REVIEW

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Pediatric nephrolithiasis: a systematic approach from diagnosis to treatment

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Abstract

Nephrolithiasis is a rare disease in children. For many years children with kidney stones have been managed like "small adults", but there are significant differences between the pediatric and the adult age in clinical presentation, etiology and treatment. Management of this condition in children has some peculiarities with respect to the adult, as it is often the sign of an underlying metabolic abnormality. Some of these metabolic alterations can lead to serious consequences, such as chronic renal failure, if not adequately diagnosed and treated. Moreover, stones in children with a metabolic abnormality can recur throughout their life, with the need for repeated surgical procedures over the years. So a systematic approach to every child with nephrolithiasis is mandatory to diagnose metabolic defects and establish a personalized therapy. Even the surgical approach in the child has changed significantly over the last two decades: open surgery has now been almost completely replaced by minimally invasive surgery due to the miniaturization of endoscopic instruments and technical advancements in optical and lithotripters systems. The goal is to obtain a stone-free status with the lowest number of minimally invasive procedures and with no complications. Many breakthroughs in our understanding of the physiopathology of renal stones and in surgical technology have been made over the last decades, but the best approach to use in a child with nephrolithiasis remains a true challenge for pediatric nephrologists and urologists.

Introduction

Nephrolithiasis is a disorder frequently seen in adults, whereas its occurrence in children is rare. While for many years children have been evaluated and managed like "small adults", there are significant differences between the pediatric and the adult age [1]. These differences mainly concern clinical presentation, the frequent recurrence rate, the presence of metabolic defects in a high number of cases with the possible association of major morbidity, such as chronic kidney disease [2].

Epidemiology and risk factors

Epidemiology

Although kidney and bladder stones have been afflicting the human race for many centuries (an Egyptian papyrus describes this condition and its management in 1550 BC), the real scope of the problem is still uncertain. Many factors such as race, geographic area, socio-economic status, and dietary habits can influence the incidence, localization within the urinary tract, and the chemical composition of stones. Moreover, these factors can vary over time in the same geographic area ("stone wave") [3]. General data on adult populations indicate that the incidence is higher in

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western countries (Europe 5–9%, North America 12–15%) than in the East (5%), whereas in people under the age of 18 years the incidence of nephrolithiasis is believed to be 5–10% of that of adults. In some areas of the Near/Middle East and North Africa (Turkey, Saudi Arabia, Egypt, and Pakistan) nephrolithiasis is an endemic disorder, affecting 10–20% of the population. Different reasons can explain these clusters, e.g. the high rates of consanguinity in these ethnic groups. Moreover the hot dry climate and high ambient temperatures increase the risk of dehydration and the deposition of stones. In northeast Thailand, for example, the high prevalence of renal tubular acidosis is associated with a high rate of renal calcium oxalate calculi and nephrocalcinosis [4]. In North India and in other regions of the world, like Florida and Ukraine, the absence of *Oxalobacter formigenes*, an intestinal oxalate degrading bacterium, can cause an absorptive hyperoxaluria leading to an increased risk of developing calcium oxalate stones [5]. In whites, the prevalence is slightly higher than in blacks, but this difference can probably be attributed more to dietary habits than to race [6].

Over the last few decades, the burden of hospital admissions, emergency department visits and surgical interventions in children with nephrolithiasis has been increasing steadily [7–9]. This trend was confirmed by a population-based study in Minnesota, which indicated an increase in incidence of 4% per calendar year over a 25-year period. This increase seemed to involve the adolescent population in particular [10].

In economically developed countries, stones are localized prevalently in the kidney or ureter, and are composed predominantly of calcium oxalate (60–90%) or calcium phosphate (10–20%). On the contrary, in low-income countries, bladder stones are more common and are formed by uric acid or ammonium [4].

Risk factors

Urinary tract malformations and infective conditions classically favor stone formation, typically those composed of struvite. In high-income countries, their frequency is decreasing, owing to the early diagnosis of malformations and better control of infections [4]. Obesity seems to be one of the most controversial potential causes [11]. In a study involving children with renal stones in Turkey, Sarica et al. [12] found that overweight children have a higher urinary concentration of lithogenic solutes and a lower urinary concentration of inhibitors of crystallization such as citrate and magnesium. The more recent paper by Dwyer et al. [11] did not confirm the relationship between body mass index and kidney stones. Dietary habits have a strong influence as they can represent the only risk factor or worsen any individual metabolic or renal disorders that are already present [13]. A decreased urine output, due to inadequate hydration, leads to an elevated concentration of urinary solutes, thus favoring the formation of non soluble crystals. Desert-dwelling Aboriginal children including infants still breastfed are at risk of kidney stone formation and even staghorn calculi. Investigation of these infants and children does not reveal metabolic abnormalities such as hypercalciuria and the stones tend not to recur as they get older. Explanations have included additional dehydrating insults on the background of a hot, dry climate such as gastroenteritis, febrile illnesses and possible carbohydrate intolerance [14].

An increase in dietary sodium intake produces higher urinary calcium excretion, which per se favors stone formation. The high intake of proteins increases urinary excretion of uric acid, oxalates, and calcium and leads to a low urinary pH, which in turn favors the precipitation of uric acid and calcium oxalate. At the same time, urinary levels of citrate, one of most powerful inhibitors of crystallization, diminish [15]. Protein intake in children in Europe and USA seems to be 3 to 5 times higher than recommended [13, 16].

