Evaluation of a child with suspected nephrolithiasis

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Purpose of review
As the incidence of nephrolithiasis in children doubles every 10 years it is becoming a common disease associated with significant morbidity along with considerable economic burden worldwide. The aim of this review is to summarize current data on the epidemiology and causes of renal stones in children and to provide a frame for the first clinical evaluation of a child with suspected nephrolithiasis.

Recent findings
Dietary and environmental factors are the driving force of changing epidemiology. Diagnosis should be based on medical history, presenting signs, examination, first laboratory and radiological workup. Ultrasound should be the initial diagnostic imaging performed in pediatric patients while low-dose computed tomography is rarely necessary for management. Metabolic factors including hypercalciuria, hypocitraturia, low fluid intake as well as specific genetic diseases should be explored after the resolution of initial signs and symptoms.

Summary
Appropriate initial evaluation, imaging technique, identification of risk factors and other abnormalities are essential for early diagnosis and prevention of stone-related morbidity in children with suspected nephrolithiasis.

Keywords
epidemiology, kidney stones, low-dose computed tomography, metabolic evaluation, nephrolithiasis, ultrasound, urolithiasis

INTRODUCTION

Nephrolithiasis is the process in which a solid foreign body (kidney stone) is formed by precipitation and aggregation of urine constituents within the kidney or the urinary tract. Stone formation occurs if the concentration of a solute surpasses its limit of solubility and is further facilitated by sites of aggregation such as Randall plaques [1,2▪▪,3▪▪] at the urinary surface of the renal papillae, bacterial or epithelial debris in the urine. Conditions leading to increased concentrations of stone forming solutes or the decrease of the inhibitory activity of urine promote stone formation [1,4].

Stones breaking loose from the kidney exit the body in the urine stream passing through the ureters, the bladder and the urethra. During the passage they can cause ureter blockage resulting in severe pain in the lower back or abdomen [5▪,6▪▪].

Herein, we will review some new aspects of the epidemiology of pediatric nephrolithiasis followed by analysis of the clinical features of acute stone disease. Signs and symptoms as well as first-line lab work and radiological approach to the disease will be discussed.

Detailed metabolic evaluation, medical and urological management and the aspects of prevention are beyond the scope of this survey and will be discussed in the following articles of this issue.

EPIDEMIOLOGY

The occurrence of kidney stone disease shows high geographical variability due to – among others – environmental, metabolic, dietary and genetic factors [7,8].

Nephrolithiasis is rather common in adults. Over the past decade incidence increased from 4% to about 9%, with a slight male preponderance (11%

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KEY POINTS

- Dietary and environmental factors are the driving force of changing epidemiology of nephrolithiasis.
- Family history and medical history should be explored, focusing on fluid intake as well as on specific genetic diseases.
- Ultrasound is the cornerstone of radiological imaging while low-dose computed tomography is rarely necessary in children.
- Detailed metabolic evaluation and analysis of stones is necessary after the resolution of initial signs and symptoms.

among men compared with 7% among women). The increase in the frequency of renal stones has been linked to the 'epidemic' of obesity [7,9,10]. A study including around 5000 adult stone patients showed that obesity and weight gain are independent risk factors for the development of nephrolithiasis in both sexes [11]. In children the occurrence of pediatric nephrolithiasis is one magnitude lower than in adults, nevertheless, incidence has been steadily growing by 6–10% annually in the past 25 years, with an estimated incidence of 36–57 per 100 000 in the United States [12–15]. Significantly, the highest increase has been reported in teenage girls [14]. Although the epidemic of obesity has reached the pediatric population as well and parallels the increase in nephrolithiasis [16,17], its direct relation to nephrolithiasis is less evident than in adults. Recent pediatric studies do not agree on this issue [15,18,19▪▪], presumably due to geographical and ethnical factors among others, moreover because of the different methodology of individual surveys. Results from a study in a network of 30 primary care pediatric practices including 110 cases and 396 matched controls from the United States [18] and a tertiary center from the United Kingdom [15] suggested that BMI should not be considered as a separate risk factor in the development of kidney stones in children. In contrast, a large epidemiologic survey from Israel found that the odds ratio for nephrolithiasis in candidates with a BMI of more than 30 kg/m^2 was 1.7 compared with candidates with a BMI of 18.5–24.9 kg/m^2 [19▪▪]. Thus, the relationship between increasing prevalence of nephrolithiasis and higher body mass should be explored further.

