Diagnosis and Management of Pediatric Nephrolithiasis

Neil J. Paloian
Kristina L. Penniston
Editors

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Foreword

Most pediatric nephrologists feel comfortable and confident providing care for children with acute kidney injury, end-stage renal disease, congenital abnormalities of the kidney and urinary tract, glomerulonephritis, hypertension, hematuria, and nephrotic syndrome given the frequency of such diagnoses in our practices. Conversely, it is common for pediatric nephrologists to feel that nephrolithiasis is an area they have not mastered despite the fact that nearly all will at some point have responsibility for the diagnostic evaluation and treatment plan for a child with nephrolithiasis. This seeming abyss exists despite the fact that the prevention and treatment of nephrolithiasis is a mature and powerful branch of practice providing benefit to those whose combination of genes and life exposure result in the formation of kidney stones.

That said, this first ever textbook dedicated to pediatric kidney stone disease attempts to bridge the gap and seeming imbalance between where we have advanced to in our knowledge and what appears to be known generally by most in our field. It is a fact that as providers, we value understanding above mere practical knowledge.

To create a reservoir of updated information regarding the epidemiology, pathophysiology, genetics, nutritional underpinnings, evaluation and treatment options for clinicians caring for children with nephrolithiasis, Drs Paloian and Penniston have assembled experts in the field to concisely and cogently document the current state of knowledge.

The editors have presciently included chapters on bone disease and vascular calcification with the intention of reminding us that our obligation to our patients extends beyond their childhood. Similarly, the examination on obesity and nephrolithiasis is a nod to the collective and inexorable plumping of the population which begins in childhood and how this demographic trend has real world consequences that impact health in ways that are more nuanced and beyond the obvious cardiovascular effects.

As Dr Paloian points out, the care of the child with nephrolithiasis requires intraspecialty collaboration. As such, being familiar with the salient aspects of both the medical and surgical approaches to this entity improves the quality of care for children with this rarer pediatric manifestation of urinary disequilibrium. While not the

stated intention of this collection, if this work benefits patients and draws a few investigators into the field and allows practitioners to have more comfort and confidence in the care of children with nephrolithiasis, it will have accomplished its task and the Editors will have done us all a service.

Respectfully,

Sharon M. Bartosh
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Preface

Caring for children with kidney stone disease is a unique challenge for which few providers are properly trained. The overall prevalence of pediatric nephrolithiasis is small, but numbers are increasing over time, and it is critical that a comprehensive medical reference be available for the healthcare providers who are taking care of these patients. While there are certainly some similarities and overlap with adult kidney stone disease, the many distinct characteristics of kidney stones in children confirm the saying in pediatric medicine that "children are not little adults." With that in mind, we are very delighted to present you with the first edition of *Diagnosis and Management of Pediatric Nephrolithiasis.*

With this text, we aspired to assemble all of the necessary information needed to successfully understand why children develop stones and what to do when presented with a child with a kidney stone. As will be exemplified throughout this textbook, treating a child with stone disease requires a complex understanding of a wide array of medical domains including basic science, physiology, laboratory medicine, pharmacotherapy, nutrition, radiology, and surgery. Accordingly, caring for these children requires a wide knowledge base and medical and surgical specialists from varied backgrounds. Our hope is that this text will serve as a valuable resource utilized by all of the various types of healthcare providers that care for children with kidney stones.

We have been very fortunate to work with a team of authors who are experts in their fields. These colleagues, who are leaders in pediatric stone research and clinical care, have collectively covered in an exceptional manner the breadth of topics required for this textbook. We are grateful that they have been able to contribute to this text, and we look forward to advancing the field of pediatric kidney stone care.

Madison, WI, USA — Neil J. Paloian
Madison, WI, USA — Kristina L. Penniston

Acknowledgments

I start by first acknowledging Neil Paloian for his tireless efforts as "lead" editor for this book. He tackled the lion's share of communications with Springer Publishing, which was no small feat amidst the COVID-19 slow-down and illnesses that affected key personnel throughout this journey. I have admired Neil's dedication to his patients during my time with him on the UW Health American Family Children's Hospital (AFCH) multidisciplinary pediatric stone clinic team. Second, I acknowledge the emphasis placed on medical nutrition therapy by all of the staff of the UW Health AFCH Pediatric Stone Clinic. They collectively ensure that patients are receptive to meeting with and listening to me. As a registered dietitian nutritionist, patients often do not appreciate the potential role of nutrition therapy unless first championed by a physician. So, thanks again to Neil for making this happen. Third, I thank the authors of the chapters of this book for their contributions, all of which ultimately help to make this book a significant contribution to the literature. Finally, while not all patients' stone disease is diet-related, I thank the patients—adult and pediatric—over my 21 years of clinical nutrition practice who allowed me to assess their diets and, if stone risk factors were identified, to consider implementing changes that appeared necessary. Nutrition therapy is not as easily executed as pharmacologic therapy—it's much easier to pop a pill!—or physical therapy, which might be something to do once a day or so. Food is something people think about and interact with multiple times in a day, and cultural and social influences frequently get in the way of change. Those who know me know that this is one reason I am passionate about "minimally invasive" nutrition therapy and about working when possible in multidisciplinary ways to treat patients with stone disease.

Kristina L. Penniston, PhD, RDN, FAND

I would like to sincerely thank my co-editor Kris Penniston for her help and guidance as we have put this text together. She has supported me as we met this project head despite many challenges. I am very proud to have her as my co-editor and could not have done this without her. Collectively, our patients in the pediatric stone clinic have served as inspiration to create this book. I am so grateful for the opportunity to be a part of the care team with our patients and for everything I have learned from them and their families.

I am thankful to all the pediatric nephrologists who have guided me over the years of training. While there are too many people to name, I am especially grateful for the mentorships of Youngki Kim, Sangeeta Hingorani, Joseph Flynn, Jordan Symons, and Sharon Bartosh. Additionally, Ceci Giachelli's laboratory is where I developed my enthusiasm for disorders of calcification. More importantly however, Dr Giachelli taught me how to ask questions and think critically as scientist. Even though I have left the lab setting, I apply her teachings in my clinical and research roles on a daily basis.

Finally, I need to acknowledge the never-ending support of my parents, Jacob and Suzanne, who have been my role models since childhood. Most importantly, I would have never been able to compile this textbook without the love and encouragement of my wife Robyn. Her sacrifice has allowed me to accomplish everything that I have professionally, including this text, and is something that I will never be able to repay and for which I am eternally grateful.

Neil J. Paloian, MD

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Chapter 1
Epidemiology of Pediatric Nephrolithiasis

Belinda Li and Douglass B. Clayton

Introduction

Across populations, urolithiasis is a steadily growing diagnosis characterized by the formation and retention of stones in the kidneys, ureters, and bladder. Globally, the estimated prevalence of urolithiasis varies by geographic region, ranging from 5–9% in Europe, 1–5% in Asia, and 7–13% in North America [1]. In the United States, the incidence is rising due to various metabolic, environmental, and dietary factors. Based on data from the National Health and Nutrition Examination Survey (NHANES), the prevalence of urolithiasis in the United States among adults rose from an estimated 3.8% in 1980 to 5.2% by 1994, and further to 8.8% by 2010 [2, 3].

While a wealth of data exists regarding the driving factors for urolithiasis in adults, urinary tract stones among children are far less common and thus less well-studied. From limited statewide databases in the United States, the overall change in incidence of urolithiasis appears to follow or surpass rates seen in adults [4, 5]. These trends provide an important perspective given the unique challenges related to the overall impact of urolithiasis management in children. Children and adolescents may be less likely than adults to experience spontaneous stone passage and therefore are more likely to require surgical intervention [4, 6]. Children remain at high risk for recurrence, radiation exposure, and morbidity over the remainder of their lifetimes [7–9], and are more likely to have underlying metabolic abnormalities [10]. Herein, we aim to describe the current epidemiologic landscape of pediatric urolithiasis in the United States as well as the important contributing factors.

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Scope of the Problem

Historically, a child presenting with a symptomatic urinary tract stone was an uncommon event. However, clinical experience and emerging data both suggest that urolithiasis is increasingly diagnosed in children. Evidence from older case series indicate that pediatric stone incidence in the United States during the 1970s–1980s was estimated to be 1 in 1000 to 1 in 7600 hospital admissions [11, 12]. More contemporary data demonstrate a rising incidence is occurring in US children. A review from a single children's hospital compared the incidence across two 3-year time periods, 1994–1996 and 2003–2005, respectively [13]. The investigators found that the number of identified cases increased from 7 in the first period to 61 in the second period, or an increase of 4.6 times higher when expressed as cases per 100 new patients.

Similar observations of rising pediatric incidence have been made through multiple population-based studies. From a statewide South Carolina medical encounter database consisting of emergency, inpatient, and surgical care data for both adults and children, the greatest increase in stone incidence out of all age groups was found in 15–19 year olds [14]. On average, the incidence among this group increased by 26% over 5 years. In a similar study investigating a South Carolina database of emergency department visits, Sas et al. found an increase in pediatric stone incidence from 7.9 per 100,000 children in 1996 to 18.5 per 100,000 in 2007 [15]. Rates of pediatric stone presentations were 2.2 times higher in the last three years of the study compared to the first three years. Supportive data are also found in several national administrative databases used to understand urolithiasis trends in the United States. A Pediatric Health Information Systems (PHIS) database study by Routh et al. compared encounters among children with urolithiasis against encounters for other common diagnoses [16]. Over a 10-year period of time, they found that encounters for children with stones increased almost sixfold compared to appendicitis and nearly eightfold compared to bronchiolitis. Bush et al. also queried the PHIS database and reported that urolithiasis comprised 1 in 685 children's hospital admissions between 2002–2007, tenfold higher than the historical reports discussed above [17]. Furthermore, evidence exists that the management of pediatric urolithiasis has shifted from inpatient to outpatient settings, signaling an even greater burden of pediatric stones not captured in these inpatient database studies [18, 19].

Yet, although there are numerous publications consistently describing this upward trend in pediatric urolithiasis, the most recent pediatric administrative dataset from the Urologic Diseases in America project published in 2019 indicates otherwise. The Optum© Clinformatics® Data Mart database utilized by the Urologic Diseases in America Project, which includes longitudinal data from inpatient, outpatient, and emergency settings, interestingly identifies a downward trend in urolithiasis rates leading into 2016 following a steady climb between 2005 and 2011 [20]. Overall rates over time were 52.8 cases per 100,000 person-years in 2005 to as high as 65.2 cases per 100,000 person-years in 2011, then dropped to 54.1 cases per 100,000 person-years in 2016. Theories to explain this latest shift have not been elucidated. Likewise, Modi et al. reported a recent decline in pediatric inpatient hospitalizations

approaching 2014 through the Nationwide Inpatient Sample, though conclusions were limited by the absence of concurrent ambulatory or outpatient data [19]; the authors propose that hospitalizations have declined as treatment has shifted more toward outpatient care. Given these dynamic patterns, it will be important to continue to follow these trends into the future to capture the evolution of this disease.

Population Characteristics

While the growing rate of pediatric urolithiasis since the new millennium is evident, clear reasons to explain such patterns are still being explored as new data emerges. Currently, we must rely on large cohorts and population-level data to better understand how stones may afflict groups of children and adolescents differently. These findings offer new perspectives around this changing epidemiology.

Sex

Patient sex does appear to play a role in stone presentation, and recent pediatric literature suggests a sex predilection for urolithiasis among children. Previously, based on data incorporating primarily adults, stones were classically noted to occur more commonly in males than in females. In a 1984 global epidemiological study accounting for 340,000 stones, women in countries in Europe and Asia reportedly made up as little as 5% of the stone population through the first half of the nineteenth century [21]. This percentage rose quickly to 30–40% into the 1980s. NHANES III data referenced earlier from 1994, which relies on reported history of stones, showed a prevalence of 6.4% among men compared to 4.1% among women in the United States; the follow-up study in 2010 showed an overall rise but consistent differential with a prevalence of 10.6% in men and 7.1% in women [2].

In contrast, the opposite trend has been developing in children, with current data showing higher rates of urolithiasis in girls than in boys. A Rochester, Minnesota-based database capturing all pediatric incident kidney stone presentations within the county over 25 years found 49 females (58%) and 35 males (42%) [5]. Adjusting for age, the incidence of stones in females was 12.6 per 100,000 person-years compared to 8.6 in males. In South Carolina, the stone incidence in 2007 for girls was 1.4 times higher than for boys [15]. Kusumi and colleagues examined discharge data from the Kids' Inpatient Database (KID) from 1997 to 2012 and found that females accounted for 60% of inpatient discharges for nephrolithiasis and ureterolithiasis [18]. Their findings confirmed those from two similar studies utilizing KID data from 2003 and 2006, in which girls comprised more diagnoses than boys at an approximately 2:1 ratio [22, 23]. Of note, while girls made up the bulk of total patients, sex distribution was not consistent throughout all age groups. In the first decade of life, urolithiasis was more common in boys than in girls. However, in the

second decade, stone prevalence was higher overall compared to the first decade, and girls made up the overwhelming majority of patients [22]. Routh et al.'s PHIS cohort of pediatric stone diagnoses showed greater parity between sexes with 47% male and 53% female, but males again made up the majority of the patients aged 11 years and under while females overwhelmingly accounted for the population aged 12–18 years [16]. Proposed theories to explain this sex predilection, particularly in the second decade of life, include the potential of lithogenic hormonal changes during puberty. In a placebo-controlled randomized trial in postmenopausal women, estrogen therapy was associated with an increased risk of nephrolithiasis possibly due to changes to urine chemistry [24]. Similar lithogenic effects of estrogen in adolescent females have yet to be identified.

Age

While the combination of age and sex clearly influence stone development, age alone demonstrates distinct epidemiologic patterns. Generally, both the prevalence and the incidence of kidney stones increases with age up to a peak between the mid-40s and mid-60s [14, 21, 25]. While the usual time of presentation is variable among children, most initially present between 5 and 15 years of age [26]. However, the risk of stone disease in children likewise increases with age, and age remains the strongest predictor of stone risk [23]. Children 2 years old or younger make up a very small percentage of patients admitted to hospitals or presenting to EDs with symptoms [15, 16]. In Bush et al.'s sample from PHIS between 2002 and 2007, children under 2 years old comprised only 3% of all stone admissions, compared to 40% of all other hospitalized diagnoses [17]. Teenagers, however, made up over 45% of stone admissions. In addition to accounting for the majority of diagnoses, teens have also seen the highest increase in incidence over the last two decades whereas the incidence in younger age groups remained relatively flat [15]. Multivariate logistic regression modeling of KID data revealed age to be the only variable significantly associated with stone disease when compared to sex and several comorbidities that have been linked to stone risk in adults [23]. Regarding stone location, older children are more likely to have ureteral stones while younger children are more likely to have renal stones [27]. The mean age for surgical intervention typically ranges between 10 and 15 years, with older age being an independent predictor for surgical intervention [8, 9, 19].

Race/Ethnicity

Within the United States, several studies support a greater likelihood for developing urolithiasis among Caucasian children compared to other ethnicities [16, 17, 20]. Caucasian children evaluated in the ED for nephrolithiasis were 5.6 times more

likely to have stones compared to African American children [15]. Caucasian children also have higher rates of surgical intervention and hospitalization. These patterns also continue into adulthood—among adults in the United States, non-Hispanic white individuals have a stone prevalence of 10.3%, compared to 6.4% in Hispanics, and 4.3% in non-Hispanic African Americans [2].

Geography and Environment

The Southeastern region of the United States has traditionally been known as the "stone belt," where rates of urolithiasis are significantly greater than in other parts of the country. The prevalence of stones in this region is as much as two times that in the Northwest according to a national survey of disease history, the Second Cancer Prevention Survey (CPS II), distributed to over one million Americans [28]. This difference has been primarily attributed to greater ambient temperatures and sunlight. While most of these data were determined from adult populations, pediatric rates appear to follow a similar pattern. Kusumi et al. [18] found that children in the southern United States made up 42% of all patients admitted with urolithiasis over a 12-year span of national administrative data collection. A plausible explanation is a greater likelihood for relative dehydration and low urine volumes from inadequate fluid intake while living in hotter climates, leading to both increased acidity of the urine and increased supersaturation of calcium oxalate and calcium phosphate in the urine [29, 30]. Indeed, often the most common abnormality on 24-hour urine collections in pediatric stone formers is low urine volume [31]. To address one aspect of this problem, Bernard and colleagues have developed an equation for adolescents to relate urine volume to water consumption [32]. Types of fluids consumed may also play a role. To examine the relationship between beverage choice and hydration in children, Bugatsas et al. collected a beverage diary over two days for 210 children aged 8–14 years with a 24-hour urine collection on the second day [33]. Only increased water and milk consumption were associated with lower 24-hour urine osmolality whereas sodas, teas, sports drinks, and energy drinks together with diminished water intake were associated with higher urine osmolality. Others have reported up to a 23% increased risk of kidney stones associated with sugar-sweetened cola beverages [34], and CPSII respondents from the Southeast reported drinking more teas and colas than those in other parts of the country, accounting for some of the increased odds of urolithiasis [28].

Over time, environmental factors will likely continue to play a progressively larger role in the epidemiology of pediatric urolithiasis in the United States. Climate change, for instance, will have far-reaching effects on multiple spheres, including social, economic, environmental, and certainly public health. The "stone belt" in the United States is projected to expand to more northern latitudes based on warming predictions, particularly in the midcontinent and upper Midwest. In 2000, 41% of the US population were considered to be within "high-risk" zones. This percentage is expected to increase to 56% and 70% in 2050 and 2095, respectively [35]. The

overall prevalence of stones attributable to climate change in the country is predicted to go up by 10% by 2050.

Additionally, childhood obesity has nearly tripled in the United States since the 1980s and is becoming more common in younger ages [36]. According to the NHANES, obesity prevalence in adolescents, the age group most commonly affected by urolithiasis, increased from 10.5% in 1998–1994 to 20.6% in 2013–2014. Children aged 2–5 years saw a sharp increase in class I obesity (BMI ≥95th percentile) over a single year, and extreme obesity (BMI ≥120% of 95th percentile) increased in children across a wide age range of 6–19 years [37, 38]. In response to these trends, some have hypothesized that the rising pediatric stone incidence is associated with the increase in childhood obesity, but several studies have failed to show a clear correlation between BMI and stone formation [4, 5, 23, 39]. In contrast, a relationship has been described in the adult population through mechanisms of altered acid/base handling and urine chemistries as a result of dietary and lifestyle habits [40]. Taylor et al. performed a prospective study involving three large cohorts of nearly 250,000 adult participants and found that weight gain, increased BMI, and waist circumference were all positively associated with incident kidney stones after adjusting for multiple factors in both men and women [41].

Underlying Conditions

An important point of distinction in the epidemiology of pediatric urolithiasis is the role of metabolic disorders and congenital anatomic anomalies in the pathophysiology of stone formation in this population. Discharge data following inpatient hospitalization for nephrolithiasis through the KID database revealed the most commonly associated diagnoses were other diseases of the kidney and ureters (37%), genitourinary symptoms and ill-defined conditions (14%), and other nutritional, endocrine, and metabolic disorders (13%) [18]. At least one metabolic abnormality on 24-hour urine collection was identified in as high as 91% of pediatric stone formers in a series of 222 children and adolescents who all underwent serum and urine collection [42]. In order of frequency, the most common urine abnormalities were low urine volume, idiopathic hypercalciuria, and hypocitraturia. Similar series have reported rates of metabolic abnormalities in children ranging from 50% to 80% [7, 31, 43]. Children with other medical conditions with metabolic effects including seizure disorders, cystic fibrosis, nephrocalcinosis, or inborn errors of metabolism also constitute many young stone formers. Children with epilepsy managed in part with ketogenic diets have a 3–10% likelihood of developing nephrolithiasis [44, 45]. Patients with cystic fibrosis have a higher prevalence of nephrolithiasis than the normal population and are predisposed to nephrocalcinosis which has been found in up to 92% of postmortem autopsies [46, 47].

While rates of urinary metabolic abnormalities are largely similar between children and adults [48, 49], there is a paucity of guidelines directing the utilization of 24-hour urine collections as a diagnostic tool to detect metabolic derangements in

children. It has been recommended that all high-risk or recurrent adult stone formers undergo 24-hour urinalysis but only 10% of these adults undergo such evaluation [50]. At present, the general recommendation is that comprehensive metabolic evaluations should be pursued in children given their high risk for recurrence. However, current guidelines on medical management and prevention of kidney stones published by the American Urological Association do not address children specifically, highlighting an area for improved consensus in the United States [51].

Congenital anomalies of the kidney and urinary tract (CAKUT) or other structural abnormalities are also frequently associated with urolithiasis as a result of stasis of urine, turbulent flow, or susceptibility to urinary tract infection [52, 53]. Some of these conditions include hydronephrosis, ureteropelvic junction obstruction, horseshoe kidney, medullary sponge kidney, autosomal dominant polycystic kidney disease, and neurogenic bladder. 11–30% of pediatric stone formers have an underlying structural abnormality according to various case series in the United States [4, 13, 43, 54, 55]. However, 95–99% of children with anatomic anomalies will not develop urolithiasis, suggesting that concurrent metabolic abnormalities play an important role in a multifactorial process in pediatric stone formers [52].

Incidental Diagnosis

The evolution of imaging studies has also certainly shaped current patterns in pediatric urolithiasis. Many urinary tract stones in children may be diagnosed incidentally because of the increasing use of advanced imaging modalities such as computed tomography (CT) for the evaluation of both suspected urolithiasis and for nonspecific abdominal complaints. A large retrospective study of computed tomography (CT) use in children between 1996 and 2010 revealed an increase from 10.5 scans to 23.9 scans per 1000 children aged between 5 and 14 years, with the greatest increase occurring in the anatomic region of the abdomen/pelvis [56]. Children undergoing evaluation specifically for nephrolithiasis in recent years were also more likely to have a CT scan. Routh et al. identified children diagnosed with urolithiasis using the PHIS database between 1998 and 2008 and found that while the overall imaging rate remained stable, the use of CT increased from 26% to 45% over the study period [16]. Furthermore, of patients who received CT, the majority (79%) completed two or more studies. However, the direct contribution of temporal trends of increasing CT utilization on rising pediatric urolithiasis rates is still difficult to confirm. One series examining the use of pediatric abdominal/pelvic CT scans in the emergency department reported a new urologic finding in 7% of all scans [57]. Nearly 60% of findings were incidental, with stones making up approximately 3% of incidental findings. A Canadian series of newly diagnosed urolithiasis in children between 1999 and 2004 revealed that more than 50% of children underwent CT imaging, and 21% of diagnoses were incidental [58]. Because children, especially those younger than 5 years old [10], can present in myriad nonclassical

ways, we can expect incidental diagnoses to continue to make up a meaningful portion of pediatric urolithiasis.

Of note in the most recent decade, overall CT use in children has seen a small decline owing in part to the Image Gently® campaign, an alliance among multiple specialty societies to reduce the exposure to ionizing radiation in children [59]. Comparing 2005 to 2016, rates of CT for pediatric urolithiasis patients were 1.5 per 120 person-days and 0.7 per 120 person-days, respectively, according to Urologic Diseases in America project data [20]. We have not yet seen if this campaign specifically has significantly impacted the rate of CT use in suspected urolithiasis. In an analysis by Streur et al. examining the impact of the campaign on CT use, children diagnosed with nephrolithiasis obtained a CT in 49% of cases before the campaign launch and 54% in the years after ($p < 0.001$) [60]. However, the authors compared trends between adults and children and found that CT has been decreasing in both groups since the launch, suggesting that Image Gently® alone does not account for this downward trend.

Recurrence

In all cases, recurrence rates increase with longer follow-ups, making children particularly vulnerable to future stone episodes. The recurrence of kidney stones in adults is very common, with up to 50% of adult incident stone formers experiencing a second occurrence within 5–10 years [61, 62]. However, the reported rates of recurrence among pediatric series are more variable, ranging from 16 to 67% at a median interval of 1–5 years between episodes [6–8, 43, 54]. The most recent institutional series in the United States included 285 children presenting with a symptomatic stone over a 7-year period, though patients with predisposing genetic or anatomic abnormalities were excluded. Sixty-eight children, or 24%, developed a recurrence within the relatively short 492 person-years of follow-up [7]. In comparison, Milliner and Murphy's 1993 series of all-comers 16 years of age and younger diagnosed with nephrolithiasis reported a recurrence rate of 67% over a mean follow-up of 5 years [43]. Notably, their series from a high-volume referral center contained 66 children (33%) with a defined genitourinary anatomic anomaly.

Among stone formers, certain children are at a higher risk of recurrence than others. The two most common underlying predisposing factors are urinary metabolic abnormalities and anatomic anomalies. Metabolic abnormalities such as hypercalciuria and hypocitraturia may increase recurrence up to fivefold compared to children without identifiable abnormalities [6, 63]. In a series of children who underwent surgical intervention for urolithiasis and developed a recurrence within 5 years, 65% with an anatomic abnormality (primarily hydronephrosis and vesicoureteral reflux) compared to 38% without had a recurrent stone ($p = 0.17$) [8]. Other factors like genetic conditions including cystinuria are less common but still place children at greater risk, while idiopathic stone formers have the lowest likelihood of

future recurrence. Together, these data emphasize the importance of the diagnosis of metabolic abnormalities and treatment directed at urolithiasis prevention.

Economic Impact

As the incidence of pediatric urolithiasis has risen, so too has the overall economic burden of the disease. Using comprehensive data from the NIH's Urologic Diseases in America project and NHANES data, estimates of the total annual costs of the diagnosis, treatment, and prevention of all urinary tract stones in the United States are projected to go from $2.1 billion in 2000 to $4.6 billion by 2030 [64, 65]. These figures are up from $1.4 billion in 1994 for over a threefold increase over the course of 30 years [64]. The primary factors contributing to these estimates are a growing population and increasing rates of diabetes and obesity in adults driving the growing prevalence of stones.

Cost estimates within pediatrics alone are somewhat limited by available data sources, but few observations have been published. Overall, children unsurprisingly make up a relatively small percentage of the nation's overall cost of urolithiasis due to lower prevalence. Inpatient charges captured by KID increased from $8.3 million in 1997 to $17.6 million in 2012 despite a small 2% decline in inpatient urolithiasis discharges [18]. The average charge for the entire hospitalization was calculated at $22,000. Even though children <5 years of age accounted for 9% of discharges, their hospital charges were on average $1680/day higher than older patients. ED charges have also increased, from a mean charge per visit of $3645 in 2006 to $5827 in 2012, possibly reflecting increased utilization of imaging in the ED [66]. Focusing on a single year (2009), Wang et al. were able to expand upon more granular data regarding inpatient hospitalization costs for urolithiasis [67]. Approximately 31% of admitted children underwent a surgical procedure, with the most common procedure being ureteral stent placement or removal (20.4%). The highest admission charges were for those undergoing percutaneous nephrolithotomy, with a median charge of $34,334, compared to approximately $18,000 for a ureteroscopy or ureteral stent only. Adding ED charges to inpatient charges, they estimated a total annual hospital-based cost of $375 million, still grossly underestimating the total economic burden that also encompasses outpatient and ambulatory surgery care. At present, knowledge of the total economic burden of pediatric urolithiasis remains undefined and is an area that will benefit from continued study.

Conclusions

The pediatric urolithiasis problem in the United States is evolving. Though we have seen a rising incidence over the last few decades, new data is emerging that this trend may be shifting. We sought to present the current climate with a focus on how

stone disease may affect our pediatric populations in different ways. Going forward, continued research efforts should be directed toward improving stone diagnosis, management, and prevention among children and adolescents to better understand the unique challenges facing these populations compared to their adult counterparts.

References

1. Sorokin I, Mamoulakis C, Miyazawa K, Rodgers A, Talati J, Lotan Y. Epidemiology of stone disease across the world. World J Urol. 2017;35:1301–20.
2. Scales CD Jr, Smith AC, Hanley JM, Saigal CS, Urologic Diseases in America Project. Prevalence of kidney stones in the United States. Eur Urol. 2012;62:160–5.
3. Shoag J, Tasian GE, Goldfarb DS, Eisner BH. The new epidemiology of nephrolithiasis. Adv Chronic Kidney Dis. 2015;22:273–8.
4. Sas DJ, Becton LJ, Tutman J, Lindsay LA, Wahlquist AH. Clinical, demographic, and laboratory characteristics of children with nephrolithiasis. Urolithiasis. 2016;44:241–6.
5. Dwyer ME, Krambeck AE, Bergstralh EJ, Milliner DS, Lieske JC, Rule AD. Temporal trends in incidence of kidney stones among children: a 25-year population based study. J Urol. 2012;188:247–52.
6. Pietrow PK, Pope JC 4th, Adams MC, Shyr Y, Brock JW 3rd. Clinical outcome of pediatric stone disease. J Urol. 2002;167:670–3.
7. Tasian GE, Kabarriti AE, Kalmus A, Furth SL. Kidney stone recurrence among children and adolescents. J Urol. 2017;197:246–52.
8. Lao M, Kogan BA, White MD, Feustel PJ. High recurrence rate at 5-year Followup in children after upper urinary tract stone surgery. J Urol. 2014;191:440–4.
9. Ristau BT, Dudley AG, Casella DP, Dwyer ME, Fox JA, Cannon GM, Schneck FX, Ost MC. Tracking of radiation exposure in pediatric stone patients: the time is now. J Pediatr Urol. 2015;11:339.e1–5.
10. Hernandez JD, Ellison JS, Lendvay TS. Current trends, evaluation, and management of pediatric nephrolithiasis. JAMA Pediatr. 2015;169:964–70.
11. Troup CW, Lawnicki CC, Bourne RB, Hodgson NB. Renal calculus in children. J Urol. 1972;107:306–7.
12. Walther PC, Lamm D, Kaplan GW. Pediatric urolithiases: a ten-year review. Pediatrics. 1980;65:1068–72.
13. VanDervoort K, Wiesen J, Frank R, Vento S, Crosby V, Chandra M, Trachtman H. Urolithiasis in pediatric patients: a single center study of incidence, clinical presentation and outcome. J Urol. 2007;177:2300–5.
14. Tasian GE, Ross ME, Song L, Sas DJ, Keren R, Denburg MR, Chu DI, Copelovitch L, Saigal CS, Furth SL. Annual incidence of nephrolithiasis among children and adults in South Carolina from 1997 to 2012. Clin J Am Soc Nephrol. 2016;11:488–96.
15. Sas DJ, Hulsey TC, Shatat IF, Orak JK. Increasing incidence of kidney stones in children evaluated in the emergency department. J Pediatr. 2010;157:132–7.
16. Routh JC, Graham DA, Nelson CP. Epidemiological trends in pediatric urolithiasis at United States freestanding pediatric hospitals. J Urol. 2010;184:1100–4.
17. Bush NC, Xu L, Brown BJ, Holzer MS, Gingrich A, Schuler B, Tong L, Baker LA. Hospitalizations for pediatric stone disease in United States, 2002–2007. J Urol. 2010;183:1151–6.
18. Kusumi K, Becknell B, Schwaderer A. Trends in pediatric urolithiasis: patient characteristics, associated diagnoses, and financial burden. Pediatr Nephrol. 2015;30:805–10.

19. Modi PK, Kwon YS, Davis RB, Elsamra SE, Dombrovskiy V, Olweny EO. Pediatric hospitalizations for upper urinary tract calculi: epidemiological and treatment trends in the United States, 2001–2014. J Pediatr Urol. 2018;14:13.e1–6.
20. Ward JB, Feinstein L, Pierce C, Lim J, Abbott KC, Bavendam T, Kirkali Z, Matlaga BR, NIDDK Urologic Diseases in America Project. Pediatric urinary stone disease in the United States: the urologic diseases in America Project. Urology. 2019;129:180–7.
21. Asper R. Epidemiology and socioeconomic aspects of urolithiasis. Urol Res. 1984;12:1–5.
22. Novak TE, Lakshmanan Y, Trock BJ, Gearhart JP, Matlaga BR. Sex prevalence of pediatric kidney stone disease in the United States: an epidemiologic investigation. Urology. 2009;74:104–7.
23. Schaeffer AJ, Feng Z, Trock BJ, Mathews RI, Neu AM, Gearhart JP, Matlaga BR. Medical comorbidities associated with pediatric kidney stone disease. Urology. 2011;77:195–9.
24. Maalouf NM, Sato AH, Welch BJ, Howard BV, Cochrane BB, Sakhaee K, Robbins JA. Postmenopausal hormone use and the risk of nephrolithiasis: results from the Women's Health Initiative hormone therapy trials. Arch Intern Med. 2010;170:1678–85.
25. Denstedt JD, Fuller A. Epidemiology of stone disease in North America. In: Urolithiasis. London: Springer; 2012. p. 13–20.
26. Clayton DB, Pope JC. The increasing pediatric stone disease problem. Ther Adv Urol. 2011;3:3–12.
27. Kalorin CM, Zabinski A, Okpareke I, White M, Kogan BA. Pediatric urinary stone disease—does age matter? J Urol. 2009;181:2267–71. discussion 2271
28. Soucie JM, Coates RJ, McClellan W, Austin H, Thun M. Relation between geographic variability in kidney stones prevalence and risk factors for stones. Am J Epidemiol. 1996;143:487–95.
29. Borghi L, Meschi T, Amato F, Novarini A, Romanelli A, Cigala F. Hot occupation and nephrolithiasis. J Urol. 1993;150:1757–60.
30. Eisner BH, Sheth S, Herrick B, Pais VM Jr, Sawyer M, Miller N, Hurd KJ, Humphreys MR. The effects of ambient temperature, humidity and season of year on urine composition in patients with nephrolithiasis. BJU Int. 2012;110:E1014–7.
31. Bevill M, Kattula A, Cooper CS, Storm DW. The modern metabolic stone evaluation in children. Urology. 2017;101:15–20.
32. Bernard J, Song L, Henderson B, Tasian GE. Association between daily water intake and 24-hour urine volume among adolescents with kidney stones. Urology. 2020; https://doi.org/10.1016/j.urology.2020.01.024.
33. Bougatsas D, Arnaoutis G, Panagiotakos DB, Seal AD, Johnson EC, Bottin JH, Tsipouridi S, Kavouras SA. Fluid consumption pattern and hydration among 8–14 years-old children. Eur J Clin Nutr. 2017;72:420–7.
34. Ferraro PM, Taylor EN, Gambaro G, Curhan GC. Soda and other beverages and the risk of kidney stones. Clin J Am Soc Nephrol. 2013;8:1389–95.
35. Brikowski TH, Lotan Y, Pearle MS. Climate-related increase in the prevalence of urolithiasis in the United States. Proc Natl Acad Sci U S A. 2008;105:9841–6.
36. Ogden CL, Flegal KM, Carroll MD, Johnson CL. Prevalence and trends in overweight among US children and adolescents, 1999–2000. JAMA. 2002;288:1728–32.
37. Ogden CL, Carroll MD, Lawman HG, Fryar CD, Kruszon-Moran D, Kit BK, Flegal KM. Trends in obesity prevalence among children and adolescents in the United States, 1988–1994 through 2013–2014. JAMA. 2016;315:2292–9.
38. Skinner AC, Ravanbakht SN, Skelton JA, Perrin EM, Armstrong SC. Prevalence of obesity and severe obesity in US children, 1999–2016. Pediatrics. 2018; https://doi.org/10.1542/peds.2017-3459.
39. Kieran K, Giel DW, Morris BJ, Wan JY, Tidwell CD, Giem A, Jerkins GR, Williams MA. Pediatric urolithiasis—does body mass index influence stone presentation and treatment? J Urol. 2010;184:1810–5.
40. Wollin DA, Skolarikos A, Preminger GM. Obesity and metabolic stone disease. Curr Opin Urol. 2017;27:422–7.

41. Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. JAMA. 2005;293:455–62.
42. Penido MGMG, Srivastava T, Alon US. Pediatric primary urolithiasis: 12-year experience at a Midwestern Children's Hospital. J Urol. 2013;189:1493–7.
43. Milliner DS, Murphy ME. Urolithiasis in pediatric patients. Mayo Clin Proc. 1993;68:241–8.
44. McNally MA, Pyzik PL, Rubenstein JE, Hamdy RF, Kossoff EH. Empiric use of potassium citrate reduces kidney-stone incidence with the ketogenic diet. Pediatrics. 2009;124:e300–4.
45. Kielb S, Koo HP, Bloom DA, Faerber GJ. Nephrolithiasis associated with the ketogenic diet. J Urol. 2000;164:464–6.
46. Matthews LA, Doershuk CF, Stern RC, Resnick MI. Urolithiasis and cystic fibrosis. J Urol. 1996;155:1563–4.
47. Hoppe B, Hesse A, Brömme S, Rietschel E, Michalk D. Urinary excretion substances in patients with cystic fibrosis: risk of urolithiasis? Pediatr Nephrol. 1998;12:275–9.
48. Eisner BH, Sheth S, Dretler SP, Herrick B, Pais VM. Abnormalities of 24-hour urine composition in first-time and recurrent stone-formers. Urology. 2012;80:776–9.
49. Karabacak OR, Ipek B, Ozturk U, Demirel F, Saltas H, Altug U. Metabolic evaluation in stone disease metabolic differences between the pediatric and adult patients with stone disease. Urology. 2010;76:238–41.
50. Bonzo JR, Tasian GE. The emergence of kidney stone disease during childhood—impact on adults. Curr Urol Rep. 2017;18:1–6.
51. Pearle MS, Goldfarb DS, Assimos DG, et al. Medical management of kidney stones: AUA guideline. J Urol. 2014;192:316–24.
52. Copelovitch L. Urolithiasis in children: medical approach. Pediatr Clin N Am. 2012;59:881–96.
53. Sas DJ. An update on the changing epidemiology and metabolic risk factors in pediatric kidney stone disease. Clin J Am Soc Nephrol. 2011;6:2062–8.
54. Diamond DA, Menon M, Lee PH, Rickwood AM, Johnston JH. Etiological factors in pediatric stone recurrence. J Urol. 1989;142(606–8):discussion 619.
55. Sternberg K, Greenfield SP, Williot P, Wan J. Pediatric stone disease: an evolving experience. J Urol. 2005; 174:1711–4; discussion 1714
56. Miglioretti DL, Johnson E, Williams A, et al. The use of computed tomography in pediatrics and the associated radiation exposure and estimated cancer risk. JAMA Pediatr. 2013;167:700–7.
57. Marietti S, Woldrich J, Durbin J, Sparks S, Kaplan G, Chiang G. Urologic findings on computed tomography of the abdomen and pelvis in a pediatric population. J Pediatr Urol. 2013;9:609–12.
58. Kit LC, Filler G, Pike J, Leonard MP. Pediatric urolithiasis: experience at a tertiary care pediatric hospital. Can Urol Assoc J. 2013;2:381.
59. Goske MJ, Applegate KE, Boylan J, et al. The image gently campaign: working together to change practice. AJR Am J Roentgenol. 2008;190:273–4.
60. Streur CS, Lin PJ, Hollingsworth JM, Kamdar NS, Kraft KH. Impact of the image Gently® campaign on computerized tomography use for evaluation of pediatric nephrolithiasis. J Urol. 2019;201:996–1004.
61. Fink HA, Wilt TJ, Eidman KE, Garimella PS, MacDonald R, Rutks IR, Brasure M, Kane RL, Ouellette J, Monga M. Medical management to prevent recurrent nephrolithiasis in adults: a systematic review for an American College of Physicians Clinical Guideline. Ann Intern Med. 2013;158:535–43.
62. Khan SR, Pearle MS, Robertson WG, Gambaro G, Canales BK, Doizi S, Traxer O, Tiselius H-G. Kidney stones. Nat Rev Dis Primers. 2016;2:16008.
63. DeFoor WR, Jackson E, Minevich E, Caillat A, Reddy P, Sheldon C, Asplin J. The risk of recurrent urolithiasis in children is dependent on urinary calcium and citrate. Urology. 2010;76:242–5.
64. Pearle MS, Calhoun EA, Curhan GC, the Urologic Diseases of America Project. Urologic diseases in America Project: urolithiasis. J Urol. 2005;173:848–57.

65. Antonelli JA, Maalouf NM, Pearle MS, Lotan Y. Use of the National Health and Nutrition Examination Survey to calculate the impact of obesity and diabetes on cost and prevalence of urolithiasis in 2030. Eur Urol. 2014;66:724–9.
66. Young BJ, Tejwani R, Wang H-HS, Wolf S, Purves JT, Wiener JS, Routh JC. Is the economic impact and utilization of imaging studies for pediatric urolithiasis across the United States increasing? Urology. 2016;94:208–13.
67. Wang H-HS, Wiener JS, Lipkin ME, Scales CD Jr, Ross SS, Routh JC. Estimating the nationwide, hospital based economic impact of pediatric urolithiasis. J Urol. 2015;193:1855–9.

Chapter 2
The Pathophysiology of Kidney Stone Formation

Scott Quarrier

Kidney Stone Formation

When blood, a liquid suspension, is filtered by the kidney in the glomerulus, the resultant filtrate is also a liquid despite the many solutes that are dissolved within the suspension. Stones represent a pathologic change in material state from the liquid filtrate to a solid. While much about stone formation and growth remains unknown, new tools and technologies show promise in being able to explain some of these unknowns. In this chapter, we provide a brief overview of the change in state - from liquid filtrate to solid - within the urinary tract. The concepts of solubility and supersaturation are explained, and stone microstructure and theories of stone formation are addressed.

Understanding the pathogenesis of kidney stone development requires a functional understanding of the kidney. The nephron is the base unit of the kidney. Blood flows into the afferent arteriole and gets filtered through the glomerulus into the proximal tubule. The glomerulus is the site of filtration where the filtrate flows from the capillaries into Bowman's capsule while the remaining unfiltered blood flows out through the efferent arteriole back into circulation. The proximal tubule filtrate fluid undergoes significant post-glomerular modification as dissolved solutes are reabsorbed back into the blood, solutes are secreted from the blood into the tubule, and water is reabsorbed as the fluid traverses the nephron segments. The nephron utilizes active and passive transport as well as steep concentration gradients from the outer cortex to inner medulla to modulate the concentration of these solutes within the uriniferous fluid.

As fluid leaves Bowman's capsule, it enters the proximal convoluted tubule where a significant amount of sodium, potassium, calcium, phosphate, bicarbonate,

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amino acids, and glucose are reabsorbed. The fluid then traverses toward the medulla in the descending limb of the loop of Henle (thick then thin) where an interstitial concentration gradient is created. The descending thick portion is lined by cuboidal epithelium that is responsible for actively transporting solutes back into the blood. The thin descending and ascending limbs are responsible for diffusion of water back into the blood. The uriniferous fluid then traverses into the distal convoluted tubule and early collecting duct which responds to hormonal signals regulating solute reabsorption. Finally, the fluid travels through the distal collecting ducts which reabsorb water from the filtrate as a direct result of the high interstitial osmolarity and under the regulation of antidiuretic hormone.

Solubility and the Role of Supersaturation

The stone-forming solutes like calcium, oxalate, phosphate, uric acid, and cystine are held in solution in the blood. These solutes are, in some cases, dissolved as salts such as calcium oxalate and calcium phosphate. Normally, these stone-forming materials exist in states below their solubility in the blood (there are pathologic exceptions that cause vascular calcification and deposition of other precipitates). They enter the filtrate in concentrations below their solubility. It is through the extraction of water while the filtrate traverses the nephron that these concentrations increase (Table 2.1). Concentrations can exceed solubility to supersaturated levels.

Supersaturation is an unstable state where salts exist above solubility concentrations and can coalesce into crystals, eventually forming precipitates, until the concentration of the material reaches solubility. Urine exists in a state above solubility even in non-stone formers and is not pathologic. Urine can range from undersaturated urine, to metastable supersaturated urine, to unstable supersaturated urine. Within the undersaturation zone (SS < 1) stones will not spontaneously form, and unstable nuclei may dissolve. As the concentration of solute increases within the solution, the solution reaches a point where the rates of dissolution and precipitation are equal. This equilibrium point is known as solubility (SS = 1).

Urine solutes above solubility (SS > 1) may or may not precipitate and are driven one way or the other by the highly variable complexity of the microenvironment of urine. Urinary salts do not exist in a pure solution but, rather, coexist with many

Table 2.1 Changes in concentration and supersaturation (SS) from filtrate in Bowman's capsule to urine leaving the collecting duct

	Filtrate	Urine
[Ca]	1 mmol/l	0.5–6 mmol/l
PO_4	1 mmol/l	0.5–10 mmol/l
Ox	0.002 mmol/l	0.05–0.3 mmol/l
SS CaP	~ 1	~ 0.5–4
SS CaOx	~ 0.01	~ 0.5–20

other molecules. A zone of concentration exists in which the urinary buffers and inhibitors prevent spontaneous nucleation but where crystals already present can grow. This zone is the metastable zone. Metastable supersaturated urine forms crystals in the presence of substrates (promoters) that provide a nucleation platform. Alternatively, crystals are formed due to the absence of stone inhibitors. These inhibitors interfere with salts, forming layers and exerting influences that slow stone growth and prevent further precipitation. Spontaneous nucleation occurs at the point when a solution becomes unstable despite the presence of inhibitors. This determines the formation product. The concentration range between solubility and the formation product varies for each stone type and with specific urinary conditions; the relative supersaturation level required for nucleation is therefore not a fixed thermodynamic constant [1].

Urine spends approximately 3 min in the renal tubules. During that three-minute period the concentration of stone-forming materials changes dramatically. The pH also changes drastically throughout the nephron, impacting solubility. Various stone-forming materials reach and exceed metastable limits in different areas of the nephron. Calcium phosphate can reach its metastable limit within the loop of Henle [2]. Calcium oxalate reaches peak supersaturation in the distal tubules and collecting ducts. Membrane-bound lipids and renal brush border membrane vesicles present a nucleation platform on which crystallization can form. The nuclei of stones can be composed of crystals whose composition is different than the majority composition. For example, calcium phosphate in plaque or tubule plugs serves as a crystallization nucleus for calcium oxalate crystals within human kidneys.

Stone Microstructure

Kidney stones vary with respect to their major mineral or pharmacologic composition. The majority of kidney stones are solid concretions composed both of crystallization and of a ubiquitous organic matrix. This matrix is present throughout the stone, within the crystals, within the inter crystalline spaces, and coating the exterior of the stone [1, 3, 4]. The matrix is composed of lipids, glycosaminoglycans, carbohydrates, and proteins [5]. The measurement of X-ray lucent voids demonstrates that this matrix composition may be as high as 3% in calcium oxalate monohydrate stones [6]. This matrix is integral to the growth kinetics of a stone. The matrix contains macromolecules that serve as both inhibitors and promoters of stone growth. Osteopontin, inter-α-inhibitor proteins, and urinary prothrombin fragment 1 are present in urine in small amounts and concentrate within the matrix [7–9]. The matrix also contains many lipid molecules which have been shown to induce crystal nucleation [10, 11]. Additionally, there is a feedback loop between crystals and the microcellular environment [12–14]. Stones have been shown to induce the production of both inhibitors and promoters of stone formation.

Sequential Schema for Stone Formation

Nucleation represents the first crystallization event. This occurs as metastable supersaturated urine crosses the threshold into unstable supersaturation. Nucleation is a molecular state change of two crystallizable substances. Nucleation can occur in the absence of other molecules (homogeneous nucleation) or in concert with crystals of other compositions or cellular components (heterogeneous nucleation) [15]. Heterogeneous nucleation requires a lower level of urinary saturation than does homogeneous nucleation. In vivo, heterogeneous nucleation is heavily favored due to the diversity of cellular material and urinary molecules. The chemical composition of crystals in stones is frequently a mixture of multiple crystal types rather than one crystal type. Even in elementally pure stones, nucleation often occurs in concert with biological elements including membranous cellular degradation products [15].

Aggregation or agglomeration is the binding of crystal nuclei to form larger concretions. Single crystals are too small to be retained in the urinary tract and thus pass in urine. It is thus through the process of aggregation that crystals reach sizes large enough to become pathologic. The urine of stone formers often has a defect in crystal aggregation inhibition that increases stone growth kinetics [16]. Urinary citrate, one of the most recognized urinary stone inhibitors, plays a central role in the modulation of inhibition of crystal aggregation [16].

Whereas aggregation is the binding of like crystals, epitaxy is the binding and interplay of dissimilar crystals. The majority of human stones are composed of mixtures of different crystal aggregates. Stones change crystalline structure based on the microenvironment surrounding them. Whereas calcium phosphate crystals form within the interstitium in the renal papilla, abetted by high concentrations exceeding the formation product, the eruption of a calcium phosphate stone into the calyceal system exposes it to a microenvironment that may favor other crystals to form. Depending on pH, either uric acid or continued calcium phosphate stones are formed. The calcium apatite base also serves as a nucleation surface for calcium oxalate monohydrate and dihydrate formation. Finally, organic matrix on stone surfaces may lead to preferential crystallization of specific crystals despite crystal solubility [17]. For example, crystal microscopy has shown that the organic matrix in mixed calcium oxalate monohydrate and dihydrate stones favors calcium oxalate monohydrate deposition despite the predominance of calcium oxalate dihydrate in urine [18].

Theories of Stone Formation

Stone formation research has many limitations that have prevented a unified stone formation theory. The heterogeneity of stone formers and stone compositions makes it unlikely that all stones follow the same pathway. Rat and mouse models of nephrolithiasis have been challenging to develop. Although it has been possible to develop hypercalciuric and hyperoxaluric models, they often present crystal deposition patterns distinct from human calculus disease [19, 20]. Only recently, in 2018, an animal

model of nephrolithiasis was created that involves concretions similar to Randall's plaque formation [21]. As such, much of the research surrounding calculus formation relies on observational analysis rather than on basic science-driven research.

Fixed Particle Theory (Randall's Plaque)

The fixed particle theory attempts to account for the relatively fast transit of filtrate through the nephron, which would be a barrier to nucleation and growth [22]. According to the theory, calcium phosphate (apatite) is deposited in the interstitium. This deposition erupts through the renal papillary surface. The erupted apatite, known as Randall's plaque, serves as a crystallization nucleus for calcium oxalate stones [23].

Contemporary work on the fixed particle theory suggests that interstitial deposition of calcium phosphate may be preceded by intratubular proximal deposition of calcium phosphate [24]. Interstitial ions and calcified nanoparticles cluster around the intratubular deposition. These calcified nanoparticles then form amorphous calcium phosphate clusters leading to erosion of the distal papilla and a fully formed Randall's plaque. This stationary plaque forms the basis for subsequent deposition of layers of calcium oxalate (growth in size) and the anchor point that prevents the developing stone from harmlessly transiting the urinary tract.

Free Particle Theory

The free particle theory requires nucleation, aggregation, and growth of the crystal to sizes that lodge within the nephron prior to excretion into the renal pelvis. Calcium phosphate, uric acid, cystine, and some iatrogenic stones form at significant rates within the nephron. These crystals can form plugs in the terminal collecting ducts, known as Randall's plugs. These plugs form the basis for further aggregation and growth as they erupt from the terminal collecting ducts into the renal pelvis. Once lodged and stationary, the plug can serve as a nucleation surface for other minerals such as calcium oxalate in a manner similar to Randall's plaques. The primary difference is the location of initial nucleation, the interstitium for Randall's plaques, and the intraluminal space for Randall's plugs.

Nanobacteria

Nanobacteria are cytotoxic, Gram-negative, atypical bacteria that can be found in human blood. The theory of nanobacteria forming nephrolithiasis builds upon Randall's plaque theory of calcium apatite units forming the initial stone nucleation

product. Nanobacteria have been shown to produce calcium apatite. Nanobacteria have also been found in 97% of stones analyzed [25]. The theory of nanobacteria causing stone formation has been under critical review due to reports that the biomineralization attributed to nanobacteria may be alternatively initiated by non-living macromolecules, rather than nanobacteria [26].

Conclusion

Kidney stone formation is a complex and incompletely understood phenomenon. Ongoing research, both at the bench and at the bedside, is required to better comprehend the process of urinary solutes transitioning from dissolved salts, to supersaturation, to crystal formation and nucleation, and finally stone development. By better understanding these processes, we will be able to develop more targeted therapies and improved strategies to decrease kidney stone risk and prevent kidney stone formation.

References

1. Khan SR, Hackett RL. Role of organic matrix in urinary stone formation: an ultrastructural study of crystal matrix interface of calcium oxalate monohydrate stones. J Urol. 1993;150(1):239–45.
2. Asplin JR, Mandel NS, Coe FL. Evidence of calcium phosphate supersaturation in the loop of Henle. Am J Phys. 1996;270(4 Pt 2):F604-13.
3. McKee MD, Nanci A, Khan SR. Ultrastructural immunodetection of osteopontin and osteocalcin as major matrix components of renal calculi. J Bone Miner Res. 1995;10(12):1913–29.
4. Ryall RL, Chauvet MC, Grover PK. Intracrystalline proteins and urolithiasis: a comparison of the protein content and ultrastructure of urinary calcium oxalate monohydrate and dihydrate crystals. BJU Int. 2005;96(4):654–63.
5. Malek RS, Boyce WH. Intranephronic calculosis: its significance and relationship to matrix in nephrolithiasis. J Urol. 1973;109(4):551–5.
6. Williams JC, et al. Variability of protein content in calcium oxalate monohydrate stones. J Endourol. 2006;20(8):560–4.
7. Atmani F, Khan SR. Role of urinary bikunin in the inhibition of calcium oxalate crystallization. J Am Soc Nephrol. 1999;10(Suppl 14):S385–8.
8. Khan SR, Kok DJ. Modulators of urinary stone formation. Front Biosci. 2004;9:1450–82.
9. Ryall RL. Macromolecules and urolithiasis: parallels and paradoxes. Nephron Physiol. 2004;98(2):37–42.
10. Khan SR, Shevock PN, Hackett RL. In vitro precipitation of calcium oxalate in the presence of whole matrix or lipid components of the urinary stones. J Urol. 1988;139(2):418–22.
11. Khan SR, et al. Presence of lipids in urine, crystals and stones: implications for the formation of kidney stones. Kidney Int. 2002;62(6):2062–72.
12. Khan SR, et al. Expression of osteopontin in rat kidneys: induction during ethylene glycol induced calcium oxalate nephrolithiasis. J Urol. 2002;168(3):1173–81.

13. Khan SR, et al. Regulation of macromolecular modulators of urinary stone formation by reactive oxygen species: transcriptional study in an animal model of hyperoxaluria. Am J Physiol Renal Physiol. 2014;306(11):F1285-95.
14. Aihara K, Byer KJ, Khan SR. Calcium phosphate-induced renal epithelial injury and stone formation: involvement of reactive oxygen species. Kidney Int. 2003;64(4):1283–91.
15. Khan SR. Calcium phosphate/calcium oxalate crystal association in urinary stones: implications for heterogeneous nucleation of calcium oxalate. J Urol. 1997;157(1):376–83.
16. Kok DJ, Papapoulos SE, Bijvoet OL. Crystal agglomeration is a major element in calcium oxalate urinary stone formation. Kidney Int. 1990;37(1):51–6.
17. Iwata H, et al. Architecture of calcium oxalate monohydrate urinary calculi. J Urol. 1985;133(2):334–8.
18. Iwata H, et al. Architecture of mixed calcium oxalate dihydrate and monohydrate stones. Scanning Microsc. 1992;6(1):231–7. discussion 237-8
19. Gorvin CM, et al. Mice with a Brd4 mutation represent a new model of nephrocalcinosis. J Bone Miner Res. 2019;34(7):1324–35.
20. Khan SR, Glenton PA. Experimental induction of calcium oxalate nephrolithiasis in mice. J Urol. 2010;184(3):1189–96.
21. Letavernier E, et al. ABCC6 deficiency promotes development of Randall plaque. J Am Soc Nephrol. 2018;29(9):2337–47.
22. Finlayson B, Reid F. The expectation of free and fixed particles in urinary stone disease. Investig Urol. 1978;15(6):442–8.
23. Randall A. Papillary pathology as a precursor of primary renal calculus. J Urol. 1940;44(5):580–9.
24. Wiener SV, et al. Novel insights into renal mineralization and stone formation through advanced imaging modalities. Connect Tissue Res. 2018;59(sup1):102–10.
25. Çiftçioglu N, et al. Nanobacteria: an infectious cause for kidney stone formation. Kidney Int. 1999;56(5):1893–8.
26. Cisar JO, et al. An alternative interpretation of nanobacteria-induced biomineralization. Proc Natl Acad Sci U S A. 2000;97(21):11511–5.

Chapter 3
Genetic Contributors to Kidney Stones in Children

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APRT Deficiency

Adenine phosphoribosyltransferase (APRT) deficiency is a rare autosomal recessive disorder of adenine metabolism. APRT is a cytoplasmatic enzyme that catalyzes the synthesis of 5-adenosine monophosphate from adenine and 5-phosphoribosyl-1-pyrophosphate (PRPP), which is the only recycling pathway in human physiology. Thus, the lack of functional APRT results in the conversion of 8-hydroxyadenine to a poorly soluble 2, 8-dihydroxyadenine (DHA) by xanthine dehydrogenase (XDH). The increase in urinary 2,8-DHA results in stone formation and crystalline nephropathy in the renal tubules and interstitium.

APRT deficiency seems to be more prevalent in Japan, Iceland, and France but it has been reported in all ethnic groups. The estimated prevalence in Japanese populations is 0.25–0.5 per 100,000 and 0.5–1 per 100,000 in the Caucasian population. These numbers are in contrast to Iceland where the prevalence of APRT deficiency is 8.9 per 100,000, possibly due to the more homogenous population [1].

Two types of APRT enzyme deficiency have been described. In Type I, which accounts for a majority of cases in Caucasians and all cases in Iceland, APRT activity in red blood cells is completely absent [2]. In Type II, which is the most common phenotype in Japan, the enzyme activity is roughly 25% of normal [1].

Clinical manifestations of APRT deficiency can present at any age. The disease typically presents with radiolucent kidney stones and crystalline nephropathy; the urinary tract appears to be the only system affected. In children the initial manifestation can be severe with acute obstructive nephropathy due to bilateral DHA stones; however, many patients remain asymptomatic during childhood and can develop progressive chronic kidney disease later in life. Possible APRT deficiency diagnosis

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should be considered in all children presenting with recurrent renal colic, AKI, poorly defined progressive renal insufficiency, radiolucent kidney stones, and in infants with reddish-brown diaper stains [3]. Uric acid stones are radiolucent as well, but are usually associated with low urine pH. Thus, radiolucent stones in the setting of an alkaline pH should raise the concern of an APRT deficiency [4]. As in many rare stone diseases, urine microscopy can be diagnostic. In APRT, polarized light microscopy will reveal crystals with a central maltase cross-pattern. Stone analysis is used to confirm diagnosis with infrared and ultraviolet spectrophotometry and/or X-ray crystallography that will distinguish DHA from uric acid and xanthine. This differentiation is not possible with standard biochemical analysis and for that reason this technique is no longer recommended [4]. Historically a diagnosis could be confirmed by analysis of APRT activity (specifically absence of activity) in red cell lysates; currently, a definitive diagnosis can be made with genetic testing and identification of biallelic pathogenic variants in the APRT gene.

Allopurinol, an XDH inhibitor, is generally used as treatment and is effective means of preventing stone formation, crystalline nephropathy and can even improve GFR in patients with advanced chronic kidney disease (CKD). Dosing is 5-10 mg/kg/day once a day or divided every 12 hours [4]. Febuxostat is an XDH inhibitor that can be used as an alternative in patients with hypersensitivity or allergy to allopurinol. In one study, comparing Allopurinol vs Febuxostat in APRT patients showed a marked decrease in DHA urine excretion with the latter compared to conventional dosing of Allopurinol [5].

Dent Disease

Dent disease is a rare, X-linked disorder that is associated with severe proximal tubular dysfunction. It was initially described in 1964 with the characterization of two unrelated cases of rickets, hypercalciuria, and tubular proteinuria [6]. The tubulopathy in Dent disease is due to mutation in CLCN5, a chloride protein exchanger or the OCRL1 gene, which are located on chromosomes Xp11.22 and Xq25, respectively. CLCN5 mutations account for 60% of Dent cases with mutations in OCRL1 present in only 15% of the cases. The genetic cause of the remaining 25% of cases has yet to be elucidated. Interestingly, some mutations of the OCRL1 gene result in Lowes syndrome instead of Dent disease.

Under normal physiological conditions, low molecular weight (LMW) proteins that are freely filtered are reabsorbed at the level of the proximal tubule by endocytosis via megalin-cubilin receptors. Mutations in CLCN5 and OCRL1 impair function of the megalin-cubilin apparatus and results in the LMW proteinuria that is a hallmark of Dent disease. In addition to this, the phenotype of Dent disease includes hypercalciuria and/or nephrolithiasis, nephrocalcinosis, rickets due to hyperphosphaturia, and progressive renal disease [7]. While there are several theories that aim to elucidate the mechanism of hypercalciuria, the exact pathophysiology remains unclear.

Due to X-linked inheritance males are more severely affected than females, with 80% of affected males developing end-stage renal disease between the third and fifth decade of life [8]. Female manifestations of the disease seem to be limited to LMW proteinuria in 50–70% of cases; rarely, severe cases of kidney stones and even end-stage renal disease (ESRD) have been reported [9].

Diagnosis of Dent disease is based on the presentation of at least 3 clinical criteria: LMW proteinuria, hypercalciuria, and one of the following: nephrocalcinosis, kidney stones, hematuria, hypophosphatemia, or renal failure.

LMW proteinuria is defined as elevation of urinary beta-2 microglobulin (B2M) or retinol-binding protein (RBP) fivefold above the upper normal limit. Screening for LMW proteinuria can be diagnostically challenging when only LMW proteins are present [10, 11]. The urine dipstick is very sensitive to albuminuria but can often miss LMW proteins and without a formal laboratory measure of proteinuria there is a potential for missed diagnoses. Additionally, Dent disease is occasionally mistakenly diagnosed as FSGS as some case reports have noted CLCN5 mutations that present with nephrotic range proteinuria and a histology compatible with focal segmental glomerulosclerosis (FSGS) [12]. The clinician does need to be aware that some cases of Dent disease can also present with albuminuria, even in the nephrotic range, so formal quantification of urinary B2M or RBP is necessary to help make the diagnosis. Hypercalciuria is defined as more than 4 mg/kg/day (>250 mg/day in adult women, >300 mg/day in adult men) of urinary calcium on a 24-h urine collection or a spot urine calcium to creatinine ratio above the age-defined limits.

As mentioned above, the presence of nephrocalcinosis, kidney stones, hypercalciuria, hematuria, hypophosphatemia, renal insufficiency, or a family history consistent with X-linked inheritance can be used to support the diagnosis in a patient with LMW proteinuria. A diagnosis can be confirmed with genetic testing and identification of pathogenic variants in CLCN5 or OCRL1. It is important to note that no genotype–phenotype correlation has been established and the severity of the disease can vary within the same family [13–15].

Treatment is supportive with thiazide diuretics used in those cases with hypercalciuria. Vitamin D and oral phosphate supplements can be used to treat rickets; however, careful monitoring with regular vitamin D levels are necessary as this therapy has the potential to increase urinary calcium. A high citrate diet seems to delay progression of renal disease and stone formation in animal models and citrate supplementation could be considered in patients with Dent disease, especially those with coexisting hypocitraturia [16].

Cystinuria

Cystinuria is a rare but notable form of inherited nephrolithiasis. Its prevalence is estimated at 1 in 7000 resulting in ~5% of stones in children [17, 18]. The disease is a result of defective reabsorption of filtered cysteine, ornithine, lysine, and arginine in the proximal tubule. There are no clinical manifestations of the urinary loss

of ornithine, lysine, and arginine; however, urinary cysteine readily forms cystine, a homodimer via a disulfide bond. Cystine is poorly soluble in the urine and easily nucleates and develops into cystine stones. As opposed to many forms of nephrolithiasis, the resulting stones can be very difficult to treat and as such several studies have shown reduced kidney function and even end-stage kidney disease in patients with cystinuria [19, 20].

In the past, cystinuria was subdivided into three phenotypes based primarily on clinical characteristics. However, as our understanding of the underlying genetic defects and ability to do genetic testing has improved, these subdivisions are less and less relevant and although the genetic underpinnings of the disease are fascinating (see below), the genotypic–phenotypic correlation is poor and rarely plays a role in clinical practice.

Pathogenic variants in one of two genes can result in cystinuria. Defects in SLC3A1 [21] which encodes a glycoprotein that forms a heterodimer with the gene product of SLC7A9 result in mislocalization of the cystine transporter. Most often this results in autosomal recessive inheritance. The other type of mutation is in SLC7A9 [22] which encodes the actual amino acid transporter. Mutations in this gene often are inherited in an autosomal dominant pattern with incomplete penetrance. Further detail regarding the molecular pathophysiology of cystinuria is included in the "Diseases and Comorbid Conditions Predisposing Children to Kidney Stones" chapter of this text.

Recently a clinical practice guideline was published by the Metabolic workgroup of the European Reference Network for Rare Kidney Disease [23]. Both surgical and medical treatment recommendations were included and were in line with past recommendations from the American Urological Association [24]. Specifically, medical therapy was subdivided into conservative and cystine-binding drugs. The medical therapy includes aggressive fluid hydration in order to maintain a cystine concentration of <250 mg/L. This often means greater than 2 L/1.73 m^2 of fluid intake and subsequent urine output. Additionally, urine alkalinization to a pH of 7.5–8 is recommended to help with cystine solubility, as cystine is more insoluble in acidic urine. In children, this is best accomplished by using potassium citrate at a dose of 60–80 meq/1.73 m^2 divided at least twice a day. In line with most dietary recommendation in the settings of nephrolithiasis a low salt diet should be encouraged. Since reduced methionine intake results in lower cystine production, foods with high methionine can be avoided [25] but is important not to restrict overall protein intake in growing children.

There are several cystine-binding drugs available such as tiopronin and d-penicillamine which cleave cystine's disulfide bond and complex with the resultant cysteine. These moieties are nearly 50x more soluble and both drugs have been shown to reduce free urine cystine levels [26]. Tiopronin has much lower serious side effect profile although both drugs have been associated with adverse effects [27]. In the case of both drugs, the target is reducing urinary cystine below 250 mg/L measured via mass-spectroscopy as other techniques cannot differentiate between cysteine and the drug–cysteine complexes. There are some interesting inhibitors of cysteine crystallization being studied. The most promising is

alpha-lipoic acid which has been shown to reduce cystine stones in a mouse model of cystinuria [28] and has shown some success, albeit in a small case series, in pediatric patients [29].

Lesch-Nyhan

Lesch-Nyhan is a rare X-linked disorder caused by a mutation in the gene encoding for hypoxanthine-guanine phosphoribosyltransferase (HPRT). It is usually characterized by hyperuricemia with subsequent hyperuricosuria and a multitude of neurological abnormalities including cognitive impairment, impulsivity, and self-injurious behavior. HPRT is a key enzyme in the uric acid and purine metabolism pathway and as such there are multiple mechanisms that contribute to hyperuricemia. HPRT mediates the catalyzation of inosine monophosphate (IMP) and guanosine monophosphate (GMP) from the purine bases hypoxanthine and guanine using 5′-phosphoribosyl-1-pyrophosphate (PRPP) as a co-substrate [30]. The lack of HPRT function leads to accumulation of hypoxanthine and guanine that in turn are converted to uric acid by xanthine oxidase. The increased availability of PRPP amidotransferase (a rate-limiting enzyme in the synthesis of purine nucleotides) and the decreased presence of its inhibitors (IMP and GMP) result in increased de novo synthesis of purine nucleotides. This combination of decreased recycling of purine bases and increased synthesis of purine nucleotides helps to explain the elevated uric acid seen in Lesch-Nyan.

Patients who present with hyperuricemia, hyperuricosuria, and neurological manifestations should raise the suspicion of an underlying HPRT deficiency. In contrast to the renal and articular symptoms that are always present, the neurological presentation can vary based on the degree and severity of enzyme deficiency. Patients are asymptomatic at birth and one of the first presentations may be orange crystal deposition on diapers. Psychomotor delay can appear around 3 months of age with more severe manifestations, such as self-mutilation behavior presenting when teeth begin to erupt.

Diagnosis is usually made using a combination of clinical findings and biochemical data. Patients with hyperuricemia with or without neurological symptoms/signs should be evaluated for HPRT deficiency. Similarly, serum uric acid measurement should be part of the evaluation of patients with psychomotor delay during the first year of life. Any degree of elevated serum uric acid should trigger further testing as some patients will have borderline hyperuricemia due to increased clearance of uric acid by the kidney. Thus, a urine uric acid to creatinine ratio is usually obtained to confirm hyperuricosuria. The results of such testing need to be interpreted using age and gender standards [31].

HPRT deficiency is confirmed by measurements of enzyme activity in intact cells (usually fibroblasts). Usually, there is a correlation between enzyme activity and neurological phenotype [32]. Genetic diagnosis can pose a challenge since documented mutations of HPRT can have a high degree of heterogenicity in type and

location within the gene with more than 300 disease-associated mutations identified to date [33].