Other risk factors are [16]:

- Preterm birth, low birth weight, and admission to neonatal care units, as renal immaturity and exposure to nephrotoxic drugs, as well as the use of diuretics, are associated with stone formation.
- Chronic bowel diseases leading to malabsorption which causes an increased intestinal absorption of oxalate.
- Neurological diseases, associated with reduced fluid intake.
- Use of drugs such as diuretics, anticonvulsants, antibiotics, and vitamin D supplementation.

Clinical presentation

Clinical manifestations in children, particularly in the first years of life, are different to those seen in adults. The lack of specific symptoms sometimes makes diagnosis difficult [17]. Moreover, nephrolithiasis can remain asymptomatic for a long time and diagnosis can be fortuitous, mostly during investigations performed for unrelated reasons. Abdominal pain remains one of the most common symptoms. Inconsolable crying and irritability are typical signs in infants. In young children, aspecific symptoms including poorly localized abdominal pain, vomiting, and constipation make differential diagnosis difficult to make between nephrolithiasis and other medical conditions [18]. The typical renal colic occurs more often in school-aged children and in adolescents. Non-glomerular gross hematuria and/or micro-hematuria, with or without flank tenderness, is a frequent mode of presentation at any age and can often precede the ultrasound diagnosis of stones [19]. Recurrent urinary tract infections and the isolated presence of leukocytes in the urinary

sediment could represent indirect signs of nephrolithiasis, especially in young children, and should be considered with a high index of suspicion. The passage or the presence of stones in the lower urinary tract can cause dysuria or voiding problems [20]. Complete urine retention with acute renal failure is a rare event, which occurs when the stone obstructs the urinary tract.

Diagnostic approach and metabolic evaluation

A complete systematic diagnostic evaluation (clinical history, laboratory and imaging investigations) is mandatory in every child presenting with a first episode, even if the etiology seems to be obvious, in order to make an adequate diagnosis and establish the appropriate course of medical and/or surgical treatment. The chances of finding a metabolic risk factor for renal damage are higher in the following instances:

– presentation during the first years of life;
– positive family history or consanguinity;
– recurrent renal stones.

Family and clinical history

Several studies have demonstrated the presence of stones in a high percentage of first degree relatives (22–75%) of children with nephrolithiasis, which can be explained by both a genetic predisposition and the influence of environmental factors and dietary habits [21]. A well-executed pedigree chart is necessary to evaluate the presence of genetic diseases, taking into consideration chronic kidney disease (CKD) or other familial diseases. The abovementioned risk factors, diet in particular, should also be evaluated.

Laboratory evaluation

Table 1 shows the first-line examinations useful to exclude the metabolic causes of renal stones. Urine analysis of a random, voided specimen provides information concerning pH and specific gravity. Microscopic evaluation is crucial and must be performed by an experienced laboratory, allowing for the study of crystals by means of polarized light

microscopy (Fig. 1). This can lead directly to the diagnosis of rare diseases, such as cystinuria or adenine phosphoribosyltransferase (APRT) deficiency if cystine or 2–8 OH adenine crystals are detected, respectively. The presence of oxalate crystals leads to the suspicion of metabolic conditions such as hypercalciuria, hyperoxaluria, hyperuricuria or hypocitraturia. Urate crystals can indicate metabolic defects of urate metabolism [22].

A 24-h urine collection (repeated 3 times) is recommended in every toilet-trained child, while maintaining habitual fluid intake and dietary habits. It provides a quantitative analysis of urinary solutes, both promoters and inhibitors of stone formation, and the assessment of daily fluid and food intake. It is important to bear in mind that concentration of substances can be underestimated when a stone is present within the urinary tract. In children who are not toilet trained the solute/creatinine ratio in a single urine sample is routinely utilized to evaluate solute excretion. Normal values per age are shown in Table 2.

Blood analysis, performed at the same time as the urine evaluation (Table 1), allows for the evaluation of kidney and tubular function. Specific second level and molecular investigations will be required in the case of the particular metabolic conditions described above [24].

The analysis of calculi obtained after spontaneous passage or surgical intervention should always be carried out. Infrared spectroscopy or X-ray diffraction are the methods of choice. They permit the analysis of fragments of even less than 1 mg obtained after lithotripsy. Stone composition can change over time and recurrent stones must always be analyzed (Fig. 1).

The diagnostic algorithm described in Fig. 2 should be used in every pediatric patient suffering from urolithiasis.

Diagnostic imaging

Ultrasound (US) is the most useful and widely used imaging modality to evaluate the presence, dimension and position of stones in the urinary tract, and it is sometimes performed in combination with a plain X-ray (to be carried out after adequate bowel preparation to eliminate intestinal bloating).

