Stone Disease in Children and Adolescents

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Stone disease is an important clinical problem in paediatric urological practice. The incidence and characteristics of stones show a wide geographical variation in children. It is quite common in some countries in the Middle East, South Asia, Africa and South America. However, recent epidemiological studies have shown that the incidence of paediatric stone disease is also increasing in the Western World at approximately 5-10% per year.

Although calcium oxalate stones seem to be the most prevalent in children there are also differences in composition of stones in different areas around the world mainly related to the primary aetiological factor in each population. Expectant management is the initial management in children with asymptomatic small size stones (< 4-5 mm) with a possibility of spontaneous clearance. Any stone not responding to expectant management, larger stones and stones with clinical symptoms and causing obstruction should be managed surgically, or by extracorporal shockwave lithotripsy.

Only a very small portion of children will require open surgery, most will be managed endoscopically, but all attempts must be made to completely remove all stones, since post-operative residual fragments pass spontaneously in only 20-25% of cases and there is a high risk of recurrence. With the advance of technology stone management has evolved into many different minimally invasive procedures with the availability of smaller size instruments for children. Deciding the type of treatment depends on the number, size, location, stone composition, the anatomy of the urinary tract and also availability of the instruments and expertise in using them.

Extracorporeal shock-wave lithotripsy (ESWL)

Extracorporeal shock-wave lithotripsy (SWL), since its introduction in both adults and children, has proven its efficacy and safety. It is a 'no-touch' treatment modality. There is little risk of bleeding and postoperative infection, however there is also little evidence for long-term follow up. It does not affect the success of auxiliary procedures. It is, of course, not without limitations, as it requires a time interval until the achievement of stone-free status.

Evidence in children showed that SWL is more beneficial in a select cohort of patients. Therefore, determination of appropriate patient is of utmost importance. Stone size appears to be important for stone-free status. Overall ESWL has a stone-free rate of 80%, which decreases with increasing size (for <1 cm: 90%, 1–2 cm: 80%, >2 cm: 60%). Another limiting factor is the location of the stone, with lower pole renal stones benefitting less. The final important factor is the composition of the stone. In most instances, it is difficult to infer composition with knowing Hounsfield units on CT scans. Children with cystine, brushite (dicalcium phosphate dihydrate), and whewellite (calcium oxalate monohydrate) stones are known to be poor- responders to ESWL treatment.

Percutaneous Nephrolithotomy (PCNL)

Having been studied as a safe procedure in adults, PCNL was first described in children by Woodside et al. in 1985, who performed in seven children with 100% stone-free rates in one session, using standard adult instruments (24–34 F).

There were initial concerns regarding potential renal damage due to percutaneous access tracts, especially in small children. This led to evolution of technique and technology in paediatric percutaneous surgery and development of miniaturized equipment, wherein the tract size reduced, and energy sources became more efficacious and safer. This in turn led to the development of techniques such as Micro-Perc and Mini-Perc. Studies have suggested that PCNL does not have any harmful effect on the growing kidney. However, because of the small size of the kidney and the collecting system in infants, the use of the smallest and least traumatic instruments with least number of renal accesses are preferred to avoid complications, especially bleeding.

If we consider the age of patient, PCNL (Micro/Mini) have shown successful outcomes in small children including infants, toddlers and pre-school children. Unlike ESWL, PCNL is not a dependent on stone composition to determine success rates, with multiples technologies available to fragment stones including with Burr hole Ultrasound, Pneumatic lithoclast and laser with excellent fragmentation potential. All are reusable, durable and very much cost effective. The standard PCNL and MINI PCNL scope are semi rigid and reusable, making the procedure very cost effective, however the Micro Perc is disposable and instruments are relatively costly. Other limitations of Micro-Perc include reduced vision compared with Mini-Perc, as the irrigation fluid is usually intermittently pushed, and because there is no regular outflow passage, the stone or its fragments might migrate in any calyx where it becomes impossible or difficult to access the stone or its fragments.

Before a discussion of surgical options, a consideration should be given to obtaining a low-dose, non-contrasted CT scan. A CT can accurately determine the burden, location, and density of stones; anatomy of the collecting system; and proximity of surrounding structures. This information would allow for a more informed decision among the surgical options and subsequent surgical planning.

