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Shockwaves and the Rolling Stones: An Overview of Pediatric Stone Disease

Naima Smeulders[1], Alexander Cho[1], Abdulelah Alshaiban[1,2], Katharine Read[1], Aisling Fagan[1], Marina Easty[1], Kishore Minhas[1], Alex Barnacle[1], Wesley Hayes[1] and Detlef Bockenhauer[1,3]

[1]Great Ormond Street Hospital National Health Service Foundation Trust, London, UK; [2]Department of Pediatrics, College of Medicine, King Saud University, King Saud University Medical City, Riyadh, Saudi Arabia; and [3]Department of Renal Medicine, University College London, London, UK

Urinary stone disease is a common problem in adults, with an estimated 10% to 20% lifetime risk of developing a stone and an annual incidence of almost 1%. In contrast, in children, even though the incidence appears to be increasing, urinary tract stones are a rare problem, with an estimated incidence of approximately 5 to 36 per 100,000 children. Consequently, typical complications of rare diseases, such as delayed diagnosis, lack of awareness, and specialist knowledge, as well as difficulties accessing specific treatments also affect children with stone disease. Indeed, because stone disease is such a common problem in adults, frequently, it is adult practitioners who will first be asked to manage affected children. Yet, there are unique aspects to pediatric urolithiasis such that treatment practices common in adults cannot necessarily be transferred to children. Here, we review the epidemiology, etiology, presentation, investigation, and management of pediatric stone disease; we highlight those aspects that separate its management from that in adults and make a case for a specialized, multidisciplinary approach to pediatric stone disease.

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The formation of a stone in the urinary tract is, in principle, a simple physicochemical process; at the heart lies the supersaturation of a solute in the urine, so that its concentration exceeds its solubility and the solute becomes a precipitate. Of course, there are many factors that contribute to this process, including which solute is elevated and why. These questions are critical for understanding stone formation and therefore inform the subsequent management. In adults, urinary stone disease is strongly linked to environmental factors, such as dietary habits and obesity.[1,2] For instance, a high intake of animal protein increases the renal acid load and thus promotes the precipitation of solutes with pH-dependent solubility, such as urate.[3] In contrast, children with kidney stones tend to have weights below the average and there is a much higher proportion of underlying Mendelian causes or anatomic abnormalities that predispose to urinary tract infections.[4,5] But even in the absence of an underlying anatomic or genetic abnormality, the recurrence risk in children for stones is high (up to 50% within 3 years of the first episode[6,7]) and many have a predisposing metabolic risk factor, such as hypercalciuria. Consequently, a comprehensive evaluation is critical and has been shown to substantially reduce the recurrence risk.[6] Prevention of future stones episodes is important not only to avoid the acute complications of stone disease, but because recurrent kidney stones are associated with an increased risk for chronic kidney disease.[8]

Still, there are many more differences between pediatric and adult stone disease as follows: adults often describe a stone episode as one of the most painful experiences in their lifetime; in younger children, less than a third may have pain as a presenting symptom and many are diagnosed incidentally.[4,9–11] Pediatric patients are also more likely to have underlying anatomic abnormalities of the urinary tract, that predispose to stone formation. In fact, a predisposing congenital anomaly was found in almost 20% of cases in our cohort[4]; this may demand further investigation and management as well as consideration in determining the strategy to remove stones. Although in

Correspondence: Detlef Bockenhauer, Department of Renal Medicine, University College London, London, UK. E-mail: d.bockenhauer@ucl.ac.uk

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principle the options for removing stones are the same as for adults, children may respond differently and require specific expertise and adaptations.

The economic burden of pediatric urolithiasis is substantial; a study from the United States estimated a minimum annual cost of $375 million for diagnosis and management of pediatric urolithiasis.[12] In this review, we discuss the epidemiology, etiology, presentation, investigation, and management of pediatric urolithiasis, highlighting specific challenges and the importance of a multidisciplinary approach in specialized center s to care for affected children.

Epidemiology

Urinary stone disease is a common problem in adults, with an estimated lifetime risk of 10% to 20% of developing a stone and an annual incidence of approximately 0.9%.[13–15] In contrast, it is a rare problem in children with an estimated incidence of approximately 5 to 36 per 100,000 children, and there appears to be a steady increase over the past 10 to 20 years.[10,11,16–18] The reasons for this are unclear. In adults, the prevalence of stone disease correlates with life style factors typical for affluent societies, such as obesity and increased intake of protein and salt.[19,20] This may in part also apply to pediatric stone disease, because the increased incidence is driven mainly by teenagers with predominantly calcium-containing stones.[11,21] Yet, interestingly, in our own experience, children with kidney stones tend to have weights below the average, arguing against obesity as a major driver for this disorder, at least in younger children.[4] In part, it may also reflect technical advances in imaging, specifically in ultrasound technology because a substantial part of referrals to our stone service concerns children who did not present with an acute stone episode, but instead were incidentally noted to have echogenic "spots" in their kidneys on ultrasound.

There are further epidemiologic differences between pediatric and adult stone disease. Whereas urolithiasis historically had a strong (2–3-fold) male predominance in adults, the sex-distribution was more even in children.[4,22,23] More recent studies suggests that the sex distribution in adults is getting more balanced,[15] whereas there appears to be a predominance of girls in pediatric stone disease.[24–26] Of note, the incidence was highest in adolescent females and these data may in part reflect the increasing prevalence of obesity, because weight appears to impart a greater risk for stone disease in females than males.[19,27] Apart from obesity, other modifiable risk factors that contribute to the stone risk in adults include diet and intake of sweetened beverages.[28] Presumably, these same risk factors become increasingly relevant also in adolescents.

