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UROLOGY - REVIEW

Diagnosis and management of non-calcium-containing stones in the pediatric population

Saritha Ranabothu[1] · Ari P. Bernstein[2] · Beth A. Drzewiecki[3]

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Abstract

Compared to adults, urolithiasis is less common in children, with a definite rise in incidence, especially among young adults (Tasian et al. in Clin J Am Soc Nephrol 11:488, 2016). In the last 25 years, the incidence in children has increased by approximately 6–10% annually, for reasons still unknown, with an associated significant increase in related health care-related expenditures (Hyams and Matlaga in Transl Androl Urol 3(3):278–83, 2014). It has been shown that there is twice as high a risk of chronic kidney disease (CKD) or end stage renal disease (ESRD) in stone formers compared to non-stone formers (Tasian et al. 2016). While calcium-containing stones are by far the most common category of stone encountered in both children and adults, non-calcium stones are more common in children than adults and have been shown in several studies to be associated with greater morbidity and lower renal function than calcium stones (Issler et al. in BMC Nephrol 18(1):136, 2017; Gambaro et al. in J Urol 198:268–273, 2017). This could be related to the challenges in the management of non-calcium-containing stones due to associated infection or metabolic derangements, further leading to recurrence and loss of renal function. There is currently a gap in our understanding of how to appropriately and effectively encounter and manage patients with non-calcium-containing stones, as such cases are encountered less frequently. Identification of stone composition and appropriate management is very important to reduce serious complications and recurrence, especially in non-calcium stones. We present a review of diagnosis and management of non-calcium-containing stones in the pediatric population, in hopes of providing more clarity to providers and promoting a consideration of non-calcium stone composition with all children presenting with urolithiasis.

Keywords Non-calcium-containing stones · Children · Challenges in management · Recurrence

Introduction

Urolithiasis is less common in children [1], accounting for 2–3% of all urinary stones; however, the incidence is rising by up to 10.6% annually [2]. The exact reasons for this are unknown, but may include changes in lifestyle, diet, and imaging modalities. In adults, obesity has been shown to be associated with increased stone prevalence, secondary to metabolic syndrome and diet [3]. The role of obesity in pediatric stones is controversial with studies showing varying results [4].

Calcium-containing stones are more common in both adults and children, constituting 70–80% of all urolithiasis. Stone composition can vary considerably with differences in age, sex, and geography [5]. Identification of stone composition and appropriate management in children is important to reduce complications and recurrence, which is almost 50%

✉ Ari P. Bernstein
abernst2@mail.einstein.yu.edu

Saritha Ranabothu
SRanabothu@uams.edu

Beth A. Drzewiecki
bdrzewie@montefiore.org

[1] Pediatric Nephrology, Arkansas Children's Hospital, University of Arkansas Medical Sciences, 1 Children's way, Little Rock, AR, USA

[2] Montefiore Medical Center, Albert Einstein College of Medicine, 1925 Eastchester Rd. Apt 23G, Bronx, NY 10461, USA

[3] Montefiore Medical Center, 3400 Bainbridge Ave, 5th Floor, Bronx, NY 10467, USA

in 3 years [6]. Genetic and anatomic abnormalities are also associated with higher incidence of urolithiasis in children.

The body of literature on pediatric urolithiasis is improving as the incidence and health care burden continues to increase. Appropriately, most of it is focused on the more common calcium-containing stones. While still rare, non-calcium-containing stones are more prevalent in the pediatric population due to anatomic, metabolic, and genetic abnormalities leading to earlier presentation of the disease, along with higher rates of recurrence. Workup and treatment of these patients can be challenging since they are not commonly encountered. We present a review of the available literature on non-calcium-containing stones that are encountered in the pediatric population including magnesium–aluminum–phosphate (struvite), cystine, uric acid, xanthine, and 2,8 dihydroxyadenine (2,8-DHA) stones. Our primary goal was to identify differences in diagnosis and management of patients with non-calcium stones, given that these patients appear to be at higher risk for renal impairment.