In the adult population, a computed tomography (CT) scan without contrast represents the gold standard and it is always used for the evaluation of patients with nephrolithiasis due to its high sensitivity and specificity for the

Table 1 First-line tests in pediatric nephrolithiasis

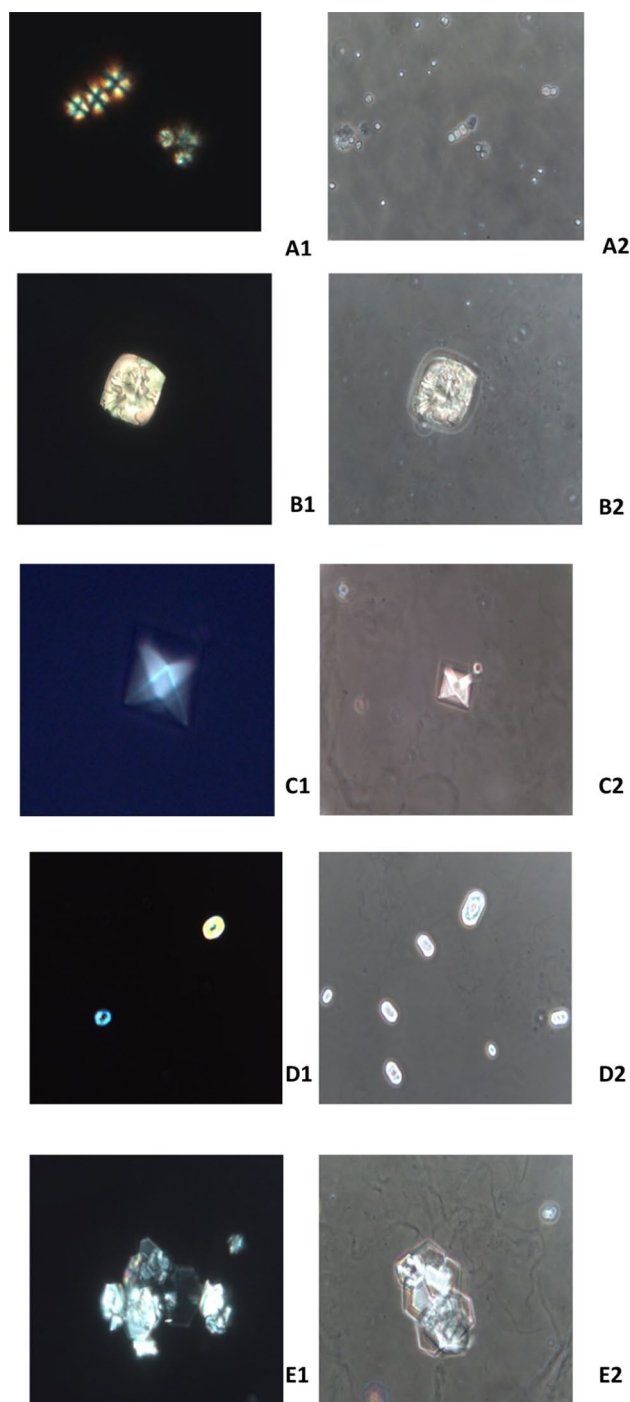|		
Urine collection	Once	Oxalates and amino acids
	3 times	Creatinine, proteins, beta2 microglobulins, Na, K, Cl, Ca, P, Mg, uric acid, citrate
Urine microscopic examination	3 times	Crystals and urinary sediment
Blood test	Once	Urea, creatinine, uric acid, Na, K, Cl, Ca, P, Mg, EAB

Fig. 1 Urinary crystals. A1, 2,8-dihydroxyadenine crystals at polarized light; 2, 2,8-dihydroxyadenine crystals without polarized light. B1, acid uric crystals at polarized light; B2, acid uric crystals without polarized light. C1, calcium oxalate dihydrate crystals at polarized light; B2, calcium oxalates dihydrate crystals without polarized light. D1, calcium oxalates monohydrate crystals at polarized light; D2, calcium oxalates monohydrate crystals without polarized light. E1, cystine crystals at polarized light; E2, cystine crystals without polarized light. Images courtesy of Dr Giuseppe Garigali, Fondazione Ca Granda, Policlinico, Milano

determination of the presence, position and size of stones. The following limitations apply to the pediatric age: radiation burden and the need for sedation. Therefore, ultra-low-dose non-contrast CT scans should be reserved for cases where US is non-diagnostic or for which the knowledge of anatomical details can be useful for the surgical strategy [25].

Metabolic risk factors and specific medical treatment

Hypercalciuria

This is the most common risk factor associated with the production of kidney stones in both adults and children. Calcium is present in urine as a free component or can form soluble and insoluble complexes, e.g. the calcium can form soluble complexes binding to citrates reducing the possibility of stone formation or conversely form insoluble complexes binding to oxalate or phosphate increasing the risk of stones.

Figure 2 shows the diseases causing hypercalciuria: normocalcemic hypercalciuria is the most frequent condition which is often due to idiopathic hypercalciuria, an apparently primitive condition, yet 45% of these children have a family history of renal stones, which supports a role for genetics, even if specific mutations have been demonstrated only in a small proportion of patients. The pathophysiology of idiopathic hypercalciuria involves complex interactions between the gastrointestinal tract, bone and the kidney: gut calcium absorption is increased but serum calcium remains normal. However, in patients on a low calcium diet hypercalciuria remains unchanged because of mobilization of calcium from bone. In fact, bone mineral density is reduced in many individuals with idiopathic hypercalciuria [26].

