Urolithiasis

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1. Introduction

Once thought of as a rare condition, pediatric urolithiasis is an increasingly common and increasingly important condition.

Key Words

Urolithiasis, nephrolithiasis, hyperoxaluria, cystinuria, citrate, nephrolithotomy, ureteroscopy, Steinstrasse, Staghorn calculus

2. Epidemiology & Economic Impact

2.1 Epidemiology

Several recent studies suggest that urolithiasis is becoming increasingly common in North American children. Population-based data has been used to estimate the incidence of pediatric urolithiasis to be **60/100,000 as of 2011, which has significantly increased over the past 25 years.**[1,2,3,4] Importantly, **nearly 50% of patients of children will recur within 3 years** of their incident stone diagnosis.[5] Adolescents (as compared to younger children) and those with a prior stone events are at greater risk for recurrence[6].

2.2 Economic Burden

One administrative database study has conservatively estimated an annual economic burden of ~$395 million in 2012, **an inflation-adjusted increase of 72% from 2006**.[7]

3. Risk Factors and Pathophysiology

3.1 Genetic Factors

Multiple genetic conditions predispose to kidney stone formation, particularly inborn errors of metabolism. These genetic conditions have highly variable pathogenetic mechanisms and include primary hyperoxaluria, cystinuria, and Lesch-Nyhan syndrome, among others[8]. A recent international study revealed that monogenic causes may underlie nearly 50% (14/30) of incident pediatric stones.[9]

3.2 Comorbid Conditions and Surgical Factors

Children who have undergone previous urological surgery are at increased risk of urolithiasis, particularly surgeries, which lead to increased bacteriuria and mucosuria such as bladder augmentation or continent urinary diversion. Metcalfe and colleagues reported that **15% of bladder augmentation patients developed bladder stones.**[10] Recent data from Indiana found risk was based on follow-up, with 18% of individuals presenting with nephrolithiasis by 20 years of follow-up. Notably, older age at augmentation was a risk factor for kidney stone formation in this population and 45% of cases were discovered on routine upper tract screening, reinforcing the importance of upper tract imaging in this population[11]. In addition, children with anatomical or functional obstruction of the urinary tract (ureteropelvic and ureterovesical junction obstructions, neurogenic bladder) are at an increased risk of urolithiasis, presumably due to urinary stasis.

3.3 Age, Gender, and Race

There is an association between increased age and increased risk of urolithiasis, even among children. **Teenage children**, **particularly teenage girls**, **are at higher risk** than younger children.[12] The mediators of this effect are as yet unknown, but may include sex-steroid dependent bone mineralization or sex-dependent susceptibility to environmental exposures[13]. Using state data from South Carolina, Sas et al reported that stone rates among African-American children did not significantly change from 1996-2007, whereas rates for Caucasian children increased significantly. Caucasian children were 5.6 times (95% CI, 4.2-7.5) more likely to be diagnosed with urolithiasis when compared with African-American children. Notably, the adolescent demographic was the fastest growing demographic within this study across the entirety of the age-spectrum (including both children and adults[14]).

3.4 Diet and Obesity

There is no definitive evidence to explain the increasing incidence of stone disease in children. However, this increase has paralleled substantial changes in diet during the last few decades, making dietary changes a suspect. Observational and pre-clinical data suggest that **stone formation is associated with dietary factors** such as increased caloric, zinc, fructose, calcium, beta-carotene, and sodium intake.[14,15,16] Despite this association, conflicting data exist as to whether obesity is associated with an increased risk of urolithiasis; two large, well-designed case-control studies produced conflicting results.[17,18] By contrast, compelling data suggest an increased risk of urolithiasis among children with severe epilepsy controlled with a ketogenic diet (up to 6% of these children will develop a kidney stone). This increased risk may be reduced through the use of potassium citrate supplements, with one study showing a 6-fold decrease in incident nephrolithiasis for children treated empirically with Polycitra K.[19] Enteral feeding via a gastrostomy tube, immobility, and seizure disorders are all identified risk factors for nephrolithiasis in children.[20,21] Children with enteral feeding regimens and nephrolithiasis have been shown to have higher rates of hyperoxaluria than kidney stone formers without enteral feeding requirements.[22] Oxalate content of enteral nutrition formulas is variable and may contribute to urinary stone risk.[23]

3.5 Medications

Several medications may increase kidney stone risk in children. Classically, furosemide has been reported as a risk-factor for nephrolithiasis especially in pre-term infants who are provided the diuretic due to respiratory distress in the newborn period.[24,25] However, a recent systematic review of 32 studies did not find a strong association with nephrolithiasis or nephrocalcinosis and furosemide use in pre-term infants, indicating that further well-designed trials are necessary to definitively assess this risk.[26] Topiramate has been linked to risk of nephrolithiasis, with a reported risk of up to 5-10% in select series. The mechanism of increased risk has been postulated to be induction of hypocitraturia and/or hypercalciuria.[27,28] While concerns regarding zonisimide, an anti-epileptic medication with a similar mechanism of action, as a risk-factor for nephrolithiasis have been raised, a large review of reported trials of zonisimide in children found a lower (1%) risk of nephrolithiasis.[29] The co-presentations of anti-epileptic medications, use of enteral feeding, immobility, and ketogenic diet must be taken into consideration when attempting to assess any of these factors as independent risks for nephrolithiasis. Corticosteroids, particularly in preterm infants, have been linked to nephrolithiasis, via a mechanism of altered calcium resorption in the bone.[30] Finally, antibiotics have been linked to nephrolithiasis-risk, both in prospective case series and larger population-based trials, perhaps related to microbiome perturbances.[31,32,33]

4. Diagnosis and Evaluation

4.1 History

Presenting symptoms differ in the pediatric population compared to adults. **Many stones are asymptomatic and do not present with typical renal colic,**[34] with one system-wide assessment of presentations suggesting 43% of all incident kidney stone diagnoses in children were incidental. If present, pain is usually non-specific abdominal pain rather than flank pain. The passage of stones or crystals may be the first manifestation in infants. Similarly, microhematuria or gross hematuria can be the first symptoms in children, even without associated pain. A history of UTI alone, rarely, may be the first indication to perform investigations that ultimately identify the presence of a stone. The history of prior nephrolithiasis, perhaps intuitively, has been shown to greatly increase the risk of identifying nephrolithiasis during presentations of acute renal colic, as has a complaint of nausea or vomiting on presentation.[35] A boy presenting with scrotal pain should obviously be examined for an acute scrotum. However, in the absence of physical exam findings consistent with scrotal pathology, consideration should be given to a distal ureteral calculus with referred pain migrating to the ipsilateral groin and scrotum.