Materials and methods

A search was made through Pubmed, Medline, Embase, and Cochrane library using terms "kidney calculi," "nephrolithiasis," "urolithiasis," and "kidney stones due to in born errors of metabolism." Our initial search was limited to ages 0–18, English language, and all articles published within the last 5 years. A second, more focused search for the individual non-calcium stones such as "uric acid urolithiasis," "cystinuria," "struvite urolithiasis," "xanthine urolithiasis," and "2,8 dihydroxyadenine (2,8-DHA) urolithiasis" was performed which did not include the restrictions of patient age or year of publication.

Results

895 journal articles met initial inclusion criteria. Of those, 125 articles were related to our review, including epidemiology, clinical features, current trends in diagnosis and treatment. Further refinement to focus on the specific non-calcium stones left 90 articles that met final inclusion criteria for review.

Background on non-calcium-containing stones

Struvite urolithiasis

Struvite stones, often termed infection stones, are magnesium-ammonium-phosphate and/or calcium carbonate apatite, forming when the urinary tract is infected with urease producing bacteria (Table 1a). Struvite stones also form in combination with calcium stones and constitute ~ 24% of staghorn calculi [7]. Though there has been shift in the cause of pediatric urolithiasis from infectious to metabolic origin, struvite stones still contribute about 10–20% of pediatric urolithiasis and carry significant morbidity [4, 8]. Predisposing factors to form struvite stones are listed in Table 1a.

Table 1 Risk factors for struvite stone formation (a) and hyperuricemia (b) in children

(a) Risk factors for struvite stones	(b) Risk factors for hyperuricemia
Younger age	Glycogen storage disease
Obstructive uropathy	Chronic diarrheal states
Chronic indwelling catheter	Myeloproliferative disorders
Urinary diversion	Severe burns
Neurogenic bladder	Tumor lysis
Urethral stricture	Probenecid
Prior urologic surgeries	Mannitol
Male gender	Radiographic contrast agents
	Losartan
	High-dose salicylates

Urease-producing organisms: *Proteus* spp., *Providencia* spp., *Klebsiella* spp., *Morganella morganii, Serratia urealyticum*

Several adult studies have shown that 20–25% of struvite stones are associated with CKD and ESRD, especially when treated conservatively [5]. A recent study in children showed a 9% risk of CKD in struvite stones compared to stones of metabolic origin [4]. Other studies have demonstrated severe papillary inflammation associated with struvite stones which could explain their increased risk of progression to CKD [9].

Clinical presentation of struvite stones varies, with the majority presenting with renal colic. Other symptoms include fever, gross hematuria, urinary tract infection (UTI)/urosepsis, or CKD [5]. Sometimes they are asymptomatic and found incidentally on ultrasonography. Struvite stones form quickly and prefer an alkaline environment, which precipitates ammonium magnesium phosphate [10].

Uric acid urolithiasis

Children have a higher urinary pH, making them less susceptible to uric acid urolithiasis. Pure uric acid stones contribute 5% of the urinary stone disease in children, with most presenting in mixed composition, and are more common in males than females [8]. Hyperuricosuria, low urine pH (< 6), and low urine volume are risk factors to develop uric acid urolithiasis [10]. Urinary uric acid secretion in children varies by age, with infants excreting higher uric acid. Normal uric acid excretion in children > 3 years is 0.56 mg/dl glomerular filtration rate or < 815 mg/1.73 m^2/24 h or < 10 mg/kg/day. One study of healthy children and adolescents found that mean values in preschool, school aged, and

adolescents on 24-h collection were 175 ± 78, 270 ± 110, and 380 ± 145 mg, respectively. Values exceeding 750 mg in adults are considered hyperuricosuria [11]. Patients with obesity, diabetes, metabolic syndrome, and monogenic metabolic disorders of purine and pyrimidine metabolism are also at increased risk [12].