Serum parathyroid hormone (PTH), vitamin D dosage and calcium levels are useful in the differential diagnosis between hyperparathyroidism, excessive vitamin D-calcium intake and vitamin D hypersensitivity, a benign genetic condition caused by CYP 21A mutation [27].

Hypercalciuria can be the principal characteristic of some tubulopathies, e.g. hereditary hypophosphatemic rickets, and it can complicate the clinical picture of other tubular diseases such as Bartter type 1 and type 2 syndromes, and Fanconi syndrome. Hypophosphatemic vitamin D-resistant rickets is the consequence of phosphate wasting by the kidney and is treated with vitamin D and phosphate supplementation. Children often develop nephrocalcinosis and/or nephrolithiasis associated not only with hypercalciuria but also with hyperphosphaturia [28].

The medical approach to the child with hypercalciuria depends on its pathogenesis. Secondary forms (iatrogenic,

Table 2 Normal urinary values in spot and 24-h urine collections. Modified from La Manna et al. [23]

Age	Urine (spot) solute/creatinine		Urine 24 h (every age)
	mg/mg	mmol/mmol	
Calcium			
0–6 months	< 0.8	< 2	≤ 4 mg/kg (< 0.1 mmol)
7–12 months	< 0.6	< 1.5	
1–3 years	< 0.53	< 1.5	
3–5 years	< 0.39	< 1.1	
5–7 years	< 0.28	< 0.8	
> 7 years	< 0.21	< 0.6	
Oxalate			
0–6 months	< 0.26	< 0.36	< 45 mg/1.73 m^2 (< 0.5 mmol)
7–24 months	< 0.11	< 0.17	
2–5 years	< 0.08	< 0.09	
5–14 years	< 0.06	< 0.08	
> 16 years	< 0.03	< 0.04	
Citrate			
0–5 years	> 0.42	> 0.25	> 365 mg/1.73 m^2 (> 1.9 mmol) [males]
> 5 years	> 0.25	> 0.15	> 310 mg/1.73 m^2 (> 1.6 mmol) [females]
Uric acid			
< 1 years	< 2.2	< 1.5	< 815 mg/1.73 m^2 (< 486 mmol)
1–3 years	< 1.9	< 1.3	
3–5 years	< 1.5	< 1	
5–10 years	< 0.9	< 0.6	
> 10 years	< 0.6	< 0.4	
Magnesium			
> 2 years	> 0.13	> 0.63	> 0.8 mg/kg (> 0.04 mmol)
Cystine			
< 10 years	< 0.07		< 13 mg/1.73 m^2 (< 55 μmol)
> 10 years			< 48 (< 200 μmol)
Adults			< 60 (< 250 μmol)

tumors, hyperparathyroidism, Bartter syndrome) require specific treatments. Idiopathic hypercalciuria must be treated by means of the dietary restriction of sodium (1–2 mEq/kg/day). Potassium citrate supplementation (0.25-1 mEq/kg/die divided into three doses) has been shown to increase the solubility of urinary calcium and is recommended in general in cases of associated hypocitraturia. The dietary restriction of calcium is never recommended, as this could cause a possible negative calcium balance and poor bone mineralization in a growing child. Thiazide diuretics are only indicated with therapy failure and stone recurrence [29].

Hypocitraturia

Hypocitraturia can be isolated or associated with other metabolic conditions such as hypercalciuria or hyperoxaluria [30]. It can also be associated with distal tubular acidosis, hypokalemia or a high protein diet. Citrate is a weak acid, partly produced within the Krebs cycle and in part introduced with the diet (lemons and limes, oranges and grapefruit, hard cheeses). Urinary citrate deficiency can be corrected by reducing protein intake or by the exogenous supplementation of potassium citrate. A dosage of 0.25–1 mEq/kg is considered safe and does not expose the patient to a risk of hyperkalemia or any other adverse events, such as stomach pain, which can disrupt the treatment adherence [31].

Hyperoxaluria

Increased urinary oxalate excretion can be due to two different conditions:

