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KIDNEY STONES: AN UPDATE ON CURRENT PHARMACOLOGICAL MANAGEMENT AND FUTURE DIRECTIONS

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Abstract

Introduction—Kidney stones are a common problem worldwide with substantial morbidities and economic costs. Medical therapy reduces stone recurrence significantly. Much progress has been made in the last several decades in improving therapy of stone disease.

Areas covered—1) effect of medical expulsive therapy on spontaneous stone passage, 2) pharmacotherapy in the prevention of stone recurrence, 3) future directions in the treatment of kidney stone disease.

Expert Opinion—fluid intake to promote urine volume of at least 2.5L each day is essential to prevent stone formation. Dietary recommendations should be adjusted based on individual metabolic abnormalities. Properly dosed thiazide treatment is the standard therapy for calcium stone formers with idiopathic hypercalciuria. Potassium alkali therapy is considered for hypocitraturia, but caution should be taken to prevent potential risk of calcium phosphate stone formation. For absorptive hyperoxaluria, low oxalate diet and increased dietary calcium intake are recommended. Pyridoxine has been shown effective in some cases of primary hyperoxaluria type I. Allopurinol is used in calcium oxalate stone formers with hyperuricosuria. Treatment of cystine stones remains challenging. Tiopronin can be used if urinary alkalinization and adequate fluid intake are insufficient. For struvite stones, complete surgical removal coupled with appropriate antibiotic therapy is necessary.

Keywords

Kidney stones; pharmacotherapy; conservative therapy; clinical trials

1. Introduction

Kidney stones are a common problem worldwide with a marked increase in prevalence over the past 20 years. According to the latest report from the National Health and Nutrition Examination Survey (NHANES 2007-2010), the prevalence of kidney stones among American adults was 8.8%: 10.6% among men and 7.1% among women [1]. It is anticipated that there will be an increase in kidney stones in the future due to global warming, lifestyle changes, diet and obesity [2-3]. The occurrence of kidney stones is costly due to both medical treatment and time lost from work [4], and is also associated with increased rates of chronic kidney disease, hypertension and myocardial infarction [5-7].

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One of the major problems with kidney stones is the high rate of recurrence: after an initial stone, there is a 50% chance of forming a second stone within 7 years if left untreated [8]. As most patients with stone disease have identifiable risk factors, it is worthwhile to evaluate for underlying causes of stone formation. The 24-hour urine collection is the cornerstone of the evaluation of patients with renal stones as it allows for calculation of urinary supersaturations for the various salts associated with lithogenesis such as calcium oxalate (CaOx), calcium phosphate (CaP), and uric acid (UA), as well as the identification of specific metabolic derangements that may be contributing to risk. Dietary modification and medical treatment aimed at lowering urinary supersaturation can significantly reduce the risk of recurrence [9]. Fluid intake and dietary modification are important interventions in all stone formers and remain the first-line in stone management. These topics are well covered elsewhere [10, 11] but outside the scope of this review. Once lifestyle changes are undertaken, repeat 24-hour-urine measurements should be obtained to guide therapy and assess the impact of the intervention. Normal ranges for urine solute excretion are suggested in table 1, but there is a great deal of overlap between stone formers and non-stone formers, and these values should be regarded as continuous risk factors.

2. Medical expulsive therapy (MET)

For patients presenting with renal colic due to ureteral stone, the most important factors predicting spontaneous stone passage are stone size and location. A meta-analysis demonstrated spontaneous passage rates of 68 and 47% for ureteral stones less than 5 mm and 5 to 10 mm, respectively [12]; the probability of passage was also related to the location in the ureter with 12, 22, and 45% of stones passing depending on whether they were in the proximal, middle, or distal ureter [13]. MET, the administration of drugs to facilitate stone passage, may obviate the need for surgical interventions.

The most common medications used for MET are α-1 blockers and calcium channel blockers. The α-1D receptor has been shown to be the most common α-adrenergic receptor in the ureter and it is most heavily expressed in the distal ureter [14]. Alpha-1 blockers decrease the force and frequency of ureteral contraction [15]. Nifedipine, a calcium channel blocker, has been shown to relax ureteral smooth muscle in vitro and its effect is predominantly seen in the distal ureter as well [16].

There are two meta-analyses evaluating the efficacy of calcium channel blockers and α-1 blockers. Hollingsworth and colleagues in a meta-analysis of 9 randomized controlled trials (RCTs) reported that patients given an α-1 blocker or a calcium channel blocker had a 65% greater likelihood of spontaneous stone passage than the control group [17]. The end point in these studies was stone passage, with treatment durations ranging from 7 days to 6 weeks. The pooled risk ratio from 9 trials was 1.90 (CI 1.51-2.40) for calcium channel blockers and 1.54 (CI 1.29-1.85) for α-1 blockers. The concomitant administration of steroids had marginal benefit [17]. In the second meta analysis including 3 studies with nifedipine and 8 with tamsulosin, published as part of the 2007 American Urological Association/European Association of Urology guidelines for the management of ureteral calculi, Preminger and associates showed that use of nifedipine resulted in only a 9% absolute increase in the rate of stone passage as compared to controls, which was not statistically significant. In contrast, α-1 blockers were shown to have a 29% absolute increase in stone passage rates versus controls, a statistically significant difference. The guidelines suggest that for patients with a ureteral stone < 10 mm and well-controlled symptoms, a period of observation along with MET is an option for initial treatment, and recommend α-1 blockers as the preferred agents for MET [12].

Although most studies of alpha-1 blockers have demonstrated beneficial effects, there are also reported unfavorable outcomes. Hermanns [18] conducted a RCT to evaluate the efficacy of MET with tamsulosin in which patients were randomized to receive either tamsulosin 0.4mg daily (n=45) or placebo (n=45) for 21 days. The stone expulsion rate was not significantly different between the tamsulosin arm (86.7%) and the placebo arm (88.9%; p=1.0). Median time to stone passage was 7 days in the tamsulosin arm and 10 days in the placebo arm (log-rank test, p=0.36), though the exact duration to stone passage was missing in 29 patients. Patients in the tamsulosin arm required significantly fewer analgesics than patients in the placebo arm (median: 3 vs 7, p=0.011). The authors concluded that tamsulosin treatment does not improve the stone expulsion rate in patients with distal ureteral stones 7 mm, though patients may benefit from a supportive analgesic effect. In a separate trial, Pedro et al evaluated the efficacy of alfuzosin as MET for distal ureteral stone passage [19]. Patients were randomized to alfuzosin group (n=34) or placebo group (n=35). There was no significant difference in the stone expulsion rate between the alfuzosin group and placebo group (73.5% vs 77.1%, respectively, p=0.83). Nevertheless, the time to stone expulsion (p=0.003) and the pain score (p=0.0005) were significantly in favor of the treatment group. The difference between these two trials and other favorable trials is the actual stone size. In the first trial, approximately 80% of the stones were 5 mm, while in the second trial the mean stone size was < 5mm. Side effects of -1 blocker therapy include dizziness, nasal congestion, ejaculatory disturbances, and hypotension. In patients undergoing cataract surgery, intraoperative floppy iris syndrome has been associated with -1 blocker therapy [20].

Use of corticosteroids has been attempted to reduce both edema and inflammation in order to facilitate stone passage. In a small trial, Dellabella and colleagues compared stone passage rates in patients who received tamsulosin, with and without deflazacort. The results showed no difference in stone passage rates, but the corticosteroid group passed stones on average 2 days sooner (p<0.05) [21]. Further larger scale trials are required before use of corticosteroids is widely implemented. Of note, deflazacort is not currently available in the United States.

