Pediatric Stone Disease
Current Trends and Future Directions

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KEYWORDS

• Kidney stones • Nephrolithiasis • Children • Calculi • Urolithiasis • Pediatrics

KEY POINTS

- The risk of recurrence for pediatric stone formers is 50% within 3 years of the first symptomatic stone, and those most at risk are adolescents and patients with a prior history of nephrolithiasis.
- Medically complex patients may have several interrelated risk factors for nephrolithiasis, particularly those with alternate routes of nutrition and immobility, warranting a multidisciplinary approach in stone prevention.
- Assessment of a child with suspected kidney stones is similar to that of an adult, although ultrasonography is the preferred initial imaging study, keeping in line with the As Low as Reasonably Achievable principle and the Image Gently Alliance.
- Emerging surgical therapies now focus on minimally invasive approaches for larger stones and reducing radiation exposure with the use of ultrasound-guided endoscopic surgeries instead of fluoroscopy.

BACKGROUND

There has been a rapid increase in the incidence of pediatric nephrolithiasis in the last several decades, with an annual increase of at least 6% to 10%.[1,2] In 2009 alone, an estimated 20 children were hospitalized and more than 90 were treated in the emergency department for urolithiasis daily.[3] A population-based study in South Carolina demonstrated that between 1997 and 2012, the 15- to 19-year-old age group had an observed increased incidence of 26% annually, with a greater increase among females.[4] Although these data reflect a rapid increases in disease incidence from the late 1990s to early 2000s, more contemporary experiences reflect the continued heightened burden of pediatric stone disease.[5] In a nationwide study looking at outpatient management of pediatric upper tract stone disease, the annual expenditure was calculated to be on average $15 million between 2011 and 2018, and this cost increased more over time, reflecting the increase in the prevalence of upper tract stones in children.[6]

The economic burdens and health care costs of pediatric nephrolithiasis are realized partly due to high recurrence rates but also due to complications relating to pain and infections requiring multimodal therapies.[7] The indirect costs and financial impact relating to pediatric urolithiasis may be even greater than what is reported in adult literature, with additional intangible human capital loss such as lost workdays for parents and extra childcare costs if the child misses multiple school days. As the majority of costs were covered by commercial insurance plans as well as government funding, employers and policymakers now have to

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anticipate increasing health care costs annually with this medical condition.[6]

Because of the overall economic impact, pediatric urologists and nephrologists alike have been working to identify genetic and environmental risk factors pertinent to the pediatric population as well as less invasive techniques to minimize stone burden and recurrence. Herein, the authors review current evidence on risk factors and prevention of stone formation, as well as emerging technologies and surgical interventions on stone treatment pertinent in the pediatric population.

RISK FACTORS

Diet and Fluid Intake

Dietary factors and reduced fluid intake can contribute to metabolic abnormalities and consequently urine supersaturation of calcium, oxalate, and phosphate.[8] There is clear evidence that poor fluid intake and excessive sodium intake, which is prevalent in the Western diet, are two of the most significant risk factors for stone formation.[9] In addition, research has demonstrated that most adolescents and children do not reach adequate fluid intake, and much of the daily intake in their diet is realized from non-water beverages and food moisture.[10] Currently, a randomized controlled trial (PUSH: Prevention of Urinary Stones with Hydration) is being conducted using smart water bottles and smartphone technology to examine the effect of financial incentives and coaching to maintain high fluid intake on the recurrence of symptomatic stones.[11]

Medications

The incidence of drug-induced urolithiasis is about 1% to 2% in the adult population, but there is a paucity of data on the influence of medications in pediatrics.[12] Nonetheless, the mechanisms by which medications can cause pediatric urolithiasis remain the same: either the drug is poorly soluble, leading to filtration of the drug itself into urine and subsequent crystallization, or the drug causes metabolic disturbances that favor urine supersaturation of stone-forming compounds.