In younger children, however, there is a much higher proportion of underlying anatomic or Mendelian causes.[4,5] Recent studies have shown that in approximately 5% of children with nephrolithiasis, potentially causative variants can be identified and this increases up to 15% if nephrocalcinosis is also assessed.[29,30] Therefore, the presence of kidney stones in prepubescent children, or the identification of specific abnormalities (see Table 1) that suggest an underlying inherited disorder, should always prompt consideration for genetic testing.

Etiology

The majority of children with kidney stones have identifiable risk factors.[4,5] In our own cohort, a metabolic predisposition was identified in one-third; and in approximately 20%, stone disease was associated with urinary tract infection.[4]

Urinary tract infection with urea splitting organisms such as *Proteus* can lead to increased ammonium in the urine, which in turn increases urine pH with consequent supersaturation of magnesium ammonium phosphate (struvite). Infective stones typically present in preschool age, especially in boys, probably reflecting congenital abnormalities of the urinary tract that impair urinary drainage and predispose to infection. In rare cases, stones can lead to chronic infection, culminating in xanthogranulomatous pyelonephritis (Figure 1) and loss of kidney function, emphasizing the importance of recognizing and treating these stones. But even in stones not initially caused by infection, bacteria may contribute to stone formation and growth by reducing urinary citrate and forming crystal-bacteria aggregates that bind to tubular epithelium, promoting inflammation and deposition of matrix proteins.[31]

There is also increasing awareness of the influence of the microbiome on the risk for urinary stones, with some bacteria being protective, such as *Oxalobacter formigenes*, which metabolizes oxalate, whereas other species, such as *Prevotella* are associated with increased stone risk.[32,33]

Hypercalciuria is the commonest biochemical abnormality associated with urinary stone disease in children, found in about half of children with a metabolic predisposition.[4] Hypercalciuria is not associated with hypercalcemia or dietary calcium intake in most children. In fact, as in adults, reducing dietary calcium intake may worsen the stone risk because of the consequent increase in oxalate and phosphate absorption.[34] Premature birth is a risk factor, probably reflecting treatment with loop diuretics and/or episodes of metabolic acidosis in the postnatal period.[35] Immobility is a further risk factor for hypercalciuria because

Table 1. List of genetic disorders associated with stone disease

Disorder	Gene	Inheritance	MIM No.	Key diagnostic parameter(s)	
				Blood	Urine
Primary hyperoxaluria	*AGXT*	AR	259900		↑Oxalate
					↑glycolate
	GRHPR	AR	260000		↑Oxalate
					↑glycerate
	HOGA1	AR	613616		↑Oxalate
					↑dihydroxyglutarate
Distal renal tubular acidosis	*ATP6V0A4*	AR	602722	↓pH	↑pH
	ATP6V1B1	AR	267300		
	SLC4A1	AR/AD	179800	↓tCO_2	↑Ca
	WDR72	AR	613214		
	FOXI1	AR	600791	↑Cl	↓citrate
Bartter syndrome	*SLC12A1*	AR	601678	↓K, ↓Cl ↑tCO_2	↑Cl ↑Ca
	KCNJ1	AR	241200		
Autosomal dominant hypocalcemia	*CaSR*	AD	601198	↑Ca	↑Ca
Cystinuria	*SLC3A1*	AR/(AD)	220100		↑Cystine, lysine, arginine, ornithine
	SLC7A9	AR			
Infantile hypercalcemia	*CYP24A1*	AR	143880	↑Ca, 1,25-↑OH-Vit D	↑Ca
	SLC34A1	AR	616963		
				↓PTH	
Hypophosphataemic rickets with hypercalciuria	*SLC34A3*	AR/(AD)	241530	↓PO_4	↑Ca
				1,25-↑OH-Vit D	
Dent disease/Lowe syndrome	*CLCN5*	XLR	300009		↑LMWP Ca↑
	OCRL	XLR	300535		
Xanthinuria	*XDH*	AR	278300	↓Uric acid	↑Xanthine
	MOCOS	AR	603592		
Adenine phosphoribosyltransferase deficiency	*APRT*	AR	614723		↑2,8-OH adenine
Familial hypomagnesemia with hypercalciuria/nephrocalcinosis	*CLDN16*	AR	248250	↓Mg	↑Mg, Ca
	CLDN19	AR	248190		
Lesch-Nyhan syndrome	*HPRT1*	XLR	300322	↑↓Uric acid	↑↓Uric acid
Renal hypouricaemia	*SLC22A12*	AR	220150	↑↓Uric acid	↑↓Uric acid
	SLC2A9	AR/AD	612076		

AR, autosomal recessive; AD, autosomal dominant autosomal dominant with incomplete penetrance; XLR, X-linked recessive; LMWP: low molecular weight proteins; MIM, Mendelian Inheritance in Man; PTH, parathyroid hormone.

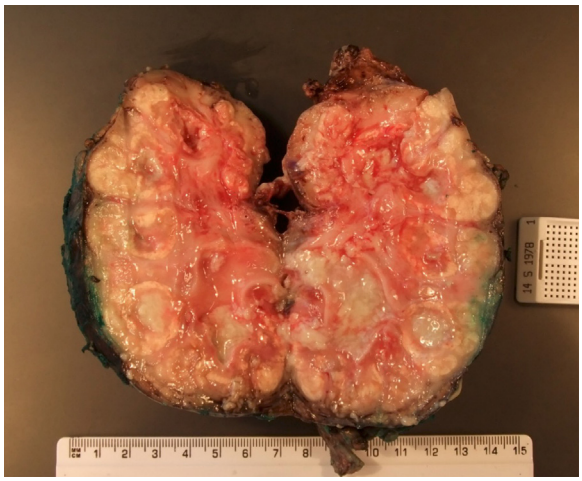

Figure 1. Xanthogranulomatous kidney secondary to UTI and urolithiasis. The external surface had been inked by the Pathology department.

of bone resorption.[36] Some seizure therapies predispose to hypercalciuria and stones; carbonic anhydrase inhibitors such as topiramate and ketogenic diets both cause acidosis, resulting in calcium resorption from bone and urinary acidification.[37] In one meta-analysis including 2795 patients on a ketogenic diet, the incidence of stone disease was about 6%.[38] Interestingly, the majority (~50%) of stones consisted of uric acid, than approximately 40% calcium-containing stones and the rest being mixed, likely reflecting low urine pH, a key risk factor for uric acid precipitation.