Treatment typically centers around the use of the xanthine oxidase inhibitor allopurinol. It is relatively effective at reducing serum and urine uric acid which can reduce renal and articular manifestations such as crystalluria, kidney stones, and gouty arthritis. Unfortunately, it has no effect on behavioral and neurological symptoms. Allopurinol should be titrated to achieve a normal serum uric acid and a urinary uric acid to creatinine ratio below 1. Attention needs to be paid to the possibility of an increased risk for xanthine stones with allopurinol treatment and thus dosing should be titrated regularly to achieve a normal serum uric acid [34]. Renal prognosis is favorable in patients who are identified early and initiate on allopurinol treatment. Long-term morbidity and mortality are mainly dictated by neurological involvement.

Primary Hyperoxaluria

Primary hyperoxaluria (PH) is a group of rare autosomal recessive disorders in which overproduction of oxalate results in nephrolithiasis, ESRD, and in some cases systemic disease (oxalosis). The prevalence of PH is largely unknown but based on data from central Europe, the estimated incidence is 1:200,000 live births with a prevalence of 1–3 per million. Notably, in areas where consanguineous marriage is more common, such as Tunisia and the Middle East, the incidence is higher and PH accounts for 1–2% of pediatric ESRD [35–38].

PH pathophysiology involves the overproduction of oxalate by the liver. The oxalate is filtered via the glomerulus and complexes with urinary calcium to form a relatively insoluble calcium oxalate salt. Early on in PH, calcium oxalate crystals accumulate and injure the renal tubules leading to both nephrocalcinosis and kidney stones. As accumulation continues, CKD develops due to progressive tubular toxicity, nephrocalcinosis, obstruction from kidney stones, and inflammation induced by calcium oxalate itself [39, 40]. The natural history of the disease involves two phases: the first one primarily affects the kidney with urolithiasis and other manifestation discussed above. However, as the GFR declines below 30 mL/min/1.73 m^2, the excretion of urinary oxalate drops leading to deposition of oxalate systemically [41]. With increasing serum levels of oxalate due to decreased filtration, calcium oxalate can deposit in many organs including the heart, blood vessels, joints, bone, and retina. This leads to a myriad of extrarenal symptoms including cardiac dysfunction, vascular disease, skeletal disease and fractures, arthritis, and decreased visual acuity.

PH is divided into 3 types based on the exact enzymatic defect. PH type 1 is caused by a deficiency of the liver-specific peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT). This pyridoxal 5-phosphate-dependent enzyme mediates the transamination of glyoxylate to glycerin. Thus, its deficiency leads to

accumulation of glyoxylate which is eventually converted to oxalate and glycolate. Mutation of the AGXT gene, which encodes the AGT enzyme, is responsible for approximately 80% of the PH cases. Interestingly, mistargeting of mitochondrial AGT can lead to hyperoxaluria even though enzyme activity is normal [42].

PH Type 2 is secondary to a mutation in GRHPR and results in a deficiency or absence of glyoxylate reductase/hydroxy pyruvate reductase (GRHPR). This enzyme catalyzes the reduction of glyoxylate to glycolate and hydroxypyruvate to D-glycerate. GRHPR is mainly an intrahepatic enzyme but is present in other tissues. When defective or deficient lactate dehydrogenase metabolizes glyoxylate to oxalate and hydroxypyruvate to L-glycerate.

PH type 3 is linked to the liver-specific mitochondrial enzyme 4-hydroxy-2oxoglutarate aldolase (HOGA). The exact mechanism that leads to accumulation of oxalate remains unclear but it is hypothesized that an enzyme substrate, HOG, is alternatively metabolized to oxalate or that HOG inhibits mitochondrial GRHPR. PH 3 is very infrequent and only comprises 10% of PH cases [43].

Clinical Presentation

The majority of the patients with PH initially present with symptoms related to urolithiasis with a median onset of 5 years of age [44]. However, a small percentage can present with nephrocalcinosis and early ESRD with no documented history of kidney stones. Unfortunately, due to the lack of awareness of this disease, up to 50% of patients have advanced CKD or ESRD at the time of diagnosis. In an estimated 10% of patients, the diagnosis is only made after disease recurs following renal transplantation.

PH type 1 presents with the most severe phenotype and can be devastating when its presents during infancy. Patients with genotype Gly170Arg or Phe152Ile tend to have a more favorable prognosis because these mutations are a response to pyridoxine (see treatment below). PH2 tends to have an insidious progression probably in part because GRHPR is not exclusive to liver and is present in other tissues. Finally, PH3 is the variant with the least severe course and even though hyperoxaluria is present ESRD is uncommon and there is rarely systemic involvement.

Diagnosis

PH should be considered in all patients who present with kidney stones at an early age or in adults with multiple episodes of urolithiasis associated with decreased GFR. Early diagnosis is vital in order to prevent long-term and irreversible damage. Evaluation should start with an analysis of urine sediment for the presence of monohydrated calcium oxalate crystals (whewellite) that are different from rhomboid

oxalate dihydrate calcium crystals. Whenever possible, a 24-h urine collection should be collected and analyzed. Elevation of 24-h urine oxalate of >0.7 mmol/1.73 m^2 or an elevated spot urine oxalate to creatinine ratio for age [45] in the absence of secondary causes of hyperoxaluria requires further investigation. Urine measurements of glycolate and glycerate are helpful but not specific, they can be advantageous in differentiating between the types of PH, see more information later in this textbook.

Genetic testing for diagnostic purposes has become standard of care now that it is readily available. Additionally, the importance of mutation identification goes beyond diagnosis as it has potential implications including treatment response. Not all genetic variants are pathologic, and variants of unknown significance require cascade testing in family members. In cases in which no mutation is identified, liver biopsy for evaluation of enzymatic activity can be informative. Functional hepatic enzyme analysis was previously the primary tool for diagnosis of PH but has been replaced by genetic testing in the majority of cases.

Serum oxalate can be measured in patients with advanced CKD or ESRD. Although normal ranges have not been established, levels above 100 umol/L are highly suggestive of PH [46].

Treatment

As mentioned above, early diagnosis is key in order to reduce disease morbidity and mortality. Initial management is focused on decreasing urinary calcium oxalate supersaturation. Fluid intake is thus a cornerstone of therapy with a recommended fluid intake of at least 2–3 L/m^2. Often this requires the placement of a gastrostomy tube in young infants and children. Oral potassium citrate (0.15 mg/kg) can help to solubilize calcium oxalate crystals [47]. Care must be used in patients with advanced CKD in order in order to avoid hyperkalemia. Most oxalate is produced endogenously so there is a minimal role in diet restriction although a low oxalate diet is usually included in the treatment plan. In some PH1 patients, pyridoxine can reduce oxalate production via multiple mechanisms. It is recommended that all PH1 patients undergo a trial of pyridoxine treatment (7–9 mg/kg/day) for at least 3 months with a response defined as >30% decrease of urinary oxalate.

Lumasiran is a novel RNA interference therapy in PH1 patients that targets glycolate oxidase. This results in reduced oxalate production by decreasing the accumulation of glyoxylate. Results from a recent Phase 3 clinical trial [48] demonstrated a significant decrease in patients that received Lumisiran compared to placebo. A majority of treated patients showed an early and sustained decrease of urinary oxalate to 1.5 times the upper limit of normal range. The only adverse reactions were mild and transient injection site reactions. Although this therapy has only recently been approved, it is possible it may significantly alter the natural history of this disease.

Dialysis

Once the GFR drops below 30 mL/min/1.73 m^2 the systemic deposition of oxalate increases dramatically and dialysis is usually initiated. Although it is readily dialyzable, endogenous production is tremendous and in patients who undergo hemodialysis 6 times a week in combination with nightly peritoneal dialysis continue to have serum oxalate levels above 30–45 umol/L [49]. Pyridoxin therapy should continue in responsive patients when they start dialysis in order to decrease oxalate production.

Transplant

Given that endogenous oxalate production occurs in the liver, pre-emptive liver transplantation is a logical consideration before patients develop advanced CKD. However, the exact timing is difficult and most patients present with some degree of CKD. Given the high recurrence rate of disease, kidney transplantation without liver transplantation is ill advised in all but the most pyridoxine-responsive patients. Thus, combined liver and kidney transplantation is the treatment of choice [50]. A staged approach in which liver transplantation occurs first in order to reduce oxalate burden can be attempted but due to logistical consideration is not often feasible. As mentioned above, advances in genetic therapy may eliminate the need for dual organ transplants in the near future.

Conclusion

There are many underlying reasons that predispose children to the development of nephrolithiasis. While rare, the primary genetic causes of kidney stones should be considered and ruled out in all children who present with stone disease. These diseases often present in childhood and cause early onset of aggressive stone disease; because of this, any provider caring for a child with kidney stones should be aware of their presentations, the role of genetic testing in diagnosis, and the unique method in which they are treated. With further advancements in the field and a better understanding of the role of genetics in these diseases, it is hopeful that further tailored therapeutics will continue to be developed for these difficult-to-manage forms of nephrolithiasis.

References

1. Bollée G, Dollinger C, Boutaud L, Guillemot D, Bensman A, Harambat J, et al. Phenotype and genotype characterization of adenine phosphoribosyltransferase deficiency. J Am Soc Nephrol. 2010;21:679–88. [PubMed: 20150536]

2. Edvardsson V, Palsson R, Olafsson I, Hjaltadottir G, Laxdal T. Clinical features and genotype of adenine phosphoribosyltransferase deficiency in Iceland. Am J Kidney Dis. 2001;38:473–80. [PubMed: 11532677]
3. Harambat J, Bollee G, Daudon M, Ceballos-Picot I, Bensman A. Adenine phosphoribosyltransferase deficiency in children. Pediatr Nephrol. 2012;27:571–9. [PubMed: 22212387]
4. Edvardsson VO, Goldfarb DS, Lieske JC, et al. Hereditary causes of kidney stones and chronic kidney disease. Pediatr Nephrol. 2013;28(10):1923–42. https://doi.org/10.1007/s00467-012-2329-z.
5. Edvardsson VO, Runolfsdottir HL, Thorsteinsdottir UA, et al. Comparison of the effect of allopurinol and febuxostat on urinary 2,8-dihydroxyadenine excretion in patients with adenine phosphoribosyltransferase deficiency (APRTd): a clinical trial. Eur J Intern Med. 2018;48:75–9. https://doi.org/10.1016/j.ejim.2017.10.007.
6. Dent CE, Friedman M. Hypercalcuric rickets associated with renal tubular damage. Arch Dis Child. 1964;39:240–9.
7. Ludwig M, Utsch B, Monnens LA. Recent advances in understanding the clinical and genetic heterogeneity of Dent's disease. Nephrol Dial Transplant. 2006;21:2708–17.
8. Devuyst O, Thakker RV. Dent's disease. Orphanet J Rare Dis. 2010;5:28. https://doi.org/10.1186/1750-1172-5-28. PMID: 20946626; PMCID: PMC2964617.
9. Wu F, Reed AA, Williams SE, Loh NY, Lippiat JD, Christie PT, Large O, Bettinelli A, Dillon MJ, Goldraich NP, Hoppe B, Lhotta K, Loirat C, Malik R, Morel D, Kotanko P, Roussel B, Rubinger D, Schrander-Stumpel C, Serdaroglu E, Nesbit MA, Ashcroft F, Thakker RV. Mutational analysis of CLC-5, cofilin and CLC-4 in patients with Dent's disease. Nephron Physiol. 2009;112:53–62.
10. De Mutiis C, Pasini A, La Scola C, Pugliese F, Montini G. Nephrotic-range albuminuria as the presenting symptom of Dent-2 disease. Ital J Pediatr. 2015;41:46.
11. van Berkel Y, Ludwig M, van Wijk JAE, Bökenkamp A. Proteinuria in Dent disease: a review of the literature. Pediatr Nephrol. 2017;32(10):1851–9. https://doi.org/10.1007/s00467-016-3499-x. Epub 2016 Oct 18. PMID: 27757584; PMCID: PMC5579149
12. Fervenza FC. A patient with nephrotic-range proteinuria and focal global glomerulosclerosis. Clin J Am Soc Nephrol. 2013;8:1979–87.
13. Ludwig M, Utsch B, Balluch B, Fründ S, Kuwertz-Bröking E, Bökenkamp A. Hypercalciuria in patients with CLCN5 mutations. Pediatr Nephrol. 2006;21:1241–50.
14. Scheinman SJ, Cox JPD, Lloyd SE, Pearce SHS, Salenger PV, Hoopers RR, Bushinsky DA, Wrong O, Asplin JR, Langman CB, Norden AGW, Thakker RV. Isolated hypercalciuria with mutation in CLCN5: relevance to idiopathic hypercalciuria. Kidney Int. 2000;57:232–9.
15. Frymoyer PA, Scheinman SJ, Dunham PB, Jones DB, Hueber P, Schroeder ET. X-linked recessive nephrolithiasis with renal failure. N Engl J Med. 1991;325:681–6.
16. Cebotaru V, Kaul S, Devuyst O, Cai H, Racusen L, Guggino WB, Guggino SE. High citrate diet delays progression of renal insufficiency in the ClC-5 knockout mouse model of Dent's disease. Kidney Int. 2005;68:642–52.
17. Chillaron J, Font-Llitjos M, Fort J, et al. Pathophysiology and treatment of cystinuria. Nat Rev Nephrol. 2010;6:424–34.
18. Daudon M. Component analysis of urinary calculi in the etiologic diagnosis of urolithiasis in the child. Arch Pediatr. 2000;7:855–65.
19. Worcester EM, Parks JH, Evan AP, Coe FL. Renal function in patients with nephrolithiasis. J Urol. 2006;176:600.
20. Prot-Bertoye C, Lebbah S, Daudon M, et al. CKD and its risk factors among patients with cystinuria. Clin J Am Soc Nephrol. 2015;10:842.
21. Calonge AUMJ, Gasparini P, Chillarón J, Chillón M, Gallucci M, Rousaud F, Zelante L, Testar X, Dallapiccola B, Di Silverio FSO. Cystinuria caused by mutations in rBAT, a gene involved in the transport of cystine. Nat Genet. 1994;6(4):420.
22. Feliubadaló AUL, Font M, Purroy J, Rousaud F, Estivill X, Nunes V, Golomb E, Centola M, Aksentijevich I, Kreiss Y, Goldman B, Pras M, Kastner DL, Pras E, Gasparini P, Bisceglia L,

Beccia E, Gallucci M, de Sanctis L, Ponzone A, Rizzoni GF, Zelante L, Bassi MT, George AL Jr, Manzoni M, De Grandi A, Riboni M, Endsley JK, Ballabio A, Borsani G, Reig N, Fernández E, Estévez R, Pineda M, Torrents D, Camps M, Lloberas J, Zorzano A, Palacín M. International Cystinuria Consortium SO. Non-type I cystinuria caused by mutations in SLC7A9, encoding a subunit (bo,+AT) of rBAT. Nat Genet. 1999;23(1):5.

23. Servais A, Thomas K, Dello Strologo L, Sayer JA, Bekri S, Bertholet-Thomas A, Bultitude M, Capolongo G, Cerkauskiene R, Daudon M, Doizi S, Gillion V, Gràcia-Garcia S, Halbritter J, Heidet L, van den Heijkant M, Lemoine S, Knebelmann B, Emma F, Levtchenko E; Metabolic Nephropathy Workgroup of the European Reference Network for Rare Kidney Diseases (ERKNet) and eUROGEN. Cystinuria: clinical practice recommendation. Kidney Int. 2021;99(1):48–58. https://doi.org/10.1016/j.kint.2020.06.035. Epub 2020 Sep 9. PMID: 32918941.
24. Pearle MS, Goldfarb DS, Assimos DG, et al. Medical management of kidney stones: AUA guideline. J Urol. 2014;192:316.
25. Bouzidi H, Daudon M. Cystinuria: from diagnosis to follow-up. Ann Biol Clin (Paris). 2007;65:473–81. [in French]
26. Effect of cystine-binding thiol drugs on urinary cystine capacity in patients with cystinuria. J Endourol. 2005;19:429–32.
27. Prot-Bertoye C, Lebbah S, Daudon M, et al. Adverse events associated with currently used medical treatments for cystinuria and treatment goals: results from a series of 442 patients in France. BJU Int. 2019;124:849–61.
28. Zee T, Bose N, Zee J, et al. α-Lipoic acid treatment prevents cystine urolithiasis in a mouse model of cystinuria. Nat Med. 2017;23:288–90.
29. Cil O, Perwad F. α-Lipoic acid (ALA) improves cystine solubility in cystinuria: report of 2 cases. Pediatrics. 2020), Article;145:e20192951.
30. Torres RJ, Puig JG. Hypoxanthine-guanine phosophoribosyltransferase (HPRT) deficiency: Lesch-Nyhan syndrome. Orphanet J Rare Dis. 2007;2:48. https://doi.org/10.1186/1750-1172-2-48. PMID: 18067674; PMCID: PMC2234399
31. Kaufman JM, Greene ML, Seegmiller JE. Urine uric acid to creatinine ratio—a screening test for inherited disorders of purine metabolism. Phosphoribosyltransferase (PRT) deficiency in X-linked cerebral palsy and in a variant of gout. J Pediatr. 1968;73:583–92.
32. Page T, Bakay B, Nissinen E, Nyhan WL. Hypoxanthine-guanine phosphoribosyltransferase variants: correlation of clinical phenotype with enzyme activity. J Inherit Metab Dis. 1981;4:203–6.
33. Official website of the Lesch-Nyhan disease Study Group [http://www.lesch-nyhan.org].
34. Brock WA, Golden J, Kaplan GW. Xanthine calculi in the Lesch-Nyhan syndrome. J Urol. 1983;130(157):159.
35. van Woerden CS, Groothoff JW, Wanders RJ, Davin JC, Wijburg FA. Primary hyperoxaluria type 1 in the Netherlands: prevalence and outcome. Nephrol Dial Transplant. 2003;18:273–9. [PubMed: 12543880]
36. Cochat P, Liutkus A, Fargue S, Basmaison O, Ranchin B, Rolland MO. Primary hyperoxaluria type 1: still challenging. Pediatr Nephrol. 2006;21:1075–81. [PubMed: 16810517]
37. Coulter-Mackie MB. Preliminary evidence for ethnic differences in primary hyperoxaluria type 1 genotype. Am J Nephrol. 2005;25:264–8. [PubMed: 15961945]
38. Harambat J, van Stralen KJ, Espinosa L, et al. Characteristics and outcomes of children with primary oxalosis requiring renal replacement therapy. Clin J Am Soc Nephrol. 2012;7:458–65.
39. Mulay SR, Kulkarni OP, Rupanagudi KV, et al. Calcium oxalate crystals induce renal inflammation by NLRP3-mediated IL-1β secretion. J Clin Invest. 2013;123:236–46.
40. Muda AO, Barsotti P, Rinaldi S, Rizzoni G, Faraggiana T. Renal pathology in hyperoxaluria. In: Sessa A, Conte F, Meroni M, Battini G, editors. Hereditary kidney diseases. Basel: Karger; 1997. p. 160–6.

41. Hoppe B, Kemper MJ, Bökenkamp A, Portale AA, Cohn RA, Langman CB. Plasma calcium oxalate supersaturation in children with primary hyperoxaluria and end-stage renal failure. Kidney Int. 1999;56:268–74.
42. Edvardsson VO, Goldfarb DS, Lieske JC, Beara-Lasic L, Anglani F, Milliner DS, Palsson R. Hereditary causes of kidney stones and chronic kidney disease. Pediatr Nephrol. 2013;28(10):1923–42. https://doi.org/10.1007/s00467-012-2329-z. Epub 2013 Jan 20. PMID: 23334384; PMCID: PMC4138059
43. Cochat P, Rumsby G. Primary hyperoxaluria. N Engl J Med. 2013;369(7):649–58. https://doi.org/10.1056/NEJMra1301564. Erratum in: N Engl J Med. 2013 Nov 28;369(22):2168.
44. Lieske JC, Monico CG, Holmes WS, et al. International registry for primary hyperoxaluria. Am J Nephrol. 2005;25:290–6.
45. Milliner DS. The primary hyperoxalurias: an algorithm for diagnosis. Am J Nephrol. 2005;25:154–60.
46. Cochat P, Hulton SA, Acquaviva C, Danpure CJ, Daudon M, De Marchi M, et al. Primary hyperoxaluria type 1: indications for screening and guidance for diagnosis and treatment. Nephrol Dial Transplant. 2012;27(5):1729–36.
47. Cochat P, Hulton SA, Acquaviva C, et al. Primary hyperoxaluria type 1: indications for screening and guidance for diagnosis and treatment. Nephrol Dial Transplant. 2012;27:1729–36.
48. Garrelfs SF, Frishberg Y, Hulton SA, Koren MJ, O'Riordan WD, Cochat P, Deschênes G, Shasha-Lavsky H, Saland JM, Van't Hoff WG, Fuster DG, Magen D, Moochhala SH, Schalk G, Simkova E, Groothoff JW, Sas DJ, Meliambro KA, Lu J, Sweetser MT, Garg PP, Vaishnaw AK, Gansner JM, McGregor TL, Lieske JC, ILLUMINATE-A Collaborators. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type 1. N Engl J Med. 2021;384(13):1216–26. https://doi.org/10.1056/NEJMoa2021712.
49. Hoppe B, Kemper MJ, Bökenkamp A, Langman CB. Plasma calcium-oxalate saturation in children with renal insufficiency and in children with primary hyperoxaluria. Kidney Int. 1998;54:921–5.
50. Bergstralh EJ, Monico CG, Lieske JC, et al. Transplantation outcomes in primary hyperoxaluria. Am J Transplant. 2010;10:2493–501.

Chapter 4
Diseases and Comorbid Conditions Predisposing Children to Kidney Stones

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Congenital Metabolic Disturbances

Hypercalciuric Disturbances

Idiopathic Hypercalciuria

Idiopathic hypercalciuria refers to the constellation of elevated urinary calcium levels with normocalcemia in the absence of an identifiable, causative disease [1]. This condition is very common with one study showing nearly one in five patients having idiopathic hypercalciuria as the sole urinary metabolic derangement [2]. Early studies suggested a genetic basis as there was a higher than predicted incidence of idiopathic hypercalciuria within families [3]. Similarly, in a recent study, more than 60% of stone formers less than 17 years of age had a positive family history in a first- or second-degree relative [2]. Multiple genes have been implicated in idiopathic hypercalciuria; however, the overall disorder appears to be multifactorial being influenced by both genetic and environmental factors [4]. Alterations in intestinal absorption, poor renal reabsorption, and bone catabolism are all non-mutually

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exclusive mechanisms that may play a role in causing hypercalciuria, rather than the classic view that each mechanism works in isolation [5].

Absorptive hypercalciuria refers to the overly avid uptake of calcium within the small intestine, the primary site of dietary calcium absorption [6–8]. Calcium presented in the small intestine may enter the body transcellularly or paracellularly [9]. The movement of calcium transcellularly is regulated by vitamin D in its active form, 1,25-dihydroxyvitamin D [10]. If not required for systemic calcium homeostasis, increasing the amount of calcium absorbed in the gut leads to increased filtration of calcium into the renal proximal tubule where it can increase the propensity to form stones. Proposed mechanisms for over absorption of intestinal calcium include hypersensitivity to vitamin D, subtle phosphate loss in the kidney leading to secondary increase in vitamin D production, and overexpression of vitamin D receptors [9, 11, 12].

Renal hypercalciuria arises from a defect within the renal tubule resulting in poor reabsorption and loss of calcium in the urine [7, 8]. As with many other solutes that are filtered in the kidney, the proximal tubule is the main site of calcium reabsorption, followed by the thick ascending limb, distal tubule, and collecting duct [13]. Hypercalciuria is not fully explained by diet alone with studies showing increased urinary calcium despite being in the fasting state [14]. There is clinical evidence to suggest that these patients may be suffering from dysfunction in both the proximal and distal nephrons [15]. Furthermore, previous rat model studies suggest that the defect may be in the thick ascending limb of the loop of Henle [16].

An important extrarenal manifestation of idiopathic hypercalciuria is the negative effects on bone health [17]. Prior work has shown a fairly clear link between loss in bone mineral density and idiopathic hypercalciuria [18]. In a prospective study, hypercalciuric patients appeared to have higher rates of bone reabsorption with normal rates of bone formation compared to normocalciuric controls [19]. Other work reinforces the fact that these children may exhibit abnormally high osteoclastic activity as evidenced by elevated levels of cytokines such as interleukin-1 [20, 21].

Dent Disease

This is a rare X-linked disorder characterized by hypercalciuria, nephrocalcinosis, and low molecular weight proteinuria [22, 23]. Nephrolithiasis occurs in approximately 50% of males [24]. There are two types, the most common being associated with mutations in the CLCN5 gene (Dent 1), located on the X-chromosome, affecting approximately 60 percent of patients. The remainder of cases are associated with mutation to the OCRL1 (Dent 2) gene or other unknown mutations [24]. Both proteins are involved in membrane trafficking and endocytosis. CLCN5 encodes a protein found on endosomal membranes, predominantly in the proximal convoluted tubule [25]. Mutations of this gene lead to loss of function and disruption of endocytosis responsible for reabsorbing filtered proteins, such as parathyroid hormone [26]. Parathyroid hormone may pass from the early proximal tubule to the late

proximal tubule and stimulate degradation of sodium-phosphate cotransporters that typically reabsorb phosphate. In turn, hyperphosphaturia will result which may contribute to stone formation. The underlying cause of hypercalciuria is still unclear. Conflicting findings have suggested increased intestinal absorption as the primary mechanism. This may be from parathyroid hormone activating 1-alpha hydroxylase and ultimately increasing 1,25-dihydroxyvitamin D related to parathyroid hormones [27, 28]. These patients unfortunately often progress to end-stage renal failure around 30–50 years of age [24].

Bartter Syndrome

Bartter syndrome is a rare condition with an estimated incidence of 1.2 per million [29]. It is characterized by defects of various proteins involved in ion transport in the thick ascending limb of the loop of Henle [30]. There have been six types described, four of which are autosomal recessive, one autosomal dominant, and one X-linked recessive [31]. Nephrocalcinosis is encountered in type 1 and type 2, which is the result of defects in the NKCC2 cotransporter and the ROMK channel, respectively (Fig. 4.1). Both channels are located on the apical membrane within the thick ascending limb. Impeded intracellular passage of sodium, potassium, and chloride via the NKCC2 cotransporter or the inability of potassium to flow into the luminal space through the ROMK channel leads to disturbances in the normal membrane potential. Without a relatively positively charged lumen, calcium is unable to be absorbed paracellularly leading to hypercalciuria. These patients may acquire

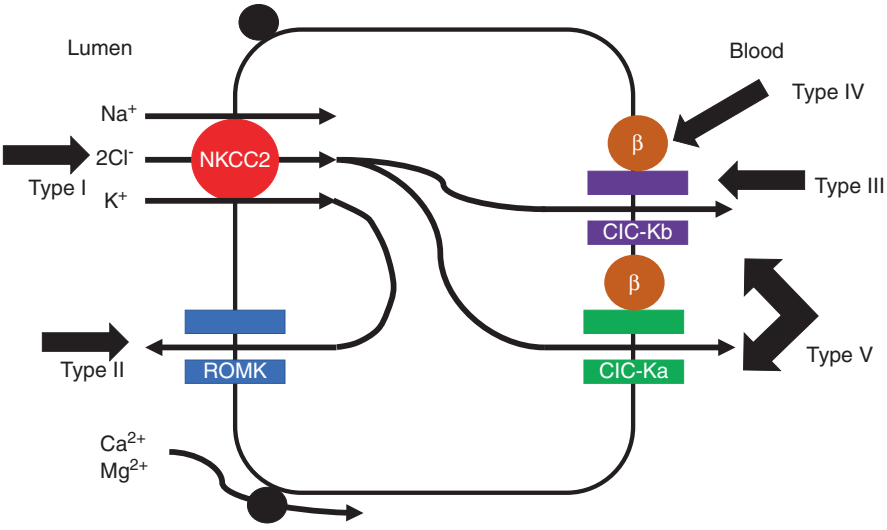

Fig. 4.1 Bartter syndrome subtypes and associated defects in ion transport within the thick ascending limb of the loop of Henle. Thin arrows demonstrate path of ions. Corresponding subtypes delineated by arrow

chronic kidney disease over time with a recent series showing 63% of patients with Bartter syndrome developing renal insufficiency [32].

Familial Hypomagnesemia with Hypercalciuria and Nephrocalcinosis

This is a rare disorder for which there are only small cohort studies available [33–35]. Mutations in the CLDN16 and CLDN19 genes, encoding claudin-16 and -19, respectively, are the most common causes of this condition and follow an autosomal recessive pattern of inheritance [36]. When mutated, these tight junction proteins prevent the normal paracellular absorption of calcium and magnesium within the thick ascending loop of Henle. In essence, the urinary profile mirrors that of loop diuretic therapy. Claudin-19 is found in the retina as well; therefore affected children may have congenital ocular disturbances [37–40]. Despite the urinary loss of magnesium, these patients tend not to manifest signs typical of profound hypomagnesemia, such as seizures [41]. Over time, hypomagnesemia may improve as a result of diminished renal function with one-third of patients progressing to chronic kidney disease by their adolescent years [41].

Distal Renal Tubular Acidosis

Inherited distal renal tubular acidosis (RTA) associated with mutations in the ATP6V1B1 and ATP6V0A4 genes may manifest with nephrocalcinosis and is inherited in an autosomal recessive fashion [42, 43]. Patients with ATP6V1B1 tend to have nephrolithiasis but both mutations result in nephrocalcinosis [44]. Both genes code for protein subunits of a vacuolar ATPase located within alpha-intercalated cells of the distal convoluted tubule [45]. With dysfunction of this proton pump, there is reduced acidification of urine and resultant acidosis. To counteract acidemia, bone is catabolized to release phosphate in order to buffer excess protons [46]. Calcium is also released at the same time, causing hypercalciuria and nephrocalcinosis [47]. In addition, the acidotic state may impair the function of calcium channels responsible for calcium reuptake in the distal tubules further adding to urine calcium loss [48]. Calcium phosphate stones tend to precipitate in the alkaline urine [49]. Extrarenally, sensorineural hearing loss may be present as the affected genes are also expressed in the inner ear [50].

On the basolateral side of the alpha-intercalated cell, there are described mutations in SLC4A1 gene that codes for the anion exchanger responsible for moving bicarbonate from the cell into the extracellular space [51]. Unlike the aforementioned genetic causes of distal RTA, defects in this gene may be inherited in either an autosomal dominant or autosomal recessive manner [49]. The inability to move bicarbonate into the body has a similar effect to not being able to secrete protons. In this case, acidosis results from not absorbing bicarbonate, which is the primary buffer in blood. The pathogenesis of stone formation then follows as previously described as a consequence of systemic metabolic acidosis. Hearing loss, however,

is not seen in these patients unlike the aforementioned mutations of ATPase [52]. Because these anion exchangers are also present on erythrocytes, peripheral blood smears may demonstrate abnormal findings such as spherocytosis [53].

Cystinuria

Cystinuria is an autosomal recessive disorder characterized by the defective resorption of the dibasic amino acids cystine, ornithine, lysine, and arginine in the proximal renal tubule and gastrointestinal tract [54]. Whereas all four amino acids can reach high urinary concentrations, precipitation of the poorly soluble cystine resulting in recurrent urolithiasis is the only phenotypic manifestation of this inborn error of metabolism [55].

Cystinuria is the cause of up to 10% of all pediatric urinary stones. While a minority of individuals with cystinuria will not develop kidney stones [56], more than half of stone formers will first experience stone formation in the first decade of life, followed by 25% to 40% of patients presenting in the second decade of life [57]. Greater disease severity has been observed in males than in females, including earlier first appearance of stones and a higher incidence of stone episodes per year [57, 58].

More than 100 mutations in each of two genes (*SLC3A1* and *SLC7A9*) encoding the renal $b^{0,+}$ amino acid transporter have been identified in cystinuria patients [59–62]. *SCL3A1* (chromosome 2p21) encodes the heavy subunit (rBAT) of the transporter and *SLC7A9* (chromosome 19q12) encodes the interacting light subunit ($b^{0,+}$AT) [54]. More than 85% of patients have detectable mutations in these genes. *SLC3A1* variants tend to follow an autosomal recessive mode of inheritance while mutations in the *SLC7A9* gene are associated with broader clinical variability, even within a single family [63] (Fig. 4.2).

Classically, cystinuria had been categorized into three subtypes based on the urinary composition of obligate heterozygotes [64]. *Type I* carriers demonstrate normal urinary cystine levels. *Types II* and *III* have elevated cystine excretion but were later condensed into *non-Type I* following new insights into the genetic and phenotypic characteristics of these individuals. More recently, the International Cystinuria

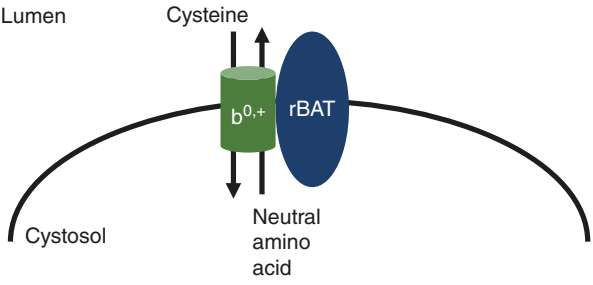

Fig. 4.2 Proximal tubule $b^{0,+}$ amino acid transporter

Consortium has promulgated a new classification based on the chromosomal location of the causative mutation. *Type A* cystinuria corresponds to the former *Type I* category of individuals with normal urinary cystine excretion and a mutation on Chromosome 2. By contrast, *Type B* mirrors *non-Type I* with a mutation on Chromosome 19. *Type AB* is reserved for cystinurics with identifiable allelic mutations to both transporter subunits [58]. To date, the clinical implications of these subtypes are not fully understood (Table 4.1).

Cystine is a dibasic amino acid with a disulfide bond that is relatively insoluble in urine at physiological pH levels. Specifically, the urine solubility of cystine is approximately 240–300 mg/L at a pH of 6.5 and increases as urine becomes more alkaline [62]. Since urine pH levels greater than 8 afford a threefold rise in cystine solubility [65], alkalinization is a mainstay therapy and treatment goal. It should be also noted that other coexisting urinary metabolic abnormalities can accompany cystinuria, including hypocitraturia, hyperoxaluria, hypercalciuria, and hyperuricosuria [55]. In a multi-institutional cohort of 125 patients, Reinstatler et al. found that nearly one-third of stone-forming cystinurics had non-cystine components in their stones, underscoring the importance of continued stone analysis to best guide treatment [66].

Primary Hyperoxaluria

The significance of oxalate as a driver of stone formulation is underscored in this rare inborn error of glyoxylate metabolism. Primary hyperoxaluria (PH) can be subdivided into three types, each of which is characterized by an autosomal recessive enzymatic defect resulting in overproduction of oxalate. The three enzymes are alanine:glyoxylate aminotransferase (AGT), glyoxylate reductase-hydropyruvate reductase (GRHPR), and 4-hydroxy-2-oxoglutarate aldolase (HOGA) corresponding to types 1, 2, and 3, respectively (Fig. 4.3). AGT, the enzyme most commonly implicated in PH, is an aminotransferase found exclusively in the liver that converts glyoxylate to glycine [68]. This reaction occurs within the peroxisome after entering the organelle as glycolate. Without this enzymatic reaction, there is an upstream accumulation of glycolate in the cytosol, which becomes susceptible to reduction

Table 4.1 Cystinuria classification

Classification[a]	Gene locus	Urinary cystine levels in heterozygotes	Former classification[b]
Type A	Chromosome 2 (SLC3A1)	Normal	Type I
Type B	Chromosome 19 (SLC7A1)	Elevated	Non-Type I (Type II and Type III)
Type AB	Chromosomes 2 and 19	Normal	

[a]International Cystinuria Consortium classification
[b]Former classification per Rosenberg et al.

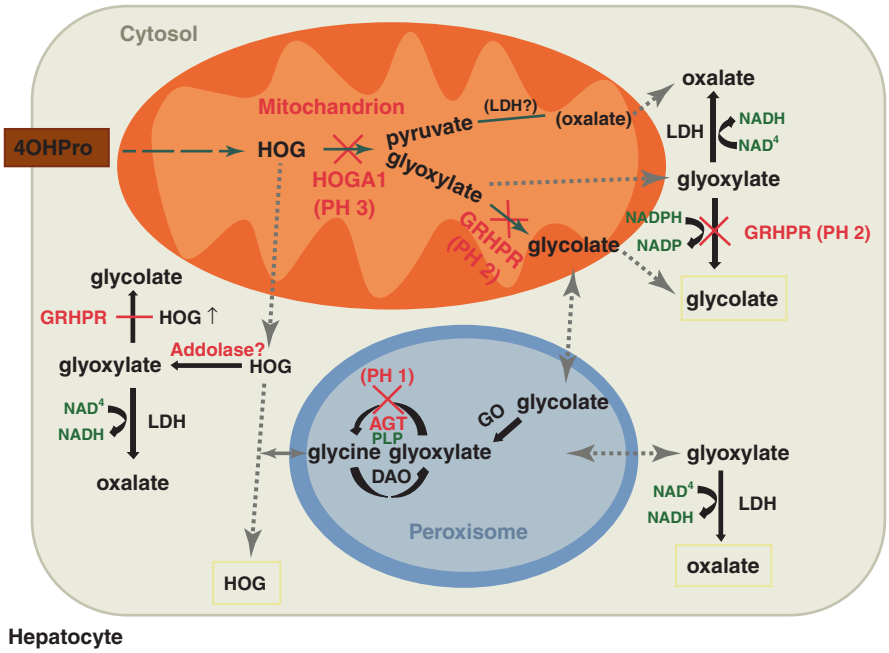

Fig. 4.3 Oxalate metabolism within the hepatocyte. Reproduced with permission from Beck and Hoppe [67]

into oxalate. This defect accounts for 70–80 percent of PH cases. The initial conversion of glyoxylate to glycolate within the cytosol requires GRHPR. In type 2 PH, when GRHPR is deficient, lactate dehydrogenase preferentially converts glyoxylate and hydroxypyruvate to oxalate and L-glycerate, instead of D-glycerate [69]. The presence of urinary L-glycerate helps to distinguish type 1 PH from type 2 PH. Type 3 PH is due to defective mitochondrial conversion of 4-hydroxy-2-oxoglutarate to glyoxylate. The exact mechanism for oxalate accumulation is not yet clear. However, one possible explanation is the mitochondrial release of 4-hydroxy-2-oxoglutarate, which is converted to oxalate via an aldolase [70]. In any event, any of these three mechanisms can result in hyperoxaluria and subsequent crystal formation. The clinical spectrum ranges from most severe with renal failure in infancy to oligosymptomatic presentation in adulthood [71]. Definitive management of PH varies by subtype and is predicated on organ transplantation. As type 1 PH is due to deficiency of a hepatic enzyme, liver transplantation is the standard curative treatment, though newer pharmacologic therapies are being developed. An important treatment consideration is combined liver and kidney transplantation, particularly in PH type 1 patients with progressive end-stage renal disease (ESRD). Treatment for type 2 PH relies on intensive medical management to reduce urinary oxalate levels but in those who progress to ESRD, renal transplantation is the recommended intervention. The role and efficacy of combined liver/kidney transplantation in these patients, however, is currently a matter of debate [72].

Purine Metabolism-Related Stones

Defects in Purine Salvage

Deficiency of hypoxanthine-guanine phosphoribosyl transferase (HGPRT) is the principal cause of Lesch-Nyhan syndrome [73]. The disease is X-linked and therefore has a predilection for males while females become carriers. This inborn error in metabolism causes accumulation of hypoxanthine, which is normally converted to inosine monophosphate. Downstream effects include decreased inhibition of the enzyme 5′-phosphoribosyl-1-pyrophosphate (PRPP) amidotransferase and increased purine synthesis precursors, all of which contribute to further accumulation of hypoxanthine (Fig. 4.4). As a result, excessive uric acid is produced, catalyzed by xanthine oxidase leading to hyperuricemia and hyperuricosuria, which may promote the development of uric acid crystals or stones within the urinary tract. In addition to urological manifestations, affected individuals may suffer from neurological deficits with self-mutilating behavior being one of the most striking features [74, 75].

A disorder closely related to Lesch-Nyhan syndrome involves defects in the enzyme adenine phosphoribosyl transferase (APRT). APRT converts adenine to adenosine monophosphate as part of the salvage pathway in purine metabolism. Accumulation of adenine will lead to increased catabolism by xanthine oxidase and the formation of insoluble 2,8-dihydroxyadenine [76]. In contrast to Lesch-Nyhan syndrome, defects in APRT have an autosomal recessive inheritance pattern and

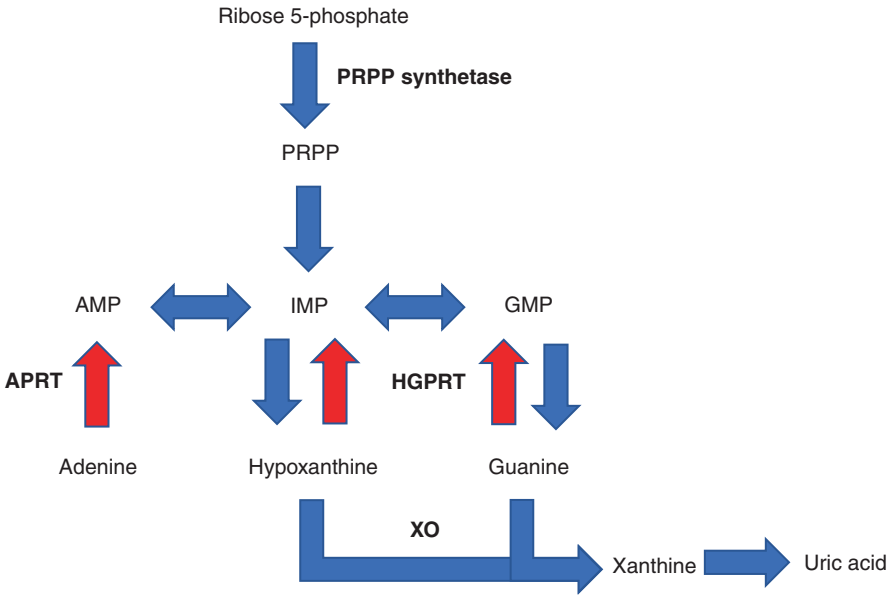

Fig. 4.4 Purine metabolism pathway

lead to the formation of 2,8-dihydroxyadenine crystals, as opposed to uric acid-based stones [77].

Phosphoribosyl Pyrophosphate Synthetase Overactivity and Overexpression

As mentioned previously, PRPP is a critical substrate in purine synthesis. Abnormally increased activity of PRPP synthetase from lack of regulation has been described [78, 79]. Additionally, overexpression of the enzyme has been also been described, which causes similar metabolic disturbances but a notable absence of neuropathy [80]. Defects are X-linked; however, females may still demonstrate hyperuricosuria but without neurologic deficits [81]. The end result of either "superactivity" or overexpression of the enzyme is increased production of xanthine and uric acid leading to hyperuricosuria and possible uric acid nephrolithiasis.

Congenital Anatomic Anomalies of the Genitourinary Tract

Ureteropelvic Junction Obstruction

Congenital obstruction of the ureteropelvic junction (UPJO) is commonly caused by intrinsic muscle deficiency or external obstruction from an aberrant lower pole renal vessel [82] (Fig. 4.5). The condition is one of the most common causes of antenatal hydronephrosis [84]. Approximately 2.1% of UPJO patients have a coincident ipsilateral stone based on a large retrospective experience [85]. One potential explanation for the relationship between UPJO and nephrolithiasis is that the blockage of urine leads to urinary stasis and concentration of solutes, thereby promoting lithogenesis. However, the work of several groups has shown that urinary stasis alone does not fully explain this relationship [85, 86]. Evaluating a cohort of patients

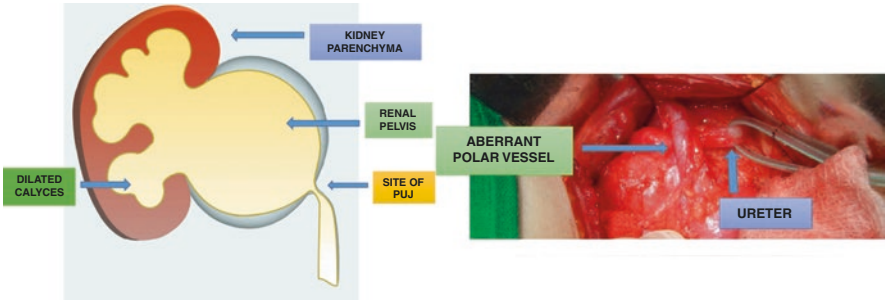

Fig. 4.5 Ureteropelvic junction obstruction due to intrinsic stenosis *(left)* and crossing vessel *(right)*. Reproduced with permission from Al-Salem [83]

less than 17 years with UPJO and a coincident ipsilateral kidney stone who underwent pyeloplasty, Husmann and colleagues found that 68% of patients had stone recurrence despite adequate repair [85]. Moreover, of patients who had non-struvite stones, 68% demonstrated an identifiable metabolic anomaly, most commonly hypercalciuria [85]. The most common stone identified was calcium oxalate followed by calcium phosphate. Therefore, the pathophysiology of stone formation in the setting of UPJO is likely multifactorial, mediated by urinary stasis and compounded by underlying urinary metabolic derangement.

Horseshoe Kidney

The most common fusion anomaly of the kidney arises when there is abnormal medial fusion of the lower pole creating a characteristic horseshoe shape [87]. Based on a large systematic review, the incidence of stones in the pediatric population with a horseshoe kidney is 3% [88]. Besides being malrotated relative to the normal kidney position and having variant blood supply, the ureter inserts relatively high on the renal pelvis which may lead to obstruction [89, 90] (Fig. 4.6). The abnormally placed ureter will hinder adequate drainage of the kidney resulting in urinary stasis. This mechanical factor is also compounded by a lithogenic urinary profile, as demonstrated by Raj et al. [91]. All patients in their cohort had at least one identifiable abnormal urinary parameter on 24-hour urinalysis with hypercalciuria being the most common derangement. Calcium oxalate is the predominant stone formed [88].

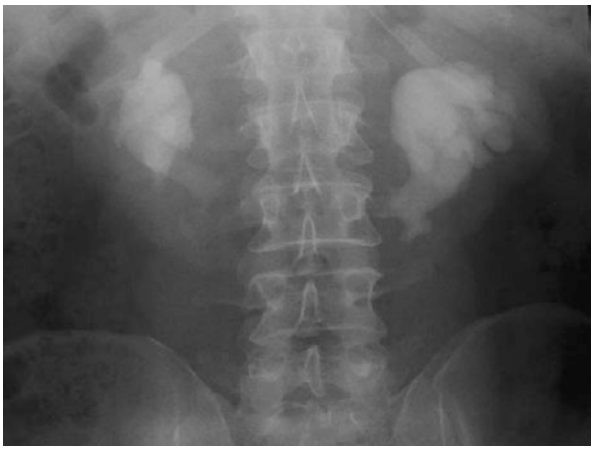

Fig. 4.6 Horseshoe kidney with high inserting ureters. Reproduced with permission from [89]

Calyceal Diverticulum

A calyceal diverticulum is a small, nonsecretory, outpouching of the collecting system [92]. Stone formation has been postulated to be secondary to urinary stasis since urine passively drains into the diverticulum via a narrow infundibulum (Fig. 4.7). Similar to the aforementioned congenital anomalies, poor drainage is only one feature of the pathophysiology. Several studies support the belief that urinary parameters promoting crystallization are also at play [94, 95]. Relative to controls, Matlaga et al. demonstrated that patients with calyceal diverticular stones have higher urinary calcium concentration and calcium oxalate supersaturation [95]. Work by Auge and colleagues found that calyceal stone formers have urinary profiles similar to those of a control cohort of stone formers [94]. Notably, these studies were performed in adults as the relevant literature is lacking in the pediatric population.

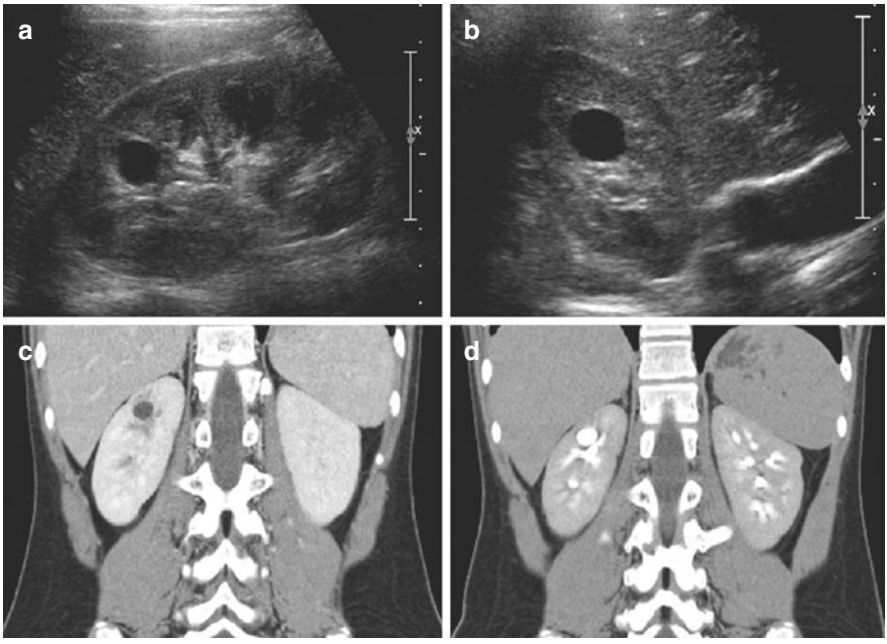

Fig. 4.7 Calyceal diverticulum visualized on ultrasound—longitudinal (**a**) and transverse (**b**)—and CT scan with contrast—nephrogram (**c**) and excretory phase (**d**). Reproduced with permission from Lee [93]

Malabsorptive Disturbances of the Gastrointestinal Tract

Cystic Fibrosis

The most common lethal genetic disease in North America is due to a mutation involving the cystic fibrosis transmembrane conductance regulator (CFTR) protein (2017). The mutation leads to a myriad of complications influencing the pulmonary, gastrointestinal, and genitourinary systems [96]. Detailed pathophysiology of the faulty receptor is beyond the scope of this chapter; however, careful consideration of the effects to the gastrointestinal tract deserves attention. Risk of nephrolithiasis is well recognized in this clinical entity with dysfunction in the gut being a main contributor [97–99]. These patients are plagued by fat malabsorption which has been well recognized [100]. The production of thick mucus causes obstruction of the exocrine pancreas eventually leading to pancreatic insufficiency from repeated episodes of pancreatitis [96]. The lack of enzymes necessary for digestion, particularly lipase, results in these patients experiencing steatorrhea [101]. The high amounts of fat saponify, thus decreasing the amount of bound oxalate as calcium participates in saponification. Furthermore, malabsorbed bile salts can increase permeability to oxalate in the colon further increasing oxalate absorption [97].

Another mechanism that may contribute to urolithiasis in cystic fibrosis patients is from disturbance of gut flora, namely reduction of *Oxalobacter formigenes* [102]. This bacterium degrades oxalate and has been implicated in hyperoxaluria [103]. Cystic fibrosis patients commonly take antibiotics thus disturbing the natural microbiota. Reduction of this helpful commensal organism has been documented to be associated with hyperoxaluria in sufferers of cystic fibrosis [98, 102]. In addition to hyperoxaluria, these patients also demonstrate hypocitraturia, which favors stone formation from diminished inhibition from urine citrate, and hypercalciuria [97, 104–106].

Short Gut Syndrome and Inflammatory Bowel Disease

Extensive resection of the intestinal tract may be required for the management of a variety of maladies afflicting the pediatric population, such as necrotizing enterocolitis, midgut volvulus, and intestinal atresia, among others [107]. Short gut syndrome is a significant potential sequela of extensive resection and the most common form of intestinal failure in the pediatric population [108]. Reduced functional intestine leads to wide-ranging complications that are outside the purview of this chapter. Importantly, malabsorption may result in enteric hyperoxaluria and a predisposition to nephrolithiasis [109, 110]. Specifically, unabsorbed fatty acids present in the gut are free to bind to calcium ions leaving unbound oxalate available to be absorbed. Excessive absorption of free oxalate eventually leads to hyperoxaluria. Chronic dehydration from malabsorption and diarrhea may further promote stone

formation in these patients as low urine volumes are a well-described risk factor. Patients can also develop hypocitraturia [111]. The underlying mechanism may be related to abnormal gut bacteria causing increased catabolism of citrate in the gut, thus diminishing reabsorption in the body. Additionally, underlying metabolic acidosis is common in these patients which decreases citrate excretion in the kidney [110, 111].

Similar to patients with short gut syndrome and malabsorptive disorders, patients with inflammatory bowel disease (IBD) are at increased risk for developing kidney stones. However, this is quite rare in the pediatric population with an incidence of 1.2% and 0.9% for Crohn's and ulcerative colitis, respectively, according to a large public database of inpatient pediatric admissions [112]. Many of the underlying reasons for stone formation are similar to those for short gut syndrome with malabsorption—steatorrhea, dehydration, and chronic acidosis [113]. Review of a large IBD registry also identified additional risk factors for lithogenesis, including low physical activity, higher disease activity, and prior history of intestinal surgery [114]. When stratified by disease type, colostomy for Crohn's disease appeared to be a significant risk factor while there was no association between prior intestinal surgery and nephrolithiasis in ulcerative colitis patients.

Acquired Metabolic Disturbances

Large-scale epidemiologic studies of adult patients have demonstrated an association between urolithiasis and lifestyle-related diseases, including hypertension [115, 116], diabetes mellitus (DM) [117], and obesity [118]. This is likely explained by disease-driven changes in the urinary milieu that promote the development of stones [118, 119]. By contrast, these diseases in childhood are likely different entities with different etiologies as compared to those in adults. As such, the potential relationships to stone disease in children stand to be quite different.

Hypertension

Although an independent association between hypertension and kidney stone disease has been shown in adults, there is limited information on this relationship in the pediatric population as children with hypertension likely represent a very small subset of those with urolithiasis [115, 116, 120, 121]. Reviewing the pooled data of over six million children in the Kids' Inpatient Database (KID), Schaeffer et al. found a significantly increased risk of kidney stone diagnosis in children with hypertension [122]. However, this relationship was only statistically significant for young children 10 years of age or younger. The authors also found a positive association between systolic blood pressure and 24-hour urine sodium, oxalate/1.73 m^2, and uric acid [123]. The lone other study to investigate hypertension and risk of

stones in children reported significantly greater blood pressures in stone formers than in non-stone formers [124]. However, Nikolis et al. failed to find that hypertension was an independent risk factor for recurrent stones in nonobese (adult) stone formers.

Similar to Schaeffer et al., the authors found blood pressure was associated with increased 24-hour urine sodium, oxalate, and uric acid excretion. Whereas hypercalciuria and increased dietary sodium intake are known risk factors for the development of kidney stones in adults [125], Nikolis et al. did not observe an association between blood pressure and urinary calcium. Unfortunately, this study was limited by small numbers of hypertensive patients, failure to distinguish between first-time and recurrent stone formers, and use of unhealthy controls as the comparator non-stone former group (2017).

Diabetes Mellitus

In adults with non-insulin-dependent (Type II) diabetes mellitus (DM), insulin resistance has been implicated as a major driver of the observed increased risk for kidney stones [126]. Specifically, DM impairs ammoniagenesis within the renal proximal tubules reducing urinary pH and promoting uric acid crystallization [127, 128]. Insulin resistance may also contribute to calcium stone formation by inducing hypocitraturia [129].

Despite a strong association between DM and urolithiasis in adults [117], this has not been reliably demonstrated in the limited pediatric literature [123, 130, 131]. Relying on a national dataset of pediatric inpatient admissions, Schaeffer et al. reported a significant association between urolithiasis and DM, though only in patients 5 years of age or younger [123]. Of note, the study did not specify the subtype of diabetes and the findings were based solely on inpatient admissions, which may represent a selected, sicker subset of patients. For example, Agrawal et al. reported a series of three children who developed urolithiasis in the setting of diabetic ketoacidosis (DKA), representing just 0.8% of all DKA cases at a single institution over a 7-year interval [131]. The authors proposed hypercalciuria due to dehydration, metabolic acidosis, and hyperglycemia with resultant glucosuria as a potential mechanism for stone formation.

Building on the work of Schaeffer et al., Kokorowski and colleagues performed a longitudinal epidemiological study of both outpatient and inpatient pediatric encounters [130]. Interestingly, the authors found an inverse relationship between insulin-dependent (Type I) DM and kidney stones while no association was observed for type II DM. Type I DM is unrelated to insulin resistance, which drives the lithogenic urinary changes that promote stone formation in adults with type II DM. Moreover, this inverse association was only significant among inpatients suggesting that other biological factors, necessitating inpatient admission, may be responsible or involved. Based on the few available studies, there is currently no

conclusive evidence that neither type 1 nor type 2 diabetes poses an increased risk of nephrolithiasis in children.

Obesity

When considering comorbid conditions that may be risk factors for the development of pediatric nephrolithiasis, it is logical to consider obesity given the parallel rise in incidence for the two conditions. In adults, several studies have shown that obesity is associated with a higher risk of developing kidney stones though others have failed to demonstrate a clear link [118, 127, 132–134]. The putative mechanism for obesity increasing stone risk is related to higher excretion of lithogenic solutes, notably uric acid, and lower urinary pH [133, 135]. With increasing obesity, urinary pH decreases and the risk of uric acid crystallization rises. Consequently, uric acid crystals in the urine may promote calcium oxalate stone formation by heterogeneous nucleation [133].

In the pediatric population, the relationship between urolithiasis risk and obesity is less clear and under-investigated. From an epidemiological perspective, there was no significant change in rates of childhood obesity or overweightness despite a significant rise in pediatric urolithiasis between 1999 and 2004 [136]. In a single-institution retrospective review of pediatric stone formers, Kieran et al. found that low body mass index (BMI) was significantly associated with earlier age of urolithiasis presentation [137]. Another review of children with recurrent stone disease stratified by BMI, De Ruysscher et al. found that a BMI >85th percentile was associated with a 15-fold lower risk of stone recurrence, in contradistinction to the relationship observed in adult stone formers [138]. This finding may be explained by differences in the metabolic profiles of pediatric stone formers compared to adults. Stone-promoting urinary abnormalities such as higher excretion of uric acid, oxalate, and citrate in combination with lower pH has a well-established association with obesity [133, 139]. In overweight pediatric stone formers, Sarica et al. reported increased oxalate excretion and hypocitraturia, findings that mirror the urinary profile of overweight adults [140]. Two other studies also found significantly higher rates of hypocitraturia in obese children with recurrent stones [141, 142]. In contrast to Sarica et al., two other studies reported elevated BMI to be associated with decreased oxalate excretion in children with stones [139, 143]. Furthermore, Murphy et al. did not observe any significant differences in urinary sodium or uric acid [139] and the several studies did not observe an association between BMI and urine pH, as described in adults [139, 142]. Collectively, these findings underscore the difficulty in assessing stone risk in children and other populations with highly variable metabolic profiles.

The aforementioned studies are heterogeneous in terms of definition of obesity, primary versus recurrent stone disease, mean patient age, and definitions for urinary parameters thus should be interpreted with caution. Taken together, there is currently a lack of strong evidence to establish a link between obesity and increased

stone risk in pediatric patients. Given the rising incidence of both urolithiasis and obesity in the pediatric population, further investigation is nevertheless warranted.

Medications Associated with Lithogenesis in Children

Medication-Inducing Nephrolithiasis

Loop Diuretics

The use of loop diuretics, including furosemide, torsemide, and bumetanide, is common in the pediatric population for the management of fluid overload from a variety of disorders [144]. Nephrocalcinosis is a known complication of loop diuretics in neonates, particularly in premature infants [145–148]. This relationship between renal calcifications and furosemide use in preterm infants was first described in 1982 based on the observation of ten infants who developed varying degrees of nephrolithiasis after receiving high-dose furosemide therapy (≥2 mg/kg) for at least 12 days [146]. The mechanism of calcium salt crystallization and aggregation within the renal tubules is multifactorial in nature, though believed to be largely driven by medication-induced hypercalciuria. This effect is mediated by the inhibition of sodium and calcium resorption in the thick ascending limb of the loop of Henle [146, 148]. The reduced glomerular filtration rate and immature hepatic function of the neonate significantly prolong the drug's half-life, which further enhances the hypercalciuric effect [147]. At the same time, risk of stone formation is promoted by renal tubular immaturity [149]. In very low birth weight (<1500 g) infants, stone formation may also be exacerbated by reduced urinary citrate excretion as a result of metabolic acidosis [150]. The calculi isolated from these patients are generally composed of calcium oxalate and/or calcium phosphate stones [145, 146, 148].

Carbonic Anhydrase Inhibitors

In general, there is a relative scarcity of data on the effects of other classes of diuretics in the pediatric population. Carbonic anhydrase inhibitors (CAI), such as acetazolamide and dorzolamide, are commonly used as adjunct therapies in a variety of pediatric conditions [148, 151]. They act by blocking the resorption of bicarbonate in the proximal tubule leading to a hyperchloremic acidosis, which potentiates the formation of calcium-based stones by urinary alkalinization and reduction of both urinary citrate and magnesium [152]. In one series of premature infants treated with concurrent furosemide and acetazolamide for post-hemorrhagic hydrocephalus, there was an observed increased risk of nephrocalcinosis and/or nephrolithiasis, which improved after discontinuing treatment [148]. A case report from Carlsen et al. described the development of kidney stones in a 17-year-old adolescent

following 2 years of dorzolamide therapy for perifoveal edema due to retinitis pigmentosa [153].

Topiramate

Topiramate is an anti-epileptic medication with a variety of clinical applications owing to its broad spectrum of pharmacological properties, including modulation of voltage-dependent sodium channels and potentiation of γ-aminobutyric acid (GABA)-mediated neurotransmission, among others [154]. As it pertains to nephrolithiasis, topiramate functions as a weak CAI. Prevention of stones is best accomplished with hydration, limited sodium intake, and citrate supplementation [155].

Zonisamide

Zonisamide is a sulfonamide-based anti-epileptic that may be mediated by blocking voltage-dependent sodium and T-type calcium channels. Like topiramate, it exerts a weak carbonic anhydrase activity despite being 100 times less potent than acetazolamide [156, 157]. Zonisamide is strongly associated with the development of urolithiasis in children [156, 158]. Though not well documented, these stones are reportedly composed of calcium oxalate and calcium phosphate [156].

Allopurinol

Allopurinol is a xanthine oxidase inhibitor that can be used in children to prevent tumor lysis syndrome prior to induction chemotherapy and to control the hyperuricemia of Lesch-Nyhan Syndrome [159, 160]. The medication reduces serum and urinary uric acid levels by blocking the conversion of xanthine to uric acid. As a result, excessive buildup of the poorly soluble xanthine in the urine (xanthinuria) can precipitate out of solution and form calculi [159]. Similar to uric acid urolithiasis, these stones are classically radioopaque and occur more frequently in the upper urinary tract [161]. Numerous cases of allopurinol-induced xanthine stones have been reported [159–162]. Prevention and treatment hinge on aggressive hydration, dose titration, and measured urinary alkalinization taking care not to excessively elevate urine pH >7, which can promote calcium phosphate stone formation [161].

Vitamins (Hypervitaminosis and Vitamin Intoxication)

Ingested vitamin C is converted, in part, into oxalate and subsequently excreted in the urine. As a result, excessive intake of supplemental vitamin C can potentially increase the risk of forming calcium oxalate stones [163, 164]. There is one reported case of a nine-year-old boy who presented with an obstructing calcium oxalate

ureteral stone and extreme hyperoxaluria (278 mg/24 h) due to vitamin C intoxication [165]. The boy had neither history of primary hyperoxaluria, enteric diseases, surgeries, nor prior stones, but had been given vitamin C supplements since the age of three. After prohibiting supplementation for 3 months, he had return of normal urinary oxalate levels with maintenance of normal oxalate excretion and no new renal stones after 3 years.

Conti et al. reported on two brothers aged 15 and 12 years, respectively, with severe hypercalcemia in the setting of vitamin D intoxication (>150 ng/mL). While the older brother was asymptomatic, the younger presented with severe abdominal pain, constipation, vomiting, renal failure, and nephrolithiasis [166]. The formation of kidney stones in hypervitaminosis D is driven by hypercalcemia, which leads to excessive excretion of calcium in the urine. Mainstays of treatment include cessation of supplements and aggressive hydration with diuretics, corticosteroids, and potassium citrate administration serving as optional adjuncts depending on severity [166, 167]. Despite the rarity of vitamin intoxication, the astute clinician should counsel family members nutritional supplements are neither completely benign nor absolutely needed in the setting of a healthy diet.

Medication-Containing Nephrolithiasis

Triamterene

Triamterene is a potassium-sparing diuretic that functions by inhibiting the resorption of sodium ions in exchange for potassium and hydrogen ions at the distal tubule. In adults, nephrolithiasis is a known potential effect of triamterene. This occurs by precipitation of the medication and its metabolites due to its high excretion and poor solubility in urine [168]. In the pediatric population, this medication may be used as an off-label treatment for hypertension. To date, there has been one reported case of triamterene stones in an adolescent [169].

Indinavir

Indinavir is a protease inhibitor commonly used in the management of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) in both adults and children. Due to its relatively poor solubility at pH >5, indinavir stones can form by precipitation and crystallization of the medication in urine [170]. While the literature has reported up to 40% of adults on prolonged therapy can harbor indinavir stones [171], owing to the rarity of HIV/AIDS in the pediatric population, indinavir stones are not well described in children but still represent a potential side effect of treatment [170–172]. These stones are characteristically radiolucent on plain X-ray. Management should focus on hydration and discontinuation/

replacement of the drug while attempting to avoid surgical intervention in this immunocompromised population [170].

Sulfonamides

Sulfonamides are poorly soluble compounds that can precipitate into crystalline aggregates in the urine. Of the sulfonamides, sulfadiazine and its acetyl derivative have particularly low urine solubility [155]. Although the phenomenon of sulfonamide-induced urolithiasis and crystalluria has been well documented in the adult literature, its known occurrence is quite rare in children [173–178]. Of note, patients with crystalluria had sulfonamide crystals and patients with observable calculi featured a sulfonamide component on stone analysis. Collectively, these findings support the lithogenic effect of these medications [175, 178]. The relative rarity of sulfonamide-associated calculi, however, highlights the obscure interplay between stone promoters and inhibitors in this stone-forming process, as opposed to supersaturation of the compound alone [173]. Management of these radiolucent stones should focus on hydration, urine alkalinization to a pH >7.5, and discontinuation of the inciting medication [155].

Ceftriaxone

Ceftriaxone is a commonly used medication in children because of its favorable safety profile, long plasma half-life, and broad spectrum of antibacterial activity. Similar to other beta-lactam inhibitors, this third-generation cephalosporin functions by inhibiting bacterial cell wall synthesis [179]. Up to two-thirds of ceftriaxone is excreted in the urine, with the remainder excreted in its unmetabolized form in the bile [180]. The drug is capable of forming an insoluble salt with calcium, which can precipitate out of solution upon exceeding its maximum solubility—both in the urinary and biliary systems [181]. Numerous cases of ceftriaxone-associated urolithiasis, crystalluria, and hypercalciuria in the pediatric population have been reported [180–185]. However, the relationship between ceftriaxone and urolithiasis and/or crystalluria has not been conclusively established, nor has the mechanism by which lithogenesis occurs. Kimata et al. suggested increased urinary calcium excretion as a possible contributor to stone formation in these patients [181]. On the contrary, Avci et al. failed to observe any change in urinary calcium levels in children treated with the medication [186].

When identified, these stones are typically radiolucent, which depends largely on the relative amount of calcium in their composition. They are characteristically small, sand-like, and detected incidentally on ultrasound [187]. Potential risk factors for ceftriaxone-induced urolithiasis have been previously described, including a family history of kidney stones, dehydration, high dosage (>100 mg/kg/day), and rapid infusion (<30 min) [182].

Other Medications Associated with Nephrolithiasis

Silica

Silica is a ubiquitously distributed element found in vegetables, whole grains, and drinking water, among other dietary sources. It is commonly used as a milk thickener (Gelopectose, containing 5.5% colloidal silicate) for children with gastrointestinal reflux, as well as in non-prescription antacids [188]. Though easily excreted in the urine, reported cases of silica stones in adults have demonstrated an association between excessive magnesium trisilicate antacid consumption and stone formation [189]. In a case report of a 6-month-old boy on silicate-containing milk thickener, bilateral nephrocalcinosis and nephrolithiasis were detected on ultrasound after the child presented with painful episodes of hematuria. Stone analysis demonstrated silica as the major component suggesting silica absorption as the possible etiology. Further, the calcifications were completely reversed after switching to silicate-free thickener [188]. By comparison, Taşdemir et al. reported three cases of silicate calculi in children without prior silicate intake or any urinary metabolic abnormalities, calling the previously suggested pathophysiology into question [190].

