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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 hypercalcemia 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 semiopaque [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/m^{2}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 $(mEq/d) = 0.49 \times protein\ (g/d) + 0.037 \times phosphorus\ (mg/d) - 0.021 \times potassium\ (mg/d) - 0.026 \times magnesium\ (mg/d) - 0.013 \times calcium\ (mg/d)$ [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 crystalized 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 m^2/24-hour, and it is usually higher than 1 mmol/1.73 m^2/24-hour. If the oxalate level in 24-hour urine is higher than 0.7 mmol/1.73 m^2/24-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 m^2 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 bonemarrow 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 alkalization 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.

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