Specific inherited disorders are rare, but are important causes of urinary stone disease in children.[39] These include disorders characterized by hypercalciuria, hyperoxaluria, cystinuria, and hyperuricosuria (Table 1).

In our own cohort, approximately a third of children had an identified metabolic abnormality and of these,

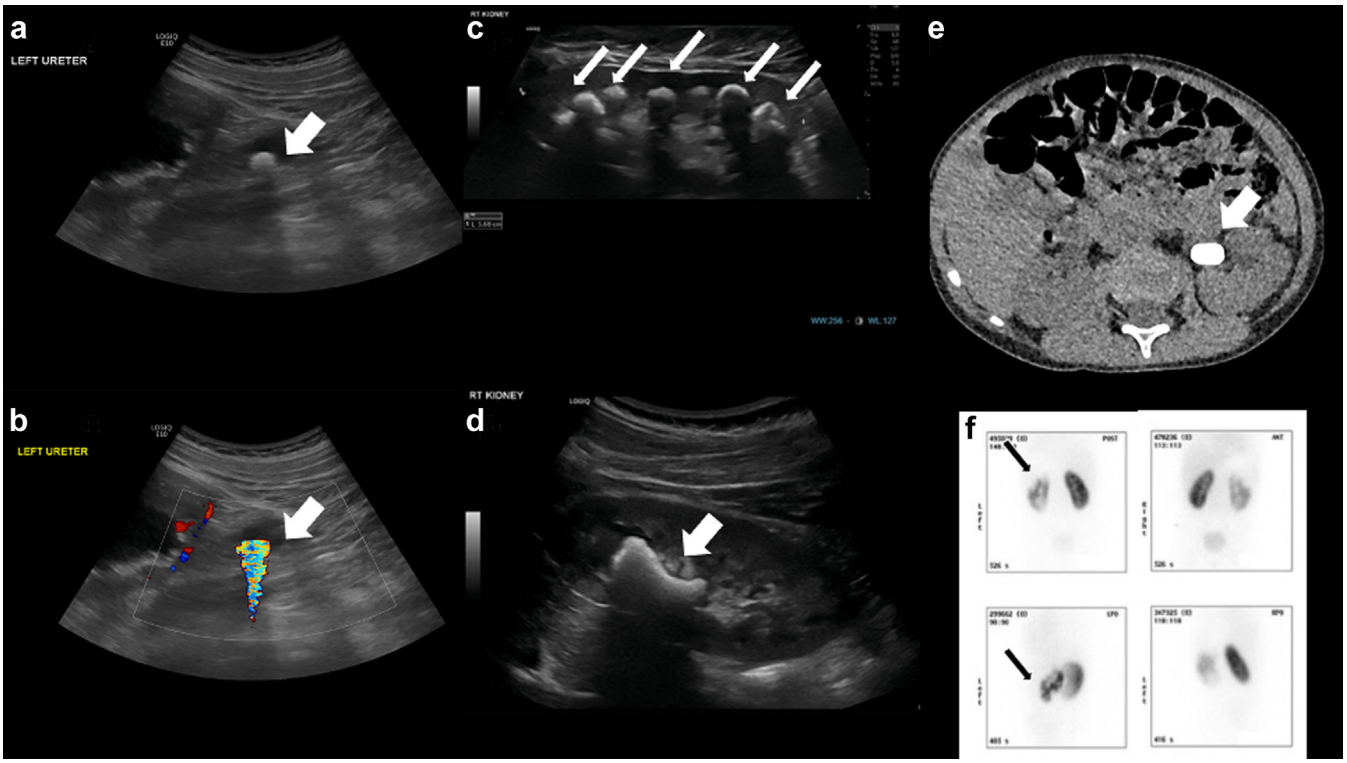

Figure 2. Examples of imaging in pediatric stone disease. (a) Ultrasound of the urinary tract. Note the echogenic focus (arrow) within the proximal ureter which demonstrates posterior acoustic shadowing, suggesting a stone. (b) Same patient, but now color Doppler applied. Note the "twinkle" artifact (arrow), a focus of alternating colors behind a reflective object. (c) Ultrasound of the right kidney in a patient with primary hyperoxaluria. Note the dense medullary nephrocalcinosis (arrows), some with acoustic shadowing, consistent with stone formation. (d) Ultrasound of the right kidney with a Staghorn calculus (arrow) occupying the renal pelvis and upper pole calyceal system. (e) Example of a large calculus (arrow) in the left pelviureteric junction, as seen on computed tomography. (f) Dimercaptosuccinic acid imaging of the same patient as in (e) shows associated focal scarring in the left upper and lower pole.

hyperoxaluria accounted for approximately 20%. Approximately half of these had primary hyperoxaluria (type 1, 2, or 3).[4] The remainder presumably had secondary hyperoxaluria resulting from increased enteral oxalate absorption, either because of dietary factors, such as excess oxalate or decreased calcium intake or because of fat malabsorption. Calcium acts as an "oxalate binder," analogous to its phosphate binding in chronic kidney disease; calcium binds to oxalate in the gut, thereby leading to precipitation, which in turn prevents enteric absorption.[40] This also explains the hyperoxaluria because of fat malabsorption, such as in congenital enteropathies, short gut syndrome, or cystic fibrosis; the increased intestinal fatty acids complex with calcium, with less calcium available to bind oxalate, thereby enhancing oxalate absorption from the gut.[41]

