Metaphylaxis in Pediatric Urinary Stone Disease

Onur Kaygısız

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Abstract

The high rate of recurrence of urinary stones after initial treatment makes metaphylaxis essential in children. Thorough assessment and planning prior to metaphylaxis enable accurate and effective treatment. Expected benefits and possible adverse conditions must be considered when deciding on dietary restrictions in growing children, as their bone development is ongoing. A diet that includes abundant hydration and avoids salt produces the optimal cost-benefit ratio. When dietary modification is not sufficient, medical treatment must be added.

Keywords: children, diet, food, and nutrition, kidney calculi, prevention, relapse

1. Introduction

The high rate of recurrence of urinary-stone disease indicates the necessity of metaphylaxis, especially in children. All lifestyle changes and medications for prevention of stone disease define the stone metaphylaxis. After stone treatment, even stone-free children showed a 25% recurrence rate during a three-year follow up [1]. In addition, after the urinary tract stone surgery, the rate of stone recurrence over five years has been observed to vary from 38 to 65% depending on the malformation of the urogenital system [2]. Children with metabolic disorders had a higher recurrence rate, so metabolic examination is essential to preventive treatment in children. In the pediatric age group, the most common metabolic disorders are hypercalciuria and hypocitraturia, with hypercalciuria more often found in the endemic areas and hypocitraturia in the nonendemic areas [3, 4]. Metaphylaxis has been found to reduce recurrence rates by about half, even in recurrent kidney stones [5].

Proper metaphylaxis must be preceded by a complete metabolic evaluation. In addition, identification of any anatomical abnormalities that may increase the risk of nephrolithiasis, a detailed dietary history, patient and family medical history, and a record of any medications used must be obtained [6].
The European Association of Urology (EAU) guidelines recommend metabolic assessment based on the type of the stones, which may be obtained spontaneously or after pediatric urolithiasis treatment [6]. However, it is not always possible to obtain stones with minimally invasive surgery, particularly in patients undergoing retrograde intrarenal surgery and shock wave lithotripsy (SWL). In this case, a general screening is required. The EAU’s pediatric urology guidelines recommend biochemical testing, including serum urea, creatinine, electrolytes, phosphorus, alkaline phosphate, uric acid, total protein, and albumin. If hypercalciemia is identified, the level of parathormone should be measured [6]. The ratio of spot urine calcium to creatinine should be analyzed, including a urinalysis and urine culture. Calcium, phosphate, magnesium, oxalate, uric acid, citrate, cysteine, protein, and creatinine clearance must be measured in a 24-hour urine [6]. In some cases, the test can be customized based on the stone type.

Renal tubular acidosis (RTA) should be suspected in calcium stones with urine pH that repeatedly tests higher than 5.5 [7]. In such patients, blood-gas levels must be analyzed. A urine pH consistently testing lower than 6 may indicate an acidic arrest [7].

Any renal anomaly responsible for the stones should be treated if there is a treatable pathology, including ureteropelvic junction obstruction. The child’s diet must be reviewed for risk factors, including anorexia, high salt intake, and excessive sugar intake. Metaphylaxis must take into consideration medically necessary diets, including ketogenic diets.

Urolithiasis of 1–2% is associated with use of some medications [8]. Detecting such risks in the medical history is important for proper treatment planning. Vitamins C and D, loop diuretics, carbonic anhydrase inhibitors, and laxatives affect the metabolism and may lead to stone formation. The mechanisms by which these drugs potentiate stone formation and the treatment approaches pertinent to them will be discussed later in this chapter [8]. Magnesium trisilicate, commonly used for gastroesophageal reflux, causes silica stones, and ciprofloxacin, sulfonamide, triamterene, indinavir, and ceftriaxone form stones [8–10] that are radiolucent or semipaque [8]. Stones that are weakly opaque or nonopaque and for which analysis results cannot be obtained should be suspected as drug-induced calculi.

Excessive use of laxatives causes formation of ammonium acid urate stones. Low urine volume and the low pH associated with chronic diarrhea increase the ammonium in urine [8]. In addition, anorexia, which is usually a postpuberty disease, is a cause of urolithiasis, with 5% of anorexia patients forming kidney stones [11], which are usually calcium oxalate, but which may be ammonium urate [12, 13]. The latter being stones that develop in cases of decreased urinary output, increased urine ammonium with hypophosphaturia, and the hyperchloremic acidosis associated with diarrhea [14]. Anorexia and any other identified primary disease should be treated before metaphylaxis.

Loop diuretics are commonly used to treat pulmonary disorders in newborns and act on the Na⁺-K⁺-2Cl⁻ pump through the thick part of Henle’s loop, inhibiting the reabsorption of magnesium and calcium with the reabsorption of sodium [15]. In infants, due to their low glomerular filtration rates and immature hepatic development, the half-life of drugs is 6–20-fold longer, the clearance is 1.2–1.4-fold lower, and volume distribution is 1.3–6-fold broader than
in adults [15]. In addition, the half-life is further increased in premature infants, with a half-life that is 6 hours in term infants and as long as 67 hours in premature infants [16]. However, increased knowledge of the pharmacokinetics and complications of using loop diuretics in infants have decreased the incidence of stones associated with these drugs [17, 18].

2. Diet

2.1. Fluid intake

Metaphylaxis of urinary stones may primarily involve regulating fluid intake and diet. Although hydration has been shown to decrease stone recurrence, the effectiveness of nutrition is controversial [19]. Increased fluid intake increases urine volume and inhibits crystal supersaturation and crystallization. In children, the fluid intake required for adequate urinary output must be calculated over 1.5 l/m² of body area [7]. Sweet-flavored liquids should be avoided, since fluid containing glucose and fructose increase excretion of calcium and oxalate [20]. In addition, fluid intake must be distributed over the entire day. Consequently, in metaphylaxis of stones, water intake is the approach that has the optimal cost-benefit ratio [21]. However, it is not possible to monitor the fluid intake of children in school, and children’s compliance in hydration is poor in general [22]. Because the need for liquids varies with temperature and activity level, parents may be recommended to monitor hydration based on urine color and urine density, if possible. Urine densities that repeatedly measure higher than 1010 indicate inadequate fluid intake [22].