With increasing occurrence, the number of hospital admissions, emergency department (ED) visits, surgical interventions and as a consequence, the economic burden increases as well [20–22,23▪].

The great geographical variability may be explained *inter alia* by environmental factors, such as arid climate, as well as dietary habits, such as the extent of salt and fluid intake, diversity of processed food and animal protein load and of vegetable and fruit consumption [24,25]. As an example, in the so-called stone belt in the southeast of the United States the prevalence of renal stones is 50% higher than in the northwest [26]. In the Afro-Asian 'stone belt' zone stretching from Morocco over Egypt to India, Indonesia and the Philippines there is also a positive correlation between nephrolithiasis prevalence and temperature. However, the high frequency of bladder stones in these regions suggests the role of possible additional factors (e.g. diet, malnutrition and infections) [27,28].

WHEN SHOULD NEPHROLITHIASIS BE SUSPECTED?

The typical stone patient's symptoms are flank pain, hematuria, nausea and vomiting [25,26,29]. However, the signs and symptoms are largely dependent on the localization of the stone, its dimensions, the degree of consequent obstruction [30] and the age of the patient [25,26,29]. In particular, young children do not present with the usual acute onset of flank pain seen in adults, therefore children are very often evaluated for other conditions before the diagnosis of nephrolithiasis is made. A diagnostic pathway for the identification of nephrolithiasis is shown in Fig. 1.

Pain and accompanying vegetative symptoms

A kidney stone formed at and fixed to the papilla is usually asymptomatic [29,31▪▪]. In a study from the United Kingdom, 13% of stones were diagnosed as accidental findings in asymptomatic patients [15]. In a Canadian report of the 244 unique children identified by radiological methods [ultrasound or computed tomography (CT)] to have renal stones, 140 (57%) were symptomatic while the other 104 patients (43%) were asymptomatic [29,31▪▪].

As the stone breaks away from the papilla and moves down the ureter it may get stuck at one of the three preformed areas of decreased luminal diameter: the pyelo-ureteral junction, the crossing site of the iliac vessels or the uretero-vesical junction, causing obstruction, consequent distension of the urinary tract and abrasion of the mucosa. In the same study, 32% of patients presented with pain, 13% had painful gross hematuria and 36% presented with urinary tract infection [31▪▪].

Due to the conjoined innervation of the gastrointestinal, genitourinary and somatic systems, patients may feel pain in the intestines, groin, bladder or