Cystinuria is an autosomal recessive disorder responsible for approximately 7% of urinary tract stones in children in our cohort.[4] It affects dibasic amino-acid reabsorption in the proximal tubule, leading to cystine crystallization and stone formation in the urinary collecting system or bladder.[42]

Urate stones are rare (~1%–2%) in children and should prompt consideration for inherited disorders of urate metabolism and transport (see Table 1).[21,43]

Disorders of purine metabolism are a rare cause of kidney stones in children, often diagnosed following biochemical analysis of kidney stones or debris. Examples include adenine phosphoribosyltransferase deficiency, which predisposes to 2,8-dihydroxyadenine stones, and xanthinuria in which xanthine stones arise from impaired metabolism of urate.[39,44]

Diagnosis

Clinical Presentation

The clinical presentation especially of younger children with stone disease may be different than in adults. Although adults and older children typically present with severe episodic flank pain,[45] younger children are often asymptomatic or only have nonspecific symptoms, such as irritability, poor feeding and incessant crying.[46] Consequently, the diagnosis can be easily missed, especially in nonverbal children who consequently may develop complications of stones, such a urinary tract obstruction and infection, even life-

Table 2. List of recommended blood and urine investigations for the initial workup of a patient with urolithiasis

Parameter	Blood	Urine
Sodium	x	x
Potassium	x	x
Chloride	x	x
Bicarbonate	x	
Urea	x	
Creatinine	x	x
Magnesium	x	x
Calcium	x	x
Phosphate	x	x
PTH	x	
Uric acid	x	x
DNA	x	
Amino acids		x
LMWP		x
Osmolality		x
Oxalate		x
Citrate		x
2,8-OH-adenine[a]		x
Xanthine[a]		x
Microscopy for crystals		x

LMWP, low molecular weight protein, such as retinol-binding protein or β-1 microglobulin; PTH, parathyroid hormone.
[a]Recommended if adenine phosphoribosyltransferase deficiency or xanthinuria are suspected, for instance because of family history.
A DNA sample can be obtained at the initial blood draw to minimize the need for further phlebotomy if an underlying genetic disorder is suspected.
The list of investigations may be adjusted individually, for instance if stone analysis is already available.
Shown is a list of recommended blood and urine investigations in the initial workup of a patient with stone disease.

threatening sepsis. Hematuria, is a common symptom across all age groups.[11]

Imaging

Imaging is critical for urinary stone diagnosis, potentially associated complications, such as obstruction and potentially underlying anatomic abnormalities.

Computed tomography (CT) is the modality of choice in the diagnosis of renal calculi in adults, but the radiation dose makes it unfavorable for routine use in children. Pediatric tissue is more sensitive to the effects of radiation with consequent higher risk for potential cancer development.[47]

Ultrasound. Ultrasound is typically the first imaging modality for suspected stone disease in children (examples are shown in Figure 2a–d). It has a up to 80% sensitivity for detecting calculi within the kidney, depending on operator skill and can rapidly provide information regarding associated obstruction.[48,49] However, because of obstruction from other body parts, stones in the mid and distal ureter are difficult to visualize and ultrasound can be challenging in patients with increased body mass index.

CT. If ultrasound is not providing a clear result, unenhanced (noncontrast) CT can be used in children. To reduce radiation dose, dedicated pediatric CT parameters are used, either on the basis of age or patient weight.

CT is the only modality which can measure the density of the calculi, thus providing an insight into the composition of the stones. Although stones in the upper ureters are usually well visualized (Figure 2e), stones at the vesicoureteric junction can be challenging to definitively identify, especially in patients with less intra-abdominal fat. As with ultrasound, dextranomer/hyaluronic acid copolymer (Deflux, Palette Life Science [www.deflux.com]) injections can mimic stones on CT.

Magnetic Resonance Imaging. Magnetic resonance imaging is infrequently used in the diagnosis of urinary tract calculi with a sensitivity of only 19% in one study.[50] Hydronephrosis is well demonstrated on magnetic resonance imaging, however, and magnetic resonance imaging can provide information about potential underlying anatomic abnormalities and adjacent abdominal organs to support surgical planning.

Nuclear Medicine. Nuclear medicine, especially dimercaptosuccinic acid scans can be helpful in decision making for patients with complex stones (e.g., Staghorn calculi), or complex anatomy (e.g., scoliosis) by providing functional information (Figure 2f).[51] If a kidney with a large complex stone demonstrates very poor function, surgical removal can be considered.

When combined with low dose CT, dimercaptosuccinic acid studies can identify whether there is functioning renal tissue overlying a stone to optimize access for percutaneous nephrolithotomy (PCNL).

Metabolic Investigation

Biochemical analysis of stone material, if available, can be diagnostic and should always be sought. For example, magnesium ammonium phosphate stones are most always infective in origin, cystine stones are diagnostic of cystinuria and 2,8 dihydroxyadenine stones are pathognomonic of adenine phosphoribosyltransferase deficiency, although erroneous diagnosis of 2,8 dihydroxyadenine stones was common in one series. [52] Similarly, xanthine stones may be misdiagnosed as urate.[53] Therefore, stone analysis may not always be diagnostic, for example also with mixed calcium oxalate and calcium phosphate stones and is not always available.[54] Biochemical evaluation of urine can be helpful, ideally with 24-hour urine collections if feasible, or spot urine samples in children not yet continent for urine. A 24-hour urine collection allows quantification of urine volume, which obviously reflects fluid intake. Moreover, ratios to urine creatinine can be misleading in children with abnormal muscle mass and therefore altered creatinine excretion.[55] However, many children fail to provide 24-hour

urine collections and even if they do, they frequently seem inaccurate, as judged by creatinine excretion.[56] Importantly, urine tests can be diagnostic, such as elevated dibasic urine amino acids for cystinuria, or elevated low molecular weight proteins for disorders of the proximal tubule such as Dent disease. A list of recommended analytes is provided in Table 2. In addition, some authors recommend including ammonia, sulfate, and urea in the urine collection to better assess the metabolic and dietary state of the patient.[57] Derivations of analytes, such as the urinary calcium to citrate ratio may be more informative than the individual values alone.[58]

Urine microscopy, specifically looking for crystals, can also provide important diagnostic clues. Blood tests to evaluate plasma electrolytes, acid-base status, bone chemistry, and parathyroid hormone levels should be undertaken in consideration of kidney tubular disorders or acidosis from other causes. DNA can also be taken at the same blood draw for subsequent genetic analysis if indicated from the biochemical results.

