



# Educational review: role of the pediatric nephrologists in the work-up and management of kidney stones

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Received: 23 August 2018 / Revised: 23 October 2018 / Accepted: 13 December 2018  
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## Abstract

**Background** The incidence of nephrolithiasis in children and adolescents is increasing and appears to double every 10 years. The most important role of the pediatric nephrologist is to diagnose and modify various metabolic and non-metabolic risk factors, as well as prevent long-term complications especially in the case of recurrent nephrolithiasis.

**Objective** The purpose of this review is to summarize the existing literature on the etiology and management of pediatric nephrolithiasis.

**Results** The incidence of kidney stones is increasing; dietary and environmental factors are probably the main causes for this increased incidence. In most pediatric patients, the etiology for the kidney stones can be identified. Metabolic factors, such as hypercalciuria and hypocitraturia, urinary tract infection, and urinary stasis, constitute leading causes. Herein, we review the etiologies, diagnostic work-up, and treatment options for the most prevalent causes of kidney stones. The detrimental effects of excessive dietary sodium, reduced fluid intake, and the benefits of plant-based over animal-based protein consumption on urinary crystal formation are discussed. We also review the long-term complications.

**Conclusions** Pediatric nephrologists have an important role in the diagnostic work-up and prevention of recurring nephrolithiasis.

**Keywords** Nephrolithiasis · Urolithiasis · Hypercalciuria · Hypocitraturia · Hyperoxaluria · Cystinuria · Hypomagnesiuria

## Introduction

Both pediatric urologists and pediatric nephrologists play a key role in the work-up and management of kidney stones in children and youths. While there is a plethora of literature available on the topic, a recent educational review outlining the specific role of the pediatric nephrologist has been lacking.

The aims of the current review are to draw attention to the growing prevalence of kidney stones in the pediatric population and provide a detailed description of the etiology, work-up, and the long-term medical management of kidney stones in children and adolescents. About half of the pediatric patients with kidney stones have a metabolic etiology, which may be either genetic or life-style related; one quarter have

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urinary tract infections and about 20% have urinary obstruction or stasis. Lastly, there is a proportion of patients where no reason can be identified [1]. In this review, we will attempt to provide a systematic and practical approach for the practicing pediatric nephrologist to identify the main causes and to plan the proper management of kidney stones in pediatric patients.

## Epidemiology

Nephrolithiasis (NL) is a common public health issue. The life-time prevalence in adults is 11.0% for men and 5.6% in women by the age of 70 [2]. Nephrolithiasis has traditionally been a disease of older men [3]. However, there has been a marked increase in the prevalence of NL in the pediatric population, particularly in teenage girls. [4]

The incidence of NL also varies widely by geographic region with a much higher incidence in arid climates [5, 6]. Ambient temperature is clearly associated with a higher incidence of NL, and the worldwide increase in NL may be related to global warming [7]. The so called “stone belt” in the south-east USA has a 50% higher prevalence of NL than the north-west, a trend predicted to increase in coming years and attributed to global warming [8]. The Afro-Asian stone belt stretches from Sudan, the Arab Republic of Egypt, Saudi Arabia, the United Arab Emirates, the Islamic Republic of Iran, Pakistan, India, Myanmar, Thailand, Indonesia to the Philippines [5], a region where a positive correlation between NL prevalence and both temperature and sunlight index has been documented [9]. However, temperature may not be the main factor. The Afro-Asian stone belt is associated with an increased frequency of bladder stones of which ammonium urate is the predominant composition. This is thought to be related malnutrition, dietary phosphate deficiency, and possibly chronic diarrhea [10].

Genetic factors also play a role. First-degree relatives of stone formers have a 2–16 times higher risk of developing NL when compared to the general population [5, 11]. Consanguinity is an additional risk factor for an increased prevalence of NL [5, 12]. A recent study identified monogenic causative mutations of NL or nephrocalcinosis (NC) in up to 21% of 106 children with a previously undetermined etiology, underscoring its potential therapeutic and preventive implications in the care of these patients [13]. To date, more than 30 single genes have been implicated in NL or NC, with different modes of inheritance including autosomal-dominant, recessive, and X-linked transmission [14]. However, regardless of the geography and heredity, there has been a substantial increase in the incidence of NL in the pediatric population, especially in developed nations [5, 6]. In South Carolina, the incidence was 7.9/100,000 in 1996 and has increased to 18.5/100,000 in 2007, with girls displaying the highest rates compared to boys (21.9 versus 15.3, respectively) [6].

Adjusted for sex and race, the greatest increase in the incidence of NL was observed in the 15- to 19-year-old adolescents, in whom the incidence increased 26% over 5 years, resulting in doubling of the risk of NL during childhood [15]. Even in colder countries like Iceland, the incidence has increased from 3.7/100,000 between 1995 and 1999 to 11.0/100,000 between 1999 and 2004. This increase was also highest in girls aged 13–17 years where it rose from 9.8/100,000 to 39.2/100,000 during those time periods [16]. A clear explanation for the observed female predominance in pediatric NL remains elusive.

## Risk factors

Some authors hypothesize that various environmental and dietary habits, such as low urinary volumes with hypomagnesuria in combination with a high-protein, high salt, low vegetable intakes often found in the typical “Western” diet, may be responsible for the recent upsurge in NL [15, 16].

### Higher ambient temperatures

The mechanism for higher temperatures causing stone disease is attributed to heat-induced sweating. Loss of extracellular fluid leads to an increase in serum osmolality that in turn causes increased secretion of vasopressin (antidiuretic hormone) by the posterior pituitary gland, leading to increased urinary concentration and reduced urinary volume. As urinary concentration increases, the concentration of relatively insoluble salts, such as calcium oxalate, increases, and once their activity exceeds their upper limit of solubility, the salts precipitate out of solution and form solid crystals that develop into stones. The mechanism for humidity contributing to stone formation is similar: when humidity is low and the air is dry, more water is lost through the skin, and again, urinary volume falls and urinary concentration increases [7].