Nonsteroidal anti-inflammatory drugs (NSAIDs) provide excellent analgesia in renal colic through inhibition of prostaglandin synthesis, which reduces glomerular filtration and renal pelvic pressure, ureteric peristalsis and ureteric edema. They are highly effective in reducing the number of new colic episodes and hospital readmission [1-3]. However, NSAIDs do not appear to have any effect on the time to stone passage or the likelihood of stone passage in renal colic. Laerum et al [22] randomized patients to 7 days of diclofenac 50mg 3 times daily (n=41) or placebo (n=39). At 3 weeks follow up, 68% of those receiving diclofenac had passed stones as compared with 74% in the placebo group. The mean time to passage was also similar in both groups, 3 days vs. 3.8 days. In another study, Kapoor et al [23] randomized patients to indomethacin suppositories 50mg every 8 hours (n=13) vs. placebo (n=13). The mean time interval to stone passage was slightly lower in the indomethacin group at 82 hours as opposed to 89 hours for placebo, but this difference was not statistically significant (p>0.10). Grenabo et al [24] used indomethacin 150mg daily (n=37) vs placebo (n=41) for 7 days and found the rate of stone passage within these 7 days was not influenced by indomethacin (22/37 and 25/41 cases, respectively). Phillips et al [25] randomized patients to 400 mg of celecoxib, followed by 200 mg every 12 hours for 10 days (n=29) or to placebo (n=24). Here as well the results showed no significant difference in the spontaneous stone passage rate (celecoxib 55.2%, placebo 54.2%, p=0.69), days to stone passage (7.0 vs 9.0, p=0.6) or size of stone passed (3.9 vs 4.6 mm, p=0.18). The authors concluded celecoxib does not facilitate stone passage or decrease narcotic requirements in patients with acute renal colic.

3 . Pharmacotherapy to prevent stone recurrence

3.1 Idiopathic Calcium Stones

Approximately 80% of patients with nephrolithiasis form calcium stones, most of which are composed primarily of CaOx or, less often, CaP [26, 27]. In some cases stones form as the result of systemic diseases such as primary hyperparathyroidism, malabsorptive syndromes, or distal renal tubular acidosis (RTA). However, the majority of calcium stones form in otherwise healthy individuals without systemic disease. In most cases, stone formation is associated with metabolic derangements that alter urine supersaturation for CaOx or CaP, the most common of which is idiopathic hypercalciuria (IH) [28]. Hyperoxaluria, hypocitraturia, persistently elevated urine pH, and increased urinary uric acid excretion can also increase risk of stone formation by raising supersaturation or decreasing the solubility of CaOx or CaP in urine.

3.1.1 Idiopathic hypercalciuria

In addition to aforementioned fluid intake and diet modification, at present, thiazide diuretics remain the major therapy for calcium stones associated with IH, and have also been used in normocalciuric stone formers. Thiazides decrease urine calcium; the presumed mechanism seems to be an increase in calcium absorption in the proximal tubule, induced by volume contraction [29]. There are at least 10 RCTs that have examined the effects of thiazide on preventing idiopathic calcium-containing kidney stone recurrence. Seven of them reported a reduction in recurrence rate in treated patients [30-36] (see table 2). Three trials showed no difference, which may in part be due to smaller sample size and shorter duration of treatment [37-39]. Although most patients in these trials made CaOx stones, an unknown number were CaP stone formers, and hypercalciuria was reported in 20-100% of the study subjects. Researchers in these trials employed various thiazide-type agents: hydrochlorothiazide (HCTZ) 25 mg twice daily [30], chlorthalidone 25-50 mg/day [33], trichlormethiazide 4 mg/day [34], indapamide 2.5 mg/day [35], and bendroflumethazide 2.5 mg thrice a day [38]. The duration and outcomes of the trials are shown in table 2.

A recent report showed that in the majority of patients treated with thiazide for stone prevention, the drugs were not being used in an evidence-based fashion [40]. Of 107 patients, 102 were treated with HCTZ, 4 with indapamide, and one with chlorthalidone. While indapamide and chlorthalidone were used at doses found effective in RCTs, only 35% of HCTZ-treated patients received 50 mg/day; in all but two patients the drug was given once a day. Fifty-two percent were prescribed 25 mg and 13% 12.5 mg of HCTZ daily, doses that have not been tested in RCTs of stone prevention. Inadequate dosing of HCTZ – either too low, or given only once daily – may be responsible for many so-called failures of thiazide in stone prevention.

The dose-dependent side effects of thiazide diuretics include hypokalemia, hyperglycemia, hyperlipidemia, hyperuricemia, hypomagnesemia, and hypocitraturia. In one short-term study of 13 patients administered thiazide for 1 week, urinary citrate excretion was substantially reduced, which returned to baseline with potassium supplementation. The effect of potassium citrate to correct hypokalemia was more pronounced than that of potassium chloride [41]. In a retrospective analysis, Odvina and associates reported long-term combined treatment with thiazide and potassium citrate in nephrolithiasis does not lead to hypokalemia or hypochloremic metabolic alkalosis [42].

IH is associated with decreased bone mineral density and increased bone resorption [43], and some have suggested that therapy aimed at decreasing urine calcium excretion may also improve bone histology in these patients. Balance studies have shown that thiazide treatment results in a positive calcium balance in stone patients [44]. Bisphosphonates are potent

inhibitors of bone resorption and a few studies have shown bisphosphonates lower urinary calcium excretion and increase bone mineral density (BMD). Heller and associates [45] noted that a short-term course of alendronate corrected fasting urinary calcium, marginally reduced 24-h urinary calcium and improved calcium balance in 9 calcium stone formers. Giusti and associates [46] in an RCT of 67 post-menopausal women with hypercalciuria associated with osteoporosis found that combination therapy with alendronate and indapamide significantly decreased 24-h urinary calcium excretion and increased BMD compared with alendronate alone, while indapamide alone failed to improve BMD. So far, no RCTs have been performed to evaluate the effects of bisphosphonates on calcium stone recurrence, and therapy with bisphosphonates cannot currently be recommended for this purpose.

3.1.2 Hypocitraturia

Citrate in urine has a protective effect on calcium crystal formation which is due both to its ability to chelate calcium ions as well as the effect it has to inhibit nucleation and growth at the crystal surface [47, 48]. Several forms of alkaline citrate have been used to treat idiopathic calcium stone disease, especially in patients with hypocitraturia. Only a small amount of ingested citrate appears in the urine intact; the remaining citrate is converted to bicarbonate in the liver, which stimulates increased clearance of filtered citrate by the kidney by changes in intracellular pH of proximal tubule cells. Potassium citrate is preferred over sodium alkali because sodium loading can increase urine calcium excretion, offsetting the benefits of raising urine citrate [49].

There are 3 major RCTs evaluating the effect of citrate administration in recurrent calcium stone formers (see table 2). Barcelo and colleagues compared the efficacy of potassium citrate with placebo in patients with hypocitraturic CaOx stones. They demonstrated a significant reduction in stone formation rate over 3 years of follow-up in patients taking potassium citrate, from 1.2 to 0.1 per patient-year (p<0.001) [50]. Ettinger et al. also found a significant reduction in the rate of CaOx stone formation in patients taking potassium-magnesium citrate compared with placebo [51]. In this study, only 20% of patients had hypocitraturia, so the benefits of raising urine citrate may not be limited to the patients with this abnormality, likely due to the ability of citrate to lower CaOx supersaturation and inhibit crystallization. However, Hofbauer and associates did not find any reduction in stone recurrence in a group of CaOx stone formers treated with sodium potassium citrate [52]; possibly the use of a mixed sodium-potassium salt blunted the antilithogenic response to citrate.

Citrate treatment can raise urine pH, and this may increase the risk for CaP stones if urine calcium remains high and fluid intake is not maintained. In the two positive citrate trials discussed above, dosages of 30-60 mEq per day were used. Usually the dose of citrate is based on the degree of hypocitraturia and treatment can typically be started with 30 mEq/day. The maximal recommended dosage is 60 mEq/day in divided doses to achieve urinary citrate excretion of > 500 mg/day. We and others recommend that treatment with citrate should typically be avoided when the urine pH is above 6.5 or if CaP supersaturation remains elevated [53].

