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Pediatric Kidney Stones—Avoidance and Treatment

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Opinion statement

Pediatric stone disease is increasing in incidence and healthcare costs. With more years at-risk for stone recurrence during their lifetimes, children with nephrolithiasis constitute a high-risk patient population that requires focused intervention through both medical and surgical means. Through high-quality future studies to compare methods of stone prevention and treatment, the burden of stone disease on the youngest members of society may be ameliorated.

Introduction

Nephrolithiasis in children has been increasingly recognized as a major source of morbidity and cost in the USA. The disease incidence has risen 6–10 % annually over the last two decades (1•, 2) with accompanying increases in frequency of hospitalizations, emergency department (ED) visits, and surgical interventions (1•, 3, 4•, 5). Population-based observational studies have estimated contemporary incidence to range from 36 to 145 per 100,000 children (1•, 3, 4•). One study noted a more than fourfold increase in incidence over a 12-year span (5). Of note, one specific subpopulation of children that appears to be at particularly higher risk is adolescent females (1•, 3, 4•, 6), though the etiology is not clear. Recent estimates of the economic burden related to

pediatric nephrolithiasis have been $229 million per year for hospital admissions and $146 million per year for emergency room encounters (7). As a result, this disease process has necessitated strategies to optimize the evaluation and treatment of children with kidney stones and to reduce recurrence risk through preventive medical and dietary management.

Presentation and diagnosis

Children with nephrolithiasis may present clinically with a spectrum of symptoms, depending on age (8). Localization of pain to the abdomen or flank is easier in adolescents and older children, while younger children may have more vague symptoms of nausea, vomiting, and irritability. Gross hematuria is not uncommon. Patients may also be diagnosed with stones as an incidental finding on imaging for other indications such as urinary tract infections (9).

In adults, use of computerized tomography (CT) with its inherent ionizing radiation is broadly considered first-line in diagnosis of nephrolithiasis given its excellent cross-sectional anatomic detail. Recently, however, a large randomized-controlled trial comparing ultrasound versus CT scan in adults with suspected nephrolithiasis showed no difference in 30-day complications between the two modalities (10••) with the ultrasound arm showing less 6-month cumulative radiation exposure. Importantly, a secondary analysis of patients in the CT arm of the trial demonstrated significant and inappropriate variability in CT radiation dosages, further emphasizing the potential harms of CT scans (11•).

In children with suspected nephrolithiasis, due to the concern for cumulative effects of radiation exposure, first-line imaging is a renal and bladder ultrasound, with CT reserved for nondiagnostic results but high clinical suspicion (12, 13•). The sensitivity, specificity, positive predictive value, and negative predictive value of ultrasound for stone detection, compared to CT as the gold standard, are 70, 100, 96, and 62 %, respectively. The stones that were missed by ultrasound could be considered to be clinically insignificant in size (14). The accuracy of ultrasound also may depend on stone location, with higher rates of detection in the kidney as opposed to the ureter alone (15).

Despite the concerns of radiation exposure, ultrasound is infrequently used as the initial imaging for suspected nephrolithiasis in children (16). Use of CT as first-line imaging modality has been directly associated with nonteaching hospitals and weekend ED visits (17), older age (17, 18, 19•), and public insurance status (18). On the contrary, certain EDs that utilized clinical care pathways emphasizing ultrasound as first-line imaging were noted to have lower odds of undergoing CT (19•), as were EDs that cared for more children (17).

Acute management

When an obstructive stone has been diagnosed in a child, management options, in addition to pain control, include observation with medical expulsive therapy (MET) or surgery. Studies on spontaneous passage rates without MET suggest higher rates of passage in older than younger children and with stones found in

the lower ureter than kidney or upper ureter (20, 21). As in adults, utilization of MET with alpha-blockers or calcium-channel blockers in children with nephrolithiasis has been increasingly employed. The rationale behind MET is the abundance of alpha-1a, alpha-1d, and calcium channel receptors found in the smooth muscle of the distal ureter. By blocking these receptors, the tone of the ureter, in theory, relaxes and thus dilates the ureter, facilitating stone passage.

While numerous trials and meta-analyses of MET exist in the adult literature, showing decrease in time to stone passage, reduced analgesic use, and increased cost-effectiveness compared to analgesics alone (22••, 23•), only a few studies have evaluated the efficacy of MET in children.