### Sodium and potassium

Up to 75% of the salt intake is due to processed food [17]. In the UK, where the salt content in processed foods undergo stricter regulations compared with those in North America, the incidence of kidney stones have not increased [11]. According to the National Academy of Science, the nutritional intake of sodium for children aged 6–11 years in the USA has increased from 200 mg in the 1970s to 3000 mg in the 2000s [18]. Current daily sodium recommendations in the USA for persons aged > 2 years are < 2300 mg for otherwise healthy individuals and < 1500 mg for at-risk populations like CKD or congestive heart failure, while 88 and 99% of persons in the above categories consumed amounts above the recommended levels [19]. The specific food categories contributing the most

to sodium consumption by different age groups revealed an average daily consumption of sodium of 3266 mg after age 2 years, with the highest daily consumption in teenagers aged 12–19 years averaging 3310 mg, of which 65% came from food obtained in a store and 25% from restaurants [20]. Efforts directed at the processed food industry and large national restaurant chains and organizations to lower the sodium in their products remain a challenge in the USA and Canada.

Urinary sodium excretion is a reliable and reproducible indicator of sodium consumption across a multitude of countries and was found to average 158 mmol/day (3641 mg/day) [21], a value very close to the estimated daily sodium consumption stated above [20]. In patients with established NL, particularly in those with hypercalciuria, higher sodium consumption may constitute a lithogenic risk, since urinary sodium and urinary calcium excretion display a close direct relationship, whereby for each 100 mmol (2300 mg) of urinary sodium the corresponding urinary calcium increased by 1 mmol (40 mg) [22], an observation confirmed in adolescents [23]. While the linkage of NL to sodium intake is not proven beyond a doubt, it is highly probable that sodium intake may be the single most important reason for the worldwide increase of kidney stones in children.

By contrast to sodium, higher urinary potassium decreases the urinary calcium/creatinine ratio [24], and low intake of potassium contributes to hypocitraturia [25]. Potassium deficiency causes intracellular acidosis and a decrease in tubular pH with stimulation of tubular citrate reabsorption [26], while a high potassium diet can attenuate the impact of a high salt diet and reduce hypercalciuria towards normal values [27].

### Overweight-obesity

The rates of overweight and obesity continue to increase in both adults and children, and studies have shown a positive association between incident stone risk and body mass index (BMI). Multiple risk factors have been proposed to explain this association including diet dependent changes in urinary composition, altered renal acid-base metabolism, and deficient ammonia production and excretion, which may all be linked to insulin resistance and impaired glucose metabolism [28]. A recent study demonstrated higher levels of urinary calcium, oxalate, sodium and uric acid, lower urinary pH and citrate, and a higher probability of stone formation in both overweight and clinically obese patients with NL compared with normal-weight stone formers [29]. Recent pediatric studies suggested that BMI should not be considered as a separate risk factor in the development of kidney stones in children [30, 31].

### Other dietary factors

Supplemental calcium, dietary oxalate, sucrose, fructose, sugar-sweetened soda, and punch were among the key risk

factors for increased incidence of NL in one of the largest ongoing epidemiologic studies [32]. As anticipated, the DASH diet was associated with a lower risk of NL. Caffeine-containing drinks have been suggested to have a preventative effect [33]; however, these drinks are not recommended for the pediatric age range.

### Special risk factors

Prematurity, use of loop diuretics for neonatal lung disease, inflammatory bowel disease, and prolonged immobilization may all promote higher concentrations of lithogenic substances with the eventual development of NC or NL [34].

### Key points

The greatest increase in the incidence of nephrolithiasis has occurred in adolescents. The reasons for this dramatic increase are multifactorial and seem to be linked to nutritional habits.

## Clinical presentation and acute management

### Presentation

Only a proportion of patients with kidney stones present with renal colic [11]. In a study from the UK, 36% of patients with NL presented with urinary tract infections, 32% presented with pain, 13% had painful gross hematuria, whereas 13% of patients were diagnosed as incidental findings in asymptomatic patients [11].

Pediatric patients with NL present with a spectrum of symptoms, which also varies with age. Adolescents would typically present with flank pain, whereas younger children would have more vague symptoms including nausea, vomiting, and irritability [35]. Additional manifestations of kidney stones in children may include failure to thrive or abdominal pain. Patients may also present with dysuria, incontinence, and/or frequency [34]. Especially patients with idiopathic hypercalciuria (IH) may present with isolated microscopic hematuria and be asymptomatic. They can also present with urinary-tract infection-like symptoms but will have negative urine cultures [36].

### Management

The acute management is beyond the scope of the present review since it is usually provided in the Emergency Room, does not differ from that in adults, frequently requires urological instrumentation, and has been extensively reviewed in the pediatric urological literature [37]. It is worth underscoring that ultrasonography should be used as the initial imaging study to evaluate children with suspected NL, with non-

contrast CT reserved for those in whom the ultrasound is non-diagnostic and the suspicion of NL remains high [38, 39] due to the higher ionizing radiation exposure from the CT [38].

## Metabolic abnormalities

One of the most important roles of the pediatric nephrologist is the identification of potentially modifiable metabolic risk factors for kidney stones. Proper identification of these factors becomes particularly important because of the high stone recurrence rate with its inherent morbidity and long-term consequences, particularly when these patients enter adulthood where recurrence rates are as high as 40% within 5 years of the initial episode of NL [3].

Whereas hypercalciuria is the most important factor, one study suggests that hypocitraturia may now account for 58% of metabolic causes, followed by hypercalciuria (48.3%), hyperuricosuria (2.2%), and hyperoxaluria (4.4%) [25]. Similar percentages were found in a cohort of children from Turkey [40]. The authors argue that this shift in metabolic trend may be a significant contributor to the increasing incidence in pediatric kidney stones [25]. Probably, dietary factors contribute to this shift owing to a low consumption of potassium and magnesium [25]. Indeed, the North American child consumes excessive amounts of animal protein, salt and sugar, and almost no vegetables, resulting in a high acid load and in reduced urinary citrate [39].

Inherited metabolic disorders are also related with NL. Phosphoribosyltransferase (APRT) deficiency, cystinuria, Dent disease, familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC), and primary hyperoxaluria should be considered in the differential diagnosis of pediatric stone disease. All of these disorders frequently cause CKD except cystinuria. Patients with these aforementioned disorders often have their initial kidney stones episode in the first decade of life and have recurrent stones [41].

APRT deficiency is a rare autosomal recessive inborn error of adenine metabolism. This entity results in the generation of large amounts of 2,8-dihydroxyadenine, which lead to stone formation in the urinary tract and crystalline nephropathy [41]. Dent disease is characterized by hypercalciuria and low molecular weight proteinuria with either NL or NC. Genetic testing for *CLCN5* and *OCRL1* can confirm the diagnosis [41]. FHHNC is caused by mutations in two genes: *CLDN16*, which is located on the long arm of chromosome 3 (3q27) and *CLDN19* on the short arm of chromosome 1 [41].