Compliance with citrate supplements is an issue. Gastrointestinal upset is the primary side effect. Citrus products have been proposed as an alternative to increase urinary citrate, but the data are conflicting [54, 55]. Hyperkalemia may occur in patients with renal insufficiency. In this situation, treatment with sodium-based alkali (sodium citrate, sodium bicarbonate) is an alternative.

3.1.3 Hyperoxaluria

Idiopathic hyperoxaluria, which is typically mild, is by far the most common type of hyperoxaluria. It may be due to excessive oxalate intake in diet, decreased dietary calcium, or increased endogenous production [56-57]. Though historically low oxalate diets were uniformly recommended for patients with CaOx disease, recent data suggest that, at least on a population level, the dietary contribution may be smaller than previously estimated [58]. Nonetheless, a thorough history is important to identify potential dietary excesses that could be contributing in a particular individual. In addition, as low dietary calcium intake is associated with increased risk of CaOx stone disease [59], a normal dietary calcium intake is encouraged.

Severe hyperoxaluria can result from primary hyperoxaluria (PH I, PH II and PH III), rare autosomal recessive genetic disorders of oxalate synthesis [60-61], and enteric hyperoxaluria, in which malabsorptive disorders such as small bowel resection, pancreatic insufficiency or bariatric surgery lead to increased absorption and renal excretion of ingested oxalate. The treatment strategy is directed at the underlying disorder. PH I, found in 80 percent of patients with PH [63], is caused by deficiency of a liver-specific enzyme, alanine glyoxylate aminotransferase (AGT), which normally converts glyoxylate to glycine. The impaired glyoxylate metabolism in the peroxisomes of hepatocytes leads to an increase in synthesis of oxalate. Pyridoxine is an essential cofactor of AGT and pharmacological doses of pyridoxine reduce hyperoxaluria in about 30% of PH I patients [64]. PH types II and III are due to other enzyme deficiencies and are somewhat less likely to result in renal failure than PH I. Genetic testing can establish both the type of PH, and also identify those patients who are likely to respond to pyridoxine supplementation [65]. Treatment is focused on reducing urinary CaOx supersaturation by intensive medical management, including high fluid intake, administration of orthophosphate, potassium citrate and/or magnesium [66]. Patients with PH need close monitoring for both stone formation and loss of renal function. Patients with very elevated urine oxalate (usually those with PH I) are at risk for renal failure; the definitive treatment is combined liver-kidney transplant [67-68].

Dietary oxalate restriction is of limited benefit in PH, but patients with enteric hyperoxaluria should be advised to avoid food with high oxalate content. If dietary measures are insufficient, oxalate binding agents can be used with meals. It should be noted, however, that limited published data exist on the pharmacologic management of this complicated disorder. Calcium supplements can reduce oxalate absorption because the calcium binds dietary oxalate in the gut lumen [69]. Cholestyramine, 2 to 4g with each meal, is even more effective as an oxalate binder, but its drawbacks include unpleasant taste and the possibility of inducing vitamin K deficiency [70]. The phosphate binder sevelamer hydrochloride has been tried to reduce oxalate absorption, but the results are inconsistent [71,72].

3.1.4 Hyperuricosuria

Hyperuricosuria decreases the solubility of CaOx and is a well-documented risk factor for CaOx stones [73,74]. Dietary purine restriction should be the first therapeutic intervention [75]. The noncompliant patients and true non-responders require alternative approaches.

In an RCT in hyperuricosuric CaOx stone formers with normocalciuria allopurinol was shown to decrease calcium stone recurrence [76]. Major drawbacks of allopurinol include rash, gastrointestinal upset, abnormal liver enzyme levels, and prolonged elimination in renal disease. Febuxostat, a nonpurine xanthine oxidase inhibitor may have advantages over allopurinol [77]. A clinical trial is ongoing to test the hypothesis that febuxostat, like allopurinol, could reduce hyperuricosuria and recurrent calcium stones.

3.1.5 Calcium phosphate stones with and without renal tubular acidosis

Stones that contain more than 50% CaP are uncommon [27]. The major determinants of CaP supersaturation are alkaline urine pH (>6.3) combined with hypercalciuria [78]. Pure CaP stones should always raise the possibility of an underlying defect in renal acid excretion, more specifically distal RTA; however most CaP stone formers do not have a disorder of acid excretion.

Treatment of CaP stones is similar to that of CaOx stones in that reduced dietary sodium and protein, high fluid intake, and thiazides are effective in our experience [53], although few trials deal specifically with this group of stone formers. The role of alkali therapy in the treatment of patients with CaP stone disease is highly controversial, as the balance of risks and benefits is likely patient-dependent. Potassium alkali can raise urine citrate levels, and may reduce urine calcium, with additional direct inhibitory effects on CaP crystal formation [79,80]. Citrate also inhibits individual crystal growth and aggregation, a beneficial effect not reflected in supersaturation calculations. These positive effects, however, are usually accompanied by a rise in urine pH which can predispose to CaP crystallization and worsening of stone disease. Which effect will be predominant in any given patient is difficult to predict. If treatment with alkali is undertaken, completion of follow up 24-hr urines to assess these differential effects is paramount.

Citrate is also a mainstay of the treatment of patients with distal RTA, in whom it is used to treat both acidosis and hypocitraturia, and the goals of therapy are stabilization of bone disease as well as stone prevention. Correction of metabolic acidosis may lower urine calcium, and improve CaP supersaturation. These patients have high urine pH at baseline, which may worsen with citrate treatment, and thiazide may need to be added to control hypercalciuria and supersaturation. However, in a study of 9 patients with incomplete distal RTA, Preminger and associates [81] found that despite a significant increase in urinary pH, treatment with potassium citrate (60-80 meq per day) led to a decrease in stone formation during 34 months of follow up compared with pretreatment rates. Urine calcium and CaOx supersaturation fell, while CaP supersaturation remained stable. However, here as well therapy with alkaline citrate should be monitored carefully with follow-up 24-hr urine collections to avoid an excessive rise in urinary pH and potential worsening of CaP supersaturation.

3.1.6 Medullary sponge kidney

Medullary sponge kidney is a congenital disorder characterized by malformation of the terminal collecting ducts in the pericalyceal region of the renal pyramids. The patients are usually asymptomatic. Most patients are discovered with a radiographic study for some other indication. Incomplete distal RTA, hypocitraturia, and hypercalciuria are common in medullary sponge kidney. Kidney stones are the major clinical presentation: about 12-20 percent of patients have recurrent calcium stone formation [82,83]. The stones are primarily composed of CaP and CaOx.

Treatment of calcium stones in patients with medullary sponge kidney is the same as in patients with idiopathic calcium stones. For example, Fabris and associates in a retrospective analysis of 97 patients with medullary sponge kidney, reported potassium citrate in a dose of 30 mEq/day for an average of 6.5 years was associated with a reduction in stone formation rate from 0.58 to 0.10 stones per patient per year [84].

3.2 Uric acid stones

The three major factors in the development of uric acid stones are low urine volume, hyperuricosuria, and abnormally acidic urine pH. However, low urinary pH is the principle

determinant in uric acid crystallization. Most idiopathic uric acid stones in adults are associated not with hyperuricosuria but rather with unduly low urinary pH [85], which may be a manifestation of insulin resistance. The solubility of undissociated uric acid is only 90 mg/L. Uric acid is a weak organic acid with a pKa of 5.5. Therefore, at low urine pH, undissociated uric acid precipitates to form uric acid stones [86]. Uric acid stones are increased in patients who have diarrheal illness [87], ileostomy [88], and metabolic syndrome [89].