PCNL is a well-established option for children with a large burden of stone. Its efficacy is much less affected by the burden, location, and density of stones as well as the anatomy of the collecting system. The main disadvantage of PCNL is its increased morbidity, of which the need for transfusion is the most significant with rates of up to 24% using standard adult equipment. With the miniaturization of endourologic equipment, the morbidity of PCNL has significantly decreased in children. Novel mini-, micro-, and ultra mini-PCNL techniques offer a lower complication rate and shorter convalescence, as well as maintain an acceptable stone-free rate for stones up to 15-20 mm.

Retrograde Intrarenal Surgery (RIRS)

Following the success of RIRS in the adult population, the rise of this technique in paediatric cohorts has been well-studied, with concomitant rates of ESWL falling by as much as 34% in some studies. RIRS allows for the simultaneous evaluation of both lower and upper urinary tract for other possible causes of hematuria, in addition to stone disease. The easy access of a pelvic stone would make the procedure much easier omitting the need for a much invasive PCNL procedure with potential complications. The most important limiting factor for the RIRS procedure is the small caliber of the ureter at this age group.

Generally, a 7.5Fr flexible ureterorenoscope (FURS) with only hydro-dilatation is enough to allow passage without the use of access sheath, which is potentially responsible for many of the ureteral injuries reported in smaller ureters. There can be other unfavorable

anatomical factors for RIRS like narrow or long infundibula and infundibulopelvic angles >45 degrees, which can restrict access to FURS, and limited maneuverability, as well as leading to surgeon ergonomic discomfort, and are predictors of failure. With that in mind, the improvements in equipment and technology have led to an expansion of the indication for RIRS. Any location in the collecting system is now potentially readily accessible to URS, including the lower pole with the use of a flexible ureteroscope that has 270 degrees of deflection.

Studies of pre- and post-pubertal children undergoing URS for upper ureteral and renal stones have demonstrated an incidence of ureteral injuries and strictures that is well less than 5%, which is comparable to other studies in adults. Whether to dilate the ureteral orifice at the time of definitive therapy or place a ureteral stent for passively dilating the ureter is still being debated. The latter decision obviously necessitates a secondary procedure for definitive therapy. Fortunately, the incidence of preoperative stenting is relatively low, even in prepubertal children. The necessity of postoperative stenting should be made on an individualized basis, depending on the experience of the surgeon, duration of the procedure, number of passes with the ureteroscope, and presence of ureteral edema or trauma at the conclusion of the procedure.

Medical Expulsive Therapy (MET)

One of the approaches for treatment of distal ureteric stone is medical expulsive therapy (MET). Several studies have reported its success both in adults and children. This might be a good choice as it avoids the risks, complications, cost of general anesthesia and surgical procedure. The ureteric smooth muscles are supplied with alpha-adrenergic receptors, especially in the distal third of the ureter. Alpha-Adrenergic blockers inhibit basal smooth muscle tone and hyper-peristaltic uncoordinated frequency, with no effect on tonic propulsive contractions. However, the majority of studies have demonstrated higher success rates of MET for distal ureteric stones up to 10 mm, with the highest rates of success for those 5mm and smaller.

Do all children with stones require a metabolic evaluation?

It is generally accepted that first time paediatric stone formers of all ages should undergo a complete metabolic evaluation. This approach is based on the high prevalence of metabolic abnormalities in children with urolithiasis (approximately 30%), of which hypercalciuria and hypocitraturia are most common. The identification of metabolic risk factors allows targeted therapy and prevents the recurrence of kidney stones.

A complete metabolic workup consists of dietary history, blood and urine tests, and stone analysis when available (Table 1). Blood tests should include measurements of sodium, potassium, chloride, calcium, magnesium, phosphorus, and bicarbonate. In contrast to adults, primary hyperparathyroidism is rare in children, and intact parathyroid hormone and 25-hydroxyvitamin D should only be measured in children with hypercalcemia. If present, vitamin D deficiency should be corrected.

Timed 24-hour urine collection should be obtained because it provides the most valuable information. There is no general consensus on the number of initial urine collections and on the time interval between collections. Two collections seem reasonable to account for the high variability of urinary lithogenic factors. The collection should be performed under usual fluid and diet intake, regular activity, free of urinary tract infection, and at least 1 month after extracorporeal shock wave lithotripsy (ESWL). Results should be interpreted with respect to weight, body surface area, and creatinine concentration. Urine creatinine is checked for the accuracy of urine collection (normal 15 to 25 mg/kg/24 hours, should be at least 15 mg/kg/day). Random urine specimens with solute to creatinine ratios are acceptable in non-toilet trained children, including children with developmental delay. Normal values vary by age and prandial state (Table 2).