## Hypercalciuria

Idiopathic hypercalciuria, defined as excess calcium excretion with normal serum calcium and without identifiable metabolic cause, is found in 40% of stone formers but has an incidence

of < 10% in the overall population [42]. Idiopathic hypercalciuria is an inherited metabolic abnormality, whereby up to 75% of children with NL have a family history of NL. Calcium can precipitate with a variety of urinary solutes, particularly oxalate forming calcium oxalate, which is insoluble. Human data indicate that while some patients have a single, specific genetic defect resulting in hypercalciuria, most do not have a specific site of mineral ion transport dysregulation. Rather, they have a systemic disorder of mineral ion homeostasis resulting in hypercalciuria, involving a combination of increased gastrointestinal calcium absorption, decreased tubular calcium reabsorption, or enhanced bone resorption along with a complex interplay of hormones including parathyroid hormone (PTH), calcitonin, 1,25-dihydroxy vitamin D, and other factors [42]. Since patients with IH have a generalized alteration of both gut and renal calcium handling, attempts to separate patients into those with primary absorptive or renal reabsorptive hypercalciuria are not clinically useful. Consistently, present in patients with IH is a reduced tubular calcium reabsorption with consequent higher urinary calcium excretion compared to normal individuals during fasting that increases greatly in the fed state [42]. Clearance studies employing lithium as a marker for proximal tubular reabsorption have demonstrated higher distal tubular calcium delivery in patients with IH compared to normal individuals, resulting in hypercalciuria as a result of a marked fall in overall tubular calcium reabsorption [43]. These findings provide the explanation for the action of thiazides to reduce hypercalciuria by increasing the rates of proximal tubular Ca reabsorption.

The diagnosis is initially established on a random urine sample by assessing the age-dependent urinary calcium/creatinine ratio. Normal values for random urine sample (calcium/creatinine) are as follows: 0–6 months: < 0.8 mg/mg or < 2 mmol/mmol, from 7 to 12 months: < 0.6 mg/mg or < 1.5 mmol/mmol, from 1 to 3 years: < 0.53 mg/mg or < 1.5 mmol/mmol, from 3 to 5 years: < 0.39 mg/mg or < 1.1 mmol/mmol, from 5 to 7 years: < 0.28 mg/mg or < 0.8 mmol/mmol, and for > 7 years: < 0.21 mg/mg or < 0.8 mmol/mmol [44]. Traditional statistical cutoffs of more than 4 mg/kg/day or urine calcium/creatinine ratios > 0.21 mg/mg are influenced by diet, ethnicity, age, and region. Please note that even higher reference intervals apply for prematurely born children. The spot urine has a sensitivity of 89% and a specificity of 59% for the diagnosis of IH confirmed by a 24-h urine [45], but this has not been uniformly confirmed by other investigators [46]. Before establishing the diagnosis of IH, other associated features should be considered, such as failure to thrive, rickets, sustained metabolic acidosis, reduced glomerular filtration rate, proteinuria, or dysmorphic features.

The first-line treatment for hypercalciuria is nutritional intervention, as discussed below [47]. If hypercalciuria is not responsive to nutritional intervention, pharmacological

treatment is indicated. Potassium citrate constitutes an appropriate first option. A major advantage of potassium citrate, as compared to hydrochlorothiazide, is its lack of major side effects. Although both sodium and potassium alkali treatment are equally effective in raising urinary pH, potassium citrate is more effective in preventing the formation of calcium stones by attenuating urinary calcium excretion [48].

For patients with persistent hypercalciuria, particularly in those with recurrent gross hematuria and history of urolithiasis, most experts recommend the use of a thiazide. Initially, thiazides work through volume contraction leading to increased calcium absorption in the proximal tubule thereby decreasing urinary calcium [49]. This effect persists even after volume contraction is corrected. The principal side-effects of hydrochlorothiazide are hypokalemia and hypochloremic metabolic alkalosis [49]. Long-term use of hydrochlorothiazide can also cause hyponatremia [50]. Regular electrolyte monitoring is required. Secondary hypocitraturia caused by the metabolic acidosis may be avoided by using both hydrochlorothiazide and potassium citrate [49].

### Hypocitraturia

Citrate is a known inhibitor of stone formation [51]. In the renal tubule, citrate complexes with calcium as a chelate complex, increasing its solubility and reducing the concentration of calcium in the urine [51]. This calcium-citrate complex limits calcium supersaturation and prevents nucleation of both calcium oxalate and calcium phosphate [51]. Furthermore, citrate acts as a buffer and alkalinizes urinary pH, which is favorable for the solubility of various crystals, including cystine and uric acid [35].

Hypocitraturia, a well-known contributor to the formation of kidney stones [51], can be idiopathic or a manifestation of systemic metabolic acidosis and hypokalemia [5], which increase the tubular citrate uptake [51]. Other conditions, such as inflammatory bowel disease, may also cause hypocitraturia [5] because of decreased intestinal absorption of citrate and increased intestinal bicarbonate wasting, resulting in metabolic acidosis. Moreover, high animal protein diets may lead to mild metabolic acidosis and reduction in urinary pH [51]. Even small decreases in tubular pH (7.4 to 7.2) significantly increase tubular reabsorption of citrate [51]. Moreover, isolated hypocitraturia may be associated with hypomagnesemia and low urinary potassium levels [52].

Normal values for citrate in spot urine from 0 to 5 years are  $> 0.42$  mg/mg or  $> 0.25$  mmol/mmol and for  $> 5$  years are  $> 0.25$  mg/mg or  $> 0.15$  mmol/mmol. For 24 h urine,  $> 365$  mg/ $1.73$  m<sup>2</sup> ( $> 1.9$  mmol) in males or  $> 310$  mg/ $1.73$  m<sup>2</sup> ( $> 1.6$  mmol) in females [44].

Another factor causing hypocitraturia may be related to vitamin D. Gene polymorphisms of the vitamin D receptor (VDR) are associated with recurrent and familial stone disease

[53]. The active form of vitamin D utilizes the VDR to modulate citrate metabolism and transport [54]. Finally, some drugs may interfere with citrate excretion, such as acetazolamide [51] and topiramate [55]. Both are carbonic anhydrase inhibitors, which are known to inhibit citrate excretion [51].