4.2 Examination

Clinical signs and symptoms of urolithiasis include an uncomfortable-appearing patient when the stone is obstructing urinary flow. The older patient may be unable to find a comfortable position and sometimes writhing in the bed. Costovertebral tenderness may be present but lower quadrant tenderness can also be present. Flank pain on examination is a documented independent risk factor for nephrolithiasis.[34]

4.3 Diagnostic Studies

4.3.1 Urinalysis

In the majority of cases of urolithiasis, urinalysis demonstrates the presence of hematuria as a result of urothelial irritation, especially quantified as greater than 3 red blood cells per high powered field on microscopic analysis.[35] However, **the absence of RBC does not preclude the presence of stone disease**. Pyuria when associated with fever and leukocytosis should alert the clinician to possible infection. Urinary tract obstruction from a urinary calculus accompanied by infection should be considered to be a serious medical condition due to the possibility of septicemia if the obstruction is not alleviated in timely fashion. Urine pH can also be helpful in determining stone composition as well as adherence/efficacy in those patients on alkalinizing medications.

4.3.2 Urine Crystal Evaluation

Microscopic analysis of urinary crystals may rarely yield significant diagnostic information. However, review of spot light microscopy could be informative in specific instances as two rare genetic diseases may be diagnosed solely based on pathognomotic urinary crystals alone. Cystinuria, an autosomal recessive defect resulting in abnormally high renal excretion of the amino acid cystine, may be diagnosed by the presence of hexagonal crystals in the urine.[36] Meanwhile, adendine phosphoribosyltransferase (APRT) deficiency results in accumulation of 2,8 dihydroxyadenine (DHA) which when crystallized creates circular brown crystals which reveal a Maltese cross pattern on polarized light microscopy.[37]

4.3.3 Metabolic Evaluation

Children are at high risk to have an identifiable metabolic disorder and to develop a stone recurrence. However, the AUA guidelines notably does not identify young age as an independent risk factor for nephrolithaisis. To this end **interested families of children with urolithiasis should be offered a metabolic evaluation in accordance with AUA Guidelines,** which should include a 24-hour urine chemistry.[38] However, several authors do recommend a more aggressive approach in children owing to the high likelihood of identifying modifiable risk factors.[39,40] Serum studies may be obtained to evaluate for renal function and calcium homeostasis. The clinical benefit of these tests, however, has been called into question as serum studies are rarely abnormal in children with nephrolithiasis.[41] A 24-hour urine study, however, is particularly important, as this test can be useful in identifying patients at increased risk of stone recurrence.[31,40] Unfortunately, this modality is underutilized in children.[42] Spot urine studies may be utilized in lieu of 24-hour urine evaluations but should be interpreted with caution as broad validation of normative values has not been pursued. The use of 24 hour urine collection after every first stone episode in children is expensive and may not change management in most patients, therefore, some suggest reserving 24 hour urine collection after recurrent stones especially in post pubertal patients but this practice is not universally accepted.[43] A simple screening test for hypercalciuria is the **spot urine calcium/creatinine ratio**. In children over 6 years of age, 0.2 mg/dL is considered the upper limit of normal; in breast-fed infants less than 6 months of age, however, ratios as high as 0.8 can be normal.While variation exists in interpretation of normal spot urine and 24-hour urine values for urinary stone risk assessment, the following tables (**Table 1** and **Table 2**) provide some reference as to normative values.[44]

Table 1: Reference ranges for 24-hour urine values in children (adapted from Hernandez et al)[45]

Urine Constituent	Age	Timed Collection
Calcium	All ages	< 4 mg/kg
Oxalate	> 2 y	< 0.45 mg/1.73 m^2
Citrate	All ages, male	> 365 mg/1.73 m^2
	All ages, female	> 310 mg/1.73 m^2
Uric Acid	All ages	< 815 mg/1.73 m^2
Creatinine	3-5 y	12-20 mg
	6-13 y	15-25 mg
	14-18 y, male	18-27 mg
	14-18 y, female	17-24 mg

Table 2: Reference ranges for spot urine values in children (adapted from Hernandez et al)[45]

Urine Constituent	Age	Value (mg/mg Creatinine)
Calcium	< 7 mo	< 0.86
	7-18 mo	< 0.6
	19 mo – 6 y	< 0.42
	> 6 y	< 0.2
Oxalate	< 6 mo	< 0.29
	6 mo – 2y	< 0.2
	> 2 – 5 y	< 0.11
	6-12 y	< 0.06
Citrate	< 5 y	0.42
	> 5y	> 0.25
Uric acid	All Ages	< 0.56 per GFR[a]
Calcium:Citrate Ratio	All Ages	< 0.6 (not normalized to creat)

a: multiply uric acid:creatinine ratio (mg/mg) with serum creatinine (mg/dL)

Serum studies such as complete blood count and renal profile are also helpful to understand the presence of possible infectious process or renal impairment, respectively, in the setting of acute renal colic. Leukocystosis may be due to inflammation; pain and stress of renal colic and is not always associated with an infectious process. Additional parameters are helpful to determine the clinical significance of the lab value. An elevated serum creatinine may be indicative of a need to pursue surgical intervention when bilateral obstructing stones or obstructing stone in solitary kidney are present. Caution must also be exercised in use of non-steroidal anti-inflammatory medications in the presence of an elevated serum creatinine given their risk of nephrotoxicity.

