum 1-α,25-dihydroxyvitamin D and intestinal calcium absorption in renal and absorptive hypercalciurias. Metabolism *29:* 13-17

[60] *Pacifici R* 1997 Idiopathic hypercalciuria and osteoporosis-distinct clinical manifestations of increased cytokine-induced bone resorption? (Editorial). J Clin Endocrinol Metab *82:* 29-31

[61] *Yu TF, Gutman AB* 1967 Uric acid nephrolithiasis and gout. Predisposing factors. Ann Intern Med *67:* 1133-1148

[62] *Coe FL, Kavalach AG* 1974 Hypercalciuria and hyperuricosuria in patients with calcium nephrolithiasis. N Engl J Med *291:* 1344-1350

[63] *Pak CYC, Waters O, Arnold L, Holt K, Cox C, Barilla D* 1977 Mechanism for calcium urolithiasis among patients with hyperuricosuria. J Clin Invest *59:* 426-431

[64] *Coe FL, Lawton RL, Goldstein RB, Tembe V* 1975 Sodium urate accelerates precipitation of calcium oxalate in vitro. Proc Soc Exp Biol Med *149:* 926-929

[65] *Pak CYC, Arnold LH* 1975 Heterogenous nucleation of calcium oxalate by seeds of monosodium urate. Proc Soc Exp Biol Med *149:* 930-932

[66] *Zerwekh JE, Holt K, Pak CYC* 1983 Natural urinary macromolecular inhibitors: Attenuation of inhibitory activity by urate salts. Kidney Int *23:* 838-841

[67] *Ham LL. Alpern RJ* 1996 Regulation of acid-base balance, citrate and urine pH. In: Coe FL, Favus MJ, Pak CYC, Parks JH, Preminger GM: Kidney Stones: Medical and Surgical Management. Lippincott-Raven, Philadelphia, pp 289-302

[68] *Pak CYC, Nicar MJ, Northcutt C* 1982 The definition of the mechanism of hypercalciuria is necessary for the treatment of recurrent stone formers. Contrib Nephrol *33:* 136-151

[69] *Kok DJ, Papapoulos SE, Bijvoet OLM* 1986 Excessive crystal agglomeration with low citrate excretion in recurrent stone-formers. Lancet *10:* 1056-1058

[70] *Nicar MJ, Hill K, Pak CYC* 1987 Inhibition by citrate of spontaneous precipitation of calcium oxalate in vitro. J Bone Miner Res *2:* 215-220

[71] *Pak CYC, Peterson R* 1986 Successful treatment of hyperuricosuric calcium oxalate nephrolithiasis with potassium citrate. Arch Intern Med *146:* 863-868

[72] *Fegan J, Khan R, Poindexter J, Pak CYC* 1992 Gastrointestinal citrate absorption in nephrolithiasis. J Urol *147:* 1212-1214

[73] *Pak CYC* 1991 Citrate and renal calculi: New insights and future directions. Am J Kid Dis *17:* 420-425

[74] *Pak CYC* 1994 Citrate and renal calculi: an update. Miner Electrolyte Metab *20:* 371-377

[75] *Pak CYC* 1987 Citrate and renal calculi. Miner Electrolyte Metab *13:* 257-266

[76] *Nicar MJ, Skurla C, Sakhaee K, Pak CYC* 1983 Low urinary citrate excretion in nephrolithiasis. Urology *21:* 8-14

[77] *Preminger GM, Sakhaee K, Skurla C, Pak CYC* 1985 Prevention of recurrent calcium stone formation with potassium citrate therapy in patients with distal renal tubular acidosis. J Urol *134:* 20-23

[78] *Pak CYC* 1989 Role of medical prevention. J Urol *141:* 798-801

[79] *Borghi L, Meschi T, Amato F, Briganti A, Novarini A, Giannini A* 1996 Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: a 5-year randomized prospective study. J Urol *155:* 839-843