However, the absolute citrate to creatinine ratio in the urine, which defines hypocitraturia, may not be as important as initially reported; as sufficient citrate needs to be present for a given urinary calcium concentration to keep the calcium complexed and prevent it from precipitating with urate or oxalate. Thus, the urinary calcium/citrate ratio may be a simpler parameter to predict stone formation and the risk of recurrences [56, 57]. Solitary stone formers had higher urinary calcium/citrate ratios compared with non-stone formers.

The cornerstone of pharmacotherapy for patients with hypocitraturia is alkalinization therapy, usually as potassium citrate [49]. Potassium citrate 1 mEq/kg per day divided into three doses after meals decreased stone recurrence and normalized urinary citrate in children [58]. The efficacy of alternative sources of citrate supplementation has not been systematically evaluated [49]. Alkali treatment is relatively safe with minor gastrointestinal side effects. In adults, in order to replace potassium citrate, lemonade consumption increases urinary citrate and may reduce stone formation [59]. One study in adults demonstrated an increase in urinary citrate levels and a decrease in the stone formation rates in 11 patients after 44 months of lemonade therapy by providing 120 ml of concentrated lemon juice (5.9-g citric acid) mixed with 2 L of water ingested throughout the day [59]. Comparing grape, orange, lime, and lemon juice both from fresh fruit and from juice concentrates showed that lime and lemon provide more citric acid per liter than grapes [60].

### Hyperoxaluria

Oxalic acid or oxalate is a widely occurring natural product of animals, plants, and other organisms. It is one of the strongest organic acids with pKa values of 1.3 to 4.3. It sometimes occurs as a free acid but is mostly bound to either sodium or potassium, ammonium, or metal cations, such as calcium and iron. Whereas ruminants (for instance goats) can handle oxalate as gut bacteria degrade oxalate into harmless formic acid and carbon dioxide, its pathological role in the formation of urinary stones has been known since the early eighteenth century [61].

The majority of urinary oxalate is derived from endogenous production of ascorbic acid and glyoxylate metabolism [5]. In normal circumstances, only 10–15% of urinary oxalate originates from dietary intake [5]. In malabsorption states, bile salts and fatty acids in the ileum may increase oxalate absorption by increasing the permeability of the colonic mucosa to oxalate [62]. Additionally, calcium may bind to fatty acids, leaving oxalate free and therefore easily absorbable [62].

Food products with high oxalate content include coffee, tea, and vegetables, such as beans, canned tomatoes, cocoa, and chocolate [5]. Ascorbic acid supplementation can increase oxalate excretion and might promote stone activity even in healthy subjects [63]. While we all excrete some oxalate in the urine, excessive oxalate formation causes severe urolithiasis.

Normal values for oxalate in spot urine sample (oxalate/creatinine) are age-dependent, from 0 to 6 months: < 0.26 mg/mg or < 0.36 mmol/mmol, from 7 to 24 months: < 0.11 mg/mg or < 0.17 mmol/mmol, from 2 to 5 years: < 0.08 mg/mg or < 0.09 mmol/mmol, from 5 to 14 years: < 0.06 mg/mg or < 0.8 mmol/mmol, and for > 16 years: < 0.03 mg/mg or < 0.04 mmol/mmol. The reference interval in a 24-h urine is < 45 mg/1.73 m<sup>2</sup> (< 0.5 mmol) for all ages [44].

Primary hyperoxaluria (PH) is an autosomal recessive hereditary disorder of the metabolism of glyoxylate [64]. This condition is inherited in an autosomal recessive pattern; therefore, the parents of an affected patient typically do not show signs and symptoms of the condition. Hepatic enzyme deficiencies result in overproduction of oxalate [41]. The enzymes involved in the three types of PH are as follows: [41]

PH1: alanine-glyoxylate aminotransferase or *AGT*

PH2: glyoxylate/hydroxy pyruvate reductase or *GR/HPR*

PH3: 4-hydroxy-2-oxoglutarate aldolase or *HOGA*

As oxalate is excreted through the kidneys, the kidney is the first organ affected. Calcium oxalate crystals form in renal tubules acting as a nidus for crystal aggregation and growth, thus initiating stone formation. Furthermore, crystals attach to renal tubular epithelial cells causing degenerative change and necrosis [65]. Health consequences include frequent formation of calcium oxalate kidney stones, as well as renal injury that leads to kidney failure in a significant proportion of affected patients [65].

The clinical difference of the three forms of PH lies in the decline of renal function over time [66]. One hundred percent of patients with type 1 PH and 20% of the patients with type 2 PH progress to end stage renal disease. By contrast, to date only one patient with Type 3 PH has been reported with end stage renal disease [66]. Secondary hyperoxalurias are described in patients with Crohn's disease, cystic fibrosis, and patients with malabsorption, such as short gut syndrome, which may include necrotizing enterocolitis as an etiology [65]. It is believed that excessive intake, increased absorption and alterations of the intestinal microflora are most responsible for the excessive absorption and subsequent urinary excretion [67].

Initial treatment aims at crystallization inhibition with potassium citrate, orthophosphate, and magnesium [65, 68, 69]. Since renal functional deterioration correlates with the degree of hyperoxaluria, reduction in urine oxalate excretion is the

most effective treatment strategy [70]. Pyridoxine is the only pharmacologic agent that has been shown to reduce oxalate excretion; however, it is only effective in 10–30% of type 1 PH patients [34].

Once CKD has been established, all the general measures are ineffective. Hemodialysis and peritoneal dialysis are ineffective at clearing oxalate generated in PH. Even though oxalate is a small molecule, the quantity of oxalate produced by the liver often exceeds the clearance of the conventional dialysis. Ideally, serum oxalate levels should be maintained below 30 μmol/L. Therefore, intensified dialysis must be used while the patient is awaiting organ transplantation [71]. Once there is a firm diagnosis of PH, the priority and potentially curative treatment is a liver transplantation, especially for type 1. For patients with advanced CKD, a combined liver and kidney transplantation should be considered [65]. Since recurrence of kidney involvement following kidney alone transplantation (KAT) in PH1 is likely, the comparative outcomes of KAT and combined liver-kidney transplantation (LKT) were analyzed in a series of 54 pediatric patients receiving a transplant in 10 French centers. Morbidity and mortality did not differ, with similar 10-year survival rates of 78% for LKT (n=33) vs 70% for KAT (n=21). First kidney graft loss, ESRD from rejection, and recurrence of oxalosis were significantly higher in the KAT group, and a second KT was required in 15 patients (71%) in the KAT group vs 4 patients (12%) in the LKT group [72]. Data from North America suggest that 100% patient survival may be possible with combined liver and kidney transplantation [73]. These results provide solid support to recommend LKT as the preferred treatment choice for PH1 patients with end-stage renal disease.