Most inborn errors of purine and pyrimidine metabolism are characterized by hyperuricosuria. Phosphoribosyl pyrophosphate (PRPP) synthetase super activity is an X-linked disorder associated with excessive uric acid production, sensorineural deafness, gout, and other neurological features. The metabolic pathway of purine metabolism and formation of uric acid are described in Fig. 1. Signs and symptoms may start during infancy. Hypoxanthine-guanine phosphoribosyl transferase (HGPRT) deficiency is an X-linked recessive disorder, which affects males, leading to accumulation of PRPP and subsequent increased production of uric acid [13]. Lesch-Nyhan syndrome is a severe form of HGPRT deficiency presenting with extra renal manifestations of dystonia, choreo-athetosis, ballismus, cognitive attention deficit, and self-destructive behavior. The excessive uric acid production leads to hyperuricosuria and stone formation. Initially, they may present with neonatal crystal nephropathy, passing orange crystals in the diaper. The absence of treatment can lead to obstructive stone disease and chronic renal insufficiency. Table 1b describes other risk factors for hyperuricemia.

Hyperuricosuria can present with microscopic or gross hematuria, orange crystalluria, urolithiasis or flank pain [14]. Uric acid can induce calcium oxalate precipitation by reducing its solubility and increasing adsorption of calcium crystal inhibitors [15].

Xanthine urolithiasis

Xanthine stones are an extremely rare form of urolithiasis in those with hereditary xanthinuria, myeloproliferative disorder, and Lesch-Nyhan syndrome subjects taking allopurinol [16]. Hereditary xanthinuria can be due to isolated xanthine oxidase deficiency (type 1) or combined xanthine oxidase and aldehyde oxidase deficiency (type 2). Type 1 patients are largely asymptomatic, but up to 1/3 of patients have urolithiasis. Type 2 patients often have neurological manifestations. Some patients may have failure to thrive, vomiting, UTI, myopathy [17]. Clinical course can progress from acute to chronic renal failure. Xanthine oxidase deficiency is usually a benign disorder; however without treatment urolithiasis recurrence rates are high.

Very little data exist on xanthine urolithiasis. When xanthinuria is associated with stones, presentation is earlier and more severe. Clinical presentation may be non-specific, thus protracting an accurate diagnosis. Few case reports exist, describing patients with early age at presentation with abdominal pain and hematuria, and acute or chronic renal