One of the most commonly researched classes of medications is antibiotics. Tasian and colleagues performed a large, population-based case-control study from the United Kingdom, using data from more than 600 general practices and more than 13 million children in a span of 10 years.[13] They discovered that cephalosporins, broad-spectrum penicillins, nitrofurantoin, fluoroquinolones, and sulfas were associated with increased chances of nephrolithiasis, even after excluding confounding conditions like urinary tract infections. The odds of nephrolithiasis diminished over time, but were still persistently higher up to 5 years from initial antibiotic administration. The greatest "window of danger" was around 3 to 6 months after exposure to the antibiotic. Children of younger ages were also more susceptible to this association. Typically, these medications precipitate into the urine, crystallize, and obstruct, without causing any metabolic disturbances.[14]

One intriguing theory linking antibiotic usage and nephrolithiasis risk is the impact of these medications on the gut microbiota via a proposed mechanism of changes in macronutrient metabolism from altered composition of the intestinal microbiome.[15] Certainly, gut bacteria is known to be dramatically and persistently reduced even months after the last antibiotic exposure.[16,17] This theory was supported by a case-control study examining the composition of gut microbial communities in patients with known calcium oxalate stone disease.[18] Kidney stone formers were found to have significantly less diverse gut microbiomes, specifically bacteria that produce butyrate and degrade oxalate. Butyrate is responsible for maintaining the gut–mucosal barrier, regulating oxalate transport, and has anti-inflammatory properties; combined with an over-abundance of oxalate from poor degradation, lower production of butyrate may produce the ideal environment for the production of calcium oxalate stones.

Disorders/Anatomic Differences

Patients with malabsorption disorders or a history of urologic reconstructive surgeries with the use of bowel segment, such as augmentation cystoplasty, or urinary stasis due to urologic anomalies or immobility, are at risk for nephrolithiasis. In a study looking at spina bifida individuals after bladder augmentation, approximately 1% of the cohort develop nephrolithiasis annually, with an incidence that is at least 10 times greater than the general population.[19] In particular, those patients were at much greater risk if the augmentation was performed at 10 years of age or older or if they had a prior history of bladder stones. This could be due to the metabolic acidosis that is inherently caused by the use of bowel segment, or mucus generated from the segment itself being refluxed to the kidney and becoming a nidus for stone formation. Other factors that could increase the risks in these patients could include hyperoxaluria due to intestinal malabsorption following bowel resection.

Complex pediatric patients dependent on enteral nutrition are also at higher risk of

nephrolithiasis. This may be related to increased sodium and oxalate content and decreased calcium content in tube feeds that predispose the risk of stones.[20] It has also been demonstrated that they have significantly higher levels of urinary oxalate excretion compared to children not on enteral feeds.[21] Further complicating the picture is that many of these patients are also non-ambulatory. Patients who are limited or non-weight bearing may have an increased risk of bone mineral disease and subsequent supersaturation of their urine.[22] In a 10-year study at a tertiary pediatric center, non-ambulatory children were more likely to require surgical interventions for their stones and were more likely to form infection-related stones such as calcium carbonate or struvite stones.[23] Many minimally ambulatory patients also have a component of neurogenic bladder and chronic bacteriuria with urea-splitting organisms, which may explain the propensity for infection-related urolithiasis. The multitude of mechanisms for urinary stone formation in these complex patients highlights the heterogeneity of nephrolithiasis in patients with multiple medical co-morbidities who will often have numerous, interrelated risk factors for stone formation.

EVALUATION

For the most part, evaluation of a symptomatic kidney stone in children is similar to managing a stone episode in an adult. A comprehensive medical history should include information regarding the amount and types of fluid intake, prescription medications, and use of supplements such as vitamins and family history of urolithiasis. Personal history of anatomic disorders of the urinary tract such as ureteropelvic junction obstruction or other disorders that can lead to stone formation such as inflammatory bowel disease should also be ascertained. Older children will have similar presenting symptoms as adults, primarily flank pain, nausea and vomiting, and lower urinary tract symptoms. However, younger or non-communicative patients may not be able to localize pain or articulate their discomfort; in these instances, the medical provider should heavily rely on diagnostic and laboratory testing.

