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EDITORIAL

Pediatric primary urolithiasis: Symptoms, medical management and prevention strategies

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Abstract

In the past few decades pediatric urolithiasis has become more frequent. The reason for this increase is not completely clear but has been attributed to changes in climate, nutritional habits and possibly other environmental factors. Although less frequent than adult stone disease, urolithiasis in the pediatric age group is also related to significant morbidity, particularly since stones tend to recur, and, thus, should not be underestimated. Most children with idiopathic stone disease have an underlying metabolic abnormality substantiating the importance of metabolic evaluation already following initial diagnosis of urolithiasis. Identification of the metabolic abnormality allows for more specific prescription of non pharmacological and pharmacological interventions aimed at preventing recurrent stone formation. A better understanding of the causes of kidney stone disease will provide better strategies for stone prevention in children.

Key words: Urolithiasis; Hypercalciuria; Cystinuria; Hyperoxaluria; Treatment; Prevention

Core tip: In the past few decades pediatric urolithiasis has become more frequent. The reason for this increase is not completely clear. Although less frequent than adult stone disease, pediatric urolithiasis is also related to significant morbidity, particularly since stones tend to recur. Most children with idiopathic stone disease have an underlying metabolic abnormality. Identification of the metabolic abnormality allows for more specific prescription of non pharmacological and pharmacological interventions aimed at preventing recurrent stone formation. A better understanding of the causes of kidney stone disease will provide better

strategies for stone prevention in children.

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INTRODUCTION

Urolithiasis (UL) is a worldwide problem and is the end product of a multifactorial process. It affects children of all ages and recurrence is a striking feature. No technique of calculi removal diminishes or alters this recurrence morbidity that in pediatric patients is directly related to surgical interventions and morphological changes resulting from possible obstructions of the urinary tract as well as to their clinical manifestations.

The incidence, composition and clinical characteristics of urinary calculi in children vary in relation to geographical location and historical periods. This variation is related to climate, genetic and dietary factors and socio-economical factors[1-3].

Recent decades studies have shown an increased incidence of kidney stones in adults[4-8]. This same trend has also been observed in children[9-14], and possibly results from increased attention to the diagnosis of UL, the routine evaluation with ultrasonography (USG) in children with specific or nonspecific symptoms, and changes in socio-economic conditions and dietetic habits of the pediatric population. However, the true incidence of pediatric UL remains unknown due to the multiplicity of etiopathogenic factors, unspecific clinical picture and lack of studies with appropriate epidemiological design. Studies conducted in different areas of the globe showed variation regarding gender and age. Sas *et al*[11] in South Carolina, United States, showed that the incidence of UL in children under 18 years was 7.9/100000 in 1996 and 18.5/100000 in 2007, higher in girls *vs* boys, and more prevalent in adolescents. In Japan, Yasui *et al*[5] showed an incidence of 17.7/100000 in males and 12.4/100000 in females in children and adolescents between 10 and 19 years of age. In Iceland, Edvardsson *et al*[15] reported that the incidence in patients younger than 18 years was 5.6/100000 on the basis of 26 new diagnoses of UL during a 6-year period among a national population of approximately 78000 children. VanDervoort *et al*[9] demonstrated that pediatric UL increased almost five times over the last decade in United States. Dwyer *et al*[13] reported that the incidence of pediatric UL in Minnesota, United States, increased from 13/100000 between 1984-1990 to 36/100000 between 2003-2008. Even in the United States, 1/685 pediatric hospitalizations are motivated by urinary calculi and over 50% are under 13 years-old individuals[10]. In 2013, Penido *et al*[14] demonstrated that the annual incidence of primary pediatric UL *per* 1000 renal clinic visits tripled from 1999 to 2010 in a children's hospital in the Midwestern United States. Data from Croatia showed that UL was responsible for 2.5/1000 pediatric hospitalizations, and its overall incidence rate in children under 18 years in 2011 was 6.5/100000[16].

UL is multifactorial and different factors are involved in its genesis, working in an interrelated way: infectious, anatomical, epidemiological, climatic, socioeconomic, dietary, genetic and metabolic. Some medications are also associated with higher risk for stone formation and among them sulfadiazine, ceftriaxone, topiramate, indinavir, triamterene, furosemide, steroids and vitamin D[17]. These risk factors, along with the physical and physiological changes in urine alter the balance between promoter elements, aggregation inhibitors and growth of crystals, resulting in the formation of stones. The evaluation of risk factors and calcium oxalate calculi formation may be evaluated through methods such as the BONN-Risk Index. This index reflects an individual balance between the promoters and inhibitors of the crystallization processes ongoing in the whole native urine[18,19]. This method is simple, cost-effective and provides accurate results. Porowski *et al*[20] showed that an increased Bonn-RiskIndex reflects the risk of calcium oxalate crystallization and may indicate early metabolic disorders leading to urolithiasis in children and adolescents.