[80] *Pak CYC, Sakhaee K, Crowther C, Brinkley L* 1980 Evidence justifying a high fluid intake in treatment of nephrolithiasis. Ann Intern Med *93:* 36-39

[81] *Robertson WG, Peacock M* 1984 Metabolic and biochemical risk factors in renal stone disease. Contrib Nephrol *37:* 1-4

[82] *Riese R, Sakhaee K* 1992 Uric acid nephrolithiasis: pathogenesis and treatment (review article). J Urol *148:* 765-771

[83] *McLeod RS, Churchill DN* 1992 Urolithiasis complicating inflammatory bowel disease (review article). J Urol *148:* 974-978

[84] *Khatchadourian J, Preminger GM, Whitson PA, Adams-Huet B, Pak CYC* 1995 Clinical and biochemical presentation of gouty diathesis: comparison of uric acid versus pure calcium stone formation. J Urol *154:* 1665-1669

[85] *Pak CYC, Sakhaee K, Fuller C* 1986 Successful management of uric acid nephrolithiasis with potassium citrate. Kidney Int *30:* 422-428

[86] *Gutman AB, Yu TS* 1965 Urinary ammonium excretion in primary gout. J Clin Invest *44:* 1474-1481

[87] *Falls WF* 1972 Comparison of urinary acidification and ammonium excretion in normal and gouty subjects. Metabolism *21:* 433-445

[88] *Gibson T, Hannan SF, Hatfield PJ, Simonds HA, Cameron JS, Potter CS, Crate CM* 1977 The effect of acid loading on renal excretion of uric acid and ammonium in gout. Adv Exp Med Biol *76B:* 46-55

[89] *Pak CYC* 1990 Hyperoxaluric calcium nephrolithiasis. In: Resnick MI, Pak CYC (eds): Urolithiasis. WB Saunders, Philadelphia, pp 65-77

[90] *Smith LH, Fromm H, Hofmann AF* 1972 Acquired hyperoxaluria, nephrolithiasis, and intestinal disease. N Engl J Med *286:* 1371-1375

[91] *Danpure CJ, Smith LH* 1996 The primary hyperoxalurias. In: Coe FL, Favus MJ, Pak CYC, Parks JH, Preminger GM: Kidney Stones: Medical and Surgical Management. Lippincott-Raven, Philadelphia, pp 859-881

[92] *Lindberg J, Harvey J, Pak CYC* 1990 Effect of magnesium citrate and magnesium oxide on crystallization of calcium salts in urine: changes produced by food-magnesium interactions. J Urol *143:* 248-251

[93] *Meyer JL, Smith LH* 1975 Growth of calcium oxalate crystals. Invest Urol *13:* 36-39

[94] *Caudarella R, Rizzoli E, Pironi L, Malavolta N, Martelli G, Poggioli G, Gozetti G, Miglioli M* 1993 Renal stone formation in patients with inflammatory bowel disease. Scanning Micros *7:* 371-380

[95] *Preminger GM, Baker S, Peterson R, Poindexter J, Pak CYC* 1989 Hypomagnesiuric hypocitraturia: an apparent new entity for calcium nephrolithiasis. J Lith Stone Dis *1:* 22-25

[96] *Danielson BG, Johansson G, Jung B, Ljunghall S, Lundqvist H, Malmborg P* 1979 Gastrointestinal magnesium absorption. Miner Electrolyte Metab *2:* 116-123

[97] *Tiselius H* 1984 A simplified estimate of the ion-activity product of calcium phosphate in urine. Eur Urol *10:* 191-195

[98] *Pak CYC, Eanes ED, Ruskin B* 1971 Spontaneous precipitation of brushite in urine: evidence that brushite is the nidus of renal stones originating calcium phosphate. Proc Natl Aca Sci USA *68:* 1456-1460