The main treatment is to increase the solubility of uric acid in urine and to reduce its concentration. Urinary alkalinization is the cornerstone of medical management of uric acid stones. Patients with known uric acid stones without significant obstruction or infection can receive a trial of oral medical dissolution, which will also serve as preventative therapy. Both potassium and sodium alkali treatment can effectively raise urinary pH, but potassium citrate is preferred over sodium citrate because sodium loads increase urinary calcium excretion. The initial recommended dosage is 30 to 40 mEq/day. Urine pH should be raised to 6.0 to 6.5.

Percutaneous or retrograde irrigation of large uric acid stones with alkalizing agents was a common practice in the past. This method was mainly used for dissolution of residual fragments after percutaneous or retrograde manipulation, or in those patients who did not tolerate systemic alkalinization. T he most commonly used agents were sodium bicarbonate solution (pH 7.0 to 8.0), tromethamine (pH 8.6) and 0.3 M tromethamine E (pH 10.5). These procedures require prolonged hospitalization and are not cost-effective [90,91].

If hyperuricosuria is present, animal protein consumption should be curtailed to less than 0.8 g/kg/day. For patients with hyperuricosuria refractory to dietary modification, xanthine oxidase inhibitors may be tried. Allopurinol is a mainstay treatment in patients with primary gout, inherited uric acid metabolism disorders, and in states of increased tissue turnover.

3.3 Cystine stones

Cystinuria is an autosomal recessive disorder of renal tubular and intestinal transport of dibasic amino acids, which results in increased urinary excretion of cystine, ornithine, lysine and arginine. Cystine is an amino acid formed by the linkage of two cysteine molecules via a disulfide bond. The limited solubility of cystine can result in stone formation. Although there are two genetically distinct forms of cystinuria, the clinical manifestations do not differ. Cystine excretion in these patients may range from 250 to over 1000 mg/day. Stones are generally composed of pure cystine although admixtures with calcium salts can occur rarely. Cystine solubility increases at higher urine pH [92,93].

Treatment of cystine stone has essentially not changed for more than 30 years [94]. Urine dilution, alkalinization and chelating therapy have remained the cornerstone of the therapeutic approach.

A reasonable goal is to keep the cystine concentration under about 240 mg/L and urine pH about 7 to maintain urine cystine supersaturation lower than 1. The goal almost always necessitates more than 4L of urine volume. Patients should awaken at least once per night to void and drink additional water in order to avoid the usual nocturnal concentration of urine. I f the urine pH is below 7, potassium citrate 10-20 mEq taken three times per day can be used to raise it. Cystine excretion may fall modestly on a sodium-restricted (<100 mmol/day) and protein-restricted (0.8 g/kg/day) diet.

If stones recur despite adequate hydration and alkaline urine pH, a cysteine-binding drug should be added. Cysteine-binding drugs have sulfhydryl groups that allow them to form

mixed disulfides with cysteine that are more soluble than the homodimer [95]. D-penicillamine and tiopronin (-mercaptopropionylglycine, -MPG) are the most commonly used thiol-binding drugs. Chow and Streem [96] studied the efficacy of D-penicillamine and -MPG in 16 patients with cystinuria. All patients received standard therapy with hydration and alkalinization. Failure of standard therapy was followed by addition of D-penicillamine (1 to 2 g) or -MPG (800 to 1200 mg) in daily divided doses. The results showed D-penicillamine and -MPG are effective in decreasing the rate of stone formation in patients in whom hydration and alkalinization failed. Both drugs have side effects including fever, arthralgias, rash, dysgeusia, leucopenia, and proteinuria, but tiopronin is better tolerated, with a lesser incidence and severity of adverse reactions.

Recurrent stones should be analyzed, because therapy may need to be adjusted to prevent the formation of stones containing CaP due to the alkaline urine pH.

3.4 Struvite stones

Struvite stones (also sometimes known as triple phosphate stones) are composed of calcium magnesium ammonium phosphate and form only in urine infected by urea-splitting bacteria, such as Proteus, Providencia, and sometimes Klebsiella, Pseudomonas, and enterococci. Because of their potential for rapid growth and substantial morbidity, early detection and eradication are essential [97]. Struvite stones are difficult to treat, and require collaboration with an expert urologist. Treatment requires both removal of all stone material and effective antibiotic therapy. Antibiotic therapy should be guided by culture of the stone itself (or renal pelvic urine obtained at the time of surgery) as well as the bladder urine. In some cases, patients have underlying metabolic causes for stone disease, as well [98].

According to the 2005 American Urological Association guideline on management of staghorn calculi [99], surgical removal of stone material is the standard therapy. There are four major surgical options recommended, including percutaneous nephrolithotomy (PNL) monotherapy, combination of PNL and shock-wave lithotripsy (SWL), SWL monotherapy and open surgery. PNL should be the first treatment for most patients. SWL monotherapy is only used in selected patients with small stone volumes who have normal collecting system anatomy. Adequate drainage of the kidney before the procedure should be established. If combination therapy with PNL and SWL is undertaken, percutaneous nephroscopy should be the last procedure to ensure that stone fragments are removed. Open surgery is only recommended in a very selected circumstances, such as patients with a large stone burden, especially if the collecting system anatomy is very distorted, or in whom who there has been a failure to remove the stone with less invasive procedures.

Culture-specific preoperative and perioperative antibiotics are critical to prevent sepsis during the surgery. Long-term, low dose culture-specific antimicrobials are important to prevent new stone growth and progression after surgery. Also by minimizing urease concentrations, small fragments after surgery may even be eradicated. Treatment with antibiotics alone is not standard of care [99].

When removal of all stone material is not possible, urease inhibitor has been used to slow or prevent stone growth. Acetohydroxamic acid (AHA) is most commonly used, although hydroxyurea is also available. In three randomized double-blind clinical trials in which AHA was used, stone growth or formation was reduced [100-102]. However, AHA requires adequate renal clearance for therapeutic efficacy and is contraindicated in patients with a serum creatinine level higher than 2 mg/dl. Its use is limited by side effects such as headache, thrombophlebitis, tremor, nausea, vomiting, and rash. AHA is also teratogenic. The starting dosage of AHA is 250 mg by mouth twice a day. If it is well tolerated for about 1 month, the dosage is increased to 250 mg by mouth three times a day.

4. Future directions

Over the past few decades, some progress has been made in the prevention of stone recurrence, especially in the calcium stone formers. Many RCTs evaluated the effects of dietary modification, potassium citrate, and thiazide in the calcium stone formation, but there is a need of further studies for comparison of pharmacotherapy vs dietary therapy, and single therapy vs combination therapy.

The treatment of cystine stones is both challenging and demanding. Minor medical improvements have been reported during recent years. Thiols remain the major treatment, but are not well tolerated. Development of effective treatment with a low profile of side effects is clearly necessary. It is possible that new techniques in molecular biology will be helpful for developing alternative forms of treatment, such as the inhibitor of cystine transporter in cultured human kidney cells that was demonstrated by antisense technology [103]. Another potential alternative approach is cystine crystal growth inhibitors, such as L-cystine dimethyl ester (L-CDME) [104]. The advantage of these inhibitors over the thiols in use is that at the low concentrations at which they seem effective they have a better safety profile and may also be more effective.

The role of oxalate-degrading bacteria, such as O. formigenes, in CaOx stone formation is a subject of current research. A pilot study showed O. formignenes reduced plasma oxalate levels and urinary oxalate excretion in the majority of PH patients [105], but the results could not be unequivocally confirmed in a recent multicenter trial . There are also inconsistent results with regard to the use of lactic acid bacteria (probiotics) to reduce urinary oxalate excretion [106]. Treatment that involves the upregulation of intestinal luminal oxalate secretion by increasing anion transporter activity (Slc26a6), or use of oxalate binders is another approach [107].

Further understanding of the potential pathogenic role of Randall's plaque as a precursor for CaOx nephrolithiasis, and the role of renal tubular crystal retention, may lead us to develop drugs that prevent the formation of Randall's plaque and/or renal tubular crystal adhesions [53]. Most importantly, however, future efforts should be aimed at understanding the molecular and genetic basis of both calcium and non-calcium kidney stones. Such an effort is necessary for the development of targeted therapy based on the underlying pathophysiological mechanisms of nephrolithiasis.