4.3.4 Genetic Evaluation

A familial preponderance for kidney stones has long been recognized, with a landmark study from Resnick et al in 1968 identifying a significant yet non-Mendalian pattern of kidney stone formation in afflicted individuals and first-degree relatives, suggesting a polygenetic source of risk.[46] More recently, Goldfarb et al performed a classic twin study identifying a 56% hereditable risk for kidney stones, with a greater hereditable risk identified in males.[47] Advances in whole exome genome sequencing and more widespread availability of genetic technologies in general have opened avenues for further investigation into monogenetic evaluations of kidney stone disease. A series of internationally-based multi-institutional studies have identified 30 genes of interest within a select cohort of children with nephrolithiasis and nephrocalcinosis. In these published experiences, 16.8% of children screen had a mutation in 14 of the 30 genes within the select gene panel. Of these mutations 44.4% were novel, indicating a relatively high prevalence for genetic variations in children with nephrolithiasis as well as underscoring the nascent understanding of genetic anomalies in these patients.[48,49] While these studies are from select experiences, one proposed algorithm for applying genetic evaluations for nephrolithiasis is to consider the patient age, consanguinity, diagnosis, and response to treatment. Children less than 5 in this approach are proposed to undergo genetic evaluation if consanguinity is present or they fail to respond to best available treatments. Children older than 5 are recommended in this approach to undergo genetic evaluation if an adequate underlying diagnosis cannot be identified or if treatment response is inadequate.[50] The relevance of family history and recurrent stone disease has not been well defined in these evaluations but such associations are ripe for future study.

4.3.5 Imaging Studies

Selection of studies to diagnose urolithiasis in the pediatric population is centered on **minimizing radiation exposure**. EAU guidelines recommend renal sonography with or without abdominal radiography as the baseline screening imaging modality among patients suspected of urolithiasis.[51] **Renal sonography** is an ideal modality to identify upper tract dilation while avoiding the use of ionizing radiation, although is operator-dependent and depending on time of presentation, may not be readily available in an acute setting. Abdominal radiography can also be helpful in cases of radiopaque calculi. In one study, 50 consecutive patients with suspected urolithiasis underwent both computerized tomography and ultrasound. **Compared to computerized tomography, ultrasound had 76% sensitivity and 100% specificity**. When evaluating clinical impact, the ultrasound/ computerized tomography discrepancy resulted in a significant change in clinical management in only 4/50 cases.[52] While computerized tomography in the adult population has become the “gold standard” for identifying urinary tract calculi, it has the disadvantage of significant radiation exposure and level 1 evidence exists in adults for use of ultrasound-first strategies to safely screen individuals for suspected renal colic.[53] In this context, ultrasound-first imaging strategies have been instituted at pediatric centers without demonstrable negative impact in missed diagnoses or emergency department revisits.[54] For preoperative planning purposes or when first-line imaging is unclear, however, CT is an appropriate second-line option in children.

4.3.6 Nephrocalcinosis in Infancy

The prevalence of nephrocalcinosis ranges from 7 to 41% among preterm infants in the neonatal intensive care unit. The etiology of nephrocalcinosis in infants is thought to be multifactorial; it is likely to be related to prematurity, particularly extreme prematurity and low birth weight, typically combined with respiratory disease such as broncho-pulmonary dysplasia and treatment with furosemide and other diuretics. Nephrocalcinosis is thought to negatively impact long-term tubular and glomerular function, although this is controversial.[54,55] Fortunately, most patients with nephrocalcinosis resolve spontaneously, with only 15% progressing to require surgical intervention.[56,57]

4.3.7 Monogenetic Kidney Stone Diseases

Several well-described monogenic diseases that potentiate kidney stone formation and/or crystalline deposition within the kidney are described and may present with greater frequency in children than adults. Although rare, recognition of these diseases is important given available medical treatments and potential for severe disease progression and renal deterioration. Three such diseases – cystinuria, primary hyperoxaluria (PH), and adenine phosphoribosyltransferase (APRT) deficiency – are described here:

Cystinuria is an autosomal recessive disease that impacts the renal amino acid transporter responsible for cysteine, ornithine, lysine, and argenine. However, only cysteine is subject to divalent bond formation and subsequent crystallization under physiologic conditions. This amino acid is a heterodimer encoded by two separate genes: SLC3A1 (on chromosome 2) and SLC7A9 (on chromosome 19),

mutations of which will lead to Type A and Type B cystinuria, respectively. Cystinuria may be diagnosed by pathognomonic hexagonal-shaped crystals or a nitroprusside test. Up to 70% of individuals will develop chronic kidney disease (CKD), underscoring the importance of life-long management of this disease. Cystine (the dimer of two cysteine molecules) has a pH-dependent solubility and at physiological urine pH has a solubility co-efficient of approximately 250 mg/L[58]. Treatment is focused on minimizing the cystine available for crystallization per liter of urine output, accomplished through four key approaches: fluid intake, diet, urinary alkalization, and cystine-binding medication. Fluid intake is typically recommended at 3-4 liters per day, in order to decrease cystine levels to less than 250 mg/L. A low protein diet (9%) may decrease methionine, a cysteine precursor, thereby reducing the available cystine load. Alkalization of the urine will increase this solubility co-efficient and typical goal pH is at least 7, and ideally 7.5 although this target is typically difficult to reach[57]. Finally, tiopronin and d-penicillimine are first and second-line cysteine binders, respectively, which reduce formation of cystine molecules by blocking the disulfide bonds. While both medications have significant side-effects, d-penicillimine is classically less well tolerated than tiopronin and thus is typically a second-line medication for cystinuria[59].

Primary hyperoxaluria (PH) is also an autosomal recessive disorder, of which there are three-subtypes, influencing metabolism of oxalate. The prevalence is 1 in 120,000 yet this disease accounts for 1-2% of all pediatric end stage renal disease. PH presents classically with calcium oxalate monohydrate stones, which typically appear dumbbell shaped on light microscopy, although such a finding is by no means pathognomonic. A summary of PH subtypes can be found in **Table 3**. Progression to CKD occurs from deposition of oxalate within the renal tubules; once the glomerular filtration rate drops below 30 mL/min, systemic deposition of oxlate ensues. As such, serum oxalate levels are not necessary to check unless the patient has CKD 4 or greater. Treatment is focused on general kidney stone preventative strategies including diet and fluid management. There are 2 notable medical management strategies for Type 1. Pyridoxime (vitamin B6) is a co-enzyme for alanine glycoxalate aminotransferase, and B6 supplementation is effective at reducing urinary oxalate in certain sub-groups of Type 1 PH[60]. Lumasiran was FDA approved in early 2021 for treatment of children and adults with Type 1 PH. This medication is an RNA inhibitor targeting the enzyme HAO-1, which converts glycoxalate to oxalate[61]. Beyond these medical therapies, classically kidney-liver transplant has been offered as treatment for PH with end stage renal disease, as the liver is prime (and in PH Type 1 the sole) driver for hyperoxaluria in these patients[60].