## Hyperuricosuria

Uric acid is an end product of purine metabolism and is excreted by the kidneys. Idiopathic renal hyperuricosuria is associated with normal serum levels of uric acid. Secondary hyperuricosuria results from a high-protein or ketogenic diet, or the use of certain medications, such as ascorbic acid, probenecid, and salicylates [58]. Hyperuricosuria associated with significant hyperuricemia is usually associated with inherited disorders of purine metabolism, lymphoproliferative disorders, and polycythemia [34].

Normal values for uric acid in spot urine sample (Uric acid/creatinine) are age-dependent, from < 1 year: < 2.2 mg/mg or < 1.5 mmol/mmol, from 1 to 3 years: < 1.9 mg/mg or < 1.3 mmol/mmol, from 3 to 5 years: < 1.5 mg/mg or < 1 mmol/mmol, from 5 to 10 years: < 0.9 mg/mg or < 0.6 mmol/mmol, and for > 10 years: < 0.6 mg/mg or < 0.4 mmol/mmol. For 24 h, the reference interval in all ages is < 815 mg/1.73 m<sup>2</sup> (485 mmol) [44].

There are three major urinary abnormalities that predispose patients to uric acid precipitation and stone formation: low

urinary pH, low urinary volume, and hyperuricosuria [74]. The solubility of uric acid is strongly pH-dependent; low urine pH (< 6.0) is the main risk factor for the development of uric acid stones [58]. The two major factors responsible for abnormally low urinary pH are a combination of increased endogenous acid production and impaired renal ammonia genesis. Ammonium buffers the titratable acidity as a compensation [74]. Furthermore, a defect in renal tubular transport of uric acid because of reduced proximal tubular reabsorption or increased secretion can cause hyperuricosuria [58]. Mutations in either the *SLC22A12* or the *SLC2A9* genes, both of which encode urate transporters expressed in the proximal tubule, are known to be causative [34].

First-line treatment for adults is dietary purine restriction and allopurinol, an inhibitor of xanthine oxidase. However, the optimal treatment for children is uncertain. The protein intake should not be restricted during childhood, and there is a lack of randomized controlled trials of alternative treatment [49].

### Cystinuria

Cystinuria is caused by mutations in either the *SLC3A1* gene for type A cystinuria or the *SLC7A9* genes for type B cystinuria [75], resulting in a disorder of amino acid transport in the proximal tubule [34]. Cystinuria is characterized by the defective reabsorption of cystine, lysine, ornithine, and arginine [76]. That defect is localized at the brush border membrane of the proximal renal tubule (S3 segment) and in the epithelial cells of the gastrointestinal tract [77]. Only the resulting urinary hyperexcretion of cystine leads to precipitation in the distal tubule and formation of cystine stones due to its low solubility at low pH [76]. This poor solubility results in the formation of renal calculi that can cause obstruction, infection, and ultimately, chronic kidney disease [77].

Normal values for cystinuria are age-dependent, for < 10 years: < 0.7 mg/mg in random spot urine sample or in 24-h urine < 13 mg/1.73 m<sup>2</sup> and for > 10 years in 24-h urine: < 48 mg/1.73 m<sup>2</sup> < 48 (< 200 μmol) [44]

Type A cystinuria is an autosomal recessive disease with 100% penetrance, which comprises 45–64% of the patients with cystinuria. Type B cystinuria may be autosomal recessive or autosomal dominant with incomplete penetrance. In rare instances, patients may have mutations in both subunits of the transporter [75]. This subtype has been named cystinuria type AB and is found in 1.2–4% of patients with cystinuria [78].

The first-line in treatment of cystinuria is increasing fluid intake and urine alkalinization [41]. In addition, although the mechanism of increased cystine excretion with increased sodium is unknown, cystinuria is also associated with high salt intake [79]. If the former therapies fail to halt stone formation, then thiol drugs are indicated [41]. The two most common

agents are D-penicillamine and α-mercaptopyronylglycine (tiopronin) [34]. Cystine is formed as a dimer of cysteine and the thiol-containing agents act by reducing the disulfide bond that bridges the two molecules of cysteine [34]. For the dosing, please see Table 1. Captopril may also be effective in reducing urinary cysteine concentration [80].

### Renal tubular acidosis

Patients with distal renal tubular acidosis (dRTA) have metabolic acidosis, which significantly reduces citrate excretion and contributes to hypercalciuria [49, 51]. The systemic and intracellular acidosis produced by this disorders leads to decreased citrate excretion [51]. dRTA is also one of the rare causes of normocalcemic hypercalciuria. In almost all cases, patients with dRTA have high urinary pH and hypercalciuria, which all contribute to the formation of calcium-phosphate stones and medullary NC [58]. Recent studies have identified a wider spectrum in the phenotype of primary dRTA patients, such as later presentation, normokalemia, and hypoacusia, caused by specific mutations in different genes [81].

Furthermore, reduced citrate concentrations and systemic acidosis occurring in complete dRTA may also cause increased calcium excretion due to the release of calcium from bone and reduced reabsorption in the nephron [51]. These patients have increased urine pH (> 6.0) [51] and often form calcium phosphate stones due to these risk factors and an inability to acidify the urine [49, 82]. Treatment with potassium citrate decreases acidemia, which contributes to hypercalciuria and hypocitraturia [49]. Additionally, potassium citrate results in normalization of calcium/creatinine and citrate/creatinine ratios [49].