Felbamate

Felbamate is a lipophilic, anti-epileptic medication characterized by poor solubility in water. To date, only three reports describe a potential relationship between this medication and urolithiasis in children. Stone analyses from these patients revealed felbamate and its metabolites as the predominant constituents [191–193]. They have been described as radiolucent unless integrated with calcium salts. While the pathophysiology of urolithiasis remains unclear, high dosages, renal dysfunction, and risk factors for other stone types have been suggested as potential contributory factors [193].

Other Antibacterial Medications

Though still an area of active investigation, exposure to oral antibiotics in children may be an important determinant of kidney stone disease. Tasian et al. previously demonstrated increased odds of developing urolithiasis following childhood antibiotic use: an association that persisted for up to 5 years after index exposure. These included sulfonamides, cephalosporins, fluoroquinolones, and broad-spectrum penicillins [194]. Moreover, the magnitude of association was greatest for exposures at younger ages. Potential mechanisms include alteration of macronutrient metabolism as a result of changes in the intestinal microbiome and selection for stone-promoting bacteria in the urinary microbiome [195, 196]. Given the concerns surrounding long-term antibiotic administration for a variety of childhood

conditions and their consequent influences on the intestinal microbiome, the majority of research in this space has focused on *Oxalobacter formigenes* [197, 198]. However, the influence of antibiotic-induced depletion of intestinal *O. formigenes* on stone disease is still an area of evolving investigation.

Hematology and Oncology

Though rare, urolithiasis is a known adverse effect of acute lymphoblastic leukemia (ALL) treatment, particularly with multiagent chemotherapy. Risk factors for stone formation include a family history of urolithiasis, immobilization, and glucocorticoid therapy [199, 200]. In the largest known cases series, from St. Jude Children's Research Hospital, glucocorticoid use was associated with a 45- and 22-fold increased risk of urolithiasis when administered during induction and continuation therapy, respectively. Of the minority with stones available for analysis, all were composed of calcium suggesting hypercalciuria in the setting of treatment-related bone demineralization as the cause 199]. Additionally, these children have a heightened risk of developing xanthine stones as xanthine oxidase therapy is routinely used to prevent excessive uric acid in the blood and urine [160, 161].

Conclusions

The etiology of pediatric nephrolithiasis is not always identified, but many children who present with stone disease have a recognizable systemic or localized disorder that increases their risk of developing kidney stones. This is a broad spectrum of diseases spanning genetic disorders with or without extra-renal manifestations, diseases not typically associated with kidney disease, congenital anatomic abnormalities, or medications themselves used to treat a myriad of conditions. Better understanding these associations, both for an individual patient as well as on a population level, will ultimately lead to targeted and effective therapy to decrease the burden of kidney stone disease.

References

1. Albright F, Henneman P, Benedict PH, Forbes AP. Idiopathic hypercalciuria: a preliminary report. Proc R Soc Med. 1953;46(12):1077–81.
2. Spivacow FR, Del Valle EE, Boailchuk JA, Sandoval Díaz G, Rodríguez Ugarte V, Arreaga ÁZ. Metabolic risk factors in children with kidney stone disease: an update. Pediatr Nephrol Berl Ger. 2020;
3. Coe FL, Parks JH, Moore ES. Familial Idiopathic Hypercalciuria. N Engl J Med. 1979;300(7):337–40.

4. Gambaro G, Vezzoli G, Casari G, Rampoldi L, D'Angelo A, Borghi L. Genetics of hypercalciuria and calcium nephrolithiasis: from the rare monogenic to the common polygenic forms. Am J Kidney Dis. 2004;44(6):963–86.
5. Vezzoli G, Soldati L, Gambaro G. Update on primary hypercalciuria from a genetic perspective. J Urol. 2008;179(5):1676–82.
6. Bronner F, Pansu D. Nutritional aspects of calcium absorption. J Nutr. 1999;129(1):9–12.
7. Pak CYC, Kaplan R, Bone H, Townsend J, Waters O. A simple test for the diagnosis of absorptive, resorptive and renal hypercalciurias. N Engl J Med. 1975;292(10):497–500.
8. Vella M, Karydi M, Coraci G, Oriti R, Melloni D. Pathophysiology and clinical aspects of urinary lithiasis. Urol Int. 2007;79(Suppl 1):26–31.
9. Frick KK, Bushinsky DA. Molecular mechanisms of primary hypercalciuria. J Am Soc Nephrol JASN. 2003;14(4):1082–95.
10. Norman AW. Vitamin D metabolism and calcium absorption. Am J Med. 1979;67(6):989–98.
11. Coe FL, Worcester EM, Evan AP. Idiopathic hypercalciuria and formation of calcium renal stones. Nat Rev Nephrol. 2016;12(9):519–33.
12. Favus MJ, Karnauskas AJ, Parks JH, Coe FL. Peripheral blood monocyte vitamin D receptor levels are elevated in patients with idiopathic hypercalciuria. J Clin Endocrinol Metab. 2004;89(10):4937–43.
13. Blaine J, Chonchol M, Levi M. Renal control of calcium, phosphate, and magnesium homeostasis. Clin J Am Soc Nephrol CJASN. 2015;10(7):1257–72.
14. Bergsland KJ, Coe FL, Gillen DL, Worcester EM. A test of the hypothesis that the collecting duct calcium-sensing receptor limits rise of urine calcium molarity in hypercalciuric calcium kidney stone formers. Am J Physiol Renal Physiol. 2009;297(4):F1017–23.
15. Worcester EM, Coe FL, Evan AP, Bergsland KJ, Parks JH, Willis LR, et al. Evidence for increased postprandial distal nephron calcium delivery in hypercalciuric stone-forming patients. Am J Physiol Renal Physiol. 2008;295(5):F1286–94.
16. Tsuruoka S, Bushinsky DA, Schwartz GJ. Defective renal calcium reabsorption in genetic hypercalciuric rats. Kidney Int. 1997;51(5):1540–7.
17. Zerwekh JE. Bone disease and hypercalciuria in children. Pediatr Nephrol Berl Ger. 2010;25(3):395–401.
18. García-Nieto V, Ferrández C, Monge M, de Sequera M, Rodrigo MD. Bone mineral density in pediatric patients with idiopathic hypercalciuria. Pediatr Nephrol Berl Ger. 1997;11(5):578–83.
19. Pavlou M, Giapros V, Challa A, Chaliasos N, Siomou E. Does idiopathic hypercalciuria affect bone metabolism during childhood? A prospective case-control study. Pediatr Nephrol. 2018;33(12):2321–8.
20. Pacifici R, Rothstein M, Rifas L, Lau KH, Baylink DJ, Avioli LV, et al. Increased monocyte interleukin-1 activity and decreased vertebral bone density in patients with fasting idiopathic hypercalciuria. J Clin Endocrinol Metab. 1990;71(1):138–45.
21. Weisinger JR, Alonzo E, Bellorín-Font E, Blasini AM, Rodriguez MA, Paz-Martínez V, et al. Possible role of cytokines on the bone mineral loss in idiopathic hypercalciuria. Kidney Int. 1996;49(1):244–50.
22. Dent CE, Friedman M. Hypercalcuric rickets associated with renal tubular damage. Arch Dis Child. 1964;39:240–9.
23. Wrong OM, Norden AG, Feest TG. Dent's disease; a familial proximal renal tubular syndrome with low-molecular-weight proteinuria, hypercalciuria, nephrocalcinosis, metabolic bone disease, progressive renal failure and a marked male predominance. QJM Mon J Assoc Physicians. 1994;87(8):473–93.
24. Devuyst O, Thakker RV. Dent's disease. Orphanet J Rare Dis. 2010;5:28.
25. Novarino G, Weinert S, Rickheit G, Jentsch TJ. Endosomal chloride-proton exchange rather than chloride conductance is crucial for renal endocytosis. Science. 2010;328(5984):1398–401.
26. Claverie-Martín F, Ramos-Trujillo E, García-Nieto V. Dent's disease: clinical features and molecular basis. Pediatr Nephrol. 2011;26(5):693–704.

27. Günther W, Piwon N, Jentsch TJ. The ClC-5 chloride channel knock-out mouse—an animal model for Dent's disease. Pflüg Arch Eur J Physiol. 2003;445(4):456–62.
28. Silva IV, Cebotaru V, Wang H, Wang X-T, Wang SS, Guo G, et al. The ClC-5 knockout mouse model of Dent's disease has renal hypercalciuria and increased bone turnover. J Bone Miner Res. 2003;18(4):615–23.
29. Koulouridis E, Koulouridis I. Molecular pathophysiology of Bartter's and Gitelman's syndromes. World J Pediatr. 2015;11(2):113–25.
30. Fulchiero R, Seo-Mayer P. Bartter syndrome and Gitelman syndrome. Pediatr Clin N Am. 2019;66(1):121–34.
31. Stechman MJ, Loh NY, Thakker RV. Genetics of hypercalciuric nephrolithiasis: renal stone disease. Ann N Y Acad Sci. 2007;1116(1):461–84.
32. Walsh PR, Tse Y, Ashton E, Iancu D, Jenkins L, Bienias M, Kleta R, Van't Hoff W, Bockenhauer D. Clinical and diagnostic features of Bartter and Gitelman syndromes. Clin Kidney J. 2018;11(3):302–9.
33. Godron A, Harambat J, Boccio V, Mensire A, May A, Rigothier C, et al. Familial hypomagnesemia with hypercalciuria and nephrocalcinosis: phenotype-genotype correlation and outcome in 32 patients with CLDN16 or CLDN19 mutations. Clin J Am Soc Nephrol CJASN. 2012;7(5):801–9.
34. Sikora P, Zaniew M, Haisch L, Pulcer B, Szczepańska M, Moczulska A, et al. Retrospective cohort study of familial hypomagnesaemia with hypercalciuria and nephrocalcinosis due to CLDN16 mutations. Nephrol Dial Transplant. 2015;30(4):636–44.
35. Weber S, Schneider L, Peters M, Misselwitz J, Rönnefarth G, Böswald M, et al. Novel paracellin-1 mutations in 25 families with familial hypomagnesemia with hypercalciuria and nephrocalcinosis. J Am Soc Nephrol JASN. 2001;12(9):1872–81.
36. Viering DHHM, de Baaij JHF, Walsh SB, Kleta R, Bockenhauer D. Genetic causes of hypomagnesemia, a clinical overview. Pediatr Nephrol Berl Ger. 2017;32(7):1123–35.
37. Faguer S, Chauveau D, Cintas P, Tack I, Cointault O, Rostaing L, et al. Renal, ocular, and neuromuscular involvements in patients with CLDN19 mutations. Clin J Am Soc Nephrol CJASN. 2011;6(2):355–60.
38. Konrad M, Schaller A, Seelow D, Pandey AV, Waldegger S, Lesslauer A, et al. Mutations in the tight-junction gene claudin 19 (CLDN19) are associated with renal magnesium wasting, renal failure, and severe ocular involvement. Am J Hum Genet. 2006;79(5):949–57.
39. Naeem M, Hussain S, Akhtar N. Mutation in the tight-junction gene claudin 19 (CLDN19) and familial hypomagnesemia, hypercalciuria, nephrocalcinosis (FHHNC) and severe ocular disease. Am J Nephrol. 2011;34(3):241–8.
40. Sharma S, Place E, Lord K, Leroy BP, Falk MJ, Pradhan M. Claudin 19-based familial hypomagnesemia with hypercalciuria and nephrocalcinosis in a sibling pair. Clin Nephrol. 2016;85(6):346–52.
41. Claverie-Martin F. Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis: clinical and molecular characteristics. Clin Kidney J. 2015;8(6):656–64.
42. Karet FE, Finberg KE, Nayir A, Bakkaloglu A, Ozen S, Hulton SA, et al. Localization of a gene for autosomal recessive distal renal tubular acidosis with normal hearing (rdRTA2) to 7q33-34. Am J Hum Genet. 1999;65(6):1656–65.
43. Ruf R, Rensing C, Topaloglu R, Guay-Woodford L, Klein C, Vollmer M, et al. Confirmation of the ATP6B1 gene as responsible for distal renal tubular acidosis. Pediatr Nephrol. 2003;18(2):105–9.
44. Alexander RT, Cordat E, Chambrey R, Dimke H, Eladari D. Acidosis and urinary calcium excretion: insights from genetic disorders. J Am Soc Nephrol JASN. 2016;27(12):3511–20.
45. Alper SL, Natale J, Gluck S, Lodish HF, Brown D. Subtypes of intercalated cells in rat kidney collecting duct defined by antibodies against erythroid band 3 and renal vacuolar H+-ATPase. Proc Natl Acad Sci. 1989;86(14):5429–33.
46. Soares SBM, de Menezes Silva LAW, de Carvalho Mrad FC, Simões e Silva AC. Distal renal tubular acidosis: genetic causes and management. World J Pediatr. 2019;15(5):422–31.

47. Besouw MTP, Bienias M, Walsh P, Kleta R, van't Hoff WG, Ashton E, et al. Clinical and molecular aspects of distal renal tubular acidosis in children. Pediatr Nephrol. 2017;32(6):987–96.
48. Nijenhuis T, Renkema KY, Hoenderop JGJ, Bindels RJM. Acid-base status determines the renal expression of Ca2+ and Mg2+ transport proteins. J Am Soc Nephrol JASN. 2006;17(3):617–26.
49. Watanabe T. Improving outcomes for patients with distal renal tubular acidosis: recent advances and challenges ahead. Pediatr Health Med Ther. 2018;9:181–90.
50. Stover EH. Novel ATP6V1B1 and ATP6V0A4 mutations in autosomal recessive distal renal tubular acidosis with new evidence for hearing loss. J Med Genet. 2002;39(11):796–803.
51. Bruce LJ, Cope DL, Jones GK, Schofield AE, Burley M, Povey S, et al. Familial distal renal tubular acidosis is associated with mutations in the red cell anion exchanger (Band 3, AE1) gene. J Clin Invest. 1997;100(7):1693–707.
52. Alonso-Varela M, Gil-Peña H, Coto E, Gómez J, Rodríguez J, Rodríguez-Rubio E, et al. Distal renal tubular acidosis. Clinical manifestations in patients with different underlying gene mutations. Pediatr Nephrol Berl Ger. 2018;33(9):1523–9.
53. Chu C, Woods N, Sawasdee N, Guizouarn H, Pellissier B, Borgese F, et al. Band 3 Edmonton I, a novel mutant of the anion exchanger 1 causing spherocytosis and distal renal tubular acidosis. Biochem J. 2010;426(3):379–88.
54. Chillarón J, Font-Llitjós M, Fort J, Zorzano A, Goldfarb DS, Nunes V, Palacín M. Pathophysiology and treatment of cystinuria. Nat Rev Nephrol. 2010;6(7):424–34.
55. Knoll T, Zöllner A, Wendt-Nordahl G, Michel MS, Alken P. Cystinuria in childhood and adolescence: recommendations for diagnosis, treatment, and follow-up. Pediatr Nephrol. 2005;20(1):19–24.
56. Goodyer P, Saadi I, Ong P, Elkas G, Rozen R. Cystinuria subtype and the risk of nephrolithiasis. Kidney Int. 1998;54(1):56–61.
57. Goldstein B, Goldfarb DS. Early recognition and management of rare kidney stone disorders. Urol Nurs. 2017;37(2):81–9, 102.
58. Dello Strologo L, Pras E, Pontesilli C, Beccia E, Ricci-Barbini V, de Sanctis L, Ponzone A, Gallucci M, Bisceglia L, Zelante L, Jimenez-Vidal M, Font M, Zorzano A, Rousaud F, Nunes V, Gasparini P, Palacín M, Rizzoni G. Comparison between SLC3A1 and SLC7A9 cystinuria patients and carriers: a need for a new classification. J Am Soc Nephrol. 2002;13(10):2547–53.
59. Botzenhart E, Vester U, Schmidt C, Hesse A, Halber M, Wagner C, Lang F, Hoyer P, Zerres K, Eggermann T. Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN). Cystinuria in children: distribution and frequencies of mutations in the SLC3A1 and SLC7A9 genes. Kidney Int. 2002;62(4):1136–42.
60. Lahme S, Bichler KH, Eggermann T, Lang F. Genomic and functional investigations of mutations of the SLC3A1 gene in cystinuria. Urol Int. 2002;69(3):207–11.
61. Schmidt C, Vester U, Hesse A, Lahme S, Lang F, Zerres K, Eggermann T. Arbeitsgemeinschaft Pädiatrische Nephrologie. The population-specific distribution and frequencies of genomic variants in the SLC3A1 and SLC7A9 genes and their application in molecular genetic testing of cystinuria. Urol Res. 2004;32(2):75–8.
62. Andreassen KH, Pedersen KV, Osther SS, Jung HU, Lildal SK, Osther PJ. How should patients with cystine stone disease be evaluated and treated in the twenty-first century? Urolithiasis. 2016;44(1):65–76.
63. Eggermann T, Venghaus A, Zerres K. Cystinuria: an inborn cause of urolithiasis. Orphanet J Rare Dis. 2012;7:19.
64. Rosenberg LE, Durant JL, Holland JM. Intestinal absorption and renal extraction of cystine and cysteine in cystinuria. N Engl J Med. 1965;273(23):1239–45.
65. Dent CE, Senior B. Studies on the treatment of cystinuria. Br J Urol. 1955;27(4):317–32.
66. Reinstatler L, Stern K, Batter H, Scotland KB, Ardekani GS, Rivera M, Chew BH, Eisner B, Krambeck AE, Monga M, Pais VM Jr. Conversion from cystine to noncystine stones: incidence and associated factors. J Urol. 2018;200(6):1285–9.
67. Beck BB, Hope B. Primary oxaluria. In: Geary D, Schaefer F, editors. Pediatric kidney disease. Berlin: Springer; 2016.

68. Danpure CJ. Molecular aetiology of primary hyperoxaluria type 1. Nephron Exp Nephrol. 2004;98(2):e39–44.
69. Johnson SA, Rumsby G, Cregeen D, Hulton S-A. Primary hyperoxaluria type 2 in children. Pediatr Nephrol. 2002;17(8):597–601.
70. Belostotsky R, Pitt JJ, Frishberg Y. Primary hyperoxaluria type III—a model for studying perturbations in glyoxylate metabolism. J Mol Med. 2012;90(12):1497–504.
71. Hoppe B, Martin-Higueras C. Inherited conditions resulting in nephrolithiasis. Curr Opin Pediatr. 2020;32(2):273–83.
72. Garrelfs SF, Rumsby G, Peters-Sengers H, Erger F, Groothoff JW, Beck BB, et al. Patients with primary hyperoxaluria type 2 have significant morbidity and require careful follow-up. Kidney Int. 2019;96(6):1389–99.
73. Torres RJ, Puig JG. Hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency: Lesch-Nyhan syndrome. Orphanet J Rare Dis. 2007;2(1):48.
74. Anderson LT, Ernst M. Self-injury in Lesch-Nyhan disease. J Autism Dev Disord. 1994;24(1):67–81.
75. Puig JG, Torres RJ, Mateos FA, Ramos TH, Arcas JM, Buño AS, et al. The Spectrum of hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency: clinical experience based on 22 patients from 18 Spanish families. Medicine (Baltimore). 2001;80(2):102–12.
76. Van Acker KJ, Simmonds HA, Potter C, Cameron JS. Complete deficiency of adenine phosphoribosyltransferase: report of a family. N Engl J Med. 1977;297(3):127–32.
77. Bollée G, Harambat J, Bensman A, Knebelmann B, Daudon M, Ceballos-Picot I. Adenine phosphoribosyltransferase deficiency. Clin J Am Soc Nephrol. 2012;7(9):1521–7.
78. Becker MA, Puig JG, Mateos FA, Jimenez ML, Kim M, Simmonds HA. Inherited superactivity of phosphoribosylpyrophosphate synthetase: association of uric acid overproduction and sensorineural deafness. Am J Med. 1988;85(3):383–90.
79. Becker MA, Raivio KO, Bakay B, Adams WB, Nyhan WL. Variant human phosphoribosylpyrophosphate synthetase altered in regulatory and catalytic functions. J Clin Invest. 1980;65(1):109–20.
80. Ahmed M, Taylor W, Smith PR, Becker MA. Accelerated transcription of *PRPS1* in X-linked overactivity of normal human phosphoribosylpyrophosphate synthetase. J Biol Chem. 1999;274(11):7482–8.
81. Balasubramaniam S, Duley JA, Christodoulou J. Inborn errors of purine metabolism: clinical update and therapies. J Inherit Metab Dis. 2014;37(5):669–86.
82. Hanna MK. Some observations on congenital ureteropelvic junction obstruction. Urology. 1978;12(2):151–9.
83. Al-Salem AH. Pelvic ureteric Junction (PUJ) Obstruction. In: An illustrated guide to pediatric urology. Chan: Springer; 2017.
84. Nguyen HT, Herndon CDA, Cooper C, Gatti J, Kirsch A, Kokorowski P, et al. The Society for Fetal Urology consensus statement on the evaluation and management of antenatal hydronephrosis. J Pediatr Urol. 2010;6(3):212–31.
85. Husmann DA, Milliner DS, Segura JW. Ureteropelvic junction obstruction with concurrent renal pelvic calculi in the pediatric patient: a long-term followup. J Urol. 1996:741–3.
86. Tekin A, Tekgul S, Atsu N, Ergen A, Kendi S. Ureteropelvic junction obstruction and coexisting renal calculi in children: role of metabolic abnormalities. Urology. 2001;57(3):542–5.
87. Natsis K, Piagkou M, Skotsimara A, Protogerou V, Tsitouridis I, Skandalakis P. Horseshoe kidney: a review of anatomy and pathology. Surg Radiol Anat. 2014;36(6):517–26.
88. Pawar A, Thongprayoon C, Cheungpasitporn W, Sakhuja A, Mao M, Erickson S. Incidence and characteristics of kidney stones in patients with horseshoe kidney: a systematic review and meta-analysis. Urol Ann. 2018;10(1):87.
89. O'Brien J, Buckley O, Doody O, Ward E, Persaud T, Torreggiani W. Imaging of horseshoe kidneys and their complications. J Med Imaging Radiat Oncol. 2008;52(3):216–26.
90. Taghavi K, Kirkpatrick J, Mirjalili SA. The horseshoe kidney: surgical anatomy and embryology. J Pediatr Urol. 2016;12(5):275–80.

91. Raj GV, Auge BK, Assimos D, Preminger GM. Metabolic abnormalities associated with renal calculi in patients with horseshoe kidneys. J Endourol. 2004;18(2):157–61.
92. Timmons JW, Malek RS, Hattery RR, Deweerd JH. Caliceal diverticulum. J Urol. 1975;114(1):6–9.
93. Lee MJ. Congenital anomalies if the upper urinary tract. In: Kim IO, editor. Radiology illustrated: pediatric radiology. Berlin: Springer; 2014.
94. Auge BK, Maloney ME, Mathias BJ, Pietrow PK, Preminger GM. Metabolic abnormalities associated with calyceal diverticular stones. BJU Int. 2006;97(5):1053–6.
95. Matlaga BR, Miller NL, Terry C, Kim SC, Kuo RL, Coe FL, et al. The pathogenesis of calyceal diverticular calculi. Urol Res. 2007;35(1):35–40.
96. Castellani C, Assael BM. Cystic fibrosis: a clinical view. Cell Mol Life Sci CMLS. 2017;74(1):129–40.
97. Hoppe B, Hesse A, Brömme S, Rietschel E, Michalk D. Urinary excretion substances in patients with cystic fibrosis: risk of urolithiasis? Pediatr Nephrol. 1998;12(4):275–9.
98. Hoppe B, von Unruh GE, Blank G, Rietschel E, Sidhu H, Laube N, et al. Absorptive hyperoxaluria leads to an increased risk for urolithiasis or nephrocalcinosis in cystic fibrosis. Am J Kidney Dis. 2005;46(3):440–5.
99. Turner MA. Oxalate and calcium excretion in cystic fibrosis. Arch Dis Child. 2000;83(3):244–7.
100. di Sant'Agnese PA, Talamo RC. Pathogenesis and physiopathology of cystic fibrosis of the pancreas: fibrocystic disease of the pancreas (mucoviscidosis). N Engl J Med. 1967;277(26):1399–408.
101. DiMagno EP, Go VLW, Summerskill WHJ. Relations between pancreatic enzyme outputs and malabsorption in severe pancreatic insufficiency. N Engl J Med. 1973;288(16):813–5.
102. Sidhu H, Hoppe B, Hesse A, Tenbrock K, Bromme S, Rietschel E, et al. Absence of Oxalobacter formigenes in cystic fibrosis patients: a risk factor for hyperoxaluria. Lancet. 1998;352(9133):1026–9.
103. Allison MJ, Cook HM, Milne DB, Gallagher S, Clayman RV. Oxalate degradation by gastrointestinal bacteria from humans. J Nutr. 1986;116(3):455–60.
104. von der Heiden R, Balestra APG, Bianchetti MG, Aebischer CC, Mullis PE, Lippuner K, et al. Which factors account for renal stone formation in cystic fibrosis? Clin Nephrol. 2003;59(03):160–3.
105. Ozçelik U, Beşbaş N, Göçmen A, Akata D, Akhan O, Ozgüç M, et al. Hypercalciuria and nephrocalcinosis in cystic fibrosis patients. Turk J Pediatr. 2004;46(1):22–7.
106. Perez-Brayfield MR, Caplan D, Gatti JM, Smith EA, Kirsch AJ. Metabolic risk factors for stone formation in patients with cystic fibrosis. J Urol. 2002:480–4.
107. Mutanen A, Wales PW. Etiology and prognosis of pediatric short bowel syndrome. Semin Pediatr Surg. 2018;27(4):209–17.
108. Fullerton BS, Hong CR, Jaksic T. Long-term outcomes of pediatric intestinal failure. Semin Pediatr Surg. 2017;26(5):328–35.
109. Carter BS, Whitworth HS. Nephrolithiasis in an infant with short-bowel syndrome. Clin Pediatr (Phila). 1994;33(12):741–2.
110. Rahman N, Hitchcock R. Case report of paediatric oxalate urolithiasis and a review of enteric hyperoxaluria. J Pediatr Urol. 2010;6(2):112–6.
111. Berman CM, Merritt RJ. Stoned-a syndrome of D-lactic acidosis and urolithiasis. Nutr Clin Pract. 2018;33(6):897–901.
112. Stark CM, Gorman GH, Nylund CM. Association of inflammatory bowel disease and urolithiasis in hospitalized pediatric patients. Inflamm Bowel Dis. 2017;23(10):1777–82.
113. Bianchi L, Gaiani F, Bizzarri B, Minelli R, Cortegoso Valdivia P, Leandro G, et al. Renal lithiasis and inflammatory bowel diseases, an update on pediatric population. Acta Biomed. 2018;89(9-S):76–80.
114. Fagagnini S, Heinrich H, Rossel J-B, Biedermann L, Frei P, Zeitz J, et al. Risk factors for gallstones and kidney stones in a cohort of patients with inflammatory bowel diseases. PLoS One. 2017;12(10):e0185193.

115. Madore F, Stampfer MJ, Rimm EB, Curhan GC. Nephrolithiasis and risk of hypertension. Am J Hypertens. 1998a;11(1 Pt 1):46–53.
116. Madore F, Stampfer MJ, Willett WC, Speizer FE, Curhan GC. Nephrolithiasis and risk of hypertension in women. Am J Kidney Dis. 1998b;32(5):802–7.
117. Taylor EN, Stampfer MJ, Curhan GC. Diabetes mellitus and the risk of nephrolithiasis. Kidney Int. 2005a;68(3):1230–5.
118. Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. JAMA. 2005b;293(4):455–62.
119. West B, Luke A, Durazo-Arvizu RA, Cao G, Shoham D, Kramer H. Metabolic syndrome and self-reported history of kidney stones: the National Health and nutrition examination survey (NHANES III) 1988-1994. Am J Kidney Dis. 2008;51(5):741–7.
120. Cappuccio FP, Strazzullo P, Mancini M. Kidney stones and hypertension: population based study of an independent clinical association. BMJ. 1990;300(6734):1234–6.
121. Gillen DL, Coe FL, Worcester EM. Nephrolithiasis and increased blood pressure among females with high body mass index. Am J Kidney Dis. 2005;46(2):263–9.
122. Schaeffer AJ, Feng Z, Trock BJ, Mathews RI, Neu AM, Gearhart JP, et al. Medical comorbidities associated with pediatric kidney stone disease. Urology. 2011;77(1):195–9.
123. Schaeffer AJ, Feng Z, Trock BJ, Mathews RI, Neu AM, Gearhart JP, Matlaga BR. Medical comorbidities associated with pediatric kidney stone disease. Urology. 2011;77(1):195–9.
124. Nikolis L, Seideman C, Palmer LS, Singer P, Chorny N, Frank R, et al. Blood pressure and urolithiasis in children. J Pediatr Urol. 2017;13(1):54.e1–6.
125. Cirillo M, Laurenzi M. Elevated blood pressure and positive history of kidney stones: results from a population-based study. J Hypertens Suppl. 1988;6(4):S485–6.
126. Pak CY, Sakhaee K, Moe O, Preminger GM, Poindexter JR, Peterson RD, Pietrow P, Ekeruo W. Biochemical profile of stone-forming patients with diabetes mellitus. Urology. 2003;61(3):523–7.
127. Daudon M, Lacour B, Jungers P. Influence of body size on urinary stone composition in men and women. Urol Res. 2006;34(3):193–9.
128. Pak CYC, Sakhaee K, Moe O, Preminger GM, Poindexter JR, Peterson RD, et al. Biochemical profile of stone-forming patients with diabetes mellitus. Urology. 2003;61(3):523–7.
129. Cupisti A, Meola M, D'Alessandro C, Bernabini G, Pasquali E, Carpi A, Barsotti G. Insulin resistance and low urinary citrate excretion in calcium stone formers. Biomed Pharmacother. 2007;61(1):86–90.
130. Kokorowski PJ, Routh JC, Hubert KC, Graham DA, Nelson CP. Association of urolithiasis with systemic conditions among pediatric patients at children's hospitals. J Urol. 2012;188(4 Suppl):1618–22.
131. Agrawal S, Kremsdorf R, Uysal S, Fredette ME, Topor LS. Nephrolithiasis: a complication of pediatric diabetic ketoacidosis. Pediatr Diabetes. 2018;19(2):329–32.
132. Chou Y-H, Su C-M, Li C-C, Liu C-C, Liu M-E, Wu W-J, et al. Difference in urinary stone components between obese and non-obese patients. Urol Res. 2011;39(4):283–7.
133. Maalouf NM, Sakhaee K, Parks JH, Coe FL, Adams-Huet B, Pak CYC. Association of urinary pH with body weight in nephrolithiasis. Kidney Int. 2004;65(4):1422–5.
134. Siener R, Glatz S, Nicolay C, Hesse A. The role of overweight and obesity in calcium oxalate stone formation. Obes Res. 2004;12(1):106–13.
135. Taylor EN, Curhan GC. Body size and 24-hour urine composition. Am J Kidney Dis. 2006;48(6):905–15.
136. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. JAMA. 2006;295(13):1549.
137. Kieran K, Giel DW, Morris BJ, Wan JY, Tidwell CD, Giem A, et al. Pediatric urolithiasis—does body mass index influence stone presentation and treatment? J Urol. 2010;184(4S):1810–5.
138. De Ruysscher C, Pien L, Tailly T, Van Laecke E, Vande Walle J, Prytuła A. Risk factors for recurrent urolithiasis in children. J Pediatr Urol. 2020;16(1):34.e1–9.

139. Murphy MO, Erpelding SG, Chishti AS, Dugan A, Ziada A, Kiessling SG. Influence of BMI in nephrolithiasis in an Appalachian pediatric population: a single-center experience. J Pediatr Urol. 2018;14(4):330.e1–8.
140. Sarica K, Eryıldırım B, Yencilek F, Kuyumcuoglu U. Role of overweight status on stone-forming risk factors in children: a prospective study. Urology. 2009;73(5):1003–7.
141. Chung JD, Kim TH, Myung SC, Moon YT, Kim KD, Chang IH. Influence of overweight on 24-hour urine chemistry studies and recurrent urolithiasis in children. Korean J Urol. 2012;53(4):268–74.
142. Bandari J, Dangle PP, Lyon TD, Lee A, Schneck FX, Cannon GM, Stephany HA, Ost MC. 24-Hour urinary parameters in overweight and obese children with urolithiasis. J Urol. 2016;196(2):526–30.
143. Eisner BH, Eisenberg ML, Stoller ML. Influence of body mass index on quantitative 24-hour urine chemistry studies in children with nephrolithiasis. J Urol. 2009;182(3):1142–6.
144. Pacifici GM. Clinical pharmacology of the loop diuretics furosemide and bumetanide in neonates and infants. Pediatr Drugs. 2012;14(4):233–46.
145. Alon US, Scagliotti D, Garola RE. Nephrocalcinosis and nephrolithiasis in infants with congestive heart failure treated with furosemide. J Pediatr. 1994;125(1):149–51.
146. Hufnagle KG, Khan SN, Penn D, Cacciarelli A, Williams P. Renal calcifications: a complication of long-term furosemide therapy in preterm infants. Pediatrics. 1982;70(3):360–3.
147. Peterson RG, Simmons MA, Rumack BH, Levine RL, Brooks JG. Pharmacology of furosemide in the premature newborn infant. J Pediatr. 1980;97(1):139–43.
148. Stafstrom CE, Gilmore HE, Kurtin PS. Nephrocalcinosis complicating medical treatment of posthemorrhagic hydrocephalus. Pediatr Neurol. 1992;8(3):179–82.
149. Gimpel C, Krause A, Franck P, Krueger M, von Schnakenburg C. Exposure to furosemide as the strongest risk factor for nephrocalcinosis in preterm infants. Pediatr Int. 2010;52(1):51–6.
150. Sikora P, Roth B, Kribs A, Michalk DV, Hesse A, Hoppe B. Hypocitraturia is one of the major risk factors for nephrocalcinosis in very low birth weight (VLBW) infants. Kidney Int. 2003;63(6):2194–9.
151. Katayama F, Miura H, Takanashi S. Long-term effectiveness and side effects of acetazolamide as an adjunct to other anticonvulsants in the treatment of refractory epilepsies. Brain and Development. 2002;24(3):150–4.
152. Gordon EE, Sheps SG. Effect of acetazolamide on citrate excretion and formation of renal calculi: report of a case and study of five normal subjects. N Engl J Med. 1957;256(26):1215–9.
153. Carlsen J. Nephrolithiasis with dorzolamide. Arch Ophthalmol. 1999;117(8):1087.
154. Mula M, Cavanna AE, Monaco F. Psychopharmacology of topiramate: from epilepsy to bipolar disorder. Neuropsychiatr Dis Treat. 2006;2(4):475–88.
155. Matlaga BR, Shah OD, Assimos DG. Drug-induced urinary calculi. Rev Urol. 2003;5(4):227–31.
156. Kubota M, Nishi-Nagase M, Sakakihara Y, Noma S, Nakamoto M, Kawaguchi H, et al. Zonisamide—induced urinary lithiasis in patients with intractable epilepsy. Brain and Development. 2000;22(4):230–3.
157. Peters DH, Sorkin EM. Zonisamide: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy. Drugs. 1993;45(5):760–87.
158. Miyamoto A, Sugai R, Okamoto T, Shirai M, Oki J. Urine stone formation during treatment with zonisamide. Brain and Development. 2000;22(7):460.
159. Shields LBE, Peppas DS, Rosenberg E. Xanthine calculi in a patient with Lesch-Nyhan syndrome and factor V Leiden treated with allopurinol: case report. BMC Pediatr. 2018;18(1):231.
160. Shiozawa Y, Sakaguchi S, Sakakibara O, Yagishita K, Saito M, Yamashiro Y. Urolithiasis in an acute lymphoblastic leukemia child during induction chemotherapy. Pediatr Hematol Oncol. 2008;25(4):359–63.

161. Pais VM, Lowe G, Lallas CD, Preminger GM, Assimos DG. Xanthine urolithiasis. Urology. 2006;67(5):1084.e9–1084.e11.
162. LaRosa C, McMullen L, Bakdash S, Ellis D, Krishnamurti L, Wu H-Y, et al. Acute renal failure from xanthine nephropathy during management of acute leukemia. Pediatr Nephrol. 2007;22(1):132–5.
163. Baxmann AC, de Mendonça OGC, Heilberg IP. Effect of vitamin C supplements on urinary oxalate and pH in calcium stone-forming patients. Kidney Int. 2003;63(3):1066–71.
164. Ferraro PM, Curhan GC, Gambaro G, Taylor EN. Total, dietary, and supplemental vitamin C intake and risk of incident kidney stones. Am J Kidney Dis. 2016;67(3):400–7.
165. Chen X, Shen L, Gu X, Dai X, Zhang L, Xu Y, et al. High-dose supplementation with vitamin C–induced Pediatric urolithiasis: the first case report in a child and literature review. Urology. 2014;84(4):922–4.
166. Conti G, Chirico V, Lacquaniti A, Silipigni L, Fede C, Vitale A, et al. Vitamin D intoxication in two brothers: be careful with dietary supplements. J Pediatr Endocrinol Metab [Internet]. 2014;27:7–8. 1 [cited 2020 Jul 19]; https://www.degruyter.com/view/j/jpem.2014.27.issue-7-8/jpem-2013-0220/jpem-2013-0220.xml
167. Manappallil RG, Shylendran S, Kakkattil A, Thomas AD. Multiple renal calculi due to hypercalcaemia induced by over-the-counter vitamin D intoxication. BMJ Case Rep. 2018:bcr-2018-225849.
168. Daudon M, Frochot V, Bazin D, Jungers P. Drug-induced kidney stones and crystalline nephropathy: pathophysiology, prevention and treatment. Drugs. 2018;78(2):163–201.
169. Watson RA, Ettinger B, Deshon GE, Agee RE, Oldroyd NO. Triamterene stone: advantage of crystallographic analysis. Urology. 1981;18(3):238–40.
170. Noble CB, Klein LT, Staiman VR, Neu N, Hensle TW, Berdon WE. Ureteral obstruction secondary to indinavir in the pediatric HIV population. Pediatr Radiol. 1998;28(8):627–9.
171. Saltel E, Angel JB, Futter NG, Walsh WG, O'Rourke K, Mahoney JE. Increased prevalence and analysis of risk factors for indinavir nephrolithiasis. J Urol. 2000;164(6):1895–7.
172. van Rossum AMC, Dieleman JP, Fraaij PLA, Cransberg K, Hartwig NG, Gyssens IC, et al. Indinavir-associated asymptomatic nephrolithiasis and renal cortex atrophy in two HIV-1 infected children. AIDS. 2001;15(13):1745–7.
173. Albala DM, Prien EL, Galal HA. Urolithiasis as a hazard of sulfonamide therapy. J Endourol. 1994;8(6):401–3.
174. Becker K, Jablonowski H, Häussinger D. Sulfadiazine-Associated nephrotoxicity in patients with the acquired immunodeficiency syndrome. Medicine (Baltimore). 1996;75(4):185–94.
175. Biorn CL. Anuria owing to urethral obstruction by sulfadiazine crystals. Calif Med. 1952;77(3):196–7.
176. Catalano-Pons C, Bargy S, Schlecht D, Tabone M-D, Deschenes G, Bensman A, et al. Sulfadiazine-induced nephrolithiasis in children. Pediatr Nephrol [Internet]. 2004;19:8. https://doi.org/10.1007/s00467-004-1519-8. [cited 2020 Jul 19]
177. Erturk E, Casemento JB, Guertin KR, Kende AS. Bilateral acetylsulfapyridine nephrolithiasis associated with chronic sulfasalazine therapy. J Urol. 1994;151(6):1605–6.
178. Winterborn MH, Mann JR. Anuria due to sulphadiazine. Arch Dis Child. 1973;48(11):915–7.
179. Zeng L, Choonara I, Zhang L, Xue S, Chen Z, He M. Safety of ceftriaxone in paediatrics: a systematic review protocol. BMJ Open. 2017;7(8):e016273.
180. Youssef DM, Sherief LM, Sherbiny HS, ElAttar MY, Sheikh ARME, Fawzy FM, et al. Prospective study of nephrolithiasis occurrence in children receiving cefotriaxone: nephrolithiasis in children receiving cefotri ceftriaxone axone. Nephrology. 2016;21(5):432–7.
181. Kimata T, Kaneko K, Takahashi M, Hirabayashi M, Shimo T, Kino M. Increased urinary calcium excretion caused by ceftriaxone: possible association with urolithiasis. Pediatr Nephrol. 2012;27(4):605–9.
182. Acun C, Erdem LO, Söğüt A, Erdem CZ, Tomaç N, Gündoğdu S, et al. Gallbladder and urinary tract precipitations associated with ceftriaxone therapy in children: a prospective study. Ann Trop Paediatr. 2004;24(1):25–31.

183. Azarfar A. Hypercalciuria following ceftriaxone a fact or myth. Hypercalciuria Ceftriaxone Fact Myth [Internet], [cited 2020 Jul 19];(3). 2015; https://doi.org/10.12861/jrip.2015.20.
184. Mohkam M, Karimi A, Gharib A, Daneshmand H, Khatami A, Ghojevand N, et al. Ceftriaxone associated nephrolithiasis: a prospective study in 284 children. Pediatr Nephrol. 2007;22(5):690–4.
185. de Moor RA, Egberts ACG, Schröder CH. Ceftriaxone-associated nephrolithiasis and biliary pseudolithiasis. Eur J Pediatr. 1999;158(12):975–7.
186. Avci Z. Nephrolithiasis associated with ceftriaxone therapy: a prospective study in 51 children. Arch Dis Child. 2004;89(11):1069–72.
187. Shen X, Liu W, Fang X, Jia J, Lin H, Xu M, Geng H. Acute kidney injury caused by ceftriaxone-induced urolithiasis in children: a single-institutional experience in diagnosis, treatment and follow-up. Int Urol Nephrol. 2014;46(10):1909–14.
188. Ulinski T, Sabot J-F, Bourlon I, Cochat P. Bilateral urinary calculi after treatment with a silicate-containing milk thickener. Eur J Pediatr. 2004;163(4–5):239–40.
189. Farrer JH, Rajfer J. Silicate urolithiasis. J Urol. 1984;132(4):739–40.
190. Taşdemir M, Fuçucuoğlu D, Özman O, Sever L, Önal B, Bilge I. Silicate calculi, a rare cause of kidney stones in children. Pediatr Nephrol. 2017;32(2):371–4.
191. Ghousheh AI, Groth TW, Fryjoff KM, Wille DF, Mandel NS, Roddy JT, et al. Urolithiasis in patients on high dose felbamate. J Urol. 2013;189(5):1865–9.
192. Meier KH, Olson KR, Olson JL. Acute felbamate overdose with crystalluria. Clin Toxicol (Phila). 2005;43(3):189–92.
193. Sparagana SP, Strand WR, Adams RC. Felbamate urolithiasis. Epilepsia. 2001;42(5):682–5.
194. Tasian GE, Jemielita T, Goldfarb DS, Copelovitch L, Gerber JS, Wu Q, et al. Oral antibiotic exposure and kidney stone disease. J Am Soc Nephrol. 2018;29(6):1731–40.
195. Barr-Beare E, Saxena V, Hilt EE, Thomas-White K, Schober M, Li B, et al. The interaction between Enterobacteriaceae and calcium oxalate deposits. Sands JM, editor. PLoS One. 2015;10(10):e0139575.
196. Cox LM, Yamanishi S, Sohn J, Alekseyenko AV, Leung JM, Cho I, et al. Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. Cell. 2014;158(4):705–21.
197. Gibney EM, Goldfarb DS. The association of nephrolithiasis with cystic fibrosis. Am J Kidney Dis. 2003;42(1):1–11.
198. Woodward M, Frank D. Postnatal management of antenatal hydronephrosis: postnatal management of antenatal hydronephrosis. BJU Int. 2002;89(2):149–56.
199. Howard SC, Kaplan SD, Razzouk BI, Rivera GK, Sandlund JT, Ribeiro RC, et al. Urolithiasis in pediatric patients with acute lymphoblastic leukemia. Leukemia. 2003;17(3):541–6.
200. Pui C-H, Roy S, Noe HN. Urolithiasis in childhood acute Leukemia and Nonhodgkin's lymphoma. J Urol. 1986;136(5):1052–4.

Chapter 5
Drug-Induced Nephrolithiasis

Rushelle Byfield and Lawrence Copelovitch

Introduction

The initiation and growth of urinary calculi require the supersaturation of certain salts in the urine. The most important determinants of urine solubility and the likelihood of solute supersaturation (crystallization) are the total urine volume, temperature, concentration of the stone-forming ions, concentration of inhibitors of crystallization, concentration of promoters of crystallization, and urine pH. Drug-induced nephrolithiasis can be divided broadly into two categories: Drugs that directly crystallize in the urine or those that promote calculi formation indirectly by altering the urinary milieu in a manner that more readily favors calcium or uric acid supersaturation. Direct drug crystallization occurs when the concentration of a specific medication or metabolite exceeds the supersaturation threshold of that specific solute resulting in precipitation or crystallization [1, 2]. Once supersaturation occurs a small number of molecules arrange in clusters through a process known as nucleation which forms as the site for further aggregation of particles and the ultimate formation of a crystal. Drugs that indirectly promote urinary calculi formation generally perturb the various urinary modulators which are normally present and serve to either inhibit or promote crystallization and subsequent stone formation. These metabolic inhibitors of stone formation include small ions, such as citrate, magnesium and pyrophosphate, urinary prothrombin fragment 1, Tamm-Horsfall protein, and macromolecules such as osteopontin/uropontin [3]. Similarly, metabolic promoters of crystallization include elevated urinary levels of calcium, oxalate, or uric acid [4].

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Medications That Result in Direct Crystallization

Sulfonamides

Sulfonamides have been used as antimicrobial agents since the 1930s. The association between sulfonamides and nephrolithiasis as well as acute kidney injury (AKI) was recognized early on and as a result current usage had been in decline for several decades. With the emergence of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) the use of one sulfonamide in particular, sulfadiazine, became indispensable as a treatment for cerebral toxoplasmosis given its excellent penetration across the blood–brain barrier. In the pediatric population, sulfadiazine has also been used for the treatment of central nervous system toxoplasmosis in the setting of immunodeficiency or solid-organ transplant [5]. The treatment of these severe infections often involves prolonged therapy with high daily doses. The metabolite of sulfadiazine, *N*-acetylsulfadiazine, is poorly soluble in the urine particularly at low pH values. Rapid crystallization of this solute in the tubules can lead to obstructive uropathy and AKI [6]. Low urine volume, dehydration, and underlying renal tubular disease or injury are additional factors that can contribute to risk of crystallization. Treatment involves aggressive hydration and urinary alkalization with a target urinary pH of >7.5 and/or cessation of the drug [5, 7].

Cephalosporins

Among the cephalosporins, ceftriaxone is widely used as an empiric treatment for children with suspected or confirmed bacterial infections. Its broad antimicrobial coverage, long half-life, and safety profile make it an attractive treatment option, especially in the treatment of suspected sepsis. Nephrolithiasis is a rarely reported side effect of ceftriaxone, which has been almost exclusively observed in the pediatric population. One prospective comparative study of ceftriaxone and cefotaxime showed similar incidence of nephrolithiasis, though it is the only report of cefotaxime induced nephrolithiasis [8]. Interestingly, the first, second, and fourth generation cephalosporins have not been reported to cause stones. Although there is some biliary excretion, ceftriaxone is primarily excreted by the kidneys. The mechanism of ceftriaxone crystal formation is poorly understood, however, it is thought to be related to interaction between ceftriaxone and calcium chloride forming an insoluble salt within the renal tubules [9]. Hypocitraturia may also contribute to ceftriaxone stone formation [10]. These stones are usually effectively managed with hydration and cessation of therapy [11–14].

Protease Inhibitors

The introduction of protease inhibitors in the early 1990s was an important breakthrough in the treatment of HIV/AIDS. AIDS is now rare in the pediatric population; however, this class of drugs remains the mainstay of treatment. Indinavir was one of the first used protease inhibitors and the one most implicated in nephrolithiasis, occurring in up to 40% of adults who used the drug [15]. While there is only ~20% renal excretion of the drug, it is poorly soluble and can form large needle shaped crystals at physiological urine pH (~5) [16, 17]. These crystals can aggregate and form calculi leading to tubular obstruction. Patients with hepatic impairment, often related to hepatitis B or C, may be at further increased risk of significant renal excretion and predisposition to calculi formation [18]. Treatment is supportive involving withdrawal of the medication whenever possible and increasing fluid intake; extra hydration is most useful at times when drug is expected to be at peak concentration (usually within an hour of administration) [19, 20].

Acyclovir

Acyclovir is a common antiviral agent used for treatment of herpes simplex virus (HSV) and varicella zoster infections, particularly in those who are immunocompromised [21]. Renal excretion of the drug accounts for 60–90% of its elimination however it is relatively insoluble in the urine, especially in areas of the nephron where urine flow is low, such as the distal tubule [22, 23]. The precipitation of acyclovir crystals in the renal collecting tubules can cause an obstructive nephropathy leading to AKI [7]. Risk factors associated with acyclovir nephrotoxicity include higher blood concentrations (usually dosages greater than 500 mg/m^2 every 8 h), rapid bolus administration, preexisting renal disease, hypovolemia, and the concomitant use of other nephrotoxic agents [23]. Precipitation can be prevented by avoiding rapid infusions of the drug and providing adequate amounts of fluids to maintain high urinary flow [24].

Foscarnet

In the pediatric population foscarnet is primarily used as a second line agent for the treatment of acyclovir-resistant HSV infections and cytomegalovirus (CMV) retinitis [25]. Initially foscarnet was known to be associated with AKI although the exact mechanism remained elusive until around 1989. The proposed mechanism was thought to be related to tubular toxicity given findings of low molecular weight

proteinuria, bland urine sediment, and ultimate resolution of renal injury [26]. Foscarnet crystals were first identified in case reports describing AIDS patients being treated for CMV retinitis who developed renal injury and AKI during the course of their treatment [27]. It has been proposed that the drug complexes with sodium and/or calcium ions to form insoluble crystals, which deposit in both the glomeruli and the tubules [27, 28]. Risk factors include high doses of the drug (6–12 g/day) and coadministration of other nephrotoxins [26, 27]. To date, despite the presence of crystalluria, definitive foscarnet containing stones have not been identified. Nevertheless, the mainstay of treatment is hydration to decrease saturation of the excreted drug in the urine.

Aminopenicillins

Aminopenicillins represent one of the most prescribed antibiotic classes in the pediatric population [29]. Amoxicillin, in particular, is popular choice for the treatment of otitis media, streptococcal pharyngitis, and community acquired pneumonia. Amoxicillin-induced nephropathy is a rare complication of medication overdose, however, the presentation can be varied, from asymptomatic to gross hematuria and rarely AKI [30–33]. In retrospective study of over 14,000 children with amoxicillin ingestion only 5 (0.03%) had renal complications [34]. Amoxicillin is primarily eliminated by the kidneys via tubular excretion, the mechanism of injury is thought to be related to deposition of crystals in the tubules. The crystals formed are bunches of thin needles that are birefringent under polarized light [35]. The development of nephropathy does not appear to be dose dependent and it is unclear what causes this rare complication. Nevertheless, the outcomes of most cases are favorable and resolve with supportive care and withdrawal of the medication [34, 36].

Methotrexate

Methotrexate is an antimetabolite that is widely used in the treatment of pediatric and adult rheumatologic diseases and cancers [37]. In particular, regimens using high dose methotrexate (>500–1000 mg/m^2) have been associated with nephrotoxicity [38]. The renal injury is likely directly related to methotrexate induced crystal nephropathy [39], although notably methotrexate crystals in urine were not reported until as recently as 2011 [40]. While almost entirely renally excreted, methotrexate and its metabolites are poorly soluble at normal urine pH. Precipitation can lead to obstruction of the tubules as well toxic damage to the renal tubular epithelium [39]. An increase in urine volume and pH can decrease precipitation by increasing solubility of methotrexate (five- to eightfold greater solubility with increase in urine pH from 6–7). This finding has led to the recommendation of urine alkalization during methotrexate administration [38].

Guaifenesin/Ephedrine

Despite AAP recommendations warning against their use in children, cough medicines remain popular over the counter purchases [41]. As ephedrine fell out of favor with the FDA, guaifenesin became the dominant ingredient in over-the-counter cough remedies due to its actions as an expectorant. In the late 1990s, the first case reports of kidney stones came to light in the setting of those abusing cough medicines for their stimulant effects [42]. Stones containing metabolites of both ephedrine and guaifenesin have been identified by mass spectrometry [43, 44]. These stones are typically radiolucent on X-ray but can be detected on CT. While ephedrine tends to precipitate in alkaline solutions, alkalization has been used as a treatment for ephedrine induced stones. The proposed mechanism is that an alkaline urine pH increases passive reabsorption of non-ionized ephedrine in the renal tubules (given ephedrine's properties as a weak base) thereby decreasing the overall urinary excretion of the drug [42, 45].

Melamine

Melamine is a nitrogen rich compound used in laminates and dishware. It rose to international prominence in September 2008 when the WHO reported an outbreak of melamine urolithiasis in children in China linked to contamination of milk products with melamine. Melamine was added to infant formulas and milk products to increase their apparent protein content. Approximately 294,000 children were affected, with 51,900 requiring hospitalization and at least 6 fatalities reported [46]. Melamine is primarily renally excreted and is poorly soluble at physiologic urine pH. While crystallization of melamine alone is inhibited at very low pH (<4.5) formation of complexes with uric acid and subsequent calculi formation is enhanced at acidic pH [47, 48]. The clinical symptoms described were variable, ranging from asymptomatic to increased fussiness, to renal colic with associated acute kidney injury. The stones were described as "grains of sand" which were relatively easy to pass or "lump like" forms that often required surgical intervention. In one 5-year follow up study at a single center following 207 children, there was no statistical difference in residual stone burden or renal function in those that underwent surgical intervention vs conservative therapy (hydration and urine alkalization, target pH 6–7) [49].

Triamterene

Triamterene is a potassium-sparing diuretic that is used for management of hypertension. Triamterene and its metabolites are excreted in the urine and have poor solubility, with close to 50% of patients developing crystalluria,

characterized by brown crystalline casts which may appear as a "Maltese cross" under polarized light [50, 51]. Actual calculi formation is less common than crystalluria. Triamterene was found in ~0.4% of stones analyzed in one large study [52]. High doses of the drug (>150 mg/day) and acidic urine pH (<5.5) were associated with increased stone formation. Treatment includes volume expansion and cessation of the drug. The utility of alkalization of the urine is less clear [53].

Promote Metabolic Effects

Calcium and Vitamin D Supplementation

Over the last few decades increased attention has been given to the role of vitamin D in various diseases related to bone health, the immune system, mental health, and cardiovascular morbidity. As a consequence, there has been an overall increase in the use of vitamin D supplementation. There have been conflicting reports about the role of vitamin D in stone formation. Most of this data comes from large-scale adult trials. While some meta-analyses [54–56] have found an association between vitamin D supplementation and risk of hypercalcemia and nephrolithiasis, others found an association with supplementation and hypercalcemia/hypercalciuria but not necessarily stone formation [57]. Overall in adults, vitamin D intake seems to be safe except perhaps in younger women with intake >1000 U per day (combined supplements and diet) [58]. Furthermore, a small study of 29 adult patients with nephrolithiasis and hypovitaminosis D suggested that vitamin D supplementation is likely safe as none of the patients developed worsening hypercalciuria after 8 weeks of therapy [59].

Vitamin C

Vitamin C is nonenzymatically metabolized into oxalate prior to being excreted in the urine. When high dose vitamin C supplementation occurs, hyperoxaluria can develop and predispose to calcium oxalate stone formation [58, 60]. There are several case reports describing children presenting with renal calculi associated with vitamin C supplementation whose symptoms completely resolved after cessation of the supplement. [61]. Importantly, although a diet high in fruits and vegetables might theoretically increase the risk of stone formation through increased urinary oxalate excretion these effects seem to be mitigated by the effects of high amounts of dietary potassium, magnesium, citrate, and phytates resulting in overall reduced risk of stone formation [62].

Carbonic Anhydrase Inhibitors: Acetazolamide, Topiramate, Zonisamide

Acetazolamide (AZM) is a carbonic anhydrase inhibitor (CAI) that blocks the reabsorption of bicarbonate in the proximal tubule. It is used in the treatment of refractory epilepsy and posthemorrhagic hydrocephalus. Both topiramate (TPM) and zonisamide (ZNS) have weak carbonic anhydrase inhibitory activity [63]. The mechanism of CAI-induced nephrolithiasis is presumed to be via the development of metabolic acidosis which ultimately contributes to the development of a secondary hypocitraturia and hypercalciuria as both the kidney and the bones attempt to maintain physiological pH and buffer the increased acid load. Calcium phosphate stones are common in this setting as the elevated urine pH which results from CAI exposure is a suitable environment for this type of stone formation. Reports on the incidence of TPM-induced nephrolithiasis are highly variable, with prevalence ranging from 5% to 20% [64, 65]. One study of nonambulatory children on TPM, who are also at risk for immobility-associated hypercalciuria, reported an incidence of nephrolithiasis of 54% [66]. Interestingly, ZNS has a lower incidence of stone formation at 1.2–1.4% [67] as compared to TPM. Notably, those who take TPM or ZNS for seizure disorder are also often prescribed the ketogenic diet which exacerbates the propensity for stone formation by further contributing to the development of metabolic acidosis. Given that children often require these medications for difficult-to-manage epilepsy discontinuation of medications may not be feasible. In such cases ensuring high fluid intake, limiting sodium intake, and treatment with citrate to correct the metabolic acidosis and improve the hypocitraturia are often recommended.

Loop Diuretics

Furosemide is a loop diuretic commonly used in the pediatric population, acutely in the management of fluid overload and chronically in children with congestive heart failure, chronic kidney disease, or chronic lung disease. Loop diuretics act at the thick ascending loop (TAL) of Henle by inhibiting the Na-K-2Cl (NKCC2) cotransporter resulting in decreased sodium reabsorption in the TAL which ultimately results in hypercalciuria as the increased urinary sodium reaches the distal convoluted tubule (DCT) and competes with calcium for reabsorption. Since the 1980s furosemide use has been associated with reports of nephrocalcinosis in both premature and full-term infants [68, 69]. Calcium oxalate is the predominant stone type although calcium phosphate stones have also been reported. If furosemide cannot be discontinued, coadministration of a thiazide diuretic can help promote increased calcium reabsorption by inhibiting the thiazide-sensitive Na-Cl cotransporter (NCC) and ultimately decrease the risk of stone formation.

Conclusion

Collectively drug-induced nephrolithiasis is a rare cause of nephrolithiasis in pediatric patients. Drugs may promote stone formation either through direct crystallization of the drug or its metabolites or via altering the urinary milieu to precipitate normally occurring solutes. Though rare, the identification of drug-induced nephrolithiasis is critical for treatment when drug removal is feasible and offers an avenue for targeted therapy in cases in which the drug cannot be eliminated.

References

1. Aggarwal KP, Narula S, Kakkar M, Tandon C. Nephrolithiasis: molecular mechanism of renal stone formation and the critical role played by modulators. Biomed Res Int. 2013;2013:292953.
2. Coe FL, Parks JH, Asplin JR. The pathogenesis and treatment of kidney stones. N Engl J Med. 1992;327(16):1141–52.
3. Daudon M, Frochot V. Crystalluria. Clin Chem Lab Med. 2015;53(Suppl 2):s1479–87.
4. Ratkalkar VN, Kleinman JG. Mechanisms of stone formation. Clin Rev Bone Miner Metab. 2011;9(3–4):187–97.
5. Molina JM, Belenfant X, Doco-Lecompte T, Idatte JM, Modai J. Sulfadiazine-induced crystalluria in AIDS patients with toxoplasma encephalitis. AIDS. 1991;5(5):587–9.
6. Sasson JP, Dratch PL, Shortsleeve MJ. Renal US findings in sulfadiazine-induced crystalluria. Radiology. 1992;185(3):739–40.
7. Catalano-Pons C, Bargy S, Schlecht D, Tabone MD, Deschenes G, Bensman A, et al. Sulfadiazine-induced nephrolithiasis in children. Pediatr Nephrol. 2004;19(8):928–31.
8. Ustyol L, Bulut MD, Agengin K, Bala KA, Yavuz A, Bora A, et al. Comparative evaluation of ceftriaxone- and cefotaxime-induced biliary pseudolithiasis or nephrolithiasis: a prospective study in 154 children. Hum Exp Toxicol. 2017;36(6):547–53.
9. Chutipongtanate S, Thongboonkerd V. Ceftriaxone crystallization and its potential role in kidney stone formation. Biochem Biophys Res Commun. 2011;406(3):396–402.
10. Cong X, Gu X, Sun X, Ning B, Shen L. Possible function of urinary pH and citrate on the ceftriaxone-induced nephrolithiasis. Urology. 2014;83(1):63–7.
11. Gargollo PC, Barnewolt CE, Diamond DA. Pediatric ceftriaxone nephrolithiasis. J Urol. 2005;173(2):577–8.
12. Stojanovic V, Djuric VG. Nephrolithiasis caused by ceftriaxone in a 3-year-old child with ureteropelvic junction obstruction. Case Rep Med. 2009;2009:365962.
13. Tasic V, Sofijanova A, Avramoski V. Nephrolithiasis in a child with acute pyelonephritis. Ceftriaxone-induced nephrolithiasis and biliary pseudolithiasis. Pediatr Nephrol. 2005;20(10):1510–1, 2–3.
14. Mohkam M, Karimi A, Gharib A, Daneshmand H, Khatami A, Ghojevand N, et al. Ceftriaxone associated nephrolithiasis: a prospective study in 284 children. Pediatr Nephrol. 2007;22(5):690–4.
15. Saltel E, Angel JB, Futter NG, Walsh WG, O'Rourke K, Mahoney JE. Increased prevalence and analysis of risk factors for indinavir nephrolithiasis. J Urol. 2000;164(6):1895–7.
16. van Rossum AM, Dieleman JP, Fraaij PL, Cransberg K, Hartwig NG, Gyssens IC, et al. Indinavir-associated asymptomatic nephrolithiasis and renal cortex atrophy in two HIV-1 infected children. AIDS. 2001;15(13):1745–7.
17. Noble CB, Klein LT, Staiman VR, Neu N, Hensle TW, Berdon WE. Ureteral obstruction secondary to indinavir in the pediatric HIV population. Pediatr Radiol. 1998;28(8):627–9.

18. Malavaud B, Dinh B, Bonnet E, Izopet J, Payen JL, Marchou B. Increased incidence of indinavir nephrolithiasis in patients with hepatitis B or C virus infection. Antivir Ther. 2000;5(1):3–5.
19. Kopp JB, Miller KD, Mican JA, Feuerstein IM, Vaughan E, Baker C, et al. Crystalluria and urinary tract abnormalities associated with indinavir. Ann Intern Med. 1997;127(2):119–25.
20. Yeh KC, Deutsch PJ, Haddix H, Hesney M, Hoagland V, Ju WD, et al. Single-dose pharmacokinetics of indinavir and the effect of food. Antimicrob Agents Chemother. 1998;42(2):332–8.
21. Becker BN, Schulman G. Nephrotoxicity of antiviral therapies. Curr Opin Nephrol Hypertens. 1996;5(4):375–9.
22. Brigden D, Rosling AE, Woods NC. Renal function after acyclovir intravenous injection. Am J Med. 1982;73(1A):182–5.
23. Sawyer MH, Webb DE, Balow JE, Straus SE. Acyclovir-induced renal failure. Clinical course and histology. Am J Med. 1988;84(6):1067–71.
24. Vachvanichsanong P, Patamasucon P, Malagon M, Moore ES. Acute renal failure in a child associated with acyclovir. Pediatr Nephrol. 1995;9(3):346–7.
25. Wang Y, Smith KP. Safety of alternative antiviral agents for neonatal herpes simplex virus encephalitis and disseminated infection. J Pediatr Pharmacol Ther. 2014;19(2):72–82.
26. Deray G, Martinez F, Katlama C, Levaltier B, Beaufils H, Danis M, et al. Foscarnet nephrotoxicity: mechanism, incidence and prevention. Am J Nephrol. 1989;9(4):316–21.
27. Maurice-Estepa L, Daudon M, Katlama C, Jouanneau C, Sazdovitch V, Lacour B, et al. Identification of crystals in kidneys of AIDS patients treated with foscarnet. Am J Kidney Dis. 1998;32(3):392–400.
28. Frochot V, Bazin D, Letavernier E, Jouanneau C, Haymann J-P, Daudon M. Nephrotoxicity induced by drugs: the case of foscarnet and atazanavir—a SEM and μFTIR investigation. C R Chim. 2016;19(11–12):1565–72.
29. Hersh AL, Shapiro DJ, Pavia AT, Shah SS. Antibiotic prescribing in ambulatory pediatrics in the United States. Pediatrics. 2011;128(6):1053–61.
30. Bright DA, Gaupp FB, Becker LJ, Schiffert MG, Ryken TC. Amoxicillin overdose with gross hematuria. West J Med. 1989;150(6):698–9.
31. Jones DP, Gaber L, Nilsson GR, Brewer ED, Stapleton FB. Acute renal failure following amoxicillin overdose. Clin Pediatr (Phila). 1993;32(12):735–9.
32. Belko J, Urueta G, Emre U. Amoxicillin overdose manifested by hematuria and acute renal failure. Pediatr Infect Dis J. 1995;14(10):917–9.
33. Labriola L, Jadoul M, Daudons M, Pirson Y, Lambert M. Massive amoxycillin crystalluria causing anuric acute renal failure. Clin Nephrol. 2003;59(6):455–7.
34. Mrvos R, Pummer TL, Krenzelok EP. Amoxicillin renal toxicity: how often does it occur? Pediatr Emerg Care. 2013;29(5):641–3.
35. Fogazzi GB, Cantu M, Saglimbeni L, Daudon M. Amoxycillin, a rare but possible cause of crystalluria. Nephrol Dial Transplant. 2003;18(1):212–4.
36. Vodovar D, Thomas L, Mongardon N, Lepeule R, Lebrun-Vignes B, Biour M, et al. Dramatic increase of amoxicillin-induced crystal nephropathy found in a cohort study of French pharmacovigilance centers. Antimicrob Agents Chemother. 2018;62(3).
37. Widemann BC, Balis FM, Kempf-Bielack B, Bielack S, Pratt CB, Ferrari S, et al. High-dose methotrexate-induced nephrotoxicity in patients with osteosarcoma. Cancer. 2004;100(10):2222–32.
38. Widemann BC, Adamson PC. Understanding and managing methotrexate nephrotoxicity. Oncologist. 2006;11(6):694–703.
39. Howard SC, McCormick J, Pui CH, Buddington RK, Harvey RD. Preventing and managing toxicities of high-dose methotrexate. Oncologist. 2016;21(12):1471–82.
40. Mallipattu SK, Ross MJ. Methotrexate in the urine. Kidney Int. 2011;80(2):226.
41. Sharfstein JM, North M, Serwint JR. Over the counter but no longer under the radar—pediatric cough and cold medications. N Engl J Med. 2007;357(23):2321–4.
42. Bennett S, Hoffman N, Monga M. Ephedrine- and guaifenesin-induced nephrolithiasis. J Altern Complement Med. 2004;10(6):967–9.