5. Conclusion

Adequate fluid intake and dietary modifications are successful in the prevention of stone recurrence. Thiazide, potassium alkali, allopurinol, and tiopronin have been shown effective in the treatment of different stones. Overall, however, few novel therapies have emerged over the past decade, and treatment of certain types of stones remains challenging. Currently, active studies evaluating pathophysiology and pathogenesis of stone disease are ongoing. These efforts will hopefully lead to the development of effective targeted therapy in the future.

Expert Opinion

In our practice, all stone formers are counseled on a low sodium diet and increasing fluid intake to facilitate at least 2-2.5L of urine volume on a daily basis, factors we believe to be absolutely crucial in the prevention of recurrent stone disease. With regard to MET, we support use of tamsulosin for medical expulsive therapy in appropriate patients due to the favorable side effect profile and the evidence for decreased time to stone passage. At this time we do not feel there is sufficient evidence to recommend addition of corticosteroid

therapy. In idiopathic calcium stone formers with recurrent disease, we evaluate for the presence of systemic disease such as primary hyperparathyroidism or RTA with a blood and urine panel. If systemic disease is ruled out, we advocate targeting of specific metabolic abnormalities for treatment based on the results of the metabolic evaluation, using both diet and pharmacotherapy as appropriate. With regard to IH, properly dosed thiazide treatment is standard in our practice, with repeat metabolic evaluations to document improvement. For hypocitraturia, we consider treatment with potassium alkali, but always with careful consideration of urine pH to avoid exacerbating potential risk of CaP stone disease. Again, repeat metabolic evaluations are crucial in this situation. Severe hyperoxaluria (> 75 mg/day) should raise the question of primary hyperoxaluria or a malabsorptive disease. If hyperoxaluria is found on the initial evaluation and primary hyperoxaluria has been ruled out, we start dietary counseling regarding increased dietary calcium intake and limiting high oxalate foods. If this is unsuccessful, we begin treatment with calcium carbonate with meals. If this fails, we initiate cholestyramine. Patients with pancreatic insufficiency may respond to treatment with pancreatic enzymes. For hyperuricosuria in the setting of CaOx stone disease, and only in this setting, we consider initiation of allopurinol therapy. Patients are counseled to watch for rash and we obtain complete blood counts (CBCs) at least yearly. At this time, we feel there are insufficient data to recommend febuxostat for this indication. For patients with uric acid nephrolithiasis, the key is urinary alkalinization. In patients with normal renal function and no history of hyperkalemia, we initiate potassium citrate 10-20 meq three times daily with a goal urinary pH of 6-6.5. In patients with a contraindication for potassium alkali, we consider use of sodium bicarbonate, despite the additional sodium load, as the benefit of alkalinization outweighs the risk of increased sodium intake. We encourage limiting dietary purine intake to 0.8-1 g/kg/day. Due to the high efficacy of urinary alkalinization, we seldom if ever utilize allopurinol for idiopathic uric acid stone disease. For cystine stone disease we initiate therapy with urinary alkalinization and increased fluid intake. If this is unsuccessful in reducing cystine supersaturation on repeat urine collections, we proceed with therapy with tiopronin, while closely monitoring for side effects. We obtain a CBC and liver function tests at least yearly while on tiopronin therapy. Close follow-up of these patients is essential to decrease stone formation. Lastly, for patients with struvite stones we strongly advocate for complete surgical removal due to the high risk of recurrence if all infected material is not cleared. Furthermore, it is critical to obtain a full metabolic evaluation, as patients often have an underlying metabolic derangement predisposing to nephrolithiasis. Given the side effect profile, we avoid use of AHA in our practice.

Reference List

1. Scales CD Jr, Smith AC, Hanley JM, Saigal CS. Prevalence of kidney stones in the United States. Eur Urol. 2012; 62:160–5. [PubMed: 22498635]

2. Romero V, Akpinar H, Assimos D. Kidney stones: A global picture of prevalence, incidence, and associated risk factors. Rev Urol. 2010; 12:e86–e96. [PubMed: 20811557]

3. Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. JAMA. 2005; 293:455–462. [PubMed: 15671430]

4. Saigal CS, Joyce G, Timilsina AR. Direct and indirect costs of nephrolithiasis in an employed population: opportunity for disease management? Kidney Int. 2005; 68:1808–14. [PubMed: 16164658]

5. Rule AD, Bergstralh EJ, Melton LJ III, et al. Kidney stones and the risk for chronic kidney disease. Clin J Am Soc Nephrol. 2009; 4:804–11. [PubMed: 19339425]

6. Madore F, Stampfer MJ, Rimm EG, Curhan GC. Nephrolithiasis and risk of hypertension. Am J Hypertens. 1998; 11:46–53. [PubMed: 9504449]

7. Rule AD, Roger VL, Melton LJ III, et al. Kidney stones associate with increased risk for myocardial infarction. J Am Soc Nephrol. 2010; 21:1641–1644. [PubMed: 20616170]

8. Sutherland JW, Parks JH, Coe FL. Recurrence after a single renal stone in a community practice. Miner Electrolyte Metab. 1985; 11:267–9. [PubMed: 4033604]

9. Parks JH, Asplin JR, Coe FL. Patient adherence to long-term medical treatment of kidney stones. J Urol. 2001; 166:2057–60. [PubMed: 11696706]

10. Goldfarb DS. Prospects for dietary therapy of recurrent nephrolithiasis. Adv Chronic Kidney Dis. 2009; 16:21–9. [PubMed: 19095202]

11. Fink HA, Akornor JW, Garimella PS, et al. Diet, fluid, or supplements for secondary prevention of nephrolithiasis: A systematic review and meta-analysis of randomized trials. Eur Urol. 2009; 56:72–80. [PubMed: 19321253]

12 *. Preminger GM, Tiselius HG, Assimos DG, et al. Guideline for the management of ureteral calculi. Eur Urol. 2007; 52:1610–31. Meta-analysis of the effect of -1 blockers and calcium channel blockers on stone passage rate. [PubMed: 18074433]

13. Miller OF, Kane CJ. Time to stone passage for observed ureteral calculi: a guide for patient education. J Urol. 1999; 162:688–90. [PubMed: 10458343]

14. Sigala S, Dellabella M, Milanese G, et al. Evidence for the presence of alpha1 adrenoceptor subtypes in the human ureter. Neurourol Urodyn. 2005; 24:142–8. [PubMed: 15690361]

15. Morita T, Wada I, Saeki H, et al. Ureteral urine transport: changes in bolus volume, peristaltic frequency, intraluminal pressure and volume of flow resulting from autonomic drugs. J Urol. 1987; 137:132–5. [PubMed: 3795356]

16. Davenport K, Timoney AG, Keeley FX. A comparative in vitro study to determine the beneficial effect of calcium channel and alpha(1)-adrenoceptor antagonism on human ureteric activity. BJU Int. 2006; 98:651–5. [PubMed: 16925767]

17. Hollingsworth JM, Rogers MA, Kaufman SR, et al. Medical therapy to facilitate urinary stone passage: a meta-analysis. Lancet. 2006; 368:1171–9. [PubMed: 17011944]

18. Hermanns T, Sauermann P, Rufibach K, et al. Is there a role for tamsulosin in the treatment of distal ureteral stones of 7 mm or less? Results of a randomised, double-blind, placebo-controlled trial. Eur Urol. 2009; 56:407–12. [PubMed: 19375849]

19. Pedro RN, Hinck B, m Hendlin K, et al. Alfuzosin stone expulsion therapy for distal ureteral calculi: a double-blind, placebo controlled study. J urol. 2008; 179:2244–7. [PubMed: 18423747]