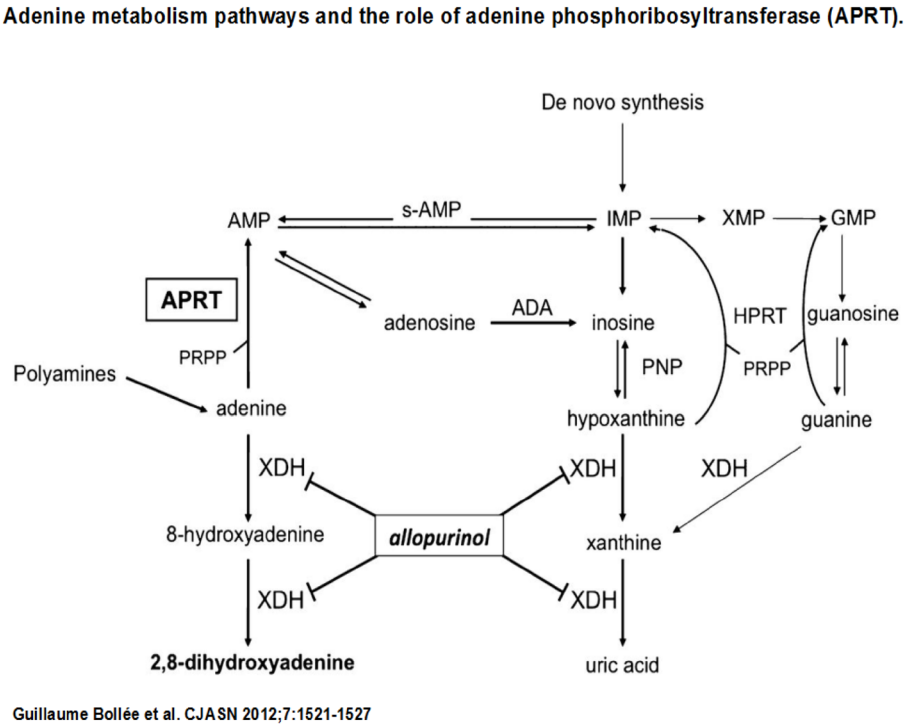

Fig. 1 Adenine metabolism pathways and the role of adenine phosphoribosyltransferase (APRT). In humans, adenine cannot be converted to adenosine as hypoxanthine to inosine; the only alternative pathway in APRT deficiency is oxidation of adenine to 2,8-dihydroxyadenine by xanthine dehydrogenase (XDH). Allopurinol acts by inhibiting XDH, thus preventing 2,8-dihydroxyadenine synthesis. *ADA* adenosine deaminase, *AMP* adenosine monophosphate, *GMP* guanosine monophosphate, *HPRT* hypoxanthine phosphoribosyltransferase, *IMP* inosine monophosphate, *PNP* purine nucleoside phosphorylase, *PRPP* 5-phosphoribyl-1-pyrophosphate

failure. Orange crystalluria may be present and can be sent for analysis [18, 19]. Xanthine urolithiasis is typically 100% pure xanthine without a mixed component to them.

Cystine urolithiasis

Cystinuria is a hereditary, heterogeneous defect in reabsorption of cystine and the dibasic amino acids ornithine, arginine, and lysine from the luminal fluid of the renal proximal tubule and small intestine [20]. Cystinuria is defined as urinary excretion of cystine > 1300 µmol/g of creatinine or sum of dibasic amino acids > 5900 µmol/g of creatinine in 24-h urine collection. Two genes have been identified in cystinuria: SLC3A1 and SLC7A9. They are inherited in an autosomal recessive fashion with incomplete dominance. Formation of cystine stones is the only clinical presentation and accounts for 6–8% of stone disease in the pediatric population [21]. Approximately 50% of patients with cystinuria will develop stones.

Clinical presentation is similar to other forms of urolithiasis, including hematuria, flank pain, nausea, UTI, or renal failure. Strong family history, hexagonal crystals or large, branched staghorn calculus should raise the suspicion of cystinuria [22]. Cystine stones are usually large at presentation and have a high recurrence rate. Males are more severely affected than females [23]. Cystine urolithiasis can lead to decreased GFR and CKD [21].

2,8 dihydroxyadenine (2,8-DHA) urolithiasis

Adenine phosphoribosyl transferase (APRT) deficiency is a rare, autosomal recessive defect of uric acid catabolism that leads to the accumulation of 2,8 dihydroxyadenine (2,8-DHA) (Fig. 1), a highly insoluble substance excreted by the kidney that precipitates in urine [24]. Intratubular deposition of crystals results in chronic tubulointerstitial nephritis with progressive sclerosis and chronic renal failure developing in adulthood. The urinary tract appears to be the only organ system affected. Early diagnosis and treatment is essential to prevent the renal failure and recurrence [25, 26].

The first stone episode often occurs in the first decade of life, sometimes with renal failure [24]. Children may present with reddish-brown diaper stains, UTIs, or hematuria. 2,8 DHA crystals are typically round and reddish-brown with central Maltese cross appearance under polarized urine light microscopy [24].

Stone assessment and management

Laboratory workup

Basic metabolic panel (BMP) and urinalysis are important to assess kidney function and urine characteristics in all presenting cases of urolithiasis. Struvite stone workup must include urine culture to evaluate for infection and identification of urease producing organisms. Uric acid stones require serum and urinary uric acid levels at presentation, as well as enzyme assays to confirm hyperuricosuria due to enzyme deficiencies [14]. A 24-h urine collection may not show hyperuricosuria, even in the presence of active uric acid stone formation, but should be obtained in all pediatric patients with urolithiasis. Low urine pH has good sensitivity and specificity in detection of uric acid stones. Xanthine stones require serum uric acid and 24-h urinary excretion of hypoxanthine, xanthine, and uric acid. Confirmatory diagnosis of hereditary xanthinuria to assess for xanthine oxidase deficiency requires tissue measurement of xanthine oxidase levels in intestinal mucosa or liver. Such patients will have very low to undetectable serum and urinary uric acid with high levels of urinary hypoxanthine and xanthine.