Ultrasonography remains the preferred initial imaging when evaluating children with suspected kidney stones. If a diagnosis cannot be reached from ultrasound alone, then an abdominal plain film or low-dose non-contrast computed tomography (CT) can be performed, particularly in cases with high clinical suspicion. Although critics of ultrasonography will argue that sensitivity of ultrasound is much lower than CT imaging (76% vs near 99%), the lower sensitivity is mostly attributed to missed small non-obstructing stones less than 3 to 4 mm that may otherwise be clinically insignificant and managed conservatively.[24] Sensitivity of ultrasound can further be improved by using adjunctive findings such as presence of ureteral jets and twinkling artifacts under Doppler settings.[25] Given that children are more vulnerable to radiation effects due to increased cell turnover, have a longer life span with greater potential for dose cumulation, and have a higher rate of recurrence than adults, every effort should be made to limit radiation exposure in this population and to follow the principles of ALARA ("As Low as Reasonably Achievable").[26] Therefore, the Image Gently Alliance was launched in 2007 by pediatric radiologists to inform and educate on the use of ionizing radiation when imaging children.[27] Since then, the use of CT imaging in children for evaluation of kidney stones has decreased significantly, such that by 2012, renal ultrasounds became more frequently used than CT.[28,29] Implementation of a clinical care pathway for kidney stones in pediatric emergency departments can also help with decreasing use of CTs, as demonstrated by a study from the Children's Hospital of Philadelphia.[30] This said, CT likely still has a role in situations of a non-diagnostic ultrasound (US) and high clinical suspicion for nephrolithiasis, and in these situations, CT dose modulation efforts should be undertaken.

MEDICAL EXPULSIVE THERAPY

Ureteral stones in children can spontaneously pass about 32% to 63% of the time, so a trial of passage is worth pursuing in the majority of cases, particularly in older children with stones <5 mm in size located in the distal ureter.[31–33] The adjunctive use of medical expulsive therapy with alpha-blockers and calcium-channel blockers has been well-documented for uncomplicated ureteral calculi in adults, and similarly, in children, tamsulosin has now been shown to increase expulsion rate in stones less than 10 mm, regardless of stone size or location.[34,35] To date, there have been six randomized controlled trials examining the role of these medications in children with distal ureteral calculi (**Table 1**).[36–41] A 2022 systematic review and meta-analysis of these six studies demonstrated that the benefits of medical expulsive therapy in children are statistically significant, although only two of these studies were placebo-controlled and none were double-blinded.[42] As well, none of these randomized controlled trials (RCTs) examined the use of calcium-channel blockers.

Table 1
Randomized controlled trials on the role of alpha-blockers in stone passage

Study	Design	Number of Patients	Primary Endpoint	Stone Characteristics	Length of Treatment, Days	Result
Aydogdu et al,[36] 2009 (Turkey, 2009)	Doxazosin (0.03 mg/kg) + ibuprofen vs ibuprofen alone	n = 19 Control = 20	Stone passage confirmed by patient	Distal ureter, <10 mm	21	No difference
Mokhless et al,[37] 2012 (Egypt, 2012)	Tamsulosin (0.2 mg for <5 yo, 0.4 mg for >5 yo) vs ibuprofen	n = 23 Control = 28	Stone passage confirmed by plain film or CT	Distal ureter, <12 mm	28	Improved passage rate with MET, improved time to passage (8.2 vs 14.5 d)
Erturhan et al,[38] 2013 (Turkey, 2013)	Doxazosin (0.03 mg/kg) + ibuprofen vs ibuprofen alone	n = 24 Control = 21	Stone passage confirmed by plain film, ultrasound, or CT	Distal ureter, any size	21	Improved passage rate with MET
Aldaqadossi et al,[39] 2015 (Egypt, 2015)	Tamsulosin (0.2 mg for <5 yo, 0.4 mg for >5 yo) + ibuprofen vs ibuprofen alone	n = 31 Control = 32	Stone passage confirmed by plain film or ultrasound	Distal ureter, <9 mm	28	Improved passage rate with MET
Elgalaly et al,[40] 2017 (Egypt, 2017)	Silodosin (4 mg) vs ibuprofen	n = 20 Control = 19	Stone passage confirmed by plain film or ultrasound	Distal ureter, <10 mm	28	Improved time to passage with MET (7 vs 10 d)
Soliman et al,[41] 2021 (Egypt, 2021)	Silodosin (4 mg) or Tamsulosin 0.4 mg vs placebo	Silodosin, n = 56 Tamsulosin, n = 55 Control = 56	Stone passage by plain film or CT	Distal ureter, <10 mm	28	Silodosin better in passage rate than tamsulosin (89% vs 75%) Tamsulosin better in passage rate than placebo (75% vs 52%)

Abbreviations: CT, computed tomography; MET, medical expulsive therapy.