2.2. Nutrition

Eating fast foods and processed foods can potentiate increased salt intake, causing hypervolemia, which leads to decreased absorption of water and sodium through the proximal tubules. This, in turn, decreases the absorption of calcium by sodium in the proximal tubules, which increases the level of calcium in the urine. The concentration of sodium in the urine is in proportion to dietary salt intake. In turn, dietary salt intake is in direct proportion to the calcium excreted in the urine [23]. In a Western-type diet, salt intake is almost 9 g/day in adults, nearly 77% of which comes from processed foods [24]. In contrast, daily salt intake should be below 3 mEq/kg [25]. Therefore, children’s consumption of fast foods should be limited to decrease dietary salt intake.

Only 10–20% of oxalate in the urine is associated with diet [26]. However, oxalate absorption through the bowels is related to dietary calcium intake [27], and restricting dietary calcium increases urinary excretion of oxalate. However, restricting salt decreases oxalate, and more significantly, the calcium excreted in the urine of those with calcium-oxalate stones [28].

Oxalate is the product of vitamin C metabolism and is excreted in urine [29]. Therefore, increased vitamin C intake may lead to hyperoxaluria. Children with hyperoxaluria should decrease consumption of high-oxalate foods [6]. In addition, oxalobacter formigenes, a probiotic, decreases urinary oxalate and is effective against hyperoxaluria [30].
Animal proteins increase the acid load, the excretion of calcium, and decrease the excretion of citrate [25]. In addition, purine metabolism increases uric acid [25], which increases the risk of calcium stones through epistaxis [31]. Despite all this, the protein restrictions recommended for adults are not suitable as part of stone metaphylaxis in children and adolescents, except in cases of definite indications [6].

Urinary excretion of citrate is affected by the system’s acid-base balance. Although acidosis decreases renal excretion of citrate and increases its reabsorption, the opposite is true in alkalosis [32]. A Western-type diet that includes decreased consumption of fruits and vegetables and increased consumption of animal products causes metabolic acidosis, resulting in lower urine pH and hypocitraturia [33]. Hypokalemia also lowers urine pH, and low potassium intake decreases urine potassium and citrate in hypokalemia and increases urinary excretion of calcium [32, 34]. Systemic alkalization increases excretion of citrate, decreases excretion of calcium, and raises urine pH [35]. Oranges, lemons, limes, and some types of mandarins are natural sources of citrate [35]. Alkaline fruits, including melons, cause urinary alkalization [36]. Grapefruits increase excretion of both citrate and oxalate [37]. The lithogenic effects of grapefruit juice and apple juice are controversial [38, 39].

Metaphylaxis benefits may be provided by increasing hydration and citrus intake and decreasing intake of sodium, oxalate, animal protein, and fructose [32]. Cranberry juice is high in oxalate and, therefore, increases urinary calcium and oxalate and decreases uric acid concentration. However, cranberry juice acidifies the urine, resulting in increased formation of calcium-oxalate and urate stones but decreased formation of calcium-phosphate stones [40]. Since cranberry juice acidifies the urine, it may be useful for infection stones that have limited options for medical treatment [41].

A study of 42,859 adults showed that high coffee and tea intake decreased the risk of symptomatic stone formation [39]. A more recent study of 6033 adults suggested that coffee intake decreased urine oxalate and uric acid, increased urine calcium and potassium, and also decreased the supersaturation of calcium oxalate by increasing urine volume [42]. However, dietary intake of coffee and tea cannot be recommended for pediatric patients because of the lack of studies of these substances in children.

Potential renal acid load (PRAL) is used to calculate the acid load of foods in adults. However, renal net acid excretion (NAE), which is based on body area, is recommended for use in pediatric patients [43]. PRAL is calculated by the formula (mEq/d) = 0.49 × protein (g/d) + 0.037 × phosphorus (mg/d) − 0.021 × potassium (mg/d) − 0.026 × magnesium (mg/d) − 0.013 × calcium (mg/d) [43]. As the formula indicates, dietary protein and phosphorus have acidic effects, whereas potassium, magnesium, and calcium have alkaline effects.

3. Medical treatment

When dietary modification is insufficient for metaphylaxis of urinary stones, medical treatment must be a part of the plan.
3.1. Alkalizing agents

Urine alkalization is used to reduce recurrence of calcium oxalate, uric acid, and cysteine stones, and urine acidification is used to reduce recurrence of infection and calcium-phosphate stones. For urine alkalization, potassium citrate is chosen instead of sodium citrate because sodium causes hypercalciuria. Potassium citrate directly dissolves calcium-oxalate crystals [44]. Therefore, it has a protective effect, even on calcium-oxalate stones that have normal citrate levels. Potassium-citrate tablets are available in 5 and 10-mEq doses, and Shohl's citrate-containing solution, which contains 1 mEq of base per millimeter, may be used for infants and children who cannot use tablets.

For calcium-oxalate stones, the targeted urine pH is 6.5, because uric acid cannot dissolve urine pH lower than 5.5, as it needs more alkalinity to dissolve. In metaphylaxis for hyperuricosuria, the targeted pH is also 6.5; however, to dissolve small uric-acid stones, the targeted pH range is 7–7.2 [7]. The daily dose may include 1–3 mEq/kg, depending on the urine pH and the primary disease, and the dose may be as high as 5–8 mEq/kg for infants with distal RTA [45]. Ideally, three doses a day should be administered, and if only one dose is possible, it should be administered in the evening [46].

Alkalization with hydration and potassium citrate has effectively decreased the risk of stones in children who are on a ketogenic diet, but these children should be referred to pediatric neurology for treatment of their primary diseases before beginning alkalization treatment [47]. Because cysteine has poor solubility and precipitates when urine pH is between 5 and 7, in alkalization therapy, the targeted value of urine pH must be higher than 7.0 [6, 48]. Alkalization accompanied by hydration has effectively prevented the recurrence of cysteine stones [49, 50].