Although various aspects of the UL have not yet explained, it is known that hypersaturation of urine is indispensable for the formation of urinary stones. Therefore, crystallization starts when the urine is supersaturated for a particular solute. If the solution is unsaturated, crystals are not formed[3]. The supersaturation depends on the ionic strength, abnormalities of the urinary pH, decreased urine volume, inability of crystallization inhibitors (citrate, magnesium, pyrophosphate, nephrocalcin, glycosaminoglycans, *etc*.) and states of hyperexcretion of calcium, uric acid, phosphorus, oxalate and cystine[3].

At this point, is necessary to mention the Randall plaque. It initially forms at the basement membrane of the thin loops of Henle before expanding to the interstitium. Randall plaque's formation has been established as an integral part of idiopathic calcium oxalate stone disease[21]. Bouchireb *et al*[22] described 25 pediatric cases of urolithiasis and Randall plaques, pointing to a prevalence of approximately 3%.

UL in children and adolescents is associated with metabolic abnormalities identified in 30% to 84% of the cases[14,23-25]. Idiopathic hypercalciuria is the most prevalent metabolic disorder in pediatric patients[9-12,14,23-25]. Besides hypercalciuria, hypocitraturia is also common and is the second most prevalent metabolic disorder in childhood UL[9,26-29]. Idiopathic hypocitraturia may present as isolated or in association with hypercalciuria, secondary to chronic diarrhea, diuretic-induced hypokalemia, renal tubular acidosis and predisposes to UL[29,30]. Less often is hyperuricosuria,

absorptive hyperoxaluria, cystinuria, and hypomagnesiuria[14,23,24].

The association between idiopathic hypercalciuria and reduced bone mineral density has been described in adult patients[31-35] and in children[36-46]. The loss of bone mass or unsuitable gain can be harmful to growth of children, because the peak bone mass occurs in childhood and at a highest rate during adolescence[47,48]. This process should occur without interference for an individual to achieve his/her optimal bone mass. Anything affecting continually a child's bone metabolism could increase the possibility of osteoporosis and fractures during adulthood[49-51]. However, alterations in childhood bone mass acquisition may not affect bone mass many decades later in late adulthood because there is a homeostatic system that tends to return to a set point after any transient perturbation[52]. Thus, workup of idiopathic hypercalciuria necessarily involves the investigation of bone mineral metabolism and the characterization of the profile of bone changes, so the physician can act objectively in prevention and treatment[40,42,43,53].

Obesity associated with metabolic syndrome is a known risk factor for UL in adults, however, this association is not well established in pediatric patients. Kieran *et al*[54] collected obesity related data from 134 patients with urinary calculi. No difference regarding stone properties was observed when BMI was considered. Another study (by Dwyer *et al*[13]) confirmed that no tendency towards obesity was associated with stone formers. This tendency was also described by Routh *et al*[12], where no different pattern of nutritional status in both pediatric stone forming and the normal population was observed. A reasonable explanation for the different nutritional trends between lithiasic pediatric patients and adults rely probably on the distinct lithogenic profiles. Uric acid stones are more common in obese adults, whereas this etiology is relatively scarce in children[7]. Stones due to hypercalciuria are not linked to obesity and can therefore explain this particularity[13,14].

Epidemiological studies have shown that diet has a major role in the pathogenesis of UL[24,30]. Diets low in animal protein but rich in cereals contribute to formation of endemic bladder stones in children[30,55]. Moreover, a high intake of animal protein predisposes hyperexcretion of uric acid, calcium, oxalate, a hypoexcretion of citrate and reduces urinary pH, all favoring the formation of calcium oxalate calculi[30]. The association between urinary sodium concentration and the calcium excretion and, consequently, the relationship between the sodium content of the diet and hypercalciuria has been described[17,56-59]. In developed countries, high consumption of processed foods far exceeds the physiological sodium needs[57]. A study showed that chloride sodium intake induces mild metabolic acidosis and may impair bone mass, as could be a risk factor for the formation of calculi[60]. On the other hand, the high potassium intake has an inverse effect on urinary calcium, *i.e.*, reduces the excretion of urinary calcium[17,56].