Table 3: Summary of Primary Hyperoxaluria Sub-Types

	Type 1	Type 2	Type 3
Enzyme	Alanine Glycoxalate Aminotransferase	Glyoxalate Reductase-Hydroxypyruvate Reductase	4-hydroxy-2-oxogluterate aldolase
By-product	Glycoxalate	Glyoxalate	Mechanism for oxalate accumulation unknown
Treatment	B6 (some genetic subtypes) Lumasiran	No specific medical treatments	No specific medical treatments
Diagnostic Pearls	Elevated urine glycolate	Urinary L-glycerate is highly specific, but less sensitive for Type 2	May also have elevated urine calcium

Adenine phosphoribosyltransferase (APRT) deficiency is a rare autosomal recessive disorder resulting in a supra-physiological build-up adenine, which is then converted via xanthine dehydrogenase to 2,8 dihydroxadenine. These 2,8 dihydroxadenine (DHA) crystals are pathognomonic for APRT deficiency (see 4.3.2 urinary crystal evaluation). Only approximately 400 individuals have been reported to suffer from this disease world-wide. However, 37 were reported to have had delays in diagnosis of a median of 7.5 years and 15% will develop renal failure. Treatment is with allopurinol, which inhibits xanthine dehydrogenase. One may monitor treatment effect by light microscopy in the clinic, with an absence of DHA crystals indicating a favorable response.[62]

5. Secondary Prevention

The risk of recurrence for children and adolescents with nephrolithiasis has been quoted at up to 50% at 3 years.[5] As such, secondary prevention of nephrolithiasis in children is essential to minimize future disease burden. Currently, risk stratification for future stone events is not well defined and recommendations are based on individualized presentations. However, secondary prevention broadly can be divided into lifestyle (i.e. fluid and dietary measures) and medication management.

5.1 Fluid and Diet Recommendations

Fluid intake is the most effective strategy in reducing future kidney stone formation, as supported by level 1 evidence arising from adult studies.[63] While complementary studies in children are limited, the low risk of hydration-based strategies and proven evidence in adults leads to strong recommendations for fluid intake in all ages with some caveats. First, infants less than 12 months of age should not be provided free water and water intake should be judicious in younger children. Second, age-based recommendations via the Institute of Medicine (IOM) and summarized in **Table 4**. Because these goals include both fluid and food intake combined, a strategy to recommend increased fluid intake for kidney stone formers is to use the IOM recommendations as a baseline for fluid intake, irrespective of ancillary intake from foods. Notably, the majority of children do not meet their typical goals for fluid intake.[64]

Table 4: Age based fluid and water intake, adapted from the Institute of Medicine (water and sodium)[65] and National Institutes of Health Office of Dietary Supplements (Calcium)[66]
Water
1-4 years: 1.3 L (about 5 cups) per day
4-8 years: 1.7 L (about 7 cups) per day
9-13 years: • Boys: 2.4 L (about 10 cups) per day • Girls: 2.1 L (about 9 cups) per day
14-18 years: • Boys: 3.3 L (about 14 cups) per day • Girls: 2.3 L (about 10 cups) per day
Sodium
1-3 years: Less than 1.5 g/day
4-8 years: Less than 1.9 g/day
9-13 years: Less than 2.2 g/day
14-18 years: Less than 2.3 g/day
Older than 18: Less than 2.5 g/day
Calcium (Recommended Daily Allowance)
1-3 years: 700 mg
4-8 years: 1000 mg
9-18 years: 1300 mg
Older Than 18 years: 1000 mg

Dietary recommendations are founded in principles of improving urinary parameters for kidney stone risk. In adults, high-level evidence supports low salt, moderate calcium, low animal protein diets to reduce risk of kidney stones[67] and similar to the fluid studies, many of these recommendations can be translated to children with important caveats. First, children should not be counseled to reduce their protein intake as their metabolic needs are different than adults, and it should be noted these dietary studies have not been reproduced in children. Second, calcium intake need vary in children (**Table 4**) and therefore moderate calcium diets should be specified so adolescents understand their recommended daily allowance of calcium actually may be greater than that of adults. However, sodium recommendations may be provided to children, as the risk of introducing reasonable sodium limitations in children is low and there may be benefits owing to the interactions of sodium and calcium reabsorption along the nephron[19].

5.2 Medical Management

Data supporting medical management for nephrolithiasis in children are limited as compared to data in adults in most instances. Notably, most medications for management or secondary prevention of nephrolithiasis are not FDA approved for those indications in children.

A summary table of all agents for medical management of pediatric urolithiasis is shown in **Table 5**. Note that all medications except alpha-adreneric antagonists are indicated for secondary prevention.

Table 5: Medical Treatments For Pediatric Urolithiasis

Therapeutic Class	Example Agents	Mechanism of Action	Outcomes	Adverse Effects	FDA Approval
Alpha-adrenergic antagonists[68]	Tamsulosin, doxazosin	– Ureteral smooth muscle relaxation	– Improved stone passage rate (71 v. 29%, p=0.005) – Reduced expulsion time (6 v 8 days, p=0.001)	Usually mild; include dizziness, headache, nausea, vomiting	Off-label for this indication in children
Thiazide diuretics[69]	Hydrochlorothiazide, chlorothiazide, chlorthalidone	– Reduce urinary calcium by increasing calcium reabsorption in distal tubule – Replenish bone calcium stores	– Decreased stone recurrences (mean difference -0.18 stones/patient/year)	Usually mild; hypokalemia and increased serum uric acid	Off-label for this indication in children
Citrate supplementation[70]	Potassium citrate	– Inhibits calcium oxalate crystallization – Inhibits spontaneous nucleation of calcium salts	– 2-4 fold risk reduction in stone recurrence	Usually mild; increased urinary pH (if severe, can cause calcium phosphate stone formation), GI upset, hyperkalemia	Off-label for this indication in children
Cysteine binders[71]	Triopronin D-penicillamine	Binds cysteine and inhibits divalent cystine bond formation	Risk reduction of stone formation 63-71%	May be severe and include proteinuria, elevated liver enzymes, bone marrow suppression	Approved in children and adults with cystinuria; Triopronin approved in children $\geq$ 20 kg
Pyridoxine[60]	Pyridoxine (B6)	Coenzyme to Alanine Glycoxalate Aminotransferase	Reduction in oxalate by 30% is considered responsive	Neuropathy at high doses	N/A – supplement

RNA Inhibitors[61]	Lumasiran	Inhibits conversion of glyoxalate to oxalate	Reduces urinary oxalate excretion by 65.4%	Mostly mild, include injection-site reactions, headache, rhinitis, upper respiratory infection	Approved for adults and children with PH Type 1

5.3 Alpha-Adrenergic Antagonists

Rationale: Alpha (α1)-blockers relax smooth muscle within the ureter, thereby helping to increase the probability of spontaneous stone passage.