20. Chang DF, Osher RH, Wang L, et al. Prospective multicenter evaluation of cataract surgery in patients taking tamsulosin (Flomax). Ophthalmology. 2007; 114:957–64. [PubMed: 17467530]

21. Dellabella M, Milanese G, Muzzonigro G. Medical expulsive therapy for distal ureterolithiasis: randomized prospective study on the role of corticosteroids used in combination with tamsulosin-simplified treatment regimen and health-related quality of life. Urology. 2005; 66:712–15. [PubMed: 16230122]

22. Laerum E, Omundsen OE, Gronseth JE, et al. Oral diclofenac in the prophylactic treatment of recurrent renal colic: A double blind comparison with placebo. Eur Urol. 1995; 28:108–11. [PubMed: 8529732]

23. Kapoor D, Weitzel S, Mowad J, et al. Use of indomethacin suppositories in the prophylaxis of recurrent ureteral colic. J Urol. 1989; 142:1428–30. [PubMed: 2685362]

24. Grenabo L, Holmlund D. Indomethacin as prophylaxis against recurrent ureteral colic. Scand J Urol Nephrol. 1984; 18:325–7. [PubMed: 6505647]

25. Phillips E, Hinck B, Pedro R, et al. Celecoxib in the management of acute renal colic: a randomized controlled clinical trial. Urology. 2009; 74:994–9. [PubMed: 19589565]

26. Johnson CM, Wilson DM, O'Fallon WM, et al. Renal stone epidemiology: a 25-year study in Rochester, Minnesota. Kidney Int. 1979; 16:624. [PubMed: 548606]

27. Coe FL, Parks JH, Asplin JR. The pathogenesis and treatment of kidney stones. N Engl J Med. 1992; 327:1141–52. [PubMed: 1528210]

28. Worcester EM, Coe FL. New insights into the pathogenesis of idiopathic hypercalciuria. Semin Nephrol. 2008; 28:120–32. [PubMed: 18359393]

29. Nijenhuis T, Vallon V, van der Kemp AW, et al. Enhanced passive Ca^{2+} reabsorption and reduced Mg^{2+} channel abundance explains thiazide-induced hypocalciuria and hypomagnesemia. J Clin Invest. 2005; 115:1651–8. [PubMed: 15902302]

30 *. Laerum E, Larsen S. Thiazide prophylaxis of urolithiasis. A double-blind study in general practice. Acta Med Scand. 1984; 215:383–89. A early RCT to show the effect of HCTZ in the prevention of calcium stone recurrence. [PubMed: 6375276]

31. Wilson DR, Strauss AL, Manuel MA. Comparison of medical treatment for the prevention of recurrent calcium nephrolithiasis. Urol Res. 1984; 12:39–40.

32. Robertson, WG.; Williams, RE.; Hargreaves, TB. A multicenter trial to evaluate three treatments for recurrent idiopathic calcium stone disease – A preliminary report. In: Schwille, PO.; Smith, LH.; Robertson, WG., et al., editors. Urolithiasis and related clinical research. Plenum Press; New York: 1985. p. 545-48.

33. Ettinger B, Citron JT, Livermore B, et al. Chlorthalidone reduces calcium oxalate calculus recurrence but magnesium hydroxide does not. J Urol. 1988; 139:679–84. [PubMed: 3280829]

34. Ohkawa M, Tokunaga S, Nakashima T, et al. Thiazide treatment for calcium urolithiasis in patients with idiopathic hypercalciuria. Br J Urol. 1992; 69:571–76. [PubMed: 1638340]

35. Borghi L, Meschi T, Guerra A, et al. Randomized prospective study of a nonthiazide diuretic, indapamide, in preventing calcium stone recurrences. J Cardiovasc Pharmacol. 1993; 22(supppl 6):S78–86. [PubMed: 7508066]

36. Fernandez-Rodriguez A, Arrabal-Martin M, Garcia-Ruiz M, et al. Role of thiazides in prophylaxis of relapsing calcium stones. Actas Urol Esp. 2006; 30:305–9. [PubMed: 16749588]

37. Mortensen JT, Schultz A, Ostergaard AH. Thiazides in the prophylactic treatment of recurrent idiopathic kidney stones. Int Urol Nephrol. 1986:265–69. [PubMed: 3533825]

38. Brocks P, Dahl C, Wolf H, et al. Do thiazides prevent recurrent idiopathic renal calcium stones? Lancet. 1981; 2:124–5. [PubMed: 6113485]

39. Scholz D, Schwille PO, Sigel A. Double-blind study with thiazide in recurrent calcium lithiasis. J Urol. 1982:903–7. [PubMed: 7176047]

40 **. Vigen R, Weideman RA, Reilly RF. Thiazide diuretics in the treatment of nephrolithiasis: are we using them in an evidence-based fashion? Int Urol Nephrol. 2011; 43:813–9. This is a key article highlighting the fact that treatment failures with thiazide use are often secondary to ineffective dosage not supported by evidence based trials. [PubMed: 20737209]

41. Nicar MJ, Peterson R, Pak CY. Use of potassium citrate as potassium supplement during thiazide therapy of calcium nephrolithiasis. J Urol. 1984; 131:430–33. [PubMed: 6699979]

42. Odvina, CV.; Preminger, GM.; Lindberg, JS., et al. Long-term combined treatment with thiazide and potassium citrate in nephrolithiasis does not lead to hypokalemia or hypochloremic metabolic alkalosis.

43. Heilberg IP, Weisinger JR. Bone disease in idiopathic hypercalciuria. Curr Opin Nephrol Hypertens. 2006; 15:394–402. [PubMed: 16775454]

44. Coe FL, Parks JH, Bushinsky DA, et al. Chlorthalidone promotes mineral retention in patients with idiopathic hypercalciuria. Kidney Int. 1988; 33:1140–6. [PubMed: 3404813]

45 *. Heller HJ, Zerwekh JE, Gottschalk FA, et al. Reduced bone formation and relatively increased bone resorption in absorptive hypercalciuria. Kidney Int. 2007; 71:808–15. An important paper highlighting bone disease as part of the spectrum of morbidity in nephrolithiasis. [PubMed: 17311067]

46. Giusti, A.; Barone, A.; Pioli, G., et al. Alendronate and indapamide alone or in combination in the management of hypercalciuria associated with osteoporosis: a randomized controlled trial of two drugs and three treatments.

47. Nicar MJ, Hill K, Pak CYC. Inhibition by citrate of spontaneous precipitation of calcium oxalate in vitro. J Bone Miner Res. 1987; 2L:215–20. [PubMed: 3455168]

48. Moe OW, Preisig PA. Duel role of citrate in urine. Curr Opin Nephrol Hypertens. 2006; 15:419–24. [PubMed: 16775456]

49. Lemann J Jr, Pleuss JA, Gray R, et al. Potassium administration decreases and potassium deprivation increases urinary calcium excretion in healthy adults. Kidney Int. 1991; 39:973–83. [PubMed: 1648646]

50 *. Barcelo P, Wuhl O, Servitge E, et al. Randomized double-blind study of potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. J Urol. 1993; 150:1761–4. An early RCT

showing the effect of potassium citrate in the idiopathic calcium nephrolithiasis. [PubMed: 8230497]

51. Ettinger B, Pak CY, Citron JT, et al. Potassium-magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. J Urol. 1997; 158:2069–73. [PubMed: 9366314]

52. Hofbauer J, Hobarth K, Szabo N, et al. Alkali citrate prophylaxis in idiopathic recurrent calcium oxalate urolithiasis-a prospective randomized study. Br J Urol. 1994; 73:362–5. [PubMed: 8199822]

53. Coe FL, Evan A, Worcester E. Pathophysiology-based treatment of idiopathic calcium kidney stones. Clin J Am Soc Nephrol. 2011; 6:2083–92. [PubMed: 21825103]