Genetic Investigation

If the metabolic investigations suggest a specific inherited disorder, such as primary hyperoxaluria, distal renal tubular acidosis, or cystinuria, genetic testing should be considered. And even with a nonspecific phenotype, such as nephrocalcinosis, genetic testing may establish a specific diagnosis in a substantial minority of patients, especially if there is a young age of onset.[29] This may directly affect management in some cases. For instance, a genetic diagnosis may be required to qualify for specific treatments, such as the novel inhibitors of oxalate production.[59] Moreover, it enables cascade screening of at-risk relatives with the possibility of providing preventative treatment before obvious symptoms manifest.[60] A list of genetic disorders associated with stone disease in children is provided in Table 1.

Treatment

Acute Medical Treatment

For those patients experiencing acute pain, analgesia with a nonsteroidal anti-inflammatory drug is recommended.[61] Use of nonsteroidal anti-inflammatory drug for renal colic has been shown in adults to be more effective than opioids with less side effects.[62] Medical expulsive therapy in the form of α-blockers (e.g., tamsulosin or doxazosin) to dilate the ureter and ureterovesical junction and hydration has been shown in adults to increase the chances of spontaneous stone passage,[61,63] and there is emerging evidence that it is similarly successful in children.[64] Antiemetics may be helpful, if nausea and vomiting is present.

Surgical Treatment

General Considerations. Decision for surgical intervention must be made on an individual basis and should take into account stone size, potential experience with previous stone passage in an individual patient and, of course, the risk for loss of kidney function, e.g., ureteric obstruction in a patient with a solitary kidney. In a study in adults, approximately 90% of stones <5 mm passed spontaneously, but this may be less especially in younger children because of their smaller anatomy.[65] Indeed, data from prepubertal children suggest that a stone size of <3 mm to 4 mm predicts a high chance of spontaneous passage.[66–68] However, in one study, spontaneous passage rate was high for stones <5 mm and similar across all age groups.[69]

Particularly for those presenting with complications of their stones, the first step is the stabilization of the child by treating potential concurrent infection and relieving obstruction by placement of a JJ stent or nephrostomy.

The goal of surgery is to clear stones by the most efficient yet least invasive manner and with the least risk of repeat procedures and complications. Particularly in view of the recurrent nature of stones in children, minimal access procedures have replaced open surgery. Though international guidance[70] on stone treatments based on stone size and location can aide decision making, in practice, the following factors are also important: the child's size, anatomy, comorbidity; the stone's complexity and composition in addition to size and location; multiplicity of stone locations within the urinary tract; the symptoms or complications caused by the stones; previous interventions and the ability to manage potential complications for a particular child; the experience of the treating team; and availability of specialized equipment. Efficiency of stone clearance is important because prolonged operative time is associated with postprocedural sepsis; therefore, a team that is familiar with the procedures and associated risks is critical to make a truly informed choice for each child.[71,72]

The aim at surgery is either to break the stone into fragments tiny enough to subsequently clear in the urine or to remove the stone and all its fragments. For the former it is essential to recognize that, in the same manner that particularly nonverbal children with urolithiasis can seem asymptomatic at the point of diagnosis, ureteric obstruction from stone fragments ("Steinstrasse") can occur silently yet risk ureteric injury and renal loss. A screening ultrasound to actively seek out this complication is advised within 10 to 14 days after any fragmentation procedure that leaves the ureter unstented. Of note, the term

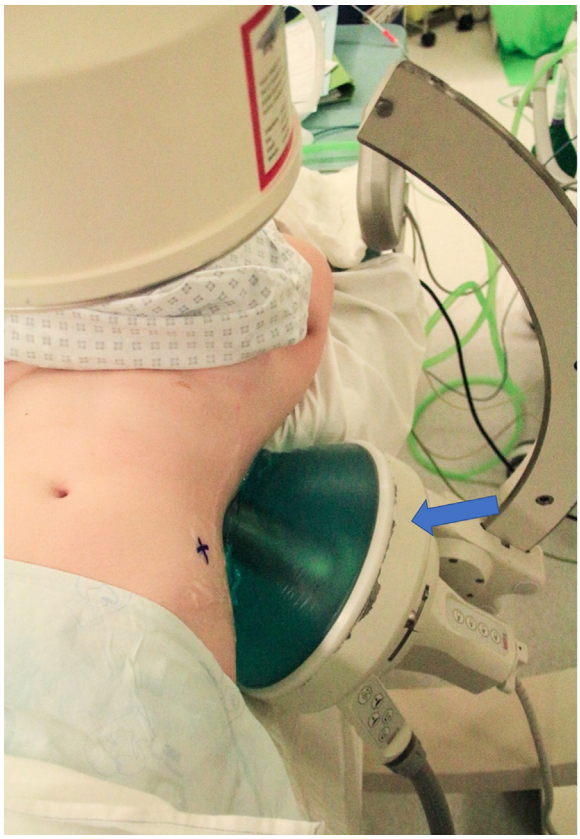

Figure 3. Child receiving extracorporeal shock wave lithotripsy under general anesthesia on a Piezolith Lithotripser: in-line ultrasound enables real-time monitoring of effectiveness and for complications (modified from[81]). Arrow indicates the shock-wavegenerator with the in-line ultrasound.