The clinical and metabolic pattern of pediatric UL has changed in recent years. Thus, specific and detailed diagnostic tests are required for each child or adolescent presenting renal calculus, even if unique. Considering that every pediatric patient is metabolically active, diagnostic steps should be directed to elucidate the pathophysiology of UL in order to prevent recurrence and reduce morbidity.

SIGNS AND SYMPTOMS

A pediatric patient can be considered acute due to a stone in the ureter, or may be diagnosed as an incidental finding of an intrarenal or intravesical stone, during workup imaging in the abdomen for any other reason. In adult patients, the most frequent clinical presentation is the classical renal colic caused by displacement of calculi or clots in the urinary tract. This clinical presentation is also observed in adolescents, however, abdominal pain is the main complaint in school children[61]. Lack of specificity related to localized pain is typical of lithiasic infants and preschool children[61]. Gross or microscopic hematuria and uncharacteristic abdominal pain are much more prevalent than the classic renal colic, which appearing in only 10% to 14% of all pediatric cases[62]. General manifestations such as nausea, vomiting, anorexia and malaise may be present.

As aforementioned, hematuria, flank or abdominal pain as well as urinary tract infection (UTI) are the most common clinical presentations. Gross or microscopic hematuria appears in 30% to 55% of all pediatric UL[9,63,64] and may remain for some time before the stone appears. Recurrent UTI or unexplained sterile pyuria should raise the level of suspicion for UL and generally should lead to the suspicion of urolithiasis in younger children[64-66]. Some authors have reported that about 10% of pediatric UL have signs and symptoms of lower urinary tract dysfunction (nocturnal and/or diurnal enuresis, urgency and/or urinary incontinence, suprapubic or urethral pain)[9,67,68]. Although the pediatric UL could have many different signs and symptoms at clinical onset, long time intervals without urinary complaints may be observed in these patients. Authors refer that 15% to 25% of children with UL, specially the younger ones, are asymptomatic and require more attention[9,63].

Lower urinary tract symptoms, *i.e.*, dysuria, urine retention, enuresis, urinary incontinence and polakiuria may be associated with distal displacement of calculi. Excessive manipulation of genitalia in preschool children may be an early sign of urethral lithiasis. Urethral obstruction due to calculi migration may be even palpable in infants. This may not allow the urine flux, resulting in pain[64].

MANAGEMENT OF ACUTE PEDIATRIC UL

Laboratory and imaging tests are needed to confirm

the diagnosis. The tests performed in the acute phase are: urine routine, bacterioscopy of uncentrifuged urine, urine culture and antibiogram, plain abdominal radiography (Rx) and kidney and urinary tract USG. Usually, blood tests are not required, however, in cases with suspected acute pyelonephritis, a complete biochemical evaluation should be performed to appropriate patient monitoring and evaluation of the severity of this clinical condition.

USG of the urinary tract usually suffices regarding diagnosis. Its main advantages include lack of exposure to radiation and potential adverse effects of contrast media, *i.e.*, in computed tomography (CT) and intravenous pyelography. These, however, are indicated in specific cases in which USG was not sufficient for a clinical decision concerning the intervention. The need of sedation is another disadvantage of CT in pediatric patients[64,69]. Calculi migration may also be followed by sequential USG, which is another advantage of this method[64]. Although the noncontrast CT scanning is considered the gold standard test for the UL diagnostic, it is a costly procedure and not always available. When obstruction is a concern or if anatomic details are necessary, the use of contrast agents may be used.

Type and stone dimension are directly related to success in diagnosing urinary stones and their position within the urinary tract. Diagnosis of small calculi depends on operator experience, but even a lithos with a diameter of just 2 mm can be observed and its position correctly described by experienced professionals[64].

Urinary stones migrating within the renal collecting system can cause pain or infection in a partially or completely obstructed urinary tract. Pain is intense and requires immediate and effective care. It is due to stimulation of receptors during dilatation of the urinary system and release of pain mediators through to local irritation and swelling of the wall of the renal pelvis or ureter. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) may be indicated as first choice, due to their higher benefits in this situation. Ureteropelvic consequences of the acute attempt to eliminate stones, such as ureteral oedema, increased peristalsis and pelvic pressure, may be effectively alleviated by nonsteroidal anti-inflammatory drugs through inhibition of prostaglandin synthesis. Hospital readmissions and new pain episodes may be avoided through these drugs, but time until complete elimination or even the likelihood of stone passing appears to be unaffected[70]. During its use, renal function should be monitored due to the risk of nephrotoxicity. Other antispasmodic and/or analgesic drugs that could be used for this acute pain control are: n-scopolamine butylbromide, amitriptyline, calcium channel blockers, steroids, morphine and analogues used in cases of intractable pain and alpha-1 blockers (*e.g.*, tamsulosin). The direct effect of alpha-1 blockers on pain is still controversial, but it is probably related to relief of ureteral spasm and promotion of stone expulsion[71].