Acetazolamide, a carbonic anhydrase inhibitor, inhibits the reabsorption of sodium bicarbonate through the proximal tubules, thus raising urine pH and potentially resulting in metabolic acidosis with prolonged use. Including acetazolamide in citrate therapy at night significantly raises urine pH in patients with cysteine and uric-acid stones, but half of these patients discontinue the drug due to side effects [51]. In addition, high urine pH may lead to calcium-phosphate stones [52, 53].

3.2. Specific treatments according to metabolic disorder

3.2.1. Hypercalciuria

3.2.1.1. Thiazide-type diuretics

Thiazide-type diuretics are especially indicated for normokalemic idiopathic hypercalciuria, which may be either absorptive or renal. Absorptive hypercalciuria may develop as three types: type 1, with direct absorption of calcium through the gastrointestinal system; type 2, with absorption of calcium associated with 1.25 dihydroxyvitamin D; or type 3, with renal calcium and phosphate absorption [54, 55]. Resorptive hypercalciuria is caused by primary hyperparathyroidism and develops with increased bone demineralization [54].
Thiazide-type diuretics act on the distal tubules, in which 10% of the sodium chloride is reabsorbed by a thiazide-sensitive Na+/Cl carrier [56]. Salt restriction during the use of thiazide-type diuretics decreases its effectiveness. The side effects of using thiazides have been reported as hypokalemia, hyperglycemia, hypercalcemia, and renal injury [57, 58]. Hypokalemia occurs with high doses [56]. Hyperglycemia may develop when thiazides are used for hypertension, but it has not been observed when they are used for hypercalciuria indications [59]. There is little evidence of renal injury with prolonged use of low or medium doses [56]. Children who develop hypercalcemia during therapy must be examined for underlying, overlooked hyperparathyroidism [58]. The initial dose of hydrochlorothiazide is 1 mg/kg. High doses are associated with side effects [60]. Starting with a dose of 0.5 mg/kg and then titrating based on urine calcium levels enables both effective treatment and avoidance of side effects [61]. However, in cases where high doses of hydrochlorothiazide are necessary, including Dent disease, close follow-up for complications is required [60].

In the presence of calcium-phosphate stones, the possibility of hyperparathyroidism and RTA should be investigated [7]. In cases of high calcium and phosphate levels, it may have brushite-type crystallization in a narrow pH range (6.5–6.8) [7]. Carbonate apatite is crystallized at pH 6.8 or higher and may present with infection stones or calcium-oxalate stones [7]. Hydrochlorothiazide is also effective on brushite stones [7]. However, patients with these require urine acidification rather than urine alkalization. Cranberry juice may be recommended for pediatric patients, because L-methionine cannot be used for them [6, 7].

In idiopathic hypercalciuria, decreased bone density may affect future bone health [62]. Thiazide-derived diuretics support bone density, even in patients with restricted calcium [63]. Studies have suggested that hydrochlorothiazide is beneficial to bone density in children with hypercalciuria, but this effect has been reported as limited in older children who are developing osteopenia [64, 65]. Controlled studies with larger populations are needed, but early hydrochlorothiazide treatment appears to be favorable for bone growth.

3.2.2. Hyperoxaluria

3.2.2.1. Pyridoxine

Pyridoxine is used for primary hyperoxaluria (PH) type 1. PH has three types: type 1, a deficiency of alanine glyoxylate aminotransferase; type 2, a deficiency of D-glycerate dehydrogenase; and type 3, a deficiency of 4-hydroxy 2-oxoglutarate aldolase [66].

In PH, due to the enzyme deficiency, glyoxylate cannot be converted into glycine in cofactors of pyridoxine (vitamin B6). Therefore, excessive oxalate is produced by the lactate dehydrogenase enzyme in the liver. Type 1 is the severest form, and accounts for 80% of PH cases [67]. Children with PH type 1 may develop nephrocalcinosis and end-stage renal failure in addition to calcium-oxalate stones. In contrast, in PH type 3, no end-stage renal failure has been reported [68]. If PH is suspected in pediatric patients, it may be diagnosed using urinary oxalate values that have been corrected for body area. In children with PH, the normal oxalate level in 24-hour urine is 0.45 mmol/1.73 m²/24-hour, and it is usually higher than 1 mmol/1.73 m²/24-hour. If the oxalate level in 24-hour urine is higher than 0.7 mmol/1.73 m²/24-hour in
repeated tests, genetic examination should be performed after excluding causes for secondary hyperoxaluria. If it is not possible to diagnose with genetic examination despite high suspicion, enzyme activity should be analyzed in a liver biopsy [69]. In patients diagnosed with PH type 1, pyridoxine therapy should be prescribed in addition to hydration and citrate therapy. In type 1 PH, pyridoxine therapy is effective in 50% of patients and decreases the urinary-oxalate level by more than 30% [70]. New studies suggesting multiple effects of pyridoxine indicate promising ways to treat patients who have not benefited from existing treatments [71]. The initial pyridoxine dose is 5 mg/kg, and depending on the response, it can be titrated to 20 mg/kg. Although rare, sensorial neuropathy may develop with high doses [72].

Hyperoxaluria may also develop due to causes that include inflammatory bowel disease, short-bowel syndrome, ethylene-glycol intoxication, and excessive intake of vitamin C. In patients with secondary hyperoxaluria, dietary oxalate and salt restrictions and alkalization therapy should be begun, and in resistant patients, pyridoxine therapy should be used [6]. The initial dose of pyridoxine may be 2–5 mg/kg/day, and it can be titrated to 8–10 mg/kg/day.

3.2.3. Hyperuricosuria

3.2.3.1. Allopurinol

Hyperuricosuria occurs when uric acid is higher than 10 mg/kg in 24-hour urine [6]. Urinary excretion of uric acid is high in infants [26]. In acidic urine, solubility of uric acid is decreased. This is more apparent when pH is lower than 5.8 [6]. Hyperuricosuria not only causes uric-acid stones but also plays a role in forming calcium-oxalate stones through epistaxis [31]. If hydration and alkalization fail, allopurinol could be begun, particularly in children who have hyperuricosuria with hyperuricemia. Allopurinol inhibits the xanthine dehydrogenase enzyme, thereby decreasing the concentration of uric acid and increasing the concentration of xanthine in the urine [26]. The pediatric dose is 10 mg/kg [6]. Skin rashes may be seen, and very rarely, allopurinol hypersensitivity syndrome (AHS) may develop [73]. AHS is a fatal side effect that also includes a rash (Stevens-Johnson syndrome, toxic epidermal necrosis), eosinophilia, leukocytosis, hepatitis, fever, and renal failure [73]. This fatal complication has no specific treatment other than termination of treatment and support therapy [73]. Therefore, it is very important to educate patients and families about symptoms and to make an early diagnosis. To prevent such complications, it may be useful to begin with a low dose and increase it [73].