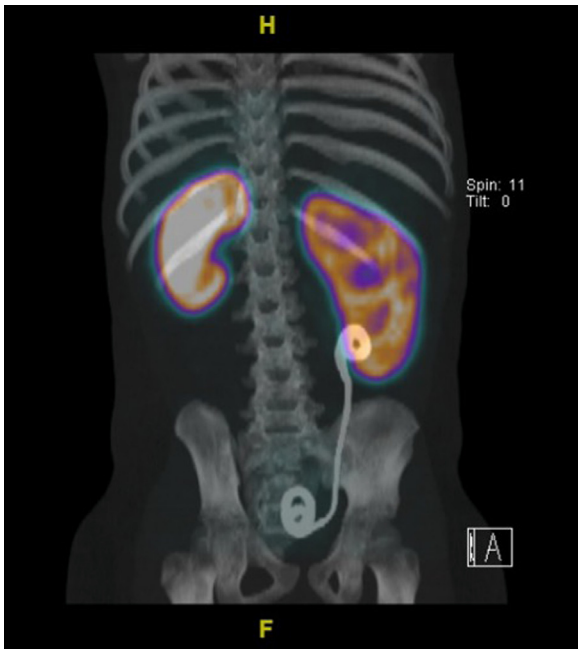

Figure 4. Image of an encrusted stent. Dimercaptosuccinic acid-SPECT showing reduced left-sided function in a "stretched" kidney and gross encrustation of a "forgotten" JJ stent after pyeloplasty surgery for a pelvi-ureteric junction obstruction. A combination of extracorporeal shock wave lithotripsy, cysto-ureteroscopy, and percutaneous nephrolithotomy were required for extraction. SPECT, single-photon emission computerized tomography.

"insignificant residual fragment" is a misnomer in children, considering that one-third will regrow over a period of 1 to 4 years, prompting further intervention.[73]

In general, sterilizing the urine ahead of interventions for urolithiasis reduces the risk of overwhelming postoperative sepsis as does administration of antibiotics (broad-spectrum or based on sensitivities of organisms grown on culture) on induction of anesthesia.[74]

Once decision for surgical intervention has been made, several options are available.

Extracorporeal Shock Wave lithotripsy (ESWL). As a noninvasive treatment, ESWL is the treatment of choice for patients with suitable stones.[75] ESWL works well for single renal pelvic stones up to 20 mm (ESWL being particularly effective for stones <10 mm, lower pole stones up to 10 mm and proximal ureteric stones).[76] In contrast to adults, stones clear from a lower pole location in children as well as from any other renal location.[34,77,78] Cystine stones, calcium oxalate monohydrate, and calcium phosphate dihydrate show poorer response to ESWL, as do stones of a density >600 to 1000 Hounsfield Units on CT.[79,80] In our experience, stone clearance by ESWL is less likely with increased stone burden, but independent of age, stone location, unilaterality or bilaterality of stones or the ambulatory status of the patient.

The first patients treated by ESWL in the 1980s were placed in a water bath and an electric spark was used to generate a shock wave. Today, pulses of shock waves are induced by rapid vibration of piezoelectric crystals or electromagnetic diaphragms. An external parabolic dish focuses the shock waves into a cone onto the stone and is transmitted through the skin ("coupling"). In-line ultrasound-guided and fluoroscopy-guided targeting systems allow real-time monitoring of the effectiveness (Figure 3). Most adults tolerate ESWL under simple analgesia. However, as the depth from the skin to the kidney stone is much shallower in children, the area of skin for coupling is significantly smaller (typically the size of a coin), making it intensely painful. This and the need to lie still for 30 to 45 minutes mean that most children benefit from general anesthesia or sedation for ESWL. Success rates in recent meta-analyses are 85% to 90%, although repeat procedures may be needed.[76,82] Close collaboration between the surgeon and lithotripsy radiographer is advised for the best results. Clearance of fragments is aided by active perioperative hydration for a good diuresis as well as removal of any previously placed ureteric stents.

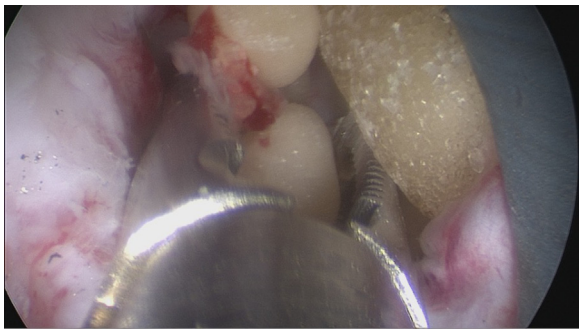

Figure 5. Extraction of cystine stones by percutaneous nephrolithotomy. Nephroscopy view through the percutaneous access into the pelvicalyceal system: stone grasping forceps have been deployed to lift out stones, which have the classical appearance of cystine stones.