Outcomes: In a recent meta-analysis, Velasquez et al found that medical expulsive therapy with alpha-adrenergic antagonists increased the odds of stone passage more than 4-fold (OR 4.06, 95% confidence interval 1.84-8.95). Mean stone size ranged from 3-8 mm; typical dose was 0.4 mg Tamsulosin or 0.03 mg/kg/d doxazosin.[72] This is similar to the results of a meta-analysis of adult data reported by Hollingsworth et al.[73]

Adverse Effects: **Most children tolerate alpha-antagonists well,** with < 1% of treated children withdrawing from studies due to adverse effects. Mild adverse effects have been reported to occur in up to 4% of patients, including somnolence, dizziness, headache, and nausea/vomiting[72].

5.4 Thiazide Diuretics

Rationale: In children, hypercalciuria can lead to urolithiasis, in addition to hematuria, frequency, dysuria, and non-specific abdominal pain. Thiazide diuretics decrease urinary loss of calcium, primarily by increasing calcium reabsorption within the distal tubule. Thiazides may also help to replenish bone stores of calcium salts, thereby reducing osteopenia rates among affected patients.

Outcomes: A Cochrane Collaboration meta-analysis of 4 randomized trials of adult patients noted a significant decrease in the number of stone recurrences in patients treated with thiazides (mean difference, -0.18 stones/patient/year, 95% confidence interval -0.30 to -0.06)[69].

Adverse Effects: Adverse effects from the prolonged use of thiazide diuretics are minor. Hypokalemia and increased uric acid values have been reported, but these changes did not reach clinical significance. In the Cochrane review, there was no reported difference in plasma levels of cholesterol, glucose and triglycerides between patients treated with thiazides and controls[68].

5.5 Citrate Supplementation

Rationale: Citrate has an inhibitory activity on calcium oxalate crystallization by binding to calcium ions in solution, and it additionally inhibits spontaneous nucleation of calcium salts.

Outcomes: Although data specific to children are lacking, 2 randomized controlled trials of adults found a 2-4 fold risk reduction in stone recurrence among patients taking citrate supplementation as compared to those taking placebo[70].

Adverse Effects: It is important to monitor urinary pH in children on citrate supplementation, as this therapy increases the urinary pH and potentially can make the urine so alkaline that calcium phosphate stones can begin to form.

5.6 Cysteine Binders

Rationale: Cysteine molecules bind to form cystine, which has a much lower solubility in physiological conditions. Binding the cysteine will prevent development of cystine.

Outcomes: Tiopronin and D-penicillamine have both been shown in retrospective studies to reduce kidney stone formation in children and adults with cystinuria[74]. In one comparative trial, tiopronin was equally as effective as D-penicillamine in reducing stone risk with a lower side effect profile[71].

Adverse Effects: While tiopronin is much better tolerated than D-penicillamine, both can have severe adverse side-effects. A comprehensive metabolic panel and urinary protein:creatine ratio should be checked prior to induction of therapy with either drug. While patients on tiopronin no longer require complete blood counts or liver function tests on surveillance, urinary protein measurements should be monitored every 3-6 months for the first year of treatment and every 6-12 months thereafter and renal function should be monitored yearly due to the general risk of renal disease with cystinuria. D-penicillamine can cause B6 deficiency, which may increase risk of hyperoxaluria and calcium oxalate calculi. As such, B6 should be monitored in these patients and pyridoxime started as supplementation if low. Additional side effects for D-penicillamine warrant monitoring of complete blood counts and liver function and include anemia, neutropenia, thrombocytopenia, and abnormal liver function[74].

5.7 Pyridoxine

Rationale: Pyridoxine is a coenzyme to alanine glycoxalate aminotransferase, which converts glyoxalate to oxalate. In certain forms of PH Type 1, pyridoxine may augment the effects this enzyme, which is otherwise insufficient, thereby reducing overall oxalate production[71].Pyridoxine is also indicated if medical-associated B6 deficiency is induced, such as treatment of cystinuria with D-penicillamine[60].

Outcomes: Overall outcomes of pyridoxine are not well reported, as this treatment is only successful in a subset of patients with the rare PH Type 1 sub-type. However, a 30% reduction in oxalate levels are considered responsive. Because the genotype to phenotype

correlation with regards to pyridoxine-responsiveness is poor, it is suggested that patients with PH Type 1 be empirically trialed on pyridoxine with a recheck of urinary oxalate approximately 1 month following treatment.

Adverse Effects: Pyridoxine is a supplement and as such, little is known regarding adverse events with this supplementation. However, at intake of > 1000 mg or more, B6 may result in neuropathy.

5.8 RNA Inhibitors

Rationale: Lumisaran is an RNA inhibitor to HAO-1, which converts glyoxalate to oxalate in PH Type 1. Inhibiting this conversion lowers the bio-available oxalate filtered through the kidneys.

Outcomes: Lumisaran has been shown to reduce urinary oxalate levels in children older than 6 and adults with PH Type 1 within 1 month of initiating treatment. Urinary oxalate levels normalized in 52% of patients on the medication and a significant decrease in plasma oxalate levels at 6 months was also noted in the treatment group.

Adverse Effects: Lumisaran is administered via monthly subcutaneous injection and accordingly, the majority of adverse effects reported were related to injection site irritation. Rhinits, headaches, and upper respiratory infections were also less commonly reported. Overall, the medication is well tolerated compared to placebo[91].