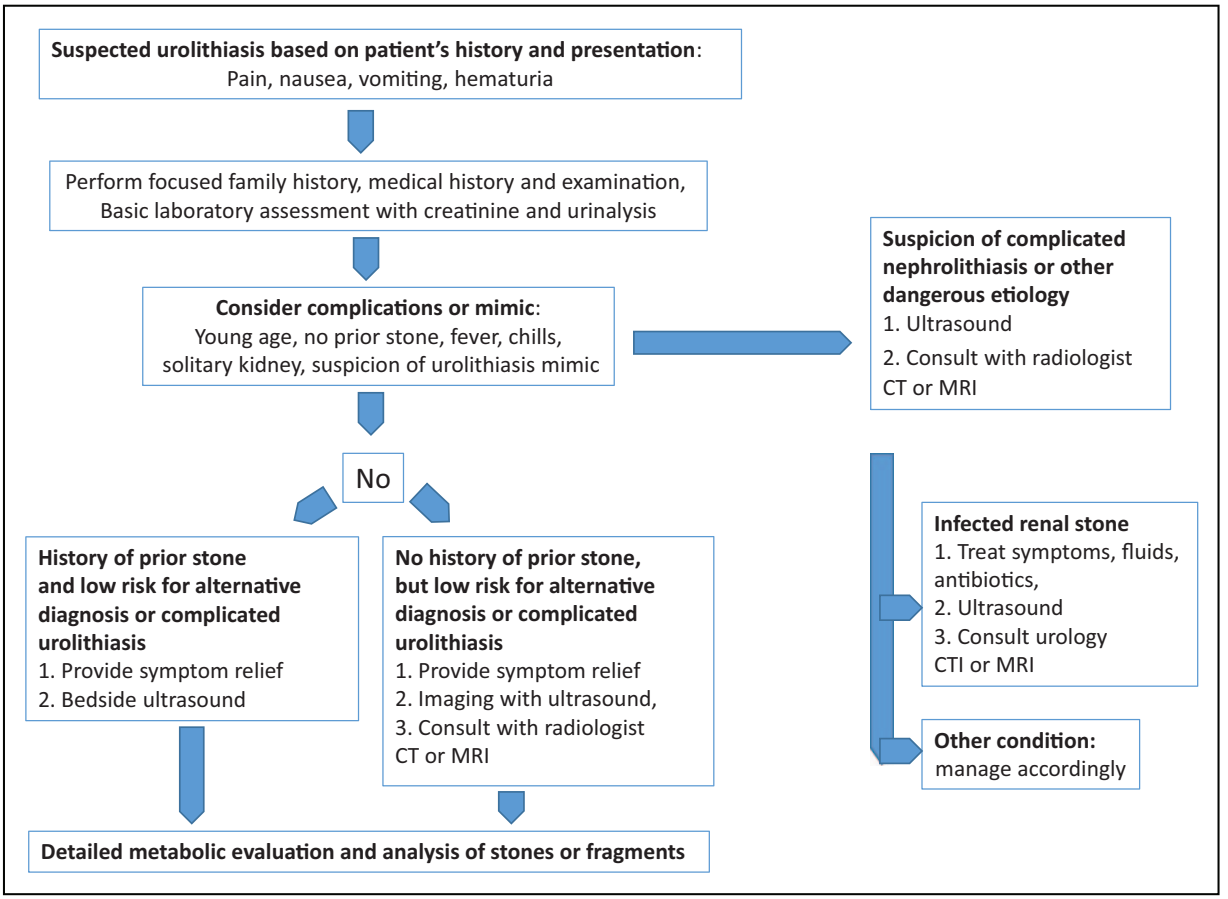

FIGURE 1. The urolithiasis diagnostic pathway (based on [5▪,23▪,25,29]).

genitalia, further vegetative signs such as nausea and vomiting frequently accompany the painful colic [32].

Dilatation of the urinary tract due to obstruction is not an obligatory diagnostic mark of the passage of a stone. According to a recent study including 248 consecutive patients presenting with ureteral colic, nearly 11% did not demonstrate any dilatation and the majority (nearly 71%) had only mild hydronephrosis. Stone diameter was related to the degree of hydronephrosis, whereas age, sex and stone location were not [30]. Smaller stone size and lower incidence of hydronephrosis could explain the lower diagnostic accuracy of ultrasound compared with CT for detecting ureteral stones [30].

Lower incidence of hydronephrosis in the case of small stones is a matter of debate and may raise the question whether the symptoms conceivably result from transient hydronephrosis which cannot be detected with imaging modalities [33].

Clinical signs are also largely dependent on the age of the child. The younger a child is the less characteristic the symptoms are. In infants, irritability, inconsolable crying, poor feeding, vomiting and in the case of urinary tract infection, signs and symptoms of sepsis may occur [25,26,29].

In young children poorly localized (often periumbilical or umbilical) abdominal pain, vomiting, diarrhea or constipation can be major challenges for the differential diagnosis. Only older children present symptoms similar to those seen in adults. The pain typically begins as waxing and waning flank pain in the acute phase [5▪,34]. Ipsilateral genital pain is a common symptom of distal ureteral stones. As renal stones not causing obstruction are usually asymptomatic, the detection of a nonobstructive stone with imaging techniques requires consideration of another etiology of the patient's symptoms [29,35].

Hematuria

Hematuria can be macroscopic or more commonly microscopic. In the case of incidentally discovered asymptomatic stones hematuria may be absent. Accordingly, using hematuria to predict the presence of urolithiasis has an accuracy of only 60% and the absence of hematuria does not rule out urolithiasis [7,36].

Microscopic hematuria may precede the appearance of kidney stones by years and is often associated with hypercalciuria [37▪,38]. Hypercalciuria is

considered to be an important contributor to stone formation; however, individual studies provide very different prevalence data, ranging from 10 to 50% [15,39,40,41▪]. Further, isolated hypercalciuria without renal stone disease is associated with an increased frequency of urinary tract infections [42]. Thus, hypercalciuria and stone disease should be considered among the risk factors for UTI and should be investigated particularly in patients with a family history of urinary stones [43▪].