### Hypomagnesuria

Urine magnesium levels are considered to be a natural protective factor for stone formation by inhibiting calcium oxalate crystal formation [83]. In the presence of magnesium, the solubility of calcium oxalate and calcium phosphate increases [44]. The potential role of magnesium to reduce the supersaturation of urine is a result of its ability to complex with oxalate and phosphate [84]. Moreover, high magnesium foods increase both urinary magnesium and citrate [83]. Consequently, hypomagnesuria may increase the risk for NL. The most important reason is familial hypomagnesuria [58]. Normal values for magnesium in spot urine from > 2 years are > 0.13 mg/mg or > 0.63 mmol/mmol, and for 24 h urine, the reference interval is > 0.8 mg/kg (> 0.04 mmol) [44]. Patients with spinal cord injury with suprapubic colostomy and short bowel syndrome may have secondary hypomagnesuria [85]. The treatment of hypomagnesuria comprises a high-magnesium diet and, if necessary, magnesium supplements. Among the over the counter magnesium

**Table 1** Medications typically prescribed for the prevention of recurrent nephrolithiasis

Medication	Dosing	Indications
Potassium citrate	0.5–1 mEq/kg/day divided in three equal doses	Hypercalciuria, hypocitraturia, cystinuria
Hydrochlorothiazide	1–2 mg/kg/day divided two or three equal doses	Hypercalciuria, hyperoxaluria
Moduretic (fixed combination of hydrochlorothiazide and Amiloride)*	1–2 mg/kg/day of the hydrochlorothiazide component divided two or three equal doses	Hypercalciuria, hyperoxaluria
Magnesium	500 mg/m <sup>2</sup> /day divided in four to six equal doses depending on diarrhea	Hypomagnesuria
Pyridoxine	7–9 mg/kg/day divided in two equal doses	PHI
Allopurinol	4 - 10 mg/kg/d divided in two equal doses	Hyperuricosuria
αMercaptopropionylglycine (tiopronin)	5 mg/kg/day tid, then adjust dose to reduce urine cystine < 250 mg/L	Cystinuria
D-Penicillamine	30 mg/kg/day divided in four equal doses	Cystinuria
Captopril	0.5–1.5 mg/kg/day divided two to four equal doses	Cystinuria

supplements, magnesium oxide may be the cheapest. Other magnesium salts including magnesium citrate are also feasible.

### Urinary tract infections

Urinary stones may present with persistent or recurrent urinary infections. Urinary infections with urease-producing organisms (*Proteus* spp., *Staphylococcus aureus*, *Klebsiella* spp., *Providencia* spp., *Pseudomonas* spp., and *Ureaplasma urealyticum*) are known to initiate the formation of struvite (magnesium ammonium phosphate) and apatite (calcium phosphate) calculi [86]. There are several important processes associated with infectious NL, including pH, bacteria, and bacterial effects on citrate. A mild process of alkalization due to a latent urinary infection by a bacteria able to produce urease may be an important step in the pathogenesis of NL [87]. Struvite calculi will only precipitate in a urinary environment with a pH of at least 7.2 [88]. Struvite stones can grow rapidly and most commonly present in a staghorn configuration [88]. This staghorn NL is characterized by a unique large-sided calculus completely filling the renal pelvis, which may be on both sides [87]. Bacteria may also produce substances capable of becoming part of the calculus matrix, or even the bacteria themselves can form the matrix [87]. Furthermore, urease-negative bacteria may induce lower urine citrate levels by the splitting of urinary citrate [87] and increasing calcium oxalates deposits, thereby contributing to a stone matrix protein [89].

Another potential link between infections and urinary stones may be related to the use of antibiotics. Antibiotics may reduce intestinal concentrations of *Oxalobacter formigenes*, which normally metabolizes intestinal oxalate, thereby reducing its absorption [88]. Women with a history of recurrent antibiotic use have been shown to have higher urinary oxalate levels, higher urinary pH, and higher urinary sodium concentrations [90].

The prevalence of urinary tract infection-related lower urinary tract stones has diminished with improved diagnosis and treatment of urinary tract infections [91]. However, they remain as a major source of morbidity in patients with spinal cord injury and neurogenic bladder [92]. The treatment of urinary tract infection-associated NL may include urological diversion, clean intermittent catheterization, antibiotic prophylaxis, and methenamine.

### Structural anomalies and stasis

Functional or anatomical obstructions of the urinary tract increase the potential for stone formation by promoting urinary stasis and infection [58]. Representative examples for these structural anomalies include ureteropelvic junction obstruction, ureterocele, horseshoe kidney, autosomal dominant polycystic kidney disease, and tubular ectasia (medullary spongy kidney) [58]. Urinary stasis associated with an abnormal anatomy may also be confounded by delayed washout of crystals, which increase the risk of urinary infections [93]. In vesicoureteral reflux, stasis and infection are major factors in stone formation, but the majority of stone-forming patients may also have concurrent metabolic abnormalities [93].

### Key points

Calcium-related derangements are among the most frequent metabolic abnormalities potentially modifiable in children and adolescents with kidney stones.

### Metabolic work-up

Twenty four-hour urine collections in children are notoriously unreliable, but fortunately, we can use random spot urine solute/creatinine ratios [94]. Most of the reference intervals for lithogenic substances in the urine are age-dependent. It



should be noted that testing should ideally occur 6 weeks after passing or treatment of a stone to avoid alterations for the stone passing [58]. Repeating the test three times is recommended [44].

A basic blood panel should be obtained for all stone formers. In addition to routine chemistry test, measurement of serum phosphorus, uric acid, and bicarbonate may also be useful. Kidney function is assessed at baseline and over the years [95]. If this initial metabolic evaluation (spot urine) do not shows an abnormality, we suggest measuring cystine, magnesium, glycolate, glycerate, and glyoxylate levels in a 24-h collection. We suggest the following flow diagram for the work-up (Fig. 1).

The analysis of calculi obtained after spontaneous passage or surgical intervention should always be carried out. Infrared spectroscopy and X-ray diffraction are the methods of choices. This can lead directly to the diagnosis of rare diseases, such as cystinuria or adenine phosphoribosyl transferase. Recurrent stones must always be analyzed as composition can change over time [44]. The normal urinary values in spot and 24-h urine collections are provided within each section above. Some distinctions will be indicated from now on.

### Urinary electrolytes, calcium, creatinine

Measurement of the urinary sodium/potassium ratio in a random urine sample is needed and should be below 2.5 [58]. The levels of calcium and magnesium excretion should be evaluated in a second urine sample collected in the morning. This measure provides a fairly accurate representation of the 24-h calcium/creatinine concentration. Hypercalciuria diagnosed in

single random urine sample should be confirmed by analysis of 24-h urine specimen [58].