During the acute phase, hydration should be increased after the diagnosis of a migrating calculus, considering it may be eliminated. The increased urine flow will be guaranteed by oral or parenteral hydration in cases with severe vomiting, diarrhea or lack of oral acceptance.

Adequate urinary flow is essential to prevent supersaturation of calcium oxalate and phosphate as well as uric acid. Urine flow equal to or higher than 1 mL/kg was shown by Lande *et al*[72] to be efficacious as protector against kidney stone formation. This water intake should be distributed throughout the 24 h, and should not exceed two liters. Clinical, laboratory and imaging evaluation should be done systematically at the patient with a migrating calculus. This interval depends on the severity of the clinical picture. The patient should be instructed to observe the elimination of the stone, because it may occur even without pain. About 60%-70% of calculi will be spontaneously eliminated and the size and characteristics of the surface limit their passage. The waiting period for stone migration without affecting the kidney function is six weeks[73,74]. After this period, it is advisable the referral to an urologist.

UL's presence does not necessarily imply surgical removal and there are criteria that help the decision. A surgical approach may be considered in cases of intractable pain, obstruction or associated infection. Indications for calculi removal in the proximal ureter include: calculi with a diameter > 5 mm; calculi with diameter < 4 mm associated with complete obstruction, urosepsis, solitary kidney, renal function deterioration, intractable symptoms, and no migration of the calculus for six weeks. In cases with involvement of the distal ureter, the indications for surgical removal of the calculus are: calculi with diameter > 7 mm; calculi with diameter < 6 mm associated with complete obstruction, urosepsis, solitary kidney, renal function deterioration, intractable symptoms, and no migration for six weeks. Therefore, the management of the stone is related to its location and its effect on the kidneys. Therapeutic options for stones that do not progress include: extracorporeal shockwave lithotripsy (ESWL), endoscopic lithotripsy with ultrasound, and percutaneous nephrolithotomy and open pyelolithotomy. ESWL can be used for treatment of children with stones and is safe with minimal complications[75,76].

Recently, Long and Srinivasan showed a significant improvement in management of pediatric UL with the miniaturization of both ureteroscopes and percutaneous nephrolithotomy equipment. These new technology possibilities have facilitated the access to the entirety of the urinary tract and have made ureteroscopy a first-line therapy option along with shock-wave lithotripsy for kidney and ureteral pediatric stones[77]. Nevertheless, larger studies with long follow-up time are required.

MANAGEMENT OF NON-ACUTE PEDIATRIC UL

After resolution of the acute phase, considering stone

elimination or removal by any technique, the pediatric patient will be conducted to the metabolic evaluation. All pediatric patient is metabolically active and, as already mentioned, rates of metabolic abnormalities in pediatric stone formers have been quoted as 30% to 84% of all cases[14,23-25]. The high recurrence rate is considered a major issue in pediatric urolithiasis. Lack of treatment results in a 50% recurrence rate within 7 years after the first colic episode[71,78]. Milliner and Murphy reported that 221 children have developed one or more kidney stones in mean follow-up of 59 mo[79]. Schwarz *et al*[80] showed a recurrence rate of UL in children equal to adults. Whereas all pediatric patients are metabolically active and that the recurrence rate is high, the metabolic study is always indicated in the pediatric UL.

All evaluations should be performed at least one month after diagnosis of the stone(s) while participants were asymptomatic and on their usual diet, normal fluid intake and physical activities[14,64]. In order to preserve the 24-h urinary sample should be used[81,82]. Pediatric metabolic testing should consist of: two 24-h urine collections analyzed for total volume, creatinine, calcium, phosphate, citrate, sodium, potassium, uric acid, oxalate; one venous blood sample analyzed for creatinine, calcium, phosphorus, uric acid, magnesium, sodium, chlorine, potassium, bicarbonate and blood gases; one random urine for urinalysis and pH. This criterion is similar to "The American Urological Association Guideline for medical management of kidney stones in adults"[83].