Three small randomized-controlled trials have been performed, all of which examined distal ureteral stones in children and included fewer than 65 patients (21, 24, 25). Although far from conclusive, two of the three trials found a significantly improved passage rate favoring alpha-blockers (21, 25). More recently, a multi-institutional retrospective cohort study demonstrated that MET was associated with 55 % spontaneous passage rate which was significantly higher compared to 44 % with analgesics alone, with over threefold increased odds of spontaneous passage (26).

Surgical management

Between 25 and 50 % of children with nephrolithiasis are estimated to undergo surgical intervention (18, 27). Current commonly used surgical options for nephrolithiasis include extracorporeal shockwave lithotripsy (SWL), retrograde intrarenal surgery (RIRS) with ureteroscopy, and percutaneous nephrolithotomy (PCNL). Open pyelolithotomy is rarely used in the contemporary era. While historically most stones in children were treated with SWL, technological advancements in miniaturization and optics of endoscopy have allowed an increase in utilization of RIRS and PCNL (28, 29). According to the American Urologic Association 2007 guidelines, RIRS is now considered first-line surgical treatment along with SWL for children with ureteral or renal calculi (22••). PCNL is usually reserved for large staghorn stones, large infection stones where clearance is essential, or renal stones in kidneys with abnormal anatomy, such as patients with horseshoe kidneys or urinary diversions (28).

Various studies have compared stone-free rates among the surgical treatment modalities. These rates for PCNL range 70–97 %, RIRS 85–88 %, and SWL 80–83 %, although the study populations were heterogeneous (30). Because the evidence in the pediatric population is limited, higher quality data may be extrapolated from the adult literature. A meta-analysis comparing SWL, RIRS, and PCNL in adults for lower pole stones <2 cm in size favored PCNL over SWL and RIRS over SWL, particularly in stones 10–20 mm in size (31•). Another meta-analysis compared PCNL to RIRS in adults for any kidney stone and noted higher stone-free rates with PCNL techniques but also higher complication rates, greater blood loss, and longer hospital stay (32•). Whether these results are applicable to children remains controversial.

One key issue that has made considerable progress recently has been the reduction of radiation exposure during surgical interventions for

nephrolithiasis. All the surgical modalities excluding open surgery typically incorporate plain films (SWL) or fluoroscopy (RIRS and PCNL), both of which carry ionizing radiation. As the radiation safety concept of as low as reasonably achievable (ALARA) emphasizes, recent techniques that utilize ultrasound for RIRS (33) and PCNL (34) have sought to minimize radiation exposure in children.

Kidney stone recurrence

A major contributor to the morbidity associated with nephrolithiasis is disease recurrence. Among adults with nephrolithiasis, up to 50 % recurrence may be expected within 10 years after the initial stone episode (35••, 36). In children, estimated nephrolithiasis recurrence rates range from 19 to 34 % at a mean follow-up of 2–3 years (20, 37). As such, children are regarded as high-risk recurrent stone formers and must be treated as such.

The primary determinant of the likelihood of kidney stone recurrence is whether there is an associated urinary metabolic abnormality with hypercalciuria and hypocitraturia being the most common (38). Other risk factors include anatomic abnormalities such as ureteropelvic junction obstruction and rare genetic conditions such as cystinuria or primary hyperoxaluria (9, 35••). Analyses of stone compositions in children have shown a similar breakdown to adults, with 70–80 % of stones containing calcium oxalate, 10 % containing calcium phosphate, 10–15 % containing struvite, and 5 % being pure uric acid (39). Nearly 70 % of children have been found to have a metabolic derangement found on 24-h urine collections that predisposes to stone formation (38). Of note, children without any identifiable metabolic abnormalities have a substantially lower risk of recurrence (20).

Prevention and medical management

After the management of acute renal colic is complete, the primary focus is the prevention of new stone formation and secondary prevention of growth of any retained stones. These preventive strategies depend on modifying the metabolic milieu that predisposes to stone formation.

It is recommend that first-time stone-formers at high-risk of stone recurrence undergo both serum and 24-h urine studies (9, 35••). Serum electrolytes should include sodium, potassium, bicarbonate, creatinine, calcium, magnesium, phosphorus, and uric acid. A 24-h urine collection should include calcium, oxalate, citrate, uric acid, sodium, creatinine, pH, cystine, volume, and supersaturation levels of calcium oxalate, calcium phosphate, and uric acid. Importantly, the accuracy of collected 24-h samples is checked using well-established 24-h creatinine values by weight, with a normal range of 15–25 mg/kg/24 h. However, normal values of creatinine excretion in children have not been published. In younger patients that have not yet been toilet trained, a “spot” urine sample can be used to test for urinary calcium, oxalate, and citrate-to-creatinine ratios. The definition of hypercalciuria varies by age, with a normal value of less than 0.2 mg/mg being established by age 6, which is the upper limit of normal for adults (40).