[99] *Coe FL, Parks J* 1976 Calcium phosphate stones and renal tubular acidosis. In: Coe FL, Parks J (eds): Nephrolithiasis: pathogenesis and treatment (2nd edition). Year Book Medical Publishers, Chicago, pp 139-171

[100] *González GB, Adams-Huet B, Pak CYC* 1996 Metabolic evaluation in patients with brushite renal stones. 79th Annual Meeting of the Endocrine Society (Abstract Book), p 487

[101] *Wang LP, Wong HY, Griffith DP* 1997 Treatment options in struvite stones. Urol Clin North Am *24:* 149-162

[102] *Elliot JS, Sharp RF, Lewis L* 1959 The solubility of struvite in urine. J Urol *81:* 366-368

[103] *Cohen TD, Preminger GM* 1996 Struvite calculi. Semin Nephrol *16:* 425-434

[104] *Sakhaee K* 1996 Pathogenesis and medical management of cystinuria. Semin Nephrol *16:* 435-447

[105] *Dent CE, Senior B* 1955 Studies on the treatment of cystinuria. Br J Urol *27:* 317-322

[106] *Pak CYC, Resnick MI, Preminger GM et al* 1997 Ethnic and geographic diversity of stone disease. Urology *50:* 504-507

[107] *Monk RD* 1996 Clinical approach to adults. Semin Nephrol *16:* 375-388

[108] *Pak CYC* 1990 General guidelines in medical evaluation. In: Resnick MI, Pak CYC (eds): Urolithiasis. WB Saunders, Philadelphia, pp 153-172

[109] *Curhan GC, Willet WC, Rimm EB, Stampfer MJ* 1993 A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. N Engl J Med *328:* 833-8

[110] *Norman DA, Fordtran JA, Brinkley L, Zerwekh JE, Nicar MJ, Strowig SM, Pak CYC* 1981 Jejunal and ileal adaptation to alterations in dietary calcium: changes in calcium and magnesium absorption and pathogenetic role of parathyroid hormone and 1,25-dihydroxyvitamin D. J Clin Invest *67:* 1599-1603

[111] *Sakhaee K, Baker S, Zerwekh J, Poindexter J, Garcia-Hernández A, Pak CYC* 1994 Limited risk of kidney stone formation during long-term calcium citrate supplementation in non-stone forming subjects. J Urol *152:* 324-327

[112] *Sakhaee K, Harvey JA, Padalino PK, Whitson P, Pak CYC* 1991 Potential role of salt abuse on the risk for kidney stone formation. J Urol *150:* 310-312

[113] *Breslau NA, Brinkley L, Hill KD, Pak CYC* 1998. Relationship role of animal protein-rich diet to kidney stone formation and calcium metabolism. J Clin Endocrinol Metab *66:* 140-146

[114] *Parivar F, Low RK, Stoller ML* 1996 The influence of diet on urinary stone disease (review article). J Urol *155:* 432-440

[115] *Wabner CL, Pak CYC* 1993 Effect of orange juice consumption on urinary stone risk factors. J Urol *149:* 1405-1408

[116] *Ramchandani P, Pollack HM* 1996 Radiologic evaluation of patients with urolithiasis. In: Coe FL, Favus MJ, Pak CYC, Parks JH, Preminger GM: Kidney Stones: Medical and Surgical Management. Lippincott-Raven Publishers, Philadelphia, pp 369-435

[117] *Brand E, Harris MM, Billon S* 1930 Cystinuria: excretion of a cystine complex which decomposes in the urine with the liberation of free cystine. J Biol Chem *86:* 315-331

[118] *Pak CYC, Skurla C, Harvey J* 1985 Graphic display of urinary risk factors for renal stone formation. J Urol *134:* 867-870

[119] *Pak CYC, Griffith DP, Menon M, Preminger GM, Resnick M* 1996 Urolithiasis. In: Glassock R (ed): Current Practice of Medicine, Vol 4. Current Medicine, Inc., Philadelphia, pp 133-134