6. Surgical Treatments

A summary table of surgical indications for pediatric urolithiasis is shown in **Table 6**. The **AUA Guidelines on Surgical Management of Stones** specifically addresses clinical scenarios of stone diagnosis and management.

Table 6: Indications for Surgical Treatments for Pediatric Urolithiasis
Uncontrollable renal colic
Intractable nausea or emesis
Obstructed and infected upper urinary tract
Obstruction resulting in impaired renal function
Persistent obstructive hydronephrosis after appropriate period of observation

6.1 Shock Wave Lithotripsy (SWL)

6.1.1 Indications and Preoperative Preparation

AUA Guidelines on Surgical Management of Stones states "Clinicians should offer ureteroscopy or SWL for pediatric patients with ureteral stones who are unlikely to pass the stones or who failed observation and/or medical expulsive therapy, based on patient-specific anatomy and body habitus." Stone size is a determinant in pediatric patients. The guidelines recommend "that with a total renal stone burden ≤ 20 mm, clinicians may offer SWL or ureteroscopy as first-line therapy whereas with a total renal stone burden > 20 mm, both PCNL and SWL are acceptable treatment options. If SWL is utilized, clinicians should place an internalized ureteral stent or nephrostomy tube."[76] European Association of Urology came out with its guidelines for pediatric stone patients which agrees with AUA guidelines except they offer PCNL for stone size more than 20 mm.[51]

Sterilization of the urine prior to the procedure may minimize infectious complications. Some lithotripters utilize fluoroscopy to identify the urinary calculus; therefore, careful review of abdominal radiograph is necessary to ensure the stone is visible to minimize difficulty with intraoperative localization. Ultrasound localization is now frequently utilized to identify and target the stone. Administration of a laxative, such as polyethylene glycol 3350, the night before the procedure to decrease the stool load can also assist with intraoperative localization. If a CT scan has been obtained the attenuation value (Hounsfield unit) of the stone offers some prognostic value with respect to stone free status following SWL.

6.1.2 Operative Considerations

The energy delivered should be commensurate with the size of the child. Modifications to ensure proper shielding, positioning of the child and appropriate dose of electrical discharge to the size of the patient are required to reduce the likelihood of complications such as hematomas or lung contusions. With regard to gating of shocks during SWL, studies have demonstrated that ungated shocks are safe in the pediatric population, and that the arrhythmias seen in adults are not likely to occur in this population. Salem et al demonstrated in a prospective randomized study in a pediatric population that a shock wave delivery of 80 versus 120 shocks per minute is associated with higher stone free rate for solitary renal stone 10-20 mm in size but one recent meta-analysis showed the quality of evidence for this to be poor. [76,77] If a staghorn calculus is being treated, placement of a ureteral stent may minimize the risk of ureteral obstruction and can be placed under the same anesthetic. To avoid significant **steinstrasse** a fractionated disintegration technique is employed in which the pelvic component of the staghorn is initially fragmented, followed by sequential fragmentation of the upper, mid and lower calyceal components.

6.1.3 Outcomes

Stone free rates are vary from 15-95%; higher rates are observed with ureteral stones compared to renal stones.[77,78,79,80] Higher success rates for SWL are dependent upon stone location, size, composition and Hounsfield units.[78,79] In one retrospective study, when patients were stratified into two groups by Hounsfield attenuation value measured with CT (<1,000 HU and ≥1,000 HU) the SWL success rates were 77% and 33%, respectively.[79] Cysteine stones are particularly hard stones and experience poor fragmentation with SWL.[78,79,80] ESWL is less effective for calcium oxalate monohydrate stones and stones in the lower pole of the kidney and the distal ureter.[81] SWL for staghorn calculi in children resulted in a stone free rate of 88% with patients less than 2 years old and 71% of children 6-11 years old in one published case series.[78] Grivas et al did a literature review for EUA which revealed a stone free rate of 43.8%-82.4% after a single session increasing to 70-90% after multiple sessions, with retreatment rates of 4-50% and complication rates up to 15%.[51] It has been shown to be a safe and effective alternative in children less than 2 years of age.[82] Marchetti et al shown equivalence between SWL and ureteroscopy but the latter leads to more morbidity.[83]

6.1.4 Surgical Complications of ESWL

The most common complications include, renal hemorrhage, subcapsular hematoma, pulmonary contusion, ureteral obstruction – steinstrasse, and urinary tract infection. Onal et al reported an incidence of steinstrasse of 7.6% in 341 renal units treated with stone burden being the only statistically significant predictor of steinstrasse.[84] In addition, SWL to a renal stone was associated with increased risk of hypertension but ureteroscopy or SWL to the ureter did not carry this risk.[85] More recent evidence looking at this in terms of biomarkers of acute kidney injury secondary to ESWL report an increase in biomarkers after ESWL but they all return to baseline.[86,87]

6.2 Ureteroscopy

6.2.1 Indications and Preoperative Preparation

Ureteroscopy is an ideal treatment modality for multiple renal stones each less than 1 cm when intervention is deemed necessary. Larger stones can be approached utilizing ureteroscopy however stone free rates are lower as stone burden increases relative to more invasive technique such as percutaneous nephrolithotomy.

AUA Guidelines recommend that in pediatric patients with a total renal stone burden ≤ 20 mm, clinicians may offer SWL or

ureteroscopy as first-line therapy. The same guidelines state that clinicians should not routinely place a stent prior to ureteroscopy.[75]

Age used to be a concern for feasibility of ureteroscopy but recent evidence shows it be safe and efficient.[88] Solitary distal ureteral calculus is another clinical situation where ureteroscopy can achieve a stone free rate in a single treatment session in over 90% of cases.[89] Sterilization of the urine prior to the procedure may minimize infectious complications.