Hypoxanthine guanine phosphoribosyl transferase (HPRT) is a purine metabolism enzyme. HPRT deficiency, the severest form of which is Lesch-Nyhan syndrome, may occur with neurologic symptoms, mental retardation, and nephropathy, and in the early stages of life, kidney stones [74]. Deficiency of glucose-6-phosphate dehydrogenase leads to hyperuricemia, increasing the intracellular phosphoribosyl pyrophosphate in type 1 [75]. In both of these metabolic diseases, allopurinol therapy is indicated for hyperuricemia and hyperuricosuria. In addition to metabolic diseases, myeloproliferative diseases may also cause hyperuricosuria, and in children with hyperuricosuria who develop new stones and for whom hydration and alkalization are insufficient, allopurinol may be begun at 10 mg/kg [6].
Furthermore, deficiency of adenosine phosphoribosyl transferase (APRT), a purine metabolism enzyme, converts adenine into 8-hydroxyadenine and xanthine dehydrogenase enzyme into 2,8-dihydroxyadenine (DHA) [76]. Transfer of DHA into the urine is high, and its solubility is low, even in alkaline urine, so DHA stones form. Alkalization therapy is not useful in such cases, and therapy must consist of 5–10 mg/kg of allopurinol and sufficient hydration [77].

Xanthinuria has two types: type 1 develops with a deficiency of xanthine dehydrogenase enzyme and type 2 develops with a deficiency of aldehyde oxidase enzyme [78]. These two types are differentiated using an allopurinol test [78]. In addition, xanthinuria may develop after Lesh-Nyhan syndrome is treated using allopurinol [79]. Xanthinuria has no specific treatment but responds well to hydration, urine alkalization, and reduction of dietary purine [80].

3.2.4. Cystine stones

3.2.4.1. Drugs containing thiol

Cystinuria is a genetic disease in which reabsorption of cysteine and other dibasic amino acids, including ornithine, arginine, and lysine, through the proximal tubules is impaired [81]. Cystinuria has two genetic types: type 1, which is caused by the SLC3A1 gene on the 2nd chromosome and type 2, which is caused by the SLC7A9 gene on the 19th chromosome [82]. Cystinuria is more common in Eastern Mediterranean populations [83]. Cysteine higher than 50 mg/1.73 m² in 24-hour urine is considered as a diagnostic for cystinuria [26]. Where hydration and alkalization fail, use of thiol-containing drugs is recommended [6]. Thiol forms a disulfide complex, which is soluble with cysteine and prevents formation of stones. Thiol-containing drugs are more effective on alkaline urine, and a study has demonstrated that dissolution in urine incubated with cysteine was low for the first 60 minutes when the pH was 6, but it was optimal when the pH was 8 [84]. However, no difference was found between pH 7 and 8 after either 60 minutes or 48 hours [84]. This indicates the importance of alkalization even when using thiol-containing drugs. However, a high urine pH may lead to phosphate crystallization; therefore, pH 7–7.5 appears to be the most appropriate target.

D-penicillamine is a chelating agent that contains thiol and increases cysteine dissolution by as much as 50-fold [85]. D-penicillamine may cause bone marrow suppression, proteinuria, skin eruptions on the neck and extremities, arthralgia, liver dysfunction, and febrile reaction [86]. Its use for metaphylaxis of cysteine stones is restricted by the fact that up to 86% of pediatric patients using it have developed side effects [87]. Although d-penicillamine use is not recommended in children, if it must be used, close follow-up for side effects is essential. In addition, to decrease side effects and increase tolerance, during the first week, the dose should be 5 mg/kg/day, and then it should be increased by 5 mg/kg/day, reaching 20 mg/kg/day at the end of four weeks [86]. Pyridoxine deficiency develops with long-term d-penicillamine therapy, so therapy should include pyridoxine [85].

Alfa mercaptopropionylglycine (AMG, thiopronin) has an effect similar to that of d-penicillamine but with fewer side effects [85]. The daily dose is 10–15 mg/kg [6]. The rate of treatment discontinuation is lower than that for d-penicillamine therapy [88]. Although thiopronin has fewer side effects than penicillamine, patients must be closely monitored for side effects, including fever, which often occurs during the first month, rash, bone marrow suppression,
and nephrotic syndrome, which improves when the drug is ceased [89, 90]. One uncontrolled study suggested that giving a low dose or a dose every other day was effective and further decreased the side effects [91]. Use of thiopronin is recommended for pediatric patients when hydration and alkalinization are not adequate to decrease cystinuria [6].

Adding captopril to cysteine makes the cysteine more than 200 times soluble in urine [86]. However, it lowers the concentration of captopril in the urine, making this treatment less effective than AMG or d-penicillamine [92, 93]. Case reports have shown that this treatment is effective in pediatric patients and has relatively few side effects, but some studies have also indicated the opposite [94–96]. The EAU’s pediatric urology guidelines do not recommend the treatment, but it may be considered when AMG cannot be used because of side effects or in children with hypertension and proteinuria [6].

3.2.5. Infection stones

Infection stones are stones of struvite, carbonate apatite, or ammonium urate. Urease-positive bacteria increase urinary bicarbonate and ammonium, making urine basic [7]. Unlike acidic stones, ammonium-urate stones form in basic environments and are associated with urinary tract infections [7]. In the case of infection stones, the carbonate-apatite form of calcium phosphate crystalizes at pH 6.8 or higher [7].

In metaphylaxis of infection stones, the primary objective is complete elimination of the stones. If a renal anomaly is causing stasis, it should be treated. Use of urease inhibitors is controversial, even in adult patients, due to their high rate of complications, and L-methionine for urine acidification is not recommended in children [6, 7]. Intake of cranberry juice may be recommended for urine acidification in pediatric patients. Antibiotic therapy and prophylaxis may be begun if required, along with urinary-culture follow-up.