1. primitive endogenous overproduction of oxalates, due to inherited oxalate metabolism defects and causing severe systemic diseases that are described in the dedicated sections of this paper.
2. secondary exogenous oxalate load, generally a benign, diet-dependent condition (high intake of ascorbic acid or food rich in oxalates: chocolate, green tea, cola, spin-
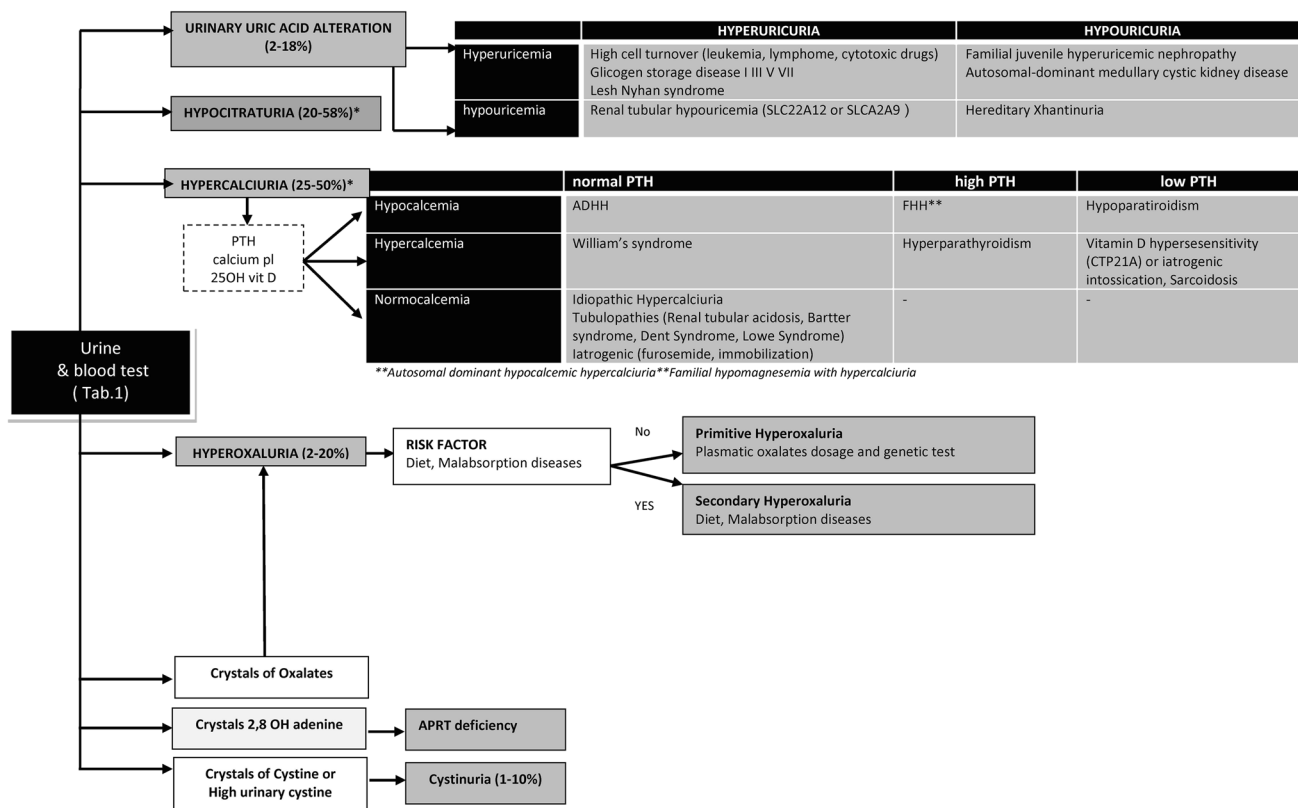
Fig. 2 Diagnostic algorithm for diagnostic evaluation of pediatric urolithiasis. Urine and blood test are described in Table 1. * Hypercalciuria and hypocitraturia can be associated with hyperoxaluria

ach and nuts or low calcium intake) or associated with chronic bowel diseases causing malabsorption. In the case of malabsorption, calcium, which normally limits intestinal oxalate absorption forming non absorbable complexes, is bound together with lipids; therefore, a much larger amount of free oxalates are absorbed. Another cause of intestinal oxalate hyper-reabsorption is the lack of *O. formigenes*, a bacterium colonizing the human colon, which metabolizes oxalate and uses it as its sole energy source. The absence of this bacterium can be either idiopathic or caused by the repeated use of antibiotics.

The solubility of calcium oxalate is reduced in the presence of hyperuricuria, hypercalciuria, hypocitraturia, and hypomagnesuria. Secondary hyperoxaluria is managed by reducing food with high oxalate bioavailability (chocolate and cola) and/or increasing their solubility in the urine with potassium citrate. A possible treatment with *O. formigenes* will be soon available, but data demonstrating clinical utility are lacking [31].

Hyperuricuria and defects in purine metabolism

Uric acid is the end product of purine degradation and is excreted mostly via the kidney. Hyperuricuria can result from elevated dietary purine/protein or fructose intake or from uricosuric drugs. Uric acid stones are quite rare because children with this condition often form calcium oxalate rather than urate stones. It can also be caused by elevated endogenous production such as excessive cellular lysis (myeloproliferative disorders), or inherited errors of metabolism, such as Lesch-Nyhan syndrome and glycogen storage disease. Dietary restriction of protein, purines and fructose and citrate administration are the major therapeutic tools, with the scope to maintain urinary pH alkaline (which reduces purine precipitation) and to reduce uric acid excretion. Allopurinol may be necessary when uric acid blood levels are elevated [32].

In the case of low serum uric acid levels (< 2 mg/100 ml) and a normal/high uric acid excretion fraction, the presence of a selective defect of uric acid tubular reabsorption can be suspected. Other rare and lesser known defects of purine

metabolism cause stones, which are often confused with those of uric acid. Such is the case with xanthine dehydrogenase deficiency, a benign condition resulting in the failure to degrade hypoxanthine and xanthine to uric acid leading to xanthine stone formation. High blood and urine levels of xanthine and hypoxanthine permit a specific diagnosis. Another more severe disease, dealt with in the next section, is APRT deficiency leading to 2,8-dihydroxyadenine.

Hereditary causes of kidney stones and chronic kidney disease

The hereditary causes of kidney stones (Table 3) are rare tubulopathies or metabolic disorders, with several common characteristics:

- Early renal stone production (generally during the first years of life) and/or nephrocalcinosis as the first clinical manifestation.
- High risk of developing progressive CKD, if not opportunely diagnosed and treated.