Microscopic analysis of urine is also important in patients with urolithiasis. In cystinuria patients, it can identify cystine crystals. The presence of xanthine and dihydroxyadenine crystals indicates adenine phosphoribosyltransferase deficiency. Dent disease is suspected in boys with low-molecular-weight proteinuria and kidney stones. If possible, stone composition should be analyzed because it guides further evaluation and targets treatment.

The goals of medical intervention are to treat the kidney stone and to prevent complications and stone recurrence. Fluid and dietary modification are the essential therapeutic and preventive measures in all children with kidney stones (Table 3). Increased fluid intake (mostly water), restricted salt, and increased potassium consumption should be recommended in all. The amount and type of fluid are important. Various ways of estimating the fluid goal have been proposed, but the urine volume appears to be the most significant determinant. Drinks containing sucrose, fructose, and phosphoric acid should be avoided. Medications that induce kidney stone formation should be discontinued. Pharmacotherapy is required in those with cystinuria, primary hyperoxaluria, recurrent kidney stones, obstruction in a solitary kidney, and in children in whom fluid and dietary modification are insufficient in controlling stone formation (Table 3). Potassium citrate, thiazides, and potassium-sparing diuretics are the most used ones. However, the optimal paediatric dose for thiazide and citrate has not been well studied.

Table 1: Initial metabolic evaluation of a child with urolithiasis

Dietary history Daily intake of fluid, sodium, potassium, calcium, oxalate and protein; Use of vitamins (C,D), minerals, herbal products, special diets (eg ketogenic diet), and medication (anticonvulsants, esp. topiramate and zonisamide, diuretics, corticosteroids, chemotherapy, antacids, protease inhibitors).
Urine Urinalysis (pH*, osmolality, microscopy, crystals) and culture Urine solute to creatinine ratios in random urine Urine solute concentrations and excrete rates in timed 24-hour urine collection (volume, pH, supersaturation profiles of calcium oxalate, calcium phosphate and uric acid, calcium, phosphorus, oxalate, citrate, uric acid, sodium, potassium, cystine and creatinine)
Serum chemistry: calcium, phosphorus, magnesium, alkaline phosphatase, sodium, potassium, chloride, bicarbonate, uric acid, creatinine, urea nitrogen
Stone analysis, when available

*Urine pH higher than 6 favors calcium phosphate; higher than 7 indicates urease productive organisms and struvite stones; lower than 6 favors cystine and uric acid.

Table 2: Normal Value for Urinary Excretion of Metabolites

Metabolite	Age	Random (mg/mg)	Timed (all ages)
Calcium	0 to 6 months 7 to 12 months >2 years	<0.8 <0.6 <0.2	<4 mg/kg per 24 hours
Oxalate	0 to 6 months 7 to 24 months 2 to 5 years 5 to 14 years >16 years	<0.26 <0.11 <0.08 <0.06 <0.32	<40 mg/1.73 m² per 24 hours
Citrate	0 to 5 years >5 years	>0.2 to 0.42 >0.14 to 0.25	<310 mg/1.73 m^2 per 24 hours in girls and 365 mg/1.73 m^2 per 24 hours in boys
Cystine	> 6 months	<0.075	<60 mg/1.73 m² per 24 hours
Uric acid	>3 years	<0.56 mg/dL*	<815 mg/1.73 m² per 24 hours

*Uric acid/Glomerular filtration rate (mg/dL)=Urinary uric acid x plasma creatinine/urinary creatinine

Special Considerations for Each Metabolic Disease

Hypercalciuria

The initial treatment should consist of low salt, high-potassium diet. Good sources of potassium are vegetables and fruits. The intake of calcium and protein should be within recommended dietary allowance (RDA). Dietary calcium and protein restriction should be avoided because it can affect the child's growth. Additionally, calcium restriction increases intestinal oxalate absorption and calcitriol levels leading to high urinary excretion of calcium and oxalate. Excessive consumption of protein should be avoided because acid production from protein metabolism will exacerbate hypercalciuria and hypocitraturia. If hypercalciuria does not resolve with a 2-month trial of dietary modification, alkali therapy (e.g., potassium citrate) and thiazide diuretics (e.g., hydrochlorothiazide) should be considered. Thiazides induce volume contraction which increases calcium absorption in the proximal tubule leading to decreased urinary calcium excretion. Therefore, they should not be used in patients with hypercalcemia. Additionally, they cause urinary potassium loss leading to citrate deficiency.