4. Conclusions

Frequent recurrence of urinary stones after initial treatment makes metaphylaxis crucial in children. Suitable metaphylaxis must be preceded by complete metabolic evaluation. Increasing fluid intake and optimizing the diet are the first steps in urinary-stone metaphylaxis. When these measures are not sufficient, medical treatment must be added. Most recommendations for metaphylaxis in children are based on studies involving adults, and, therefore, more studies involving children are called for.

Author details

Onur Kaygısız

Address all correspondence to: onurkygsz@yahoo.com

Faculty of Medicine, Department of Urology, Uludağ University, Bursa, Turkey
References

[1] Abhishek, Kumar J, Mandhani A, Srivastava A, Kapoor R, Ansari MS. Pediatric urolithiasis: Experience from a tertiary referral center. Journal of Pediatric Urology. 2013 Dec;9(6 Pt A):825-830. DOI: 10.1016/j.jpurol.2012.11.003

[2] Lao M, Kogan BA, White MD, Feustel PJ. High recurrence rate at 5-year followup in children after upper urinary tract stone surgery. Journal of Urology. 2014 Feb;191(2):440-444. DOI: 10.1016/j.juro.2013.09.021.

[3] Elmacı AM, Ece A, Akın F. Pediatric urolithiasis: Metabolic risk factors and follow-up results in a Turkish region with endemic stone disease. Urolithiasis. 2014 Oct;42(5):421-426. DOI: 10.1007/s00240-014-0682-z

[4] Ertan P, Tekin G, Oger N, Alkan S, Horasan GD. Metabolic and demographic characteristics of children with urolithiasis in Western Turkey. Urological Research. 2011 Apr;39(2):105-110. DOI: 10.1007/s00240-010-0306-1

[5] Tekin A, Tekgul S, Atsu N, Bakkaloglu M, Kendi S. Oral potassium citrate treatment for idiopathic hypocitruria in children with calcium urolithiasis. Journal of Urology. 2002 Dec;168(6):2572-2574

[6] Tekgül S, Dogan HS, Erdem E, Hoebepke P, Kocvara R, Nijman R, et al. European Society Guidelines for Paediatric Urinary Stone Disease. Urology Limited Update March; EAU 2015. pp. 51-58

[7] Straub M, Strohmaier WL, Berg W, Beck B, Hoppe B, Laube N, 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 Journal of Urology. 2005;23(5):309-323. Epub 2005 Nov 29. Review.)

[8] Daudon M, Jungers P. Drug-induced renal calculi: Epidemiology, prevention and management. Drugs. 2004;64(3):245-275

[9] Matlaga BR, Shah OD, Assimos DG. Drug-induced urinary calculi. Reviews in Urology. 2003 Fall;5(4):227-231

[10] Chutipongtanate S, Thongboonkerd V. Ceftriaxone crystallization and its potential role in kidney stone formation. Biochemical and Biophysical Research Communications. 2011 Mar 18;406(3):396-402. DOI: 10.1016/j.bbrc.2011.02.053

[11] Herzog W, Deter HC, Fiehn W, Petzold E. Medical findings and predictors of long-term physical outcome in anorexia nervosa: A prospective, 12-year follow-up study. Psychological Medicine. 1997 Mar;27(2):269-279

[12] Komori K, Arai H, Gotoh T, Imazu T, Honda M, Fujioka H. A case of ammonium urate urinary stones with anorexia nervosa. Hinyokika Kiyo. 2000 Sep;46(9):627-629. Review. Japanese
[13] Leaf DE, Bukberg PR, Goldfarb DS. Laxative abuse, eating disorders, and kidney stones: A case report and review of the literature. American Journal of Kidney Diseases. 2012 Aug;60(2):295-298. DOI: 10.1053/j.ajkd.2012.02.337

[14] Bouquegneau A, Dubois BE, Krzesinski JM, Delanaye P. Anorexia nervosa and the kidney. American Journal of Kidney Diseases. 2012 Aug;60(2):299-307. DOI: 10.1053/j.ajkd.2012.03.019

[15] Pacifici GM. Clinical pharmacology of furosemide in neonates: A review. Pharmaceuticals (Basel). 2013 Sep 5;6(9):1094-1129. DOI: 10.3390/ph6091094

[16] Young TE, Mangum B, Neofax A. Manual of Drugs used in Neonatal Care. Cardiovascular. 23rd ed. Montvale, NJ, USA: Thomson Reuters; 2010. pp. 248-249

[17] Hufnagle KG, Khan SN, Penn D, Cacciarelli A, Williams P. Renal calcifications: A complication of long-term furosemide therapy in preterm infants. Pediatrics. 1982 Sep;70(3):360-363

[18] Chang HY, Hsu CH, Tsai JD, Li ST, Hung HY, Kao HA, Chang JH, Chung HY, Wang HK. Renal calcification in very low birth weight infants. Pediatrics and Neonatology. 2011 Jun;52(3):145-149. DOI: 10.1016/j.pedneo.2011.03.004

[19] Fink HA, Akornor JW, Garimella PS, MacDonald R, Cutting A, Rutks IR, Monga M, Wilt TJ. Diet, fluid, or supplements for secondary prevention of nephrolithiasis: A systematic review and meta-analysis of randomized trials. European Urology. 2009 Jul;56(1):72-80. DOI: 10.1016/j.eururo.2009.03.031.Review

[20] Nguyen NU, Dumoulin G, Henriet MT, Regnard J. Increase in urinary calcium and oxalate after fructose infusion. Hormone and Metabolic Research. 1995 Mar;27(3):155-158

[21] Lotan Y, Buendia Jiménez I, Lenoir-Wijnkoop I, Daudon M, Molinier L, Tack I, Nuijten MJ. Increased water intake as a prevention strategy for recurrent urolithiasis: Major impact of compliance on cost-effectiveness. Journal of Urology. 2013 Mar;189(3):935-939. DOI: 10.1016/j.juro.2012.08.254