Moreover, all these disorders are rare, not well known among physicians, and thus with a high risk of remaining undiagnosed [33, 34].

APRT deficiency

This is caused by an APRT gene mutation, which results in a deficiency in APRT, a cytoplasmic enzyme involved in the catabolism of uric acid, leading to the generation of 2,8-dihydroxyadenine, a highly insoluble metabolite which precipitates in the urine producing renal stones or nephrocalcinosis. The prevalence of homozygotes estimated on heterozygote frequency in the general population should be 1–2 in 100,000 [35], but only a few cases have been diagnosed to date. If not diagnosed and adequately treated, the disease causes progressive CKD which can recur after kidney transplant. Diagnosis of APRT deficiency should be considered in all children with radiolucent kidney stones and/or nephrocalcinosis, or in children with recurrent stones and CKD, taking into account that metabolic blood and 24-h urine tests do not show abnormalities: only stone analysis by means of infrared spectroscopy or the presence of the typical reddish-brown 2,8-dihydroxyadenine crystals at microscopic

Table 3 Hereditary causes of kidney stones

Disease	Prevalence	Transmission	Locus gene (OMIM)	Protein	Phenotype
APRT deficiency	Estimated 1–2/100,000* Few cases described	AR	16q24 (102600)	APRT	Renal: 2,8 dihydroxyadenine stones and nephrocalcinosis
Cystinuria					
Type A	1:7000–1:100,000	AR/AD	2p21 (220100)	SLC3A1	Renal: cystine stones
Type B			19q13.11 (220100)	SLC7A9	
FHHNC	Few cases	AR	3q27 (248250)	CLDN 16	Renal: hypercalciuria with oxalate calcium stones, hypomagnesemia, proximal tubulopathy
			1p34.2 (248190)	CLDN19	Renal: hypercalciuria with oxalate calcium stones, hypomagnesemia, proximal tubulopathy
					Ocular: coloboma, pigmentary retinitis, nystagmus
DENT disease					
DENT 1	Few cases	XLR	Xp11.23 (300009)	CLCN5	Renal: hypercalciuria with oxalate calcium stones, proximal tubulopathy, proteinuria and segmental glomerulosclerosis
DENT 2			Xq26.1	OCRL1	Renal: like DENT 1
					Mental retardation
Hyperoxaluria	1:120,000				
Type 1		AR	2q37.3 (259900)	AGXT	Renal: hyperoxaluria with oxalate calcium stones, nephrocalcinosis
					Multiorgan failure due to calcium oxalate deposition
Type 2		AR	9p13.2 (260000)	GRHPR	Renal: hyperoxaluria with oxalate calcium stones, nephrocalcinosis
Type 3		AR	10q24.2 (613616)	HOGA1	

APRT adenine phosphoribosyltransferase, *FHHNC* familial hypomagnesemia with hypercalciuria and nephrocalcinosis

urinalysis (Fig. 1) make diagnosis possible. APRT activity in the red cells and gene analysis will confirm the diagnostic suspicion [36]. Medical treatment consists of the use of a xanthine dehydrogenase inhibitor (allopurinol: 5–10 mg/kg/day) in addition to a high oral water intake. Febuxostat has recently been introduced as an alternative treatment in children intolerant to allopurinol [37].

Cystinuria

This is a defect of reabsorption in the renal proximal tubule and in the gastrointestinal tract, selective for cystine, lysine, ornithine and arginine [33]. Excessive urinary excretion of cystine, a molecule with low solubility, leads to the formation of stones [38]. The presence of the typical flat hexagonal cystine crystals in the urine (Fig. 1) is pathognomonic of cystinuria. High concentrations of urinary cystine or the demonstration of cystine when stone analysis is performed permit diagnosis if crystals are absent. Treatment consists in increasing the cystine solubility by alkalinization of the urine (pH between 7 and 8) with potassium citrate and in transforming cystine into more soluble drug-cystine complexes by tiopronin. High oral fluid intake and a low sodium diet decrease the supersaturation of urinary cystine [33]. The prognosis has dramatically improved in the last few years, thanks to medical therapies and prophylactic regimens [39].

Dent disease or "X-linked hypercalciuric nephrolithiasis"

This is a group of renal tubular diseases [40] responsible for impaired chloride channel function on the proximal tubule, cortical collecting duct and thick ascending limb. High levels of tubular protein (LMW: 10–100 times above normal), calcium and phosphorus excretion with nephrocalcinosis and/or stones are the typical aspects of the disease [33, 34]. Sometimes hypophosphatemic rickets and glomerular proteinuria or nephrotic syndrome in various degrees of severity can be present. The progression of CKD can start between the 3rd–5th decades of life. At present, no effective treatment has been clearly defined. Thiazide diuretics are often used to decrease calcium excretion and angiotensin converting enzyme inhibitors and angiotensin receptor blockers are utilized to reduce proteinuria and slow down the progression of CKD.