54. Seltzer MA, Low RK, McDonald M, et al. Dietary manipulation with lemonade to treat hypocitraturic calcium nephrolithiasis. J Urol. 1996; 156:907–9. [PubMed: 8709360]

55. Penniston KL, Steele TH, Nakada SY. Lemonade therapy increases urinary citrate and urine volumes in patients with recurrent calcium oxalate stone formation. Urology. 2007; 70:856–60. [PubMed: 17919696]

56. Hagler L, Herman RH. Oxalate metabolism. I. Am J Clin Nutr. 1973; 26:758–65. [PubMed: 4576881]

57. Holmes RP, Goodman HO, Assimos DG. Contribution of dietary oxalate to urinary oxalate excretion. Kidney Int. 2001; 59:270–76. [PubMed: 11135080]

58. Taylor EN, Curhan GC. Determinants of 24-hour urinary oxalate excretion. Clin J Am Soc Nephrol. 2008; 3:1453–60. [PubMed: 18650406]

59 **. Curhan GC, Willett WC, Rimm EB, et al. A prospective study of dietary calcium and other nutrients and risk of symptomatic kidney stones. N Engl J Med. 1993; 328:833–38. A landmark paper demonstrating the relationship of low dietary calcium intake to stone disease. [PubMed: 8441427]

60. Danpure CJ. Advances in the enzymology and molecular genetics of primary hyperoxaluria type 1. Prospects for gene therapy. Nephrol Dial Transplant. 1995; 10(suppl 8):24. [PubMed: 8592621]

61. Seargeant LE, deGroot GW, Dilling LA, et al. Primary oxaluria type 2 (L-glyceric aciduria): a rare cause of nephrolithiasis in children. J Pediatr. 1991; 118:912. [PubMed: 2040928]

62. Belostotsky R, Seboun E, Idelson GH, et al. Mutations in DHDPSL are responsible for primary hyperoxaluria type III. Am J Hum Genet. 2010; 87:392. [PubMed: 20797690]

63. Hoppe B, Langman CB. A United States survey on diagnosis, treatment, and outcome of primary hyperoxaluria. Pediatr Nephrol. 2003; 18:986. [PubMed: 12920626]

64. Leumann E, Hoppe B. The primary hyperoxalurias. Semin Nephrol. 2008; 28:152–62. [PubMed: 18359396]

65. Monico CG, Rossetti S, Olson JB, et al. Pyridoxine effect in type I primary hyperoxaluria is associated with the most common mutant allele. Kidney Int. 2005; 67:1704. [PubMed: 15840016]

66. Rumsby, G. Primary hyperoxaluria type 2. Pagon, RA.; Bird, TD.; Dolan, CR., et al., editors. University of Washington, Seattle; GeneReviews. Seattle: 1993-2008.

67. Millan MT, Berquist WE, So SK, et al. One hundred percent patient and kidney allograft survival with simultaneous liver and kidney transplantation in infants with primary hyperoxaluria: a single-center experience. Transplantation. 2003; 76:1458. [PubMed: 14657686]

68. Jeyarajah DR, McBride M, Klintmalm GB, et al. Combined liver-kidney transplantation: what are the indications? Transplantation. 1997; 64:1091. [PubMed: 9355821]

69. Hess B, Jost C, Zipperle L, et al. High-calcium intake abolishes hyperoxaluria and reduces urinary crystallization during a 20-fold normal oxalate load in humans. Nephrol Dial Transplant. 1998; 13:2241–47. [PubMed: 9761503]

70. Smith LH, Fromm H, Hofmann AF. Acquired hyperoxaluria, nephrolithiasis, and intestinal disease: description of a syndrome. N Engl J Med. 1972; 286:1371–5. [PubMed: 5030020]

71. Caravaca F, Ruiz AB, Escola JM, et al. Either calcium carbonate or sevelamer decreases urinary oxalate excretion in chronic renal failure patients. Nefrologia. 2007; 27:466–71. [PubMed: 17944584]

72. Lieske JC, Regnier C, Dillon JJ. Use of sevelamer hydrochloride as an oxalate binder. J Urol. 2008; 179:1407–10. [PubMed: 18289565]

73. Coe FL. Hyperuricosuric calcium oxalate nephrolithiasis. Kidney Int. 1978; 13:418–26. [PubMed: 661071]

74. Pak CY, Barilla DE, Holt K, et al. Effect of oral purine load and allopurinol on the crystallization of calcium salts in urine of patients with hyperuricosuric calcium urolithiasis. Am J Med. 1978; 65:593–99. [PubMed: 707519]

75. Coe FL, Parks JH. Hyperuricosuria and calcium nephrolithiasis. Urol Clin North Am. 1981; 8:227–44. [PubMed: 7268958]

76. Ettinger B, Tang A, Citron JT, et al. Randomized trial of allopurinol in the prevention of calcium oxalate calculi. N Engl J Med. 1986; 315:1386–9. [PubMed: 3534570]

77. Pacher P, Nivorozhkin A, Szabo C. Therapeutic effects of xanthine oxidase inhibitors: renaissance half a century after the discovery of allopurinol. Pharmacol Rev. 2003; 58:87–114. [PubMed: 16507884]

78. Parks JH, Worcester EM, Coe FL, et al. Clinical implications of abundant calcium phosphate in routinely analyzed kidney stones. Kidney Int. 2004; 66:777–85. [PubMed: 15253733]

79. Lemann J Jr, Bushinsky DA, Hamm LL. Bone buffering of acid and base in humans. Am J Physiol Renal Physiol. 2003; 285:F811–F832. [PubMed: 14532161]

80. Greischar A, Nakagawa Y, Coe FL. Influence of urine pH and citrate concentration on the upper limit of metastability for calcium phosphate. J Urol. 2003; 169:867–70. [PubMed: 12576801]

81. Preminger GM, Sakhaee K, Skurla C, et al. Prevention of recurrent calcium stone formation with potassium citrate therapy in patients with distal renal tubular acidosis. J Urol. 1985; 134:20–3. [PubMed: 4009822]

82. Hilderbrandt, F.; Sayer, JA.; Jungers, P., et al. Nephronophthisis-Medullary Cystic and Medullary Sponge Kidney Disease. In: Schrier, RW., editor. In: Diseases of the kidney & urinary tract. 8th. Philadelphia; Lippincott, Williams & Wilkins: 2007. p. PP478

83. Parks JH, Coe FL, Strauss AL. Calcium nephrolithiasis and medullary sponge kidney in women. N Engl J Med. 1982; 306:1088–91. [PubMed: 7070404]

84. Fabris A, Lupo A, Bernich P, et al. Long-term treatment with potassium citrate and renal stones in medullary sponge kidney. Clin J Am Soc Nephrol. 2010; 5:1663–8. [PubMed: 20576821]

85. Maalouf NM, Cameron MA, Moe OW, et al. Novel insights into the pathogenesis of uric acid nephrolithiasis. Curr Opin Nephrol Hypertens. 2004; 13:181–89. [PubMed: 15202612]

86. Sakhaee K, Adams-Huet B, Moe OW, et al. Pathophysiologic basis for normouricosuric uric acid nephrolithiasis. Kidney Int. 2002; 62:971–9. [PubMed: 12164880]

87 *. Parks JH, Worcester EM, O'Connor RC, et al. Urine risk factors in nephrolithiasis patients with and without bowel disease. Kidney Int. 2003; 63:255–65. This paper highlights the unique urinary risk factors in a population of patients with bowel disease. [PubMed: 12472791]

88. Clarke AM, Mckenzie RG. Ileostomy and the risk of urinary uric acid stones. The Lancet. 1969; 294:395–7.

89. Abate N, Chandalia M, Cabo-Chan AV Jr, et al. The metabolic syndrome and uric acid nephrolithiasis: novel features of renal manifestation of insulin resistance. Kidney Int. 2004; 65:386–92. [PubMed: 14717908]