Nonetheless, current evidence has thus far proved that medical expulsive therapy is safe and effective in children and may help decrease the risk of additional surgery in young children who may have smaller anatomy and increased difficulty navigating the ureter with ureteroscopy. Of note, the use of tamsulosin or alternative alpha-adrenergic antagonists or calcium-channel blockers would be considered 'off-label' use, which should be addressed with the patient and family during counseling. One additional proposed benefit of alpha-blockade is the relaxation of ureteral smooth muscle to facilitate future ureteral access during endoscopy. Preliminary results from McGee and colleagues utilizing preoperative tamsulosin 1 week before surgery suggested that patients who were given preoperative tamsulosin 1 week before surgery had lower rates of failed ureteroscopy.[43] This complementary role of alpha-blockers can potentially decrease the number of trips to the operating room, and in the future, should be an area of focus in clinical and patient outcomes research for pediatric stones.

EMERGING SURGICAL TECHNOLOGIES

There are several anatomic differences unique to children that should be taken into consideration when evaluating for surgery. First, the smaller body habitus and ureteral diameter may make ureteroscopy and use of adult-sized ureteroscopic instruments challenging, especially with primary ureteral access (ie, before ureteral stenting). For these reasons, Ellison and Yonekawa proposed six characteristics of an ideal surgical modality to guide treatment selection: (1) high rate of monotherapeutic success; (2) low risk for complications; (3) ability to return the child to baseline activity; (4) minimized radiation exposure; (5) minimized anesthesia exposure; (6) no need for ancillary procedures.[44]

Patient-centered selection for the ideal surgical modality should include consideration of the patient and stone factors, surgeon experience and resource availability, and perhaps most importantly, patient-driven goals of care. Given the lack of comparative effectiveness data that currently exist within the surgical space of nephrolithiasis, a current patient-centered and expansive observational clinical trial comparing success and patient-reported outcomes across ureteroscopy (URS), shock wave lithotripsy (SWL), and PCNL (the Pediatric KIDnet Stone Care Improvement Network trial— NCT04285658) will complete accrual in May 2023.[45]

A small number of endourology nomograms and scoring systems has recently been developed to predict success rate and surgical outcomes for pediatric patients. There are currently two pediatric nomograms predicting successful treatment with SWL.[46,47] Several studies comparing these two tools have demonstrated that both had good accuracy in their predictions, although the Dogan nomogram had a higher specificity and therefore is considered slightly superior to the Onal nomogram.[48,49] Both scoring systems utilize a combination of gender, age, stone size, and location to predict success, but neither system investigated any correlation with postoperative complications. There are two nomograms for percutaneous nephrolithotomy (PCNL): the stone-kidney size score (SKS) and the Capital Medical University Nomogram (CMUN).[50,51] The SKS only relies on stone-to-kidney size ratio and number of stones and does not factor in staghorn anatomy or location of stones. When comparing it to adult PCNL nomograms, SKS is able to somewhat accurately predict stone-free rate and complications. The CMUN, on the other hand, used data collected from micro and mini PCNL as well as ureteroscopy, and used CT to measure stone burden as opposed to ultrasonography. It has not been externally validated or compared to other nomograms, including the SKS. Because of the heterogeneous data, the CMUN scoring system is more biased and therefore more difficult to generalize and less predictive.

Ureteroscopy is a mainstay for surgical stone treatment, and recent modifications and improved laser technology have made this surgical option even more favored among surgeons. Thulium laser technology was recently introduced in adult endourology and has since been widely adopted after validation of its safety and ease of use.[52] A study from Boston Children's demonstrated improved stone clearance in 109 children with no differences in postoperative complications over 5 years.[53] Although there was no difference in the total operative time in this study, there was a significant difference in laser time, with the longer laser time in the thulium group likely related to low ablation efficiency. Another territory recently explored is ultrasound-guided ureteroscopy, in an effort to decrease radiation exposure during endoscopic surgery. A feasibility study from Morrison and colleagues demonstrated for the first time that laser lithotripsy can be safely performed using ultrasound on patients with lower average BMI.[54] The authors were able to position the ultrasound probe to visualize guidewires, dual-lumen catheters, and ureteroscope throughout the upper urinary tract. Although there would be an expected learning curve to reading real-time ultrasounds intraoperatively, the study offers hope in lowering radiation

exposure in these children without compromising stone-free rates or increasing the risk of complications.