In patients with hypercalciuria, serum PTH, vitamin D dosage, and blood calcium levels are useful in the differential diagnosis between hyperparathyroidism, excessive vitamin D-calcium intake, and vitamin D hypersensitivity. [44]

### Urinary oxalate, glycolate, glycerate and glyoxylate

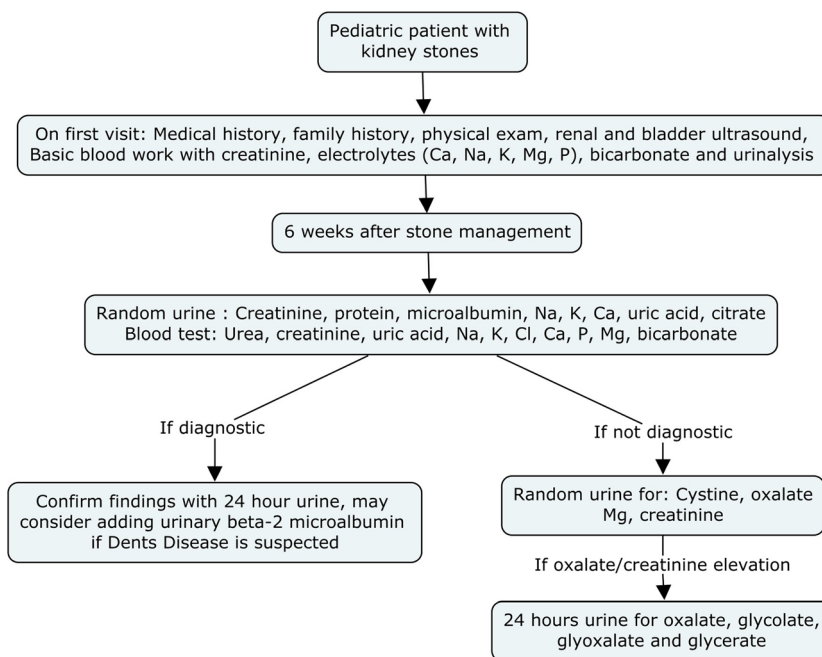
Urine oxalate should be measured in a 24-h urine collection, if possible. If 24-h urine oxalate is not feasible, a spot urinary oxalate/creatinine ratio can be performed but must be interpreted according to age. This ratio is highest in premature newborns and decreases rapidly in the first year of life [96]. It should be noted that children with markedly reduced GFR (< 30 ml/min/1.73 m<sup>2</sup>) may have normal urinary oxalate excretion [96]. Oxaluria must be confirmed using two urine samples [67].

PH is characterized by urinary oxalate excretion > 1.0 mmol/1.73 m<sup>2</sup> per 24 h in a majority of patients and in some cases, may exceed 2.0 mmol/1.73 m<sup>2</sup>/24 h. In patients with hyperoxaluria > 0.8 mmol/1.73 m<sup>2</sup> per 24 h, urinary glycolate, glycerate, and glyoxylate levels should be measured [67]. About two thirds of PH-I patients have elevated urinary glycolate levels, while urinary glycerate levels are high in PH-II patients and glyoxylate is elevate in PH-III [97].

### Urinalysis, urine pH, and specific gravity

Urinalysis, specific gravity, and urine pH aid in the diagnosis, etiology, and possible compositions of kidney stones.

**Fig. 1** Proposed flow chart for the work-up of nephrolithiasis



Macroscopic or microscopic hematuria has been observed in as many as 85% to 90% of children with urolithiasis [98]. A urine sediment may reveal crystals and may lead to the recognition of drug-induced crystalluria. Uric acid crystals are seen in acidic urine, usually 5.5 or less, and calcium phosphate crystals in more alkaline urine, usually 6.5 to 7 [95].

## Interventions

Dietary interventions should come first, before medical interventions. As outlined under the individual diagnoses, there are multiple medical interventions and lifestyle interventions.

### Diet, fluid intake, and stone prevention

The composition of urine is ultimately determined by the diet of the child. An improper diet, as discussed previously, plays a significant role in the formation of kidney stones; on the other hand, a properly modified diet can also be used for stone prevention. However, studies in pediatrics regarding the effectiveness of diet modification are limited. The recommendations put forth are primarily extrapolated from studies on adults.

Irrespective of dietary considerations, it is important to note that the intervention most supported by evidence is that of increased fluid intake. The mechanism of action for this intervention is the reduction of the concentration of stone-forming solutes in the urine. As such, a decrease in water intake within the pediatric population may be a contributing factor towards the observed increased prevalence of nephrolithiasis in children [91].

In a randomized controlled trial by Borghi et al., the authors demonstrated that low urine volume was a risk factor for nephrolithiasis and that increased fluid intake as an initial therapy was effective at reducing stone recurrences [99]. In pediatrics, children with urolithiasis have been shown to have low urine volumes compared with normal children [100]. Thus, recommendations for fluid intake aim at maintaining a urine output greater than 750 mL per day in infants, greater than 1000 mL per day for children less than 5 years, greater than 1500 mL per day for children between 5 and 10 years of age, and greater than 1500 mL per day for children older than 10 years [91]. The potential influence of urine volume on urinary supersaturation, a useful tool for predicting risk of stone recurrence and defined as the ratio of the concentration of dissolved salt to its solubility in urine, was elevated in 56% of children with newly diagnosed urolithiasis and was highly prevalent in those with urine volumes < 1 mL/kg/h [101]. Stone forming children have higher supersaturation of calcium oxalate than non-stone-forming children [102], a lithogenic condition potentially amenable to intervention with increased fluid intake.

Dietary modifications to prevent stone recurrence are dependent on the type of kidney stone, as well as the metabolic abnormalities present in the child. The general dietary recommendations based on metabolic abnormalities in 24-h urinary excretion are as follows: [26]

- Hypercalciuria: calcium 800–1200 mg per day, avoid oxalate-rich foods, decrease sodium intake and increase potassium to > 120 mEq, increase citrate and fluid intake.
- Hyperoxaluria: calcium 800–1200 mg or more per day, reduce oxalate-rich foods and sodium intake, and increase citrate and fluid intake.
- High sodium excretion: calcium 800–1200 mg per day, reduce sodium intake and increase potassium, citrate, and fluid intake.
- High uric acid excretion: calcium 800–1200 mg per day, reduce sodium intake and increase potassium, citrate, and fluid intake.
- Low pH: calcium 800–1200 mg per day, adequate sodium intake and increase potassium, citrate, and fluid intake.
- Low citrate: calcium 800–1200 mg per day, reduce sodium intake and increase potassium, citrate and fluid intake.

Overall, to reduce stone recurrence, children should maintain a diet that contains a recommended daily allowance of calcium and less than 2300 mg of sodium, while increasing intakes of potassium and citrate.