43. Assimos DG, Langenstroer P, Leinbach RF, Mandel NS, Stern JM, Holmes RP. Guaifenesin- and ephedrine-induced stones. J Endourol. 1999;13(9):665–7.
44. Pickens CL, Milliron AR, Fussner AL, Dversdall BC, Langenstroer P, Ferguson S, et al. Abuse of guaifenesin-containing medications generates an excess of a carboxylate salt of beta-(2-methoxyphenoxy)-lactic acid, a guaifenesin metabolite, and results in urolithiasis. Urology. 1999;54(1):23–7.
45. Hoffman N, McGee SM, Hulbert JC. Resolution of ephedrine stones with dissolution therapy. Urology. 2003;61(5):1035.
46. Wen JG, Liu XJ, Wang ZM, Li TF, Wahlqvist ML. Melamine-contaminated milk formula and its impact on children. Asia Pac J Clin Nutr. 2016;25(4):697–705.
47. Guan X, Deng Y. Melamine-associated urinary stone. Int J Surg. 2016;36(Pt D):613–7.
48. Poon NW, Gohel MD, Lau C, Hon EK, Leung PC, Ng CF. Melamine crystallization: physico-chemical properties, interactions with other lithogenic salts and response to therapeutic agents. J Urol. 2012;187(4):1483–90.
49. Chang H, Wu G, Yue Z, Ma J, Qin Z. Melamine poisoning pediatric urolithiasis treatment in Gansu, China 5-year follow-up analysis. Urology. 2017;109:153–8.
50. Fairley KF, Birch DF, Haines I. Abnormal urinary sediment in patients on triamterene. Lancet. 1983;1(8321):421–2.
51. Triamterene and the kidney. Lancet. 1986;1(8478):424.
52. Ettinger B, Oldroyd NO, Sörgel F. Triamterene nephrolithiasis. JAMA. 1980;244(21):2443–5.
53. Carr MC, Prien EL, Babayan RK. Triamterene nephrolithiasis: renewed attention is warranted. J Urol. 1990;144(6):1339–40.
54. Avenell A, Mak JC, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. Cochrane Database Syst Rev. 2014;(4):CD000227.
55. Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Krstic G, Wetterslev J, et al. Vitamin D supplementation for prevention of cancer in adults. Cochrane Database Syst Rev. 2014;(6):CD007469.
56. Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, et al. Vitamin D supplementation for prevention of mortality in adults. Cochrane Database Syst Rev. 2014;(1):CD007470.
57. Malihi Z, Wu Z, Stewart AW, Lawes CM, Scragg R. Hypercalcemia, hypercalciuria, and kidney stones in long-term studies of vitamin D supplementation: a systematic review and meta-analysis. Am J Clin Nutr. 2016;104(4):1039–51.
58. Ferraro PM, Taylor EN, Gambaro G, Curhan GC. Vitamin D intake and the risk of incident kidney stones. J Urol. 2017;197(2):405–10.
59. Leaf DE, Korets R, Taylor EN, Tang J, Asplin JR, Goldfarb DS, et al. Effect of vitamin D repletion on urinary calcium excretion among kidney stone formers. Clin J Am Soc Nephrol. 2012;7(5):829–34.
60. Taylor EN, Stampfer MJ, Curhan GC. Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. J Am Soc Nephrol. 2004;15(12):3225–32.
61. Chen X, Shen L, Gu X, Dai X, Zhang L, Xu Y, et al. High-dose supplementation with vitamin C—induced pediatric urolithiasis: the first case report in a child and literature review. Urology 2014;84(4):922–4.
62. Meschi T, Maggiore U, Fiaccadori E, Schianchi T, Bosi S, Adorni G, et al. The effect of fruits and vegetables on urinary stone risk factors. Kidney Int. 2004;66(6):2402–10.
63. Kossoff EH, Pyzik PL, Furth SL, Hladky HD, Freeman JM, Vining EP. Kidney stones, carbonic anhydrase inhibitors, and the ketogenic diet. Epilepsia. 2002;43(10):1168–71.
64. Mahmoud AA, Rizk T, El-Bakri NK, Riaz M, Dannawi S, Al TM. Incidence of kidney stones with topiramate treatment in pediatric patients. Epilepsia. 2011;52(10):1890–3.
65. Dell'Orto VG, Belotti EA, Goeggel-Simonetti B, Simonetti GD, Ramelli GP, Bianchetti MG, et al. Metabolic disturbances and renal stone promotion on treatment with topiramate: a systematic review. Br J Clin Pharmacol. 2014;77(6):958–64.

66. Goyal M, Grossberg RI, O'Riordan MA, Davis ID. Urolithiasis with topiramate in nonambulatory children and young adults. Pediatr Neurol. 2009;40(4):289–94.
67. Wroe S. Zonisamide and renal calculi in patients with epilepsy: how big an issue? Curr Med Res Opin. 2007;23(8):1765–73.
68. Gimpel C, Krause A, Franck P, Krueger M, von Schnakenburg C. Exposure to furosemide as the strongest risk factor for nephrocalcinosis in preterm infants. Pediatr Int. 2010;52(1):51–6.
69. Saarela T, Lanning P, Koivisto M, Paavilainen T. Nephrocalcinosis in full-term infants receiving furosemide treatment for congestive heart failure: a study of the incidence and 2-year follow up. Eur J Pediatr. 1999;158(8):668–72.

Chapter 6
Nutritional Contributors to Nephrolithiasis in Children

Kristina L. Penniston

Introduction

Urolithiasis is a common problem. Its incidence is rising in both men and women, including in regions with historically lower rates [1]. In the United States, urolithiasis in children has risen particularly dramatically [2, 3]. The causes for this are unknown. Urolithiasis is a multifactorial disease. Contributors include genetics; altered anatomy, physiology, and metabolism; environmental factors (e.g., exposures to specific foods or dietary patterns, medications, and hot temperatures); and patient behaviors. One or more of these factors in combination may be responsible depending on the individual. Urolithiasis is variably expressed. Some patients begin to form stones early in life, others later. Some form stones in both kidneys, others in only one. Some form many stones and recur frequently, others only once, even those exposed to and/or expressing the same risk factors. Patients form different types of stones, including mixtures of different materials. Calcium oxalate stones may occur as monohydrate or dihydrate, and stones are frequently mixtures, variably including calcium phosphate (carbonate apatite or brushite), hydroxyapatite, and ammonium urate. In the United States, calcium oxalate stones predominate in both children and adults.

Because urolithiasis is multifactorial, diet is only one of many possible contributors. In patients without genetic, physiologic, metabolic, or other etiologies, diet may be suspected. Lithogenic dietary factors may comingle with any of the above and with underlying medical conditions that predispose to urolithiasis. Nutritional factors affect kidney stone risk directly by affecting urine supersaturation, the first required step in crystal formation. This chapter reviews aspects of children's diets that might contribute to stone formation and growth. The mechanisms for dietary

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factors' influence on stone risk, specifically urinary parameters, are described as are their diagnostic indications. Because cutoffs for urinary risk factors are defined variably, risk is generally described as "higher" or "lower." Therapeutic interventions to address dietary risk factors are described in a companion chapter elsewhere in this book. This chapter begins by reviewing the role of nutritional balance in children's health and societal and familial influences on children's diets.

Nutrition Needs of Children

Children's diets must meet growth and development needs even if dietary changes are necessary to manage a disease process. Above all, children must be in a state of positive nitrogen balance. This means that the intake of nitrogen, a key component of dietary protein, must be greater than their loss of nitrogen. Children's protein needs, as well as energy and other nutrient needs, are higher per kilogram (kg) of body weight. For example, a healthy child from birth to 1 year should consume around 100 kilocalories (kcals) per kg daily. Compare this to energy needs for adults, which, depending on lifestyle, nutritional status, and energy expenditure, is approximately one-quarter of that. As children progress through infancy to the toddler stage and beyond, their energy needs per body weight become progressively lower and then stabilize when maximum stature and maturity are reached. Micronutrients are required by children in similarly higher amounts per body weight. To support skeletal growth, for example, children must be in positive calcium and phosphorus balance. During years of accelerated bone growth, children's needs for calcium are higher than for adults.

Micronutrients Vitamins and minerals must be present in the diet because the human body cannot synthesize them. Micronutrients do not provide energy (kcals), although some participate in chemical reactions in vivo that produce energy. Recommended intake levels differ by age group and life stage (Table 6.1). Balance is important—micronutrients have adverse effects when consumed in excess as well as when consumed in insufficient amounts. An example of adverse effects due to insufficient intake is scurvy, which is caused by inadequate vitamin C. Accounts of scurvy in children with autism spectrum disorder, who frequently have low or limited food repertoires, are reported [4, 5]. Zinc deficiency in boys results in hypogonadism and pubertal arrest. Insufficient calcium intake in childhood leads to decreased peak bone mass, increasing risk for osteopenia/osteoporosis in adulthood. Additionally, insufficient intake of vitamins or minerals that are cofactors for metabolic reactions leads to specific disorders related to impaired metabolism. On the other hand, excessive micronutrient intake is also associated with adverse events. Excessive vitamin A consumption in children may lead to altered skeletal development [6] and is linked with refractory hypercalcemia [7]. While vitamin A deficiency is a problem in many underdeveloped nations, a random sample within the United States found that 97% of toddlers taking multivitamins were ingesting preformed (active) vitamin A in amounts above the Tolerable Upper Intake Level

Table 6.1 Dietary Reference Intakes (DRIs) for micronutrients (vitamins and minerals) issued by the United States Food and Nutrition Board of the Institute of Medicine, National Academy of Sciences [46]. The DRIs include Recommended Dietary Allowances (RDAs) for nutrients with the most scientific evidence to support setting specific amounts and Adequate Intakes[a] (AIs) for nutrients with less evidence

	Infants		Children		Adolescents	
	0–5.9 months	6–11.9 months	1–3 years	4–8 years	9–13 years	14–18 years
Minerals						
Calcium, mg	200*	260*	700	1000	M: 1300 F: 1300	M: 1300 F: 1300
Chloride, g	0.18*	0.57*	1.5*	1.9*	M: 2.3* F: 2.3*	M: 2.3* F: 2.3*
Chromium, mcg	0.20*	5.5*	11*	15*	M: 25* F: 21*	M: 35* F: 24*
Copper, mcg	200*	220*	340	440	M: 700 F: 700	M: 890 F: 890
Fluoride, mg	0.01*	0.50*	0.70*	1.0*	M: 2.0* F: 2.0*	M: 3.0* F: 3.0*
Iodine, mcg	110*	130*	90	90	M: 120 F: 120	M: 150 F: 150
Iron, mg	0.27*	11	7	10	M: 8 F: 8	M: 11 F: 15
Magnesium, mg	30*	75*	80	130	M: 240 F: 240	M: 410 F: 360
Manganese, mg	0.003*	0.60*	1.2*	1.4*	M: 1.9* F: 1.6*	M: 2.2* F: 1.6*
Molybdenum, mcg	2*	3*	17	22	M: 34 F: 34	M: 43 F: 43
Phosphorus, mg	100*	275*	460	500	M: 1250 F: 1250	M: 1250 F: 1250
Potassium, mg	400*	860*	2000*	2300*	M: 2500* F: 2300*	M: 3000* F: 2300*
Selenium, mcg	15*	20*	20	30	M: 8 F: 8	M: 11 F: 9
Sodium, mg	110*	370*	800*	1000*	M: 1200* F: 1200*	M: 1500* F: 1500*
Zinc, mg	2*	3	3	5	M: 8 F: 8	M: 11 F: 9
Vitamins						
Vitamin A, mcg	400*	500*	300	400	M: 600 F: 600	M: 900 F: 700
Vitamin B1, mg	0.20*	0.30*	0.50	0.60	M: 0.90 F: 0.90	M: 1.2 F: 1.0
Vitamin B2, mg	0.30*	0.40*	0.50	0.60	M: 0.90 F: 0.90	M: 1.3 F: 1.0
Vitamin B3, mg	2*	4*	6	8	M: 12 F: 12	M: 16 F: 14

(continued)

Table 6.1 (continued)

	Infants		Children		Adolescents	
	0–5.9 months	6–11.9 months	1–3 years	4–8 years	9–13 years	14–18 years
Vitamin B6, mg	0.10*	0.30*	0.50	0.60	M: 1.0 F: 1.0	M: 1.3 F: 1.2
Vitamin B12, mcg	0.40*	0.50*	0.9	1.2	M: 1.8 F: 1.8	M: 2.4 F: 2.4
Folate, mcg	65*	80*	150	200	M: 300 F: 300	M: 400 F: 400
Pantothenic acid, mg	1.7*	1.8*	2*	3*	M: 4 F: 4	M: 5 F: 5
Vitamin C, mg	40*	50*	15	25	M: 45 F: 45	M: 75 F: 65
Vitamin D, mcg	10*	10*	15	15	M: 15 F: 15	M: 15 F: 15
Vitamin E, mg	4*	5*	6	7	M: 11 F: 11	M: 15 F: 15
Vitamin K, mcg	2.0*	2.5*	30*	55*	M: 60* F: 60*	M: 75* F: 75*
Biotin, mcg	5*	6*	8*	12*	M: 20* F: 20*	M: 25* F: 25*
Choline, mg	125*	150*	200*	250*	M: 375* F: 375*	M: 550* F: 400*

Values shown are RDAs and AIs per day in grams (g), milligrams (mg), or micrograms (mcg). AIs are identified with asterisks.

[a] Adequate Intake (AI) is a term for the estimation of nutrient needs for which scientific data to support setting a Recommended Dietary Allowance (RDA) is limiting

(TUL) [8]. Excess zinc intake, which is reported in children consuming fortified foods such as ready-to-consume breakfast cereals [9], can prevent copper absorption and subsequently induce anemia as copper is essential for iron absorption from the digestive tract. If caught early enough and addressed, these problems may be reversed without inducing permanent damage.

Macronutrients Macronutrients include fats (chains of individual fatty acids), protein (chains of amino acids), carbohydrates (long chains of "sugar" molecules, such as mono-, di-, and polysaccharides), fiber (nondigestible carbohydrates), and water. In contrast to micronutrients, macronutrients provide energy. The US Department of Agriculture (USDA) 2020–2025 Dietary Guidelines for Americans (Table 6.2) encourage children and adolescents to "maintain calorie balance to support normal growth and development without promoting excess weight gain" and provide guidelines for energy intake as well as for consumption of specific foods [10]. Foods to be encouraged include dairy (if consistent with family and cultural preferences) to provide carbohydrates as well as fat and protein. Meats, fish, and poultry are encouraged (again, if consistent with preferences and familial dietary patterns) for their high-biological value protein. For all children, fruits, vegetables, and whole grains

Table 6.2 ***Dietary Guidelines for Americans 2020–2025, developed by the US Department of Agriculture and US Department of Health and Human Services*** [10]. Values shown are suggested energy intakes (kcals) for infants 12 months of age to adulthood. Depending on the food group, recommended consumption is by cup/ounce gram equivalents (eq) either per day or per week (wk)

	INFANTS	CHILDREN	ADOLESCENTS	
	12–23 months	2–8 years	9–13 years	14–18 years
FOOD GROUP	700 to 1,000 kcals	1,000 to 2,000 kcals	1,400 to 26,00 kcals	1,800 to 3,200 kcals
Vegetables, cup eq/day	⅔ to 1	1 to 2½	1½ to 3½	2½ to 4
Vegetable subgroups in weekly amounts				
Dark green leafy vegetables, cup eq/wk	½ to 1	½ to 1½	1 to 2½	1½ to 2½
Red and orange vegetables, cup eq/wk	1 to 2½	2½ to 5½	3 to 7	5½ to 7½
Beans, peas, lentils, cup eq/wk	½ to ¾	½ to 1½	½ to 2½	1½ to 3
Starchy vegetables, cup eq/wk	1 to 2	2 to 5	3½ to 7	5 to 8
Other vegetables, cup eq/wk	¾ to 1c	1½ to 4	2½ to 5½	4 to 7
Fruits, cup eq/day	½ to 1	1 to 2	1½ to 2	1½ to 2½
Grains, ounce eq/day	1¾ to 3	3 to 6	5 to 9	6 to 10
Whole and refined grains by subgroup				
Grains, whole; ounce eq/day	1½ to 2	1½ to 3	2½ to 4½	3 to 5
Grains, refined; ounce eq/day	¼ to 1	1½ to 3	2½ to 4½	3 to 5
Dairy, cup eq/day	1⅔ to 2	2 to 2½	3	3
Protein foods, ounce eq/day	2	2 to 5½	4 to 6½	5 to 7
Protein foods by subgroup in weekly amounts				
Meats, poultry, eggs; ounce eq/wk	7 to 8¾	10 to 26	19 to 31	23 to 33
Seafood, ounce eq/wk	2 to 3	2 to 8	6 to 10	8 to 10
Nuts, seeds, soy products, ounce eq/wk	1 to 1¼	2 to 5	3 to 5	4 to 6
Oils, grams/day	9 to 13	15 to 24	17 to 34	24 to 51

are encouraged to provide the basis of carbohydrate intake and also to provide fiber. In order to avoid displacement of healthier foods and/or excess energy consumption, limited consumption of foods with added sugars, processed meats, and refined grains is recommended [11]. Children whose diets are excessive for energy, particularly from fat and carbohydrates, are at risk of becoming overweight and developing obesity. In particular, overconsumption of fructose, which is widespread in sugary beverages and many processed foods, is linked in children with overweight and obesity [12] as well as fatty liver [13]. Current estimates show that 17% of US chil-

dren aged 6–11 years are presenting with obesity, and 21% of adolescents aged 12–19 years are obese [14].

While avoidance of excess energy intake is paramount, it is also important that children's diets provide high-biological value protein at recommended levels by age group (Table 6.3). Children whose overall dietary patterns are insufficient for protein are at risk for malnutrition, even if carbohydrate and fat intakes are ample. In its most extreme version, protein deficiency in children results in kwashiorkor, a form of protein-calorie malnutrition that most often occurs amidst famine. In less extreme conditions, protein deficiency leads to slow growth and short stature, diminished muscle development, slow wound healing, and immune compromise. According to data from the National Health and Nutrition Examination Study (NHANES), one in

Table 6.3 Dietary Reference Intakes (DRIs) for water and macronutrients issued by the United States Food and Nutrition Board of the Institute of Medicine, National Academy of Sciences [46]. The DRIs include Recommended Dietary Allowances (RDAs) for nutrients with the most scientific evidence to support setting specific amounts and Adequate Intakes[a] (AIs) for nutrients with less evidence

	Infants		Children		Adolescents	
	0–5.9 months	6–11.9 months	1–3 years	4–8 years	9–13 years	14–18 years
Total water,[b] liters/day	0.70*	0.80*	1.3*	1.7*	M: 2.4* F: 2.1*	M: 3.3* F: 2.3*
Carbohydrate, grams/day	60*	95*	130	130	M: 130 F: 130	M: 130 F: 130
Total fiber, grams/day	ND[c]	ND[c]	19*	25*	M: 31* F: 26*	M: 38* F: 26*
Fat, grams/day	31*	30*	ND[c]	ND[c]	M: ND F: ND	M: ND F: ND
Linoleic acid, grams/day	4.4*	4.6*	7*	10*	M: 12* F: 10*	M: 16* F: 11*
α-Linolenic acid, grams/day	0.50*	0.50*	0.70*	0.90*	M: 1.2* F: 1.0*	M: 1.6* F: 1.1*
Protein,[d] grams/day	9.1*	11	13	19	M: 34[e] F: 34[e]	M: 52[e] F: 46[e]

[a] Adequate Intake (AI) is a term for the estimation of nutrient needs for which scientific data to support setting a Recommended Dietary Allowance (RDA) is limiting

[b] Includes all water contained in food, beverages, and drinking water

[c] Not determined

[d] Based on grams (g) protein per kilogram (kg) of body weight for the reference body weight; for children 9 years of age and adults, this is 0.8 g/kg body weight. For children up to 9 years of age, the RDA for protein per kg body weight is higher

[e] Body weight is key for determining individualized protein requirements. In estimating daily protein needs, the reference weight for adolescent males and females 9–13 years is 42.5 kg (94 pounds). For males and females 14–18 years, reference weights are 65 kg (143 pounds) and 57.5 kg (127 pounds), respectively. Thus, recommended protein consumption (g/day) may vary from data shown in the table

Values shown are RDAs and AIs per day. AIs are identified with asterisks

seven children in the United States between 6 and 13 years consumes insufficient protein [15].

How Children's Diets Are Influenced

Eating behaviors evolve during the first years of a child's life and are shaped by biological, familial, social, and cultural influences. Food preferences develop over time and are influenced by multiple factors, including flavors. Interestingly, dietary flavors appear to be experienced by the fetus in utero [16]; flavor familiarity of the postpartum infant is theorized [17]. If the infant is breastfed, sensory properties of breast milk may influence the acceptance and consumption of solid foods [18]. As children age, they rely on adults to feed them whether at home, school, or childcare. Young children are frequently fed by someone other than a parent. Influences on children's diets thus diversify depending on the multiple eating habits and norms to which they are exposed. In childcare and school settings, children observe the eating behavior of others and are influenced by them. Evidence supports, for example, that a child's selection and consumption of vegetables are influenced by siblings, peers, and the adults around them [19]. Food marketing and advertising also shape children's food choices as they are particular targets of campaigns for sugary breakfast cereals, sugar-sweetened beverages, and candy. In 2017, food companies spent $11 billion on television ads, and 80% of this was spent on the unhealthiest of offerings, e.g., processed foods, fast foods, sugary sodas, candy, and unhealthy snacks [20]; youth-targeted marketing represented a substantial proportion of this [21]. Not surprisingly, exposure to food marketing of unhealthy foods increases children's preferences for and consumption of these foods [22]. Economic factors may also affect children's diets. Although highly variable, healthier diets may cost more than less healthy diets for some families. In one meta-analysis, the cost of the healthiest compared to the least healthy diet (as defined by various diet quality indices), was approximately $550 higher per year [23]. Indeed, in parts of the United States, access to fruits and vegetables differs by socioeconomic status, suggesting that cost is a factor [24, 25].

Role of Nutrition in Urolithiasis

Diet is considered a modifiable factor in the management of many health conditions and disorders. As with urolithiasis, diet is usually a component of secondary prevention, i.e., prevention of disease progression, exacerbation, or recurrence. Many people with unhealthy diets, children included, never form kidney stones, pointing to other influences that comingle with diet to tip the balance toward urolithiasis. Thus, primary prevention with diet is not usually justified. Medical nutrition therapy practiced by a registered dietitian nutritionist (RDN) is the application of

evidence-based, personalized nutrition care—including setting goals for change and providing strategies to achieve them—to prevent and manage diseases. An alternative to the RDN's individualized approach is the recommendation of general dietary strategies, ideally based on guidelines derived from high-quality evidence. While the former is targeted at each individual's unique risk factors, nutritional needs, health status, food preferences, barriers to change, and other personal factors, the latter is not.

Diet is implicated in many patients with urolithiasis [26, 27]. But due to its multifactorial etiology, this is not always the case. Children may have risk factors for stones, such as high urine calcium, for example, without a dietary contributor(s). This is true for other urinary risk factors as well and underscores the multifactorial nature of urolithiasis. A careful dietary assessment is the best way to identify whether an observed stone risk factor is linked with diet. If dietary influences are not identified, no amount of dietary change is likely to reduce stone recurrence risk. If dietary influences are identified, they can be generally grouped into two categories: excessive and insufficient intake.

Excessive Intake and Urolithiasis

When consumed in excess, several dietary habits contribute to calcium-containing (calcium oxalate and calcium phosphate) and uric acid stones, the types of stones most frequently formed by children. Dietary factors related to excessive consumption are described; indications for making the nutrition diagnoses are explained (Table 6.4).

Excess Energy Excessive energy leads to overweight and obesity, which increases the risk for all types of urinary tract stones. The mechanism(s) for this association is unclear but may have to do in part with insulin resistance, which may be exacerbated by higher fructose intake [12]. Children have increased their energy intake over time, and this is attributed to dietary behaviors such as eating more food away from home, drinking more sugar-sweetened and other calorie-laden beverages, and consuming more calories from between-meal snacks [28]. More children with stones thus also present with overweight or obesity [14].

Excess Dietary Acid Load The prototypic Western diet is a pattern that induces higher net endogenous acid production. In this setting, renal citrate reabsorption increases and less is excreted. The reduction of citrate in urine contributes to higher urinary supersaturation for calcium stones. In addition to reducing renal citrate excretion, diets with high potential renal acid load (PRAL) can lead to metabolic acidosis if consumed chronically, inducing calcium resorption from bone. If calcium resorption overwhelms metabolic capacity to maintain homeostasis, then renal calcium excretion rises, potentially leading to higher urinary calcium excretion. Diets with high PRAL can also reduce urine pH, which increases the risk for uric

Table 6.4 Nutrition diagnoses related to urolithiasis

Nutrition problem statement...	…related to	…evidenced by	…and
Excessive bioactive substance intake (high dietary acid load) related to…	…insufficient intake of bicarbonate precursors from fruits/vegetables (and/or excessive intake of acidogenic foods) as evidenced by…	…low urine citrate, and/or overly acidic urine, and/or higher urine calcium, and…	…diet assessment
Excessive mineral intake (calcium) related to…	…excessive supplementation as evidenced by…	…higher urine calcium and…	…diet assessment
Excessive mineral intake (sodium and chloride) related to…	…high intake of salt-rich foods and their potential for expansion of extracellular volume as evidenced by…	…higher urine calcium and…	…diet assessment
Excessive vitamin intake (vitamin D) related to…	…excessive supplementation as evidenced by…	…higher urine calcium and/or high 25(OH)D and…	…diet assessment
Excessive vitamin intake (vitamin C) related to…	…excessive supplementation contributing to higher oxalate biosynthesis as evidenced by…	…higher urine oxalate and…	…diet assessment
Excessive carbohydrate intake (refined carbohydrates or added sugar) related to…	…higher intake of commercially-processed (or sugar-sweetened) foods as evidenced by…	…higher urine calcium and…	…diet assessment
Inadequate bioactive substance intake (bicarbonate precursors) related to…	…suboptimal intake of fruits/vegetables as evidenced by…	…low urine citrate, and/or overly acidic urine, and/or higher urine calcium, and…	…diet assessment
Inadequate fluid intake related to…	…not drinking enough to produce ample urine as evidenced by…	…low urine output and…	…diet assessment
Inadequate calcium intake related to…	…insufficient consumption of foods/beverages rich in calcium needed to bind oxalate as evidenced by…	…higher urine oxalate and…	…diet assessment
Inadequate prebiotic intake related to…	…low intake of fiber-rich foods containing prebiotics for oxalate-degrading probiotics in digestive tract as evidenced by…	…higher urine oxalate and…	…diet assessment

The table lists common nutrition diagnoses that might be identified by a registered dietitian nutritionist after diet assessment. Diet assessment is required in order to determine the likelihood of specific dietary factors (the nutrition problem) on observed urinary risk factors (evidence). The presence of 24-h urinary risk factors does not in and of itself confirm a dietary etiology.

acid precipitation and stone formation. While dietary protein derived from animal sources is most often implicated in diets high for PRAL, it is not the only factor. Foods higher for PRAL include not only meats of all types, poultry, fish, seafood, eggs, and cheeses—all of which are animal sources—but also grains [29]. Grains are often neglected as a contributor to PRAL but, if intake is excessive and not

opposed by ample intake of dietary bicarbonate precursors, they can significantly increase dietary acid load. Interestingly, dairy milk, kefir, and yogurt are not high for PRAL even though they come from animals. Importantly, these are also key dietary sources of calcium. Calcium is required for bone growth and also binds dietary oxalate and reduces its intestinal absorption. Thus, when dietary PRAL is a target for nutrition therapy to prevent stones, limitation of these foods in children is not only ill-advised but also does nothing to reduce PRAL. Protein-rich foods can and should be included in a dietary pattern that is suitably controlled for PRAL as long as the intake of fruits and vegetables, which contain organic acids that are converted in the liver to bicarbonate, are consumed in sufficient quantity to reduce PRAL. If lower urine citrate and/or higher urine calcium are present and cannot be accounted for by other factors, a diagnosis of high dietary PRAL may be considered (Table 6.4).

Added Sugar There is evidence that dietary patterns high in carbohydrates, especially from refined sources, increase calcium stone risk by impairing insulin regulation and lowering renal calcium reabsorption, leading to higher urinary calcium excretion [30, 31]. Additionally, in children with or at risk for diabetes mellitus, high carbohydrate loads may potentiate insulin resistance and lead to impaired ammoniagenesis. This reduces urine pH and increases uric acid stone risk [32]. Children's intake of sugar in the United States is high; advertising campaigns aimed at children, greater accessibility to processed and convenience foods, and increased snacking have contributed to higher sugar intake over time [21, 22]. One study showed that in the late 1970s the average younger child ate one between-meal snack per day; this increased to 3 per day by 2014 [33]. If urinary calcium excretion is high and cannot be explained by other factors, excess intake of added sugars may be suspected in the nutrition diagnosis (Table 6.4).

Excess Fat Diets high in fat are frequently higher for energy, which may lead to overweight or obesity, both of which are associated with higher stone risk [34]. Fat is critically important in children's diets, but intake exceeds recommendations for many [35], especially in children who more frequently consume processed and energy-dense foods. Excessive fat in the gastrointestinal tract can lead to higher permeability and absorption of oxalate. If the absorption of diet-derived oxalate is not impeded (e.g., bound by calcium or degraded by bacteria), it is excreted by the kidneys as there is no human need for oxalate. Higher urinary oxalate excretion is a primary risk factor for calcium oxalate stones. There is also recent evidence that high-fat diets, particularly those with excess arachidonic acid (a polyunsaturated omega-6 fatty acid consumed primarily in meats, including fish, poultry, and eggs), may increase urinary excretion of both calcium and oxalate. Although Taylor et al. found no association between arachidonic acid intake and incident kidney stones [36], Baggio et al. found that higher plasma phospholipid arachidonic acid content was associated with hypercalciuria, which they attributed to alterations in calcium-regulating hormones, higher intestinal calcium absorption, and bone turnover [37]. A purported link between high arachidonic

acid intake and hyperoxaluria was found by Messa et al., who observed higher arachidonic acid content in the red blood cell membranes of hyperoxaluric stone formers [38]. Interestingly, other polyunsaturated fatty acids, specifically eicosapentaenoic and docosahexaenoic acids, may serve as competitive substrates for arachidonic acid and may thus be therapeutic in patients with hypercalciuria and/or hyperoxaluria [39].

Excess Salt There are many dietary "salts," neutral compounds of cationic minerals and anionic minerals or organic acids, most of which are not associated with excessive intake or adverse effects. Examples are calcium salts (such as calcium carbonate, which is used in adding calcium to foods and beverages), lithium salts (consumed in small amounts in cereals and in some vegetables and spices), magnesium salts, and potassium salts. Sodium salts are also consumed, primarily as sodium chloride (NaCl), commonly known as "table salt." Excess NaCl induces expansion of extracellular volume which in turn reduces renal calcium reabsorption and increases urinary calcium excretion. This leads to a higher risk for calcium stones and, if unchecked over time, premature bone loss [40]. Interestingly, when sodium is complexed with other anions (e.g., bicarbonate, citrate, and sulfate) there is less or no increase in plasma volume and thus minimal effect on calciuria [41]. Children's intake of NaCl has increased over time. In children aged 6–18 years, data from the 2011–2012 NHANES estimated that average intake of sodium from NaCl was 3256 mg/day, not including any added salt [42]. Foods comprising the bulk of children's NaCl intake were pizza, Mexican mixed dishes, sandwiches (including burgers as well as deli meat sandwiches and sub sandwiches), breads, cold cuts, soups, savory snacks, and cheese. Of these, nearly 60% came from grocery store purchases, 16% came from fast food purchases, and 10% from school cafeterias [43]. Evidence shows that taste preferences formed during childhood for high-salt foods follow them into adulthood [44]. If urine calcium is high, and if NaCl intake features prominently in diet assessment, then excessive intake could be diagnosed (Table 6.4). Note that habitual intake of NaCl may be high even if 24-hour urine sodium and chloride are below risk cutoffs. This may be due to variable intake throughout the week and to the 24-hour urine collection being completed on a "low salt" day. The converse is also true, i.e., 24 h-hour urine sodium and chloride may appear high, but habitual NaCl intake may be assessed as generally well-controlled or even habitually low.

Uric Acid Precursors Overly acidic urine (pH <6.0) is the primary driver of uric acid stone formation. Thus, even in the setting of higher urinary uric acid excretion, control of urine pH is the main strategy to prevent uric acid stones. Urine uric acid is generated from exogenous purines (uric acid precursors) and also from endogenous sources, primarily the degradation of nucleic acids from normal cellular turnover. Dietary purines presumably increase uric acid stone risk by inducing higher uric acid synthesis and, subsequently, hyperuricosuria. While purines are found in meats and meat products (including poultry, fish, and seafood) as well as certain vegetables, the purines in vegetables have been shown to have no or negligible

effect on uric acid synthesis [45]. There is no recommended dietary intake level for purines. Although overly acidic urine is the primary driver of uric acid stone formation, if uric acid overproduction is thought to contribute to higher urine uric acid, and if intake of meats, fish, seafood, and/or poultry is excessive, then a diagnosis of excessive purine intake could be considered.

Excess Calcium and/or Vitamin D Excessive intake of these micronutrients from foods alone (diet) is usually not observed. In fact, insufficient intake of both calcium and vitamin D in children is more common. However, excessive supplementation of calcium and/or vitamin D is not unheard of. Both lead to higher urinary calcium excretion by way of higher gastrointestinal calcium absorption. The TUL for calcium is 2500 mg/day [46]. For vitamin D, the safe upper intake limit is 4000 IU/day (250 mcg) [46]. These should rarely be exceeded by anyone, including children, particularly those with a history of calcium stones or positive family history for stones, which may indicate greater susceptibility to hypercalciuria. If high urine calcium is present (especially if corroborated by elevated vitamin D status and/or serum calcium) and cannot be explained by other factors, and if calcium and/or vitamin D are supplemented in high amounts, excessive intake could be diagnosed (Table 6.4).

Excess Vitamin C (Ascorbic Acid) As with calcium and vitamin D, excessive intake of vitamin C from foods alone is nearly unheard of. However, when supplementing, it is not difficult to overwhelm the body's ability to use ascorbic acid—the higher end of which is estimated to be approximately 200 mg/day—leading to the obligate degradation of large amounts of ascorbic acid. The end product of degradation is oxalate; thus, ascorbic acid is a precursor to oxalate biosynthesis. Evidence confirms that excessive vitamin C supplementation can lead to hyperoxaluria [47]. Because vitamin C deficiency is quite rare in the United States, it is usually possible to meet vitamin C needs with as little as 1–2 servings of certain fruits, fruit juices, or vegetables daily. Thus, supplementation is rarely indicated. But vitamin C "megadosing" has for decades been promoted as a "magic bullet" for a variety of ailments, including cancer, the common cold, and several more serious immune-compromising illnesses. If higher urinary oxalate excretion cannot be explained by other dietary factors, and if the child is using a vitamin C supplement, excessive vitamin C intake could be the nutrition diagnosis (Table 6.4).

Insufficient Intake and Urolithiasis

When consumed in insufficient quantity, several dietary habits contribute to calcium-containing (calcium oxalate and calcium phosphate) and uric acid stones, the types of stones most frequently formed by children. Dietary factors related to inadequate consumption are described; indications for making the nutrition diagnoses are explained (Table 6.4).

Fluids In the majority of situations, fluid intake determines urine output. All fluids contribute to urine production. While foods with high water content also contribute to urine production, the ingestion of fluids from beverages accounts for the majority of urine volume. The initial driving force for crystal formation and growth in urine is supersaturation, which is dependent on urine volume. If high enough, urine volume may outweigh the influence of urinary crystal promoters, depending on the magnitude of their expression. But if urine volume is insufficient to compensate for urinary stone risk factors, urine reaches supersaturation, and crystals precipitate. Maintaining adequate hydration status is important for optimal physiologic function and cognitive performance. Among children 4–17 years of age in 13 different countries, 60% did not meet recommendations for fluid intake [48]. Plain water intake by children is lower than recommended in the United States. Among adolescents, plain drinking water accounted for only 33% of total water intake [49], which may account for less than optimal fluid intake and lower urine output. While fluids other than water contribute toward urine output, they may contain energy, added sugar, or salt, any of which if consumed in excess could outweigh the benefit. Nonetheless, all fluids raise urine output. In the presence of low urine volume, low fluid intake is diagnosed (Table 6.4).

Dietary Bicarbonate Precursors As described earlier, the typical Western diet confers a net acid load. Dietary bicarbonate precursors consumed from fruits and vegetables oppose this acid load. Insufficient consumption of fruits and vegetables thus contributes to high dietary acid load or PRAL. "Insufficient" intake is variably defined but is essentially that which is unable to compensate for a given dietary acid load. The USDA Dietary Guidelines for Americans (Table 6.2) recommend anywhere from 2 to >5 servings of fruits/vegetables daily. Children's intake of fruits and vegetables varies with family and cultural influences, but the majority of studies suggest suboptimal intake overall [50]. Of children aged 6–18 years, <25% met recommendations for fruit and vegetable intake [51]. In 2017, only 7% of US high school students met recommendations for fruit intake, and only 2% met vegetable intake recommendations. Among all children aged 2–17 years, 10% ate no fruits or vegetables daily [52]. In the presence of low urine citrate and/or overly acidic urine—and/or hypercalciuria as described earlier—and if the diet assessment reveals suboptimal intake, low intake of bicarbonate precursors from fruits and vegetables may be diagnosed (Table 6.4).

Insufficient Calcium Insufficient calcium consumption by children is endemic [53], especially when daily need rises to 1300 mg/day, as in children 9–19 years of age. With respect to urolithiasis, insufficient calcium intake increases the amount of oxalate absorbed from foods as there is less calcium in the digestive tract to bind with oxalate and reduce its intestinal absorption. Low calcium intake may also paradoxically contribute to hypercalciuria. In several studies, when adults with idiopathic hypercalciuria were placed on low calcium diets, most were unable to reabsorb calcium as efficiently as normal subjects, leading in some cases to increased bone resorption in order to maintain normal serum calcium [54]. It is therefore pos-

sible that insufficient calcium intake in children with such alterations in renal mineral handling could lead to hypercalciuria. Calcium was designated a nutrient of public health concern in the 2015–2020 USDA Dietary Guidelines for Americans as data showed that many Americans, especially older children and adolescents, do not meet their needs. Even when using supplements, female adolescents ages 12–19 years were at the highest risk for calcium underconsumption [55, 56]. Certainly, in the presence of higher urinary oxalate excretion, consider insufficient calcium intake as a diagnosis. As the oxalate content of the diet increases, such as with ample intake of healthy fruits, vegetables, and whole grains, the need for calcium to bind oxalate rises simultaneously. But even if oxalate intake is not high, suboptimal calcium intake should be considered as an etiology for high urine oxalate (Table 6.4).

Insufficient Vitamin D Insufficient vitamin D intake, if it leads to low vitamin D status, is associated with secondary hyperparathyroidism, leading potentially to higher renal filtered calcium load, calcium resorption from bone, and hypercalciuria. Among children and adolescents aged 2–18 years, 81% do not meet the daily recommended intake [57]. In children with concomitant insufficient calcium intakes, the potential for secondary hyperparathyroidism and hypercalciuria is potentiated. Obesity may be a complicating factor in the setting of insufficient vitamin D consumption. A recent study in obese children found an inverse association of vitamin D status with body mass and a direct association with parathyroid hormone (PTH) [58]. Interestingly, these alterations were normalized after weight loss. Some studies have reported that vitamin D supplementation by obese individuals has favorable effects on PTH and bone resorption [59]. While Vitamin D supplementation by individuals with low vitamin D status is not associated with hypercalciuria [60] and in fact may correct it (if the etiology was secondary hyperparathyroidism), supplementation by already replete individuals should be avoided.

Insufficient Magnesium In the United States, magnesium is considered a nutrient of "public health concern" [61] as 60% of Americans [62] and 70–80% of older adults have insufficient intake [63]. The same is observed in children, with estimates that upwards of 30% of children, especially "picky eaters," have low magnesium intake [61]. The 24-h urinary excretion of magnesium is directly related to magnesium status and is a better measure of status than serum magnesium [64], which, like calcium, does not drop until severe deficiency. Lower urine magnesium increases the risk for calcium oxalate stone formation because magnesium is less available to bind with oxalate. When magnesium and oxalate bind in urine, they form a much more soluble complex than calcium and oxalate. Thus, insufficient magnesium consumption among children may contribute to higher calcium oxalate stone risk. If 24-hour urine magnesium is low, then insufficient magnesium status should be diagnosed.

Insufficient Fiber/Prebiotics Children need fiber (Table 6.3) for the same reasons as do adults. It helps to regulate bowel function, is involved in normal lipid metabolism, and is associated with lower risk for diabetes, heart disease, and some cancers. With respect to urolithiasis, certain compounds in dietary fiber, such as uronic acids present in cellulose-containing foods, reduce calcium absorption from the gastrointestinal tract [65]. While this effect may be modest [66], it may actually be helpful in individuals with suspected absorptive hypercalciuria. Thus, low fiber intake could be implicated in certain forms of hypercalciuria. Another property of dietary fiber is that it is the primary source of prebiotics, phytochemicals, and other compounds that serve as substrate for probiotics, healthy microbes that inhabit the normal digestive tract. Lower fiber intakes compromise the ability of the gut microbiome to contribute to healthy gastrointestinal tract function [67]. Importantly, many of the microbes that normally inhabit the gut can degrade oxalate within multispecies collaborative networks [68, 69]. The gut microbiome is thus gaining attention as an important mechanism in controlling oxalate absorption and urinary excretion [70]. Exposure to oral antibiotics as a contributor to oxalate-related dysbiosis is documented [71]. While first noted in children with cystic fibrosis [72], the frequent use of antibiotics in children for transient conditions, such as ear infection or respiratory tract infection, is increasingly recognized as a risk factor for hyperoxaluria and calcium oxalate stone formation [73]. In sum, children's intake of fiber is generally low, as is adults' [74]. In the setting of higher urinary oxalate excretion, if dysbiosis is suspected as a contributor, then low fiber intake may be an appropriate nutrition diagnosis (Table 6.4).

Conclusion

Dietary factors influence the risk for urolithiasis directly, such as contributing to higher calcium excretion, or indirectly, such as contributing to overweight and obesity. But diet is one of only several factors that causes urolithiasis. When diet is correctly identified as the etiology for stone risk, such as when suboptimal calcium intake is identified as a primary contributor to hyperoxaluria, dietary change is a potent means to reduce risk. However, when diet is incorrectly attributed to a stone risk factor, changing the diet will not resolve or reduce stone risk and increases the possibility of unfavorable effects on nutrient balance and nutrition quality.

References

1. Raheem OA, Khandwala YS, Sur RL, Ghani KR, Denstedt JD. Burden of urolithiasis: trends in prevalence, treatments, and costs. Eur Urol Focus. 2017;3:18–26.
2. Bowen DK, Tasian GE. Pediatric stone disease. Urol Clin North Am. 2018;45:539–50.

3. Clayton DB, Pope JC. The increasing pediatric stone disease problem. Ther Adv Urol. 2011;3:3–12.
4. Kinlin LM, Blanchard AC, Silver S, Morris SK. Scurvy as a mimicker of osteomyelitis in a child with autism spectrum disorder. Int J Infect Dis. 2018;69:99–101.
5. Nastro A, Rosenwasser N, Daniels SP, Magnani J, Endo Y, Hampton E, et al. Scurvy due to selective diet in a seemingly healthy 4-year-old boy. Pediatrics. 2019;144:e20182824.
6. Conaway HH, Henning P, Lerner UH. Vitamin A metabolism, action, and role in skeletal homeostasis. Endocr Rev. 2013;34:766–97.
7. Lorenzo M, Nadeau M, Harringon J, Gill PJ. Refractory hypercalcemia owing to vitamin a toxicity in a 4-year-old boy. CMAJ. 2020;192:E671–5.
8. Butte NF, Fox MK, Briefel RR, Siega-Riz AM, Dwyer JT, Deming DM, Reidy KC. Nutrient intakes of US infants, toddlers, and preschoolers meet or exceed dietary reference intakes. J Am Diet Assoc. 2010;110:S27–37.
9. Rangan AM, Samman S. Zinc intake and its dietary sources: results of the 2007 Australian National Children's nutrition and physical activity survey. Nutrients. 2012;4:611–24.
10. U.S. Department of Agriculture and U.S. Department of Health and Human Services. Dietary Guidelines for Americans, 2020–2025. 9th Edition. December 2020. Available at https://www.dietaryguidelines.gov/sites/default/files/2020-12/Dietary_Guidelines_for_Americans_2020-2025.pdf. Accessed 09 Feb 2021.
11. Cena H, Calder PC. Defining a healthy diet: evidence for the role of contemporary dietary patterns in health and disease. Nutrients. 2020;12:334.
12. Patterson ME, Yee JK, Wahjudi P, Mao CS, Lee W-NP. Acute metabolic responses to high fructose corn syrup ingestion in adolescents with overweight/obesity and diabetes. J Nutr Intermed Metab. 2018;14:1–7.
13. DiStefano JK, Shaibi GQ. The relationship between excessive dietary fructose consumption and paediatric fatty liver disease. Pediatr Obes. 2020;e12759 [online ahead of print].
14. Sanyaolu A, Okorie C, Qi X, Locke J, Rehman S. Childhood and adolescent obesity in the United States: a public health concern. Glob Pediatr. Health. 2019;6:2333794X19891305.
15. Hess J, Slavin J. Snacking for a cause: nutritional insufficiencies and excesses of U.S. children, a critical review of food consumption patterns and macronutrient and micronutrient intake of U.S. children. Nutrients. 2014;6:4750–9.
16. Mennella JA, Jagnow CP, Beauchamp GK. Prenatal and postnatal flavor learning by human infants. Pediatrics. 2001;107:E88.
17. Cooke L, Fildes A. The impact of flavour exposure in utero and during milk feeding on food acceptance at weaning and beyond. Appetite. 2011;57:808–11.
18. Harris G, Coulthard H. Early eating behaviors and food acceptance revisited: breastfeeding and introduction of complementary foods as predictive of food acceptance. Curr Obes Rep. 2016;5:113–20.
19. Johnson SL. Developmental and environmental influences on young children's vegetable preferences and consumption. Adv Nutr. 2016;7:220S–31S.
20. Andreyeva T, Kelly IR, Harris JL. Exposure to food advertising on television: associations with children's fast food and soft drink consumption and obesity. Econ Hum Biol. 2011;9:221–33.
21. Powell LM, Harris JL, Fox T. Food marketing expenditures aimed at youth: putting the numbers in context. Am J Prev Med. 2013;45:453–61.
22. Smith R, Kelly B, Yeatman H, Boyland E. Food marketing influences on children's attitudes, preferences and consumption: a systematic critical review. Nutrients. 2019;11:875.
23. Rao M, Afshin A, Singh G, Mozaffarian D. Do healthier foods and diet patterns cost more than less healthy options? A systematic review and meta-analysis. BMJ Open. 2013;3:e004277.
24. Darmon N, Drewnowski A. Does social class predict diet quality? Am J Clin Nutr. 2008;87:1107–17.
25. Dubowitz T, Heron M, Bird CE, Lurie N, Finch BK, Basurto-Dávila R, et al. Neighborhood socioeconomic status and fruit and vegetable intake among whites, blacks, and Mexican Americans in the United States. Am J Clin Nutr. 2008;87:1883–91.

26. Vieira MS, Francisco PC, Hallal ALLC, Penido MGMG, Bresolin NL. Association between dietary pattern and metabolic disorders in children and adolescents with urolithiasis. J Pediatr. 2020;96:333–40.
27. Hernandez JD, Ellison JS, Lendvay TS. Current trends, evaluation, and management of pediatric nephrolithiasis. JAMA Pediatr. 2015;169:964–70.
28. Savage JS, Fisher JO, Birch LL. Parental influence on eating behavior: conception to adolescence. J Law Med Ethics. 2007;35:22–34.
29. Remer T, Manz F. Potential renal acid load of foods and its influence on urine pH. J Am Diet Assoc. 1995;95:791–7.
30. DiNicolantonio JJ. Not salt but sugar as aetiological in osteoporosis: a review. Mo Med. 2018;115:247–52.
31. Schwille PO, Rumenapf G, Kohler R. Blood levels of glucometabolic hormones and urinary saturation with stone forming phases after an oral test meal in male patients with recurrent idiopathic calcium urolithiasis and in healthy controls. J Am Coll Nutr. 1989;8:557–66.
32. Schaeffer AJ, Feng Z, Trock BJ, Mathews RI, Neu AM, Gearhart JP, Matlaga BR. Medical comorbidities associated with pediatric kidney stone disease.
33. Barrera CM, Moore LV, Perrine CG, Hamner HC. Number of eating occasions and source of foods and drinks among young children in the United States: NHANES, 2009-2014. Nutrients. 2019;11:897.
34. Poore W, Boyd CJ, Singh NP, Wood K, Gower B, Assimos DG. Obesity and its impact on kidney stone formation. Rev Urol. 2020;22:17–23.
35. Shan Z, Rehm CD, Rogers G, Ruan M, Wang DD, Hu FB, et al. Trends in dietary carbohydrate, protein, and fat intake and diet quality among US adults, 1999-2016. JAMA. 2019;322:1178–87.
36. Taylor EN, Stampfer MJ, Curhan GC. Fatty acid intake and incident nephrolithiasis. Am J Kidney Dis. 2005;45:267–74.
37. Baggio B, Budakovic A, Nassuato MA, Vezzoli G, Manzato E, Luisetto G, Zaninotto M. Plasma phospholipid arachidonic acid content and calcium metabolism in idiopathic calcium nephrolithiasis. Kidney Int. 2000;58:1278–84.
38. Messa P, Londero D, Massarino F, Paganin L, Mioni G, Zattoni F, Cannella G. Abnormal arachidonic acid content of red blood cell membranes and main lithogenic factors in stone formers. Nephrol Dial Transplant. 2000;15:1388–93.
39. Rodgers AL, Siener R. The efficacy of polyunsaturated fatty acids as protectors against calcium oxalate renal stone formation: a review. Nutrients. 2020;12:1069.
40. Frassetto LA, Morris RC Jr, Sellmeyer DE, Sebastian A. Adverse effects of sodium chloride on bone in the aging human population resulting from habitual consumption of typical American diets. J Nutr. 2008;138:419S–22S.
41. Pinheiro VB, Baxmann AC, Tiselius H-G, Heilberg IP. The effect of sodium bicarbonate upon urinary citrate excretion in calcium stone formers. Urology. 2013;82:33–7.
42. Quader ZS, Gillespie C, Sliwa SA, Ahuja JKC, Burdg JP, Moshfegh A, et al. Sodium intake among US-school-aged children: National Health and nutrition examination survey, 2011-2012. J Acad Nutr Diet. 2017;117:39–47.
43. Quader ZS, Zhao L, Gillespie C, Cogswell ME, Terry AL, Moshfegh A, Rhodes D. Sodium intake among persons aged ≥2 years – United States, 2013-2014. MMWR Morb Mortal Wkly Rep. 2017;66:324–38.
44. Ventura AK, Worobey J. Early influences on the development of food preferences. Curr Biol. 2013;23:R401–8.
45. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Purine-rich foods, dairy and protein intake, and the risk of gout in men. N Engl J Med. 204;350:1093–103.
46. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium; Ross AC, Taylor CL, Yaktine AL, et al., editors. Dietary Reference Intakes for Calcium and Vitamin D. Washington (DC): National Academies Press (US); 2011. 6, Tolerable Upper Intake Levels: Calcium and Vitamin D. Available from: https://www.ncbi.nlm.nih.gov/books/NBK56058/. Accessed 29 Mar 2021.

47. Baxmann AC, Mendonça DOG, C, Heilberg IP. Effect of vitamin C supplements on urinary oxalate and pH in calcium stone-forming patients. Kidney Int. 2003;63:1066–71.
48. Bottin JH, Morin C, Guelinckx I, Perrier ET. Hydration in children: what do we know and why does it matter? Ann Nutr Metab. 2019;74(suppl 3):11–8.
49. Patel AI, Shapiro DJ, Wang YC, Cabana MD. Sociodemographic characteristics and beverage intake of children who drink tap water. Am J Prev Med. 2013;45:75–82.
50. Eliason J, Acciai F, deWeese RS, Vega-Lopez S, Ohri-Vachaspati P. Children's consumption patterns and their parent's perception of a healthy diet. Nutrients. 2020;12:2322.
51. Kim SA, Moore LV, Galuska D, Wright AP, Harris D, Grummer-Strawn LM, et al. Vital signs: fruit and vegetable intake among children – United States, 2003-2010. MMWR Morb Mortal Wkly Rep. 2014;63:671–6.
52. Lange SJ, Moore LV, Harris DM, Merlo CI, Lee SH, Demissie Z, Galuska D. Percentage of adolescents meeting federal fruit and vegetable intake recommendations – youth risk behavior surveillance system, United States, 2017. MMWR Morb Mortal Wkly Rep. 2021;70:69–74.
53. Lappe JM, McMahon DJ, Laughlin A, Hanson C, Desmangles JC, Begley M, Schwartz M. The effect of increasing dairy calcium intake of adolescent girls on changes in body fat and weight. Am J Clin Nutr. 2017;105:1046–53.
54. Worcester EM, Coe FL. New insights into the pathogenesis of idiopathic hypercalciuria. Semin Nephrol. 2008;28:120–32.
55. Banna J, O'Driscoll J, Boushey CJ, Auld G, Olson B, Cluskey M, et al. Parent and household influences on calcium intake among early adolescents. BMC Public Health. 2018;18:1390.
56. US Department of Agriculture Agricultural Research Service. 2019. Usual nutrient intake from foods and beverages, by gender and age, what we eat in America, NHANES 2013–2016. Available from: www.ars.usda.gov/nea/bhnrc/fsrg. Accessed 11 Apr 2021.
57. Taylor SN. Vitamin D in toddlers, preschool children, and adolescents. Ann Nutr Metab. 2020;76(suppl 2):30–40.
58. Reinehr T, de Sousa G, Alexy U, Kersting M, Andler W. Vitamin D status and parathyroid hormone in obese children before and after weight loss. Eur J Endocrinol. 2007;157:225–32.
59. Migliaccio S, Di Nisio A, Mele C, Scappaticcio L, Savastano S, Colao A. Obesity and hypovitaminosis D: causality of casualty? Int J Obes Suppl. 2019;9:20–31.
60. Penniston KL, Jones AN, Nakada SY, Hansen KE. Vitamin D repletion does not alter urinary calcium excretion in healthy postmenopausal women. BJU Int. 2009;104:1512–6.
61. DeNicolantonio JJ, O'Keefe JH, Wilson W. Subclinical magnesium deficiency: a principal drive of cardiovascular disease and a public health crisis. Open Heart. 2018;5:e000668.
62. Workinger JL, Doyle RP, Bortz J. Challenges in the diagnosis of magnesium status. Nutrients. 2018;10:1202.
63. de Baaij JHF, Hoenderop JGJ, Bindels RJM. Magnesium in man: implications for health and disease. Physiol Rev. 2015;95:1–46.
64. Ennis JL, Asplin JR. The role of the 24-h urine collection in the management of nephrolithiasis. Int J Surg. 2016;36(Pt D):633–7.
65. Shah M, Chandalia M, Adams-Huet B, Brinkley LJ, Sakhaee K, Grundy SM, Garg A. Effect of a high-fiber diet compared with a moderate-fiber diet on calcium and other mineral balances in subjects with type 2 diabetes. Diabetes Care. 2009;32:990–5.
66. Buchowski MS. Calcium in the context of dietary sources and metabolism, in calcium: chemistry, analysis, function and effects. 2015. p. 3–20. https://doi.org/10.1039/9781782622130-00003
67. Wegh CAM, Schoterman MHC, Vaughan EE, Belzer C, Benninga MA. The effect of fiber and prebiotics on children's gastrointestinal disorders and microbiome. Expert Rev Gastroenterol Hepatol. 2017;11:1031–45.
68. Miller AW, Choy D, Penniston KL, Lange D. Inhibition of urinary stone disease by a multispecies bacterial network ensures healthy oxalate homeostasis. Kidney Int. 2019;96:180–8.
69. Stern JM, Moazami S, Qiu Y, Kurland I, Chen Z, Agalliu I, et al. Evidence for a distinct gut microbiome in kidney stone formers compared to non-stone formers. Urolithiasis. 2016;44:399–407.

70. Ticinesi A, Nouvenne A, Meschi T. Gut microbiome and kidney stone disease: not just an Oxalobacter story. Kidney Int. 2019;96:25–7.
71. Tasian GE, Jemielita T, Goldfarb DS, Copelovith L, Gerber JS, Wu Q, Denburg MR. Oral antibiotic exposure and kidney stone disease. J Am Soc Nphrol. 2018;29:1731–40.
72. Sidhu H, Hoppe B, Hesse A, Tenbrock K, Brömme S, Rietschel E, Peck AB. Absence of Oxalobacter formigenes in cystic fibrosis patients: a risk factor for hyperoxaluria. Lancet. 1998;352:1026–9.
73. Denburg MR, Koepsell K, Lee J-J, Gerber J, Bittinger K, Tasian GE. Perturbations of the gut microbiome and metabolome in children with calcium oxalate kidney stone disease. JASN. 2020;31:1358–69.
74. Kranz S, Brauchla M, Slavin JL, Miller KB. What do we know about dietary fiber intake in children and health? The effects of fiber intake on constipation, obesity, and diabetes in children. Adv Nutr. 2012;3:47–53.

Chapter 7
Urological Surgery in Children with Nephrolithiasis

John Weaver, Jonathan S. Ellison, and Gregory E. Tasian

History and Physical

Pediatric patients with nephrolithiasis can often present with vague, nebulous symptoms. Unlike adults, prepubescent children often do not present with classic flank pain localized to the affected kidney. Rather, nonspecific abdominal pain is often the initial presenting complaint. Thus, it is critical for the physician to possess a high degree of suspicion in these cases, particularly if the patient has a prior history of kidney stones. Children presenting with their initial stone event often present an even greater diagnostic dilemma. A comprehensive flowsheet from the Children's Hospital of Philadelphia illustrating a standard care pathway for pediatric patients presenting with a non-emergent kidney stone can be found in Fig. 7.1 [1]. The evaluation of a child with a suspected ureteral stone should begin with a thorough history to determine the location, quality, quantity, and duration of the pain. Inciting and alleviating factors should be assessed. As previously mentioned, children may not be able to localize their pain as well as adults or pinpoint an inciting factor. Children with a history of symptomatic stones may be able to identify recurrent episodes by drawing on their prior lived experience. Patients will often also report nausea and vomiting since the onset of their pain. Some patients will endorse gross hematuria [2]. Children complaining of fevers and chills during an acute stone episode should be evaluated urgently as a febrile child with an obstructing ureteral stone is a surgical emergency requiring prompt diagnosis. Should these children present with an obstructed urinary tract in conjunction with infected urine, they are at high risk of decompensating quickly and developing sepsis. As such, immediate

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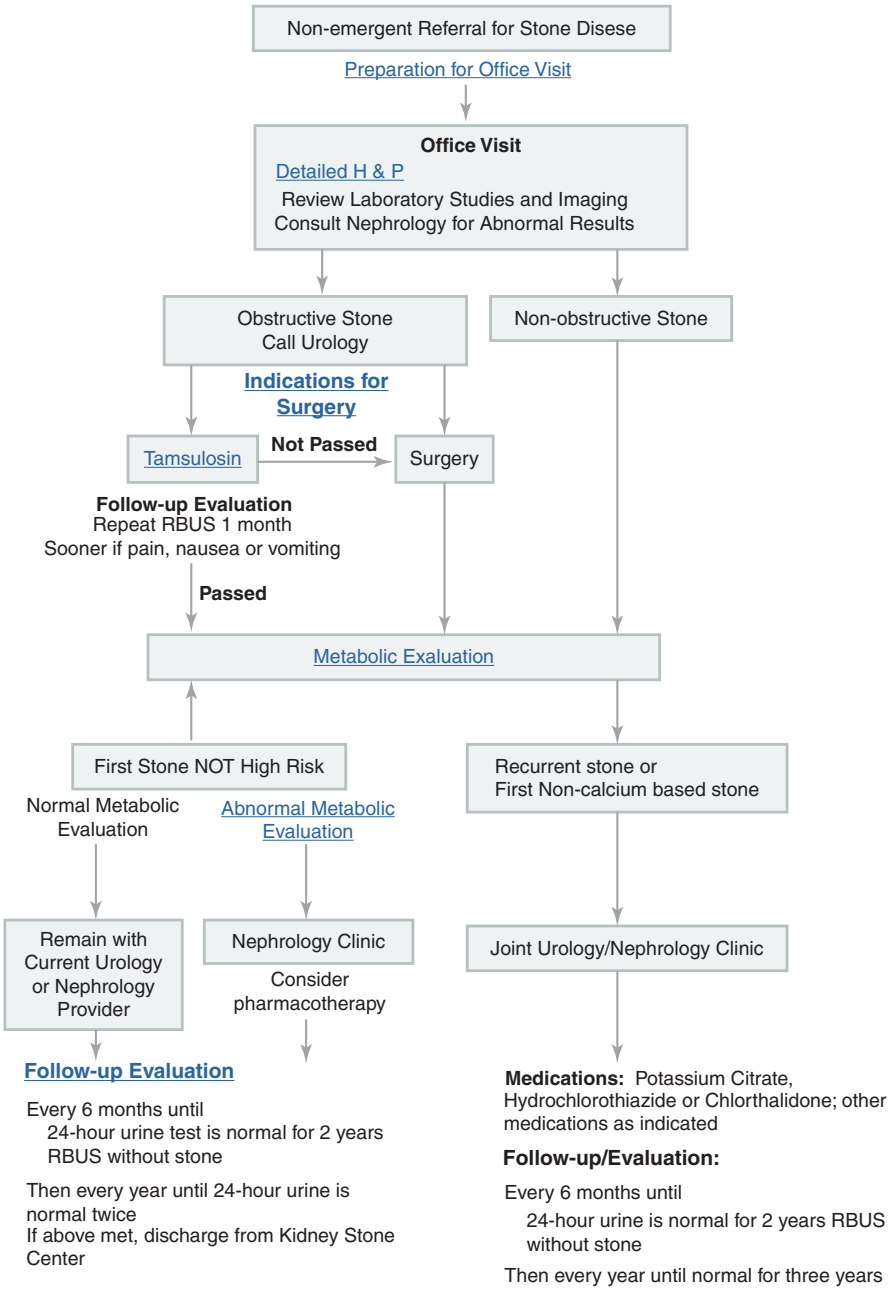

Fig. 7.1 Standard care pathway for patients presenting with a non-emergent kidney stone [17]

decompression of the obstructed urinary system with either the placement of a ureteral stent or nephrostomy tube is warranted, with plans to delay definitive stone treatment until after the infection has been treated. For these acutely ill patients, Fig. 7.2 summarizes an emergency room treatment pathway [3].

A thorough family history of nephrolithiasis should be obtained from any patient being evaluated for kidney stones. Inherited metabolic or genetic conditions that increase risk for nephrolithiasis include disorders such as cystinuria, primary hyperoxaluria, CYP24A1 gene mutations, or Dent's disease. A complete dietary history should also be obtained including daily fluid intake, salt intake, vitamin, and mineral supplementation as well as if the patient is on a special diet, such as a ketogenic diet. Certain medications can also place patients at an increased risk for stones. These include, but are not limited to, corticosteroids, diuretics (furosemide, acetazolamide), protease inhibitors (indinavir), antibiotics, and anti-epileptics (topiramate) [4, 5]. A thorough past medical history with an emphasis on genitourinary

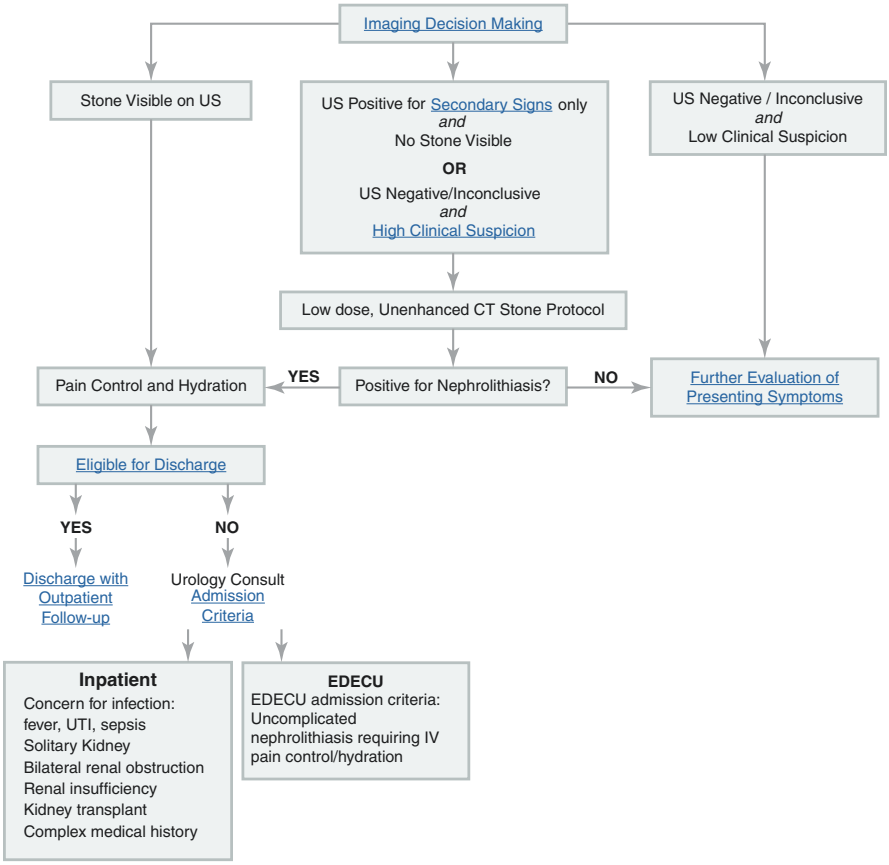

Fig. 7.2 Emergency Department Pathway for Evaluation and Treatment of Children with Suspected Nephrolithiasis (used with permission of Children's Hospital of Philadelphia, 2022)

issues should be obtained. A history of urinary tract infections or urinary tract abnormalities resulting in urinary stasis can put a patient at increased risk for nephrolithiasis. Additionally, patients with a history of intestinal malabsorption or chronic immobility are at increased risk for stone formation.

A focused physical exam evaluating for kidney stones includes a complete abdominal exam while also checking for costovertebral tenderness bilaterally. Patients may endorse costovertebral or lower quadrant tenderness on the affected side. A genitourinary exam is necessary as well. If the stone has migrated into the distal ureter the patient may complain of frequency, irritation, and dysuria with voiding. They may experience bladder spasms that localize to the tip of the penis in males and the external genitalia in females. In boys, a distal ureteral calculus may mimic testicular pain concerning an acute scrotum. Detailed physical examination looking for dysmorphic features (William syndrome), rickets (Dent's disease, hereditary hypophosphatemic rickets with hypercalciuria), or gout (hypoxanthine-guanine phosphoribosyltransferase deficiency, phosphoribosyl pyrophosphate synthetase superactivity) can be helpful.

Preoperative Diagnostic Studies

A urinalysis is a critical component of the nephrolithiasis work-up. There will often be red blood cells present as a result of urothelial irritation. However, the presence of red blood cells on the urinalysis is not 100% sensitive. The absence of red blood cells in the urine does not rule out the presence of a kidney stone [2].

Finding bacteria in a urine specimen suggests the presence of a UTI. The threshold for the classic definition of bacteriuria is 5+, which is roughly equivalent to 100,000 colony-forming units (CFUs)/mL [6]. Nitrites will be positive if an organism that reduces nitrate is present within the urine. However, one must consider that not all urinary pathogens are nitrate reducers, such as *Pseudomonas* and Gram-positive organisms. Nonetheless, a positive test is specific for bacterial presence. The presence of any amount of bacteria in the setting of a kidney stone should trigger awareness as to a potential infection. Pyuria, defined as urine WBC >10 or positive leukocyte esterase, indicates the presence of inflammation. Pyuria may be present in the absence of an infection as it is not specific for infection and has a low positive predictive value. However, pyuria is sensitive to infection and its absence virtually eliminates the presence of an infection, with a negative predictive value of nearly 90% [6, 7].

It should be noted that a urinalysis that is negative for infection does not completely rule out the presence of an infection, as urine proximal to an obstructing stone can become infected. This urine may not be able to pass into the bladder as a result of the obstruction and a urine specimen from the bladder would hence be sterile. Thus, in the setting of a urinalysis that is negative for leukocytes and nitrites, one should still maintain a concern for obstructed pyelonephritis when a febrile

illness, systemic inflammatory response syndrome, or other systemic signs of infection are present.

A basic metabolic panel should also be obtained when evaluating a patient for a potential stone episode. A patient with a ureteral stone may be found to have elevated creatinine as a result of obstruction of a renal unit and/or dehydration from associated nausea and vomiting. Electrolytes may also be significantly abnormal depending on how long the patient has been symptomatic. In cases where the entire functional renal system is obstructed (i.e., an obstructed solitary kidney or bilateral ureteral calculi in a child with two functioning renal units), prompt decompression with or without definitive initiation treatment is warranted.

Imaging

When a practitioner's index of suspicion for a kidney stone is high, imaging is necessary to establish the diagnosis. Non-contrast computed tomography (CT) is exceptionally accurate for diagnosing urinary stones with nearly 100% sensitivity and specificity. Nonetheless, because CT scans deliver ionizing radiation, which is associated with an increased risk for malignancy later in life, efforts have been made to use ultrasonography as the first-line imaging modality for nephrolithiasis in children [8]. In fact, recent studies have found that although ultrasound (US) is less sensitive and specific than CT, US accurately identifies clinically significant kidney stones in children with 70% sensitivity and >95% specificity [9, 10]. Hence, the European Association of Urology guidelines for the evaluation of pediatric nephrolithiasis state: *Despite CT's high diagnostic accuracy, its use should be reserved for cases with non-informative US with or without plain abdominal radiograph unless there are anatomic features that decrease the diagnostic performance of ultrasound* (e.g., *obesity* and *spinal anomalies*). If ultrasound is non-diagnostic, but the suspicion for a ureteral stone remains high, a low dose CT protocol should be performed [11]. A technical paper by the American Urological Association (AUA) also supports using US as the initial imaging study for children with suspected nephrolithiasis and obtaining a non-contrast CT scan for children with the non-diagnostic US in whom the clinical suspicion for stones remains high [12–14]. The attributable risk for cancer from a single CT scan performed for kidney stones is small (0.2% to 0.3% above baseline), but the cumulative risk is higher for those undergoing repeated studies [8, 15].