Infection

Urinary tract infections may be present in up to 30% of patients with urolithiasis. Age below 2 years at diagnosis, the presence of a metabolic risk factors and size of stone above 5.3 mm are significant risk factors for infection [43▪].

Fevers and chills are not common in uncomplicated urolithiasis, but if present, should raise concern for an infected stone [25,44].

DIAGNOSTICS

Initial evaluation depends on the situation in which the stone is discovered and includes laboratory testing and radiological imaging.

Laboratory testing

In the ED laboratory testing and imaging should focus on the detection of the suspected renal stone and its eventual acute consequences, such as obstruction, infection, and occasionally pre and/or post renal failure [5▪,25].

A more detailed metabolic evaluation [40,41▪] including urine osmolarity, excretion of solutes such as calcium, sodium, oxalate, urate, citrate, magnesium, cysteine, urine pH, etc., should take place after the resolution of the initial violent signs and symptoms, or in the case of an accidentally discovered 'silent' stone, because in the acute phase dehydration (due to vomiting) and therapeutic measures (intravenous fluids with NaCl load) can significantly influence urinary concentration and excretion of solutes.

Blood tests

Dehydration due to vomiting can lead to a transient rise in serum creatinine of prerenal origin [5▪,36]. More severe creatinine elevation may be detected in patients with solitary kidney or cases with bilateral obstruction (postrenal mechanism) [45], advanced chronic kidney disease at baseline (acute on chronic mechanism). Eventually drug-induced crystal nephropathy may induce serious acute kidney injury [46▪▪,47▪,48]. Medication may further be associated with renal stone disease and increase incidence by influencing the enteral microbiome [49▪▪].

Parameters indicative of inflammation, such as increment of neutrophil count or C reactive protein, may help to differentiate complicated urolithiasis with infection from an uncomplicated stone [5▪,29,36]. However, as an increase in neutrophil count can also be due to a stress reaction, it should be considered rather as a supplement to clinical decision-making [36].

Urinalysis

Urinalysis reveals the presence of hematuria. However, hematuria may be absent in the case of a silent stone or in a patient with complete obstruction. Urinary crystals are common in healthy patients. As the voided urine specimen cools down during storage on room temperature, the solubility of urine components decreases leading to in-vitro crystal formation. Thus, the presence of crystals *per se* is insufficient for the diagnosis of urolithiasis. As exception to the general rule, specific crystal forms (e.g. cystine) are informative of the metabolic condition leading to stone disease [1]. The presence of urinary white blood cells under light microscopy, a positive leukocyte esterase reaction and nitrites on the test strip are suggestive for urinary tract infection. However, urolithiasis can cause sterile ureteral inflammation, thus urinalysis should always be evaluated together with clinical symptoms and the result of urine culture [43▪].

Diagnostic imaging

While native abdominal radiography and intravenous urography were the standard methods to detect urolithiasis and consequent urinary obstruction in adults as well as in children for decades, with the arrival of ultrasound and CT diagnostic algorithms have undergone fundamental changes. In adult urology CT has become the standard for stone imaging. Low-dose CT scans can now be performed with a similar or less amount of radiation as plain radiographs, without the need for intravenous contrast [50]. In pediatrics however, both the American Urological Association and the European Society for Pediatric Radiology recommend ultrasound as the initial imaging modality [51,52]. Accordingly, abdominal radiography is not used routinely in children anymore. If clinical suspicion of urolithiasis is high enough ideally ultrasound is usually chosen for imaging [53▪] (Figs. 2–4).

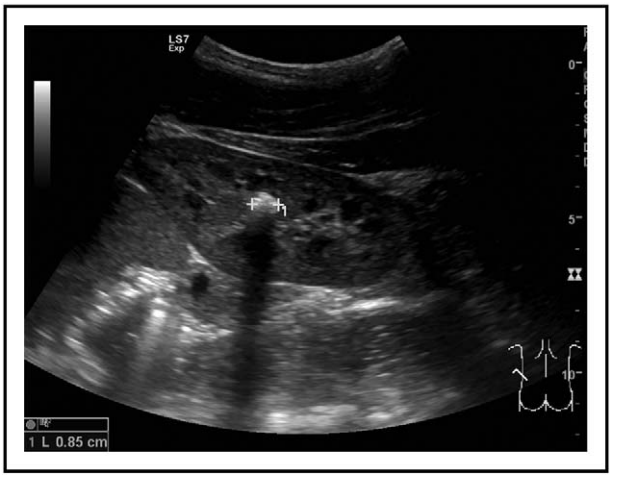

FIGURE 2. A nonobstructive hyperechogenic renal stone with acoustic shadow is seen in the pyelum.