Hypocitraturia

Potassium citrate is used to treat children with hypocitraturia and calcium oxalate stones. Citrate binds with calcium and lowers urinary calcium supersaturation. Additionally, citrate has a direct inhibitory effect on growth and aggregation of crystals. Moreover, citrate therapy prevents stone recurrence and slows growth of residual stones following ESWL. Studies in adults showed benefits with high lemon intake, but this has not yet been studied in children.

Hyperoxaluria

Children with hyperoxaluria should be advised to decrease consumption of chocolate and cola, two well-known oxalate rich foods that have been associated with hyperoxaluria in adults. Restriction of other oxalate-rich foods is not recommended due to lack of evidence that it will prevent hyperoxaluria and will decrease the risk of recurrent stone formation. Administration of potassium citrate, magnesium, and pyrophosphate helps prevent calcium oxalate crystallization in patients with hyperoxaluria. Excess vitamin C intake should be avoided due to its effect on oxalate metabolism.

Cystinuria

Dietary modifications in children with cystinuria consist of low- protein (< 20 g/day), low-salt

(<2g/day), and high-fluid intake (> 3 liters/day). This is difficult to achieve in children and is not sufficient to prevent the recurrence of stones. Urinary alkalinization with potassium citrate is needed in order to maintain a urine pH between 7 and 7.5. Cystine chelation therapy with either Alpha- mercaptopropionylglycine (tiopronin) or D-penicillamine is used in children with poor response to hydration and alkalinization. Both drugs work equally well by increasing the solubility of cystine crystals, but tiopronin has fewer side effects and therefore is better tolerated.

Hyperuricosuria

Increased consumption of animal protein causes high acid pro- duction leading to excessive excretion of urinary calcium and hypocitraturia. High intake of purines increases urinary uric acid. However, protein should not be restricted in children because it impairs their growth. Uric acid decreases the solubility of calcium ox- alate causing calcium urolithiasis. Children with hyperuricemia require therapy with Allopurinol, an inhibitor of xanthine oxidase which reduces uric acid production. Urinary alkalinization with potassium citrate increases urinary pH facilitating the excretion of uric acid. Sodium citrate and sodium bicarbonate should be avoided because of sodium induced calcium excretion.

Table 3: Dietary and pharmacologic intervention in pediatric urolithiasis

Condition	Dietary	Pharmacologic
Hypercalciuria	• High fluid intake* • Restricted sodium** • High potassium diet • RDA for calcium • RDA animal protein***	• Hydrochlorothiazide (0.5 to 2 mg/kg per day, older children 25-100 mg/day) • Potassium citrate (2 to 4 mEq/kg/day divided in 3 doses after meals, older children 30 to 90 mEq/day)
Hypocitraturia	• High fluid intake • RDA animal protein • High lemon intake	• Potassium citrate (2 to 4 mEq/kg/day, older children 30 to 90 mEq/day)
Hyperoxaluria	• Very high fluid intake (PH) • Moderate oxalate restriction • High magnesium and potassium supplements • Low-fat diet • Avoid excessive vitamin C • RDA for calcium	• Potassium citrate (2 to 4 mEq/kg/day, older children 30 to 90 mEq/day) • Pyridoxine (8 to 10 mg/kg per day) for primary hyperoxaluria (PH)
Hyperuricosuria	• High fluid intake • Moderate animal protein • Restricted sodium	• Potassium citrate (2 to 4 mEq/kg/day, older children 30 to 90 mEq/day) • Allopurinol (4-10 mg/kg/day, older children 300 mg per day) ***
Cystinuria	• Very high fluid intake (day and night)	• Potassium citrate (2 to 4 mEq/kg/day, older children 30 to 90 mEq/day) **** • Tiopronin (starting dose of 100 mg BID) • D-penicillamine (30 mg/kg/day divided in 4 doses) • Captopril (0.5-1.5 mg/kg/day divided in 4 doses)

***Fluid goal is targeted to maintain an age-related daily urinary volume:** Infants ≥750 mL, small children below five years of age ≥1000 mL, children between 5 and 10 years of age ≥1500 mL, children greater than 10 years of age ≥2000 mL.
**Less than 2-3 mEq/kg/day
***Reserved for children with a known disorder of uric acid metabolism
****Dose targeted to achieve a urine pH equal to or above 7.0
*****Avoid excessive protein intake