[120] *Barcelo P, Wuhl O, Servitge E, Rousand A, Pak CYC* 1993 Randomized double-blind study of potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. J Urol *150:* 1761-1764

[121] *Harvey JA, Zobitz MM, Pak CYC* 1989 Bioavailability of citrate from two different preparations of potassium citrate. J Clin Pharmacol *29:* 338-341

[122] *Costanzo LS, Weiner IM* 1974 On the hypocalciuric action of chlorothiazide. J Clin Invest *54:* 628-637

[123] *Yendt ER, Cohanim M* 1978 Prevention of calcium stones with thiazide. Kidney Int *13:* 397-409

[124] *Nicar MJ, Peterson R, Pak CYC* 1984 Use of potassium citrate as potassium supplement during thiazide therapy of calcium nephrolithiasis. J Urol *131:* 430-433

[125] *Leppla D, Browne R, Hill K, Pak CY* 1983 Effect of amiloride with or without hydrochlorothiazide on urinary calcium and saturation of calcium salts. J Clin Endocrinol Metab *57:* 920-924

[126] *Pak CYC, Peterson R, Sakhaee K, Fuller C, Preminger GM, Reisch J* 1985 Correction of hypocitraturia and prevention of stone formation by combined thiazide and potassium citrate therapy in thiazide-unresponsive hypercalciuric nephrolithiasis. Am J Med *79:* 284-288

[127] *Ruml L, Pearle MS, Pak CYC* 1997 Calcium oxalate urolithiasis. Urol Clin North Am *24:* 117-133

[128] *Koening K, Padalino P, Alexandrides G, Pak CYC* 1991 Bioavailability of potassium and magnesium and citraturic response from potassium-magnesium citrate. J Urol *145:* 330-334

[129] *Pak CYC, Koening K, Khan R, Haynes S, Padalino P* 1992 Physicochemical action of potassium-magnesium citrate in nephrolithiasis. J Bone Min Res *7:* 283-287

[130] *González GB, Pak CYC, Adams-Huet B, Taylor R, Bilhartz LE* 1998 Effect of potassium-magnesium citrate on upper gastrointestinal mucosa. Alim Pharmacol Therapy *12:* 105-110

[131] *Preminger GM, Pak CYC* 1987 Eventual attenuation of hypocalciuric response to hydrochlorothiazide in absorptive hypercalciuria. J Urol *137:* 1104-1109

[132] *Breslau NA, Padalino P, Kok DJ, Kim YC, Pak CYC* 1993 Physicochemical effects of a new slow-release potassium phosphate preparation (UroPhos-K) in absorptive hypercalciuria. J Bone Min Res *10:* 394-400

[133] *Heller HJ, Reza Albarrán AA, Breslau NA, Pak CYC* 1996 Long-term physiologic effects of UroPhos-K in absorptive hypercalciuria. Eighth International Symposium on Urolithiasis. In: Urolithiasis. Millet the Printer, Dallas (Abstract Book), pp 434-436

[134] *Pak CYC, Sakhaee K, Fuller C* 1986 Successful management of uric acid nephrolithiasis with potassium citrate. Kidney Int *30:* 422-428

[135] *Sakhaee K, Nicar M, Hill K, Pak CYC* 1983 Contrasting effects of potassium citrate and sodium citrate therapies on urinary calcium chemistries and crystallization of stone-forming salts. Kidney Int *24:* 348-352

[136] *Klee LW, Brito CG, Lingeman JE* 1991 The clinical implications of brushite calculi. J Urol *145:* 715-718

[137] *National Institutes of Health* 1991 Consensus development conference statement on primary hyperparathyroidism. J Bone Min Res *6:* S9-S13

[138] *Worcester EM* 1996 Stones due to bowel disease. In: Coe FL, Favus MJ, Pak CYC, Parks JH, Preminger GM: Kidney Stones: Medical and Surgical Management. Lippincott-Raven, Philadelphia, pp 883-903