[22] Alon US, Zimmerman H, Alon M. Evaluation and treatment of pediatric idiopathic urolithiasis-revisited. Pediatric Nephrology. 2004 May;19(5):516-520

[23] Ticinesi A, Nouvenne A, Maalouf NM, Borghi L, Meschi T. Salt and nephrolithiasis. Nephrology Dialysis Transplantation. 2016 Jan;31(1):39-45. DOI: 10.1093/ndt/gfu243

[24] Mattes RD, Donnelly D. Relative contributions of dietary sodium sources. The Journal of the American College of Nutrition 1991;10:383-393

[25] Tasian GE, Copelovitch L. Evaluation and medical management of kidney stones in children. Journal of Urology. 2014 Nov;192(5):1329-1336. DOI: 10.1016/j.juro.2014.04.108

[26] Copelovitch L. Urolithiasis in children: Medical approach. Pediatric Clinics of North America. 2012 Aug;59(4):881-896. DOI: 10.1016/j.pcl.2012.05.009
[27] von Unruh GE, Voss S, Sauerbruch T, Hesse A. Dependence of oxalate absorption on the daily calcium intake. Journal of the American Society of Nephrology. 2004 Jun;15(6):1567-1573

[28] Nouvenne A, Meschi T, Prati B, Guerra A, Allegri F, Vezzoli G, Soldati L, Gambaro G, Maggiore U, Borghi L. Effects of a low-salt diet on idiopathic hypercalciuria in calcium-oxalate stone formers: A 3-mo randomized controlled trial. Am J Clin Nutr. 2010 Mar;91(3):565-70. DOI: 10.3945/ajcn.2009.28614

[29] Curtin CO, King CG. The metabolism of ascorbic acid-1-C14 and oxalic acid-C14 in the rat. Journal of Biological Chemistry. 1955 Oct;216(2):539-548

[30] Jairath A, Parekh N, Otano N, Mishra S, Ganpule A, Sabnis R, Desai M. Oxalobacter formigenes: Opening the door to probiotic therapy for the treatment of hyperoxaluria. Scandinavian Journal of Urology. 2015 Feb 2:1-4

[31] Sarig S. The hyperuricosuric calcium oxalate stone former. Mineral and Electrolyte Metabolism. 1987;13(4):251-256

[32] Zuckerman JM, Assimos DG. Hypocitraturia: Pathophysiology and medical management. Reviews in Urology. 2009 Summer;11(3):134-144

[33] Adeva MM, Souto G. Diet-induced metabolic acidosis. Clinical Nutrition. 2011 Aug;30(4):416-421. DOI: 10.1016/j.clnu.2011.03.008

[34] Domrongkitchaiporn S, Stitchantrakul W, Kochakarn W. Causes of hypocitraturia in recurrent calcium stone formers: Focusing on urinary potassium excretion. American Journal of Kidney Diseases. 2006 Oct;48(4):546-554

[35] Heilberg IP, Goldfarb DS. Optimum nutrition for kidney stone disease. Advances in Chronic Kidney Disease. 2013 Mar;20(2):165-174. DOI: 10.1053/j.ackd.2012.12.001. Review

[36] Baia Lda C, Baxmann AC, Moreira SR, Holmes RP, Heilberg IP. Noncitrus alkaline fruit: A dietary alternative for the treatment of hypocitraturic stone formers. Journal of Endourology. 2012 Sep;26(9):1221-1226. DOI: 10.1089/end.2012.0092

[37] Goldfarb DS, Asplin JR. Effect of grapefruit juice on urinary lithogenicity. Journal of Urology. 2001 Jul;166(1):263-267

[38] Curhan GC, Willett WC, Rimm EB, Spiegelman D, Stampfer MJ. Prospective study of beverage use and the risk of kidney stones. American Journal of Epidemiology. 1996 Feb 1;143(3):240-247

[39] Hönow R, Laube N, Schneider A, Kessler T, Hesse A. Influence of grapefruit-, orange- and apple-juice consumption on urinary variables and risk of crystallization. British Journal of Nutrition. 2003 Aug;90(2):295-300

[40] Gettman MT, Ogan K, Brinkley LJ, Adams-Huet B, Pak CY, Pearle MS. Effect of cranberry juice consumption on urinary stone risk factors. Journal of Urology. 2005 Aug;174(2):590-594

[41] Kessler T, Jansen B, Hesse A. Effect of blackcurrant-, cranberry- and plum juice consumption on risk factors associated with kidney stone formation. European Journal of Clinical Nutrition. 2002 Oct;56(10):1020-1023
[42] Ferraro PM, Taylor EN, Gambaro G, Curhan GC. Caffeine intake and the risk of kidney stones. The American Journal of Clinical Nutrition. 2014 Dec;100(6):1596-1603. DOI: 10.3945/ajcn.114.089987

[43] Remer T, Dimitriou T, Manz F. Dietary potential renal acid load and renal net acid excretion in healthy, free-living children and adolescents. The American Journal of Clinical Nutrition. 2003 May;77(5):1255-1260

[44] Shang YF, Xu M, Zhang GN, Ouyang JM. Concave urinary crystallines: Direct evidence of calcium oxalate crystals dissolution by citrate in vivo. Bioinorganic Chemistry and Applications. 2013;2013:637617. DOI: 10.1155/2013/637617

[45] Batlle D, Haque SK. Genetic causes and mechanisms of distal renal tubular acidosis. Nephrology Dialysis Transplantation. 2012 Oct;27(10):3691-3704. DOI: 10.1093/ndt/gfs442. Review

[46] Berg C, Larsson L, Tiselius HG. Effects of different doses of alkaline citrate on urine composition and crystallization of calcium oxalate. Urological Research. 1990;18(1):13-16

[47] Sampath A, Kossoff EH, Furth SL, Pyzik PL, Vining EP. Kidney stones and the ketogenic diet: Risk factors and prevention. Journal of Child Neurology. 2007 Apr;22(4):375-378

[48] Claes DJ, Jackson E. Cystinuria: Mechanisms and management. Pediatric Nephrology. 2012 Nov;27(11):2031-2038. DOI: 10.1007/s00467-011-2092-6. Epub 2012 Jan 27. Review