6.2.2 Operative Considerations

Instrumentation of the urinary tract is performed under direct vision with the endoscope or with fluoroscopic assistance to minimize the chances of injury to the patient. Recently efforts are being made to make this procedure amenable to ultrasound guidance but they are in their preliminary stages.[90] At times a standard rigid ureteroscope may not be able to be safely passed retrograde into distal ureter due to narrow lumen found in the pediatric patient. In these circumstances it is safest to place a double J ureteral sent to allow for passive ureteral dilation and wait a few weeks until the ureter can more easily accommodate the ureteroscope to minimize the risk of ureteral injury. Some recent evidence suggests tamsulosin use pre-operatively might improve successful passage of ureteroscope without pre-stenting.[91] In adults, pre-stenting is associated with decreased operative time and improved ability to place ureteral access sheath.[92] Semirigid ureteroscopes commonly used are 7-8 French in size however there are smaller ones available (4.5/4.9 French) that are very helpful in the pediatric population or small luminal diameter ureter. Rigid ureteroscopes should be used primarily for the distal ureter while flexible ureteroscopes used for proximal (proximal to the iliac vessels) and intrarenal ureteroscopy. Single-use ureteroscopes are now being used in pediatric urological practice with reports of similar success rates as reusable ones, and these have been shown to be cost effective.[93,94]

Placement of a “safety” guide wire into the ureter assists the surgeon while navigating the ureteroscope through the ureter. Ureteral access sheaths allow the surgeon to pass the flexible ureteroscope per urethra into the kidney easily while attempting to lower the intrapelvic pressures that accompany instrumentation. These sheaths can be placed under fluoroscopic guidance over a guide wire. Recent evidence suggests use of ureteral access sheaths is safe and effective in children.[95,96] Access sheaths with suction attachments can be used to clear residual fragments after lithotripsy and thus improve residual fragment rate.

Once the stone is identified with the ureteroscope, depending upon the size of the stone, a stone retrieval basket or lithotripter can be passed through the working sheath of the scope. If the stone is small enough the basket is deployed and the stone ensnared. It is critical that the stone within the basket is visualized along with the lumen of the ureter upon withdrawal of the scope. This is to minimize the risk of the basket becoming caught in the ureter and inadvertent traction resulting in injury to the ureter. If the stone is too large to be removed, then a lithotripter device is passed. The Holmium laser is the most commonly used device in United States and can be used in both rigid and flexible ureteroscopes although more recently Thullium laser has been adopted for this use. Stones can either be fragmented into dust particles to be passed spontaneously or into smaller fragments that are amenable to basket stone extraction. Newer laser technology reduces retropulsion of stones during lithotripsy and thus reduces operative times.[97]

Placement of a double J ureteral sent following the ureteroscopic procedure is not mandatory in all cases. However, it is recommended to place a stent when ureteral mucosa injury, ureteral orifice dilation, ureteral perforation or treatment of impacted ureteral stone is encountered.

6.2.3 Outcomes

Stone free rates vary from 75-95%.[89,98,99,100] A recent systematic review by Ishii et al showed that stone free rate was 88% with a mean stone burden of 9.8 mm.[89] Stone free rates for lower pole renal calculi treated with flexible ureteroscopy was reported to be 76% in a series by Cannon et al.[98] This is in contrast to higher stone free rates for mid to distal ureteral calculi treated with rigid ureteroscopy.[89,99,100] In a recent review by Grivas et al., semi-rigid ureteroscope was found to have a stone free rate of 81-98%, retreatment rate of 6.3-10% and complication rates of 1.9-23%. In comparison the same numbers for flexible ureteroscope were 76-100%, 0-19% and 0-28% respectively. They found younger age, cysteine stones, larger stones and lack of presenting symptoms predispose to failure of intervention in children.[54] Atar et al.[99] compared use of a 4.5 Fr mini-ureteroscope with use of a 7.5 Fr standard ureteroscope for treatment of ureteric stones in 69 preschool children; the stone free rate was significantly higher (93% vs 79%) for children treated with the mini-ureteroscope. The youngest children treated in the study was 2 years old.[99]

6.2.4 Surgical Complications of Ureteroscopy

Complications include those occurring intraoperatively: hemorrhage, ureteral perforation, ureteral avulsion and those occurring postoperatively: urinary tract infection, ureteral obstruction from stone fragment/mucosal edema, ureteral stricture. A systematic review of pediatric ureteroscopy in total of 1718 procedures in nearly 1500 children reported that a relatively small proportion of the study population (8.7%) had minor complications; with the most serious being Clavien grade III complications.[89] The most frequently reported complication is ureteral perforation and this occurs in 4-6%.[89,100] A NSQIP database study looking at post-operative outcomes after ureteroscopy reports an unplanned visit rate of 16.5% and the most reasons for the visit are urinary tract infection, new or unresolved stone and pain.[101]

6.3 Percutaneous Nephrolithotomy (PCNL)

6.3.1 Indications and Preoperative Preparation

A larger stone burden (> 2 cm), staghorn calculus, significant sized cysteine stones are accepted indications for PCNL. A reconstructed lower urinary tract that precludes retrograde access to ureterovesical junction is another indication for percutaneous antegrade access to treat mid to distal ureteral calculi when SWL is ineffective or inappropriate. Another scenario to consider PCNL is in malrotated kidneys and horseshoe kidneys where both SWL and ureteroscopy may not be feasible due to position and rotational concerns. Sterilization of the urine prior to the procedure minimizes infectious complications. Obtaining a type and screen is prudent given the risk of bleeding requiring transfusion is higher for PCNL compared to other stone removal techniques.

AUA Guidelines state: “In pediatric patients with a total renal stone burden > 20 mm, both PCNL and SWL are acceptable treatment options” and it is strongly recommended “Clinicians should obtain a low-dose CT scan on pediatric patients prior to performing PCNL.[75]

6.3.2 Key Operative Points

Percutaneous access can be obtained prior to PCNL or at the same setting using either fluoroscopy or ultrasound. Dilation of the tract is accomplished under fluoroscopic guidance using either serial coaxial dilators or balloon dilator over a guide wire. Once the tract is dilated to a sufficient size, a working sheath is left in place to allow for passage of either a rigid or flexible nephroscope. The sheath size should be larger than the scope being utilized to allow for adequate irrigation. The sheath also minimizes bleeding by providing a tamponade effect on the parenchyma. Excessive torque of the kidney while maneuvering the nephroscope should also be avoided to minimize tearing and subsequent bleeding. Recently the concept of small percutaneous tracts to minimize the bleeding that can accompany tract dilation have been more widely utilized with the microperc and miniperc techniques.The advent of miniaturization of instruments ushered in smaller scopes, smaller retrieval devices, and energy sources. These miniaturized instruments and accessories may obviate the need to dilate the tract beyond 20 Fr. Access sheaths that can have suction connected to it may improve residual fragmentation rate and aid cleaner fields of vision.