New techniques and instrumentation for PCNL have allowed for the use of smaller sheaths, with new techniques named based on the size of the tract: mini (14–24 F), ultra-mini (11–13F), super-mini (10–14F) and even micro (<5F) PCNL.[55] Current evidence has shown the safety and efficacy of these techniques in children regardless of age or size of the stone, with a lower risk of complications for bleeding with smaller sizes.[56,57] A systematic review of micro- and ultra-mini PCNL in children noted that reported stone clearance has ranged from 80% to 100%, with complication rates around 11% to 14%, most relating to extravasation and blood loss with larger tract sizes.[52]

For children with complex medical conditions, contracted body habitus, or ectopically positioned kidneys, conventional approaches with URS, SWL, and PCNL may be challenging. In children who cannot tolerate prone positions or for those with issues related to airway access, the supine PCNL has been successfully performed in children.[58,59] Historically, in situations where endoscopic approaches are not feasible to enable reliable stone clearance, open surgery would be considered. With recent advances in laparoscopic and robotic-assisted techniques, these open approaches have fallen out of favor and perhaps opened additional avenues to consider minimally invasive treatments for upper tract stone disease. Those with complicated renal anatomy such as ureteropelvic junction obstruction requiring pyeloplasty should be considered for robotic surgery for simultaneous nephrolithotomy and upper tract reconstruction.[60,61] Stone clearance in these patients has been shown to be at least 96%.[62]

RECURRENCE AND PREVENTION

In adults, the recurrence rate of a symptomatic stone is 50% within 5 to 10 years of the first episode.[63] In children, this recurrence rate is even more dramatic, with the probability of a recurrent symptomatic stone episode within 3 years.[5] Multiple studies have demonstrated that adolescents and those with a prior history of stone formation are at increased risk for subsequent stone events.[64,65] In a cohort of 200 children from a multi-institutional study, Medairos and colleagues discovered that the incidence of a symptomatic stone event was 41% within 1.5 years and that adolescents had a significantly higher chance of stone events than younger children.[64] They emphasized that this at-risk group in particular should have close follow-up for future stone events. Similarly, results from the Registry for Stones of the Kidney and Ureter also demonstrated that those patients who formed a stone before age 20 are more likely to have recurrent stone events compared to those who formed their first stone later in life.[66]

Ultimately, these patients with a complex disease process should be under multidisciplinary care involving a nutritionist, nephrologist, and urologist. Per American Urological Association (AUA) Guidelines, periodic 24-hour urine studies and basic metabolic panels should be obtained during workup and follow-up of recurrent stone formers and interested first-time stone patients.[67] However, the utility of a full metabolic evaluation with a serum chemistry panel and 24-hour urine studies in a first-time pediatric stone former remains controversial. Although completion of 24-hour urine studies has been shown to help with decreased recurrence of future symptomatic stones, it is expensive, difficult to perform correctly in children with adequate volume, and oftentimes does not lead to increased compliance to prescribed treatments.[68] In a study of 800 patients at a high-volume tertiary care center, nearly 50% completed a 24-hour urine study, which admittedly is higher than reported literature.[69] Those who were older in age, who had renal colic with first stone presentation, and who had a family history of stones were more likely to complete the 24-hour urine analyses, but those on government-subsidized insurance were less likely.