Side effects of transient hematuria (8%), pain (3%), and petechiae are common.[83] In infants, shock wave transmission to the chest, precipitating pulmonary hemorrhage and haemoptysis, can be prevented by placing a sheet of paper between the ESWL cushion and the patient's chest. Subcapsular hematoma and life-threatening sepsis are rare. Ureteric obstruction from stone fragments occurs in approximately 5%.[76,83] Concerns regarding ESWL's potential impact on immature organs have been resolved by a long-term follow-up study extending to over 10 years, showing no effect on renal growth or on the incidence of hypertension and diabetes.[84]

Uretero(reno)scopy. The first line treatment for distal ureteric stones, ureteroscopy is also popular for proximal ureteric stones in children.[85] Approximately 90% stone-free rates at first treatment can be achieved.[86] Complication rates are consistently <10%, mostly low grade and self-limiting, although prolonged operative time remains an independent predictor of complications.[87]

Holmium-YAG laser energy is the preferred modality for stone fragmentation in view of the small size of probes allowing their passage through the smallest of ureteroscopes and carries the least risk of stone retropulsion.[87] In the absence of ureteric or vesicoureteric junction edema, stone fragments can be cleared under direct vision with a basket and sent for stone analysis. The stone fragment for analysis must be sufficiently small to pass easily through the vesico-ureteric junction because large fragments risk ureteric avulsion by basket extraction. Very small stone fragments or stone dust may be left to pass spontaneously.

Retrograde Intrarenal Surgery. The advent of small flexible ureteroscopes has enabled retrograde access to the pelvicalyceal system, although at maximal deflection, stone baskets and laser fibers cannot always be deployed, so that stones in the lowest calyces may remain inaccessible for retrograde endoscopic interventions. Successful stone clearance in >90% of cases has been reported.[81] The need for prestenting and/or poststenting mean that most children undergoing retrograde intrarenal surgery need >1 general anesthetic.[88] Stents "forgotten" after retrograde intrarenal surgery may result in severe encrustation, recurrent stone formation, and urinary tract infection (Figure 4), risking loss of kidney function.[89] In patients with a history of urolithiasis, stents should be removed within 4 to 6 weeks of their placement to avert this complication.

PCNL. PCNL was first described in 1976.[90] Almost 10 years later, the first pediatric cohort (school age) was reported.[91] In PCNL, a percutaneous tract into the kidney close to the stone is established, through which various instruments (e.g., a lithoclast, laser, or stone grasping forceps) can be inserted for stone fragmentation and/or removal (Figure 5). PCNL has been shown to be effective also in preschool children, and age or weight is no longer a limitation.[92] Today, PCNL is the first line treatment modality for Staghorn stones, renal stones >20 mm, lower pole stones >10 mm, cystine, or struvite stones.[93] Where there is a residual stone after PCNL, this can be treated by ESWL, "second-look" PCNL and/or uretero-renoscopy.[92,94–96] Successful stone clearance in >90% of cases has been reported.[82] Close cooperation between the interventional radiologist establishing the initial tract and urologist performing the lithotomy is key to successful clearance and avoidance of complications. This is especially relevant in children with distorted anatomy, such as severe scoliosis, where the percutaneous access needs to be planned carefully beforehand. The main concern in the use of PCNL is the potential impact of tract and instrument sizes on the kidney. However, in a series of 72 PCNLs using tracts up to 30FR (1cm diameter) in children aged 0.75 to 16 years, no scars could be seen on postoperative dimercaptosuccinic acid imaging, suggesting that there is no substantial loss of functional kidney tissue.[94] Today, the trend is toward smaller tract sizes; however, this does impact the operative instruments that can be deployed through the operating telescope and hence stone clearance and operative time.[97] The increased use of super-mini-PCNL in adults, particularly for lower pole stones, has not achieved the same degree of popularity in pediatric practice, in view of the effectiveness of ESWL even for lower pole stones in children.

Preventative Strategies

Hydration. Regardless of etiology, increased urinary water excretion will reduce the concentration of all solutes and thereby reduce the risk of supersaturation

Table 3. List of medications commonly used in the treatment of urinary stone disease

Drug	Indication	Typical dosage range	Frequency
Potassium citrate	Metabolic acidosis, Urine alkalinization	1–5 mEq/kg/d	Divide in >2 doses/d
Chlorothiazide	Hypercalciuria	10–20 mg/kg	Twice daily
Bendroflumethiazide	Hypercalciuria	50–200 mcg/kg	Once daily
Tiopronine	Cystinuria	15–40 mg/kg	Divide in 3 doses/d
D-penicillamine		20–30 mg/kg	Divide in 2–3 doses/d
Allopurinol	Hyperuricosuria	10–40 mg/kg/d	Daily
Tamsulosin	Stone expulsion	0.2–0.4 mg/kg/d	Daily
Doxazosin	Stone expulsion	30–100 mcg/kg/d	Daily
Ibuprofen	Ureteric colic	10–15 mg/kg	Every 8 h
Keterolac	Ureteric colic	0.5–1 mg/kg IV	Every 6 h

Given is a list of medications commonly used in the treatment if urinary stone disease, as well as the indication, dosage and frequency. Dosage information is from the British National Formulary for Children (https://bnfc.nice.org.uk), except for tiopronine and tamsulosin, where dosage was sourced from the literature.[93,108] IV, intravenous.

and stone formation. A fluid intake of >1.5 l/d/m^2 body surface area is recommended and some patients may benefit from even higher intake.[39,98] Fluid intake should be maintained throughout, including at night, to avoid periods of increased urinary concentration. Unfortunately, despite the apparent simplicity, adherence to this treatment is challenging,; making patients drink when they are not thirsty is difficult.[99] In our own unpublished experience with patients providing 24-hour urines for metabolic analysis, volume is typically well below the target of 1.5 l/d/m^2, even though patients may be more likely to remember to have a high fluid intake during the collection period. Forced aquaresis, using Arginine Vasopressin Receptor 2 receptor blockers (''vaptans'') could help to reduce urine concentration, but only limited data on the use of these medications in stone disease are available.[100]

Alkalinization. Urinary alkalinization is commonly used to reduce the risk of supersaturation of uric acid, cystine, and calcium oxalate. The pKa of uric acid is about 5.3, a urine pH <5.5 therefore markedly increases the risk of uric acid crystallization.[101]

The role of urine pH in calcium oxalate precipitation is complex, but alkaline supplementation reduces the reabsorption of citrate, which is a major inhibitor of calcium crystal formation.[102] Therefore, alkaline supplementation also reduces the risk of calcium oxalate precipitation.