Once again, a variety of energy modalities can be utilized through the scope such as Holmium laser, pneumatic or ultrasonic lithotripters depending upon availability or surgeon preference. Fragments are removed with care so as not to dislodge the working sheath and subsequent loss of the percutaneous access.

A planned staged/second look PCNL may be appropriate with large stone burden and placement of a nephrostomy tube to preserve the percutaneous tract is needed. Alternatively, it may be reasonable to proceed with a “tubeless” PCNL postoperatively and not leave a nephrostomy tube through the percutaneous tract when the patient is rendered stone free at the end of the procedure. However, a nephrostomy tube can also provide drainage of the kidney and access for subsequent postoperative radiographic study of the upper urinary tract as well. Whichever type of tube is chosen, the tube is placed under fluoroscopic guidance over a guide wire known to be within the renal collecting system.

Most pediatric patients are admitted to hospital following PCNL. When a nephrostomy tube is in place, an antegrade nephrostogram can assist in determining if any distal obstruction from residual stone fragment/blood clot is present. Removal of the nephrostomy tube may be appropriate dependent upon the nephrostogram findings or residual stone burden. As with other treatment strategies, renal imaging, either renal ultrasound or KUB, should be performed to quantify the success of the PCNL in rendering the patient stone free. Residual stone burden can be managed according to the discretion of the treating physician.

6.3.3 Outcomes

Stone free rates range from 60-98%with PCNL.[100,102,103,104] Higher success rates are associated with lesser stone burden and the absence of staghorn calculus.[100] When a randomized control trial compared PCNL to ureteroscopy for children with renal calculi > 2 cm, stone free rates were 96% vs. 71%, respectively.[103] Grivas et al in their work for EAU guidelines quote initial stone free rates of 70-90% increasing to 84.6-97.5% after a second look. Overall complication rate was at 20%.[51] Daw et al published their experience with miniperc in 26 children less than 6 years old with renal calculi < 5 cm through 14Fr sheath using a ureteroscope with laser lithotripsy. The authors reported a primary stone free rate, stone free rate after retreatment, and stone free rate after auxiliary ESWL of 77%, 85%, and 92%, respectively. Retreatment rate was 8%.[104]

6.3.4 Complications of PCNL

Complications include those occurring intraoperatively: inability to dilate percutaneous tract to access the collecting system, loss of percutaneous tract, renal pelvis perforation; and those occurring postoperatively: urinary tract infection/sepsis, ureteral obstruction from stone fragment, delayed hemorrhage from renal pseudoaneurysm, or arteriovenous malformation. Onal et al in a multi institutional series showed an intraoperative complication rate of 9.7% and 20% postoperative complication rate.[102] In multivariate logistic regression analysis operation time, sheath size (> 20 Fr), mid calyceal puncture and partial staghorn formation were found to be the statistically significant parameters affecting complication rates.[102] Samad et al demonstrated sustained damage to the kidney in only 5% of

patients[105] Cicekbilek et al used DMSA scans before and after PCNL to show no change in kidney function using 12-24 Fr tracts.[106] When comparing a group of patients with similar stone burden, complications occurred more frequently in PCNL compared to ureteroscopy (41% vs 10%) in one study with fever and blood transfusions comprising the majority of such complications.[103]

7. Clinical Care & Postoperative Pathway

Outpatient management is appropriate in the patient whose pain is well controlled, who is able to tolerate oral intake and who is without signs of infection (fever, leukocytosis). Close clinical follow-up is necessary to monitor for stone passage and to determine if change in management strategy (surgery) is indicated (**Table 7**, **Table 8**, and **Table 9**).

If surgery is pursued than postoperative pain control is accomplished with non-narcotic analgesics and narcotics as needed for the severity of the pain. Anticholinergics and alpha-blockers have been described to address bothersome bladder symptoms secondary to indwelling ureteral stent but are off label uses. Large rectal stool burden can result in increased bladder symptoms, which make assessment for and control of constipation important in symptom control.

Renal imaging, either renal ultrasound or KUB, should be performed to quantify the success of the stone procedure. Residual stone burden can be managed at the discretion of the treating physician, as many will pass spontaneously, however residual fragments can lead to symptoms and additional surgeries. If a ureteral stent was placed following the ureteroscopic procedure, then its removal to avoid complications is mandatory. The length of duration of ureteral stenting varies according to the indication for stenting. In the absence of injury to the ureter during ureteroscopic procedure, any ureteral mucosal edema is usually resolved after a few days and the stent can be removed. A longer duration of ureteral stenting is prudent for a stent placed because of ureteral perforation or treatment of impacted ureteral stone as stenting may affect the incidence of ureteral stricture.

Once again given the high recurrence rate in pediatric stone formers[5] and the fact that children are at high risk to have an identifiable metabolic disorder, **all children with urolithiasis should undergo a metabolic evaluation,** which should include a complete blood count, renal panel and a 24-hour urine chemistry.[39,40] (**Table 7**)

Table 7: Recommended Metabolic Workup for Pediatric Urolithiasis

Stone Analysis	Serum Studies	Urine Studies†
Stone composition	BUN Creatinine Bicarbonate Calcium Phosphorous Magnesium Uric Acid Parathyroid hormone Total Protein Albumin Alkaline Phosphatase Vitamin D	Total Volume Creatinine pH Sodium Potassium Calcium Oxalate Citrate Uric Acid Cysteine Magnesium Protein

† Two separate 24 hour urine collections are ideal

Table 8: Indications for Inpatient Admission
Uncontrolled pain refractory to oral analgesia
Persistent nausea or emesis
Fever
Bilateral obstructing ureteral calculi or obstructing stone in solitary kidney
Impaired renal function

Table 9: Factors to Consider when Selecting a Treatment Modality
Stone Burden
Stone Location
Single or Multiple Stones
Suspected Stone Composition (Cysteine)
Hounsfield Units (if known)
Access to ureter if there is history of lower urinary tract reconstruction
Co-existing ipsilateral congenital anomalies like UPJO, horse-shoe kidney, malrotated kidney

Videos

Flexible ureteroscopy with laser lithotripsy and basket stone extraction

Rigid ureteroscopy with laser lithotripsy and retrograde ureteral stent placement

Presentations

Urolithiasis (pediatrics) Presentation 1

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