In 2010, Routh et al. examined 7921 children with kidney stones treated at hospitals within the Pediatric Hospital Inpatient Sample and observed that more than 2600 children underwent a median of two CT scans for a single kidney stone episode [16]. Patients with a history of nephrolithiasis are at a high risk of recurrence, and therefore, at high risk of needing additional imaging in the future. The risk of cumulative radiation exposure is particularly concerning for children because of their long life expectancy and the greater sensitivity of developing abdominal organs and tissues to the effects of radiation. Figure 7.3 depicts the authors' diagnostic

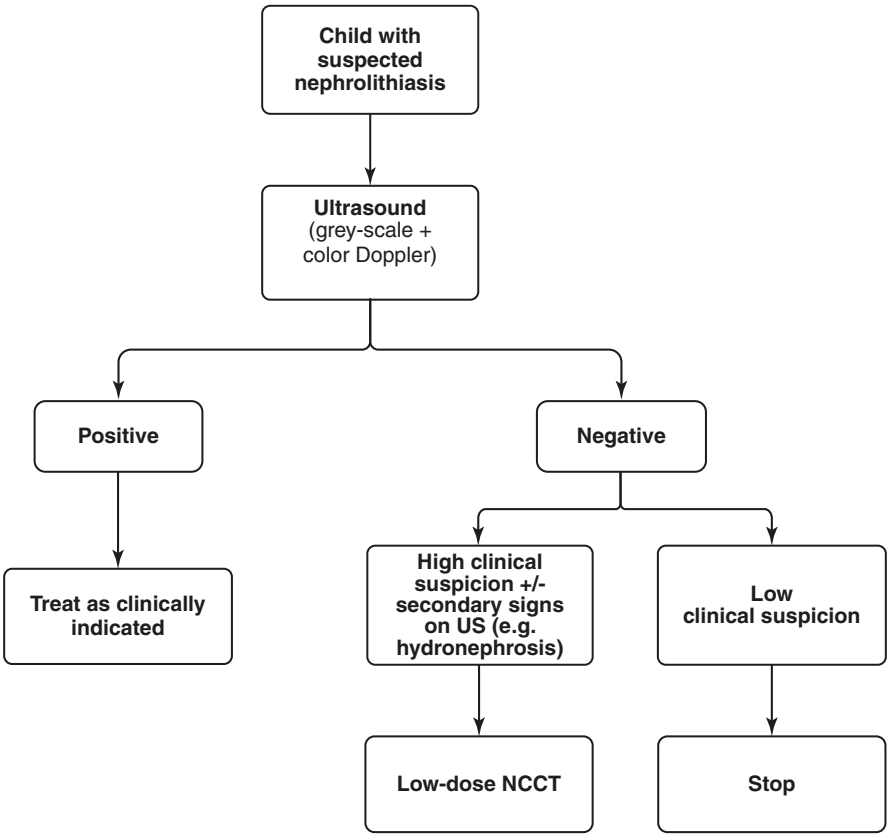

Fig. 7.3 Diagnostic imaging algorithm for pediatric patients with suspected kidney or ureteral calculi

imaging algorithm for pediatric patients with suspected kidney or ureteral stones [17].

Treatment Decision-Making

All pediatric patients presenting with a symptomatic obstructing ureteral calculi need treatment in the acute setting. Management options include observation with pain control, medical expulsive therapy, and urinary diversion with a ureteral stent or nephrostomy tube.

Conversely, when a patient presents with an incidental finding of an asymptomatic, non-obstructing renal calculi they may not require any treatment in the acute setting. The AUA published a guideline for this clinical scenario in which they state: *In pediatric patients with asymptomatic and non-obstructing renal stones,*

clinicians may utilize active surveillance with periodic ultrasonography [18]. This recommendation is based solely on expert opinion. When we elect to follow these patients in our practice, we initially obtain an ultrasound every 6 months. If a stone begins to increase in size or becomes symptomatic while on surveillance we offer surgery as an option. When a patient does require surgery, three surgical interventions can be pursued: ureteroscopy (URS), shockwave lithotripsy (SWL), and percutaneous nephrolithotomy (PCNL). These will all be discussed in depth in this chapter.

Medical Expulsive Therapy

Medical expulsive therapy is the use of medication, primarily alpha-blockers, combined with high fluid intake to facilitate passage of a ureteral stone. The AUA guidelines, with respect to medical expulsive therapy, state: *In pediatric patients with uncomplicated ureteral stones less than or equal to 10 mm, clinicians should offer observation with or without MET using alpha-blockers* [18]. This recommendation was based on Grade B Evidence. Grade B Evidence as described by the AUA is "moderate quality evidence: randomized control trials with some weaknesses; generally strong observational studies." Specifically, this rating is based upon four small, poor-quality, randomized controlled trials of alpha-blockers for children with distal ureteral stones less than 12 mm. These studies generally demonstrated that alpha-blockers improved stone passage [19–22]. The most recent trial from Aldaqadossie et al. found that patients treated with the alpha-blocker tamsulosin passed their stones 87% of the time compared to 63% in children not treated with an alpha-blocker ($p = 0.025$) [21]. Those treated with tamsulosin passed their stones in a much shorter amount of time (7.7 vs. 18.0 days; $p < 0.001$). Additionally, a multi-institutional retrospective cohort study demonstrated that tamsulosin was associated with higher stone passage (56%) compared with those treated with analgesics alone (44%) [23]. These results were pooled in a systemic review and meta-analysis, which demonstrated that MET with an alpha-blocker was associated with increased odds of stone passage compared with placebo or analgesic alone (OR 2.21, 95% CI, 1.4 to 3.49) (Velazquez et al. 2015). MET in the adult population is controversial and likely benefits a select population; the corollary in children is unknown. Additional studies will be needed to refine MET in children. When prescribing MET, the provider should note the use of alpha-blockers in children remains off-label for this indication. However, these medications are well tolerated, 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 [24]. The duration of MET required for optimal stone passage rates is unknown. In our practice, we will generally re-evaluate a patient after roughly 2 weeks of MET to determine if surgical intervention is required.

Surgical Management

The three surgical options for patients with stone disease include SWL, URS, and PCNL. Open or laparoscopic stone removal is still warranted in patients with stones concurrent with anatomic abnormalities such as a ureteropelvic junction obstruction, wherein successful treatment with one of the standard treatment modalities may not be possible. When choosing the optimal modality for a given patient, many factors must be considered. Physicians need to take into account the size and location of the stone, patient anatomy, patient comorbidities, composition of the stone, equipment availability, and patient and provider preference.

At this time, the comparative effectiveness of surgical interventions for pediatric patients with kidney stones is unclear, and the evidence for or against any given surgery is especially poor. There are currently eight guidelines that have been published by the AUA with respect to treatment for pediatric patients with ureteral or renal stones. Of these eight guidelines, none were guided by level A evidence and four were based on expert opinion alone [18]. This paucity of high-quality research has led the 2017 National Urology Research Agenda to prioritize studies of pediatric patients with kidney stones. To address this knowledge gap, the Patient Centered Outcomes Research Institute (PCORI) is currently funding the Pediatric KIDney Stone (PKIDS) Care Improvement Network. This multi-institutional, prospective cohort study seeks to compare stone clearance, re-treatment, unplanned healthcare encounters, and the lived patient experience in the postoperative period for URS, SWL, and PCNL (ClinicalTrials.gov Identifier: NCT04285658) [25].

One of the greatest dilemmas with respect to pediatric stone management is defining and assessing stone clearance. Stone clearance is widely considered the most important clinical outcome of surgery. Throughout the pediatric stone literature, the method of assessing stone clearance varies by study and ranges from visual inspection at the time of URS to postoperative ultrasound or CT. Postoperative CT scans are commonly used to assess residual stone burden in adults; however, as described above, the associated ionizing radiation exposure with CT limits the appeal of this modality in children. Residual fragments equate to worse clinical outcomes, as they have the potential to grow and become symptomatic requiring additional interventions. In adults, residual calculi less than 4 mm are typically considered “clinically insignificant fragments” [26]. At this time, the size cut off at which point fragments can be considered clinically insignificant, particularly when assessed by ultrasound, is not clear. Children may have a greater capacity to clear residual fragments than adults, so it is difficult to generalize findings in the adult literature with respect to what size stone fragments can be considered clinically insignificant [27]. However, studies looking at residual fragments of 4 mm or less have found a higher than acceptable rate of clinically significant adverse outcomes ranging from 31 to 69%, particularly in children with a history of multiple prior stone episodes [28–30].

Shockwave Lithotripsy

SWL was originally introduced in the early 1980s and was first performed successfully in children in 1986 [31]. Interpreting comparative effectiveness for SWL is made difficult due to variations in lithotripter model, technique, patient selection, and differing definitions of procedural success Nevertheless, a few of the key factors that one needs to take into account when considering a patient for SWL are stone size, location, stone composition, and body habitus of the patient. Generally, body habitus is less of a factor in children as compared to adults as the skin to stone distance in children is usually shorter [32]. Stone size is an important factor when evaluating patients for SWL. Elsobky et al. reported a 91% stone clearance for mean stone diameter less than 10 mm versus 75% stone clear for stone size greater than 10 mm [33]. Stone location is also critical with lower-pole stones having lower clearance with SWL. A recent systematic review and meta-analysis comparing SWL, URS, and PCNL in adults for lower-pole stones less than 2 cm in size favored PCNL over SWL and URS over SWL, particularly in stones 10–20 mm in size [34]. Additional factors that have been found to be associated with SWL failure include increased infundibular length and infundibulopelvic angle greater than 45 degrees [35, 36]. Nomograms have been created to predict outcomes of pediatric shockwave lithotripsy. These nomograms were developed using predictors of treatment failure including prior stone history, stone location, stone burden, gender, and age [37, 38].

There are currently multiple AUA guidelines that specify when it is appropriate to utilize SWL. With respect to ureteral stones the AUA recommends: *Clinicians should offer URS or SWL for pediatric patients with ureteral stones who are unlikely to pass the stones or who failed observation and/or MET, based on patient-specific anatomy and body habitus. Additionally, in pediatric patients with a total renal stone burden of less than or equal to 2 cm, the AUA advises that clinicians may offer SWL or URS as first-line therapy.* Interestingly, for patients with a renal stone burden over 2 cm the AUA states both PCNL and SWL are acceptable treatment options. However, if SWL is utilized, they recommend, based on expert opinion, that clinicians place an internalized ureteral stent or nephrostomy tube. Al-Busaidy et al. showed that 23 patients who underwent pre-stenting prior to ESWL for staghorn calculi had fewer major complications and shorter hospital stays than the 19 patients who were not pre-stented [39]. Because of the abundance of studies that have demonstrated poor efficacy of SWL for large renal stone burdens in adults and the safety and high efficacy of PCNL in this setting, it is the authors' practice not to perform SWL for stones greater than 15 mm in pediatric patients [18].

If a patient has a preoperative CT scan, the Hounsfield units (HU) of the stone should be measured. Stone attenuation of less than 1000 HU is associated with treatment success in children [40, 41]. Certain types of stone, such as cystine and brushite, are known to have higher attenuation and are notoriously difficult to treat with SWL given their increased density.

The energy delivered during SWL 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. Increased shock frequency have been associated with lower stone clearance among adults, but the optimal settings for children are unknown [42]. A retrospective cohort study of children treated with SWL in Turkey reported similar stone clearance and complications for shock frequencies of 60 and 90 shocks per minute [43]. However, Salem et al. found that 80 shocks per minute were associated with greater stone clearance rates when compared to 120 shocks per minute [44].

Complications associated with SWL include hematuria (up to 44%) and subcapsular or perirenal hematoma [45]. Additionally, by definition, children will need to pass stone fragments and are at risk for intermittent renal colic. The overall rate of steinstrasse (ureteral obstruction caused by stone fragments following SLW) has been quoted in a recent meta-analysis and systematic review to be 6% [46]. Accordingly, steinstrasse, particularly following the treatment of large stones, is a risk and may require further intervention to treat obstructing residual calculi. Issues with focusing SWL can lead to injury to adjacent structures such as colon, vasculature, lung, spleen, and pancreas [45]. Krambeck et al. reported an increased risk for hypertension and diabetes mellitus related to bilateral treatment, number of administered shocks, and treatment intensity [47]. Another recent study of adults also demonstrated that SWL was associated with a 40% increased risk for incident hypertension. It is our practice to discuss with patients and caregivers the potential risk for hypertension associated with SWL during the shared decision-making process considering the possibility that children's kidneys may be more vulnerable to injury, the independent association between kidney stone disease and hypertension, and the longer lifespan over which hypertension may develop following surgical treatment.

Ureteroscopy

In the past, URS was not considered a primary treatment option for upper tract renal calculi in children because of the high risk of complications. Over recent years the surgical equipment used for URS has advanced tremendously and the miniaturized equipment places patients at a much lower risk for complications. Current standard endourology equipment includes 7.5 and 8 Fr flexible ureteroscopes, which can be fiberoptic or digital. Semirigid ureteroscopes that can be 4.5 Fr or 6.5 Fr. Standard wires can come as 0.035 inch, 0.025 inch, and 0.018 inch, and ureteral stents range in size from 3.7 Fr to 8 Fr. Importantly, the size of the working channel within the cystoscope or ureteroscope will influence the available ureteral access catheters and

ureteral stents, which will then influence the surgeon's choice for wires. For example, a 4-F ureteral access catheter and/or 3.7 F ureteral stent will only accommodate a 0.025-inch wire. Understanding the equipment limitations and adaptability of the endoscopic equipment for the pediatric patient is essential for efficient ureteroscopic access. A recent systemic review reported the results of 14 studies of children and found the average stone clearance was 87.5% and 10% of patients experienced complications less than or equal to Clavien III [48]. As a result of these technological advancements, the utilization of URS has been rising while the utilization of SWL has been declining in both adults and children [49, 50].

A recent multi-institutional study comparing URS to SWL in pediatric patients found that stone clearance and rates of residual stone fragments <4 mm after final procedure for SWL were 77.0% and 90.8% and for URS were 78.5% and 91.7%, respectively. Re-treatment rates for both procedures were not significantly different (17.9% SWL vs. 18.9% URS, $P = 0.85$). Children who underwent SWL had lower rates of emergency room visits for infections (0% vs. 5.1%, $P = 0.03$) and flank pain (3.6% vs. 10.9%, $P = 0.05$) and required fewer general anesthetics per treatment (1.2 vs. 2.0, $P < 0.01$) than those who underwent URS [51].

While URS has progressed significantly over time limitations still remain. Although the efficacy of URS is less dependent on stone position than SWL, stone location can still modify the efficacy of URS. Cannon et al. reported only a 76% stone clearance rate in 21 children with lower-pole calculi and a mean stone diameter of 12 mm [52]. The smaller kidneys and tighter infundibulopelvic angles of the renal collecting system provide less room for surgeon maneuverability in the pediatric patient (Fig. 7.4). Younger patients also pose a significant challenge. Children younger than 6 years of age have been reported to have lower treatment success and higher complications (24.0% vs. 7.1%) [52]. Among children weighing less than 20 kg, Berrettini et al. reported that 37% of patients undergoing URS had complications, with a greater risk reported for younger and smaller children [53]. Additionally, even modern ureteroscopes may not be small enough to atraumatically navigate through the ureteral orifices of young children. In these cases, pre-placement of a ureteral stent will aid to passively dilate the tract prior to returning again for stone treatment for subsequent treatment. Unfortunately, two anesthetics are required when a patient undergoes staged treatment.

Once a stone is encountered in the ureter or the kidney, it may be removed intact or the surgeon may utilize a laser (typically a holmium: YAG) to fragment the stone into smaller pieces for clearance. There are two main techniques that can be used to fragment a stone. Laser dusting utilizes high pulse frequency and low pulse energy to break the stone into small <1-mm particles to enable spontaneous passage of the dust. While efficient, a dusting approach may not be adequate for children who are sedentary or who have anatomical considerations which result in urinary stasis (i.e., hydronephrosis). Alternatively, laser fragmentation and extraction technique (low frequency, high energy) involve fragmenting stones into 1–4 mm sized pieces that are then extracted from the kidney with a basket. One downside of the fragmentation technique is the requirement for multiple passes through the ureter, which poses an additional risk for ureteral trauma. As a result, many urologists will use a ureteral

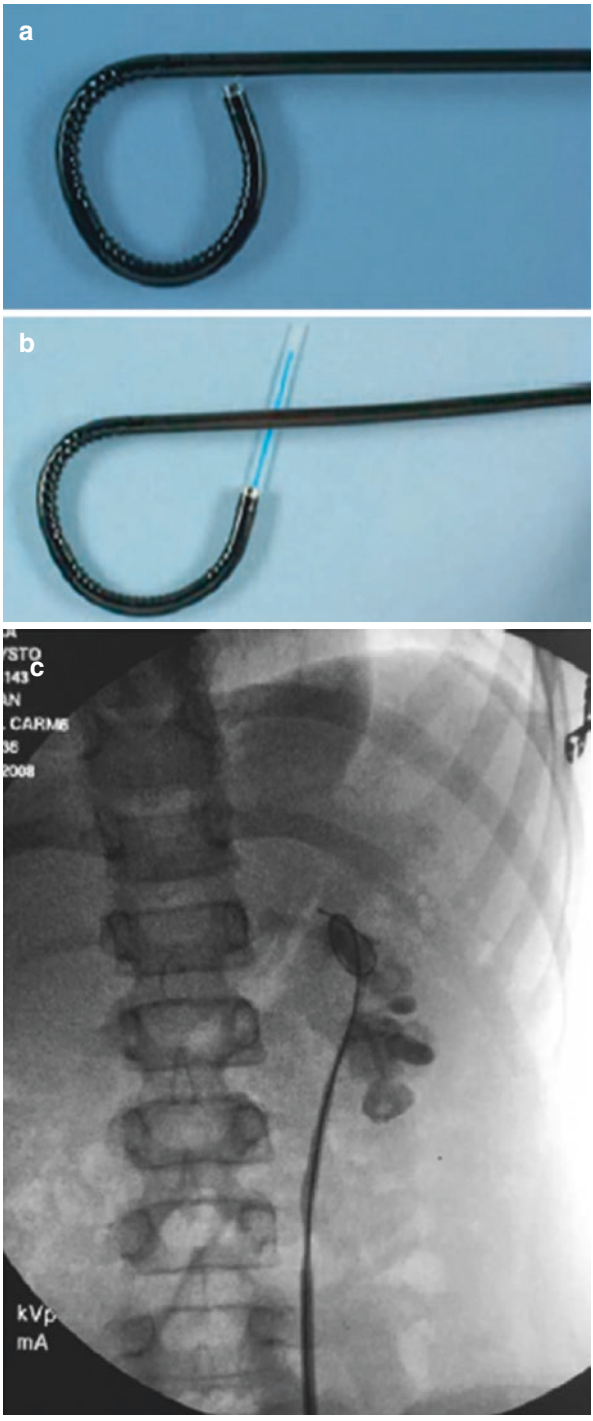

Fig. 7.4 Flexible ureteroscope displaying its 270-degree deflection at its distal tip (**a**). The degree of tip deflection becomes restricted when a laser fiber is passed through the scope (**b**). Significant deflection is required for the ureteroscope to handle the sharp angles that lead to a lower pole calyx (**c**)

access sheath. Ureteral access sheaths facilitate repetitive upper tract access while reducing intrarenal pressures, decreasing operative time, and improving stone clearance in adults [54]. These sheaths come in a multitude of sizes with an inner sheath ranging from 9 Fr to 12 Fr and an outer sheath that can range from 11 Fr to 14 Fr. Access sheaths may also facilitate flexible ureteroscopy when altered anatomy or tortuous ureters are encountered. However, caution is required when using a ureteral access sheath as some ureters are not large enough to accommodate a sheath and resultant injury to the ureter can occur. Whether or not access sheaths result in improved stone clearance in the pediatric population remains unclear. As Berrettini et al. showed that they are beneficial while Wang et al. found the opposite [52, 55].

Once a stone has been adequately treated, the surgeon must determine if a ureteral stent should be left in place at the conclusion of the procedure. The decision to place a ureteral stent postoperatively is based on the duration of the procedure, the number of passes with the ureteroscope, and the degree of visible ureteral trauma or edema at the conclusion of the procedure. We make the decision on an individual patient basis. If the child can tolerate leaving a urethral string in place for 5–7 days, the patient's parents are asked to remove the stent at home; otherwise, the stent is removed under brief anesthesia after 7 days via cystoscopy. Some children with a ureteral stent in place will develop bladder spasms postoperatively and these patients may benefit from anticholinergic medications while the stent remains in place.

Complications during URS include bleeding, ureteral perforation, or even ureteral avulsion. Postoperative complications include urinary tract infections, ureteral stricture formation, and ureteral obstruction from stone fragment passage or from residual mucosal edema. If there is a concern for a potential ureteral injury during a case a ureteral stent should be placed and the case should be immediately aborted with plans to come back at a later date to evaluate the ureter [48, 56].

Percutaneous Nephrolithotomy

PCNL is currently our treatment of choice for patients with a stone burden greater than 2 cm. When PCNL was first introduced, urologists were reluctant to treat pediatric patients, as there were concerns regarding the potential for severe parenchymal damage to the small kidneys of children. Despite this concern, after PCNL was found to be a successful treatment option in adults, some urologists attempted PCNL in children using adult-sized instruments. In the earliest study, Woodside et al. rendered seven patients stone free without complications [57]. Since that time pediatric PCNL has become widely adopted and the miniaturization of instruments has facilitated this process. PCNL is considered first-line therapy for renal stones greater than 20 mm in children with stone clearances of approximately 90% [18]. In order to decrease the morbidity of the procedure, mini- and micro-PCNL have become more popular for both children and adults. Mini-PCNL was first described in 1998 as a new technique for the treatment of stones in pediatric patients [58]. It has since been adopted as a treatment option for adults as well. Mini-PCNL

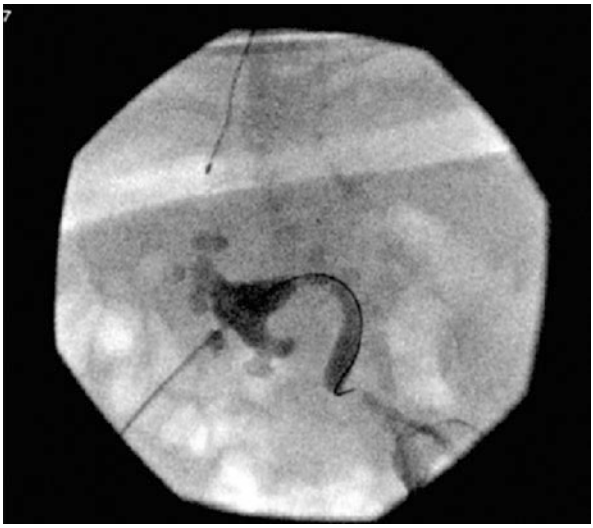

Fig. 7.5 Mid-pole access for mini-PCNL for a renal pelvis stone in an infant

typically refers to tracts of less than 20–24 Fr (Fig. 7.5) [17]. Micro-PCNL typically refers to tracts less 10 Fr. An "all-seeing needle" optical puncture system has been described for micro-PCNL. While not FDA approved in the United States this method has shown promise with low complications and high stone-free rates in trials abroad [59]. The comparative effectiveness of and indications for newer techniques such as mini-PCNL, and micro-PCNL among pediatric patients is an active area of investigation.

Preoperative planning is required prior to undertaking the endeavor of percutaneous stone surgery. The AUA guidelines recommend a CT scan for preoperative planning prior to performing PCNL [18]. A CT accurately depicts stone size and location as well as identifies any aberrant renal anatomy such as malrotation. Nearby structures such as colon, lung, liver, and spleen will also be seen on CT allowing the surgeon to determine if their location will complicate percutaneous access to the kidney. By viewing the CT images, the surgeon can ultimately determine the optimal calyx to access the stones safely. Additionally, the urine should be sterilized prior to proceeding with PCNL. A preoperative urine culture should be obtained 2–3 weeks prior and treated if positive.

It is critical that the surgeon have a detailed discussion regarding informed consent with parents prior to proceeding with a PCNL. All risks must be reviewed including bleeding requiring transfusion, delayed renal hemorrhage requiring angioembolization, sepsis, pneumothorax, hemothorax, urothorax, incomplete stone clearance, and injuries to adjacent organs.

We begin the procedure by performing cystoscopy and placing a 4 or 5 Fr open-ended ureteral catheter just below the ureteropelvic junction, which can be used for retrograde pyelograms or instillation of saline to distend the collecting system. The patient is then placed in the prone position and a 16- or 18-gauge spinal needle is placed into the desired calyx with the assistance of fluoroscopy or ultrasound. The

authors obtain access using ultrasound as described by Chu et al. [60]. Once we have accessed our desired calyx, the tract is dilated using an 18-Fr balloon dilator and PTFE sheath for renal access. Children's kidneys, and especially infant's kidneys, are more mobile than adult kidneys and often push away when obtaining initial needle access and placing the access sheath. After obtaining access, we use a 15-Fr rigid nephroscope and a lithotripter that uses both ultrasonic and mechanical energy to fragment and remove the stone(s). While we use a 15-Fr nephroscope, it should be noted that nephroscopes come as small as 12 Fr. We use a flexible pediatric cystoscope or flexible ureteroscope to confirm stone clearance and remove any residual calyceal stones. We routinely place a nephrostomy tube at the end of the procedure. Postoperatively, we generally remove the nephrostomy tube after the urine clears around the time of discharge, which is usually postoperative day 1.

Complications following PCNL are not rare, with reports of 10% and 20% for intraoperative and postoperative complications, respectively. Complications include those occurring intraoperatively: inability to dilate percutaneous tract to access the collecting system, acute hemorrhage, 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. A large multicenter study demonstrated that the most significant determinants affecting complication raters were operative time, sheath size, midcalyceal puncture, and partial staghorn calculi [61].

Follow-Up

Approximately 50% of patients who develop kidney stone disease during childhood will develop a recurrent stone within 3–5 years [62–64]. This is similar to or higher than rates reported for adults [65, 66]. Additionally, children with an identifiable metabolic abnormality have an up to fivefold increased risk for recurrence compared with children with no identifiable metabolic disorder [67]. Consequently, all children should undergo a comprehensive metabolic evaluation. Following a stone episode, all patients should be offered a 24-h urine collection that is then analyzed for calcium, oxalate, uric acid, sodium, citrate, creatinine, volume pH, and cystine (cyanide-nitroprusside screening test). In the author's practice families are generally encouraged to do their initial 24-h urine within 2–3 months of their surgery as we have found this tends to yield high compliance. Results are evaluated with respect to weight, body surface area, or creatinine to be properly interpreted in children. Urine creatinine excretion (normal 15–25 mg/kg/day for adults) is useful in assessing the adequacy of the urine collection. Younger children will have lower creatinine excretions, although it is important to note that normal creatinine ranges have not yet been established. Supersaturations for calcium oxalate, calcium phosphate, and uric acid can be calculated from computer models based on the results of the urine collection. Obtaining a 24-h urine collection from patients who are not toilet trained can be difficult, but analysis of a random spot urine sample measuring

the ratio of calcium, uric acid, citrate, and oxalate to creatinine can be performed instead.

Pediatric stone patients should all be followed with regular imaging postoperatively. Ultrasound is sufficient to screen for stone recurrence and silent hydronephrosis due to obstruction without putting the patient at risk for radiation. The imaging schedule is generally dependent on the risk of recurrence, but can range from every 6 months to annually.

Patients with kidney stone disease are at risk for development of comorbidities such as decreased bone mineral density, chronic kidney disease, hypertension, and heart disease [68–71]. It is critical for practitioners to be aware of these associations when following these patients. While most of the studies that found these connections included adult patients, children may be at particular risk because early onset of nephrolithiasis may represent a more severe phenotype, and children have a long lifetime over which comorbid disease may develop.

Conclusion

The prevalence of nephrolithiasis in children is rising, and the presentation of these patients can often be drastically different from that of adults. Special considerations including patient size must be taken into account when discussing treatment options, particularly surgical interventions, and only an experienced, pediatric trained urologist should attempt surgical stone extraction on a child with kidney stones. Additionally, the underlying etiologies in children are often vastly different from those of adults. Children are more likely to possess an innate metabolic abnormality, and as such are more prone to recurrence [62–64]. They have a long lifetime over which recurrence and comorbid disease may develop, which illustrates why strict follow up is so critical for these patients.

References

1. Tasian GE, Copelovitch L, Plachter N, Ashcroft K, et al. Outpatient clinical pathway for the evaluation/treatment of child with nephrolithiasis. Children's Hospital of Philadelphia Center for Healthcare Quality and Analytics; 2013. https://www.chop.edu/clinical-pathway/nephrolithiasis-outpatient-specialty-care-clinical-pathway
2. Persaud AC, Stevenson MD, McMahon DR, Christopher NC. Pediatric urolithiasis: clinical predictors in the emergency department. Pediatrics. 2009;124(3):888–94.
3. Zonfrillo M, Lavelle J, Piro J, Kim S, Darge K. ED pathway for evaluation and treatment of children with suspected nephrolithiasis. Children's Hospital of Philadelphia Center for Healthcare Quality and Analytics; 2018. https://www.chop.edu/clinical-pathway/nephrolithiasis-suspected-emergent-care-clinical-pathway
4. Shorvon SD. Safety of topiramate: adverse events and relationships to dosing. Epilepsia. 1996;37(Suppl 2):S18–22.

5. Tasian GE, Jemielita T, Goldfarb DS, et al. Oral antibiotic exposure and kidney stone disease. J Am Soc Nephrol. 2018;29:1731.
6. Simerville JA, Maxted WC, Pahira JJ. Urinalysis: a comprehensive review. Am Fam Physician. 2005;71:1153–62.
7. Gordon LB, Waxman MJ, Ragsdale L, Mermel LA. Overtreatment of presumed urinary tract infection in older women presenting to the emergency department. J Am Geriatr Soc. 2013;61:788–92.
8. Katz SI, Saluja S, Brink JA, et al. Radiation dose associated with unenhanced CT for suspected renal colic impact of repetitive studies. Am J Roentgenol. 2006;186(4):1120–4.
9. Johnson EK, Faerber GJ, Roberts WW, et al. Are stone protocol computed tomography scans mandatory for children with suspected urinary calculi? Urology. 2011;78(3):662–6.
10. Passerotti C, Chow JS, Silva A, et al. Ultrasound versus computerized tomography for evaluating urolithiasis. J Urol. 2009;182(4 Suppl):1829–34.
11. Kwon JK, et al. Usefulness of low-dose nonenhanced computed tomography with iterative reconstruction for evaluation of urolithiasis: diagnostic performance and agreement between the urologist and the radiologist. Urology. 2015;85:531.
12. Turk C, Knoll T, Petrik A, et al. Guidelines on Urolithiasis. 2013. https://uroweb.org/wp-content/uploads/21_Urolithiasis_LRV4.pdf. Accessed 9 Feb 2013.
13. Turk C, Petrik A, Sarica K, et al. EAU guidelines on interventional treatment for urolithiasis. Eur Urol. 2016;69(3):475–82.
14. Fulgham PE, Assimos DG, Pearle MS, et al. Clinical effectiveness protocols for imaging in the management of ureteral calculous disease: AUA technology assessment. J Urol. 2013;189(4):1203–13.
15. Kuhns LR, Oliver WJ, Christodoulou E, et al. The predicted increased cancer risk associated with a single computed tomography examination for calculus detection in pediatric patients compared with the natural cancer incidence. Pediatr Emerg Care. 2011;27(4):345.
16. Routh JC, Graham DA, Nelson CP. Epidemiological trends in pediatric urolithiasis at United States freestanding pediatric hospitals. J Urol. 2010;184(3):1100–4.
17. Tasian GE, Copelovitch L. Management of pediatric kidney stone disease. 12th ed. Campbell Walsh Wein Urology; 2020.
18. Assimos D, Krambeck A, Miller NL, et al. Surgical management of stones: American urological association/Endourological society guideline. J Urol. 2016;196(4):1161–9.
19. Aydogdu O, Burgu B, Gucuk A, et al. Effectiveness of doxazosin in treatment of distal ureteral stones in children. J Urol. 2009;182(6):2880–4.
20. Mokhless I, Zahran AR, Youssif M, et al. Tamsulosin for the management of distal ureteral stones in children: a prospective randomized study. J Pediatr Urol. 2012;8(5):544–8.
21. Aldaqadossi HA, Shaker H, Saifelnasr M, et al. Efficacy and safety of tamsulosin as a medical expulsive therapy for stones in children. Arab J Urol. 2015;13(2):107–11.
22. Erturhan S, Bayrak O, Sarica K, et al. Efficacy of medical expulsive treatment with doxazosin in pediatric patients. Urology. 2013;81(3):640–3.
23. Tasian GE, Cost NG, Granberg CF, et al. Tamsulosin and spontaneous passage of ureteral stones in children: a multi-institutional cohort study. J Urol. 2014;192(2):506–11.
24. Velazquez N, Zapata D, Wang HH, et al. Medical expulsive therapy for pediatric urolithiasis: systematic review and meta-analysis. J Pediatr Urol. 2015;11(6):321–7.
25. Ellison JS, Lorenzo M, Beck H, et al. Pediatric KIDney Stone Care Improvement Network. Comparative effectiveness of paediatric kidney stone surgery (the PKIDS trial): study protocol for a patient-centred pragmatic clinical trial. BMJ Open. 2022;12(4):e056789. https://doi.org/10.1136/bmjopen-2021-056789. PMID: 35383073; PMCID: PMC8983998.
26. Chew BH, et al. Natural history, complications and re-intervention rates of asymptomatic residual stone fragments after ureteroscopy: a report from the EDGE research consortium. J Urol. 2006;195(4 Part 1):982–6.

27. Gofrit ON, Pode D, Meretyk S, et al. Is the pediatric ureter as efficient as the adult ureter in transporting fragments following extracorporeal shock wave lithotripsy for renal calculi larger than 10 mm. J Urol. 2001;166:1862.
28. Afshar K, McLorie G, Papanikolaou F, Malek R, Harvey E, Pippi-Salle JL, et al. Outcome of small residual stone fragments following shock wave lithotripsy in children. J Urol. 2004;172:1600–3.
29. Dincel N, Resorlu B, Unsal A, Tepeler A, Silay MS, Armağan A, et al. Are small residual stone fragments really insignificant in children? J Pediatr Surg. 2013;48:840–4.
30. El-Assmy A, El-Nahas AR, Harraz AM, El Demerdash Y, Elsaadany MM, El-Halwagy S, et al. Clinically insignificant residual fragments: is it an appropriate term in children? Urology. 2015;86:593–8.
31. Newman DM, Coury T, Lingeman JE, et al. Extracorporeal shock wave lithotripsy experience in children. J Urol. 1986;136:238.
32. Kurien A, Symons S, Manohar T, et al. Extracorporeal shock wave lithotripsy in children: equivalent clearance rates to adults is achieved with fewer and lower energy shock waves. BJU Int. 2009;103:81.
33. Elsobky E, Sheir KZ, Madbouly K, et al. Extracorporeal shock wave lithotripsy in children: experience using two second-generation lithotripters. BJU Int. 2000;86:851.
34. Donaldson JF, Lardas M, Scrimgeour D, et al. Systematic review and meta-analysis of the clinical effectiveness of shock wave lithotripsy, retrograde intrarenal surgery, and percutaneous nephrolithotomy for lower-pole renal stones. Eur Urol. 2015;67(4):612–6.
35. Onal B, Demirkesen O, Tansu N, et al. The impact of caliceal pelvic anatomy on stone clearance after shock wave lithotripsy for pediatric lower pole stones. J Urol. 2004;172:1082.
36. Ozgur Tan M, Karaoglan U, Sen I, et al. The impact of radiological anatomy in clearance of lower calcyeal stones after shcok wave lithotripsy in pediatric patients. Eur Urol. 2003;43:188.
37. Onal B, Bulent, et al. Nomogram and scoring system for predicting stone-free status after extracorporeal shock wave lithotripsy in children with urolithiasis. BJU Int. 2013;111(2):344–52.
38. Dogan HS, et al. A new nomogram for prediction of outcome of pediatric shock-wave lithotripsy. J Ped Urol. 2015;11(2):84–e1.
39. Al-Busaidy SS, Prem AR, Medhat M. Pediatric staghorn calculi: the role of extracorporeal shock wave lithotripsy monotherapy with special reference to ureteral stenting. J Urol. 2003;169(2):629–33.
40. El-Assmy A, El-Nahas AR, Abou-El-Ghar ME, et al. Kidney stone size and hounsfield units predict successful shockwave lithotripsy in children. Urology. 2013;81:880.
41. McAdams S, Kim N, Dajusta D, et al. Preoperative stone attenuation value predicts success after shock wave lithotripsy in children. J Urol. 2010;184:1804.
42. Ozkan B, Dogan C, Can GE, et al. Does ureteral stenting matter for stone size? A retrospective analyses of 1361 extracorporeal shock wave lithotripsy patients. Cent European J Urol. 2015;68(3):358–64.
43. Kaygisiz O, Kilicarslan H, Mert A, et al. Comparison of intermediate and low frequency shock wave lithotripsy for pediatric kidney stones. Urolithiasis. 2018;46(4):391–5.
44. Salem HK, et al. Slow vs rapid delivery rate shock wave lithotripsy for pediatric renal urolithiasis: a prospective randomized study. J Urol. 2014;191(5):1370–4.
45. Yucel S, Akin Y, Danisman A, et al. Complications and associated factors of pediatric extracorporeal shock wave lithotripsy. J Urol. 2012;187(5):1812–6.
46. Lu P, Wang Z, Song R, et al. The clinical efficacy of extracorporeal shock wave lithotripsy in pediatric urolithiasis: a systematic review and meta-analysis. Urolithiasis. 2015;43(3):199–206.
47. Krambeck AE, LeRoy AJ, Patterson DE, et al. Long-term outcomes of percutaneous nephrolithotomy compared to shock wave lithotripsy and conservative management. J Urol. 2008;179:2233.
48. Ishii H, Griffin S, Somani BK. Ureteroscopy for stone disease in the pediatric population: a systematic review. BJU Int. 2015;115(6):867–73.

49. Wang H-HS, et al. Shock wave lithotripsy vs ureteroscopy: variation in surgical management of kidney stones at freestanding children's hospitals. J Urol. 2012;187(4):1402–7.
50. Ellison JS, et al. Risk factors for repeat surgical intervention in pediatric nephrolithiasis: a pediatric health information system database study. J Pediatr Urol. 2018;14(3):245–e1.
51. Marchetti KA, Lee T, Raja N. Extracorporeal shock wave lithotripsy versus ureteroscopy for management of pediatric nephrolithiasis in upper urinary tract stones: multi-institutional outcomes of efficacy and morbidity. J Pediatr Urol. 2019;15(5):516e1–8.
52. Cannon GM, Smaldone MC, Wu HY, et al. Ureteroscopic management of lower-pole stones in a pediatric population. J Endourol. 2007;21:1179.
53. Berrettini A, Boeri I, Montanari E, et al. Retrograde intrarenal surgery using ureteral access sheaths is a safe and effective treatment for renal stones in children weighing <20 kg. J Pediatr Urol. 2018;14(1):59e1–59.e6.
54. Singh A, Shah G, Young J, et al. Ureteral access sheath for the management of pediatric renal and ureteral stones: a single center experience. J Urol. 2006;175:1080.
55. Wang H-H, et al. Use of the ureteral access sheath during ureteroscopy in children. J Urol. 2001;186(4S):1728–33.
56. Smaldone MC, Docimo SG, Ost MC. Contemporary surgical management of pediatric urolithiasis. Urol Clin North Am. 2010;37:253.
57. Woodside JR, Stevens GF, Stark GL, et al. Percutaneous stone removal in children. J Urol. 1985;134:1166.
58. Jackman SV, et al. Percutaneous nephrolithotomy in infants and preschool age children: experience with a new technique. Urology. 1998;52(4):697–701.
59. Jiang K, Chen H, Yu X, Chen Z, et al. The “all- seeing needle” micro-PCNL versus flexible ureterorenoscopy for lower calyceal stones of < 2 cm. Urolithiasis. 2019;47(2):201–6.
60. Chu C, Masic S, Usawachintachit M. ET AL: ultrasound-guided renal access for percutaneous nephrolithotomy: a description of three novel ultrasound-guided needle techniques. J Endourol. 2016;30(2):153–8.
61. Onal B, Dogan HS, Satar N, et al. Factors affecting complications rates of percutaneous nephrolithotomy in children: results of a multi-institutional retrospective analysis by the Turkish Pediatric Urology Society. J Urol. 2014;191:777.
62. Lao M, Kogan BA, White MD, et al. High recurrence rate at 5-year follow up in children after upper urinary tract stone surgery. J Urol. 2014;191(2):440–4.
63. Tasian GE, Kabarriti AE, Kalmus A, et al. Kidney stone recurrence among children and adolescents. J Urol. 2017;197(1):246–52.
64. Tekin A, Tekgul S, Atsu N, et al. Oral potassium citrate treatment for idiopathic hypocitraturia in children with calcium urolithiasis. J Urol. 2002;168(6):2572–4.
65. Ljunghall S, Danielson BG. A prospective study of renal stone recurrences. Br J Urol. 1984;56(2):122–4.
66. Johnson CM, Wilson DM, O’Fallon WM, et al. Renal stone epidemiology: a 25 year study in Rochester, Minnesota. Kidney Int. 1979;16(5):624–31.
67. Pietrow PK, Pope JC 4th, Adams MC, et al. Clinical outcome of pediatric stone disease. J Urol. 2002;167(2 Pt 1):670–3.
68. Letavernier E, Traxer O, Daudon M, et al. Determinants of osteopenia in male renal-stone-disease patients with idiopathic hypercalciuria. Clin J Am Soc Nephrol. 2011;6(5):1149–54.
69. Asplin JR, Donahue S, Kinder J, et al. Urine calcium excretion predicts bone loss in idiopathic hypercalciuria. Kidney Int. 2006;70(8):1463–7.
70. Denburg MR, Jemielita TO, Tasian GE, et al. Assessing the risk of incident hypertension and chronic kidney disease after exposure to shock wave lithotripsy and ureteroscopy. Kidney Int. 2016;89(1):185–92.
71. Ristau BT, Dudley AG, Casella DP, et al. Tracking of radiation exposure in pediatric stone patients the time is now. J Pediatr Urol. 2015;11(6):339.e331–5.

Chapter 8
The Role of Imaging in Management of Stone Disease

Jonathan S. Ellison and Pooja Thakrar

Introduction

As the incidence of pediatric nephrolithiasis has risen over the past few decades, so too has the attention given to pediatric-specific imaging considerations [1, 2]. Children pose many unique imaging opportunities and challenges as compared to adults. Increased susceptibility to ionizing radiation at a young age should prompt providers to consider the "as low as reasonably achievable" (ALARA) principle when employing imaging strategies to detect and characterize urinary tract calculi [3]. Meanwhile, the smaller body habitus and lower adiposity typically seen in the pediatric population may provide more favorable conditions for minimizing or eliminating ionizing radiation, such as with low-dose computed tomography (LDCT) or ultrasonography (US) [4, 5]. This chapter will appraise the current state of imaging for pediatric nephrolithiasis, discuss pediatric-specific considerations for individual imaging modalities, and review imaging strategies for specific clinical scenarios.

Imaging Utilization and Practice Patterns

The majority of children with nephrolithiasis present symptomatically, most often with lateralizing, relapsing and remitting flank pain (renal colic); hematuria; or

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nausea and vomiting [6]. Accordingly, a large proportion of these cases are seen through the emergency department, with most ultimately managed without admission [7]. Due to the centralization of pediatric health care services, mostly focused in major metropolitan areas and/or academic medical centers, up to 90% of children with an initial episode of nephrolithiasis may present to a community hospital without pediatric specialization [8]. Given the importance of minimizing ionizing radiation in the pediatric population, the choice of initial imaging modality for nephrolithiasis has been evaluated as a potential quality of care measure. Nationwide assessments of initial imaging strategies suggest higher utilization of computed tomography (CT) as compared to US, with 63–87% of children receiving a CT during the acute evaluation [2, 9]. Following an acute care visit for nephrolithiasis, 35% of children may undergo CT scanning in follow-up, including a small proportion of children for whom multiple CT scans are performed during evaluation of a single episode of renal colic [10]. Additionally, the imaging burden may increase when surgical intervention is required. Although not necessary in all cases, many children will receive additional studies utilizing ionizing radiation prior to surgical intervention [11, 12]. Exposure to ionizing radiation also occurs during and following surgical intervention, with the degree of exposure varying in response to several factors, including the type of procedure [12, 13]. Understanding the crucial time points in evaluation of pediatric nephrolithiasis and the indications for imaging at each interval assessment is key in determining the optimal imaging modality while minimizing ionizing radiation exposure and health care resource utilization (Fig. 8.1). Imaging

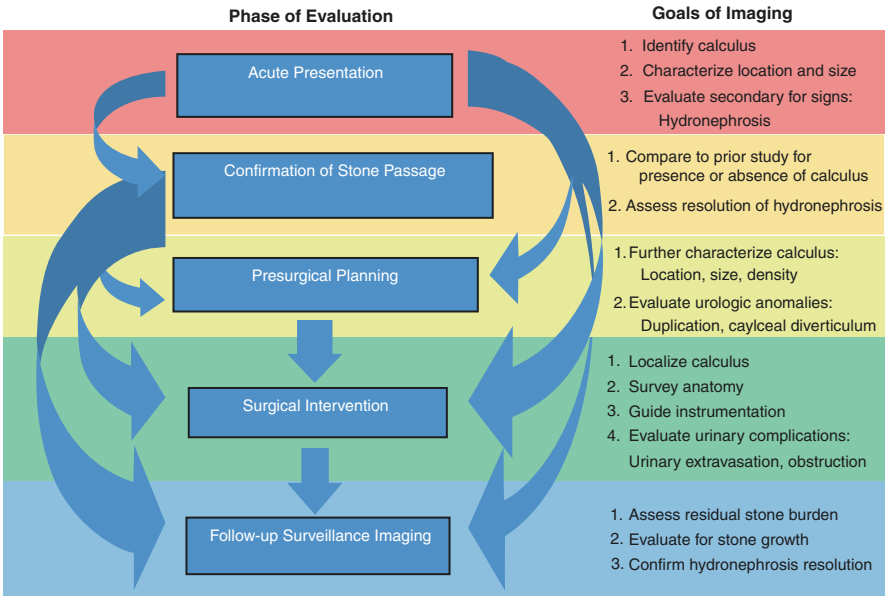

Fig. 8.1 Phases of evaluation in nephrolithiasis, progressing from acute presentation to follow-up surveillance. Imaging may not be necessary in each phase. Note the goals of imaging, which vary across the phases of evaluation

may not be required at each phase. When imaging is indicated, the information sought varies according to the clinical course, and imaging studies should be selected accordingly.

Risks of Ionizing Radiation in Children

Children and young adults are at increased risk for malignant complications secondary to ionizing radiation exposure. This risk has been attributed to rapid cell turnover in pediatric organ systems, smaller body surface area, and a longer lifespan over which such events may be realized [3, 14, 15]. Early studies on the risks of ionizing radiation in children focused on CT imaging. Brenner et al. in 2001 reported that malignancy risks in children receiving CT scans were at least an order of magnitude higher than in adults, with an incidence of 1 in 10,000 to 1 in 1000 depending on the body site imaged and the patient age. In this sentinel study, the authors estimated that based on annual CT rates in children, up to 500 potentially fatal pediatric malignancies per year may be induced by CT imaging [16]. Importantly, such estimates are based on the linear no-threshold (LNT) model of radiation exposure, which relies on two main assumptions regarding radiation exposure and risk. The first presumes that the risks for radiation-associated complications exhibit a linear relationship to radiation dose. The second presupposes that there is no threshold below which radiation exposure is safe (i.e., not associated with risk), nor is there a threshold above which the radiation-associated risk becomes saturated. Notably, while the LNT model is widely accepted in the medical community, it is not accepted universally, and controversy surrounding radiation exposure and risk exists [17, 18]. Contemporary data regarding CT dose reduction strategies spurred by Brenner's initial report suggest a smaller but still significant risk of solid organ tumors attributable to CT imaging. Meulepas et al., in a large cohort study from the Netherlands, found that each additional 100 mGy of cumulative radiation exposure conferred a 2% increase in relative risk for development of brain tumors [19]. Meanwhile, an evaluation of CT imaging practices from the United Kingdom estimated contemporary lifetime risks of imaging-associated malignancy to be 50–70% less than historical estimates, largely as a result of efforts to minimize radiation exposure. In contrast to Brenner's landmark study, the authors projected approximately 290 imaging-related pediatric malignancies annually, including both fatal and survivable cancers, using the same CT rates first reported by Brenner et al. [20].

Accordingly, the ALARA principle has arisen to help providers choose the optimal imaging strategy in children, balancing the sometimes competing interests of minimizing radiation exposure and providing adequate imaging resolution for appropriate clinical management. Included in this principle are two key concepts for imaging stewardship. First, in settings where multiple imaging modalities demonstrate similar clinical effectiveness, providers should favor the modality which uses the least ionizing radiation. Second, when ionizing radiation is required for imaging, strategies should be put in place to minimize exposure to the individual [3]. The latter

principle is especially relevant for modalities such as CT, which can impart high radiation doses but often have variable dosing parameters. For instance, according to a study by Miglioretti et al., patients who received radiation doses in the highest quartile during CT scanning could realize up to a 40% reduction in radiation-associated malignancies by employing dose reduction methods [21]. However, other authors have argued that the basic assumptions upon which such estimates have been made (namely the LNT model) are flawed and caution against over applying ALARA at the cost of diagnostic uncertainty, misdiagnosis, and increased burden of health care utilization [22]. In pediatric nephrolithiasis, decisions must often be individualized, accounting for patient factors and health system context, to strike the appropriate balance and choose the "best" imaging for the patient.

Ultrasound Imaging

In many ways, US is an ideal initial imaging modality for pediatric nephrolithiasis. US has the ability to provide highly specific images to identify and localize urinary calculi without using ionizing radiation [2]. However, US is operator-dependent, meaning that the quality of the acquired images relies on the skill of the sonographer. In addition, the availability of US may be limited in nonpediatric facilities, especially during off-hours or within acute care settings [9]. A thorough understanding of test performance and imaging characteristics will enable the most effective use of sonographic imaging for nephrolithiasis.

Characteristics of Calculi on Ultrasound Imaging

A urinary calculus can be identified by three key features on US: an echogenic focus, the presence of "twinkle" artifact on Doppler imaging, and posterior acoustic shadowing. The echogenic focus is the most readily recognized feature, produced by the reflection of acoustic waves at the interface between the relatively dense urinary calculus and the adjacent urine or soft tissue, the latter of which are more penetrable to the ultrasound beam [23]. In the absence of other sonographic features of nephrolithiasis, an echogenic focus may represent a false positive finding. These false positive findings may result from imaging artifact, calcium deposits within the renal parenchyma, or calcifications lining the collecting system (such as Randall's plaques). In addition, accurately measuring the size of the urinary calculus represented by the echogenic focus may be difficult. Imaging artifact at the fluid-calculus interface can magnify the echogenic focus, making it appear larger than the actual size of the calculus [24].

The addition of twinkle artifact, posterior acoustic shadowing, or both may enhance the test characteristics of US [25]. Twinkle artifact arises from what is termed "phase jitter" upon activation of Doppler technology during imaging. The

"twinkle" appears as a focus of rapidly alternating colors along the Doppler spectrum. A color "comet tail" of alternating Doppler signal may also be appreciated immediately deep to the calculus [26]. The origin of this artifact has been hypothesized to be the generation of microbubbles across a rough or uneven surface, such as that of a urinary calculus. Twinkle artifact may be seen in all common forms of urinary calculi, but characterizations of the artifacts are not detailed enough to distinguish stone type [27].

Posterior acoustic shadowing is an additional useful sonographic finding seen with urinary calculi. The dense surface of a urinary calculus reflects nearly all the ultrasound waves it encounters, resulting in minimal acoustic penetrance. Posterior acoustic shadowing develops from the consequent dearth of transmitted sound waves deep to the target. The "shadow" is best appreciated approximately 1 cm beyond the echogenic focus (Fig. 8.2) [28, 29].

Sensitivity and Specificity of Ultrasound for Nephrolithiasis

US has long been compared unfavorably to CT in the evaluation of nephrolithiasis, largely as a result of poorer performance characteristics or limited sensitivity in certain clinical scenarios [30, 31]. However, as ultrasound quality has improved and the use of adjunct imaging findings such as twinkle artifact and posterior acoustic shadowing has developed, US has gained popularity for evaluation of nephrolithiasis [32]. The sensitivity of US is dependent upon imaging quality, operator skill, and the patient's body habitus, among other factors [4, 33]. These same factors may favorably influence the accuracy of US in the pediatric realm. First, children typically have lower abdominal wall adiposity than adults. Second, US is often more

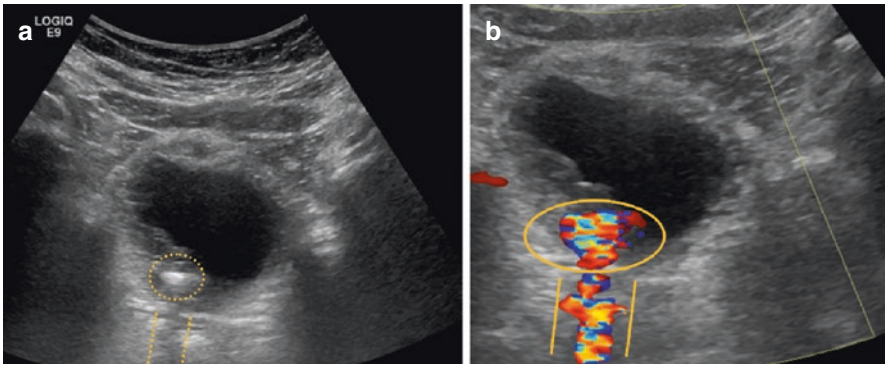

Fig. 8.2 Sonographic findings of a distal ureteral calculus at the ureterovesical junction. (**a**) The echogenic focus (dashed circle) causes posterior acoustic shadowing (dashed lines). (**b**) Twinkle artifact (solid ellipse) is seen within the calculus, while an associated color comet tail (solid lines) is present deep to the calculus

Table 8.1 Diagnostic capabilities of ultrasound for detection of nephrolithiasis using CT as the reference standard

Study	Sensitivity	Specificity	PPV	NPV
Passerotti et al. 2009	62%	98%	97%	74%
Roberson et al. 2018	67%	97%	95%	79%
Verhagen et al. 2019	84.3%	N/A[a]	NR	NR
Palmer et al. 2005	62.5%	100%	100%	25%

[a]No true negative was reported, so specificity was not calculated
PPV positive predictive value, *NPV* negative predictive value, *NR* not reported, *N/A* not applicable

broadly used in pediatric systems, improving operator performance as well as enabling availability of higher quality imaging systems.

US sensitivity, as compared to CT, ranges between 62 and 84% (Table 8.1). Of note, there is significant selection bias for positive US studies when comparing CT and US. Positive US studies may not warrant further imaging by CT, skewing the specificity toward favorable results [25, 30, 31, 34]. The sensitivity for sonographic identification of urinary calculi is most limited in the ureter, although false negative evaluation can also occur in the kidneys [25, 30, 34]. Sonography evaluating for twinkle artifact alone may increase the positive predictive value of finding a calculus anywhere along the urinary tract to upwards of 75%. However, the accuracy of twinkle artifact to localize a specific calculus, as compared to CT imaging, is only about 50% [26]. Twinkle artifact is most useful for localization of urinary calculi in situations where the stone is isoechoic to surrounding tissues, as it can occur up to 50% of the time. In these situations, the echogenic focus itself may be difficult to identify without the adjunct of obvious twinkling on Doppler [35]. The addition of posterior acoustic shadowing to sonographic criteria profoundly improves diagnostic specificity to 95–100%, but at a substantial cost in sensitivity (31–60%) [25, 36]. This trade-off is likely due to the limitations of identifying the posterior acoustic shadow, which may only be seen in up 70% of all urinary calculi in children. However, the sensitivity of this measure increases with increasing stone size. Calculi ≥9 mm in size reliably demonstrated acoustic shadowing in a study by Verhagen et al. [25]

Size Estimation of Urinary Calculi Using Ultrasound

The echogenic focus on US representing a urinary calculus is subject to imaging artifact which can spuriously increase its size. Although not well studied in children, the size discrepancy between calculi measured on US as compared to CT (a modality which more accurately estimates the size of urinary calculi) is approximately 2 mm for calculi less than 10 mm in size. A greater proportional size discrepancy is seen in smaller calculi (≤5 mm) [37]. Overestimation of stone size can significantly alter treatment recommendations [38]. In vitro studies have demonstrated size discrepancies between the calculus and the echogenic focus to be

dependent upon the image gain and the depth of penetration. Posterior acoustic shadowing, although not seen with all urinary calculi, is not subject to the same imaging artifact and may therefore more accurately approximate the size of the calculus [39]. Identification and measurement of the posterior acoustic shadow is a learnable skill which could be applied at the point of care [28].

Additional Sonographic Findings

Additional information provided by sonography may aid in medical decision making. For example, renal pelvicaliectasis identified on US could indicate either urinary stasis or active obstruction. In such a setting, comparison with previous imaging studies is often helpful to distinguish between the acute findings arising from an obstructing urinary calculus and more chronic, often congenital, processes. Similarly, the identification of a dilated ureter proximal to a ureteral calculus can be useful in confirming a diagnosis. The presence of hydronephrosis and concern for obstruction may dictate the timing of surgical management. Even in the setting of obstruction, however, a trial of observation and medical therapy to allow spontaneous stone passage is appropriate for children without concomitant urinary tract infection, provided their pain is well controlled [40].

The absence of ureteral jets on sonography is often reported to suggest ureteral obstruction. However, the presence of ureteral jets is dependent upon a concentration gradient between urine in the ureter and urine in the bladder. Normal ureteral jets can therefore be undetectable if the patient has recently voided, limiting the specificity of absent ureteral jets [41, 42]. Interestingly, a small study by Yıldırım et al. demonstrated an association between diminished ureteral jet dynamics and increased risk of nephrolithiasis in children. However, this study has not been externally validated, and the clinical use of such parameters is not well defined [43].

The presence of bladder sediment on US has been shown to be a significant predictor of positive urine culture [44]. While this finding should not supplant urinalysis and culture, the presence of bladder sediment on US should prompt the clinician to evaluate for a urinary tract infection, especially in the setting of a ureteral calculus or planned surgical intervention.

Computed Tomography

CT is a mainstay for evaluation of nephrolithiasis across the age spectrum owing to its high sensitivity and specificity, its ability to readily characterize additional genitourinary and nongenitourinary pathologies, and its near-ubiquitous availability. However, concerns regarding radiation exposure have led to a disavowal of indiscriminate CT use in children with suspected nephrolithiasis [9]. Nuanced study alterations such as dose adjustment, use or absence of intravenous contrast, and

specific imaging protocols may affect test performance and should be considered when interpreting the imaging.

Modifiable Computed Tomography Scanning Parameters

Tube current, tube voltage, and gantry rotation time are CT scanning parameters which, when altered, can affect radiation dose and image quality. Tube current refers to the rate at which photons are produced by the X-ray tube, while tube voltage reflects the energy of those photons. Gantry rotation time is the length of time required for the X-ray source and detectors to cycle once around the patient. Decreasing any of these parameters will reduce the amount of radiation to which a patient is exposed. In particular, radiation output is proportional to the square of the tube voltage, meaning that even small decreases in tube voltage can yield substantial reductions in dose. Meanwhile, reductions in gantry rotation time and tube current yield proportionate decreases in radiation dose [45]. The ability to achieve substantial dose reduction while still obtaining a meaningful image is in large part based on patient size. Both tube voltage and tube current can and should be decreased in smaller patients such as children, as fewer photons and less photon energy are needed to achieve diagnostic quality images [46]. Newer CT scanners employ automatic tube current modulation to modify the tube current based on the size and attenuation of the body part being scanned [47].

Diagnostic Accuracy of Stone Protocol Computed Tomography

While the specific protocol for CT will vary by institution and hospital setting, the term "stone protocol CT" often refers to a noncontrast CT (NCCT) scan of the abdomen and pelvis. Intravenous contrast is not used because it may result in renal enhancement or excretion of contrast into the collecting system, which could obscure an otherwise visible renal or ureteral calculus [48]. Specific attention must be paid to the slice thickness, especially in the axial plane, as thicker sections (e.g., 5 mm) may result in false negative studies for calculi $\leq$3 mm in size [49]. When accounting for these technical factors, a standard dose NCCT carries a 98% specificity and 97% sensitivity for diagnosis of nephrolithiasis [48]. Indeed, many studies in the pediatric population use CT as the reference standard for comparing US performance [25, 30]. Aside from technical factors, false negatives may arise in specific clinical situations. Certain protease inhibitors such as atazanavir or indinavir can induce formation of renal calculi which are radiolucent on CT, creating a diagnostic dilemma and the need for high clinical suspicion when evaluating patients on these medications [50]. Additionally, imaging artifact created by orthopedic hardware such as spinal rods or hip prostheses can obscure visibility of the upper or lower urinary tract, respectively (Fig. 8.3).

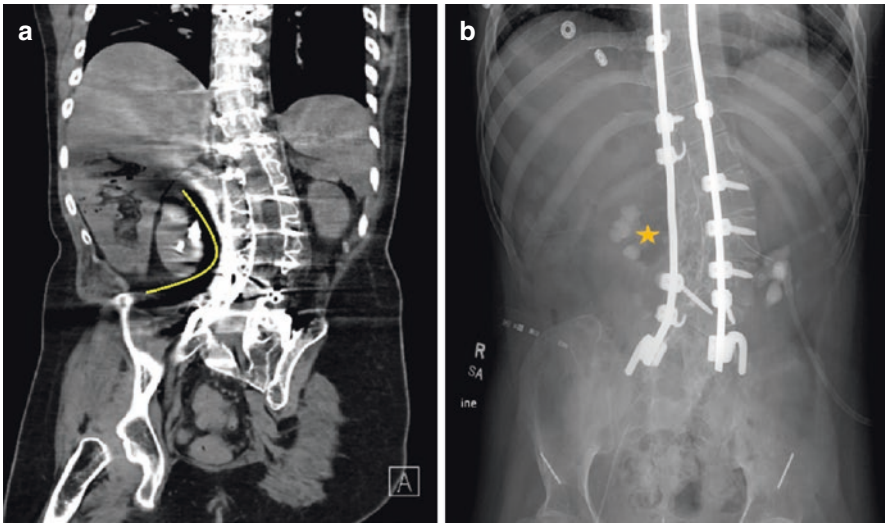

Fig. 8.3 Artifact from spinal rods on a CT image (**a**) obscures full assessment of right renal calculus burden (yellow curve). The corresponding abdominal radiograph (**b**) shows the full extent of the right renal staghorn calculus (orange star)

Low-dose Computed Tomography

Concerns regarding radiation exposure during pediatric CT imaging have existed for over two decades. Accordingly, a multitude of dose reduction strategies have been employed in order to improve the safety profile of these examinations. By accounting for patient size, prior exposures, and study indication, patient-specific protocols can reduce radiation exposure by up to 84% for abdominal imaging without loss in image quality [51].

"Low-dose" CT (LDCT) scans are obtained by decreasing the tube voltage and tube current to levels at which the image may be "noisy" or have low resolution but evaluation of high-contrast structures remains possible. At lower tube voltage settings, elements with higher atomic numbers, such as calcium, demonstrate increased attenuation. This effect is not seen in tissues such as muscle and fat, which leads to better contrast between calcifications and soft tissues. The increased contrast can yield equivalent or even improved contrast-to-noise ratios for calcium-containing structures compared to standard tube voltages, an effect which can be useful for detection of renal calculi [52]. In addition, reduction of the tube current from the standard setting to 80 mA can yield a substantial dose reduction without loss of imaging quality. In children weighing less than 50 kg, reducing tube current to 40 mA can reduce the effective dose even further without a significant impact to image quality, though image quality may be impacted in larger children [5].

LDCT is likely underutilized in the adult population; settings yielding exposures of <200 mGy-cm are used in the minority of CT studies performed to evaluate

nephrolithiasis [53]. These practices may permeate into the pediatric population as well, as an analysis of all-cause pediatric CT scans found significantly lower doses in those performed in pediatric as compared to adult centers [54]. Nearly 90% of initial evaluations for pediatric nephrolithiasis occur outside of pediatric-specific centers. Thus, it is important to consider these settings as opportunities to improve radiation exposure [8].

Dual-energy Computed Tomography

Pediatric renal calculi can form from a variety of substrates, including calcium oxalate, calcium phosphate, struvite, cystine, and uric acid. Identification of the specific stone type can be helpful to guide patient management. In particular, unlike other urinary calculi which may need to be removed or fragmented if they do not pass spontaneously, uric acid stones can be treated medically with urine alkalinization [55]. While differentiation of stone types is limited on a standard NCCT, dual-energy CT (DECT), which involves simultaneous image acquisition at high- and low-energy X-ray spectra, allows differences in tissue composition to be determined. DECT therefore permits classification of uric acid and nonuric acid stones with much greater accuracy [56, 57]. In addition, because calcium oxalate, calcium phosphate, struvite, and cystine stones also have distinct compositions, DECT can be used to distinguish these calculi by applying additional filtration to the high-energy spectrum [58]. As the various subtypes of calcium stones have different degrees of fragility, identification of the particular stone type may aid in determination of the most appropriate surgical procedure. Of note, because exact attenuation values are difficult to obtain in small structures, the accuracy of DECT for characterization of renal calculi is decreased when stone size is less than 3–5 mm. However, these smaller calculi ultimately may not require surgical intervention, and DECT may therefore be of limited additional benefit in these cases. Finally, mixed composition calculi may be misclassified because of overlapping dual-energy characteristics [59].

DECT can also be used to create virtual nonenhanced images from a contrast-enhanced study, allowing otherwise obscured renal and ureteral calculi to be detected. The sensitivity for detecting calculi in the collecting systems on the virtual nonenhanced images is reported to be 53–87%, decreased compared to a true NCCT and further lessened in the setting of small calculi [5, 6]. Detection of these small calculi on the virtual nonenhanced images is limited by beam-hardening and increased noise from dense contrast material on the native images [59].

Though it has not been studied specifically for pediatric nephrolithiasis, DECT can reportedly be performed with similar or lower radiation exposure compared to standard dose CT. Most DECT systems include automated dose-reduction technologies, and two recent studies which have included DECT of the abdomen in children demonstrated dose reductions of 12.5–24% compared to single-energy exams [60, 61]. However, further study is warranted to determine opportunities for DECT dose reduction in children with nephrolithiasis [60].

Additional Findings on Computed Tomographic Imaging

As with US, surrounding soft tissue structures can be seen on CT, providing information regarding hydronephrosis or hydroureter. Additionally, the three-dimensional stone configuration and the relationship of the kidney to adjacent viscera may be important for complex surgical planning [62]. In contrast to US, stone density can be measured on CT and may provide a suggestion of the stone composition. Calculi with Hounsfield units below 490 are more likely to represent uric acid stones [63]. As mentioned previously, this has important implications for management, as dissolution therapy for uric acid calculi in children has been shown to be equally efficacious to surgical intervention [55]. Furthermore, higher Hounsfield units, indicative of a denser stone, are predictive of poorer surgical outcomes [64]. Finally, the scout image is often a useful adjunct to assess the visibility of the calculus on radiography. Up to 50% of calculi may be seen on a CT scout image, and these calculi are reliably identified on plain radiography as well (Fig. 8.4) [65]. Hence, a urinary calculus which is visible on the CT scout image may be followed with radiographic rather than CT imaging and may be localized using fluoroscopy for surgical intervention.