[49] Izol V, Aridogan IA, Karsli O, Deger M, Satar N. The effect of prophylactic treatment with Shohl's solution in children with cystinuria. Journal of Pediatric Urology. 2013 Dec;9(6 Pt B):1218-1222. DOI: 10.1016/j.jpurol.2013.05.017

[50] Kizilöz H, Kaygisiz O, Çanakli F, Bilen CY, Erkan I, Tekgül S. The Effect of cystine level and urinary PH on the recurrence of cystine stones. Journal of Pediatric Urology. 2009 Apr;5(supp 1):s33

[51] Sterrett SP, Penniston KL, Wolf Jr JS, Nakada SY. Acetazolamide is an effective adjunct for urinary alkalization in patients with uric acid and cystine stone formation recalcitrant to potassium citrate. Urology. 2008 Aug;72(2):278-281. DOI: 10.1016/j.urology.2008.04.003

[52] Grases F, Zelenková M, Söhnel O. Structure and formation mechanism of calcium phosphate concretions formed in simulated body fluid. Urolithiasis. 2014 Feb;42(1):9-16. DOI: 10.1007/s00240-013-0611-6

[53] Kamel KS, Shafiee MA, Cheema-Dhadli S, Halperin ML. Studies to identify the basis for an alkaline urine pH in patients with calcium hydrogen phosphate kidney stones. Nephrology Dialysis Transplantation. 2007 Feb;22(2):424-431

[54] Bataille P, Fardellone P, Ghazali A, Cayrolle G, Hottelart C, Achard JM, Fournier A. Pathophysiology and treatment of idiopathic hypercalciuria. Current Opinion in Rheumatology. 1998 Jul;10(4):373-388

[55] Srivastava T, Schwaderer A. Diagnosis and management of hypercalciuria in children. Current Opinion in Pediatrics. 2009 Apr;21(2):214-219. DOI: 10.1097/MOP.0b013e3283223db7. Review
[56] Ellison DH, Loffing J. Thiazide effects and adverse effects: Insights from molecular genetics. Hypertension. 2009 Aug;54(2):196-202. DOI: 10.1161/HYPERTENSIONAHA.109.129171

[57] Frenkel NJ, Vogt L, De Rooij SE, Trimpert C, Levi MM, Deen PM, van den Born BJ. Thiazide-induced hyponatraemia is associated with increased water intake and impaired urea-mediated water excretion at low plasma antidiuretic hormone and urine aquaporin-2. Journal of Hypertension. 2015 Mar;33(3):627-633. DOI: 10.1097/HJH.0000000000000423

[58] Wermers RA, Kearsns AE, Jenkins GD, Melton LJ. Incidence and clinical spectrum of thiazide-associated hypercalcemia. 3rd. American Journal of Medicine. 2007 Oct;120(10):911.e9-15. Epub 2007 Apr 16

[59] Singh P, Knoedler JJ, Krambeck AE, Lieske JC, Bergstralh EJ, Rule AD. Thiazide diuretic prophylaxis for kidney stones and the risk of diabetes mellitus. Journal of Urology. 2014 Dec;192(6):1700-1704. DOI: 10.1016/j.juro.2014.06.078

[60] Blanchard A, Vargas-Poussou R, Peyrard S, Mogenet A, Baudouin V, Boudailliez B, Charbit M, Deschesnes G, Ezzhair N, Loirat C, Macher MA, Niaudet P, Azizi M. Effect of hydrochlorothiazide on urinary calcium excretion in dent disease: An uncontrolled trial. American Journal of Kidney Diseases. 2008 Dec;52(6):1084-1095. DOI: 10.1053/j.ajkd.2008.08.021

[61] Choi JN, Lee JS, Shin JI. Low-dose thiazide diuretics in children with idiopathic renal hypercalciuria. Acta Paediatrica. 2011 Aug;100(8):e71-e74. DOI: 10.1111/j.1651-2227.2011.02191.x

[62] Zerwekh JE. Bone disease and hypercalciuria in children. Pediatric Nephrology. 2010 Mar;25(3):395-401. DOI: 10.1007/s00467-009-1338-z

[63] Pak CY, Heller HJ, Pearle MS, Odvina CV, Poindexter JR, Peterson RD. Prevention of stone formation and bone loss in absorptive hypercalciuria by combined dietary and pharmacological interventions. Journal of Urology. 2003 Feb;169(2):465-469

[64] Moreira Guimarães Penido MG, de Sousa Tavares M, Campos Linhares M, Silva Barbosa AC, Cunha M. Longitudinal study of bone mineral density in children with idiopathic hypercalciuria. Pediatric Nephrology. 2012 Jan;27(1):123-130. DOI: 10.1007/s00467-011-1952-4

[65] García-Nieto V, Monge-Zamorano M, González-García M, Luis-Yanes MI. Effect of thiazides on bone mineral density in children with idiopathic hypercalciuria. Pediatric Nephrology. 2012 Feb;27(2):261-268. DOI: 10.1007/s00467-011-1987-96

[66] Lorenzo V, Torres A, Salido E. Primary hyperoxaluria. Nefrologia. 2014 May 21;34(3):398-412. DOI: 10.3265/Nefrologia.pre2014.Jan.12335.[Article in English, Spanish]

[67] Fargue S. Factors influencing clinical outcome in patients with primary hyperoxaluria type 1. Kidney International. 2014 Dec;86(6):1074-1076. DOI: 10.1038/ki.2014.280

[68] Cochot P, Rumsby G. Primary hyperoxaluria. The New England journal of Medicine. 2013 Aug;369(7):649-658. DOI: 10.1056/NEJMra1301564. Review
[69] Milliner DS. The primary hyperoxalurias: An algorithm for diagnosis. American Journal of Nephrology. 2005 Mar–Apr;25(2):154-160

[70] Hoyer-Kuhn H, Kohbrok S, Volland R, Franklin J, Hero B, Beck BB, Hoppe B. Vitamin B6 in primary hyperoxaluria I: First prospective trial after 40 years of practice. Clinical Journal of the American Society of Nephrology. 2014 Mar;9(3):468-477. DOI: 10.2215/CJN.06820613