If clinical suspicion of cystine urolithiasis is high, a sodium-cyanide-nitroprusside test offers a rapid qualitative determination of cystine concentration prior to 24-h urine collection. Cyanide reduces the cystine to cysteine, binding to nitroprusside and causing a color change to red–purple. Genetic testing can be performed to identify patients with cystinuria who are high risk for forming stones due to the underlying genetic abnormality. Siblings of an index patient should be screened [23]. 2,8 DHA stone workup should consist of evaluating APRT activity in red blood cells and renal biopsy. The complete absence of activity in red blood cells is diagnostic, whereas lower levels of activity might indicate heterozygosity and novel mutations. Renal biopsy can reveal 2,8 DHA crystalline nephropathy in the intratubular, intracellular, or interstitial regions.

In patients where the urolithiasis has a hereditary component, parents should be offered genetic counseling and screening when appropriate.

Ultimately, stone analysis is the most sensitive and specific test for all stone compositions and must be performed in stones that are passed or extracted, with infrared and UV spectrophotometry recommended.

Imaging

Struvite stones often have a mixture of calcium components and therefore can be identified with sonography and/or roentgenography (X-ray). Cystine stones are radiopaque, but less dense than calcium stones with a ground glass appearance on roentgenography. Sonography alone or in combination with roentgenography can be successful in identifying cystine stone burden. If struvite or cystine staghorn calculi are identified, CT imaging may be required for preoperative planning. In a single center study of cystinuric pediatric patients, the median number of imaging tests was > 3 per year, over half of them associated with radiation.

Staghorn calculi were more highly associated with need for helical CT scan [27].

Uric acid, xanthine, and 2,8 DHA stones are radiolucent; thus, diagnosis with roentgenography is not possible. Renal sonography can provide information regarding hydroureteronephrosis, and non-obstructing stones, but diagnosis of acute, obstructing ureteral stones of these compositions is limited with this modality. Non-contrast CT provides superior diagnostic sensitivity for detection of obstructing uric acid, xanthine, and 2,8 DHA urolithiasis; however, this must be weighed against the increase risk of radiation to children [28]. When possible, dual energy CT scans and low-dose protocols should be utilized to afford better definition of calcium versus non-calcium urolithiasis as well as reducing radiation exposure.

Treatment

Struvite stone intervention involves complete stone removal followed by antibiotic treatment, although no guidelines exist for sufficient antibiotic duration. Urosepsis risk is prevented with pre/postoperative antibiotics following a positive urine culture, even in the absence of symptoms. Retrograde intrarenal stone surgery (RIRS), also known as ureteroscopy and laser lithotripsy, is safe and effective in children with large stones of any composition (> 2 cm) in the renal pelvis or ureter [20–22]. This may require preliminary stenting of the ureter for 1–2 weeks to allow for passive dilation in order to allow the ureter to accommodate the ureteroscope without injury to the ureter. Percutaneous nephrolithotomy (PCNL) has higher stone-free rates in these larger stones but at the increased risk of longer hospitalization, higher blood loss, increased radiation, urine leak or pain. Extracorporeal shock wave lithotripsy (ESWL) can provide very high stone-free rates in smaller stones (< 2 cm) that are not in the lower pole, and can be easily repeated. Minimally invasive PCNL has been developed for smaller stones that are located in the lower poles to reduce the complications [29]. Other adjuvant or alternative therapies such as the use of a urease inhibitor (acetohydroxamic acid, hydroxyurea), dissolution techniques, and urine acidification methods have only minimal benefit and are currently less commonly utilized [30]. Few studies evaluate recurrence rate of struvite stones in the pediatric population, with rates varying from 1 to 14%; however, adult studies have shown 10% recurrence following complete removal which increased to 85% with persistence of residual stone [6, 21]. Complete extraction of stones at time of surgery is of key importance, as well as identification of underlying bladder and bowel dysfunction, and prevention of future urinary tract infections.