A reduction in animal protein is not recommended for a growing child, rather the child should follow the Dietary Guidelines from the US Department of Agriculture [103]. Furthermore, the sodium contents of selected foods are also reported in the same guidelines [103]. Calcium restriction should be discouraged, especially in children, due to risk of bone demineralization [104]. It is also important to inform the families that they should avoid a low-calcium diet to prevent secondarily increased oxalate uptake and increased urinary oxalate excretion. The daily allowance of calcium is age dependent; for infants, the recommended allowance ranges between 200 and 260 mg and is dependent on weight; 700 mg for children between 1 and 3 years; while children between 4 and 8 years, 1000 mg is prescribed; lastly, for pediatric patients older than 8 years old, a daily allowance of 1300 mg of calcium is recommended [105].

Although the evidence for the efficacy of oxalate restriction remains contentious, reduced oxalate intake should be prescribed for children with hypercalciuria and hyperoxaluria [26, 106]. Foods such as cocoa powder, beets, soy flour, spinach, and rhubarb are very high in oxalate, while other such as potato chips, lasagna with meat, walnuts, and French fries contain high levels of oxalate. Lastly, vegetables form a substantial source of dietary citrate and potassium and children should also be encouraged to increase their vegetable consumption as a preventative measure for kidney stones.

## Medical interventions

For convenience, we are listing the most commonly used medical interventions below in Table 1. Please note that some medications, for instance Moduretic®, which is a fixed combination of amiloride and hydrochlorothiazide, are not available everywhere.

## Key points

Children with kidney stones should generally be encouraged to increase water intake, reduce sodium intake, maintain normal unrestricted dietary calcium, and increase consumption of both potassium and citrate, preferably through eating more fruits and vegetables. However, dietary recommendations should be further guided by the child's underlying metabolic abnormality, age, and weight.

## Long-term complications

Several studies have demonstrated reductions in bone mineral density (BMD) in adults with IH as compared to non-hypercalciuric controls, suggesting that persistent hypercalciuria may lead to decreased bone mass and increased risk of fractures [104]. Similar associations of IH and bone loss have been identified in children with or without hematuria or NL, raising concerns that life-long hypercalciuria might be an important contributor to reduced peak bone mass and earlier onset of adult osteoporosis. Employing dual photon and dual energy X-ray densitometric techniques, several studies have clearly demonstrated reduced BMD in children with IH in different world geographic locations, such as Brazil, the Canary Islands, USA, and Europe [107]. The possibility that the BMD changes may be genetically determined was suggested by the demonstration that children of mothers with BMD considered osteopenic displayed significantly lower spine BMD than did children of mothers with normal BMD [108]. Epidemiologic studies have shown that osteoporotic fractures occur more frequently in patients with nephrolithiasis as compared to the general population [109]. In the largest cohort study of adults and children with history of urolithiasis, the highest incidence and highest hazard ratio of first fracture were documented in boys aged 10–19 years [110]. Since the median time from initial diagnosis of urolithiasis to first fracture was a decade, pediatric nephrologists caring for young patients could conceivably be able to intervene during the critical years of bone mineral accretion in childhood and adolescence to reduce the risks of future fractures.

Recent reports have shown that NL may entail and increased risk of cardiovascular disease, [111] myocardial infarction [112], and cardiovascular events [113]. Two recent large meta-analysis revealed, with virtually identical results, that NL was associated with a 20% increased adjusted risk estimate for coronary heart disease and a 40% increase in stroke [114, 115]. These findings may be linked to increased arterial stiffness in patients with NL [116], perhaps as a result of chronic inflammation and bone Ca resorption in patients with IH. Similarly, the CARDIA study showed a positive association between NL and atherosclerosis in young adults [117]. Furthermore, higher carotid artery intima-media thickness, an early marker of atherosclerosis, was shown to be higher in young children with NL [118]. Stone formers had also a significantly higher cumulative risk of CKD compared to matched control subjects [119]. Finally, the theoretical risk of malignancies in patients with recurrent NL due to excessive radiation exposure from multiple life-long repeated CT scan examinations must be considered during prolonged follow-up [120].

## Conclusions

The incidence of kidney stones in children and adolescents is increasing, mostly owing to dietary factors. The role of the pediatric nephrologist in the acute presentation is limited. However, all children with nephrolithiasis should be referred to pediatric nephrologists for a thorough work-up and intervention, especially in repeat stone formers. Dietary and fluid intake modification is the first line. Depending on the results of the work-up, specific medical intervention may be indicated. The pediatric nephrologist needs to be knowledgeable in the diagnostic work-up and plays a major role in the medical treatment of recurrent nephrolithiasis.

## Multiple choice questions (answers are provided following the reference list)

- Which one of the following amino acids is not increased in urine in patients with cystinuria?
  - Cystine
  - Ornithine
  - Lysine
  - Arginine
  - Glutamine
- Which of the following statements is **TRUE**?
  - The diagnosis of hyperoxaluria does not necessitate a 24-h urine collection.

- b) Most urinary solutes have age-dependent reference intervals.
- c) Higher muscle mass can cause overestimation of solute to creatinine ratios in urine.
- d) A single spot urine at the time of presentation will suffice for the work-up of nephrolithiasis.
3. Which of the following statements is **NOT TRUE**?
- a) Kidney stone formation can be multifactorial, including urinary tract infections, stasis, and metabolic reasons.
- b) Hypercalciuria is a monogenetic disorder.
- c) Increased urinary sodium excretion leads to urinary calcium wasting.
- d) A urinary sodium/potassium ratio should be less than 2.5 in children with a propensity for kidney stones.
4. Please select the **FALSE** statement:
- a) To date, we know of three different forms of primary hyperoxaluria.
- b) In primary hyperoxaluria type I, the genetic defect results in reduced or absent alanine-glyoxylate aminotransferase.
- c) In primary hyperoxaluria type III, progression to end-stage renal disease is rare.
- d) In primary hyperoxaluria type III, the genetic defect results in deficiency or absence of the enzyme glyoxylate reductase/hydroxy pyruvate reductase.
5. Please select the **FALSE** statement:
- a) The incidence of nephro- and urolithiasis in children and adolescents is increasing due to dietary changes and increasing ambient temperature.
- b) The incidence of kidney stones in children is higher in arid climates.
- c) The increase of kidney stones among children and adolescents was not observed in countries with laws promoting lower salt content in processed food.
- d) Boys are always more affected than girls across all ages.

### Compliance with ethical standards

**Conflict of interest** The authors declare that there is no conflict of interest.

**Financial disclosure** None.

**Answers** 1. e; 2. b; 3. b; 4. d; 5. d

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