Cystine solubility is poor below pH 7 and in one retrospective study, maintaining urine pH >7.5 was associated with the lowest risk of detecting cystine crystals in the urine.[103] However, it is unclear how well the visualization of crystals in the urine correlates with stone formation. Moreover, in the same study, they saw increased frequency of phosphate precipitation with alkaline urine pH, because phosphate precipitation is also pH dependent, increasing with rising urine pH. Therefore, the benefit with respect to preventing one form of crystallization needs to be balanced against the risk of calcium phosphate stone formation in each individual case. For example, in a patient with uric acid stones, maintaining a urine pH around 6 may be sufficient to prevent further uric acid stones without substantially increasing the risk of calcium phosphate stones. Conversely, in a patient with cystinuria and recurrent cystine stones, a target urine pH of ≥7.5 may be justified, because the benefit with regard to reducing the recurrence risk for cystine stones may outweigh the risk for calcium phosphate stone formation.

Urine alkalinization can be achieved in different ways, including dietary modification (reducing animal protein intake) and alkali supplementation.[104] Though the type of alkali should make no difference with regards to raising urine pH, there is a theoretical concern that sodium-containing alkali salts could lead to an increase in urine calcium excretion and most clinicians therefore use potassium-alkali salts, typically potassium citrate.[105] Acceptance of this treatment in children may be improved if lemonade is used for citrate provision, but the results of clinical trial have been varied.[106,107] A reason for this may be the low pH of lemon juice, so that citrate exists primarily in the form of citric acid and thus provides little, if any alkali load.[104]

A list of medications commonly used in the treatment of urinary stone disease, including citrate, is provided in Table 3. The dose should be distributed throughout the day, as much as possible, unless delayed-release formulations are used. Large, infrequent doses may lead to spikes in urinary pH that increase the risk of phosphate precipitation and the urine may become acidic again, when the drug has worn off. In our own practice, we typically use liquid citrate formulations and encourage the children to add the daily dose to their drinking bottles, so that they have small amounts with each sip of water.

Prophylactic use of citrate (2 mEq/kg/d) has been advocated for children starting on a ketogenic diet and was associated with a reduced incidence of kidney stones from 10.6% to 0.9% in one study.[109]

Reducing Urinary Calcium Excretion. For patients with hypercalciuria and/or calcium-containing stones, medical treatment typically aims at reducing urinary calcium excretion. The first measure is usually dietary modification, i.e., limiting sodium intake. In the proximal tubule, calcium passively follows sodium reabsorption. Consequently, excess sodium intake reduces proximal sodium and therefore also calcium reabsorption.[110,111] Conversely, reduced sodium intake

leads to enhanced proximal sodium and therefore also increased calcium uptake. Unfortunately, in our own unpublished experience, adherence to a low sodium diet is challenging, when assessed by 24-hour urine sodium excretion, especially for teenagers, even though patients may be more likely to remember the dietary advice during the urine collection. Though sodium excretion is subject to infradian changes, a 24-hour urine still provides a reasonable approximation of sodium intake.[112]

For those with persistent hypercalciuria despite dietary advice, thiazide treatment can help reduce urinary calcium. The mechanism is thought to be enhanced proximal sodium (and therefore calcium) reabsorption because of thiazide-induced hypovolemia.[113]

Treatment of Uric Acid Stones. Most uric acid stones in children are due to metabolic disorders with excess urate production, and urate lowering drugs such as allopurinol are recommended to reduce the concentration of uric acid in blood and consequently urine, in addition, to the general treatments of hydration and urine alkalinization.[114] Similarly, rasburicase dramatically lowers uric acid levels, but except for some case reports, there are no good data on the long-term use of this drug in stone disease.[115]

Treatment of Cystinuria. The mainstay of treatment of cystinuria is hydration and urine alkalinization, as detailed above. In addition, there are data that suggest that reduced sodium intake is associated with reduced cystine excretion and consequently, a reduced sodium intake is advisable.[116,117] Yet, patients who continue to have recurrent stone episodes may benefit from cystine binding drugs, such as tiopronin or D-penicillamine. These are thiol compounds that facilitate cleavage of cystine into cysteine to form mixed disulphides, which have much better solubility than cystine.[108,118] Unfortunately, both drugs can have severe side effects, including proteinuria, even nephrotic syndrome, as well as thrombocytopenia and neutropenia. Regular monitoring is therefore advised. Captopril is another thiol compound used in cystinuria, but data are contradictory[119,120] and sufficient dosing may be limited by its blood pressure lowering effect.

Specific New Treatments. New small interfering RNA treatments for primary hyperoxaluria have shown promising results in clinical trials to date, with one primary hyperoxaluria type 1 treatment, lumasiran, recently being licensed. Lumasiran is a small interfering RNA drug administered by subcutaneous injection which degrades messenger RNA for glycolate oxidase, thereby reducing liver oxalate overproduction and urinary oxalate levels by 65%.[121] Nedosiran is a further small interfering RNA treatment which targets hepatic lactate dehydrogenase and is currently under evaluation for the treatment of primary hyperoxaluria type 1 and 2 in children in clinical trials. An oral glycolate oxidase inhibitor is also being assessed.[122] These drugs may render liver transplantation obsolete in children with severe primary hyperoxaluria.

Conclusions

Urinary stone disease is rare in children and consequently there are only few centers with experience and expertise in its treatment. Specialized equipment is necessary for surgical treatment to accommodate pediatric anatomy. An underlying risk factor can be identified in most children with stone disease and a comprehensive workup is mandatory to facilitate specific treatment to minimize the risk of stone recurrence.

DISCLOSURE

All the authors declared no competing interests.

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