An adequate 24-h urine collection may be impracticable in patients without sphincter control. Random urine quantification and its proportion per mg of urine creatinine may allow the identification of the metabolic abnormality[64]. The following analytes should be quantified: oxalate, sodium, potassium, magnesium, uric acid, phosphate, citrate and calcium[64]. Qualitative determination of cystine through the nitroprusside test is acceptable, since the sensibility of the test is near to the level accepted as the limit for cystinuria. Amino acids chromatography remains, however, the gold standard for the diagnosis. When a stone is available, clinicians should obtain a stone analysis at least once. Stone composition of a single element is the exception, leading to the need of determination of the multiple components of the calculus. Despite the possibility of quantification of small amounts of a constituent (less than 1 mg, *i.e.*,) through infrared spectroscopy or X-ray diffraction, the exact stone analysis is prone to errors[64].

The metabolic diagnosis will enable appropriate treatment. Therefore, this will result in preventing the formation of new and growth of existing stones, inducing the patient to metabolic inactivation. A small percentage of pediatric patients forming urinary stones presents no metabolic abnormality[14]. Table 1 shows abnormal values for the excretion of various substances[17,81]. Interruption of the growth process involving preexisting calculi as well as development of new ones should be the goal of the medical treatment. Identification of the underlying metabolic cause, adequate treatment with supplements (potassium citrate), drugs (thiazides) and dietary modification mean prevention, and all these measures together are assigned as metaphylaxis.

To date there is no known medical treatment to determine the healing of UL. Those existing are directed to restore the biochemical and urinary physical chemistry. The UL treatment consists of long-term general measures (hydration, nutrition, physical activity) and specific measures (pharmacological intervention). Free urinary flux and adequate hydric ingestion compose the mainstay of urine supersaturation avoidance. It must be ensured a urinary flow at least 1.0 mL/kg per hour to reduce the urinary concentration[72] but ideally 2.0 to 3.0 mL/kg per hour. If there are higher expenses (insensitive and sweating loss), there should be an increase of this intake. The amount of liquid intake should be distributed throughout the day for good and constant urinary flow maintenance. About half of net quantity must be water and the other half, can be chosen by the patient (juices, teas, *etc*.). Hydric ingestion is well bellow the desired range in the vast majority of children with urolithiasis[56]. Beverage constituents should be monitored, since they can act as pro-lithiasic beverages (apple and grapefruit juice)[84] or anti-lithiasic (coffee, tea and alcoholic beverages)[84,85]. The reason for those associations is unknown.

The use of soda based beverages and urolithiasis is controversial[84,85]. Studies in adult populations showed no relation, but the discontinuation of this kind of drink was described as protective against stone recurrence in others, particularly those containing phosphoric acid[86]. For children it would be appropriate to allow the use of soda drinks only in special occasions. Severe dietary restrictions are contraindicated. First because they can hinder adherence to treatment; second, because they can determine nutritional deficiencies that may be more significant than the UL *per se* (reduced bone mineral density, height and weight loss, multiple vitamin deficiency, other). The diet should be corrected and appropriate to the child or adolescent's needs and recommended normal diet for calcium, calories and proteins according to RDA.

The ideal daily intake of sodium varies according to age: 1.2 g for 4-8 years old children, 1.5 g for those aged 9-18 years. The corresponding upper limits are 1.9 g and 2.3 g, above which health risk may be attributable[87]. Potassium is mostly provided as dairy products, vegetables and fruits. Its optimal recommendations also vary according to age: 3.8 for 4-8 years old children and 4.5 g for those between 9 and 18 years[87]. This is roughly equivalent to 3 units a day.

Monitoring of adequate ingestion of these elements can be achieved through determination of urine Na/K ratio, which should be under 2.5[88]. Higher ingestion of sodium-containing food is associated with increased natriuria, which can determine hypercalciuria, a stone predisposing condition[88]. All patients with hypercalciuria should have the Na/K ratio checked and

Table 1 Normal values for random urine and 24-h urine factors for children and adolescents