[71] Fargue S, Rumsby G, Danpure CJ. Multiple mechanisms of action of pyridoxine in primary hyperoxaluria type 1. Biochimica et Biophysica Acta. 2013 Oct;1832(10):1776-1783. DOI: 10.1016/j.bbadis.2013.04.010

[72] Cochat P, Hulton SA, Acquaviva C, Danpure CJ, Daudon M, De Marchi M, et al. OxalEurope. Primary hyperoxaluria Type I: Indications for screening and guidance for diagnosis and treatment. Nephrology Dialysis Transplantation. 2012 May;27(5):1729-1736. DOI: 10.1093/ndt/gfs078

[73] Stamp LK, Taylor WJ, Jones PB, Dockerty JL, Drake J, Frampton C, et al. Starting dose is a risk factor for allopurinol hypersensitivity syndrome: A proposed safe starting dose of allopurinol. Arthritis & Rheumatology. 2012 Aug;64(8):2529-2536. DOI: 10.1002/art.34488

[74] Torres RJ, Puig JG. Hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency: Lesch-Nyhan syndrome. Orphanet Journal of Rare Diseases. 2007 Dec 8;2:48. Review

[75] Nicoletta JA, Lande MB. Medical evaluation and treatment of urolithiasis. Pediatric Clinics of North America. 2006 Jun;53(3):479-491

[76] Sahota AS, Tischfield JA, Kamatani N, Simmonds HA. Adenine phosphoribosyltransferase deficiency and 2, 8-dihydroxyadenine lithiasis. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Vogelstein B, Childs B, editors. The Metabolic and Molecular Bases of Inherited Disease. 8th ed. New York, NY: McGraw-Hill; 2001. pp. 2571-2584

[77] Harambat J, Bollée G, Daudon M, Ceballos-Picot I, Bensman A; APRT Study Group.. Adenine phosphoribosyltransferase deficiency in children. Pediatric Nephrology. 2012 Apr;27(4):571-579. DOI: 10.1007/s00467-011-2037-0

[78] Gok F, Ichida K, Topaloglu R. Mutational analysis of the xanthine dehydrogenase gene in a Turkish family with autosomal recessive classical xanthinuria. Nephrology Dialysis Transplantation. 2003 Nov;18(11):2278-2283

[79] Brock WA, Golden J, Kaplan GW. Xanthine calculi in the Lesch-Nyhan syndrome. Journal of Urology. 1983 Jul;130(1):157-159

[80] Gargah T, Essid A, Labassi A, Hamzaoui M, Lakhoua MR. Xanthine urolithiasis. Saudi Journal of Kidney Diseases and Transplantation. 2010 Mar;21(2):328-331

[81] Mattoo A, Goldfarb DS. Cystinuria. Seminars in Nephrology. 2008 Mar;28(2):181-191. DOI: 10.1016/j.sennephrol.2008.01.011

[82] Goodyer P, Boutros M, Rozen R. The molecular basis of cystinuria: An update. Experimental Nephrology. 2000 May–Jun;8(3):123-127
Saravakos P, Kokkinou V, Giannatos E. Cystinuria: Current diagnosis and management. Urology. 2014 Apr;83(4):693-699. DOI: 10.1016/j.urology.2013.10.013. Review

Asplin DM, Asplin JR. The Interaction of thiol drugs and urine pH in the treatment of cystinuria. Journal of Urology. 2013 Jun;189(6):2147-2151. DOI: 10.1016/j.juro.2012.12.031

Biyani CS, Cartledge JJ. Cystinuria-diagnosis and management. EAU-EBU Update Series. 2006;4:175-183

DeBerardinis RJ, Coughlin 2nd CR, Kaplan P. Penicillamine therapy for pediatric cystinuria: Experience from a cohort of American children. Journal of Urology. 2008 Dec;180(6):2620-2623. DOI: 10.1016/j.juro.2008.08.057

Nihon Asanuma H, Nakai H, Takeda M, Shishido S, Kawamura T, Nagakura K, Yamafuji M. Clinical study on cystinuria in children--the stone management and the prevention of calculi recurrence. [Article in Japanese] Hinyokika Gakkai Zasshi. 1998 Sep;89(9):758-765

Pak CY, Fuller C, Sakhaee K, Zerwekh JE, Adams BV. Management of cystine nephrolithiasis with alpha-mercaptopropionylglycine. Journal of Urology. 1986 Nov;136(5):1003-1008

Tasic V, Lozanovski VJ, Ristoska-Bojkovska N, Sahpazova E, Gucev Z. Nephrotic syndrome occurring during tiopronin treatment for cystinuria. European Journal of Pediatrics. 2011 Feb;170(2):247-249. DOI: 10.1007/s00431-010-1315-3

Zheng Z, Xue Y, Jia J, Wei L, Shang W, Lin S. Tiopronin-induced membranous nephropathy: A case report. Renal Failure. 2014 Oct;36(9):1455-1460. DOI: 10.3109/0886022X.2014.926754

Berio A, Piazzal. Prophylaxia of cystine calculosis by alpha-mercaptopropionylglycine administered continuously or every other day. Boll Soc Ital Biol Sper. 2001 Apr–Jun;77(4-6):35-41

Goldfarb DS, Coe FL, Asplin JR. Urinary cystine excretion and capacity in patients with cystinuria. Kidney International. 2006 Mar;69(6):1041-1047

Chow GK, Streem SB. Medical treatment of cystinuria: Results of contemporary clinical practice. Journal of Urology. 1996 Nov;156(5):1576-1578

Printza N, Koukourgianni F, Papathanasiou A, Augoustides-Savvopoulou P, Papachristou F. Efficacy of captopril therapy in cystinuria lithiasis. A case report. Hippokratia. 2007 Apr;11(2):83-85

Conde Sánchez JM, Reina Ruiz C, Amaya Gutiérrez J, Camacho Martínez E, Vega Toro P, García Pérez M. Cystine calculi. Prevention with captopril. Clinical case. [Article in Spanish] Actas Urológicas Españolas. 2000 Feb;24(2):190-196

Seyedzadeh A, Mamtaz HE, Moradi MR, Moradi A. Pediatric cystine calculi in west of Iran: A study of 22 cases. Urology Journal. 2006 Summer;3(3):134-137