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC)

This disorder depends on two different mutations encoding proteins claudine‑16 and claudine‑19 expressed on the thick ascending limb of Henle. Claudine‑19 is also present in the retina [41]. The renal defect of both mutations is similar and involves a high magnesium, calcium and phosphorus excretion leading to hypomagnesemia, hypermagnesuria, and hypercalciuria with consequent early nephrocalcinosis and calcium oxalate renal stones. Hypocalcemia, incomplete distal acidosis, and hypocitraturia can be associated with variable severity. Impairment of renal function is already severe during childhood with progressive evolution to end-stage renal disease (ESRD). No effective therapeutic treatment is available. The administration of magnesium supplements could be useful to correct hypomagnesemia, while thiazide use is controversial [42].

Primary hyperoxaluria (PH)

This is a group of diseases involving the metabolic pathway of oxalates. The deficiency of three different hepatic enzymes is responsible for three types of PH, type 1 being the most frequent and severe form. PH is characterized by the overproduction of oxalate and glycolate. The high concentration of oxalate in the urine leads to the formation of calcium oxalate, which tends to crystallize in the tubules and renal interstitium causing stones and nephrocalcinosis. Stones are typically composed of calcium oxalate monohydrate, sometimes mixed with calcium oxalate dihydrate (Fig. 1).

The clinical picture is variable, in the most severe cases stones and nephrocalcinosis are diagnosed prenatally by US and CKD is present at birth. Sometimes, recurrent renal stones can be the only clinical sign for many years. The constant presence of high levels of oxalate in the urine, in the absence of secondary causes, leads to clinical suspicion. High urine glycolate and L-glycerate levels confirm the diagnosis. Genetic testing can establish the type of PH. There is no specific therapy. High fluid intake, even by means of an enteral tube, and the use of calcium oxalate crystal formation inhibitors, such as citrate, are useful to limit calcium oxalate deposits in the kidney. A diet low in oxalates will not influence clinical evolution because of the hepatic origin of oxalate production. Only a group of patients with PH type 1 seems to have responded to a pharmacological dose of pyridoxine (vitamin B6). The efficacy of the administration of *O. formigenes* is being tested in experimental protocols [43]. For PH type 1 patients with progressive CKD who are non responders to pyridoxine, liver and kidney transplantation are the only forms of treatment [44].

Treatment

General measures of treatment

It is common to think that spontaneous stone passage is more likely in children than in adults because the ureter

has more compliance, but no study has ever demonstrated this and pediatric studies are lacking. The medical treatment indicated in all forms of renal stones is adequate hydration. This is a general measure which lowers the urinary concentration of all solutes, preventing the growth of the stones already in situ and/or favoring their expulsion. The volume of fluid intake (water) should be adjusted to the weight of the patient and should be 70–100 ml/kg/day [16]. Adequate hydration and increased fluid intake is an ideal in all children with stone disease. Unfortunately, compliance with increased fluid intake, particularly in younger children, is extremely difficult. Fluid intake in children is dictated by thirst and the likelihood of compliance to a prescribed fluid intake in the long term is small. An important time for increasing fluid intake is when the child suffers a dehydrating insult such as fever or diarrhea. In those predisposed to stones there should be a low threshold for short-term intravenous rehydration therapy.

Indications for treating children are similar to those for adult patients. The decision is usually based on clinical and radiographic aspects: pelvic or ureteral obstruction caused by a stone, particularly in a solitary or transplanted kidney or in the presence of fever, pain refractory to oral analgesics, increasing inflammatory index, or sepsis.

In recent years, a medical expulsive therapy (MET) with alpha-blockers or calcium channel blockers has been commonly used in pediatric patients to relax ureteral smooth muscle and enlarge the distal third of the ureter. Two recent systematic reviews and meta-analyses showed that treatment with MET results in an increased odds of spontaneous ureteral stone passage and it is a safe and effective choice for ureteral stones in pediatric patients [45, 46]. This solution is used when the patient has a non-obstructive and small (< 10 mm) stone in the distal part of the ureter (2 cm before the ureterovesical junction).

Surgical management

The management of pediatric stones has changed significantly during the last two decades: open surgery has now been almost completely replaced by minimally invasive surgery, due to the miniaturization of endoscopic instruments and the technical advancement of optical and lithotripter systems. The goal is to obtain a stone-free status with the lowest number of most minimally invasive procedures and with no complications. Surgical indications in children are similar to those in adults. The main difference and disadvantage is that all procedures—extracorporeal shockwave lithotripsy (ESWL), placement or removal of ureteral stents, etc.—have to be performed under general anesthesia. Moreover stones can recur, with the need for repeated surgical procedures over the years.

Figure 3 illustrates the surgical techniques in relation to the size and site of the stone in the urinary tract. The majority of stones can be successfully managed with ESWL, ureteroscopy/retrograde intrarenal surgery (RIRS), percutaneous nephrolithotomy (PCNL), or a combination of these treatments. Open surgery is currently indicated in very few selected cases, in the presence of: associated structural abnormalities (pelvi-ureteric or ureterovesical junction obstruction), a large burden of infective and staghorn stones, or large bladder calculus particularly in augmented bladder [47, 48]. Stone location, composition, size, anatomy of the collecting system, presence of obstruction or infection status and the preferences of the surgeon are important aspects to consider when selecting the best strategy. The European Society for Pediatric Urology (ESPU) guidelines recommend the use of ESWL as the first option, while a number of recent papers have introduced the use of endourological techniques even in infants and preschool children, because of the availability of smaller instruments.