	24-h urine	Random urine corrected by creatinine		Random urine factored for GFR
Volume	⩾ 1.0 mL/kg per hour			
Creatinine	2 to 3 yr: 6 to 22 mg/kg > 3 yr: 12 to 30 mg/kg			
Calcium	< 4.0 mg/kg (0.10 mmol/kg)	Age 0-6 mo 6-12 mo 1-2 yr 2-18 yr	mg/mg; mmol/mmol < 0.80; < 2.24 < 0.60; < 1.68 < 0.40; < 1.12 < 0.21; < 0.56	< 0.10
Citrate	⩾ 400 mg/g creatinine	⩾ 0.28 (mmol/L/mmol/L)		> 0.18 (mg/L/mg/L)
Calcium/Citrate	< 0.33	< 0.33		
Na/K	⩽ 3.5	⩽ 3.5		
Uric acid	< 815 mg/1.73 m^2 BS	< 0.65		< 0.56 mg < 0.03 mmol
Cystine	< 60 mg/1.73 m^2 BS	< 0.02 (mg/mg) < 0.01 (mmol/mmol)		
Magnesium	> 88 mg/1.73 m^2 BS			
Oxalate	< 50 mg/1.73 m^2 BS < 0.49 mmol/1.73 m^2 BS	Age 0-6 mo 7 mo-4 yr > 4 yr	(mg/mg) < 0.30 < 0.15 < 0.10	
Phosphate		TP/GFR: > 2.8 and < 4.4 mg/dL[1]		

[1]Phosphate tubular reabsorption by glomerular filtration rate. GFR: Glomerular filtration rate; BS: Body surface.

natriuria considered as an important dietary factor to be modified, in case of an inadequate urinary finding. Another possible dietary intervention is the reduction of animal derived protein intake (such as red meat)[85-87]. Protein metabolism end-products result in increased acidity, which should be buffered by bone-released bicarbonate[89-91]. When the bone resorption is excessive, decreased bone mineral density and hypercalciuria may appear[89-91]. Stone formation is also associated with ingestion of other sugars (sucrose, fructose), vitamins (vitamin C), while magnesium and phytate may impair calculus formation[92].

Fats and sugars need to be avoided, because they may predispose to obesity, lead to increased incidence of hypercalciuria and hyperoxaluria associated stones. Some errors in dietary guidelines are very common as the elimination of tomatoes, dairy products, chocolate, teas, *etc*. These are held beliefs in the population and difficult to change.

Exercise must be regular, since the incidence of stones is directly proportional to physical inactivity and obesity (in adults). However, we must emphasize the care with fluid replacement after exercise so as not to encourage the concentration and urinary saturation.

PHARMACOLOGICAL INTERVENTION

Idiopathic calcium stones

Hypercalciuria: The initial approach to hypercalciuric children consists of adequate high fluid intake, low sodium diet and the recommended ingestion (RDA) of protein and calcium[46,87,93-95]. Dietary compliance is particularly difficult in children and adolescents, leading to usage of pharmacotherapy[56]. Pharmacological therapy is typically added if dietary treatment fails[93-95].

A randomized controlled trial pointed to beneficial effects of citrate use in adults with Urolithiasis[96]. Improvement of bone mineral density was also described by Pak *et al*[97] in adults with calcium oxalate stones after long-term use of potassium citrate. Modifications regarding increased urine pH as well as citrate and potassium levels were described during treatment. Urolithiasis in the pediatric age group had the prognosis definitely changed by citrate, due to a decrease in recurrence rate, growth of residual lithiasic fragments after lithotripsy and in children with hypocitraturia[98,99]. In hypercalciuric osteopenic adults, both thiazide diuretics and potassium citrate were previously demonstrated to be effective in simultaneously reversing hypercalciuria and improving reduced BMD[100,101].

The first line therapy in pediatric urolithiasis consists of potassium citrate. The main reason is the fact of being considered as a supplement, but studies with more detailed information on its effects in the pediatric population are lacking[102]. Studies by Reusz *et al*[103] and Schwaderer *et al*[104] demonstrated the beneficial effects of thiazides and/or potassium citrate on bone mineral density in children with IH. According to Srivastava *et al*[102], drug therapy should be reserved for children with symptomatic hypercalcuria and/or rare monogenic disorders. In 2012, Moreira Guimarães Penido *et al*[46] demonstrated an improvement of bone mineral density Z-score in 84 pediatric hypercalciuric patients after treatment with potassium citrate and thiazides, suggesting a beneficial effect and potential need for treatment. The use of thiazides in adult patients, albeit normocalciuric patients in many cases, still remains a

prevalent option of drug treatment. The absorption of calcium in the proximal tubule is enhanced, probably due to volume contraction[105].

Hypocitraturia: The choice of potassium citrate over the alkaline preparation is warranted because the sodium load may interfere with calcium excretion, minimizing the impact of urine citrate increase[71]. Compared to placebo, administration of citrate in hypercalciuric stone formers led to significative reduction in stone forming[106,107].