Uric acid stones respond well to medical management with low-likelihood of stone recurrence. Medical treatment involves alkalinization of urine with potassium citrate or potassium bicarbonate (1–2 meq/kg/day) and aggressive fluid intake to produce urine output ~ 2 L per day or 1 ml/kg/h. Pre-existing stones can be dissolved with medical management. Some patients with significantly elevated plasma uric acid levels (> 1000 µmol/L) may require allopurinol to

Table 2 Cystine stone treatment guidelines

Conservative
Hydration and diet
Hydration (2 L/m^2/day or 3–5 L/day)
Diet with low methionine intake (protein restriction is not advisable in children), increase intake of fruits, vegetables (to increase pH) and reduce salt intake
Pharmacological treatment
Alkali supplementation (to keep urine pH 7–7.5)
Thiols
D-Penicillamine (pediatric: 20–40 mg/kg/day, adult: 0.5–2 g/day)
α-mercaptopropionylglycine (alpha-MPG also known as tiopronin) (pediatric: 10–15 mg/kg/day, adult initial dose: 250 mg/day, gradual increase to 400–1200 mg/day, max dose: 2 g/day)
Adverse effects: fever, rash, arthralgia, leukopenia, gastrointestinal intolerance, proteinuria, and nephritic syndrome. Long-term therapy may lead to vitamin B-6 (pyridoxine) deficiency, vitamin B-6 supplementation (50 mg/day) is recommended
Captopril: (patients intolerant to thiols) 50 mg three times a day
Surgical management
Chemolysis (THAM (tris-hydroxymethyl-aminomethane) or the chelating solution acetylcysteine 2%)
Shock wave lithotripsy (SWL) especially stones with rough morphology compared to smooth morphology
Ureterorenoscopic stone removal (URS)
Percutaneous nephrolithotomy (PNL) (large and branched cystine stones)
Open or laparoscopic surgery

reduce levels below 400 μmol/L. 95% of urinary uric acid will be soluble at a urinary pH of 7. Reduction of purine dietary intake (red meat, poultry, fish, and legumes) is imperative [21]. Intermittent urinalysis is recommended to maintain desirable urinary pH. Surgical intervention is required when large stones cause acute obstruction, sepsis, and severe pain. Surgery options include ESWL, RIRS, and PCNL, depending on stone burden, location, and patient characteristics as previously described.

2,8 DHA stones are also medically treated with allopurinol with great success [17]. Treatment may cause dissolution of pre-existing stones and improve renal function [18]. A low purine diet and high fluid intake can result in permanent absence of stones. Surgery is only indicated for large, obstructing stones, and intervention would be based on clinical presentation.

Xanthine stone treatment is similar to uric acid stones, including low purine diet and high fluid intake [14]. Alkalinization of urine has been used but has been only modestly effective in the increase of xanthine solubility. Potassium citrate is recommended with concomitant hypocitraturia. Allopurinol is also used to block conversion of hypoxanthine to xanthine, as hypoxanthine is soluble in urine (Fig. 1). Surgical intervention is required for obstructing or growing xanthine stones. These stones are soft and responsive to ESWL, RIRS, and PCNL. Stones must be easily visible on sonography for ESWL. Pyelolithotomy has been historically required due to large stone burden and chronic obstruction.