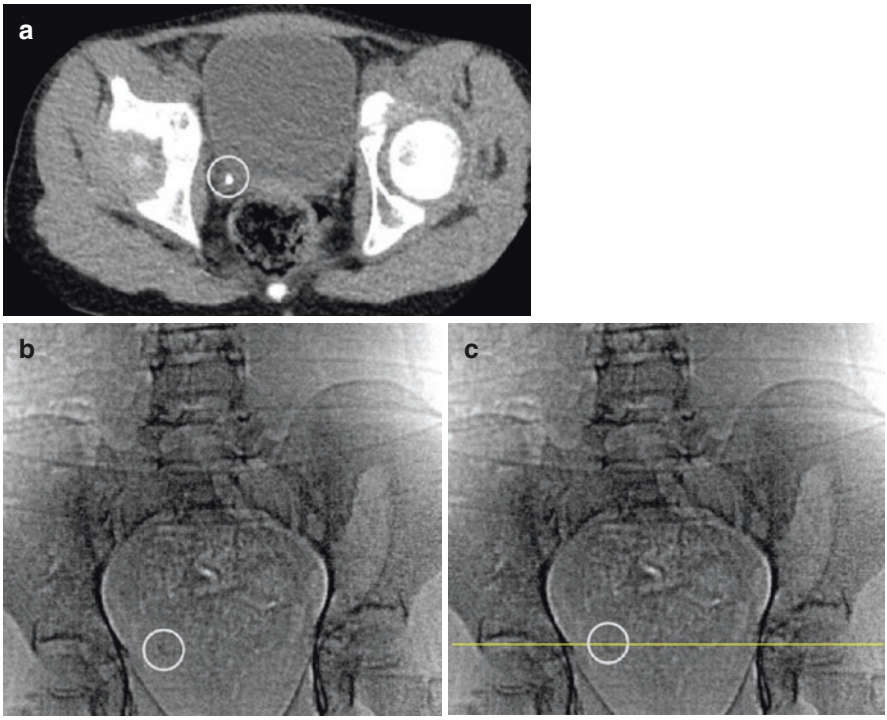

Fig. 8.4 Axial CT (**a**) and CT scout (**b** and **c**) images of a right distal ureteral calculus (gray circle). Note the use of "scout line mode" on the preliminary image (yellow line in "C") to aid in localizing the calculus in the vertical plane

Additional Imaging Strategies

Abdominal Radiography

An abdominal radiograph capturing the kidneys, ureters, and bladder (KUB) is less commonly used than either US or CT but still has a useful role as an adjunct imaging strategy [9, 10]. One reason for this limited utilization is the general low yield of abdominal radiography in the pediatric population, irrespective of indication [66]. Although associated with a lower radiation dose than even a low-dose CT, the radiation exposure of an abdominal radiograph may be up to 35 times that of a chest radiograph. Thus, when obtaining a KUB, limiting imaging to a single-shot radiograph will be most effective to control radiation exposure [67]. As an adjunct to US, a KUB can be useful to demonstrate radiopaque calculi in the anticipated areas of the kidneys, ureters, and bladder. However, soft tissues are not well defined on radiography, and as such, characterization of the calculus is limited to its size and general location. Data regarding the imaging effectiveness of KUB are limited in children. In adults, a KUB may add marginal benefit to the sensitivity and specificity of US as a routine adjunct imaging modality and is especially ineffective at identifying calculi less than 5 mm in size [68]. Additionally, some calculi, including those composed of uric acid, are radiolucent on radiography irrespective of stone size, further limiting the utility of the KUB. However, these stone types account for less than 2% of all cases of pediatric nephrolithiasis [69].

The KUB does have potential benefit in greater visibility of the mid-ureteral region than on US. In addition, visibility of a urinary calculus on CT scout images suggests that the calculus could be followed by radiography instead of with repeat CT. Finally, certain surgical modalities, such as shock wave lithotripsy (SWL), often rely upon fluoroscopic imaging of the calculus. As such, the visibility of a calculus on KUB at least indicates feasibility of fluoroscopy-guided SWL as a treatment option.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has been identified as a potential imaging strategy for nephrolithiasis in certain circumstances, such as pregnancy [70]. This modality, though attractive due to its lack of ionizing radiation, has several drawbacks in the evaluation of children with nephrolithiasis. Most significantly, calculi are typically not visible by MRI but are instead identified by the focal absence of signal during excretory urography [71]. Additionally, the length of the study and the requirement for the patient to remain stationary for the duration may be prohibitive without sedation for younger children [72]. Thus, while identification of incidental nephrolithiasis has been reported on MRI in children, the role of MRI for nephrolithiasis remains limited at present [73].

Intravenous Pyelography

Intravenous pyelography (IVP) was the historical study of choice for evaluation of nephrolithiasis. The study entails the injection of intravenous contrast followed by sequential radiographic imaging of the abdomen. This strategy allows radiopaque calculi to be identified similar to a KUB but also permits opacification of the collecting system in order to evaluate stone location more precisely and to assess for filling defects which could indicate radiolucent calculi [74]. However, this study is less sensitive than CT and requires the additional burdens of multiple sequential images and administration of intravenous contrast [75]. While the mention of IVP in this text is largely an homage to imaging history, there may be rare occasions in which this technique proves valuable in contemporary practice, such as the use of contrast to opacify the renal collecting system for a better understanding of anatomy during fluoroscopy-guided SWL.

Choice of Imaging Based on Clinical Context

As is clear from the above review of imaging modalities, US and CT are the mainstays for evaluation of children with nephroureterolithiasis, with occasional benefit from KUB as an adjunct study. The choice of the "optimal" imaging strategy is based on the clinical context and the information needed balanced against the risks of ionizing radiation exposure.

Imaging for Suspected Nephrolithiasis in Children

Acknowledging the need to reduce radiation exposure in children, US is often cited as the preferred first-line strategy for imaging of suspected renal or ureteral calculi in children [48, 76, 77]. These recommendations are supported by high-level evidence evaluating the clinical effectiveness of both US and CT in adults. In a randomized controlled trial of CT and US for suspected nephrolithiasis in adults, Smith-Bindman et al. reported no difference in adverse outcomes or significant missed diagnoses between these modalities [78]. While US remains inferior to CT in its sensitivity for detecting urinary calculi, it is nevertheless a safe first-line option and screening tool which minimizes radiation exposure. This balance is important, as the majority of CT scans performed for suspected nephrolithiasis will be negative for urinary calculi [79]. Many considerations may influence imaging choice, including: patient factors such as age, gender, and medical comorbidities, the provider's familiarity with pediatric care, and even the day of the week [2, 9]. This last variable may be indicative of the relative availability of after-hours CT and US in some health care systems. Many of these factors are not modifiable. The presence of a

"kidney stone pathway" through the pediatric emergency department has been associated with reduced use of initial CT imaging for nephrolithiasis and has been shown to be effective, without adverse events such as increased readmissions or return visits to acute care settings [80, 81]. Because the majority of ureteral calculi may pass spontaneously, even a nondiagnostic US in the appropriately selected clinical scenario may be sufficient for acute care decision making, provided timely urological follow-up (typically within 2–4 weeks) is ensured [82]. Using this paradigm, a CT scan would be obtained in situations where the clinical diagnosis was in doubt and defining the presence, location, and size of a urinary calculus would guide emergent management. Thus, children with a nondiagnostic US and a continued high index of suspicion for obstructive nephrolithiasis should receive a CT during initial evaluation in the emergency department only if urgent urological intervention may be needed. Such settings include concern for concomitant urinary tract infection and pain that cannot be safely managed at home. An alternative paradigm uses identified risk factors for nephrolithiasis to enable selection of children with a higher pretest probability to receive a first-line CT scan. Persaud et al. reported on four independent risk factors for nephrolithiasis in children presenting to emergency care: the presence of nausea or vomiting; a personal history of nephrolithiasis; microscopic hematuria (≥3 red blood cells per high powered field) or gross hematuria; and lateralizing flank pain on evaluation [79]. While the merits of these paradigms have not been compared, a combination of both is likely useful in daily clinical practice (Fig. 8.5). Regardless of the imaging strategy chosen, the use

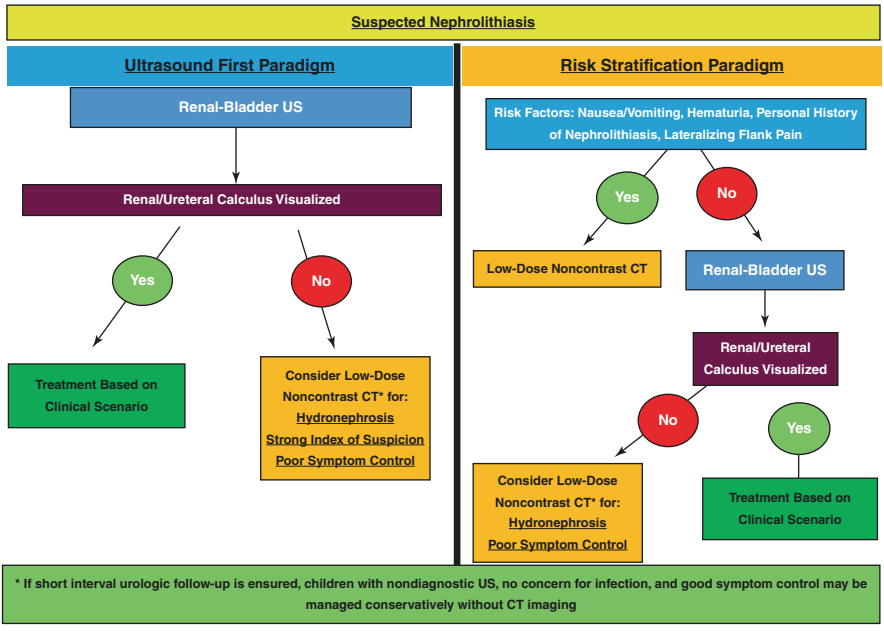

Fig. 8.5 Two paradigms for initial imaging in suspected pediatric nephrolithiasis: ultrasound first vs. risk stratification

of low-dose CT should be supported, provided patient and hospital factors enable a high-quality examination.

Follow-up Imaging for Acute Nephrolithiasis

Following an acute evaluation for nephrolithiasis, repeat imaging is indicated to assess for persistence versus passage of the calculus [48]. Short-interval imaging, within 2–4 weeks, is particularly important for evaluating children in one of two circumstances: a radiologically proven ureteral calculus or a nondiagnostic US with a high degree of suspicion for nephrolithiasis (especially in the setting of concomitant hydronephrosis or ureteral dilation). In either setting, follow-up imaging is used to document stone passage and to ensure that there is no persistent silent obstruction which could result in irreversible renal injury. Notably, although both self-reported stone passage and resolution of symptoms are highly predictive of successful stone passage, neither can ensure the absence of residual calculus. For this reason, repeat imaging is recommended even when symptoms have resolved [83]. The choice of imaging in follow-up care is dependent upon the initial imaging modality and the clinical context. In general, a "like with like" approach is preferred in order to ensure visibility of the previously diagnosed calculus [10, 48]. However, this strategy may become problematic if the initial diagnosis is made by CT, given the risks of repeated exposure to ionizing radiation [10]. As mentioned earlier in this chapter, a calculus seen on the CT scout can be reliably seen on a KUB as well, the latter being a reasonable choice for follow-up imaging. In the setting of a nondiagnostic US at initial evaluation, US remains reasonable for follow-up imaging if symptoms and microscopic hematuria have resolved. If this approach is chosen, the family must be counseled that repeat symptoms should be re-evaluated with NCCT.

Imaging for Preoperative Preparation

Multiple surgical options exist to treat nephrolithiasis, including shock wave lithotripsy (SWL), ureteroscopy (URS), percutaneous nephrolithotomy (PCNL), and rarely open or laparoscopic stone removal. Stone size and location, patient factors, and urinary tract anatomy can all influence surgical decision making [84]. For small and moderate-sized calculi up to approximately 1.5 cm in diameter, URS and SWL offer similar stone clearance [85]. In these circumstances, CT offers little additional information beyond what US can provide [11]. Conversely, as the risks of surgical intervention are greater than the potential risks from radiation exposure, preoperative CT is indicated if the diagnosis is in doubt [86]. While SWL can be performed via US guidance, this is facility-dependent. If fluoroscopy-guided SWL is used, the surgeon must confirm the visibility of the calculus on KUB before proceeding to

treatment. Some specific clinical scenarios may warrant additional cross-sectional or functional imaging prior to surgical intervention.

1. PCNL: PCNL is performed by gaining percutaneous access into the renal collecting system via the flank. The access tract traverses the retroperitoneum, and gaining access poses risks to perinephric structures such as a retrorenal colon, the spleen, or the liver. As such, a preprocedural CT scan is sometimes recommended to evaluate intra-abdominal anatomy and aid in PCNL preparation, especially if US will be used to gain access (see below) [62].
2. Concern for poorly functioning or obstructed renal units: Initial imaging findings such as parenchymal thinning may suggest poor renal function. Nuclear medicine renography should be considered to assess split renal function prior to surgical intervention. In the case of a poorly functioning kidney (i.e., providing ≤10% of total renal function) with a symptomatic renal or ureteral calculus, nephrectomy may be a more appropriate surgical option than stone removal or fragmentation. Similarly, diuretic renography can be used if concomitant ureteropelvic junction obstruction is suspected. A surgical option which manages the obstruction as well as the renal calculi, such as pyeloplasty with pyelolithotomy, would then be preferred.
3. Need to define urinary anatomy: In the setting of possible ureteral duplication or suspected calyceal diverticulum, excretory urography (typically with CT or MR urography) can be useful to delineate anatomy prior to surgical intervention. Notably, the need for imaging depends on the surgical approaches being considered. For instance, ureteral duplication has minimal impact on SWL success and can often be identified and safely accounted for at the time of intervention via retrograde URS. However, preprocedural identification of a duplicated collecting system would be of utmost importance when planning access for a PCNL. Similarly, a calyceal diverticulum may be suspected on US, suggested by a dilated calyx with fluid surrounding the calculus of interest (Fig. 8.6). With a high index of suspicion, URS may be successful even without preoperative

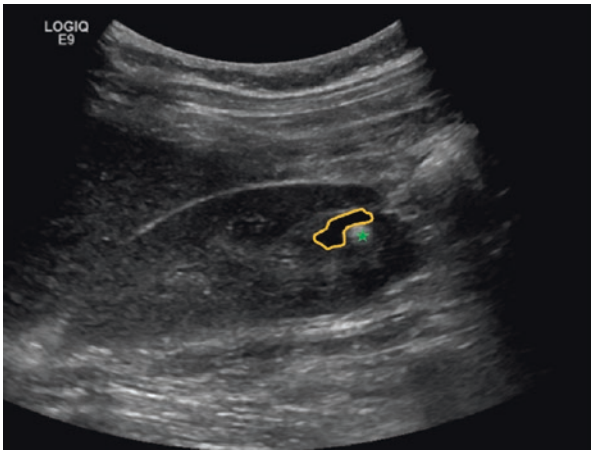

Fig. 8.6 Findings of lower pole hydronephrosis or a reported cyst-like structure with a focal calcification should prompt consideration of possible calyceal diverticulum. In this figure, a fluid-filled structure (orange outline) is seen adjacent to a calcification (green star)

excretory imaging. However, if an alternative approach to treatment of a calyceal diverticulum, such as percutaneous ablation or robotic/laparoscopic excision, is planned, further definition of the anatomy (e.g., the size of the diverticulum, the thickness of the overlying parenchyma, and the length of the infundibular stenosis) may be useful for surgical selection [87].

Intraoperative Imaging

Approximately 30% of children presenting acutely with nephrolithiasis will require surgical intervention [82]. These children may be exposed to a substantial amount of radiation intraoperatively owing to the use of fluoroscopy to localize calculi and to guide placement of surgical instruments [12]. In keeping with the ALARA principles, the two main strategies to minimize intraoperative radiation exposure include avoidance of ionizing radiation when possible and mitigation of dose when not. In order to reduce fluoroscopic dose, several strategies may be established in the operating room. All involved members of the surgical team should be provided appropriate protective equipment and should have agreed-upon terminology for obtaining imaging. Most C-arm machines have dose settings which can be lowered as needed for pediatric patients. Additionally, using pulsed fluoroscopy will reduce the number of images taken, thereby decreasing dose. Continuous fluoroscopy may be reserved for situations when surgical movements or three-dimensional anatomy must be assessed in real time. In order to reduce scatter and improve focused energy delivery, the space between the image intensifier and the patient should be minimized and should be devoid of any unnecessary radiopaque surgical equipment. Institution of a preoperative checklist including many of these modifications has been shown to significantly decrease effective radiation dose to both the patient and the operative team [88, 89].

1. SWL: A variety of lithotripters exist, all of which depend upon the ability to identify the calculus for targeted energy delivery [90]. While fluoroscopic guidance is the most common imaging adjunct, US-guided SWL has been reported to be equally or more effective [91]. One benefit of US guidance is the ability to provide real-time monitoring of stone location during inspiration and expiration.
2. URS: Ureteroscopic treatment allows direct endoscopic visualization of the urinary tract and urinary calculi. Imaging can therefore be selective and limited to key steps in the procedure. Retrograde pyelography provides an overview of the urinary tract anatomy. Fluoroscopic imaging during the passage of guidewires, access sheaths, or the ureteroscope itself can then ensure that these instruments remain within the ureter and renal collecting system during manipulation. In the event that a calculus is difficult to localize by ureteroscopy, imaging can provide the surgeon with an understanding of the stone location in relation to the ureteroscope. Finally, imaging enables the surgeon to confirm appropriate indwelling ureteral stent position if one has been placed during the procedure. Notably,

based on surgeon experience and patient factors, URS can be achieved safely with the use of minimal to no fluoroscopy, with the only absolute need for imaging being at the time of stent placement [92]. US-guided URS has been reported in select pediatric cases, resulting in safe and effective treatment. While this modality is attractive, the limitations include a learning curve for sonographic identification of surgical equipment and the need for additional personnel and equipment in the operating room [93].

3. PCNL: Percutaneous access during PCNL is typically the most imaging-intensive aspect of surgical management for nephrolithiasis and accordingly carries a high burden of potential radiation exposure [12]. Unlike URS, PCNL access should not be attempted without imaging guidance. However, US has proven to be a useful adjunct to or even replacement for fluoroscopy during renal access and tract dilation. Reports of US-guided PCNL access in children have arisen from high-volume centers, showing promising results with surgical outcomes and complication rates similar to those seen with fluoroscopic guidance [94–96]. Although operator-dependent, US guidance has the benefit of reducing radiation exposure even during the learning period [97]. US-guided PCNL access has several additional advantages over fluoroscopic guidance, including the ability to easily identify posterior calyces as well as key structures at risk for injury such as bowel, liver, spleen, or pleura [98]. For children with complex anatomy, such as those with pelvic kidneys or prior lower urinary tract reconstruction, cross-sectional guidance with CT may be necessary to gain safe percutaneous access, as has been described for certain transgluteal approaches [99]. Advances in CT have led to development of Dyna-CT (Siemens Healthcare Solutions, Erlangen, Germany), which can provide real-time three-dimensional cross-sectional imaging within the operating room. While several parameters important for optimal application of this technology in the pediatric population have yet to be defined, Dyna-CT provides yet another tool in the armamentarium of urologists managing complex stone disease [100].

Postoperative Imaging

As with short-interval follow-up imaging subsequent to an acute stone event, imaging following surgical intervention is used to assess for residual calculi and obstruction of the collecting system. Accordingly, “like with like” imaging strategies are preferred, such that follow-up imaging employs the same modality as the initial evaluation, depending upon feasibility and radiation exposure [48]. When considering postoperative imaging strategy, one must also account for the surgical intervention used and the risks associated with imaging [13].

Following SWL, a KUB is appropriate for evaluation, particularly if the calculus was radiopaque and visible on preoperative KUB and/or intraoperative fluoroscopy. Routine US imaging following SWL is not necessary. The ureter is typically not manipulated during SWL treatment, making the risk for ureteral injury much lower than with URS [48]. If there was preoperative hydronephrosis, US or CT could be

considered in addition to or in place of the KUB to document resolution. From a practical perspective, these situations can be managed with a KUB to assess for residual stone burden and US to evaluate for persistent hydronephrosis.

In contrast, the surgeon is able to directly visualize the calculus being treated and removed during URS. Some authors have therefore advocated against routine imaging after straightforward URS [101]. Others have concluded that routine imaging is not cost-effective, even with a known low risk of silent obstruction secondary to iatrogenic ureteral stricture. However, those same authors acknowledge that the consequences of losing a kidney in such circumstances are incalculable beyond standard modeling of health care costs [102]. Others have shown substantial morbidity associated with postoperative ureteral stricture following URS [103]. Consequently, routine US is recommended by many experts to assess for postoperative hydronephrosis [48]. It should be noted that the aforementioned studies were performed in adults. The rate of ureteral stricture disease following URS in children is poorly defined, in part due to the relatively low incidence of this complication and in part due to challenges in obtaining long-term follow-up in pediatric cohorts. The rate of new-onset hydronephrosis following URS has been reported at 12–26%, due either to postoperative ureteral edema or to residual stone fragments. In two small studies of patients with hydronephrosis following URS, postoperative edema was assumed to be the cause of hydronephrosis in the patients without documented residual stone fragments. Hydronephrosis in these patients resolved spontaneously following a period of observation. Of those children with documented residual obstructing stone fragments, one-third ultimately required repeat surgical intervention [104, 105]. Notably, none of the children in either study had documented ureteral strictures. Because the majority of new-onset hydronephrosis following URS will resolve spontaneously, it is reasonable to monitor these findings in asymptomatic patients with short-interval ultrasonography (i.e., 4–6 weeks) before obtaining a CT scan to evaluate for residual stone fragments.

There is a similar risk of postoperative obstruction after PCNL which typically warrants imaging follow-up to evaluate for hydronephrosis. Additionally, PCNL is often performed for larger and more complex renal calculi, including those in staghorn or partial staghorn configurations, which can further increase the risk of lingering stone fragments. The potential for residual stone fragments is particularly concerning in situations where infection-related, or struvite, calculi are present. In the setting of residual struvite calculi following stone treatment, the recurrence of clinically significant calculi has been reported to be 80% or more. When struvite calculi are known or suspected, one may want to evaluate the collecting system postoperatively with the most sensitive imaging modality, namely CT, to assess for residual fragments. The threshold for retreatment in those cases may be much lower [106].

Routine Surveillance Imaging

Of all indications for imaging in nephrolithiasis, routine follow-up imaging for asymptomatic children remains the least well understood in terms of clinical

efficacy, choice of imaging modality, and required frequency. The recurrence rate for pediatric nephrolithiasis has been reported to be 50% at 3 years, meaning that a large proportion of these children may develop recurrent stone disease while still under pediatric care [107]. However, the rates of symptomatic versus asymptomatic recurrence have not been reported. Overall, symptomatic and asymptomatic presentations for newly diagnosed nephrolithiasis occur at similar frequencies; hence, a reliance on symptoms alone may be insufficient for detection [6]. Additionally, when a residual calculus is present, documenting stone growth as well as new stone formation is important to guiding future surgical management. Larger stone sizes portend a greater risk for future symptoms and need for surgical intervention [108, 109]. Similar to evaluations for symptomatic presentations, most asymptomatic children can be safely managed with surveillance US to assess for new stone formation and/or stone growth. Exceptions include significant calculi that are not visible on US and/or select patients for whom the risk of recurrence is exceptionally high and a more sensitive imaging modality is required.

Conclusions

Though nephrolithiasis has become more common in children, it remains a relatively infrequent diagnosis in the pediatric realm which requires a high index of suspicion and a focused evaluation. Due to the need for multiple imaging studies across the clinical course for nephrolithiasis, which includes initial evaluations, perioperative assessments, and follow-up surveillance, the potential for cumulative radiation exposure is high. At each step of the evaluation, an effort to determine the optimal imaging strategy must be made. There should be a continual focus on balancing radiation exposure, imaging needs, and the specific clinical context. Future work should explore barriers to implementation of US-first protocols and low-dose CT imaging across complex health systems, risk stratification of children based on clinical presentation and index of suspicion, and clinically effective surveillance protocols.

References

1. Tasian GE, Ross ME, Song LH, Sas DJ, Keren R, Denburg MR, et al. Annual incidence of nephrolithiasis among children and adults in South Carolina from 1997 to 2012. Clin J Am Soc Nephrol. 2016;11(3):488–96.
2. Tasian GE, Pulido JE, Keren R, Dick AW, Setodji CM, Hanley JM, et al. Use of and regional variation in initial CT imaging for kidney stones. Pediatrics. 2014;134(5):909–15.
3. Shah NB, Platt SL. ALARA: is there a cause for alarm? Reducing radiation risks from computed tomography scanning in children. Curr Opin Pediatr. 2008;20(3):243–7.

4. Pichler R, Skradski V, Aigner F, Leonhartsberger N, Steiner H. In young adults with a low body mass index ultrasonography is sufficient as a diagnostic tool for ureteric stones. BJU Int. 2012;109(5):770–4.
5. Karmazyn B, Frush DP, Applegate KE, Maxfield C, Cohen MD, Jones RP. CT with a computer-simulated dose reduction technique for detection of pediatric nephroureterolithiasis: comparison of standard and reduced radiation doses. AJR Am J Roentgenol. 2009;192(1):143–9.
6. Cassim R, Van Walraven C, Lavallee LT, McAlpine K, Highmore K, Leonard MP, et al. Systematic radiologic detection of kidney stones in Canadian children: a new era of asymptomatic stones? J Pediatr Urol 2019;15(5):467 e1- e7.
7. Kusumi K, Becknell B, Schwaderer A. Trends in pediatric urolithiasis: patient characteristics, associated diagnoses, and financial burden. Pediatr Nephrol. 2015;30(5):805–10.
8. Kurtzman JT, Song L, Ross ME, Scales CD Jr, Chu DI, Tasian GE. Urology consultation and emergency department revisits for children with urinary stone disease. J Urol. 2018;200(1):180–6.
9. Johnson EK, Graham DA, Chow JS, Nelson CP. Nationwide emergency department imaging practices for pediatric urolithiasis: room for improvement. J Urol. 2014;192(1):200–6.
10. Ellison JS, Merguerian PA, Fu BC, Holt SK, Lendvay TS, Gore JL, et al. Follow-up imaging after acute evaluations for pediatric nephrolithiasis: trends from a national database. J Pediatr Urol. 2018;14(6):525–31.
11. Johnson EK, Faerber GJ, Roberts WW, Wolf JS Jr, Park JM, Bloom DA, et al. Are stone protocol computed tomography scans mandatory for children with suspected urinary calculi? Urology. 2011;78(3):662–6.
12. Ristau BT, Dudley AG, Casella DP, Dwyer ME, Fox JA, Cannon GM, et al. Tracking of radiation exposure in pediatric stone patients: the time is now. J Pediatr Urol. 2015;11(6):339. e1-e5.
13. Ellison JS, Merguerian PA, Fu BC, Holt SK, Lendvay TS, Shnorhavorian M. Postoperative imaging patterns of pediatric nephrolithiasis: opportunities for improvement. J Urol. 2019;201(4):794–801.
14. Brody AS, Frush DP, Huda W, Brent RL, American Academy of Pediatrics Section on R. Radiation risk to children from computed tomography. Pediatrics. 2007;120(3):677–82.
15. Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation exposure. N Engl J Med. 2007;357(22):2277–84.
16. Brenner D, Elliston C, Hall E, Berdon W. Estimated risks of radiation-induced fatal cancer from pediatric CT. AJR Am J Roentgenol. 2001;176(2):289–96.
17. Tubiana M, Feinendegen LE, Yang CC, Kaminski JM. The linear no-threshold relationship is inconsistent with radiation biologic and experimental data. Radiology. 2009;251(1):13–22.
18. Martin CJ. The LNT model provides the best approach for practical implementation of radiation protection. Br J Radiol. 2005;78(925):14–6.
19. Meulepas JM, Ronckers CM, Smets A, Nievelstein RAJ, Gradowska P, Lee C, et al. Radiation exposure from pediatric CT scans and subsequent cancer risk in the Netherlands. J Natl Cancer Inst. 2019;111(3):256–63.
20. Journy NM, Lee C, Harbron RW, McHugh K, Pearce MS, de González AB. Projected cancer risks potentially related to past, current, and future practices in paediatric CT in the United Kingdom, 1990–2020. Br J Cancer. 2017;116(1):109–16.
21. Miglioretti DL, Johnson E, Williams A, Greenlee RT, Weinmann S, Solberg LI, et al. The use of computed tomography in pediatrics and the associated radiation exposure and estimated cancer risk. JAMA Pediatr. 2013;167(8):700–7.
22. Siegel JA, Sacks B, Pennington CW, Welsh JS. Dose optimization to minimize radiation risk for children undergoing CT and nuclear medicine imaging is misguided and detrimental. J Nucl Med. 2017;58(6):865–8.
23. Ortiz SHC, Chiu T, Fox MD. Ultrasound image enhancement: a review. Biomed Signal Process Control. 2012;7(5):419–28.
24. Dunmire B, Lee FC, Hsi RS, Cunitz BW, Paun M, Bailey MR, et al. Tools to improve the accuracy of kidney stone sizing with ultrasound. J Endourol. 2015;29(2):147–52.

25. Verhagen MV, Watson TA, Hickson M, Smeulders N, Humphries PD. Acoustic shadowing in pediatric kidney stone ultrasound: a retrospective study with non-enhanced computed tomography as reference standard. Pediatr Radiol. 2019;49(6):777–83.
26. Dillman JR, Kappil M, Weadock WJ, Rubin JM, Platt JF, DiPietro MA, et al. Sonographic twinkling artifact for renal calculus detection: correlation with CT. Radiology. 2011;259(3):911–6.
27. Wood BG, Urban MW. Detecting kidney stones using twinkling artifacts: survey of kidney stones with varying composition and size. Ultrasound Med Biol. 2020;46(1):156–66.
28. Dai JC, Dunmire B, Liu Z, Sternberg KM, Bailey MR, Harper JD, et al. Measurement of posterior acoustic stone shadow on ultrasound is a learnable skill for inexperienced users to improve accuracy of stone sizing. J Endourol. 2018;32(11):1033–8.
29. Dunmire B, Harper JD, Cunitz BW, Lee FC, Hsi R, Liu Z, et al. Use of the acoustic shadow width to determine kidney stone size with ultrasound. J Urol. 2016;195(1):171–7.
30. Roberson NP, Dillman JR, O'Hara SM, DeFoor WR Jr, Reddy PP, Giordano RM, et al. Comparison of ultrasound versus computed tomography for the detection of kidney stones in the pediatric population: a clinical effectiveness study. Pediatr Radiol. 2018;48(7):962–72.
31. Palmer JS, Donaher ER, O'Riordan MA, Dell KM. Diagnosis of pediatric urolithiasis: role of ultrasound and computerized tomography. J Urol. 2005;174(4 Pt 1):1413–6.
32. Streur CS, Lin PJ, Hollingsworth JM, Kamdar NS, Kraft KH. Impact of the image gently(R) campaign on computerized tomography use for evaluation of pediatric nephrolithiasis. J Urol. 2019;201(5):996–1004.
33. van Randen A, Lameris W, van Es HW, van Heesewijk HP, van Ramshorst B, Ten Hove W, et al. A comparison of the accuracy of ultrasound and computed tomography in common diagnoses causing acute abdominal pain. Eur Radiol. 2011;21(7):1535–45.
34. Passerotti C, Chow JS, Silva A, Schoettler CL, Rosoklija I, Perez-Rossello J, et al. Ultrasound versus computerized tomography for evaluating urolithiasis. J Urol. 2009;182(4 Suppl):1829–34.
35. Cunitz BW, Harper JD, Sorensen MD, Haider YA, Thiel J, May PC, et al. Quantification of renal stone contrast with ultrasound in human subjects. J Endourol. 2017;31(11):1123–30.
36. Masch WR, Cohan RH, Ellis JH, Dillman JR, Rubin JM, Davenport MS. Clinical effectiveness of prospectively reported sonographic twinkling artifact for the diagnosis of renal calculus in patients without known urolithiasis. AJR Am J Roentgenol. 2016;206(2):326–31.
37. Sternberg KM, Eisner B, Larson T, Hernandez N, Han J, Pais VM. Ultrasonography significantly overestimates stone size when compared to low-dose, noncontrast computed tomography. Urology. 2016;95:67–71.
38. Ganesan V, De S, Greene D, Torricelli FCM, Monga M. Accuracy of ultrasonography for renal stone detection and size determination: is it good enough for management decisions? BJU Int. 2017;119(3):464–9.
39. Dai JC, Dunmire B, Sternberg KM, Liu Z, Larson T, Thiel J, et al. Retrospective comparison of measured stone size and posterior acoustic shadow width in clinical ultrasound images. World J Urol. 2018;36(5):727–32.
40. Preminger GM, Tiselius H-G, Assimos DG, Alken P, Buck C, Gallucci M, et al. 2007 guideline for the management of ureteral calculi. J Urol. 2007;178(6):2418–34.
41. Kremer H, Dobrinski W, Mikyska M, Baumgartner M, Zollner N. Ultrasonic in vivo and in vitro studies on the nature of the ureteral jet phenomenon. Radiology. 1982;142(1):175–7.
42. Baker SM, Middleton WD. Color Doppler sonography of ureteral jets in normal volunteers: importance of the relative specific gravity of urine in the ureter and bladder. AJR Am J Roentgenol. 1992;159(4):773–5.
43. Yıldırım D, Gürses B, Kocaoğlu M. Doppler characteristics of the ureteric jet-streams in patients with non-obstructive nephrolithiasis: mechanism of dysfunctional propagation of the peristaltic activity from the pelvic pacemaker to the ureterovesical sphincter. Turk J Urol. 2010;36(3)
44. McQuaid JW, Kurtz MP, Logvinenko T, Nelson CP. Bladder debris on renal and bladder ultrasound: a significant predictor of positive urine culture. J Pediatr Urol. 2017;13(4): 385 e1-e5.

45. Lira D, Padole A, Kalra MK, Singh S. Tube potential and CT radiation dose optimization. AJR Am J Roentgenol. 2015;204(1):W4–10.
46. Frush DP. Pediatric CT: practical approach to diminish the radiation dose. Pediatr Radiol. 2002;32(10):714–7. discussion 51-4
47. Kalra MK, Maher MM, Toth TL, Schmidt B, Westerman BL, Morgan HT, et al. Techniques and applications of automatic tube current modulation for CT. Radiology. 2004;233(3):649–57.
48. Fulgham PF, Assimos DG, Pearle MS, Preminger GM. Clinical effectiveness protocols for imaging in the management of ureteral calculous disease: AUA technology assessment. J Urol. 2013;189(4):1203–13.
49. Memarsadeghi M, Heinz-Peer G, Helbich TH, Schaefer-Prokop C, Kramer G, Scharitzer M, et al. Unenhanced multi–detector row CT in patients suspected of having urinary stone disease: effect of section width on diagnosis. Radiology. 2005;235(2):530–6.
50. Grant MT, Eisner BH, Bechis SK. Ureteral obstruction due to radiolucent atazanavir ureteral stones. J Endourol Case Rep. 2017;3(1):152–4.
51. Singh S, Kalra MK, Moore MA, Shailam R, Liu B, Toth TL, et al. Dose reduction and compliance with pediatric CT protocols adapted to patient size, clinical indication, and number of prior studies. Radiology. 2009;252(1):200–8.
52. Nagayama Y, Oda S, Nakaura T, Tsuji A, Urata J, Furusawa M, et al. Radiation dose reduction at pediatric CT: use of low tube voltage and iterative reconstruction. Radiographics. 2018;38(5):1421.
53. Weisenthal K, Karthik P, Shaw M, Sengupta D, Bhargavan-Chatfield M, Burleson J, et al. Evaluation of kidney stones with reduced–radiation dose CT: progress from 2011–2012 to 2015–2016—not there yet. Radiology. 2018;286(2):581–9.
54. Strauss KJ, Somasundaram E, Sengupta D, Marin JR, Brady SL. Radiation dose for pediatric CT: comparison of pediatric versus adult imaging facilities. Radiology. 2019;291(1):158–67.
55. Elderwy AA, Kurkar A, Hussein A, Abozeid H, Hammodda HM, Ibraheim AF. Dissolution therapy versus shock wave lithotripsy for radiolucent renal stones in children: a prospective study. J Urol. 2014;191(5 Suppl):1491–5.
56. Siegel MJ, Ramirez-Giraldo JC. Dual-energy CT in children: imaging algorithms and clinical applications. Radiology. 2019;291(2):286–97.
57. Boll DT, Patil NA, Paulson EK, Merkle EM, Simmons WN, Pierre SA, et al. Renal stone assessment with dual-energy multidetector CT and advanced postprocessing techniques: improved characterization of renal stone composition—pilot study. Radiology. 2009;250(3):813–20.
58. Fung GSK, Kawamoto S, Matlaga BR, Taguchi K, Zhou XD, Fishman EK, et al. Differentiation of kidney stones using dual-energy CT with and without a tin filter. Am J Roentgenol. 2012;198(6):1380–6.
59. Kaza RK, Ananthakrishnan L, Kambadakone A, Platt JF. Update of dual-energy CT applications in the genitourinary tract. AJR Am J Roentgenol. 2017;208(6):1185–92.
60. Siegel MJ, Curtis WA, Ramirez-Giraldo JC. Effects of dual-energy technique on radiation exposure and image quality in pediatric body CT. AJR Am J Roentgenol. 2016;207(4):826–35.
61. Siegel MJ, Ramirez-Giraldo JC, editors. Pediatric diagnostic reference ranges for dual-energy dual-source abdominopelvic CT. Radiological Society of North America 2018 Scientific assembly and annual meeting; 2018; Chicago, IL.
62. Assimos D, Krambeck A, Miller NL, Monga M, Murad MH, Nelson CP, et al. Surgical management of stones: American urological association/Endourological society guideline, PART I. J Urol. 2016;196(4):1153–60.
63. Spettel S, Shah P, Sekhar K, Herr A, White MD. Using Hounsfield unit measurement and urine parameters to predict uric acid stones. Urology. 2013;82(1):22–6.
64. El-Assmy A, El-Nahas AR, Abou-El-Ghar ME, Awad BA, Sheir KZ. Kidney stone size and hounsfield units predict successful shockwave lithotripsy in children. Urology. 2013;81(4):880–4.
65. Johnston R, Lin A, Du J, Mark S. Comparison of kidney-ureter-bladder abdominal radiography and computed tomography scout films for identifying renal calculi. BJU Int. 2009;104(5):670–3.

66. Rothrock SG, Green SM, Hummel CB. Plain abdominal radiography in the detection of major disease in children: a prospective analysis. Ann Emerg Med. 1992;21(12):1423–9.
67. Kwon H, Jung JY. Effectiveness of a radiation reduction campaign targeting children with gastrointestinal symptoms in a pediatric emergency department. Medicine (Baltimore). 2017;96(3):e5907.
68. Kanno T, Kubota M, Funada S, Okada T, Higashi Y, Yamada H. The utility of the kidneys-ureters-bladder radiograph as the sole imaging modality and its combination with ultrasonography for the detection of renal stones. Urology. 2017;104:40–4.
69. Gabrielsen JS, Laciak RJ, Frank EL, McFadden M, Bates CS, Oottamasathien S, et al. Pediatric urinary stone composition in the United States. J Urol. 2012;187(6):2182–7.
70. McAleer SJ, Loughlin KR. Nephrolithiasis and pregnancy. Curr Opin Urol. 2004;14(2):123–7.
71. Rothpearl A, Frager D, Subramanian A, Bashist B, Baer J, Kay C, et al. MR urography: technique and application. Radiology. 1995;194(1):125–30.
72. Ahmad R, Hu HH, Krishnamurthy R, Krishnamurthy R. Reducing sedation for pediatric body MRI using accelerated and abbreviated imaging protocols. Pediatr Radiol. 2018;48(1):37–49.
73. Kavanagh EC, Ryan S, Awan A, McCourbrey S, O'Connor R, Donoghue V. Can MRI replace DMSA in the detection of renal parenchymal defects in children with urinary tract infections? Pediatr Radiol. 2005;35(3):275–81.
74. Shine S. Urinary calculus: IVU vs. CT renal stone? A critically appraised topic. Abdom Imaging. 2008;33(1):41–3.
75. Yilmaz S, Sindel T, Arslan G, Ozkaynak C, Karaali K, Kabaalioglu A, et al. Renal colic: comparison of spiral CT, US and IVU in the detection of ureteral calculi. Eur Radiol. 1998;8(2):212–7.
76. Association AU. Choosing wisely: 15 things patients and physicians should question 2017 [updated 2017. Available from: http://www.choosingwisely.org/societies/american-urological-association/
77. Riccabona M, Avni FE, Dacher JN, Damasio MB, Darge K, Lobo ML, et al. ESPR uroradiology task force and ESUR paediatric working group: imaging and procedural recommendations in paediatric uroradiology, part III. Minutes of the ESPR uroradiology task force minisymposium on intravenous urography, uro-CT and MR-urography in childhood. Pediatr Radiol. 2010;40(7):1315–20.
78. Smith-Bindman R, Aubin C, Bailitz J, Bengiamin RN, Camargo CA Jr, Corbo J, et al. Ultrasonography versus computed tomography for suspected nephrolithiasis. N Engl J Med. 2014;371(12):1100–10.
79. Persaud AC, Stevenson MD, McMahon DR, Christopher NC. Pediatric urolithiasis: clinical predictors in the emergency department. Pediatrics. 2009;124(3):888–94.
80. Ziemba JB, Canning DA, Lavelle J, Kalmus A, Tasian GE. Patient and institutional characteristics associated with initial CT use for children presenting to the emergency department with kidney stones. J Urol. 2015;193(5 Suppl):1848.
81. Ellison JS, Crowell CS, Clifton H, Whitlock K, Haaland W, Chen T, et al. A clinical pathway to minimize computed tomography for suspected nephrolithiasis in children. J Pediatr Urol. 2019;15(5):518 e1-e7.
82. Ellison JS, Merguerian PA, Fu BC, Holt SK, Lendvay TS, Gore JL, et al. Use of medical expulsive therapy in children: an assessment of nationwide practice patterns and outcomes. J Pediatr Urol. 2017;13(5):509 e1-e7.
83. McLarty R, Assmus M, Senthilselvan A, Schuler T, Wollin T, De S. Patient reported outcomes predicting spontaneous stone passage may not have acceptable accuracy. J Urol. 2020. https://doi.org/10.1097/JU.0000000000001030.
84. Hernandez JD, Ellison JS, Lendvay TS. Current trends, evaluation, and management of pediatric nephrolithiasis. JAMA Pediatr. 2015;169(10):964–70.
85. Marchetti KA, Lee T, Raja N, Corona L, Kraft KH, Wan J, et al. Extracorporeal shock wave lithotripsy versus ureteroscopy for management of pediatric nephrolithiasis in upper

urinary tract stones: multi-institutional outcomes of efficacy and morbidity. J Pediatr Urol. 2019;15(5):516 e1-e8.
86. Ishii H, Griffin S, Somani BK. Flexible ureteroscopy and lasertripsy (FURSL) for paediatric renal calculi: results from a systematic review. J Pediatr Urol. 2014;10(6):1020–5.
87. McGarry L, Sahadev R, Hogan G, Long C, Otero H, Srinivasan AK, et al. Calyceal diverticula in children: laparoscopic marsupialization is the optimal intervention. J Pediatr Urol. 2020.
88. Kokorowski PJ, Chow JS, Strauss KJ, Pennison M, Tan W, Cilento B, et al. Prospective systematic intervention to reduce patient exposure to radiation during pediatric ureteroscopy. J Urol. 2013;190(4 Suppl):1474–8.
89. Elkoushy MA, Shahrour W, Andonian S. Pulsed fluoroscopy in ureteroscopy and percutaneous nephrolithotomy. Urology. 2012;79(6):1230–5.
90. Silay MS, Ellison JS, Tailly T, Caione P. Update on urinary stones in children: current and future concepts in surgical treatment and shockwave lithotripsy. Eur Urol Focus. 2017;3(2–3):164–71.
91. Goren MR, Goren V, Ozer C. Ultrasound-guided shockwave lithotripsy reduces radiation exposure and has better outcomes for pediatric Cystine stones. Urol Int. 2017;98(4):429–35.
92. Hsi RS, Harper JD. Fluoroless ureteroscopy: zero-dose fluoroscopy during ureteroscopic treatment of urinary-tract calculi. J Endourol. 2013;27(4):432–7.
93. Morrison JC, Van Batavia JP, Darge K, Long CJ, Shukla AR, Srinivasan AK. Ultrasound guided ureteroscopy in children: safety and success. J Pediatr Urol. 2018;14(1):64 e1-e6.
94. Xiao B, Hu WG, Zhang X, Chen S, Li YH, Li JX. Ultrasound-guided mini-percutaneous nephrolithotomy in patients aged less than 3 years: the largest reported single-center experience in China. Urolithiasis. 2016;44(2):179–83.
95. Penbegül N, Tepeler A, Sancaktutar AA, Bozkurt Y, Atar M, Yıldırım K, et al. Safety and efficacy of ultrasound-guided percutaneous nephrolithotomy for treatment of urinary stone disease in children. Urology. 2012;79(5):1015–9.
96. Sharifiaghdas F, Tabibi A, Nouralizadeh A, Sotoudeh M, Ayanifard M, Pakmanesh H, et al. Our experience with totally ultrasonography-guided percutaneous nephrolithotomy in children. 2015.
97. Usawachintachit M, Masic S, Allen IE, Li J, Chi T. Adopting ultrasound guidance for prone percutaneous nephrolithotomy: evaluating the learning curve for the experienced surgeon. J Endourol. 2016;30(8):856–63.
98. Lojanapiwat B. The ideal puncture approach for PCNL: fluoroscopy, ultrasound or endoscopy? Indian J Urol. 2013;29(3):208–13.
99. Alomar M, Alenezi H. Computed tomography-guided transgluteal percutaneous nephrolithotripsy in an ectopic pelvic kidney: novel technique. J Endourol. 2013;27(4):398–401.
100. Vicentini FC, Botelho LA, Braz JL, Almeida ES, Hisano M. Use of the Uro Dyna-CT in endourology–the new frontier. Int J Brazilian Urol. 2017;43(4):762–5.
101. Karadag MA, Tefekli A, Altunrende F, Tepeler A, Baykal M, Muslumanoglu AY. Is routine radiological surveillance mandatory after uncomplicated ureteroscopic stone removal? J Endourol. 2008;22(2):261–6.
102. Weizer AZ, Auge BK, Silverstein AD, Delvecchio FC, Brizuela RM, Dahm P, et al. Routine postoperative imaging is important after ureteroscopic stone manipulation. J Urol. 2002;168(1):46–50.
103. May PC, Hsi RS, Tran H, Stoller ML, Chew BH, Chi T, et al. The morbidity of ureteral strictures in patients with prior Ureteroscopic stone surgery: multi-institutional outcomes. J Endourol. 2018;32(4):309–14.
104. Gökce MI, Telli O, Özkıdık M, Akıncı A, Hajıyev P, Soygür T, et al. Evaluation of postoperative hydronephrosis following ureteroscopy in pediatric population: incidence and predictors. Urology. 2016;93:164–9.
105. Resorlu B, Kara C, Resorlu EB, Unsal A. Effectiveness of ultrasonography in the postoperative follow-up of pediatric patients undergoing ureteroscopic stone manipulation. Pediatr Surg Int. 2011;27(12):1337–41.

106. Preminger GM, Assimos DG, Lingeman JE, Nakada SY, Pearle MS, Wolf JS Jr, et al. Chapter 1: AUA guideline on management of staghorn calculi: diagnosis and treatment recommendations. J Urol. 2005;173(6):1991–2000.
107. Tasian GE, Kabarriti AE, Kalmus A, Furth SL. Kidney stone recurrence among children and adolescents. J Urology. 2017;197(1):246–51.
108. Telli O, Hamidi N, Bagci U, Demirbas A, Hascicek AM, Soygur T, et al. What happens to asymptomatic lower pole kidney stones smaller than 10 mm in children during watchful waiting? Pediatr Nephrol. 2017;32(5):853–7.
109. Dos Santos J, Lopes RI, Veloso AO, Harvey E, Farhat WA, Papanikolaou F. Outcome analysis of asymptomatic lower pole stones in children. J Urol. 2016;195(4 Pt 2):1289–93.

Chapter 9
Workup, Testing, and Interpretation When Evaluating the Child with Stones

Neil J. Paloian

Introduction

Once thought to be a relatively rare phenomenon, it is now understood that pediatric kidney stone disease is not an uncommon occurrence [1, 2]. While childhood nephrolithiasis is not as prevalent as it is in the adult population, it is potentially more important to identify the underlying cause of a stone in a pediatric patient [3]. These children have a much longer lifespan ahead of them, and therefore many more years to form recurrent stones. Additionally, children have a very high chance of having an identifiable metabolic derangement that is causative of the underlying stone formation [4]. To be able to prevent recurrence of stones in these young children, it is essential that every child who presents with a stone has a full evaluation to try and elucidate the cause of the stone. It is equally important to understand how to interpret these results in the context of the growing child; laboratory results in pediatrics are often different than in adults and nephrolithiasis is no exception. Only with proper testing and analysis can the provider formulate an individual treatment plan that minimizes the risk of future stones for these children.

History and Physical

Determining the underlying cause of a pediatric kidney stone begins in the same manner as any other medical diagnostic dilemma: with a detailed history and physical exam. Unlike adults with nephrolithiasis who typically present with severe flank pain, children can present with a range of symptoms including flank pain,

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generalized abdominal pain, gross hematuria, UTI, or they can be completely asymptomatic [5]. Understanding the clinical symptoms of a child with an acute stone is helpful in making the initial diagnosis of nephrolithiasis, but does not help clarify why the child developed the stone. Ideally, this next evaluation to determine the etiology of the stone takes place in an outpatient setting, with the child and family present, when the child is pain-free and all participants can concentrate and engage in what can be a lengthy discussion. The emergency department or inpatient unit is not an appropriate setting to be having this conversation. Additionally, it can be helpful to have laboratory work, such as serum and/or urine testing, completed ahead of time to discuss results with the family. Importantly, some of this testing must be completed when the child is on their home nutrition and fluid regimen, and these results may be distorted if collected in the hospital when the child is receiving intravenous fluids or ordered to take nothing by mouth.

The metabolic derangements leading to stone disease are formally diagnosed with a stone analysis or with blood or urine testing; however, a thorough history will direct the provider to arrange for appropriate testing, while avoiding unnecessary or unhelpful tests. A first step is to obtain a complete dietary history. While the provider should inquire about nutritional intake, it is optimal to have this performed by a registered dietician or nutritionist that is well versed in kidney stone disease. This analysis should include fluid intake, both the quantity of fluids ingested daily and the type and content of those fluids, specifically addressing fluids containing caffeine and alcohol. Additionally, a detailed dietary recall should include components such as dietary sodium intake, calcium intake, consumption of oxalate containing foods and whether or not these are taken with calcium or magnesium foods or supplements, and foods with a high dietary acid load [6]. It is also important to factor in if the child receives a non-infant formula or is being treated with a ketogenic diet [7, 8].

The rest of the history should be focused on the remaining identifying factors that place the child at risk for stone disease. While some of these risk factors may be non-modifiable, it is still important to recognize these as they may aid the provider in determining a treatment plan. These include a past history of stones in the child as well as a family history of stones [9, 10]. A young child with recurrent stones is very likely to have a significant metabolic derangement causing the stones and is more likely to have an inherited or genetic disease. Additionally, it is likely that this child will continue to have more stones over time and an aggressive therapy plan should be determined to keep the child stone free in the future. A positive family history for stones can help the provider determine the likelihood of an inherited or genetic disease. Even in the absence of a heritable cause of the stones, a positive family history is a risk factor for future stones in the child and should be managed accordingly.

During the history taking, it is important to determine the ambulation status of the child and the activity level of the child; while some of the data linking decreased activity to nephrolithiasis has come from the adult literature, it is likely still applicable to the pediatric patient with stones [11, 12].

A thorough medication history should be obtained; there are many medications implicated in the formation of nephrolithiasis (these will be discussed in more detail elsewhere in this text). The provider should specifically focus on pharmaceuticals that are known to increase the chance of kidney stones such as certain diuretics (furosemide, acetazolamide, triamterene), anti-epileptics (felbamate, topiramate, zonisamide), uricosuric agents (colchicine, probenecid), protease inhibitors (indinavir sulfate), and corticosteroids [13]. It is also important to discuss over-the-counter supplement use with the patient, such as vitamin D, vitamin C, and calcium.

The child's past medical history is equally important in determining causes and potential treatments of their kidney stones. A history of any urologic abnormalities is especially significant with a focus on neurogenic bladder and bladder augmentation [11, 14]. Additionally, a history of frequent fractures, bow leggedness, or significant dental complications could signify an underlying disorder of mineral metabolism that could lead to recurrent stones [15]. Finally, there are many other associated medical conditions that can be associated with nephrolithiasis. Some of these include underlying diseases that are well known to cause frequent stones, such as Lesch–Nyhan syndrome, and others such as cerebral palsy, cystic fibrosis, and diabetes where there is an increased risk of stones [16, 17]. These co-morbid medical illnesses will be covered in their own chapters in this textbook.

Finally, a thorough physical exam is essential in evaluating the child presenting with a history of urinary calculi. Certain findings such as rickets or an abnormal neurologic exam may aid the provider determine the underlying cause of the stone such as an underlying neurologic disease or systemic mineral disorder. Additionally, other co-morbid conditions such as hypertension or obesity can be assessed. While the link between cardiovascular health, obesity, and nephrolithiasis is not well established in the pediatric population, this association is clear in adults [1, 3]. Therefore, if hypertension or obesity is discovered on exam, this would be a good time to address these concerns given the current epidemic of obesity in children [18].

Urine Studies

Children with nephrolithiasis have a greater than a 50% chance of having an underlying and identifiable metabolic disturbance contributing to their stone formation; therefore, it is generally agreed that all children presenting with a stone undergo a full metabolic workup [19]. As mentioned, a thorough history and physical is an essential beginning to the workup of the child with stones; however, the majority of the diagnostic answers are found by examining the urine of these children. A urinalysis is easy to obtain, inexpensive, and widely available at most laboratories. While it is typically one of the most useful tests in the nephrologist's armamentarium, a urinalysis is of somewhat less use when evaluating the child with stone disease. Despite this, there are certain helpful details that can be acquired from the urinalysis. The presence of hematuria is useful in the acute stage when deciding whenever or not a child has as stone, but this finding is not specific to stone types

and would not affect chronic treatment decisions, which is the main objective of the provider in clinic. The urine specific gravity can be useful as a gauge to assess urine concentration. This can be helpful in determining how urine volume plays into stone formation and how well the child is adhering to their fluid therapy plan, but these are better assessed on a 24-hour urine study as the specific gravity will fluctuate throughout the day based on fluid intake and the solute excretion needs of the child during the day. The presence of protein in the urine should also be an indication to the provider to further evaluate tubular function, as proteinuria can be seen in certain hereditary diseases such as Dent disease [20].

Urine pH can be assessed on the urinalysis. While this is not diagnostic of any stone type, certain stones form more strongly in acidic urines and some form more strongly in alkaline urines. The urinary pH can aid in ruling in or ruling out certain stone types and should be followed when the goal is to acidify or alkalinize the urine. Like the urine concentration, this is best analyzed on a 24-hour urine sample to minimize the variability of urinary acid excretion throughout the day.

The presence of urinary crystals on a urinalysis can be helpful in identifying the stone type in a patient with known stones. Ideally, the provider is able to view a spun down, fresh, first morning urine sample themselves in the clinic vicinity. Visible stone crystals can be characterized by their unique microscopic properties (Table 9.1) [21]. This is particularly helpful in cystinuria, where the presence of pathognomonic hexagonal cystine crystals is diagnostic for the disease [22]. In addition, in a patient with known nephrolithiasis, identifying certain other crystal types can help approximate the supersaturation of those mineral salts and can help guide the diagnostic workup and treatment plan. Crystalluria is commonly found in non-stone formers

Table 9.1 Identification of urinary crystals by type

Crystal mineral	Microscopy findings
Calcium oxalate monohydrate (whewellite)	Oval or dumbbell shape
	Positive birefringence under polarized light
Calcium oxalate dihydrate (weddellite)	Octahedral or dodecahedral shape
	Positive birefringence under polarized light
Calcium orthophosphates	Amorphous shape
Dicalcium phosphate dihydrate (brushite)	Asymmetric rod shape
	Can form rosettes
Uric acid	Diamond or rhomboid shape
	Yellow/red/brown in color
Struvite	Rod or coffin shape
	Positive birefringence under polarized light
Cystine	Flat hexagon shape
2,8-dihydroxyadenine	Spherical shape
	Black Maltese cross under polarized light
Xanthine	Granule or stick shape

Data taken from reference [21]

and the finding may or may not be of any clinical significance when evaluating a patient without a stone [23].

Leukocytes and nitrites in the urine can help distinguish whether or not there is a concurrent infection, which is very important in the acute phase, but in the absence of struvite stone disease this is of less use in determining stone type and long-term treatment plan. If a urine culture were to be positive for a urea splitting bacteria, the suspicion for struvite stones would be increased [24]. If a child has known struvite stones and a co-existing urinary tract infection with a causative organism, the overall treatment plan will consist in part of appropriate antimicrobials to eradicate the bacteria; therefore, identifying the organism and its antibiotic sensitives is of significant importance [25].

There are scenarios where the provider has to devise a treatment plan without knowing the exact composition of stone that the patient has formed. Some of the treatments for nephrolithiasis are uniform for all stone formers, but many of the therapies are specific to the type of the stone the child has. The provider can make a good estimate of this by looking at the properties of the urine including mineral concentrations and supersaturations. Despite this, it is always preferable to analyze the stone itself after spontaneous passage or surgical extraction. Determining the specific stone material composition is the ideal method to narrow the differential diagnosis. For example, a cystine stone verifies the diagnosis of cystinuria and the finding of a uric acid stone should prompt the provider to investigate for disorders of purine metabolism. Additionally, knowing the stone composition can facilitate the appropriate preventive management. This will be discussed in other chapters of this text, but one instance of this would be when stone is recognized to be a calcium phosphate stone; alkalization of the urine would be expected to further worsen stone formation. Stone analysis is also critical in diagnosing some of the rare inherited stone diseases; a stone comprised of 2,8-dihydroxyadenine is consistent with adenine phosphoribosyl transferase deficiency and a stone comprised of xanthine is diagnostic of xanthine oxidase deficiency [26, 27].

The most important part of the complete workup for any child with kidney stone disease includes a urinary metabolic evaluation. Ideally this is done with a 24-hour urine collection [28]. In clinical care however, this is not always possible. There are many instances in the pediatric clinic when children are unable to properly collect the 24-hour urine sample due to age, behavioral issues, or neurologic disease. While an in-dwelling urinary catheter can be placed for this purpose, it is not without its disadvantage. The risks and benefits of catheter placement for specimen collection must be discussed in depth with the patient or parent/caregiver and an individualized plan agreed upon. If it is not reasonable or desirable to undergo catheterization for a 24-hour urine collection, spot urine samples can be obtained and analyzed. Urinary excretion of calcium, phosphorus, oxalate, and uric acid can be assessed. Normal values for age are listed in Table 9.2 [29–31].

There are additional circumstances where specialized spot urine tests are helpful, typically when evaluating children for hereditary causes of nephrolithiasis. In a child with significant hyperoxaluria and calcium oxalate stones, a child with stones and renal insufficiency, or a child with stones and a family history of hyperoxaluria,

Table 9.2 Normal urinary solute values in random urine samples

Urine solute	Age	Value
Calcium	<7 months	<0.86 mg calcium/mg creatinine
	7–18 months	<0.6 mg calcium/mg creatinine
	19 months–6 years	<0.42 mg calcium/mg creatinine
	>6 years	<0.2 mg calcium/mg creatinine
Oxalate	<6 months	<400 mg oxalate/g creatinine
	7 months–1 year	<300 mg oxalate/g creatinine
	2–6 years	<150 mg oxalate/g creatinine
	7–10 years	<100 mg oxalate/g creatinine
	>11 years	<75 mg oxalate/g creatinine
Citrate	<5 years	>0.42 mg citrate/mg creatinine
	>5 years	>0.25 mg citrate/mg creatinine
Uric acid	>3 years	0.56 mg uric acid/dL of glomerular filtrate[a]
Cystine	0–2 months	<870 μmol/g creatinine
	3–11 months	<300 μmol/g creatinine
	1–2 years	<150 μmol/g creatinine
	3–5 years	<125 μmol/g creatinine
	6–11 years	<100 μmol/g creatinine
	>12 years	<150 μmol/g creatinine

Data taken from references [29–31]
[a]Calculated as: urine uric acid X serum creatinine/urine creatinine

Table 9.3 Normal urinary glycolate byproducts values in random urine sample

Urine Solute	Age	Value
Glycolate	<18 years	<75 mg glycolate/g creatinine
	>18 years	<50 mg glycolate/g creatinine
Glycerate	<31 days	<75 mg glycerate/g creatinine
	>1 month–4 years	<125 mg glycerate/g creatinine
	5–10 years	<55 mg glycerate/g creatinine
	>11 years	<25 mg glycerate/g creatinine
4-hydroxy-2-oxogluturate (HOG)	All	<10 mg HOG/g creatinine

Data taken from reference [32]

there should be a high suspicion for primary hyperoxaluria. In these cases, it is recommended to obtain a urine hyperoxaluria panel. This test, collected as a spot urine sample, evaluates urinary levels of oxalate, glycolate, glycerate, and 4-hydroxy-2-oxogluturate; normal values are listed in Table 9.3 [32]. In the patient with hyperoxaluria, elevated urinary glycolate is suggestive of primary hyperoxaluria type I, elevated urinary glycerate is suggestive of primary hyperoxaluria type II, and elevated urinary 4-hydroxy-2-oxogluturate is suggestive of primary hyperoxaluria type III. If all of the measured oxalate metabolites except for oxalate are within normal limits, the causes of secondary hyperoxaluria should be further explored.

Table 9.4 Normal urinary solute values in 24-hour urine samples

Urine solute	Age	Value
Calcium	All	<4 mg calcium/kg body weight
Oxalate	> 2 years	<0.45 mg oxalate/1.73 m^2
Citrate	All, male	>365 mg citrate/1.73 m^2
	All, female	>310 mg citrate/1.73 m^2
Uric acid	All	<815 mg uric acid/1.73 m^2
Cystine	All	<60 mg cystine/1.73 m^2
Creatinine	All, male	18–24 mg creatinine/kg body weight
	All, female	15–20 mg creatinine/kg body weight

Data taken from references [20, 31, 33, 35]

Additionally, in the child where a stone has not yet been obtained and identified, cystinuria should be ruled out. This can be done with a spot urine sample for cystine; normal values are included in Table 9.2 [33]. Depending on the laboratory used, the result may include isolated urinary cystine levels or may include urinary quantities of the four amino acids (cystine, ornithine, lysine, and arginine) affected in cystinuria [22].

The optimal metabolic workup in a patient with kidney stones includes the collection of a 24-hour urine risk profile [34]. These tests allow for a more accurate assessment of urinary excretion of minerals and electrolytes including: calcium, oxalate, phosphate, citrate, magnesium, sodium, uric acid, and potassium. This test should be performed when the child is at home, on their normal diet, and not receiving intravenous fluids. Normal values for urinary mineral levels are presented in Table 9.4 [20, 31, 33, 35]. Additionally, markers of protein metabolism such as urinary urea nitrate and sulfate levels are typically available, which may be helpful when creating a treatment plan and prescribing dietary modifications. Properties of the urine such as total volume and pH can be accurately measured. One very useful result on the 24-hour urine collection is the supersaturation of mineral salts. This is not directly measured, but is calculated from the properties of the urine sample including both promoters and inhibitors of stone formation to give the provider an estimate of the likelihood of a patient forming a specific type of stone [36]. Supersaturations are useful when it is unclear what type of stone that a patient has formed; when the calculus has not been collected and/or analyzed, an elevated supersaturation of a certain type of stone forming solute can aid the provider in working up specific risk factors for that stone type. Furthermore, supersaturation is very helpful when monitoring a treatment plan and predicting a patient's response to dietary or medical management and the ongoing risk of developing further stones.

The 24-hour urine study is the gold standard of urinary metabolic evaluation in the patient with stones, but it can be a difficult test to complete properly [37]. This is likely even more true for a child; therefore, it is very important to assess the validity of the study by analyzing the 24-hour urine creatine excretion which is included as part of this comprehensive test [38]. Assuming the child has normal creatinine production for age and normal creatinine clearance, the total amount of creatine

excretion in the 24-hour period can be estimated based on the child's weight (Table 9.4). A urinary creatinine that is lower than expected would suggest an undercollection and a creatinine higher than expected suggests an overcollection. If the child does not have normal creatinine production (for example has much lower or higher muscle mass than expected for age) or does not have normal creatinine elimination, the reference values for urinary creatinine are harder to interpret and may not be as useful.

There is significant intra-individual variation in the 24-hour urine mineral and electrolyte results due to dietary and environmental fluctuations. To mitigate this, it is recommended that adults completing the test complete two separate collections which are both analyzed [39, 40]. This has not been comprehensively studied in children, but it is assumed that the same variability would exist in children and this strategy of performing two 24-hour urine collections is used at some pediatric centers. Because the test is cumbersome and can be difficult to perform correctly, the decision to obtain one versus two 24-hour urine tests should be left to the provider or pediatric center to determine the optimal test protocol.

The 24-hour stone risk urine study includes a comprehensive set of tests that are more than adequate for treating most patient with kidney stones, but these are insufficient for evaluating and managing children with cystinuria. In these patients, a 24-hour cystine level must be obtained, often as part of a separate test. Normal values for cystine excretion are listed in Table 9.4 [33]. One substantial issue with this test is that it does not differentiate between cystine and thiol drugs bound to cysteine (which is much more soluble). In those patients with cystinuria being treated with thiol containing drugs, cystine supersaturation and cystine capacity measured on an adjunct 24-hour urine cystine tests can be instrumental in determining response to therapy and risk of future cystine stones [41].

Blood Testing

Children often have basic chemistry testing when they present acutely with a kidney stone. This is helpful mostly for assessing renal function in the setting of significant obstruction and resulting acute kidney injury. A basic chemistry panel is less helpful in diagnosing the cause of the kidney stone; however, there are a few instances where abnormalities on a basic or comprehensive metabolic panel can be very valuable. A low total carbon dioxide level especially with co-existing hyperchloremia should prompt further workup for renal tubular acidosis [42]. Hypokalemia may be associated with an inherited renal tubulopathy such as Bartter syndrome or could be related to medication effects on renal tubular function [43, 44].

When the child with kidney stones presents to clinic for a formal assessment, especially those with hypercalciuria, it is important to perform a more thorough systemic evaluation for disorders of mineral metabolism; this includes serum concentrations of calcium, magnesium, and phosphorus. The provider should assess calcium blood levels based on total calcium and ionized calcium as certain

conditions such as hypoalbuminemia, hypophosphatemia, or hyperphosphatemia can distort total calcium levels [45]. Normal serum calcium levels can be higher in young children than in adults and this needs to be taken into consideration when evaluating a child for abnormalities in serum calcium [46]. Ideally local laboratories while having their reference ranges stratified by age as normal values ultimately will be lab specific.

The presence of hypercalciuria should prompt the provider to further explore the vitamin D-parathyroid (PTH) axis. Examples of such disorders include hypo- or hyperparathyroidism, vitamin D toxicity, and inherited disorders such as Williams syndrome and CaSR (calcium sensing receptor) mutations [43]. Fully investigating the vitamin D-PTH pathway includes checking serum levels of PTH, 25-OH vitamin D, and 1,25-OH_2 vitamin D (calcitriol). Normal values for these are generally supplied by the laboratory that is running the test; however, the clinician will need to assess these thoroughly in the context of the rest of the lab results. For instance, a normal PTH level in the setting of significant hypercalcemia is inappropriate, and conditions such as primary hyperparathyroidism should be considered. 1,25-OH_2 vitamin D levels should be interpreted similarly, with focus on the relationship between PTH and calcitriol levels. Since PTH is the main catalyst of the 1-α-hydroxy enzyme, discordant PTH and calcitriol levels should be investigated further [47].

Optimal levels of 25-OH vitamin D in children are not entirely clear, but it is reasonable to consider values between at least 20 ng/ml and 80 ng/ml as acceptable for normal bone mineralization [48, 49]. 25-OH vitamin D less than 20 mg/ml should be supplemented given the association of vitamin D deficiency and renal stones; despite some concern that this can worsen hypercalciuria, this is not typically observed, at least in adults [50]. Elevated 25-OH vitamin D levels, however, are known to promote hypercalciuria and lead to stones; in children hypervitaminosis D is considered when 25-OH vitamin D levels exceed 100 ng/ml and vitamin D intoxication occurs when 25-OH vitamin D is greater than 150 ng/ml [51, 52]. When discovered, elevated vitamin D levels should be evaluated and addressed promptly.

Additional important serum mineral levels to assess in the child with stones include magnesium and phosphorus. Hypomagnesemia can be seen in several inherited forms of nephrolithiasis including familial hypomagnesemia with hypercalciuria and nephrocalcinosis [43]. Similarly, hypophosphatemia is seen in several genetic stone diseases such as hereditary hypophosphatemic rickets with hypercalciuria. FGF-23 levels can also be helpful in assessing disorders of phosphate homeostasis, though normal levels are not well established and levels need to be correlated with dietary phosphate intake and with renal function [53]. Serum alkaline phosphatase levels are occasionally useful as well, with elevated levels consistent with disorders of increased osteoclast activity such as hyperparathyroidism and low alkaline phosphatase levels suggestive of undermineralization, such as that seen with hypophosphatasia [54, 55].

The serum level of uric acid is often critical to differentiate disorders of purine metabolism from disturbances in renal tubular uric acid transport in the child with hyperuricosuria. Conditions that cause overproduction of uric acid, such as

Lesch–Nyhan syndrome, will often present with hyperuricemia [56]. The presence of uric acid stones and hypouricemia suggest a renal tubular disorder such as hereditary renal hypouricemia, most often caused by defects in the human urate 1 transporter (URAT1) [57]. Additionally, if a child develops a xanthine stone, a markedly depressed serum uric acid level is consistent with xanthinuria [26].

Plasma oxalate levels may be helpful in those patients with renal insufficiency or renal failure and concerns for primary hyperoxaluria [32]. This is especially important in monitoring the primary hyperoxaluria patient who has evidence of systemic oxalosis.