Treatment of calcium stones should include not only citrate, which may raise urinary pH and propitiate calcium stone formation, but also maintain adequate fluid intake. Initial dose for children is 0.25-0.5 mEq/kg two times a day in order to increase urinary levels to a minimum of 180 mg/g creatinine (Table 1)[17,81]. Urinary acidity should be monitored and should not exceed 6.5[108]. An important side effect of citrate is stomach pain, which can sometimes disrupt the treatment adherence[71]. Increased ingestion of citrus (*i.e.*, orange and lemon juices) may modify the profile of citrate excretion, acting as an alternative to citrate preparations[71].

Hyperoxaluria: Increased urinary levels of oxalate may be due to primary hyperoxaluria. Different mechanisms, resembling distinct enzymatic defects, lead to classification of this genetic entity into 3 forms, namely primary hyperoxaluria Ⅰ (PH1), Ⅱ (PH2) and Ⅲ (PH3). Deficient production of the enzyme alanine-glyoxylate aminotransferase by the liver is responsible for the more serious form of the illness, leading to end-stage renal disease[71]. High fluid intake, thiazides diuretics, citrate, pyrophosphates and magnesium oxide compose the mainstay treatment[17]. Liver-kidney or sequential liver and kidney transplantation are the best medical options after diagnosis is confirmed. Discussion upon the most appropriate moment of transplantation still remains.

The hepatic enzymatic defect is the hallmark of hyperoxaluria and restriction of dietary oxalate rich-food does not play a pivotal role in the treatment. Ingestion of food with high oxalate content, *i.e.*, spinach, rhubarb, brown rice, berries and dark teas should be avoided, as well as ascorbic acid. Adequate calcium intake must be encouraged[17]. It is also recommended, reducing fat intake and avoid use of vitamin C.

Hepatocytic peroxisomes are dysfunctional, leading to an increased synthesis of oxalate due to impaired glyoxylate metabolism. Vitamin B6 (piridoxine) is a cofactor of AGTX and its supplementation on a minimal pharmacological dose of 30 mg twice a day is recommended in order to achieve reduction of urinary oxalate levels (possible in up to 30% of PHI patients)[109]. PH 2 is linked to glyoxylate reductase/hydroxypyruvate reductase defficiency. PH3 is a more benign form of disease and is caused by mutations in the 4-hydroxy-2-oxoglutarate aldolase 1[110].

Another therapeutic option to enhance colonic secretion of oxalate involves probiotics. Studies with a naturally occurring bacterium, *Oxalobacter formigenes*, showed an inverse association with the presence of calcium oxalate stones. Nevertheless, degradation of intestinal oxalate also acts sinergystically with the colonic secretion, reducing blood and urine oxalate levels[111-113]. Colonization or intestinal recolonization with Oxalobacter formigenes would be an attractive therapeutic or prophylactic strategy to prevent or limit the formation of calcium oxalate stones, however, more studies are necessary[113].

Absorptive hyperoxaluria may also be idiopathic or secondary to malabsorptive disorders, *i.e.*, pancreatic insufficiency and small bowel resection. Under these circumstances, the absorption of ingested oxalate is augmented as well as the renal excretion. Another situation (which is rare in children and adolescents) that may lead to a similar physiological behavior of the gut is bariatric surgery. Restriction of oxalate intake in the forementioned conditions is primordial[17,71].

Lactic acid bacteria (LAB) are Gram-positive organisms that produce lactic acid as a final product of carbohydrate fermentation. This group includes Lactobacillus, Enterococcus, Lactococcus among others. Experimentally, LAB can degradate oxalate. However, in vivo results are contradictory. Goldfarb *et al*[114] found that lactic acid bacteria are ineffective in patients with absorptive hypercalciuria. Effective reduction in urine oxalate excretion was described by Lieske *et al*[115] in patients with secondary absorptive hyperoxaluria associated with fat malabsorption. Drugs that act primarily as phosphate binders, such as sevelamer hydrochloride, were unsuccessful in reducing oxalate absorption[116,117].

Uric acid stones: A combination of diverse factors, *i.e.*, low urine output, hyperuricosuria and abnormal reduced urine pH leads to uric acid (UA) stone formation. Notwithstanding, the main determinant of uric acid precipitation remains low pH. This factor is remarkable in adult patients (which are mainly not hyperuricosuric) and may be a biochemical manifestation of insulin resistance[71]. Alkalinization is the pillar of treatment of UA stones. Potassium citrate preparations are preferred due to a possible increased calcium excretion secondary to sodium load in sodium citrate.