Cystine stone management is described in Table 2. Thiol-containing medications can dissolve stones, although obstruction and high stone burden at presentation make surgical intervention often necessary. Alkalinization of the urine with pH between 7.0 and 7.5 is targeted [27]. Effect is dose dependent and should be titrated. Long-term usage of DP can lead to pyridoxine deficiency, and co-treatment with pyridoxine is suggested [31]. Captopril may also be used in patients that are refractory to DP or alpha-MPG, but also requires titration and is not recommended in patients that have risk factors for renal insufficiency. Surgical management is necessary for high stone burden or obstruction. ESWL may be preferred for smaller stones ≤ 1.5 cm in the upper calyces or proximal ureter. Cystine stones are considered dense and somewhat resistant to fragmentation with ESWL, but concomitant treatment with thiol medications may make stones more susceptible. In a review of their experience with cystinuric patients at Children's Hospital Boston, 16 ESWLs were performed in 6 patients, with 5 of them requiring a repeat procedure [32].

RIRS is an option for patients with cystine stone burdens less than 1.5–2 cm as a primary or secondary procedure, and is ideal for obstructing distal stones. Stones larger than 2 cm or complex staghorn calculi require PCNL or even open or laparoscopic (with or without robotic assistance) nephrolithotomy. The morbidity of cystine urolithiasis is significant, requiring life-long treatment, and has a 60% recurrence rate. A summary of laboratory workup, imaging and treatment interventions is provided in Table 3.

Conclusion

The burden of non-calcium-containing stone disease is more evident in the pediatric population compared to adults. Clinical presentation may be variable depending on the underlying disease process, and all children who present with urolithiasis should undergo metabolic workup to rule out non-calcium-containing and less common sources of urolithiasis. Diagnosis should not be delayed and radiologic imaging is usually necessary. Stone analysis must be performed to properly identify the composition and genetic analyses conducted to identify potential underlying causes. Many stones will not be radiopaque and knowing how to properly investigate these stones while minimizing radiation is critical. Children with recurrent stones or non-calcium-based stones should be treated at pediatric centers with expertise in urolithiasis. When young children present with urolithiasis, atypical stone disease should be considered.

Table 3 Evaluation and management of non-calcium-containing stones

	Struvite	Uric acid	Xanthine	Cystine	2,8 PHA
Laboratory	UA/UCx	UA for pH	UA	UA	UA
	24-h urine collection	Serum/urinary uric acid	Serum uric acid	24-h urinary cystine	Stone/crystal analysis
	BMP, Ca, PTH	BMP	BMP	BMP	BMP
		24-h urine collection	24-h Urinary xanthine, hypoxanthine, uric acid	Sodium-cyan-nitroprusside test	Renal biopsy
		Enzyme assay	24-h urine collection	Genetic testing for SLC3A1, SLC7A9 mutation	APRT activity RBCs
			Tissue measurement of xanthine oxidase		
Radiologic	RBUS + KUB	Sonogram		RBUS + KUB	RBUS
	CT (individual cases)	CT if presence of hydroureteronephrosis with negative KUB for stone		CT (individual cases)	CT (individual cases)
	Struvite	Uric acid	Xanthine	Cystine	2,8 DHA
Medical	Abx	Urinary alkalinization (pH > 6)	Urinary alkalinization (pH > 7)	Urinary alkalinization (pH 7.0–7.5)	
	Rear underlying metabolic abnormalities	Fluid hydration	Fluid hydration	Fluid hydration	Fluid hydration
		Low purine diet	Low purine diet	Low methionine diet	Low purine diet
		Allopurinol (5–10 mg/kg/day, single or divided doses)		Thiol medications (D-penicillamine; pediatric: 20–40 mg/kg/day, adult: 0.5–2 g/day + pyridoxine supplementation), α-mercaptopropionylglycine pediatric: 10–15 mg/kg/day, adult initial dose: 250 mg/day, gradual increase to 400–1200 mg/day, max close: 2 g/day)	Allopurinol (5–10 mg/kg/day, single or divided doses)
				Captopril (50 mg PO TID)	
Surgical	ESWL	ESWL	ESWL	ESWL	Infrequently required
	RIRS	RIRS	RIRS	RIRS	
	PCNL		PCNL	PCNL	
	Treatment of obstructive urologic disease		Pyelolithotomy		

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Compliance with ethical standards

Conflict of interest One author has a financial relationship with Astellas, mentioned by name in our cover letter. We have no other conflicts to disclose.

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