Genetic Testing

The exact prevalence of monogenic causes of nephrolithiasis remains unknown, though recent studies and advances in genetic testing have started to shed some light on this matter. It is clear that pediatric stone formers have at least a 10% chance of having genetic kidney stone disease identified [58]. This is likely an underestimation given that not all pediatric stone patients undergo genetic testing and even in those patients that do have genetic testing performed, the testing may not be comprehensive, especially as new causal genes or new variants are constantly being discovered that are pathogenic for kidney stone formation. As novel therapies are created for certain monogenic forms of stone disease, it is important to correctly identify these since understanding the molecular diagnosis can dramatically alter the therapeutic approach. It is therefore reasonable to screen all pediatric stone patients for genetic diseases. The suspicion for one of these rare forms of stone disease should be particularly high when the patient presents before adolescence, when they have an unexplained chronic kidney disease or proteinuria, in the presence of a strong family history, when a rare crystal or stone type is discovered, or have evidence of a systemic disorder of mineral metabolism [20].

There are limitations to this approach including access to and affordability of testing as well as difficulty in deciphering the significance of variants of uncertain significance. In circumstances where genetic testing is more difficult to obtain, it is reasonable to reserve focused single gene testing for those patients with a higher suspicion for a specific monogenic stone disease, such as those patients with hyperoxaluria and elevated levels of urinary glycerate, glycolate, or 4-hydroxy-2-oxogluturate [32]. A list of genetic diseases that can be associated with stones is displayed in Table 9.5 [20, 43, 58, 59].

Tissue Studies

Although not common, there are rare instances where biopsy specimens play a role in the diagnosis of nephrolithiasis. Historically a liver biopsy was critical to making the diagnosis of primary hyperoxaluria. In these instances, the activity of the

Table 9.5 Genetic causes of nephrolithiasis

Condition	Gene involved	Inheritance pattern
Primary hyperoxaluria type I	AGXT	AR
Primary hyperoxaluria type II	GRHPR	AR
Primary hyperoxaluria type III	HOGA1	AR
Cystinuria	SLC3A1/ SLC7A9I	AD/AR
Autosomal dominant hypocalcemia with hypercalciuria	CASR	AD
Bartter syndrome		
Type I	SLC12A1	AR
Type II	KCNJ1	AR
Type III	CLCNKB	AR
Type IV	BSND	AR
Type V	CASR	AD
Type VI	CLCN5	XR
Dent's disease	CLCN5	XR
Lowe's syndrome	OCRL1	XR
Hereditary hypophosphatemic rickets with hypercalciuria	SLC34A1	AR
Nephrolithiasis, osteoporosis, and hypophosphatemia	SLC34A3	AD
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis	PCLN1/ CLDN16	AR
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis with ocular abnormalities	CLDN19	AR
Distal renal tubular acidosis	SCL4A1	AD
Distal renal tubular acidosis with sensorineural deafness	ATP6B1/ ATPV16B1	AR
Distal renal tubular acidosis with preserved hearing	ATP6N1B/ ATP6V0A4	AR
Hypophosphatasia	ALPL	AR
Familial idiopathic hypercalciuria	ADCY10	AD
Infantile hypercalcemia	CYP24A1	AR
Adenine phosphoribosyltransferase deficiency	APRT	AR
Xanthinuria	XDH/MOCOS	AR
Renal hypouricemia	SLC22A12	AR
Familial hypouricemia	SLC2A9	AR
Lesch–Nyhan syndrome	HPRT1	XR

AD = autosomal dominant, AR = autosomal recessive, XR = x-linked recessive
Data taken from references [20, 43, 58, 59]

enzymes alanine:glyoxylate aminotransferase (AGT) and/or glyoxylate reductase/hydroxypyruvate reductase (GRHPR) can be assessed directly from hepatic tissue. Reduced activity of AGT is consistent with a diagnosis of primary hyperoxaluria I and reduced activity of GRHPR is consistent with primary hyperoxaluria type II [32]. Presently there is little role for performing a liver biopsy in a pediatric stone disease patient given the invasive nature of the procedure and the improvement in

the ability to successfully diagnose or rule out primary hyperoxaluria with genetic testing.

Renal biopsies are performed routinely in patients with underlying renal disorders. The procedure has no recommended role in the evaluation of nephrolithiasis; however, occasionally a patient with renal failure or proteinuria and no clinical history of stones will undergo a diagnostic renal biopsy and tubular crystals will be identified on histology. In these cases, the provider should use this information to assist in determining the underlying type and cause of the crystals and their relationship to the original kidney disease that prompted the biopsy. Calcium can be stained directly with an alizarin red stain, but calcium crystals are also typically seen well on hematoxylin and eosin (H&E) stained slides [60]. Calcium oxalate crystals on renal histology appear fan or rose shaped; importantly, they appear birefringent under polarized light [61]. Intermittent calcium oxalate tubules may be of little clinical significance, but extensive calcium oxalate tubules in the setting of renal dysfunction should prompt further evaluation for causes of oxalate nephropathy such as primary hyperoxaluria or ethylene glycol poisoning. In contrast to calcium oxalate crystals, calcium phosphate crystals fail to polarize and the presence of phosphate can be confirmed by a von Kossa stain [60]. Calcium phosphate crystals can also be seen on biopsy specimens without significant co-morbid pathology, but their detection in the setting of depressed renal function should encourage exploration of causes of phosphate nephropathy such as tumor lysis syndrome or phosphate containing medication overdose.

Supplemental Imaging

Imaging is an important part of the workup both for acute and chronic stone diseases. The majority of this consists of imaging modalities evaluating the urinary system and the stone itself; those tests will be covered in their own chapter of this text. Occasionally additional radiology studies can be useful when evaluating and caring for the child with kidney stone disease. In children who present with stones and any evidence of rickets on physical exam, it is important to pursue X-ray testing to assess the properties of the joint spaces. This can reveal irregularities such as widening of the physis or metaphyseal cupping that would support a diagnosis of rickets [62]. Long leg X-rays can also help diagnose and monitor the degree of genu varum or genu valgum in affected children.

Children with stone disease, and specifically those with hypercalciuria, are at increased risk for low bone density [63]. This is especially true for those patients with certain genetic conditions or with abnormalities of systemic mineral homeostasis. For those pediatric patients with hypercalciuria, it is recommended to obtain regular screening bone density testing [64]. This should be done with DXA (dual-energy X-ray absorptiometry) [65]. The provider should make sure that scan is done in a center that is experienced in DXA technique and interpretation in children.

Conclusion

The evaluation of a child with pediatric nephrolithiasis is critical in detecting rare diseases that can lead to frequent stone formation and to end stage renal disease. Additionally, the child who presents with stones is likely to have future stones events; in order to create an appropriate therapy plan it is important to understand why the child developed the stone. Every diagnostic dilemma in medicine begins with the basics of a thorough history and physical, which may alert the physician to possible underlying metabolic issues that need to be explored further. The most essential part of the evaluation involves a thorough study of the urine, including factors that both cause and inhibit stone formation. Ideally this is done with a 24-hour urine study and it is critical that all of these tests are interpreted by a provider who understands that normal values in children are not the same as those in adults. Further blood tests are often indicated and also need to be interpreted in the context of the growing child. Finally, the increase in the use of genetic testing in all aspects of medicine applies to pediatric nephrolithiasis; this is an exciting new tool for the diagnosis of underlying inherited causes of kidney stones in children, but there are certainly pitfalls to this method and the results must be deciphered by a provider who understands the advantages and disadvantages of these tests.

References

1. Dwyer ME, Krambeck AE, Bergstralh EJ, Milliner DS, Lieske JC, Rule AD. Temporal trends in incidence of kidney stones among children: a 25-year population based study. J Urol. 2012;188(1):247–52.
2. Tasian GE, Ross ME, Song L, Sas DJ, Keren R, Denburg MR, et al. Annual incidence of nephrolithiasis among children and adults in South Carolina from 1997 to 2012. Clin J Am Soc Nephrol. 2016;11(3):488–96.
3. Scales CD Jr, Smith AC, Hanley JM, Saigal CS, Urologic Diseases in America P. Prevalence of kidney stones in the United States. Eur Urol. 2012;62(1):160–5.
4. Perrone HC, dos Santos DR, Santos MV, Pinheiro ME, Toporovski J, Ramos OL, et al. Urolithiasis in childhood: metabolic evaluation. Pediatr Nephrol. 1992;6(1):54–6.
5. Alpay H, Ozen A, Gokce I, Biyikli N. Clinical and metabolic features of urolithiasis and microlithiasis in children. Pediatr Nephrol. 2009;24(11):2203–9.
6. Penniston KL, Nakada SY. Updates in the metabolic management of calcium stones. Curr Urol Rep. 2018;19(6):41.
7. Penniston KL, Palmer EA, Medenwald RJ, Johnson SN, John LM, Beshensky DJ, et al. Oxalate content of enteral nutrition formulas. J Pediatr Gastroenterol Nutr. 2019;69(5):e135–e40.
8. Sampath A, Kossoff EH, Furth SL, Pyzik PL, Vining EP. Kidney stones and the ketogenic diet: risk factors and prevention. J Child Neurol. 2007;22(4):375–8.
9. Schwarz RD, Dwyer NT. Pediatric kidney stones: long-term outcomes. Urology. 2006;67(4):812–6.
10. Coward RJ, Peters CJ, Duffy PG, Corry D, Kellett MJ, Choong S, et al. Epidemiology of paediatric renal stone disease in the UK. Arch Dis Child. 2003;88(11):962–5.
11. Stephany HA, Clayton DB, Tanaka ST, Thomas JC, Pope JC, Brock JW, et al. Development of upper tract stones in patients with congenital neurogenic bladder. J Pediatr Urol. 2014;10(1):112–7.

12. Ramey SL, Franke WD, Shelley MC 2nd. Relationship among risk factors for nephrolithiasis, cardiovascular disease, and ethnicity: focus on a law enforcement cohort. AAOHN J. 2004;52(3):116–21.
13. Matlaga BR, Shah OD, Assimos DG. Drug-induced urinary calculi. Rev Urol. 2003;5(4): 227–31.
14. Kisku S, Sen S, Karl S, Mathai J, Thomas RJ, Barla R. Bladder calculi in the augmented bladder: a follow-up study of 160 children and adolescents. J Pediatr Urol. 2015;11(2):66 e1–6.
15. Schwaderer AL, Oduguwa A, Kusumi K. Urinary stone disease in pediatric and adult metabolic bone clinic patients. Urolithiasis. 2018;46(2):173–8.
16. Taylor EN, Stampfer MJ, Curhan GC. Diabetes mellitus and the risk of nephrolithiasis. Kidney Int. 2005;68(3):1230–5.
17. Chidekel AS, Dolan TF Jr. Cystic fibrosis and calcium oxalate nephrolithiasis. Yale J Biol Med. 1996;69(4):317–21.
18. Styne DM, Arslanian SA, Connor EL, Farooqi IS, Murad MH, Silverstein JH, et al. Pediatric obesity-assessment, treatment, and prevention: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2017;102(3):709–57.
19. Spivacow FR, Negri AL, del Valle EE, Calvino I, Fradinger E, Zanchetta JR. Metabolic risk factors in children with kidney stone disease. Pediatr Nephrol. 2008;23(7):1129–33.
20. Edvardsson VO, Goldfarb DS, Lieske JC, Beara-Lasic L, Anglani F, Milliner DS, et al. Hereditary causes of kidney stones and chronic kidney disease. Pediatr Nephrol. 2013;28(10):1923–42.
21. Daudon M, Frochot V. Crystalluria. Clin Chem Lab Med. 2015;53(Suppl 2):s1479–87.
22. Mattoo A, Goldfarb DS. Cystinuria. Semin Nephrol. 2008;28(2):181–91.
23. Frochot V, Daudon M. Clinical value of crystalluria and quantitative morphoconstitutional analysis of urinary calculi. Int J Surg. 2016;36(Pt D):624–32.
24. Bichler KH, Eipper E, Naber K, Braun V, Zimmermann R, Lahme S. Urinary infection stones. Int J Antimicrob Agents. 2002;19(6):488–98.
25. Diri A, Diri B. Management of staghorn renal stones. Ren Fail. 2018;40(1):357–62.
26. Kudo M, Moteki T, Sasaki T, Konno Y, Ujiie S, Onose A, et al. Functional characterization of human xanthine oxidase allelic variants. Pharmacogenet Genomics. 2008;18(3):243–51.
27. O'Toole TE, Wilson JM, Gault MH, Kelley WN. Human adenine phosphoribosyltransferase: characterization from subjects with a deficiency of enzyme activity. Biochem Genet. 1983;21(11–12):1121–34.
28. Ennis JL, Asplin JR. The role of the 24-h urine collection in the management of nephrolithiasis. Int J Surg. 2016;36(Pt D):633–7.
29. Stapleton FB, Nash DA. A screening test for hyperuricosuria. J Pediatr. 1983;102(1):88–90.
30. Sargent JD, Stukel TA, Kresel J, Klein RZ. Normal values for random urinary calcium to creatinine ratios in infancy. J Pediatr. 1993;123(3):393–7.
31. Hoppe B, Kemper MJ. Diagnostic examination of the child with urolithiasis or nephrocalcinosis. Pediatr Nephrol. 2010;25(3):403–13.
32. Milliner DS. The primary hyperoxalurias: an algorithm for diagnosis. Am J Nephrol. 2005;25(2):154–60.
33. Gillespie RS, Stapleton FB. Nephrolithiasis in children. Pediatr Rev. 2004;25(4):131–9.
34. Yagisawa T, Chandhoke PS, Fan J. Comparison of comprehensive and limited metabolic evaluations in the treatment of patients with recurrent calcium urolithiasis. J Urol. 1999;161(5):1449–52.
35. Ghazali S, Barratt TM. Urinary excretion of calcium and magnesium in children. Arch Dis Child. 1974;49(2):97–101.
36. Prochaska M, Taylor E, Ferraro PM, Curhan G. Relative supersaturation of 24-hour urine and likelihood of kidney stones. J Urol. 2018;199(5):1262–6.
37. Miler M, Simundic AM. Low level of adherence to instructions for 24-hour urine collection among hospital outpatients. Biochem Med (Zagreb). 2013;23(3):316–20.

38. Remer T, Neubert A, Maser-Gluth C. Anthropometry-based reference values for 24-h urinary creatinine excretion during growth and their use in endocrine and nutritional research. Am J Clin Nutr. 2002;75(3):561–9.
39. Nayan M, Elkoushy MA, Andonian S. Variations between two 24-hour urine collections in patients presenting to a tertiary stone clinic. Can Urol Assoc J. 2012;6(1):30–3.
40. Parks JH, Goldfisher E, Asplin JR, Coe FL. A single 24-hour urine collection is inadequate for the medical evaluation of nephrolithiasis. J Urol. 2002;167(4):1607–12.
41. Goldfarb DS, Coe FL, Asplin JR. Urinary cystine excretion and capacity in patients with cystinuria. Kidney Int. 2006;69(6):1041–7.
42. Lopez-Garcia SC, Emma F, Walsh SB, Fila M, Hooman N, Zaniew M, et al. Treatment and long-term outcome in primary distal renal tubular acidosis. Nephrol Dial Transplant. 2019;34(6):981–91.
43. Stechman MJ, Loh NY, Thakker RV. Genetic causes of hypercalciuric nephrolithiasis. Pediatr Nephrol. 2009;24(12):2321–32.
44. Hufnagle KG, Khan SN, Penn D, Cacciarelli A, Williams P. Renal calcifications: a complication of long-term furosemide therapy in preterm infants. Pediatrics. 1982;70(3):360–3.
45. Payne RB, Carver ME, Morgan DB. Interpretation of serum total calcium: effects of adjustment for albumin concentration on frequency of abnormal values and on detection of change in the individual. J Clin Pathol. 1979;32(1):56–60.
46. Colantonio DA, Kyriakopoulou L, Chan MK, Daly CH, Brinc D, Venner AA, et al. Closing the gaps in pediatric laboratory reference intervals: a CALIPER database of 40 biochemical markers in a healthy and multiethnic population of children. Clin Chem. 2012;58(5):854–68.
47. Hewison M, Zehnder D, Bland R, Stewart PM. 1alpha-hydroxylase and the action of vitamin D. J Mol Endocrinol. 2000;25(2):141–8.
48. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 dietary reference intakes for calcium and vitamin D: what dietetics practitioners need to know. J Am Diet Assoc. 2011;111(4):524–7.
49. Wagner CL, Greer FR, American Academy of Pediatrics Section on B, American Academy of Pediatrics Committee on N. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. Pediatrics. 2008;122(5):1142–52.
50. Johri N, Jaeger P, Ferraro PM, Shavit L, Nair D, Robertson WG, et al. Vitamin D deficiency is prevalent among idiopathic stone formers, but does correction pose any risk? Urolithiasis. 2017;45(6):535–43.
51. Conti G, Chirico V, Lacquaniti A, Silipigni L, Fede C, Vitale A, et al. Vitamin D intoxication in two brothers: be careful with dietary supplements. J Pediatr Endocrinol Metab. 2014;27(7–8):763–7.
52. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M, Drug, et al. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. Pediatrics. 2008;122(2):398–417.
53. Portale AA, Wolf M, Juppner H, Messinger S, Kumar J, Wesseling-Perry K, et al. Disordered FGF23 and mineral metabolism in children with CKD. Clin J Am Soc Nephrol. 2014;9(2):344–53.
54. Kollars J, Zarroug AE, van Heerden J, Lteif A, Stavlo P, Suarez L, et al. Primary hyperparathyroidism in pediatric patients. Pediatrics. 2005;115(4):974–80.
55. Fallon MD, Teitelbaum SL, Weinstein RS, Goldfischer S, Brown DM, Whyte MP. Hypophosphatasia: clinicopathologic comparison of the infantile, childhood, and adult forms. Medicine (Baltimore). 1984;63(1):12–24.
56. Lesch M, Nyhan WL. A familial disorder of uric acid metabolism and central nervous system function. Am J Med. 1964;36:561–70.
57. Sperling O. Hereditary renal hypouricemia. Mol Genet Metab. 2006;89(1–2):14–8.
58. Braun DA, Lawson JA, Gee HY, Halbritter J, Shril S, Tan W, et al. Prevalence of monogenic causes in pediatric patients with nephrolithiasis or nephrocalcinosis. Clin J Am Soc Nephrol. 2016;11(4):664–72.

59. Cameron MA, Sakhaee K, Moe OW. Nephrolithiasis in children. Pediatr Nephrol. 2005;20(11):1587–92.
60. Cathro HP, Shen SS, Truong LD. Diagnostic histochemistry in medical diseases of the kidney. Semin Diagn Pathol. 2018;35(6):360–9.
61. Pizzolato P. Histochemical recognition of calcium oxalate. J Histochem Cytochem. 1964;12:333–6.
62. Chatterjee D, Gupta V, Sharma V, Sinha B, Samanta S. A reliable and cost effective approach for radiographic monitoring in nutritional rickets. Br J Radiol. 2014;87(1036):20130648.
63. Moreira Guimaraes Penido MG, de Sousa TM. Bone disease in pediatric idiopathic hypercalciuria. World J Nephrol. 2012;1(2):54–62.
64. Schwaderer AL, Cronin R, Mahan JD, Bates CM. Low bone density in children with hypercalciuria and/or nephrolithiasis. Pediatr Nephrol. 2008;23(12):2209–14.
65. Gordon CM, Leonard MB, Zemel BS, International Society for Clinical D. 2013 Pediatric position development conference: executive summary and reflections. J Clin Densitom. 2014;17(2):219–24.

Chapter 10
Medical Management of Pediatric Stones

Michelle A. Baum

Treatment of Urinary Metabolic Abnormalities

Hypercalciuria

If dietary interventions including high fluid intake and sodium reduction do not improve 24-hour urine parameters, or the child continues to have ongoing stone formation, pharmacologic treatment of hypercalciuria may be indicated [1]. This treatment aims to reduce urinary calcium excretion with subsequent decreases in supersaturation for calcium oxalate and calcium phosphate. Evidence for use of thiazide diuretics to reduce urinary calcium dates back to the 1950s and 1960s [2]. Thiazide diuretics and non-thiazide sulfonamides result in increased renal tubular calcium reabsorption and hence lower urinary calcium excretion [3, 4]. Small randomized clinical trials in adults have shown decreased recurrence of kidney stones with use of thiazide diuretics [3, 5–8]. Furthermore, in both adult and pediatric patients, use of thiazide diuretics in hypercalciuria has been associated with increased bone mineral density and decreased fracture risk [9, 10]. Studies suggest that in addition to hypocalciuric actions, thiazide may have direct stimulation of osteoblastic bone formation and inhibition of osteoclastic bone reabsorption [10].

Several options for thiazide treatment include hydrochlorothiazide, chlorothiazide, and chlorthalidone (Table 10.1). Side effects of thiazides include hypokalemia, hyponatremia, and thiazide-induced hypomagnesemia and hypocitraturia [21]. Hence after initiation, laboratory studies should be followed within several weeks of beginning therapy. As with all treatments for stone prevention, 24 hour urine should be followed 4–8 weeks after initiation, with ongoing adjustment in the regimen if abnormalities persist.

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Table 10.1 Pediatric dosing guidelines. In all cases, please refer to most up-to-date dosing guidelines in Lexicomp [11]

Drug name	Pediatric starting dose	Maximum dose
Potassium citrate/potassium bicarbonate	2–4 meq/kg/day in 3–4 divided doses	Follow urine and serum parameters
Hydrochlorothiazide	1–2 mg/kg/day in 1–2 divided doses	50 mg
Chlorothiazide	10–20 mg/kg/day in 2 divided doses	375 mg
Chlorthalidone	Off label 0.3 mg/kg/day once daily	50 mg
Amiloride	0.4–0.625 mg/kg/day daily or divided twice daily	20 mg
Allopurinol	5–10 mg/kg/day daily or divided twice daily	300 mg–600 mg
Febuxostat	No pediatric dosing guidelines	Adult dosing 40–80 mg
Tiopronin	15 mg/kg/day divided three times daily	50 mg/kg/day divided three times daily
Penicillamine	20–40 mg/kg/day divided tid or qid	1500 mg/day

Data taken from [1, 11–20]

There is limited data to suggest that amiloride may enhance the hypocalciuric effect of thiazide diuretics when used together [22, 23]. Alone, amiloride does not result in a significantly decreased urinary calcium excretion compared to a thiazide. In occasional cases where there is significant hypokalemia or persisting hypercalciuria and supersaturation, amiloride might be considered to add to a thiazide (Table 10.1).

Hypomagnesuria

Magnesium inhibits calcium oxalate crystallization as magnesium oxalate is more soluble than calcium oxalate in the urine. Magnesium also binds oxalate in the gut and reduces its intestinal absorption [24]. Hence magnesium supplements may be an additional agent for prevention of kidney stones especially in the setting of low urinary magnesium excretion. Magnesium oxide and gluconate are formulations that are generally better tolerated with fewer side effects, with the main complaints being abdominal pain, nausea, vomiting, and diarrhea. Limited data suggest potassium-magnesium citrate formulations seem to have increased effect on urinary magnesium, urinary citrate, and reduced calcium oxalate supersaturation and may be a superior choice in thiazide-induced hypokalemia and hypocitraturia [25, 26].

Hypocitraturia

Treatment with alkali therapy to increase urine citrate has been shown to reduce stone formation in patients with hypocitraturia as well as in other calcium oxalate stone formers [27–29]. Citrate complexes with urinary calcium and this molecule is much more soluble in urine than calcium oxalate or calcium phosphate; citrate has inhibitory effects on urine crystallization by inhibiting crystal growth of calcium phosphate and calcium oxalate. Recent studies have also suggested citrate can actually decrease urine calcium excretion as well. Citrate therapy has been shown to increase urine pH, increase urinary citrate excretion, and decrease recurrence of calcium stones. Lastly, potassium citrate supplementation increases solubility of uric acid due to urinary alkalization and hence helps prevent uric acid stones [12]. Alkali therapy is also indicated in prevention of nephrolithiasis in secondary hypocitraturia resulting from ketogenic diet, zonisamide, topiramate or acetazolamide use [30–32]. Lastly, alkali therapy is used in treatment of renal tubular acidosis [13].

Potassium-based alkali is preferred in most cases to avoid increasing the dietary and renal tubular sodium load and worsening of hypercalciuria. The dose required may vary and a typical starting dose can be 2–4 meq/kg/day of potassium citrate; this should be adjusted based on serum studies (total carbon dioxide and potassium levels) and urine pH and urine citrate (Table 10.1). Potassium bicarbonate can be considered if the main objective is to increase urinary pH or correct underlying metabolic acidosis.

Hyperuricosuria

Uric acid stones are uncommon in pediatrics and when identified are typically caused by elevated urinary uric acid levels. The most important preventative measure for uric acid stones is urinary alkalization, with a goal of increasing the urine pH above 6.5. Hence potassium citrate or potassium bicarbonate should be initiated. Although allopurinol (an inhibitor of xanthine dehydrogenase) is used for treatment of hyperuricemia and hyperuricosuria in gout, it is unclear if this prevents uric acid stone prevention any further once alkalization is achieved. Monitoring for allopurinol should include complete blood count and liver function tests. The provider should also be aware of the rare risk of increased xanthine production resulting in xanthinuria/xanthine stones. Febuxostat is a newer xanthine dehydrogenase agent also used in hyperuricemia/gout though data is lacking as an agent for nephrolithiasis prevention [12, 14, 33]. Lastly, in Lesch–Nyhan syndrome, significant hyperuricemia may result in hyperuricosuria with orange staining in the diaper and recurrent uric acid stones. This is typically managed with urinary alkalization with potassium citrate/bicarbonate and reduction in serum uric acid with allopurinol or febuxostat [15].

Treatment of Specific Genetic Disorders

Primary Hyperoxaluria

Historically, treatment for primary hyperoxaluria (PH) has proven very challenging and many patients will have countless episodes of kidney stones and will eventually develop chronic kidney disease and/or end stage renal disease. High fluid intake can help to decrease stone burden and partially mitigate progression of kidney disease, but these patients often continue to form recurrent stones. Targeted pharmacologic therapy has generally been limited, although newer therapies are showing promise in treating this difficult to manage disease.

Pyridoxine is a cofactor for the alanine-glyoxylate aminotransferase (AGT) enzyme that is deficient or inactive in primary hyperoxaluria type 1 [15, 34, 35]. There exist specific genotypes in primary hyperoxaluria type 1 in which pyridoxine increases the activity of the mistargeted AGT enzyme and decreases oxalate production [35, 36]. Pyridoxine should be prescribed in all patients in whom PH is a diagnostic consideration pending genetic testing; determination regarding continuation of pyridoxine can be made by following urinary oxalate excretion on treatment and when genetic testing results return. About 30% of patients with PH1 will have some degree of response to pyridoxine and may even have complete normalization of urinary oxalate excretion. Response to pyridoxine has been defined as a 30% reduction in urinary oxalate [15]. Initial pyridoxine dose is 5 mg/kg/day (most suggest maximum of 10 mg/kg/day, but in some rare cases up to 20 mg/kg/day has been used) [15, 34].

Pyridoxine prescription should be followed up with a 24-hour urine collection to assess impact on 24-hour oxalate excretion after a trial of at least 3 months. In patients with reduced glomerular filtration rate (GFR), evaluating response to pyridoxine using urinary oxalate excretion is more difficult. In such patients, trial of pyridoxine should still be attempted until genetic testing for genotypes associated with pyridoxine sensitivity is obtained.

Potassium citrate/potassium bicarbonate is also used to reduce urinary calcium oxalate crystallization/supersaturation [15, 34, 35]. In cases where GFR is reduced, sodium citrate should be used due to the risk of hyperkalemia.

Renal replacement therapy is initiated earlier in PH patients compared to other disorders where GFR guides initiation timing. In PH, increased plasma oxalate levels result in risk of systemic oxalosis with significant concern for oxalosis when plasma oxalate levels exceed 30 μmol/L. Very aggressive intermittent hemodialysis regimens are instituted as oxalate production exceeds the ability of hemodialysis to clear oxalate. Often patients require daily dialysis [15, 34, 35]. The overall goal should be to get patients to transplant as soon as possible to reduce systemic oxalosis.

Liver/kidney transplant should be considered early in patient's course with signs of declining GFR [15, 34, 35]. While there historically have been disagreements on timing of organ transplantation in PH, current guidelines should be reviewed closely

for patients with a new diagnosis of primary hyperoxaluria and revisited throughout their clinical course [34, 37]. Pre- and post-transplant dialysis should continue post transplantation while following plasma oxalate levels until levels determined safe to discontinue. Liver transplant has been utilized in both PH1 and PH2, but not yet reported in PH3 [34, 37, 38].

A new therapy for PH1 was recently approved and additional new therapies for primary hyperoxaluria are currently in development and undergoing clinical trials [39]. For PH1, inhibition of glycolate oxidase (GO) can reduce production of glyoxylate and hence oxalate production and subsequent hyperoxaluria [39, 40]. An RNA inhibition agent, lumasiran, was recently approved by the FDA for reduction of urinary oxalate in primary hyperoxaluria type 1 [41]. Inhibition of the hepatic lactate dehydrogenase A (LDHA) pathway also has been shown to decrease oxalate production and is under clinical trial in PH1 and PH2, and PH3 [39, 42]. Gene therapy options are also under investigation and pre-clinical [39, 43]. The use of molecular chaperones (similar to pyridoxine) for AGT is also currently being studied [39, 44–46]. These would seek to prevent the mistargeting of AGT and restore AGT to the peroxisome where it can function normally. CRISPER/CAS9 to disrupt the gene encoding for GO has been studied in PH1 mice and was associated with decreased urine oxalate excretion. Similar CRISPER/CAS technology could be applied to other gene editing for all forms of PH [39].

Lastly, Oxalobacter formigenes, an oxalate metabolizing intestinal bacteria, has been studied in both animal models and in patients with primary hyperoxaluria and could ultimately prove to be a useful adjunctive therapy option in patients with PH [39, 47, 48].

Cystinuria

In addition to high fluid intake, patients with cystinuria should be started on alkalinization therapy. Solubility of cystine increases when the urine pH exceeds 7–7.5. Potassium-based citrate or bicarbonate is preferred as sodium-based citrate or bicarbonate as urine sodium excretion increases urinary cystine glomerular filtration and excretion [16, 49, 50]. Potassium citrate or potassium bicarbonate ideally should be given three times a day and urine pH should be monitored. 24-hour urine profiles should be reassessed once patient is receiving high fluid intake, reduced sodium diet, and alkalinization therapy. Further details of how to monitor urinary parameters in patients with cystinuria are discussed elsewhere in this text.

For ongoing stone formation or ongoing 24-hour urine profile appearing high risk for future stone formation, cystine binding thiol drugs can be prescribed. For cystinuria, two options for cystine binding thiol drugs are alpha-mercaptopropionyl glycine (tiopronin) and D-penicillamine. Each contains a thiol group that results in a disulfide exchange with cystine, forming a soluble drug-cystine complex [16–18, 51]. Pediatric dosing for tiopronin begins at 15 mg/kg/day up to 50 mg/kg/daily and is divided three times daily. Adverse effects include hypersensitivity reactions,

gastrointestinal distress, and proteinuria with nephrotic syndrome or membranous nephropathy. Tiopronin is recommended by the American Urological Association as the agent of choice for cystinuria patients that have failed treatment with high fluid intake, low sodium diet and urinary alkalization. D-penicillamine is dosed at 20–40 mg/kg/day divided three or four times daily (maximum adult dose 1500 mg/day). D-penicillamine has a very significant side effect profile including allergic reactions (rash, fever, lymphadenopathy, arthralgias), bronchiolitis obliterans, increased skin friability and bleeding, cytopenias, hepatotoxicity, and glomerulopathy/glomerulonephritis with hematuria and proteinuria. It is also known to cause vitamin B6 deficiency. In the United States, D-penicillamine has been issued a boxed warning by the Food and Drug Administration; it is recommended that it only be prescribed by a physician experienced with its use and aware of the toxicity profile and under close supervision. With penicillamine, pyridoxine (B6) should be given to prevent deficiency. A small study demonstrated improvement in 24 h urine cystine capacity measurement with use of cystine binding thiol drugs [52]. The ACE inhibitor Captopril does contain a thiol group as well and is a proposed treatment option for cystinuria; however, it has not been shown to significantly decrease cystine stone formation and attempting to do so often causes hypotension [16].

As with other changes to the regimen, 24 h urine should be reassessed in a short interval of 4–8 weeks to guide ongoing management. Given the risk of proteinuria and membranous nephropathy with cystine binding thiol drugs, urine protein excretion should be assessed at baseline and then every 6–12 months. Serum B6, as well as serum LFTs and CBC with differential should be monitored while on D-penicillamine. No blood test monitoring is currently in the package insert for the new enteric coated formulation of tiopronin [16].

Alpha-lipoic acid (ALA) has also been proposed as a therapy for cystinuria. Animal models have demonstrated that ALA increases solubility of urinary cystine but robust trials in humans are lacking. A case series has outlined two pediatric patients with cystinuria who responded favorably to ALA, but further studies are needed to determine the efficacy of ALA in treating cystinuria [53].

APRT Deficiency

In patients with adenine phosphoribosyltransferase (APRT) deficiency, both allopurinol and febuxostat have been shown to decrease 2,8-dihydroxyadenine synthesis. Both have been shown to prevent crystal deposition, stone formation, and development of renal failure, and can actually result in resolution of stones and improvement in GFR [54]. In a comparison pilot clinical trial in APRT where patients received allopurinol, followed by a washout, and then febuxostat, febuxostat was shown to be more effective than allopurinol in reducing 2,8-dihydroxyadenine [19]. Even on allopurinol, 2,8-dihydroxyadenine levels were substantial, and the study suggested that potentially higher doses of allopurinol might be needed to achieve further reduction of 2,8-dihydroxyadenine. Allopurinol dosing is 5–10 mg/kg/day

either daily or divided BID. Dosing for febuxostat in the pilot clinical trial was not reported in mg/kg, but all patients received 80 mg of febuxostat. Hypersensitivity reaction to febuxostat is also reported to be rare compared to allopurinol. Side effects for allopurinol were higher in the registry population compared to febuxostat [55].

Renal transplantation is a treatment for APRT deficiency for those who develop end stage renal disease [56]. Allograft function was superior in patients who started treatment with allopurinol pre-transplant compared to those who did not receive any treatment or started it after transplant. Premature allograft loss due to disease recurrence or chronic allograft dysfunction has been associated with lack of allopurinol use at the time of transplant. Large doses of allopurinol may be necessary to prevent recurrence. As an alternative to allopurinol, febuxostat can also be used. Hence it is critical to start treatment with a xanthine oxidoreductase agent prior to transplant [56].

Dent Disease

At present, there are no specific treatments for Dent disease. Pharmacologic management is aimed at potentially reducing proteinuria to slow CKD progression as well as to reduce hypercalciuria [57–59]. Thiazides can be used to treat hypercalciuria as they would for other patients with elevated urinary calcium levels, though this has only been studied in very small population of patients with Dent disease and the long-term efficacy is unclear [60]. Thiazide use is often limited by a higher side effect profile in patients with Dent disease including hypokalemia and hypotension. Angiotensin converting enzyme inhibitors or angiotensin receptor blockers have been used to treat proteinuria, but may only truly impact glomerular proteinuria and not the prominent feature in this disorder of tubular proteinuria. They may be more applicable in the population manifesting focal global glomerulosclerosis.

A report of a transplantation of wild-type bone marrow into CLcn5 $^{Y/-}$ mice resulted in improved proximal tubular dysfunction with decreased tubular proteinuria, glycosuria, polyuria, and decreased urine calcium excretion [61]. Bone marrow transplantation remains an interesting treatment choice for many hereditary metabolic disorders, though the treatment is associated with significant morbidity and mortality and further studies are needed before it can be recommended for treatment of any pediatric kidney stone disease.

Glycogen Storage Disease Type 1

Glycogen storage disease type 1 (historically known as von Gierke disease) has many clinical manifestations but can result in systemic acidosis, hypocitraturia, hypercalciuria, and/or hyperuricemia and is associated with nephrocalcinosis/

nephrolithiasis [62, 63]. Guidelines for monitoring and treatment of patients with glycogen storage disease type 1 have been published and should be followed [63, 64]. Hence, children with glycogen storage disease type 1 should have monitoring for development of nephrolithiasis and nephrocalcinosis with periodic renal ultrasound. Serum studies to assess for acidosis and hyperuricemia should be obtained and urine should be assessed for hypercalciuria or hypocitraturia. Oral potassium citrate supplementation, thiazides, and allopurinol and low purine diet can be used where indicated.

Conclusion

Pharmacologic management of pediatric stone disease should be considered after appropriate dietary and fluid management and tailored to specific etiologies of stone disease or based on a genetic diagnosis. At present, the majority of treatment options involve correcting the metabolic derangements to limit stone recurrence risk. For certain genetic conditions, targeted therapies do exist with more being developed. Ongoing research into medical treatments for pediatric nephrolithiasis is critical to further develop well-tolerated therapies that decrease the burden of kidney stone disease in children.

References

1. Pearle MS, Goldfarb DS, Assimos DG, Curhan G, Denu-Ciocca CJ, Matlaga BR, et al. Medical management of kidney stones: AUA guideline. J Urol. 2014;192(2):316–24.
2. Yendt ER, Gagné RJ, Cohanim M. The effects of thiazides in idiopathic hypercalciuria. Am J Med Sci. 1966;251(4):449–60.
3. Coe FL, Parks JH, Bushinsky DA, Langman CB, Favus MJ. Chlorthalidone promotes mineral retention in patients with idiopathic hypercalciuria. Kidney Int. 1988;33(6):1140–6.
4. Bergsland KJ, Worcester EM, Coe FL. Role of proximal tubule in the hypocalciuric response to thiazide of patients with idiopathic hypercalciuria. Am J Physiol Renal Physiol. 2013;305(4):F592–9.
5. Laerum E, Larsen S. Thiazide prophylaxis of urolithiasis. A double-blind study in general practice. Acta Med Scand. 1984;215(4):383–9.
6. Ettinger B, Citron JT, Livermore B, Dolman LI. Chlorthalidone reduces calcium oxalate calculous recurrence but magnesium hydroxide does not. J Urol. 1988;139(4):679–84.
7. Borghi L, Meschi T, Guerra A, Novarini A. Randomized prospective study of a nonthiazide diuretic, indapamide, in preventing calcium stone recurrences. J Cardiovasc Pharmacol. 1993;22(Suppl 6):S78–86.
8. Reusz GS, Dobos M, Tulassay T, Miltényi M. Hydrochlorothiazide treatment of children with hypercalciuria: effects and side effects. Pediatr Nephrol. 1993;7(6):699–702.
9. Schwaderer AL, Kusumi K, Ayoob RM. Pediatric nephrolithiasis and the link to bone metabolism. Curr Opin Pediatr. 2014;26(2):207–14.
10. Sakhaee K, Maalouf NM, Kumar R, Pasch A, Moe OW. Nephrolithiasis-associated bone disease: pathogenesis and treatment options. Kidney Int. 2011;79(4):393–403.

11. Lexicomp. 2020;Wolters Kluwer, Philadelphia. http://online.lexi.com. Accessed 6/10/21
12. Mehta TH, Goldfarb DS. Uric acid stones and hyperuricosuria. Adv Chronic Kidney Dis. 2012;19(6):413–8.
13. Pelletier J, Gbadegesin R, Staples B. Renal tubular acidosis. Pediatr Rev. 2017;38(11):537–9.
14. Copelovitch L. Urolithiasis in children: medical approach. Pediatr Clin N Am. 2012;59(4):881–96.
15. Hoppe B, Martin-Higueras C. Inherited conditions resulting in nephrolithiasis. Curr Opin Pediatrics. 2020;32(2):273–83.
16. Eisner BH, Goldfarb DS, Baum MA, Langman CB, Curhan GC, Preminger GM, et al. Evaluation and medical management of patients with cystine nephrolithiasis: a consensus statement. J Endourol. 2020.
17. Pak CY, Fuller C, Sakhaee K, Zerwekh JE, Adams BV. Management of cystine nephrolithiasis with alpha-mercaptopropionylglycine. J Urol. 1986;136(5):1003–8.
18. Remien A, Kallistratos G, Burchardt P. Treatment of cystinuria with Thiola (alpha-mercaptopropionyl glycine). Eur Urol. 1975;1(5):227–8.
19. Edvardsson VO, Runolfsdottir HL, Thorsteinsdottir UA, Sch Agustsdottir IM, Oddsdottir GS, Eiriksson F, et al. Comparison of the effect of allopurinol and febuxostat on urinary 2,8-dihydroxyadenine excretion in patients with adenine phosphoribosyltransferase deficiency (APRTd): a clinical trial. Eur J Intern Med. 2018;48:75–9.
20. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017;140(3)
21. Huen SC, Goldfarb DS. Adverse metabolic side effects of thiazides: implications for patients with calcium nephrolithiasis. J Urol. 2007;177(4):1238–43.
22. Maschio G, Tessitore N, D'Angelo A, Fabris A, Pagano F, Tasca A, et al. Prevention of calcium nephrolithiasis with low-dose thiazide, amiloride and allopurinol. Am J Med. 1981;71(4):623–6.
23. Costanzo LS, Weiner IM. Relationship between clearances of Ca and Na: effect of distal diuretics and PTH. Am J Phys. 1976;230(1):67–73.
24. Massey L. Magnesium therapy for nephrolithiasis. Magnes Res. 2005;18(2):123–6.
25. Pak CY, Koenig K, Khan R, Haynes S, Padalino P. Physicochemical action of potassium-magnesium citrate in nephrolithiasis. J Bone Miner Res. 1992;7(3):281–5.
26. Odvina CV, Mason RP, Pak CYC. Prevention of thiazide-induced hypokalemia without magnesium depletion by potassium-magnesium-citrate. Am J Ther. 2006;13(2):101–8.
27. Song Y, Hernandez N, Shoag J, Goldfarb DS, Eisner BH. Potassium citrate decreases urine calcium excretion in patients with hypocitraturic calcium oxalate nephrolithiasis. Urolithiasis. 2016;44(2):145–8.
28. Barcelo P, Wuhl O, Servitge E, Rousaud A, Pak CY. Randomized double-blind study of potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. J Urol. 1993;150(6):1761–4.
29. Pak CY, Fuller C, Sakhaee K, Preminger GM, Britton F. Long-term treatment of calcium nephrolithiasis with potassium citrate. J Urol. 1985;134(1):11–9.
30. Daudon M, Frochot V, Bazin D, Jungers P. Drug-induced kidney stones and crystalline nephropathy: pathophysiology. Prevent Treatm Drugs. 2018;78(2):163–201.
31. Mahmoud AAH, Rizk T, El-Bakri NK, Riaz M, Dannawi S, Al TM. Incidence of kidney stones with topiramate treatment in pediatric patients: kidney stones with topiramate. Epilepsia. 2011;52(10):1890–3.
32. Jhagroo RA, Wertheim ML, Penniston KL. Alkali replacement raises urinary citrate excretion in patients with topiramate-induced hypocitraturia. Br J Clin Pharmacol. 2016;81(1):131–6.
33. Williams-Larson AW. Urinary calculi associated with purine metabolism. Uric acid nephrolithiasis. Endocrinol Metab Clin N Am. 1990;19(4):821–38.
34. Rumsby G, Cochat P. Primary hyperoxaluria. N Engl J Med. 2013;369(22):2163.
35. Sas DJ, Harris PC, Milliner DS. Recent advances in the identification and management of inherited hyperoxalurias. Urolithiasis. 2019;47(1):79–89.

36. Fargue S, Rumsby G, Danpure CJ. Multiple mechanisms of action of pyridoxine in primary hyperoxaluria type 1. Biochim Biophys Acta. 2013;1832(10):1776–83.
37. Garrelfs SF, Rumsby G, Peters-Sengers H, Erger F, Groothoff JW, Beck BB, et al. Patients with primary hyperoxaluria type 2 have significant morbidity and require careful follow-up. Kidney Int. 2019;96(6):1389–99.
38. Dhondup T, Lorenz EC, Milliner DS, Lieske JC. Combined liver-kidney transplantation for primary hyperoxaluria type 2: a case report. Am J Transplant. 2018;18(1):253–7.
39. Weigert A, Martin-Higueras CM, Hoppe B. Novel therapeutic approaches in primary hyperoxaluria. Expert Opin Emerg Drugs. 2018;23(4):349–57.
40. Liebow A, Li X, Racie T, Hettinger J, Bettencourt BR, Najafian N, et al. An investigational RNAi therapeutic targeting glycolate oxidase reduces oxalate production in models of primary hyperoxaluria. J Am Soc Nephrol. 2017;28(2):494–503.
41. Saland J, Groothoff J, Fishberg Y, Hulton S, Koren M, Overcash J, Sellier-Leclerc A, et al. 12-month analysis of ILLUMINATE-A, a phase 3 study of Lumasiran: sustained oxalate lowering and kidney stone event rates in primary hyperoxaluria type 1. Am Soc Nephrol. 2020. Abstract/Poster 2637.
42. Lai C, Pursell N, Gierut J, Saxena U, Zhou W, Dills M, et al. Specific inhibition of hepatic lactate dehydrogenase reduces oxalate production in mouse models of primary hyperoxaluria. Mol Ther. 2018;26(8):1983–95.
43. Castello R, Borzone R, D'Aria S, Annunziata P, Piccolo P, Brunetti-Pierri N. Helper-dependent adenoviral vectors for liver-directed gene therapy of primary hyperoxaluria type 1. Gene Ther. 2016;23(2):129–34.
44. Miyata N, Steffen J, Johnson ME, Fargue S, Danpure CJ, Koehler CM. Pharmacologic rescue of an enzyme-trafficking defect in primary hyperoxaluria 1. Proc Natl Acad Sci U S A. 2014;111(40):14406–11.
45. Oppici E, Dindo M, Conter C, Borri Voltattorni C, Cellini B. Folding defects leading to primary hyperoxaluria. Handb Exp Pharmacol. 2018;245:313–43.
46. Oppici E, Fargue S, Reid ES, Mills PB, Clayton PT, Danpure CJ, et al. Pyridoxamine and pyridoxal are more effective than pyridoxine in rescuing folding-defective variants of human alanine:glyoxylate aminotransferase causing primary hyperoxaluria type I. Hum Mol Genet. 2015;24(19):5500–11.
47. Hatch M, Gjymishka A, Salido EC, Allison MJ, Freel RW. Enteric oxalate elimination is induced and oxalate is normalized in a mouse model of primary hyperoxaluria following intestinal colonization with oxalobacter. Am J Physiol Gastrointest Liver Physiol. 2011;300(3):G461–9.
48. Milliner D, Hoppe B, Groothoff J. A randomised phase II/III study to evaluate the efficacy and safety of orally administered Oxalobacter formigenes to treat primary hyperoxaluria. Urolithiasis. 2018;46(4):313–23.
49. Fjellstedt E, Denneberg T, Jeppsson JO, Tiselius HG. A comparison of the effects of potassium citrate and sodium bicarbonate in the alkalinization of urine in homozygous cystinuria. Urol Res. 2001;29(5):295–302.
50. Edvardsson VO, Goldfarb DS, Lieske JC, Beara-Lasic L, Anglani F, Milliner DS, et al. Hereditary causes of kidney stones and chronic kidney disease. Pediatr Nephrol. 2013;28(10):1923–42.
51. DeBerardinis RJ, Coughlin CR, Kaplan P. Penicillamine therapy for pediatric cystinuria: experience from a cohort of American children. J Urol. 2008;180(6):2620–3.
52. Dolin DJ, Asplin JR, Flagel L, Grasso M, Goldfarb DS. Effect of cystine-binding thiol drugs on urinary cystine capacity in patients with cystinuria. J Endourol. 2005;19(3):429–32.
53. Cil O, Perwad F. α-Lipoic acid (ALA) improves cystine solubility in cystinuria: report of 2 cases. Pediatrics. 2020;145(5).
54. Edvardsson VO, Sahota A, Palsson R. Adenine Phosphoribosyltransferase Deficiency. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJ, Stephens K, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993 [cited 2020 May 5]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK100238/

55. Runolfsdottir HL, Palsson R, Agustsdottir IM, Indridason OS, Edvardsson VO. Kidney disease in adenine phosphoribosyltransferase deficiency. Am J Kidney Dis. 2016;67(3):431–8.
56. Runolfsdottir HL, Palsson R, Agustsdottir IMS, Indridason OS, Li J, Dao M, et al. Kidney transplant outcomes in patients with adenine phosphoribosyltransferase deficiency. Transplantation. 2019.
57. Ehlayel AM, Copelovitch L. Update on dent disease. Pediatr Clin N Am. 2019;66(1):169–78.
58. Anglani F, Gianesello L, Beara-Lasic L, Lieske J. Dent disease: a window into calcium and phosphate transport. J Cell Mol Med. 2019;23(11):7132–42.
59. Lieske JC, Milliner DS, Beara-Lasic L, Harris P, Cogal A, Abrash E. Dent disease. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJ, Stephens K, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993 [cited 2020 Aug 15]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK99494/
60. Raja KA, Schurman S, D'mello RG, Blowey D, Goodyer P, Van Why S, et al. Responsiveness of hypercalciuria to thiazide in Dent's disease. J Am Soc Nephrol. 2002;13(12):2938–44.
61. Gabriel SS, Belge H, Gassama A, Debaix H, Luciani A, Fehr T, et al. Bone marrow transplantation improves proximal tubule dysfunction in a mouse model of dent disease. Kidney Int. 2017;91(4):842–55.
62. Weinstein DA, Somers MJ, Wolfsdorf JI. Decreased urinary citrate excretion in type 1a glycogen storage disease. J Pediatr. 2001;138(3):378–82.
63. Kishnani PS, Austin SL, Abdenur JE, Arn P, Bali DS, Boney A, et al. Diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics. Genet Med. 2014;16(11):e1.
64. Visser G, Rake J, Labrune P, Leonard J, Moses S, Ullrich K, et al. Consensus guidelines for management of glycogen storage disease type 1b - European study on glycogen storage disease type 1. Eur J Pediatr. 2002;161(0):S120–3.

Suggested Reading

Daga A, Majmundar AJ, Braun DA, Gee HY, Lawson JA, Shril S, et al. Whole exome sequencing frequently detects a monogenic cause in early onset nephrolithiasis and nephrocalcinosis. Kidney Int. 2018;93(1):204–13.

Parks JH, Coe FL. Evidence for durable kidney stone prevention over several decades. BJU Int. 2009;103(9):1238–46.

Fink HA, Wilt TJ, Eidman KE, Garimella PS, MacDonald R, Rutks IR, et al. Medical management to prevent recurrent nephrolithiasis in adults: a systematic review for an American College of Physicians Clinical Guideline. Ann Intern Med. 2013;158(7):535–43.

Chapter 11
Nutritional Prevention of Nephrolithiasis in Children

Kristina L. Penniston

Introduction

Nutrition-related contributors to urolithiasis are addressed elsewhere in this book. Although not addressed further in this chapter, a brief review of dietary contributors is shown (Table 11.1). Here forward, this chapter primarily describes the use of diet to reduce the recurrence risk of calcium and uric acid containing stones in children. Primary hyperoxaluria and cystinuria are only briefly addressed as diet is causative in neither condition and specific nutrition recommendations have only limited effect. In all other children with kidney stone disease, the ability of dietary changes to mitigate stone risk and reduce recurrence depends on: (1) confirmation that diet is a contributor to stone risk factor(s); (2) correct identification of the dietary habit(s) that explains stone risk(s); (3) application of the appropriate dietary change(s) that address stone risk; and (4) the patient's and parents' implementation of the recommended change(s). Nutritional approaches to preventing stones include general recommendations that may be given to all patients, steering them toward dietary patterns that reduce stone risk; these are described in this chapter. Alternatively, individual recommendations based on each patient's specific stone-related risk factors (Fig. 11.1) may be selectively prescribed; these are also described in this chapter.

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Table 11.1 Dietary contributors to urolithiasis are grouped into two categories—excessive and insufficient intake. Additional data show the type(s) of stones most associated with each dietary factor, their mechanism(s) of action, and result on urinary stone risk factors

	Dietary factor	Stone type	Mechanism of action
Excessive intake	Energy	All crystal types	Unknown [44]
	Dietary patterns high for potential renal acid load	Calcium, all crystal types Uric acid Cystine	Higher net endogenous acid production and renal citrate reabsorption (lower excretion); lower urine pH
	Carbohydrates (particularly added sugar)	Calcium, all crystal types	Impaired insulin regulation and lower renal calcium reabsorption (higher excretion)
		Uric acid	Insulin resistance and impaired renal ammoniagenesis (lower pH); also fructose may enhance uric acid biosynthesis
	Fat	Calcium oxalate	Higher gastrointestinal tract permeability to oxalate (higher excretion)
	Uric acid precursors[a]	Uric acid	Higher uric acid biosynthesis and excretion
	Oxalate[b]	Calcium oxalate	Higher oxalate absorption and renal excretion
	Salt (as sodium chloride)	Calcium, all crystal types	Expansion of extracellular volume and lower renal calcium reabsorption (higher excretion)
	Calcium, vitamin D	Calcium, all crystal types	Higher calcium absorption and renal excretion
	Vitamin C and other oxalate precursors[c]	Calcium oxalate	Higher oxalate biosynthesis and excretion
Insufficient intake	Fluids	All crystal types	Higher urine supersaturation
	Dietary patterns low for renal alkaline potential	Calcium, all crystal types Uric acid Cystine	Higher net endogenous acid production and renal citrate reabsorption (lower excretion); lower urine pH
	Calcium, vitamin D	Calcium, all crystal types	Calcium resorption from bone, higher renal filtered load and excretion
	Magnesium	Calcium oxalate	Higher renal reabsorption (lower excretion)
	Fiber	Calcium oxalate	Lower prebiotic intake and potential for lower microbial oxalate degradation in digestive tract (higher oxalate excretion)

[a]Purines, xanthine, alcohol, fructose [18, 19]

[b]Refers to oxalate-rich foods, especially if consumed in setting of lower calcium intake, and to dietary supplements that provide oxalate (e.g., turmeric, cinnamon, potentially other plant-derived substances)

[c]Examples include collagen, hydroxyproline

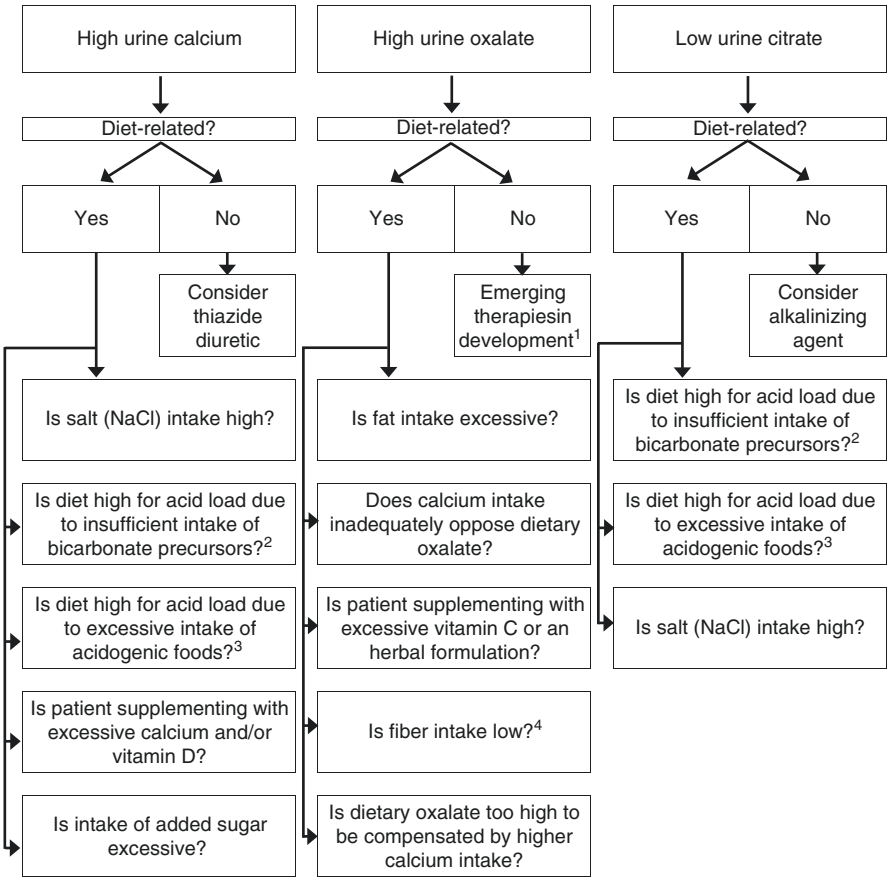

Fig. 11.1 Key questions providers may ask in order to identify dietary contributors to common lithogenic risk factors for calcium-containing stones. Refer to Table 11.1 for dietary mechanisms of action on 24-h urine parameters and to Table 11.3 for specific dietary recommendations that address the dietary contributors identified in this model. [1]Emerging pharmacologic therapies for hyperoxaluria include oxalate degrading enzymes, probiotics, and RNA interference agents [20, 61]. [2]Most all fruits and vegetables and their juices (note that milk, yogurt, and kefir are basically neutral for acid load). [3]All meats (including fowl and fish), all grains and foods made with grains; also cheeses and eggs. [4]Fiber is the source of prebiotics required by gut microbes, not only microbes that degrade oxalate but also those whose presence in the gut is required for optimal oxalate degradation by oxalotrophs [29]

General Dietary Approaches to Stone Prevention

Dietary Patterns Studies of overall dietary patterns and stone risk are inconsistent. Nonetheless, on the basis of observational studies, some have proposed the Dietary Approaches to Stop Hypertension (DASH) [1] or Mediterranean dietary patterns for stone prevention [2, 3]. The 2020–2025 US Department of Agriculture (USDA) Dietary Guidelines for Americans [4] have also been suggested for stone prevention (Table 11.2). These patterns could indeed provide the basis for a stone

Table 11.2 Comparison of dietary recommendations. Recommended consumption of foods by food group is compared between three dietary patterns, all of which have been promoted for general stone prevention

Food group	Dietary approaches to stop hypertension diet	USDA Dietary Guidelines for Americans, 2020–2025[a]	Mediterranean diet[b]
Vegetables	**4–5 servings/day**	**2½ cups/day**	**At every meal**
	All encouraged; specific types of vegetables are not usually recommended over others	*Dark green—1½ cups/wk* *Red, orange—5½ cups/wk* *Legumes[c]—1½ cups/wk* *Starchy—5 cups/wk* *Other—4 cups/wk*	*All encouraged; specific types of vegetables are not usually recommended over others*
Fruits	**4–5 servings/day**	**2 cups/day**	**At every meal**
Grains	**7–8 servings/day**	**6 ozs/day**	**At every meal**
	Preponderance of whole grains are recommended	*Whole—≥3 ozs/day* *Refined—≥3 ozs/day*	*Mostly (or all) whole grains are recommended*
Dairy[d]	**2–3 servings/day**	**3 cups/day**	**"Moderate portions" weekly**
	Low- or nonfat sources	*Specific forms of dairy are not specified*	*Yogurt and cheese[e] are recommended sources*
Protein foods	**≤2 servings/day**	**34 ozs/week**	**Varies;** see below
	Lean meats, poultry, and fish	*Fish, seafood—8 ozs/week* *Meats, poultry, eggs—26 ozs/week*	*Fish, seafood—Often, at least twice/week* *Poultry, eggs—Moderate portions weekly* *Meats—Eat less often*
Nuts, seeds, soy	**4–5 servings/week**	**5 ozs/week**	**At every meal** *(nuts and seeds)*
Oils	**2–3 servings/day** *(fats and oils)*	**27 grams/day** *(oils)*	**At every meal** *(olive oil)*
Sweets	**5 servings/week**	**Intake should amount to no more than 10% of kcals/day**	**Consume less often**

[a]Recommendations shown are for individuals requiring 2000 kcals per day. Recommendations for vegetarian dietary patterns and for other calorie levels (from 1000–3200 kcals/day) are available at https://www.dietaryguidelines.gov/sites/default/files/2020-12/Dietary_Guidelines_for_Americans_2020-2025.pdf. The USDA Dietary Guidelines also provide extrapolations at each calorie level for a Mediterranean-style dietary pattern

[b]There are several accepted versions of the Mediterranean diet. Presented herein is what is considered the "standard" pattern

[c]Beans, peas, peanuts

[d]All of the dietary patterns described in the table reference non-dairy calcium-fortified foods and beverages as surrogates for dairy, suggesting that the primary purpose of a "dairy" recommendation is for calcium

[e]The Mediterranean diet does not list milk as a recommended dairy source

prevention diet that is good for overall health, cardiovascular health, and optimizing nutritional status. As such, some advocate these dietary patterns for all patients who form stones, reasoning that, no matter the type of stone or individual dietary risk, all patients could benefit from them. However, there are drawbacks to general dietary approaches to stone prevention, especially for children.

Drawbacks to the DASH Diet The DASH diet is complex and difficult to practice, as systematically reviewed by others [5], especially for certain demographic subpopulations [6] and for children [7] and families whose starting point (i.e., their baseline dietary pattern) is significantly divergent. Depending on one's energy needs, the DASH diet recommends up to 12 servings of fruits and vegetables daily (approximately 5–6 cups; Table 11.2). Accordingly, a 7-year-old boy or girl requiring 1500–1800 kcals/day, depending on body weight and activity level, would need 7–8 servings of fruits and vegetables per day. For most patients, especially children whose preferences for fruits and vegetables are not optimal, getting them to simply consume 5 servings a day (approximately 2–3 cups) is a significant challenge; overall, >90% of people in the USA fail to meet this goal [8]. Moreover, there may be contradictions within the DASH diet for children with certain comorbidities, such as food intolerances (e.g., gluten, lactose), food allergies (e.g., milk protein, nuts), diabetes, or obesity—all of which may make DASH diet guidelines difficult to incorporate. Finally, the DASH diet is criticized for its lack of cultural sensitivity. A study that evaluated the effectiveness of the DASH diet alone and in combination with weight reduction measures found that, compared to whites, African Americans had lower DASH diet adherence scores over time even though they increased their intake of DASH foods [9]. Investigators concluded that, due to "strong cultural influences on food preferences, food preparation, and perceptions about eating practices," it might be more effective to modify traditional recipes and integrate foods with high cultural relevance into a DASH-like plan instead of recommending the DASH diet guidelines as typically presented. Similar findings in Korean, Japanese, and other East Asian populations [10] suggest a "one-size-fits-all DASH diet" is not practical. In each of the above scenarios, the DASH diet could be adapted and individualized, but that would require specialized knowledge and additional time, thus undermining the simplicity of recommending a general dietary pattern to all.

Drawbacks to the Mediterranean Diet Similar drawbacks exist with the Mediterranean dietary pattern. The diet deviates significantly from the typical Western diet, the latter of which includes much more meat and far fewer fruits and vegetables. The magnitude of the changes required, not to mention the number of changes, may thus be difficult to achieve, especially by children whose current diets fall far below recommended goals and for children in families that are not open to adopting broad-sweeping diet changes. Adherence over time to the Mediterranean diet is challenging [11]. Even in countries from which the Mediterranean diet originated, compliance is reportedly low [12]. This is thought to be due to societal changes, notably socioeconomic [13], but possibly other factors. One study demonstrated that among children and adolescents living in southern European countries,

roughly 50% had "average adherence" to the Mediterranean dietary pattern while the other 50% had "scarce adherence" with a trend toward poorer adherence over time [14]. The Mediterranean diet is also questioned with regard to its appropriateness for children. Calcium and iron, for example, may be difficult to consume in adequate amounts on a daily basis [15]. Strict adherence to the Mediterranean diet may result in under-consumption of protein. In one study, subjects on the Mediterranean diet consumed an average of only 14% of their daily calories from protein [16]. For children ages 9 years and older, recommended protein intakes approach 30% of daily calories [17]. As with the DASH diet, adaptation of the Mediterranean diet to suit individual needs is possible, but that requires nutrition expertise and thus undercuts the ability to recommend one diet for all children who form stones.

Dietary Guidelines Targeted to Stone Risk An alternative to recommending wholescale dietary patterns is to provide general dietary recommendations using guidelines such as those developed by the American Urological Association [18]. General guidelines like these may be provided by anyone who is familiar with them. In clinical practice, a list of the guidelines is typically provided (or verbally described) to each patient regardless of his/her metabolic risk factors or stone history. An advantage of general recommendations is that there is no need to assess patients' diets or to parse out specific recommendations or sets of recommendations to different patients. Often, a single written handout can accommodate the needs of all. Another advantage is that extra time spent explaining or customizing dietary recommendations to each patient is avoided. Compared with the DASH or Mediterranean diets, stone-targeted dietary guidelines may not require wholescale dietary changes and may thus be more easily incorporated into one's existing diet.

But there are drawbacks to providing patients with lists of general dietary guidelines. These include the possibility of (1) recommending dietary changes when the patient's stone risk is not diet-related, (2) too many recommendations to be remembered or followed, (3) unnecessary dietary recommendations (such as a change that is not capable of addressing actual stone risk), or (4) recommending something the patient is already doing. In the first scenario, no amount of dietary change can alter the course of a patient's stone disease if the cause is not diet-related. Another concern is that attempts to control non-dietary factors with dietary changes result in delayed application of more appropriate medical therapies. In the second scenario, long lists of recommendations tend to be confusing or forgotten by patients [19], risking low or no compliance and adherence over time. In the third scenario, a patient making a dietary change that has no effect on his/her stone risk (because it addressed no actual risk factor) may be unlikely to accept or adhere to future dietary and medical recommendations. Such patients may lose faith in the potential of nutrition and other therapies to prevent stones, especially if they comply with recommendations and then continue to make new stones. In the fourth scenario, the patient who already conforms to the recommended dietary changes is essentially offered no therapy, again potentially delaying effective preventive care. Finally,

there are psychological, biological, physical, economic, cultural, social, and behavioral barriers that influence long-term dietary habits and food choices. Without assistance in overcoming these barriers, making many changes and sticking to them may be difficult whereas successfully making one or two changes might be possible.

Personalized Nutritional Stone Prevention Personalized medicine centers around tailored treatments based on composites of each patient's unique characteristics, which vary greatly, even among those with shared disease diagnoses. These characteristics include factors related to environment, lifestyle, personality, personal preferences, and diet, as well as demographic, physical, physiological, biochemical, and genomic factors. Evidence confirms that targeted, personalized dietary approaches for the management of many medical conditions are effective [20]; this is likely true for urolithiasis as well [19, 21, 22]. Just as the urologic surgeon individualizes his/her procedural stone treatment to patients' preferences, anatomy, stone composition, stone location, etc., individualized nutritional approaches are endorsed by clinical nutrition experts. In the same way that evaluation of each patient's metabolic stone risk enables specific factors to be ruled in or out, a nutrition assessment can rule diet in or out as a stone risk. Without learning about each patient's baseline diet, the very need for dietary modification, let alone the type and number of recommendations to be provided, is unknown. Just as pharmacologic therapy is driven by metabolic risk factors obtained from medical assessment, nutrition therapy is driven by nutrition-related risk factors from diet assessment. Benefits of individual diet assessment include: (1) ability to personalize dietary recommendations and avoid long lists of general recommendations, some of which may not be helpful to an individual; (2) ability to tie specific nutritional factors to specific urinary stone risk factors, which may improve patients' and families' coherence of their stone disease process; (3) avoidance of unnecessary dietary changes that may decrease patients' motivation for prevention; and (4) in the event that diet is ruled out as a contributor to stones, more effective therapy can be put into place sooner rather than later.