ESWL remains the first choice for stones < 1.5 cm within the renal pelvis and upper or middle calices, while

Fig. 3 Surgical management in pediatric urolithiasis
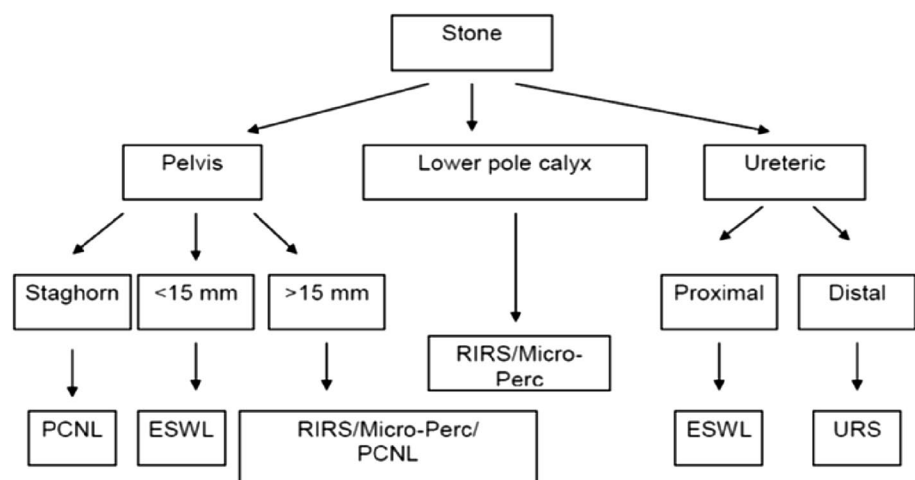
its efficacy is limited in the lower calices. Multiple treatments are often required for stones > 1.5 cm. This technique presents a number of significant disadvantages, such as the need for general anesthesia, a lower success rate for bigger stones, the presence of stones unresponsive to treatment and the unknown long-term effects of the shock waves on the developing kidney.

Miniaturization of percutaneous access has led to the development of a "micro-perc" system: a 4.85 Fr "all-seeing needle" is used for direct access with no need for dilatation. This technique presents many advantages, such as a lower transfusion and complication rate and shorter hospital stay. Stones are fragmented by a holmium laser fiber in a "dusting" setting, without the possibility of extracting the fragments, which should clear spontaneously, though this makes it difficult to perform a complete metabolic evaluation of the stone composition. The stone-free rate of micro-perc has been reported as being between 83 and 90%, but the success rate decreases if micro-perc is used for stones > 2 cm and those in an obstructed collecting system [49, 50].

Ureteroscopy/retrograde intrarenal surgery with the use of flexible ureteroscopy is a potentially less invasive technique than the percutaneous renal surgery, with a success rate between 58 and 100% [26], especially for stone sizes < 2 cm or stones located in the lower pole calices, where ESWL is contraindicated. With this technique, the use of the ureteral access sheath is mandatory to allow for removal of the fragments, avoid a high intrarenal pelvic pressure, and to reduce the risk of major complications such as urosepsis and urinary extravasation. Two points remain controversial: the need for ureteric pre-stenting and the use of a ureteral access sheath in infants and smaller patients. In the literature, some studies, in both adult and pediatric populations, have reported cases in which a ureteral access sheath could not be advanced easily and produced some ureteral injuries. For this reason, some authors recommend the application of a double-J stent, leaving it in place for 2–3 weeks before repeating the treatment in order to achieve a passive ureteral dilatation to decrease the risk of complications [22]. Because of its size (9.5–11.5 Fr), the use of a ureteral access sheath in infants is still debated. A recent study has reported the use of a ureteral access sheath in pediatric patients < 20 kg without any major complications [51, 52].

Percutaneous nephrolithotomy (percutaneous access to the kidney under US and C-arm fluoroscopic guidance) has a significantly higher stone-free rate (> 90%) but it is an invasive approach, with the risk of injury to other organs, renal pelvis perforation, urosepsis or severe bleeding in > 10% of cases. Factors influencing the transfusion rate in the pediatric population are the presence of stone burden, major size of the sheath (12–24 Fr), need for multiple renal punctures, and a longer operative time [53].

Conclusion

The increasing global prevalence of nephrolithiasis will become a rising medical and economic burden, especially for high-income countries. Major efforts to prevent the disease, such as modifications of cultural and dietary habits, will have to be implemented worldwide. In childhood, nephrolithiasis must be considered as a symptom indicating one of a number of medical conditions which needs a precise diagnostic definition and adequate therapy. Some of these diseases have dramatic consequences on kidney health if not diagnosed and treated. In our opinion, some of these often remain underdiagnosed and are not as rare as once thought.

Many breakthroughs in our understanding of the physiopathology of renal stones and in surgical technology have been made over the last decades, but what is the best approach to use in a child with nephrolithiasis remains a true challenge for pediatric nephrologists and urologists. The presence of a highly-skilled multidisciplinary team (including radiologists, dieticians, and geneticists), an experienced general laboratory, and a specialized biochemical and molecular diagnosis laboratory is absolutely necessary in order to obtain the best results in terms of the prevention of renal damage.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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