Preventive measures should first focus on risk factors that are modifiable. Increasing fluid intake is often the first step in prevention.[70] This is particularly important in patients who live in hot climates or during the summer months when children are more likely to play outdoors in the sun. In a study looking at drinking behaviors in adolescents and response to fluid intake during school, it was noted that this age group is particularly unaware of their daily water intake and is also slow to respond to thirst.[71] Although there is no consensus on how much fluid intake is appropriate for prevention, some base their recommendations on daily urine volumes: infants should maintain a volume greater than 750 mL, children younger than 5 should have greater than 1000 mL, those between 5 and 10 years old should have greater than 1500 mL, and adolescents should aim for greater than 2 L.[72] Researchers have also used 24-h urine collections to develop an equation to help achieve increased urine output goals in adolescents with stones.[73] This equation, known as the fluid prescription, determines the additional fluid intake needed to produce the desired increase in urine output by dividing the desired urine output by

Table 2
Dietary recommendations and weight-based medications for selective metabolic abnormalities

Metabolic Abnormality	Dietary Changes	Pharmaceutical Therapies	Mechanism of Action	Side Effects	FDA-Approved?
Hypocitraturia	Increase potassium- and citrate-rich vegetables and fruits, such as pineapples, tomatoes, bananas	Potassium citrate 2–4 mEq/kg/d	Raises urine pH by providing an alkali load; raises urine citrate excretion	Hyperkalemia, GI discomfort (nausea, diarrhea, vomiting)	Off-label
Hypercalciuria	Low-sodium diet <2 g/d	Hydrochlorothiazide 1–2 mg/kg/d, up to 25–50 mg daily Chlorthalidone initial 0.3 mg/kg/d, up to 2 mg/kg/d or 50 mg/d	Promotes release of sodium into urine and reabsorption of calcium	Hypokalemia, hyponatremia, hypercalcemia	Off-label
Hyperuricosuria	Decrease non-dairy protein and sodium	Allopurinol 4–10 mg/kg/d	Lowers serum and urine uric acid (xanthine oxidase inhibitor)	Hepatotoxicity, delayed hypersensitivity reactions (Stevens-Johnson syndrome)	Off-label
Cystinuria	Decrease sodium intake Higher fluid intake	Alpha-mercaptopropionyl glycine (tiopronin)	Increases solubility of cystine	Fatigue, rash, oral mucosal ulcers, GI discomfort (nausea, diarrhea)	Yes
Hyperoxaluria	Limit daily oxalate Maintain high calcium intake	Lumasiran (for primary hyperoxaluria type 1) Calcium supplementation for enteric hyperoxaluria	Reduces levels of glycolate oxidase enzyme, which reduces the amount of glyoxylate (substrate for oxalate production)	Injection site reaction, abdominal pain	Yes

0.71. For instance, if a child, based on their urine collection results, needs to increase their 24-hour urine output by 500 cc to reach a goal of 2 L, then the recommended increase in the daily fluid intake is 704 mL. Children should also aim for a low-sodium diet and a healthy daily number of citrate-heavy fruits and vegetables. Restriction on animal protein intake is usually not indicated and may adversely affect the linear growth and development of young children. Additionally, as calcium reduction paradoxically increases stone risk and may negatively impact bone health and development, moderate calcium intake is recommended. If dietary changes are not sufficient, pharmacologic therapies may be necessary to decrease recurrence (**Table 2**).

SUMMARY

Pediatric nephrolithiasis is now a public health burden and a looming crisis due to the meteoric increase in incidence within the last several decades. A significant effort in the research community has thus focused on identifying modifiable risk factors, such as environmental exposures, dietary contributors, and effects of medications on gut microbiome, to help educate the medical community and the public on the prevention of stones. We now know that children have a 50% chance of a recurrent stone episode within 3 years. We also know that adolescents and those with complex chronic medical conditions are particularly vulnerable to kidney stone formation. Careful selection of management therapies with a strong emphasis on preventive measures is essential in curbing recurrent stone episodes in pediatric patients, and future research should focus on minimally invasive surgical techniques that minimize ionizing radiation and repeated exposure to general anesthesia.

CLINICS CARE POINTS

- The risk of recurrence for pediatric stone formers is 50% within 3 years of first symptomatic stone, and those most at risk are adolescents and patients with prior history of nephrolithiasis.
- Medically complex patients may have several interrelated risk factors for nephrolithiasis, particularly those with alternate routes of nutrition and immobility, warranting a multidisciplinary approach in stone prevention.
- Assessment of a child with suspected kidney stones is similar to that of an adult, although ultrasonography is the preferred initial imaging study, keeping in line with the ALARA principle and the Image Gently Alliance.
- Emerging surgical therapies now focus on minimally invasive approaches for larger stones and reducing radiation exposure with use of ultrasound-guided endoscopic surgeries instead of fluoroscopy.

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