If any underlying metabolic abnormalities are diagnosed, the next step is often prevention through dietary modification, followed by pharmacologic intervention if dietary changes are insufficient. In adults with hypercalciuria and recurrent stones, diets containing normal calcium levels, low protein, and low sodium were shown to reduce recurrence risk (41, 42•, 43). In children, the recommendations regarding protein restriction should not be strictly followed, given how important protein is for normal growth and a paucity of data in this age group. In general, children should consume the recommended dietary allowance of calcium, as calcium restriction may increase intestinal oxalate absorption and stone risk. Pediatric stone-formers also are encouraged to eat fruits and vegetables, which are high in citrate and potassium, two known inhibitors of stone formation (42•, 43). Lastly, limiting sodium intake has been strongly associated with lower urinary calcium excretion in hypercalciuric stone formers (44).

Of note, one of the most important dietary modifications to reduce stone recurrence risk is adequate fluid intake to increase urinary volume and decrease urinary supersaturation and crystal formation (9, 35••, 41, 42•, 43, 45•, 46). In adults, the recommended minimal intake is 2 L per day or enough fluids to generate over 2.5 L of urine output per day (9, 35••, 42•, 45•, 46). In children, some authors have recommended a minimum fluid intake of 750 mL per day in infants, 1000 mL per day in children up to age 5, 1500 mL per day in children up to age 10, and over 2000 mL per day in older children and adolescents (47). The Institute of Medicine also has dietary references for water intake by age, ranging from 700 mL per day in infants to 3300 mL in 14–18 year-olds (48).

In patients in whom dietary modifications alone fail, pharmacologic intervention may be indicated. The specific therapies depend on the underlying metabolic abnormalities as detected on the stone composition and 24-h urine collections (9, 35••, 46, 49). In patients with calcium-based stones, which constitute the majority of children with nephrolithiasis (39), the underlying metabolic abnormalities often include hypocitraturia and hypercalciuria (38). Citrate is a known direct inhibitor of stone formation and furthermore alkalinizes urinary pH to increase the solubility of various crystals, including cystine and uric acid. As such, alkali therapy, usually in the form of potassium citrate, constitutes a major class of targeted pharmacologic therapy for stone prevention.

Two prospective cohort studies in children with hypocitraturia and calcium-based stone burden have found that administration of potassium citrate was significantly associated with decreased stone recurrence (37, 50). Other indications for potassium citrate include hyperuricosuria with pure uric acid stones, cystinuria, and distal renal tubular acidosis (9, 35••).

The second major class of pharmacologic interventions is thiazide diuretics, which work by reducing urinary calcium excretion within the distal convoluted tubules of the nephron. They are recommended in patients with calcium stones and hypercalciuria but do require limiting dietary sodium load to optimize success. While the data examining thiazide efficacy in children is lacking, several trials in adults show

approximately 50 % reduced risk of recurrent calcium stone formation compared to placebo or control (46).

Conclusion

Overall, the quality and quantity of studies in pediatric patients with nephrolithiasis remain limited. Much of the evidence driving current clinical practice is extrapolated from the adult literature. Key similarities to adults exist in the treatment of primary stone episodes among children, with MET and advancements in technology enabling less invasive techniques for stone removal. Preventive strategies to reduce recurrence, including adequate fluid intake, dietary changes, and select use of pharmacologic therapies, also may be applicable to pediatric stone patients. However, children do simultaneously represent a very different risk population than adults. Unnecessary radiation exposure must be reduced given a child's greater years at risk for stone recurrence and additional diagnostic imaging or treatment. Additionally, with the rising incidence of pediatric nephrolithiasis, the disease burden on society can be expected to increase, both clinically and financially. Future research directions should include comparative effectiveness studies of various primary and secondary treatment strategies and randomized trials evaluating efficacy and safety of MET and pharmacologic interventions.

Compliance with Ethical Standards

Conflict of Interest

David I. Chu has received grant number T32-DK07785 from the National Institute of Diabetes and Digestive and Kidney Diseases.

Gregory E. Tasian and Lawrence Copelovitch declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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