Treatment of children with uric acid stones is complex due to the need of multiple interventions. The initial dose of potassium citrate is 0.5 to 1.5 mEq/kg per day and urine pH should be between 6.0-6.5. Dietary purine restriction is also indicated (seafood, small fish - especially sardines, beans, peas, chicken liver, heart, guts) when urinary urate excretion is high. When the hyperuricosuria is refractory to these measures, attempt with xantine oxidase inhibitors, *e.g.*, allopurinol may be tried (50 mg daily for children younger than 10 years

and 100 mg for older patients)[71].

Cystine stones: The transport of dibasic amino acids (*i.e.*, cystine, lysine, arginine and ornithine) is essential to maintain adequate solubility of these compounds. Defective tubular and intestinal transport of cystine leads to cystinuria, a cause of recurrent urolithiasis in up to 4% of pediatric urinary stone formers. In areas where consanguinity is high, this proportion may be even higher[14].

Cystinuric patients produce stones with a high degree of cystine content. Infrequently, mixed content with calcium salts may occur[118]. Daily excretion of 250 to more than 1000 mg leads to a permanent need for urine dilution, alkalinization and chelation. Cystine should stay in a urine suspension with particular chemical conditions: concentration under 250 mg/L and urine pH around 7. There is an apparent correlation between urine volume and cystine excretion: in order to excrete 750 mg of cystine, 3 L of urine output are necessary. Fluid intake must be constant and well distributed along the day. Potassium citrate (1.0-3.0 mEq/kg) is recommended to raise pH up to 7.0. In case of stone recurrence despite these measures, cysteine-binding compounds may be added. Modification of the chemical structure of cystine is possible through re-arrangement of disulfide bonds with thiol-binding drugs, *i.e.*, D-penicillamine and tiopronin (alpha-mercaptopropionylglycine_alpha-MPG). Resulted compounds are 50-times more soluble than original cystine. D-penicillamine as well as alpha-MPG proved to be efficient in decreasing stone formation in cystinuric patients in whom hydration and the use of alkalis showed to be ineffective[17,71].

The use of D-penicillamine must be judicious, regarding its potential side effects, such as its anti-pyridoxine effect[119]. Supplementation with pyridoxine (vitamin B6) 25-50 mg, daily, is advocated. Despite the better availability of D-penicillamine, tiopronin carries a better profile regarding incidence as well as severity of adverse reactions. Conflicting results with ACE-inhibitors (Captopril), which is a sulfhydryl agent, were already reported. The potential hypotensive effect of this drug resulted in an indication of "rescue therapy", where other measures failed[17].

The development of new techniques allowed the conceivement future of alternative treatments for cystinuria. Inhibition of the cystine transporter[120] and of the cystine crystal growth (L-cystine dimethyl ester_L-CDME) are promising measures to prevent cystine Urolithiasis[121,122]. They appear to be effective even at low concentrations, improving the safety profile of this sort of treatment. Dietary modifications, such as sodium and protein-restriction (0.8-1.0 g/kg per day), may lead to a modest decrease of cystine excretion. Once eliminated, stone analysis in cystinuric patients should be performed. Admixture with calcium salts is possible when urine pH is above 7.0[71].

CONCLUSION

The belief that pediatric urolithiasis is rare has lead to delayed etiological diagnosis in the past. The complete metabolic investigation of every infant or child with stones is mandatory. General measures involving adequate fluid intake and dietary modifications are considered general metaphylaxis for all kind of stones. Novel treatment modalities are scarce and the challenge of treating certain types of stone-forming diseases, *i.e.*, cystinuria, still remains.

Additionally, hypercalciuria has been evaluated in many studies during the last decade. Emphasis was laid mainly on the effects of dietary modification, alkali use (particularly potassium citrate) and thiazides, regarding calcium stone formers. However, more studies are warranted to compare pharmacotherapy and dietary changes, single *vs* combination therapies, among others. New approaches such as the use of probiotics like *Oxalobacter formigenes*, which act as oxalate-degraders, appear to be promising in calcium oxalate stone formers. However, the results are not consistent[114,115]. Future alternative treatments of hyperoxaluria involve upregulation of intestinal secretion through the increase of the anion transporter activity (S1c26a6)[118]. Studies on the pathogenesis of pediatric urolithiasis and the potencial pathogenic role of Randall's plaque and the tubular retention of crystals are currently on the way[108].

Individualized approaches to stone forming conditions will be available in a near future and will allow the start of early and adequate treatment to prevent recurrence, reduce morbidity and prevent progression to end-stage kidney disease[2,3,17].

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