Indeed, ultrasound evaluation has its limits. In a pediatric comparative study from 68 renal stones detected by CT 30 were not recognized by ultrasound. Altogether, ultrasound was 66.7% (48.8–80.8%) sensitive and 97.4% (86.8–99.9%) specific for detecting stones. However, of the 30 stones not detected by ultrasound, only three were more than 3 mm according to CT. Thus, in the clinical practice, ultrasound has high specificity for detecting nephrolithiasis in children but only moderate sensitivity for stones more than 3 mm, where false negatives are common [54▪]. The sensitivity of ultrasound can be enhanced by the color Doppler technique using the stone-triggered artifact called twinkling artifact. The twinkling artifact is a mixture of rapidly alternating red and blue pixels behind a strongly reflective object (e.g. calculus) resembling turbulent blood flow. This phenomenon is thought to be secondary to intrinsic machine 'noise' within the color Doppler circuitry of the ultrasound device [55,56▪▪,57▪] (Fig. 5a and b).

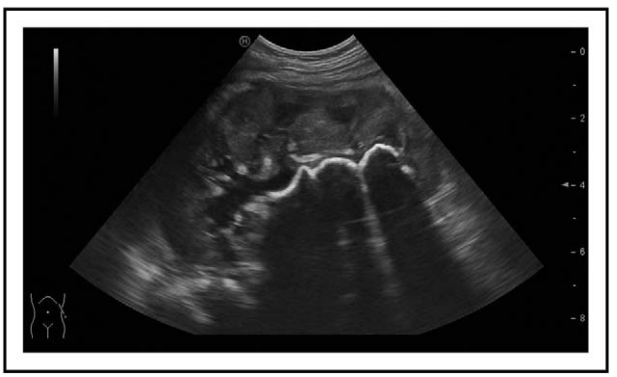

FIGURE 3. Staghorn stone filling the pyelum seen in a cystinuria patient. Please note the marked acoustic shadow. The pyelum and some of the chalices are markedly dilated.

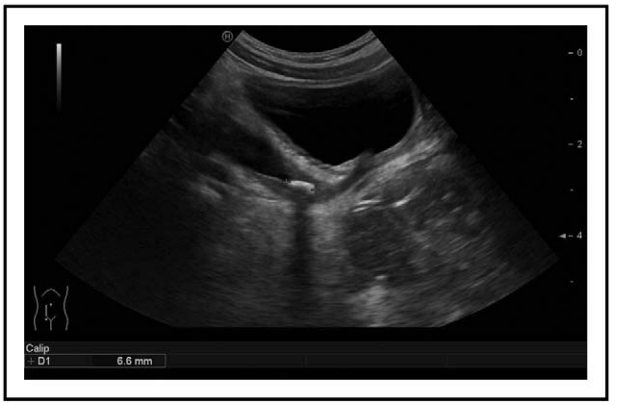

FIGURE 4. An ureterolith with an acoustic shadow is seen in the ureter near the ureterovesical junction. As part of the consequent obstruction, a dilated ureter is visible behind the bladder.

Meanwhile, thanks to continuous technical progress the radiation burden of CT has also decreased substantially; however, it is indeed still not negligible [50]. Thus, there is a constant effort to