90. Straub M, Strohmaier WL, Berg W, et al. Diagnosis and metaphylaxis of stone disease. Consensus concept of the National Working Committee on stone disease for the upcoming German urolithiasis guideline. World J Urol. 2005; 23:309–23. [PubMed: 16315051]

91. Shekarriz B, Stoller ML. Uric acid nephrolithiasis: current concepts and controversies. J Urol. 2002; 168:1207–14.

92. Hall PM. Nephrolithiasis: treatment, causes, and prevention. Cleve Clin J Med. 2009; 76:583–91. [PubMed: 19797458]

93. Worcester EM, Coe FL. Nephrolithiasis. Prim Care. 2008; 35:369–91. [PubMed: 18486720]

94. Mattoo A, Goldfarb DS. Cystinuria. Semin Nephrol. 2008; 28:181–91. [PubMed: 18359399]

95. Crawhall JC, Scowen EF, Watts RW. Effect of penicillamine on cystinuria. Br Med J. 1963; 1:588–90. [PubMed: 14023737]

96. Chow GK, Streem SB. Medical treatment of cystinuria: results of contemporary clinical practice. J Urol. 1996; 156:1576–8. [PubMed: 8863541]

97. Rodman JS. Struvite stones. Nephron. 1999; 81:50–59. [PubMed: 9873215]

98. Lingeman JE, Siegel YI, Steele B. Metabolic evaluation of infected renal lithiasis: clinical relevance. J Endourol. 1995; 9:51. [PubMed: 7780431]

99. Preminger GM, Assimos DG, Lingeman JE, et al. Chapter 1: AUA guideline on management of staghorn calculi: diagnosis and treatment recommendation. J Urol. 2005; 173:1991–2000. [PubMed: 15879803]

100. Griffith DP, Gleeson MJ, Lee H, et al. Randomized, double-blind trial of lithostat (acetohydroxamic acid) in the palliative treatment of infection-induced urinary calculi. Eur Urol. 1991; 20:243–7. [PubMed: 1726639]

101. Williams JJ, Rodman JS, Peterson CM. A randomized double-blind study of acetohydroxamic acid in struvite nephrolithiasis. N Engl J Med. 1984; 311:760–4. [PubMed: 6472365]

102. Griffith DP, Khonsari F, Skurnick JH, et al. A randomized trial of acetohydroxamic acid for the treatment and prevention of infection-induced urinary stones in spinal cord injury patients. J Urol. Aug; 1988 140(2):318–24. [PubMed: 3294442]

103. Wendt-Nordahl G, Sagi S, Bolenz C, et al. Evaluation of cystine transport in cultured human kidney cells and establishment of cystinuria type 1 phenotype by antisense technology. Urol Res. 2008; 36:25–9. [PubMed: 18074125]

104. Rimer JD, An Z, Zhu Z, et al. Crystal growth inhibitors for the prevention of L-cystine kidney stones through molecular design. Science. 2010; 330:337–41. [PubMed: 20947757]

105. Hoppe B, Beck B, Gatter N, et al. Oxalobacter formigenes: a potential tool for the treatment of primary hyperoxaluria type 1. Kidney Int. 2006; 70:1305–11. [PubMed: 16850020]

106. Lieske JC, Goldfarb DS, De Simone C, et al. Use of a probiotic to decrease enteric hyperoxaluria. Kidney Int. 2005; 68:1244–49. [PubMed: 16105057]

107. Hassan HA, Cheng M, Aronson PS. Cholinergic signaling inhibits oxalate transport by human intestinal T84 cells. Am J Physiol Cell Physiol. 2012; 302:C46–58. [PubMed: 21956166]

Article Highlights

*Stone disease is common and has high morbidity. Medical therapy is effective in decreasing stone recurrence

*Therapy with alpha-1 blockers such as tamsulosin is effective in promoting stone passage and decreasing stone passage time. NSAIDs can be used concomitantly for their analgesic effects.

*Hypercalciuria is common in calcium stone formers and is effectively treated with thiazide diuretics

*Treatment with alkaline citrate is effective in prevention of stone recurrence in idiopathic calcium stone formers. Caution is warranted with use of citrate in patients with CaP stone disease and high urine pH.

*Alkali therapy for urinary alkalinization is a cornerstone of management of uric acid stone disease

Table 1

24-hour urine stone chemistries used for kidney stone evaluation

Analyte	Units	Normal values (mean±SD) in non-stone formers (Adults)
PH		5.8-6.2
Calcium	mg/d	<250 (F), M300 (M), <4mg/kg or <140mg/g creatinine (both sexes)
Oxalate	mg/d	30-50
Citrate	mg/d	>550 (F), >450 (M)
Uric Acid	mg/d	<750 (F), <800 (M)
Phosphate	mg/d	500-1500
Magnesium	mg/d	50-150
Sulfate	mmol/d	20-80
Ammonia	mmol/d	15-60
Sodium	mmol/d	50-150
Potassium	mmol/d	20-100
Creatinine	mg/kg/d	15-19 (F), 20-24 (M)
Cystine	mg/d	<75
Calcium Oxalate Supersaturation		<8
Calcium Phosphate Supersaturation		0.5-1.5
Uric Acid Supersaturation		0-1

Abbreviations: F, female; GFR, glomerular filtration rate; M, male

Data from University of Chicago Stone Clinic (for adults)

The data as calculated by the Equal2 program

Table 2

Major clinical trials in pharmacotherapy of kidney stones

Authors Year (ref.)	Treatment	Population Studied	Study Duration (Years)	Treated/Placebo	Design	Recurrence (%) Treated/Control	Finding RR
Thiazide Therapy							
Brocks 1981 (38)	Bendroflumethiazide 2.5 mg TID	CaSF (n=62)	1.6	33/29	RCD	24/16	NS
Scholz 1982 (39)	HCTZ 25 mg BID	CaSF (n=51)	1	25/26	RCD	24/23	NS
Laerum 1984 (30)	HCTZ 25 mg BID	CaSF (n=50) (M/F=38/12)	3	25/25	RCD	20/48	0.39
Wilson 1984 (31)	HCTZ 100 mg daily	CaSF (n=44)	2.8	23/21	RC	21/44	0.48
Robertson 1985 (32)	Bendroflumethiazide 2.5 mg TID	CaSF (n=22)	3 to 5	13/9	RC		0.38
Mortensen 1986 (37)	Bendroflumethiazide 2.5 mg TID + KCl TID	CaSF (n=22) (M=22)	2	12/10	RCD	40/40	NS
Ettinger 1988 (33)	Chlorthalidone 25/50 mg daily	CaOx SF (n=73) (M/F=63/10	3	19(25mg)/ 23(50mg)/ 31(placebo)	RCD	14/46	0.23
Ohkawa 1992 (34)	Triclormethiazide 4mg daily	CaSF (n=175)	2.1 to 2.2	82/93	RC		0.42
Borghi 1993 (35)	Indapamide 2.5mg daily	CaOx SF (n=75)	3	43/14	RCD	15/43	0.21
Fernandez-Rodriguez 2006 (36)	HCTZ 50 mg daily	CaSF (n=100)	3	50/50	RC		0.56
Citrate Therapy							
Barcelo 1993 (50)	Potassium Citrate 30-60 mEq/d	Hypocit CaSF (n=57) (M/F=25/32	3	18/20	RCD	28/80	
Ettinger 1997 (51)	Potassium Mg Citrate 60 mEq/d	CaOx SF (n=64) (M/F=50/14)	3	31/33	RCD	13/64	
Hofbauer 1994 (52)	Sodium K Citrate Variable dose to Keep urine pH 7-7.2	CaOX SF (n=50) M/F=31/19	3	25/25	RCD	69/73	NS

CaOx, calcium oxalate; SF, stone former; M, male; F, female; RC, randomized controlled; RCD, randomized controlled double blind; HCTZ, hydrochlorothiazide; Hypocit, hypocitraturic; RR, relative risk; NS, no significance