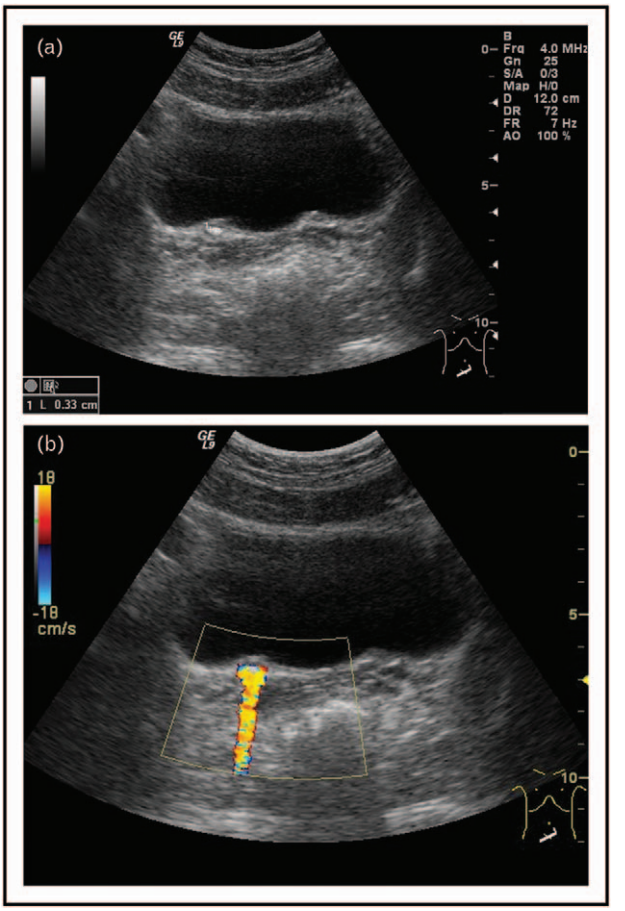

FIGURE 5. A nonobstructive small stone is shown at the ureterovesical junction (a). A stone-triggered artifact called twinkling artifact is seen (in the same patient) with color Doppler imaging (b).

assist clinical diagnostics with appropriate imaging algorithms [52,53▪,58] to reduce rates of initial and overall CT utilization without adversely impacting downstream care.

Evaluating risk factors of stone formation

The risk factors should be assessed in two steps.

The first examination is intended to support general orientation. History of underlying structural abnormalities of the kidney and urinary tract should be explored together with the history of nephrolithiasis in parents and siblings, as the offspring of renal stone formers may carry several metabolic risk factors similar to their parents and which are predisposing to stone formation [59]. Further, cystinuria and hyperoxaluria may show increased occurrence in consanguineous families. Perinatal medical history with focus on prematurity, vitamin D supplementation, conditions leading to immobilization, dietary habits with special focus on salt and animal protein intake should be explored, daily fluid intake should be evaluated [60▪,61▪].

Further questions concerning medical history should refer to medications associated with stone formation [46▪▪,47▪,48] and history of recurrent urinary tract infection, especially when caused by a urease-producing organism, such as Proteus or Klebsiella [28,62].

The patient should be examined for the presence of manifest or latent malabsorptive intestinal diseases and conditions, such as Crohn's disease, ulcerative colitis and short gut syndrome as they increase the risk of stone formation [63,64,65▪].

In a second step, following the resolution of the acute symptoms a more detailed metabolic evaluation should take place.

While maintaining habitual fluid intake and dietary habits, a quantitative analysis of urinary solutes, both promoters and inhibitors of stone formation, and the assessment of daily fluid and food intake urine analysis should be performed [66].

The most appropriate method of urine collection is still a matter of debate. 24-h urine collection [67] can be achieved in toilet-trained children, whereas in children who are not toilet-trained the solute/creatinine ratio in a single spot urine can be utilized to assess solute excretion. Alternatively, the use of 12 h urine collection and second morning sampling or afternoon single spot urine has also been proposed. Pediatric normal values for the constituents, such as calcium, oxalate and citrate are available and should be used as reference [67–70].

Using the concentration of urine constituents, different equations have been constructed to predict the risk of crystal precipitation [67,71,72▪]. Further, laboratory methods to explore the point of supersaturation and crystal formation have been designed [73▪]. However, these are not part of the everyday clinical practice.

The analysis of stones or fragments of stones obtained after spontaneous passage or surgical intervention should always be performed. As stone composition can change over time, recurrent stones should always be analyzed as well [66]. The methods of choice for analysis are radiograph diffraction or infrared spectroscopy [74]. This can lead directly to the diagnosis of rare diseases, such as cystinuria or adenine phosphoribosyl transferase defect.

CONCLUSION

The diagnosis of suspected nephrolithiasis is based on medical and family history, presenting signs, physical examination, first laboratory and radiological workup. Ultrasound should be the initial diagnostic imaging performed in pediatric patients while low-dose CT is rarely necessary for management. Metabolic factors including hypercalciuria, hypocitraturia, low fluid intake as well as specific genetic diseases should be explored after the resolution of initial signs and symptoms.

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Conflicts of interest

There are no conflicts of interest.

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