Individual Stone-Targeted Dietary Recommendations Personalized medical approaches are increasingly possible due to the breadth and amount of patient-specific data that are routinely collected. These data can be used to deliver a regimen tailored to each individual and targeted to his/her primary risk factors. Individual nutrition recommendations should be provided by someone who understands metabolic stone risk factors and how they are influenced by diet. In urolithiasis, the rationale for individual dietary recommendations is that patients form stones for different reasons and thus have different risk factors. Moreover, not all stones are diet-related. Ideally, individualized nutrition recommendations are targeted to each patient's 24-hour urinary risk factors and stone composition, if available, and informed by diet-related lithogenic risk factors identified in diet assessment (Fig. 11.1). Tools for screening patients' diets for several dietary risk factors [e.g., potential acid load of diet [23], sodium chloride (NaCl) intake [24, 25], calcium intake [26]] are available for use by those who are not nutrition experts and are a

Table 11.3 Targeted dietary recommendations individualized to the most common urinary stone risk factors. Information in the table begins—from left to right—with "If…" a risk factor from 24-hour urine collection results exists "And…" findings from diet assessment reveal a potential contributor to it, "Then…" quantify consumption and patient-related factors related to consumption, and "Recommend…" strategies to address the dietary contributor. While strong evidence for each and every nutrition recommendation is lacking, all of the recommendations listed have some level of support as described in the guidelines of several organizations [18, 60, 61]

IF…	AND…	THEN…	RECOMMEND…
Low urine volume	Fluid intake is limited or low; or, intake is insufficient to compensate for extra-renal losses	Identify barriers to consumption	Strategies to address barriers, which might include expanding repertoire of recommended beverages, suggesting a fluid intake schedule or reminder system, use of non-caloric or low-calorie flavor enhancers, fluid delivery by enteral nutrition support routes (e.g., for very young patients)
High urine calcium	Diet assessment demonstrates excessive salt intake (sodium chloride)	Identify sources and pattern of consumption	Strategies to reduce amount and/or frequency of intake Strategies to replace highest-salt foods with lower-salt alternatives Strategies to balance higher-salt meals or days with lower-salt meals or days
	Calcium supplementation is excessive	Quantify intake, add dietary contribution to estimate total intake	Discontinue entirely or reduce dosage if some amount of supplement is needed to meet calcium needs Address misconceptions about health benefits
	Vitamin D supplementation is excessive	Quantify intake; check 25(OH)D to evaluate magnitude of effect	Discontinue or reduce dosage Address misconceptions about health benefits
	Diet assessment reveals high dietary acid load	Identify whether intake of bicarbonate precursors is low and/or if intake of acidogenic foods is high	Strategies to increase intake of fruits, vegetables, and high-alkali beverages Combine above with smaller portions or lower frequency of intake of acidogenic foods as needed
	Diet is excessive for added sugars	Identify sources and pattern of consumption	Strategies to eliminate or reduce amount and/or frequency of intake

Table 11.3 (continued)

IF…	AND…	THEN…	RECOMMEND…
High urine oxalate	Diet is low for calcium; or, intake is insufficient to compensate for malabsorption	Quantify intake, identify timing of consumption and barriers to consumption	Strategies to overcome barriers to adequate calcium intake Consume calcium-containing foods/beverages with meals (supplements may be needed in some cases)
	Diet not low for calcium but oxalate intake is high	Identify sources	Increase calcium intake, especially with meals, to compensate for high oxalate intake Reduce portion sizes and/or frequency of intake of the highest-oxalate foods
	Patient is supplementing with vitamin C	Quantify intake	Discontinue or reduce dosage Address misconceptions about health benefits from supplement
	Patient supplements with herbal or other over-the-counter plant supplements	Identify sources	Discontinue or reduce number or amount of supplements Address misconceptions about health benefits from supplements
	Diet is low for fiber/low for prebiotics	Quantify fiber intake, identify barriers to consumption	Strategies to overcome barriers to higher fiber consumption
Low urine citrate (with or without low urine pH)	Diet assessment reveals high dietary acid load	Identify whether intake of bicarbonate precursors is low and/or if intake of acidogenic foods is high Identify if salt (NaCl) intake is high	Strategies to increase intake of fruits, vegetables, and high-alkali beverages Combine above with smaller portions or lower frequency of intake of acidogenic foods as needed Consider over-the-counter urinary alkalinizing agents (e.g., baking soda, commercially available products); lemon or lime juice Employ strategies to reduce NaCl intake (as described above)
Low urine magnesium	Diet is low for whole grains, leafy green vegetables; or, intake is insufficient to compensate for malabsorption or medication-induced reductions in magnesium absorption	Quantify intake, identify barriers to consumption	Strategies to increase intake Magnesium supplement may be required, depending on magnitude of hypomagnesiuria

good option when a nutrition clinician is not available. Selective, individualized dietary recommendations may then be provided (Table 11.3).

Advantages of individual dietary recommendations include low risk of unnecessary or ineffectual dietary changes, assuming that the appropriate dietary change(s) was/were recommended. This is important because, as with other therapies, nutrition therapy should aim for the highest level of effectiveness with the least possible cost and burden to the patient. Depending on the recommended dietary change(s), patients may find themselves spending more in grocery purchases. Minimizing the number of recommended changes lowers this possibility. Moreover, as diet changes are frequently difficult to make, patient burden is minimized when the number of recommended changes is limited to those most needed. Another advantage is the ability to tie nutrition recommendations to specific metabolic risk factors. This may have the side effect of increasing patients' understanding of the relationship between stones and diet and thus enhancing their self-efficacy. Finally, individualized dietary recommendations can accommodate a child's food likes and dislikes, a family's diet-related cultural preferences, unique nutrient needs (e.g., lactose-free, higher protein, higher calorie for catch-up growth), and can target changes to specific stone risk factors.

Drawbacks to individualized dietary recommendations include the need for more provider time with each patient, which may require changes to clinic scheduling. Another drawback is that physicians and physician extenders (e.g., nurse practitioners, physician assistants) are not experts in nutrition. Just as a metabolic assessment to determine patients' stone risk factors requires specific testing and expert interpretation, a diet assessment to identify dietary contributors to stone risk requires specialized knowledge and interpretive skills. For example, depending on the patient and his/her metabolic risk factors, diet assessment might entail quantifying the intake of specific dietary components, such as calcium, oxalate, and salt, and/or of the effect of the dietary pattern as a whole on acid-base balance and the gut microbiome. If a qualified clinical nutritionist is not part of the provider team, a thorough diet assessment, which provides the basis for individualized nutrition therapy, may not be possible.

Nutritional Stone Prevention for Children with Special Needs

Stone prevention in children with special needs is complex and typically requires input from a team of providers. In many cases, a team from pediatric nephrology, pediatric urology, and clinical nutrition is required. Some of the most common pediatric special needs that predispose or are otherwise associated with urolithiasis are now reviewed.

Children with Primary Hyperoxaluria In inherited nephrolithiasis, the etiology of stone formation is not diet-related. Similarly, the primary treatment for each is not diet-related. But dietary modification may be useful to a moderate degree in

reducing the frequency of occurrence and/or the number and size of stones formed. In primary hyperoxaluria, the primary source of urinary oxalate excretion is hepatic oxalate biosynthesis, not oxalate absorbed from the intestinal tract. Nevertheless, efforts to reduce the bioavailability of dietary oxalate should be incorporated, and this may include pairing calcium-containing foods and beverages with meals and/or calcium supplements with meals. Furthermore, avoidance of vitamin C supplementation and use of herbal supplements should be advised as ascorbic acid is an oxalate precursor, and herbal supplements may provide oxalate and add to overall dietary oxalate load (Table 11.1). Nutritional methods to maintain suitably low urinary calcium excretion should also be in place (Table 11.3) if the child is prone to higher urine calcium. Finally, higher fluid intakes to push urine production and output as high as possible should be recommended to decrease the urinary supersaturation of calcium salts. In very small children whose stone disease is very aggressive, this may require fluid delivery via nasogastric or gastrostomy tube [27].

Children with Cystinuria For children with cystinuria, the diet should be as high as possible for fluids, ample for fruits and vegetables, and low for salt. High fluid intake promotes higher urine output, which lowers urine supersaturation. Fruits and vegetables provide bicarbonate precursors that may help to increase (alkalinize) urine pH and are thus recommended because cystine precipitates in overly acidic urine. If fruit and vegetable intake is consistently high enough, lower dosages of prescriptive urinary alkalinizing agents (frequently used in patients with cystinuria) may be possible. Dietary NaCl increases urinary cystine excretion [28], and a lower-salt diet is thus recommended. However, the importance of this recommendation among patients with cystine stones has been questioned [29]. Finally, methionine, an essential amino acid consumed from foods high in protein, is a precursor to cysteine biosynthesis and urinary cystine excretion. Thus, in adults with cystinuria, some advocate methionine restriction [30] the effectiveness of this dietary modification is questioned [29]. Because children are growing and require ample methionine, limitation of foods containing methionine is not recommended.

Seizure Disorders Children with seizure disorders are at high risk for nephrolithiasis for many reasons. Some of these children form stones after starting topiramate [31], an anti-epileptic carbonic anhydrase inhibitor that severely lowers urinary citrate excretion and raises urine pH, increasing calcium phosphate stone formation risk. Prescriptive urinary alkalinizing agents that raise urine citrate offset the effect of the topiramate [32] and should thus be considered; the ability of nutrition therapy to adequately alkalinize urine pH in this scenario is limited. Another risk-enhancing seizure control mechanism is the ketogenic diet and variations thereof. These are increasingly employed in seizure prevention with good effect [33]. Because the ketogenic diet is extremely limited for carbohydrates and high for fat and protein, it causes similar urinary effects as carbonic anhydrase inhibitors due to the nearly complete absence of dietary bicarbonate precursors and high dietary acid load. As aforementioned, urinary alkalinizing agents are helpful. Other risk factors for calcium urolithiasis are also conferred by the ketogenic diet. These include low fiber/

prebiotic intake, low magnesium intake, and higher NaCl intake. When children on ketogenic diets are enrolled in clinically supervised health centers where RDNs familiar with the diet are integrally involved, the inherent low fiber content of the diet is addressed with approved fiber supplements that fit with each child's prescribed ketogenic ratio [34]. While this may address a child's susceptibility to constipation, it may not adequately address the effect of low prebiotic intake on the gut microbiome. Studies demonstrate that the ketogenic diet contributes to dysbiosis in infants and children with seizure disorders [34, 35]. While ketogenic diets are not typically high for oxalate, the disruption in gut microbial form and function may alter not only bacterial oxalate degradation but also other functions of the gut microbiome that influence kidney stone disease [36]. In addition, while the propensity for magnesium depletion while on the ketogenic diet is typically mitigated with supplementation [37], children may quickly develop depletion on unsupervised regimens devoid of appropriate supplementation, resulting in lower urinary magnesium excretion and higher calcium oxalate stone risk (Table 11.3). Finally, because suboptimal NaCl intake is a concern in the setting of ketosis (particularly diabetic ketoacidosis) [38], patients are frequently, and sometimes unnecessarily, told to add salt to foods and to consume salty bone broths, salted nuts and seeds, and cheese. In unsupervised or unmanaged situations, salt consumption may become excessive, risking the development of hypercalciuria (Table 11.1). In these cases, specific strategies to control NaCl intake should be implemented. These include introducing low-salt alternatives to foods typically consumed in the ketogenic diet, such as switching from salted to unsalted nuts and seeds, replacing cured and processed meats with uncured/unprocessed versions, and using unsalted soups and broths.

Cystic Fibrosis Chronic antibiotic use by children with cystic fibrosis results in significant shifts in the gut microbiome and its function [39], including ability to degrade oxalate. Additionally, malabsorption is a characteristic feature of cystic fibrosis depending on the extent of gastrointestinal tract involvement [40]. These factors, either alone or in combination, increase the risk for calcium oxalate stones as both result in higher absorption of dietary oxalate and subsequent higher urinary oxalate excretion. If altered oxalate degradation by microbes (dysbiosis) is suspected, therapies might include fecal microbiota transplant or probiotic supplements. Unfortunately, neither are clinically proven as of yet. While fecal microbiota transplants have been done in individuals with *Clostridium difficile* infections (including in children) [41], they are not approved and have recently been scrutinized by the Food and Drug Administration due to cases of transmission of various *Escherichia coli* bacterium [42] and, more recently, SARS-CoV-2 [43]. This method of enhancing bacterial oxalate degradation in children with cystic fibrosis is thus untested. The effectiveness of probiotic supplements to enhance bacterial oxalate degradation in the digestive tract has been examined. However, results are thus far equivocal [44], likely due to the heterogeneous nature of study participants and to the use of different probiotic formulations. Optimizing calcium intake from foods and beverages, pairing them with all meals, and calcium supplements with meals

are strategies that may help to reduce oxalate absorption and urinary excretion in children with cystic fibrosis. The amount of calcium needed to maintain suitably low urinary oxalate excretion depends on the oxalate content of the diet. Chewable or liquid forms of calcium supplements may be most appealing to children. Any form of calcium—calcium carbonate, calcium citrate, calcium glycinate—may be used. Although some forms are better absorbed than others, the purpose of calcium supplementation in this scenario is to bind oxalate, not to be absorbed.

Children on Enteral Nutrition Support Most complete and intact (polymeric) tube feeding formulas are built up from corn or soy, both of which contain oxalate. A handful of formulas recently analyzed for oxalate content revealed that some do indeed provide appreciable amounts, especially in patients requiring larger formula volumes [45]. Thus, higher urinary oxalate excretion may develop; cases of this are documented [46]. However, it is not clear that calcium oxalate stones comprise the majority of stones in children on enteral nutrition support, even in the setting of hyperoxaluria. Rather, struvite and calcium phosphate stones may be more commonly observed, especially in children prone to urinary tract infections [46, 47]. Nonetheless, children with high urine oxalate whose nutrition support regimens involve bolus feedings may be managed with calcium tablets crushed and administered with each feeding; alternatively, liquid calcium may be used. The amount of calcium given should be informed by following 24-h urine oxalate and adjusting the dosage as needed. If nutrition is delivered by continuous feeding, it may be effective to administer crushed calcium tablets or liquid calcium several times daily via syringe on the assumption that the more often calcium is available in the digestive tract, the more opportunities there are to bind oxalate. Again, efficacy should be determined with follow-up 24-h urine collections. Children on enteral nutrition support whose urine output is low may benefit from additional water flushed through feeding tubes as tolerance for volume allows.

Children with Gastrointestinal Disorders Gastrointestinal diseases such as Crohn's and Celiac disease, as well as non-celiac gluten sensitivity and other digestive disorders, are often associated with malabsorption [48]. Diarrhea, which typically occurs in malabsorption, induces bicarbonate wasting which, in turn, increases renal citrate reabsorption and reduces its excretion, resulting in a net increase in calcium oxalate stone risk [49]. Urine pH may also decline, increasing risk for uric acid stones [50]. Efforts to manage and control a child's chronic diarrhea is the primary way to reduce calcium oxalate stone risk. There are several nutrition-related ways to address diarrhea, including modification of the amount and types of dietary fiber consumed, use of fiber supplements, and avoidance of fatty foods and other dietary triggers. Higher consumption of foods and beverages with bicarbonate precursors can mitigate the fall in urine citrate. A primary characteristic of malabsorption is also higher oxalate absorption and urinary excretion [48, 51]. This is due to the sequestration of minerals, such as calcium and magnesium, by fatty acids, rendering less calcium and magnesium available to bind dietary oxalate. In children

with gastrointestinal disorders and with high urine oxalate, chewable calcium or liquid calcium supplements with meals may help to reduce the bioavailability of dietary oxalate.

Children with Lactose Intolerance or Milk Protein Allergy While there are many non-dairy sources of calcium, children with lactose intolerance or milk protein allergy may struggle to obtain sufficient calcium. Calcium intake insufficient to balance oxalate consumption contributes to higher urinary oxalate excretion. In these cases, expanding the child's food and beverage repertoire to include calcium-fortified non-dairy foods and beverages is helpful. These may include fruit juices and plant-based milks (e.g., soy, rice, almond, cashew, oat, coconut, macadamia, hemp, flaxseed). While there may be concern about the purported oxalate content of some of these milks, calcium fortification in these products is usually quite ample, even exceeding the amount of calcium in cow's milk on a gram for gram basis. As such, any oxalate in the product would likely be of low bioavailability. If, on the other hand, calcium supplements are to be used, they should be distributed so that no more than 300 mg of calcium is delivered at a time, preferably with meals to optimize the opportunities to bind with dietary oxalate.

Children with Autism Spectrum Disorders In the child with any form of autism and kidney stones, dietary modification may be challenging. Hypersensitivity to textures prompts refusal of foods with certain mouthfeel properties, limiting the repertoire of foods and beverages the child consumes [52]. Strong flavor and aromatic aversions, objections to certain colors, and anxiety about trying new foods are frequent autism-associated problems [52–54] and further limit the food repertoire. Some food limitations may explain the manifestation of stone risk factors. For example, children with aversions to liquids may have chronically low urine output and high urine supersaturation of stone forming solutes. The diets of children with aversions to fruits and vegetables, which is common in those with autism spectrum disorder [54], may be high for acid load, contributing to lower urinary citrate excretion. Calcium intake may be compromised in children refusing dairy, especially if non-dairy calcium sources are also refused, leading to higher urinary oxalate excretion if dietary oxalate is not adequately opposed. Although small and cross-sectional in design, results of one study demonstrated higher plasma oxalate in children with autistic spectrum disorders compared to non-autistic controls [55]. Investigators could not determine whether the oxalate was endogenously or exogenously derived; there was no effort to assess the children's diets. Finally, some children with autism prefer to eat mostly or even exclusively snack foods [53, 56], which are frequently high in NaCl. Because of the effect of NaCl on renal calcium reabsorption (Table 11.1), hypercalciuria could develop. Mitigation of all of these risk factors may be addressed with specific dietary modifications (Table 11.3), but a multidisciplinary approach that involves clinical nutritionists and behavioral specialists with experience in children with autism spectrum disorders is likely required.

Medical Nutrition Therapy and the Nutrition Care Process of Registered Dietitian Nutritionists

RDNs in the Clinical Setting Personalized nutrition regimens for kidney stone prevention are prescribed by registered dietitian nutritionists (RDNs) working in concert with or with input from nephrologists and/or urologists. RDNs utilize medical nutrition therapy (MNT) as part of the nutrition care process in the "application of nutritional diagnostic, therapy, and counseling services for the purpose of disease management" [57] (Fig. 11.2). The nutrition care manual of the Academy of Nutrition and Dietetics includes a chapter on MNT for kidney stones, which RDNs

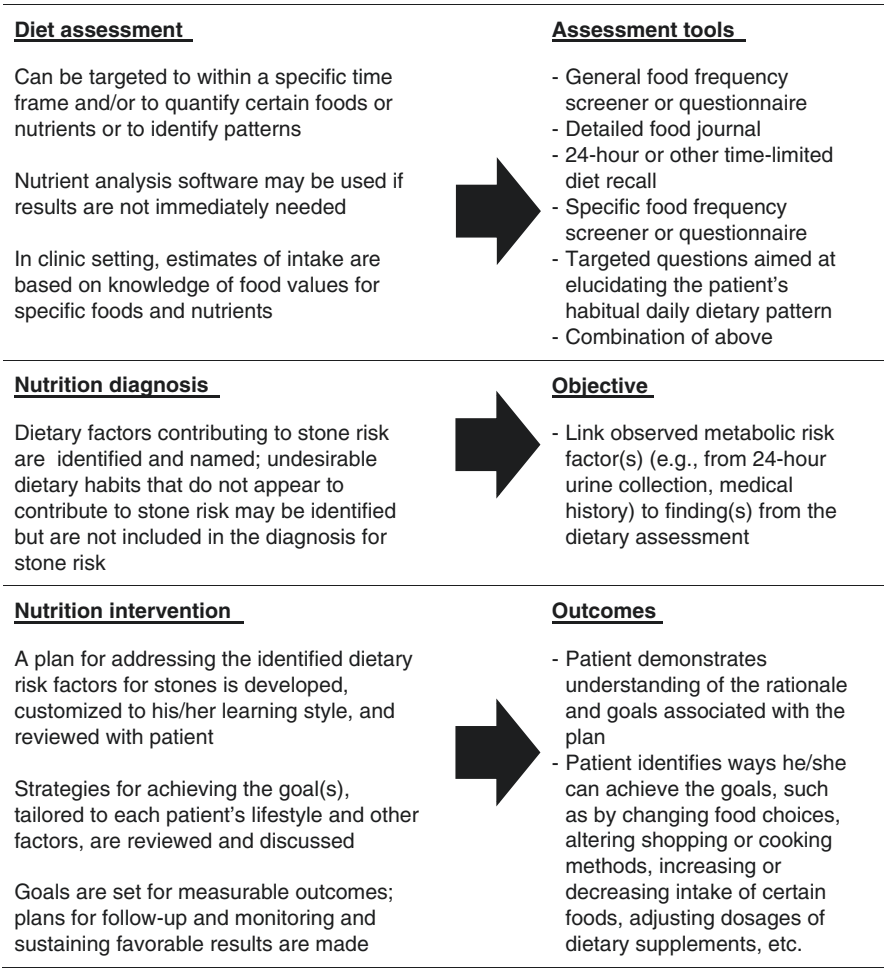

Fig. 11.2 Stone-related aspects of the Nutrition Care Process practiced by registered dietitian nutritionists

may use as a reference in clinical practice. In providing MNT, RDNs utilize a process that involves assessment of current diet and nutrient status, diagnosis of diet-related contributors to disease, and customized intervention to address contributors and mitigate their effects on the disease process. At each step in the nutrition care process (Fig. 11.2), the RDN draws from the conglomerate of information acquired from the patient's diet history and his/her demographic, anthropometric, and metabolic profile and from other medical information relevant to urolithiasis. RDNs have particular expertise in designing nutrition interventions that uniquely address each patient's holistic nutrition needs and integrate, as needed, nutrition recommendations prescribed for multiple comorbidities. RDNs further utilize their knowledge of nutrition and behavioral science to work with patients to develop acceptable and practical strategies for achieving the goals of the nutrition intervention. There are many examples that demonstrate favorable effects of MNT, including a recent systematic review and meta-analysis which described the potential of salt-lowering MNT provided by a RDN among patients with chronic kidney disease [58].

RDNs in the Community When needed, RDNs utilize nutrition partners and resources outside of the clinic to enhance patients' self-efficacy in managing their disease. This is especially important when time for education in the clinical encounter is limited and/or when more hands-on learning is required. For example, for a child whose dietary kidney stone risk factors include high urinary calcium excretion thought to be related to a diet high in NaCl, the RDN may refer the patient and his/her family to a local supermarket that has an RDN on staff for education on replacing processed foods, prepared meals, and salty snacks with healthier alternatives. Supermarket RDNs, also known as retail RDNs, offer customized grocery store tours and answer specific food-related questions [59]. Openings for retail RDNs are multiplying rapidly, creating new potential pathways for clinical-community nutrition care. In one store in the southeast USA, the RDN has offered for two decades a hands-on, education-based "field trip" for children ages 4–12 years. The tours aim to cultivate healthy grocery shopping habits, introduce and sample new foods, and make the link between food and health. Supermarket RDNs frequently host classes on healthy food preparation techniques and provide customer-friendly educational materials. In some cases, the clinical RDN provides a "prescription" for the child and his/her family for the retail RDN to "fill." A kidney stone-related nutrition prescription could, for example, request the grocery store RDN to address a family's specific educational needs related to diet and urolithiasis, e.g., how to shop for and prepare lower-salt meals, finding and identifying non-dairy calcium sources, preparing quick and convenient snacks based on fruits and vegetables, and creating daily menus that meet the desired clinical recommendations.

Conclusion

Diet contributes to urolithiasis in several ways (Table 11.1) but does not contribute to all kidney stones. Prior to dispensing dietary recommendations, clinicians should

use all of the biochemical and other data available to determine the appropriate nutrition intervention. In the presence of 24-hour urinary stone risk factors, specific questions about patients' diets can be asked to estimate dietary involvement (Fig. 11.1). In cases for which diet is thought to contribute to stone risk, general dietary patterns (Table 11.2) may be recommended. However, conforming to them may require (1) multiple dietary changes, some of them complex; (2) changes to how grocery shopping is done, (3) adaptations to remain consistent with cultural and family-specific food-related norms; and (4) food substitutions to accommodate special health needs. Moreover, some of the changes required may have no impact on the course of a patient's urinary stone disease. Rather than recommending wholescale dietary changes, which in a child's case likely involves buy-in and significant effort by the entire family, stone-targeted dietary recommendations may be made. These can be based on guidelines developed by medical organizations (e.g., the American Urological Association) or on specific evidence-based dietary approaches for specific urinary stone risk factors (Table 11.3). In order to avoid unnecessary dietary changes, such as those from which no reduction in stone risk is likely to occur, RDN members of the clinical team can assess patients' diets to identify linkages with urinary stone risk factors and recommend the minimal number of the most appropriate changes that alter risk. In addition, RDNs can help a child and his/her family identify practical strategies to achieve the desired goals, utilizing resources outside of the clinic and in the patient's own locale as needed.

Modern healthcare is complex. The biomedical literature is increasingly difficult to stay atop. More data than ever are available in patients' electronic health records and continues to rise exponentially, sometimes making it difficult for one provider to identify and accumulate all relevant information for each and every patient. No one provider can be expected to absorb and use all of this information, and rarely does a patient now receive care from a single provider. Multi- and interdisciplinary approaches to treating many diseases have thus emerged and, depending on the medical condition, incorporate a variety of health professionals. In any child with kidney stones, individualized treatment plans utilizing the nutrition care process provided by RDNs (Fig. 11.2) should be considered.

References

1. Taylor EN, Fung TT, Curhan GC. DASH-style diet associates with reduced risk for kidney stones. J Am Soc Nephrol. 2009;20:2253–9.
2. Prieto RM, Rodriguez A, Sanchis P, Morey M, Fiol M, Grases F, et al. Association of adherence to the Mediterranean diet with urinary factors favoring renal lithiasis: cross-sectional study of overweight individuals with metabolic syndrome. Nutrients. 2019;11:1708.
3. Leone A, Fernández-Montero A, de la Fuente-Arrillaga BS, Battezzati A, Bes-Rastrollo M. Adherence to the Mediterranean dietary pattern and incidence of nephrolithiasis in the Seguimiento Universidad de Navarra follow-up (SUN) cohort. Am J Kidney Dis. 2017;70:778–86.

4. Beara-Lasic L, Goldfarb DS. Recurrent calcium kidney stones. Clin J Am Soc Nephrol. 2019;14:1388–90.
5. Kwan MW, Wong MC, Wang HH, Liu KQ, Lee CL, Yan BP, et al. Compliance with the dietary approaches to stop hypertension (DAS) diet: a systematic review. PLoS One. 2013;8:378412.
6. Folsom AR, Parker ED, Harnack LJ. Degree of concordance with DASH diet guidelines and incidence of hypertension and fatal cardiovascular disease. Am J Hypertens. 2007;20:225–32.
7. Paula BL, Poltronieri F, Fernandes R, Retondario A, de Moraes Trindade EBS, de Vasconcelos FAG. Effects of the dietary approach to stop hypertension (DASH) diet on blood pressure, overweight and obesity in adolescents: a systematic review. Clin Nutr ESPEN. 2018;28:1–11.
8. Lee-Kwan SH, Moore LV, Blanck HM, Harris DM, Galuska D. Disparities in state-specific adult fruit and vegetable consumption – United States, 2015. MMWR Morb Mortal Wkly Rep. 2017;66:1241–7.
9. Epstein DE, Sherwood A, Smith PJ, Craighead L, Caccia C, Lin PH, et al. Determinants and consequences of adherence to the DASH diet in African American and white adults with high blood pressure: results from the ENCORE trial. J Acad Nutr Diet. 2012;112:1763–73.
10. Song Y, Lobene AJ, Wang Y, Gallant KM. The DASH diet and cardiometabolic health and chronic kidney disease: a narrative review of the evidence in East Asian countries. Nutrients. 2021;13:984.
11. Scannell N, Villani A, Mantzioris E, Swanepoel L. Understanding the self-perceived barriers and enablers toward adopting a Mediterranean diet in Australia: an application of the theory of planned behaviour framework. Int J Environ Res Public Health. 2020;17:9321.
12. Bracale R, Vaccaro CM, Coletta V, Cricelli C, Gamaleri FC, Parazzini F, Carruba M. Nutrition behavior and compliance with the Mediterranean diet pyramid recommendations: an Italian survey-based study. Eat Weight Disord. 2020;25:1789–98.
13. Cavaliere A, De Marchi E, Banterle A. Exploring the adherence to the Mediterranean diet and its relationship with individual lifestyle: the role of healthy behaviors, pro-environmental behaviors, income, and education. Nutrients. 2018;10:141.
14. Grosso G, Galvano F. Mediterranean diet adherence in children and adolescents in southern European countries. NFS J. 2016;3:13–9.
15. Rubio-López N, Llopis-González A, Picó Y, Morales-Suárez-Varela M. Dietary calcium intake and adherence to the Mediterranean diet in Spanish children: the ANIVA study. Int J Environ Public Health. 2017;14:637.
16. Grammatikopoulou MG, Daskalou E, Hatzopoulou M, Sourtzinou L, Tsigga M. Comparing diet composition and growth of children living in two limitary Greek islands (Samos and Corfu). Public Health Nutr. 2009;12:1284–9.
17. Summary Report of the Dietary Reference Intakes. National Academy of Sciences. https://www.nationalacademies.org/our-work/summary-report-of-the-dietary-reference-intakes; accessed March 20, 2021.
18. Pearle MS, Goldfarb DS, Assimos DG, Curhan G, Denu-Ciocca CJ, Matlaga BR, et al. Medical management of kidney stones: AUA guideline. J Urol. 2014;192:316–24.
19. Penniston KL, Wertheim ML, Nakadaa SY, Jhagroo RA. Factors associated with patient recall of individualized dietary recommendations for kidney stone prevention. Eur J Clin Nutr. 2016;70:1062–7.
20. Jinnette R, Narita A, Manning B, McNaughton SA, Mathers JC, Livingstone KM. Does personalized nutrition advice improve dietary intake in healthy adults? A systematic review of randomized controlled trials. Adv Nutr. 2020:nmaa144. https://doi.org/10.1093/advances/nmaa144.
21. Penniston KL, Nakada SY. Updates in the metabolic management of calcium stones. Curr Urol Rep. 2018;19:41.
22. Penniston KL. The nutrition consult for recurrent stone formers. Curr Urol Rep. 2015;16:47.
23. Trinchieri A. A rapid food screener ranks potential renal acid load of renal stone formers similarly to a diet history questionnaire. Urolithiasis. 2013;41:3–7.
24. McLean RM, Farmer VL, Nettleton A, Cameron CM, Cook NR, Campbell NRC. Assessment of dietary sodium intake using a food frequency questionnaire and 24-hour urinary sodium excretion: a systematic literature review. J Clin Hypertens (Greenwich). 2017;19:1214–30.

25. Cooper M, Simpson JR, Klutka R. Development and validation of a sodium analysis tool (SALT). Nutr J. 2020;19:55.
26. Macdonald HM, Garland A, Burr J, Strachan A, Wood AD, Jamil NA, et al. Validation of a short questionnaire for estimating dietary calcium intakes. Osteoporos Int. 2014;25:1765–73.
27. Irving SW, Rempel G, Lyman B, Sevilla WMA, Northington L, Guenter P. Pediatric nasogastric tube placement and verification: best practice recommendations from the NOVEL project. Nutr Clin Pract. 2018;33:921–7.
28. Lindell A, Denneberg T, Edholm E, Jeppsson JO. The effect of sodium intake on cystinuria with and without tiopronin treatment. Nephron. 1995;71:407–15.
29. Siener R, Bitterlich N, Birwé H, Hesse A. The impact of diet on urinary risk factors for cystine stone formation. Nutrients. 2021;13:528.
30. Rodman JS, Blackburn P, Williams JJ, Brown A, Pospischil MA, Peterson CM. The effect of dietary protein on cystine excretion in patients with cystinuria. Clin Nephrol. 1984;22:273–8.
31. Mahmoud AAH, Rizk T, El-Bakri NK, Riaz M, Dannawi S, Al TM. Incidence of kidney stones with topiramate treatment in pediatric patients. Epilepsia. 2011;52:1890–3.
32. Jhagroo RA, Wertheim ML, Penniston KL. Alkali replacement raises urinary citrate excretion in patients with topiramate-induced hypocitraturia. Br J Clin Pharmacol. 2016;81:131–6.
33. Sondhi V, Agarwala A, Pandey RM, Chakrabarty B, Jauhari P, Lodha R, et al. Efficacy of ketogenic diet, modified Atkins diet, and low glycemic index therapy diet among children with drug-resistant epilepsy: a randomized clinical trial. JAMA Pediatr. 2020;174:944–51.
34. Dahl WJ, Niebergal EJ, Owen RJ. Implications of fiber inadequacy in the ketogenic diet: a case study. ICAN. 2011;3:288–90.
35. Lindefeldt M, Eng A, Darban H, Bjerkner A, Zetterström CK, Allander T, et al. The ketogenic diet influences taxonomic and functional composition of the gut microbiota in children with severe epilepsy. npj Biofilms Microbiomes. 2019;5:5.
36. Miller AW, Choy D, Penniston KL, Lange D. Inhibition of urinary stone disease by a multispecies bacterial network ensures healthy oxalate homeostasis. Kidney Int. 2019;96:180–8.
37. Christodoulides SS, Neal EG, Fitzsimmons G, Chaffe HM, Jeanes YM, Aitkenhead H, Cross JH. The effect of the classical and medium chain triglyceride ketogenic diet on vitamin and mineral levels. J Hum Nutr Diet. 2012;25:16–26.
38. Su D, Li J, Guo M, Li Y, Ma S. Clinical analysis of electrolyte disorders in patients with diabetic detoacidosis. Clin Lab. 2021;67:1.
39. Thavamani A, Salem I, Sferra TJ, Sankararaman S. Impact of altered gut microbiota and its metabolites in cystic fibrosis. Meta. 2021;11:123.
40. Li L, Somerset S. Digestive system dysfunction in cystic fibrosis: challenges for nutrition therapy. Dig Liver Dis. 2014;46:865–74.
41. Hourigan SK, Ahn M, Gibson KM, Pérez-Losada M, Felix G, Weidner M, et al. Fecal transplant in children with *clostridioides difficile* gives sustained reduction in antimicrobial resistance and potential pathogen burden. Open Forum Infect Dis. 2019;6:ofz379.
42. Gupta S, Mullish BH, Allegretti JR. Fecal microbiota transplantation: the evolving risk landscape. Am J Gastroenterol. 2021;116:647–56.
43. Yadav D, Khanna S. Safety of fecal microbiota transplantation for *Clostridioides difficile* infection focusing on pathobionts and SARS-CoV-2. Ther Adv Gastroenterol. 2021;14:17562848211009694.
44. Borghi L, Nouvenne A, Meschi T. Probiotics and dietary manipulations in calcium oxalate nephrolithiasis: two sides of the same coin? Kidney Int. 2010;78:1063–5.
45. Penniston KL, Palmer EA, Medenwald RJ, Johnson SN, John LM, Beshensky DJ, Saeed IA. Oxalate content of enteral nutrition formulas. J Pediatr Gastroentrol Nutr. 2019;69:e135–40.
46. Johnson EK, Lightdale JR, Nelson CP. Risk factors for urolithiasis in gastrostomy tube fed children: a case-control study. Pediatrics. 2013;132:e167–74.
47. Edvardsson V. Urolithiasis in children. In: Avner E, Harmon W, Niaudet P, Yoshikawa N, Emma F, Goldstein S, editors. Pediatric nephrology. Berlin, Heidelberg: Springer; 2016. https://doi.org/10.1007/978-3-662-43596-0_53. accessed December 13, 2020.

48. Bianchi L, Gaiani F, Bizzarri B, Minelli R, Cortegoso Valdivia P, Leandro G, et al. Renal lithiasis and inflammatory bowel diseases, an update on pediatric population. Acta Biomed. 2018;89:76–80.
49. Zuckerman JM, Assimos DG. Hypocitraturia: pathophysiology and medical management. Rev Urol. 2009;11:134–44.
50. Ngo TC, Assimos DG. Uric acid nephrolithiasis: recent progress and future directions. Rev Urol. 2007;9:17–27.
51. Mutalib M. Renal involvement in paediatric inflammatory bowel disease. Pediatr Nephrol. 2021;36:279–85.
52. Chawner LR, Blundell-Birtill P, Hetherington MM. Among children and adults with developmental disorders: a systematic review. J Autism Dev Disord. 2019;49:3504–25.
53. Cermak SA, Curtin C, Bandini LG. Food selectivity and sensory sensitivity in children with autism spectrum disorders. J Am Diet Assoc. 2010;110:238–46.
54. Chung LMY, Law QPS, Fong SSM. Using physical food transformation to enhance the sensory approval of children with autism spectrum disorders for consuming fruits and vegetables. J Altern Complement Med. 2020;26:1074–9.
55. Konstantynowicz J, Porowski T, Zoch-Zwierz W, Wasilewska J, Kadziela-Olech H, Kulak W, et al. A potential pathogenic role of oxalate in autism. Eur J Paediatr Neurol. 2012;16:485–91.
56. Good P. Do salt cravings in children with autistic disorders reveal low blood sodium depleting brain taurine and glutamine? Med Hypotheses. 2011;77:1015–21.
57. Rhodes KS, Kirkpatrick C. The value of incorporating medical nutrition therapy by a registered dietitian nutritionist in clinical practice. J Clin Lipidol. 2018;12:1109–10.
58. Rozga M, Burrowes JD, Byham-Gray LD, Handu D. Effects of sodium-specific medical nutrition therapy from a registered dietitian nutritionist in individuals with chronic kidney disease: an evidence analysis center systematic review and meta-analysis. J Acad Nutr Diet. 2021; S2212-2672:227-236
59. Yoder AD, Proaño GV, Handu D. Retail nutrition programs and outcomes: an evidence analysis center scoping review. J Acad Nutr Diet. 2020; S2212-2672:31201-31206
60. Prezioso D, Strazzullo P, Lotti T, Bianchi G, Borghi L, Caione P, et al. Dietary treatment of urinary risk factors for renal stone formation. A review of CLU working group. Arch Ital Urol Androl. 2015;87:105–20.
61. Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, Straub KT. EQU guidelines on diagnosis and conservative management of urolithiasis. Eur Urol. 2016;69:468–74.

Chapter 12
Mechanisms and Catalysts Related to Achieving Lifestyle Changes in Pediatric Kidney Stone Prevention

Cassandra M. Vanderwall

Introduction

Independent of age and stage of life, lifestyle change requires an integration of physical, mental, emotional, and social behaviors. The registered dietitian nutritionist (RDN) is well prepared to support pediatric patients with urolithiasis achieve lifestyle changes that will foster stone prevention. Facets of this patient- and family-centered care includes motivational interviewing (MI) and shared decision making. A thorough assessment is necessary prior to engaging the patient and their caregivers in change. This assessment would include a focus on medical and surgical histories, food and nutrition habits, physical activity, mental well-being, and social determinants of health. During the assessment, it is vital that the clinician maintains a compassionate learner's posture that is non-judging and considerate of a patient and family's independent needs. Assessment is critical because behavior change is two-pronged and includes efforts to achieve and maintain a new habit [1].

Self-Awareness and Readiness to Change

The transtheoretical model offers comprehensive, theoretical scaffolding for determining readiness to change and promoting individualized nutrition interventions [1, 2]. The stages of change include [2]:

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1. **Pre-Contemplation**: In this first stage, individuals do not recognize the need for change and are not considering change within the next six months. The goal is to guide the individual into a discussion on the benefits of change and to explore hurdles for the patient and family.
2. **Contemplation**: In the second stage, individuals are considering change and intend to change within the next 6 months; however, ambivalence may remain. It is beneficial for the clinical team to support the pediatric patient in their change talk and lead them to the resources that promote the change.
3. **Preparation:** In this pivotal stage, patients are ready to attempt change and take action within the next month. Patients are supported in the change by helping them to identify small steps towards the change, and dialog on how this change can support improvements in their health.
4. **Action:** Patients in this stage have embarked on a change within the last 6 months and intend to sustain it. The clinician can be supportive by helping the patient identify the benefits of change, sources of support and strategies for sustaining the change.
5. **Maintenance:** Patients have now sustained their behavior change for more than 6 months and desire to maintain the change. Clinicians can be most helpful by preventing relapse by celebrating this success and identifying present or anticipated hurdles for maintaining the change.
6. **Termination:** This final stage is rarely achieved. In this stage, people have no desire to return to their previous behaviors or habits and are confident that they will not wane. The role of the clinician in this stage is comparable to the maintenance stage but also can be to support the identification of next steps or future change.

Individuals may move forward and backward throughout the stages based on their readiness to change a specific behavior [1]. Their stage of change may also differ for different habits. For example, the patient may have championed drinking water and reducing sugar-sweetened beverages (Maintenance) but remains contemplative in regard to reducing excess salt, or sodium, in their meals and snacks.

Motivation to change behaviors is not synonymous with motivation to engage in a health-related intervention. Adherence difficulties are encountered with patients who engage in lifestyle change with little or no awareness of the problem that needs to be changed, or the rationale for change [3]. These patients may include those who chronically underestimate their sodium, calcium or fluid intake, or lack the social support from their caregivers to achieve change. Our pediatric patients who do not adhere may show ambivalence about whether the problematic behavior really needs to change, since the perceived cost may not yet outweigh the benefits they are stalled in their change [4].

Motivational Interviewing

Motivational interviewing (MI) is an evidence-based counseling approach to behavior change which is described by its founders Miller and Rollnick (2013) as a "c*ollaborative, goal-oriented style of communication with particular attention to the*

language of change. It is designed to strengthen personal motivation for and commitment to a specific goal by eliciting and exploring the person's own reasons for change within an atmosphere of acceptance and compassion." Key facets include guiding versus directing and empowering individuals in a respectful and curious manner. MI can be especially beneficial with patients who are highly ambivalent about change, have low confidence and desire for change and do not consider that change to be important [5]. Core skills of MI are referred to as OARS, which is an acronym for strategies that attend to the language of change in the exchange of information:

- Open-ended questioning: Questions that guide individuals to reflect and consider the meaning of change.
- Affirmation: Recognition and confirmation of effort and strengths towards change that foster the patient's consideration for change.
- Reflection: Active listening strategy where the listener repeats and rephrases what they here to offer a deeper perspective.
- Summarizing: Another active listening strategy that confirms shared understanding and reinforces key points from the dialog [5].

These OARS are utilized to progress through the fundamental process of MI, permitting patients to move in a bi-directional fashion through the process:

- Engaging: Building rapport and establishing a productive relationship through active listening.
- Focusing: Can be described as shared decision making, where the clinician, patient, and family agree upon a shared agenda and purpose.
- Evoking: The process of using active listening and open-ended questions to draw a person to explore and identify their "why," or rationale for change.
- Planning: In this phase of the process, the clinician and patient explore how the change will be achieved. This is an ideal time for individualized education and training as is necessary to achieve the targeted change [5].

The motivational interviewing skill set when used alongside additional psychosocial metrics can permit a robust tailoring of education and counseling to improve health. Change will originate and be sustained within the patient and not the clinician. Clinicians who use motivational interviewing are tour guides for patients and their families who can unbiasedly help them focus on their health parameters as well as on their readiness to change, internal motivation, and competing demands that may pose hurdles to engagement and change.

Incorporating Psychosocial Metrics into Practice

The ability to achieve and maintain health behavior changes, such as healthful eating habits, may be compromised by poor psychosocial health, particularly lower self-efficacy or underlying mental illness [6]. A healthcare environment that supports an individual's autonomy, competence, and self-efficacy can reliably facilitate

change and foster greater internalization and integration of self-concepts, such as readiness to change a health behavior [7]. Psychosocial barriers are common reasons for not engaging in health-related changes [6, 7]. Motivation for taking action varies from individual to individual and family to family; the literature supports the need for healthcare providers to explore these psychosocial constructs and health-related values to identify the patient's and the caregivers' personal and health-related priorities [5, 8, 9], Clinicians have the opportunity to incorporate psychosocial assessment tools or screeners into their practice to promote an environment that's conducive to change. Explore accepted validated tools available to you and your practice that assess depression, anxiety, self-harm behaviors and/or eating disorders in pediatric populations. Examples of these tools and guidance for their use are available from organizations such as the American Academy of Pediatrics and the US Preventive Services Task Force.

Individualizing recommendations in a patient- and family-centered discussion focuses on health behaviors to prevent stone formation and reoccurrence, which may be more appropriate to facilitate education than relying on general education. The use of visual tools, such as food models, measuring utensils, or food labels may support the assessment and intervention steps of the change process. Readiness and confidence rulers may facilitate positive dialog between clinicians, patients, and caregivers and provide insight into future motivation and adherence [10–12]. Use of these tools will likely result in the identification of issues, competing demands, beliefs, attitudes, or behaviors earlier in the process, increasing the opportunity for discussion around these variables. This will enable use of strategies to overcome potential barriers to change efforts. These tools also can help facilitate discussions about influences on perceptions of both present health and change, which may limit a person's readiness to engage in healthful behaviors. These discussions may permit clinicians to explore the full range of consequences of change and lack of change, including consequences and detriments to both mental and physical well-being.

Summary

These understandings lay the groundwork for incorporation of MI, shared decision making, and the assessment of psychosocial variables in clinical practice to identify the patient's readiness to change, misperceptions related to change and to individualize care, education, and counseling to foster change and reduce subsequent risk that may result from unawareness or lack of change. The motivational interviewing skillset has potential to greatly influence healthcare by providing a framework for more constructive conversations about health-related priorities in the primary care and specialty care settings and in the community. It is also vital to understand that while it is important for parents and caregivers to have accurate perceptions of their child's health, correct observations may not translate into action. Interventions are most effective when they are individualized using facets of motivational

interviewing [5–10]. Therefore, clinicians have the potential to be key figures in the change process by facilitating an environment conducive to self-assessment, self-discovery, and self-efficacy, which could make efforts towards health behavior change efforts more effective and sustainable.

References

1. Prochaska JO, Norcross JC, Fowler JL, Follick MJ, Abrams DB. Attendance and outcome in a work site weight control program: processes and stages of change as process and predictor variables. Addict Behav. 1992;17(1):35–45.
2. Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment; Department of Health and Human Services. Enhancing motivation for change in substance abuse treatment. https://www.ncbi.nlm.nih.gov/books/NBK64967/pdf/Bookshelf_NBK64967.pdf. Updated 2012.
3. Pietrabissa G, Manzoni GM, Corti S, Vegliante N, Molinari E, Castelnuovo G. Addressing motivation in global obesity treatment: a new challenge for clinical psychology. Front Psychol. 2012;3:317.
4. McEvoy PM, Nathan P. Perceived costs and benefits of behavioral change: reconsidering the value of ambivalence for psychotherapy outcomes. J Clin Psychol. 2007;63(12):1217–29.
5. Motivational Interviewing Network of Trainers, MINT. MI Guidance Documents. 2019. https://motivationalinterviewing.org/mi-guidance-documents.
6. Gillespie J, Midmore C, Hoeflich J, Ness C, Ballard P, Stewart L. Parents as the start of the solution: a social marketing approach to understanding triggers and barriers to entering a childhood weight management service. J Hum Nutr Diet. 2015;28(Suppl 1):83–92.
7. Stewart L, Chapple J, Hughes AR, Poustie V, Reilly JJ. Parents' journey through treatment for their child's obesity: a qualitative study. Arch Dis Child. 2008;93(1):35–9.
8. Miller WR, Rollnick S. Motivational interviewing: helping people to change. 3rd ed. Guilford Press; 2013.
9. Dawson AM, Brown DA, Cox A, et al. Using motivational interviewing for weight feedback to parents of young children. J Paediatr Child Health. 2014;50(6):461–70.
10. Schwarzer R. Social-cognitive factors in changing health-related behaviors. Curr Dir Psychol Sci. 2001;10(2):47.
11. Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and Well-being. Am Psychol. 2000;55(1):68–78.
12. Readiness Ruler. Case Western Reserve University, Center for Evidence-Based Practices website. https://www.centerforebp.case.edu/resources/tools/readiness-ruler

Chapter 13
The Role of the Multidisciplinary Team in Pediatric Nephrolithiasis

Neil J. Paloian

Introduction

Children with kidney stone disease require long-term medical support as they are at high risk of having an identifiable metabolic abnormality and are at high risk for recurrence of stone events [1, 2]. Caring for these children in a comprehensive fashion cannot be reasonably performed by a single provider given their complex medical, surgical, and dietary needs. By combining resources and skillsets into a unified clinic team, pediatric nephrolithiasis patients can receive optimal care in an efficient and cost-effective manner.

The Multidisciplinary Clinic

A multidisciplinary clinic can have different definitions depending on the clinical environment and institution, but the general concept of a multidisciplinary clinic applies anytime a group of healthcare providers collaborate to deliver efficient care and manage complex medical conditions [3]. There is no strict requirement regarding what type or how many providers are present in a multidisciplinary clinic, but the providers will have expertise in different areas of medical and/or surgical care. This can include, but is not limited to, physicians, nurse practitioners, physician assistants, nurses, dieticians, physical/occupational/speech therapists, genetic counselors, pharmacists, and psychologists [4, 5].

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The multidisciplinary clinic likely has its origins in the medical home concept. This term was first used in 1967 by the American Academy of Pediatrics (AAP) in reference to the acknowledged challenges in caring for children with complex and chronic medial illness [6]. At that time, it was becoming obvious that care for these children was often fractured amongst specialists who practiced in separate locations and had little communication between themselves and the various members of the medical team. The suggestion made by the AAP was that all records should be centralized and coordinated in a meaningful way as this prevents both errors and redundancy in medical care. Initially this task was assigned to the pediatrician or family physician, but later shifted to include a care team made up of a variety of healthcare members that were familiar with these medically complex children and their unique care coordination [7]. From this model came the concept of the specialty care team, which relocates the overall care management from primary care to the specialty setting. This care team, like the modern multidisciplinary clinic, involves multiple specialists from across different medical fields and backgrounds who all contribute to the care of the patient with chronic illness and have a responsibility to communicating regularly [5]. The overall goal of these specialty care teams is to improve health outcomes while reducing costs; when executed correctly with the committed participation of medical specialists, this model has proven to be very effective in meeting these objectives [8].

Benefits of Multidisciplinary Care

The medical field continues to evolve and over time patient care has become much more complex [9]. This has led to significant improvements in healthcare outcomes, but has also created a healthcare delivery system that has increased inefficiencies and waste [10]. While the solution to this problem is not simple or straightforward, the multidisciplinary clinic has emerged as one part of the answer to this problem.

There are several benefits of utilizing a multidisciplinary clinic that make it an attractive option for many types of chronic medical care. One of these benefits is the improvement in care coordination. Patients with complex medical conditions often see multiple medical providers as part of their routine evaluations and treatment; though necessary, this leads to fragmentation of care [11]. This division of care produces avoidable patient hardships and medical complications when providers and health systems cannot communicate easily and effectively. When all providers, team members, and resources are incorporated into the same physical location and the same health system, care coordination is much more successful [12].

Another important component of improved care coordination is the potential for cost savings. This is especially important given the global concern for rapidly increasing healthcare costs. Multiple models of multidisciplinary care have noted cost savings when compared to traditional care examples. This has been noted in countries across the world with very different reimbursement styles [13–15]**.** Additionally, the financial benefits of these multidisciplinary systems have been

well defined in many types of medical practices including diabetes, arthritis, and cardiology, just to name a few [16–18].

An additional benefit of the multidisciplinary care team is the improvement in the patient and family experience. It seems instinctive that both patients and their caregivers would appreciate the chance to visit with all of their providers together coordinated with all necessary education, imaging, and testing during the same encounter. Indeed, when surveyed, patients themselves have found enhanced satisfaction, improved access to care, and superior adherence to recommended treatments following transition to a multidisciplinary care system [19, 20]. Similarly, parents of children who are cared for in a multidisciplinary clinic have described improved navigation through the clinic space, more efficient time spent in clinic, and overall high levels of satisfaction with these approaches.

The most important advantage of the multidisciplinary clinic is to better patient care. Multidisciplinary care teams have been developed for almost all types of chronic disease and overwhelmingly they have been shown to enhance patient outcomes. Examples of this include in chronic pain management where disease education was improved, in brain injury patients where earlier gain in neurologic function has been noted, and in colorectal cancer where the use of multidisciplinary teams has shown an increase in patient survival [21–23]. This also holds true for pediatrics multidisciplinary care teams; children with complex sleep apnea show improved sleep disordered breathing in a multidisciplinary clinic, obese children and adolescent have greater reduction in BMI when enrolled in a multidisciplinary weight loss program, and pediatric intestinal failure patients in a multidisciplinary rehab program have fewer septic episodes and decreased mortality [24–26]. These examples listed demonstrate only a small fraction of the patient outcomes benefits of the multidisciplinary clinic teams that are being utilized or created in almost every medical specialty.

One value of the multidisciplinary clinic that may be overlooked initially is the ability to generate easier research projects and further medical knowledge. By combining all patients with a similar underlying disease into a single medical home, it is more straightforward to see patterns emerge in care, to retrospectively analyze data as part of the standard of care practice, and easier to implement, consent, and follow patients prospectively. While this may be an ancillary benefit of the clinic, it does further support the academic mission of most children's hospitals and medical schools. While the patients may not benefit directly, all children with stone disease will be able to take advantage of further research in the field, which is vitally needed.

As the kidney stone disease is often managed jointly by urology and nephrology, it is a condition that lends itself naturally to a multidisciplinary clinic. Many academic centers and children's hospitals have multidisciplinary pediatric kidney stones clinics in place. At the time of the writing of this textbook, one center has formally assessed their experience. The members of the pediatric kidney stone clinic at the Cincinnati Children's Hospital Medical Center effectively outlined the benefits unique to running a multidisciplinary clinic focused on pediatric nephrolithiasis. Two hundred sixty-four patients with kidney stone disease evaluated in the clinic between 2014 and 2018 were included in this retrospective cohort study.

Several noteworthy outcome improvements were identified in this population including decreased frequency of surgical procedures, decreased emergency department (ED) visits, and less use of ionizing computerized tomography (CT) scans after enrollment in the clinic [27]. This data strongly suggests that a pediatric multidisciplinary kidney stone clinic is a meaningful approach to improve care coordination and advance clinical outcomes in this population.

Components of a Successful Kidney Stone Clinic

With rising prevalence of pediatric stone disease and the known benefits of multidisciplinary clinics, it is reasonable that the majority of children with nephrolithiasis receive their care in a dedicated pediatric kidney stone clinic. Establishing a pediatric kidney stone clinic can be a significant undertaking and begins with identifying the appropriate participants to be involved in the clinic. While all pediatric kidney stone clinics may be structured uniquely to best fit their local needs, below is an outline that can be utilized to ensure a productive and effective multidisciplinary clinic. It is important that whomever is chosen to participate maintain consistency in the clinic to gain mastery of their role both from a medical and logistical standpoint.

One of the key members of the pediatric kidney stone clinic is the pediatric urologist. Within the scope of this clinic, it is the responsibility of the urologist to monitor for the development or passage of new stones, observe the growth/passage/resolution of established stones, monitor for the resolution of pelviectasis and/or ureterectasis associated with an acute stone event, and follow-up on any postoperative needs of any child requiring surgical stone extraction. The urologist should dictate the modality and timing of the necessary follow-up imaging, which often can be coordinated immediately prior to the stone clinic. As no procedures occur within the context of the clinic (excluding interpretation of imaging studies), it is reasonable that this role could be filled by an advanced practice provider (APP) such as a nurse practitioner or physician's assistant. In this case, the APP would require an excellent understanding of which patients may necessitate surgical intervention and they must have efficient communication with a urologist should the child have need of operative stone removal.

A pediatric nephrologist is also a requirement in any pediatric stone clinic. The nephrologist is tasked with ordering any necessary laboratory testing. Blood and spot urine samples may be able to be obtained at an on-site laboratory. If the patient requires any 24-hour urine testing completed, all arrangements should be made to ensure that results of the test are available to the provider at the time of the appointment. This should be anticipated prior to the clinic date recognizing that the process of receiving finalized test results is a lengthy process: the patient will need access to collection materials, must complete the test in a timely manner, the urine sample must be transported to the laboratory for analysis, and finally the results need to be transmitted to the clinic or provider. After a thorough history and physical and

analysis of all laboratories obtained, the nephrologist can then make an assessment of the risk factors that led to the underlying stone. With that information, the nephrologist can formulate a dietary and/or medication plan to lessen the probability of forming future stones and can follow and adjust this plan over time as needed. As with the urologist, this role potentially can be fulfilled by a pediatric nephrology APP who is well versed in risk factor identification and stone prevention.

As noted previously, many of the risk factors for pediatric stone disease involve the patient's dietary choices and many treatments involve nutritional modifications. As such, it is valuable to have a registered dietician (RD) actively participating in the stone clinic. The RD should have extensive nephrology/urology training and be able to procure a thorough dietary history with attention to nutritional risk factors specific to stone disease. Additionally, they should be proficient in interpretation of metabolic studies including 24-h urine samples and be able to devise a comprehensive dietetic treatment plan, which is often the most vital component of stone prevention. The RD should be familiar with a broad range of nutrition regimens in children of all ages and neurodevelopmental abilities which should include formula (infantile, juvenile, adult, and specialty formulas), specialty diets (ketogenic, vegan, and gluten-free diets), and nuances of certain age ranges (i.e., toddler or teenager diets). It is critical that the dietician be adept at working with both the child and parents, as often the child with stones has limited control over their dietary intake.

A highly functional multidisciplinary pediatric stone clinic requires specific nursing skills to operate properly. Often this will be implemented by a registered nurse (RN) who possesses a strong background in either pediatric urology or pediatric nephrology nursing. The role of the RN in this clinic is vital and includes proper identification and triaging of patients, coordination of appointments and imaging studies, and the arrangement of all laboratory testing. This includes specialty lab testing such as 24-hour urine stone risk profiles, which is a test unique to stone disease that is only offered by certain specialty clinical laboratories. Understanding the nuances of ordering and obtaining this test correctly is vital as it is the most important tool the nephrologist has in their evaluation and treatment plan of the child with stone disease. Additionally, the RN must have excellent communication skills as the lead coordinator of the providers and as the primary correspondent to the patient and family for all pre- and post-clinic needs.

As the underlying etiology of stone disease in children becomes better understood, it is apparent that up to 50% of pediatric patients with nephrolithiasis have an identifiable monogenic cause of their kidney stones [28]. Therefore, it is very advantageous to have a geneticist involved in the pediatric kidney stone clinic who is familiar with genetic causes of nephrolithiasis and disorders of systemic mineral homeostasis. It is the responsibility of the geneticist to identify the proper genetic testing in the appropriate patients and interpret those tests in the context of determining a final diagnosis. Including an expert in this field is critical as genetic testing results can be very difficult to decipher and should be performed by someone who has a mastery in the field. Improper analysis of variants of uncertain significance or misunderstandings of disease inheritance can lead to misdiagnosis and incorrect treatments. In addition to having a skilled provider to interpret genetic testing, it is

equally important to work with a genetic counselor who is well versed in the logistics of obtaining this very specialized testing, which often requires complex insurance preapprovals and other unique logistical considerations. A trained genetic counselor is also capable of obtaining detailed pedigrees as part of the diagnostic evaluation and is knowledgeable in reviewing inheritance of confirmed diseases in respect to family planning with patients and their parents. The role of the geneticist and genetic counselor in the pediatric stone clinic is most beneficial around the time of initial evaluation and diagnosis; therefore, it may not be necessary to have them physically in the clinic space, but they should be able to see the patients as needed whenever there is concern for a genetic cause of stones. Since they might not be consistent in the clinic space, it is important to have a dedicated genetics team who excels in the evaluation of these children with nephrolithiasis.

The pediatric radiologist is another specialty member of the team who is likely not present in the clinic. It is very valuable to work with a radiologist who is fellowship trained in pediatric radiology and to be able to work with them in real time as providers are seeing patients in the clinic who may have had radiographic studies obtained just prior to their clinic appointment. Additionally, the pediatric radiologist should be comfortable using and interpreting ultrasound images for the evaluation of stone disease as ultrasonography is the preferred imaging modality in pediatrics, unlike in adult medicine where computerized tomography scans (CT) are the gold standard [29].

One underrecognized participant in the multidisciplinary pediatric kidney stone clinic is the learner. Medical students, pediatrics and urology residents, and pediatric nephrology and urology fellows can all benefit greatly from involvement in this specialty clinic. If properly executed, the pediatric stone clinic can serve as a model example of multidisciplinary care to medical students. Additionally, residents or fellows who are fine-tuning their skills prior to practicing on their own, have the chance to learn from experts in the field by participating in the care of relatively rare patients [30]. Fortunately, involving learners in a multidisciplinary clinic does not hinder patient care and does not obstruct the workflow of the clinic [31].

Another component of the multidisciplinary pediatric kidney stone clinic that might not be readily apparent is the adult medical and surgical counterparts who will care for the patients as they age out of the pediatric practice. Stone disease can be considered a lifelong illness as any patient who forms a stone is at some level of risk for forming a subsequent stone and will likely require ongoing follow-up throughout their lifetime. With this in mind, it is important to transition their care to providers who are well versed in adult nephrolithiasis management. The details of this will vary significantly based on the institution and the region, but it is very important to understand where these patients will get their ongoing care and to have a dependable relationship with these providers. It is clear that the transition period during adolescence for children with chronic disease is a risky time, significant possibility of deterioration of the patient's health [32]. Ideally, a uniform transition protocol can be established where the pediatric patients are seamlessly integrated into the adult stone clinic when they are of the appropriate age. If logistic barriers prevent this or if a suitable adult nephrolithiasis clinic does not exist in the

geographic area, the pediatric kidney stone clinic should be aware of community nephrologists and urologists who would be able to successfully provide ongoing care.

Workflow of a Pediatric Kidney Stone Clinic

Making sure that a multidisciplinary clinic functions efficiently is just as critical as assembling a high-quality team of participants. Each clinic and institution will need to create a clinic workflow that maximizes their physical space and available resources, but there are certain logistical strategies that can help ensure that the clinic runs as effectively as possible.

Effective preparation for a pediatric kidney stone clinic is critical in making sure that the clinic is both beneficial to the patient and family as well as an efficient use of the providers' time. This will typically be performed by the clinic nurse, though it can vary from institution to institution. Most of the preparatory work involves ensuring that all necessary testing is completed and available for review at the time of the clinic. The primary laboratory test that must be completed prior to the clinic time is the 24-h urine stone profile. The urine collection kits often come from a centralized lab and need to be mailed to families. Additionally, due to the nature of the test collection, the child cannot be in school or busy with multiple activities outside the home; a date that works for the urine collection may require waiting weeks until the family's schedule allows. The test needs to be mailed back to the central lab. Finally, this complex metabolic test needs to be processed and results finalized. This test can take weeks or months to complete from start to finish and therefore it is imperative that the clinic preparations take this into account.

Clinic planning will also involve making sure that all radiology needs are taken care of for the upcoming patient encounter in the kidney stone clinic. Images may be obtained at outside facilities, either when the patient presents for acute evaluation at their local hospital or because logistics or insurance dictate that the studies should be completed at a specific medical center. In these cases, it is important to have all radiology reports and images transmitted to the clinic ahead of time, so that they can be reviewed by the providers prior to and/or with the clinic visit. If radiology studies are needed on the day of the clinic, this must be scheduled far enough in advance to ensure they can be timed appropriately with the child's clinic visit.

Ideally, all of the pediatric stone clinic providers are able to meet ahead of the clinic to discuss in detail the upcoming clinic. This is an excellent time for the providers to review the child's clinical history and available studies. The providers can then collectively determine which patients require further laboratory or imaging testing. Additionally, this is an ideal time to determine which providers will be evaluating which patients during the clinic visit. Depending on certain circumstances, one of the team members may not need to participate in the visit. For instance, if the patient was recently assessed by urology for an acute issue, the urologist may not need to be involved in this particular patient's upcoming visit. Alternatively, if

pre-clinic planning reveals that a patient's urine stone risk profile is suggestive of excellent compliance to the prescribed dietary changes, that patient may not need to physically meet with the dietician for that encounter. If there are multiple members of a specialty participating from a division, this is also an excellent opportunity to designate who will be seeing each patient during the clinic visit; this ensures a more efficient clinic where all providers know their roles ahead of time. As telemedicine clinic visits are increasing in frequency over time, it can also be determined if any patients are appropriate for evaluation via telehealth.

The flow of the clinic itself should be determined by the providers ahead of time. This ensures that everyone's time is used efficiently and to make sure that the patients are not waiting unnecessarily before or between visits from the different providers. It should be decided prior to the clinic which providers will see which patients, and in what order they will evaluate them. In addition, it should be determined if multiple providers will see patients together or if they will be seen separately. Separate patient evaluations provide more flexibility to the clinic schedule while combined patient evaluation with multiple providers in the room ensures that all participants (including the family and patient) are in clear understanding of the final plan. If visits are performed separately, it is imperative that the different specialists communicate promptly after each visit is concluded. Ideally, the clinic workroom is physically large enough to accommodate all of the providers during the length of the clinic. This also helps to make certain that communication is easy and efficient.

Conclusion

Multidisciplinary clinical care offers many advantages to the providers participating as well as the patients and their families. For this reason, multidisciplinary clinics are being created for the treatment of almost all types of medical ailments. Pediatric kidney stone disease is an excellent example of care that is likely to be enhanced with a multidisciplinary clinic. Nephrolithiasis requires optimization of medical, nutritional, and surgical management. In children, this level of care requires treatment from experts in the field; however, even with the most experienced clinicians, care overall is significantly enhanced by combining all resources into a single clinic. With the correct participants and an optimized workflow, the pediatric multidisciplinary kidney stone clinic is an excellent model for how to deliver optimal care for patients.

References

1. DeFoor W, Asplin J, Jackson E, Jackson C, Reddy P, Sheldon C, et al. Urinary metabolic evaluations in normal and stone forming children. J Urol. 2006;176(4S):1793–6.
2. Tasian GE, Kabarriti AE, Kalmus A, Furth SL. Kidney stone recurrence among children and adolescents. J Urol. 2017;197(1):246–52.

3. Tyler KH, Haverkos BM, Hastings J, Hu E, Philips R, Gru AA, et al. The role of an integrated multidisciplinary clinic in the management of patients with cutaneous lymphoma. Front Oncol. 2015;5:136.
4. Austin B, Wagner E, Hindmarsh M, Davis C. Elements of effective chronic care: a model for optimizing outcomes for the chronically ill. Epilepsy Behav. 2000;1(4):S15–20.
5. Wagner EH. The role of patient care teams in chronic disease management. BMJ. 2000;320(7234):569–72.
6. Sia C, Tonniges TF, Osterhus E, Taba S. History of the medical home concept. Pediatrics. 2004;113(5 Suppl):1473–8.
7. Wagner EH, Austin BT, Von Korff M. Organizing care for patients with chronic illness. Milbank Q. 1996;74(4):511–44.
8. Taylor D, Lahey M. Increasing the involvement of specialist physicians in chronic disease management. J Health Serv Res Policy. 2008;13(Suppl 1):52–6.
9. Braithwaite J. Changing how we think about healthcare improvement. BMJ. 2018;361:k2014.
10. Berwick DM, Hackbarth AD. Eliminating waste in US health care. JAMA. 2012; 307(14):1513–6.
11. Shrank WH, Rogstad TL, Parekh N. Waste in the US health care system: estimated costs and potential for savings. JAMA. 2019;322(15):1501–9.
12. Grosse SD, Schechter MS, Kulkarni R, Lloyd-Puryear MA, Strickland B, Trevathan E. Models of comprehensive multidisciplinary care for individuals in the United States with genetic disorders. Pediatrics. 2009;123(1):407–12.
13. Voong KR, Liang OS, Dugan P, Torto D, Padula WV, Senter JP, et al. Thoracic oncology multidisciplinary clinic reduces unnecessary health care expenditure used in the workup of patients with non-small-cell lung cancer. Clin Lung Cancer. 2019;20(4):e430–e41.
14. Chen YR, Yang Y, Wang SC, Chou WY, Chiu PF, Lin CY, et al. Multidisciplinary care improves clinical outcome and reduces medical costs for pre-end-stage renal disease in Taiwan. Nephrology (Carlton). 2014;19(11):699–707.
15. Stone CJL, Johnson AP, Robinson D, Katyukha A, Egan R, Linton S, et al. Health resource and cost savings achieved in a multidisciplinary lung cancer clinic. Curr Oncol. 2021;28(3):1681–95.
16. Sosa-Rubi SG, Contreras-Loya D, Pedraza-Arizmendi D, Chivardi-Moreno C, Alarid-Escudero F, Lopez-Ridaura R, et al. Cost-effectiveness analysis of a multidisciplinary healthcare model for patients with type-2 diabetes implemented in the public sector in Mexico: a quasi-experimental, retrospective evaluation. Diabetes Res Clin Pract. 2020;167:108336.
17. Nisar MK. Early arthritis clinic is cost-effective, improves outcomes and reduces biologic use. Clin Rheumatol. 2019;38(6):1555–60.
18. Thrysoee L, Kidholm K, Rasmussen MK, Brandes A. Cost analysis of a dedicated outpatient clinic in patients with newly diagnosed atrial fibrillation. J Cardiovasc Nurs. 2021;
19. Hoffman C, Yuan M, Boyke A, Perera I, Rabbin-Birnbaum C, O'Connor A, et al. Impact of a multidisciplinary craniofacial clinic for patients with craniofacial syndromes on patient satisfaction and outcome. Cleft Palate Craniofac J. 2020;57(12):1357–61.
20. Lagan NC, Mc Grane F, Huggard D, Sharkey J, Purcell C, Balfe J, et al. Implementation of a health surveillance clinic for children with down syndrome. Arch Dis Child Educ Pract Ed. 2021;106(1):60–2.
21. Joypaul S, Kelly F, McMillan SS, King MA. Multi-disciplinary interventions for chronic pain involving education: a systematic review. PLoS One. 2019;14(10):e0223306.
22. Turner-Stokes L, Pick A, Nair A, Disler PB, Wade DT. Multi-disciplinary rehabilitation for acquired brain injury in adults of working age. Cochrane Database Syst Rev. 2015;12:CD004170.
23. MacDermid E, Hooton G, MacDonald M, McKay G, Grose D, Mohammed N, et al. Improving patient survival with the colorectal cancer multi-disciplinary team. Color Dis. 2009;11(3):291–5.
24. DeVries JK, Nation JJ, Nardone ZB, Lance SH, Stauffer JA, Abichaker GM, et al. Multidisciplinary clinic for care of children with complex obstructive sleep apnea. Int J Pediatr Otorhinolaryngol. 2020;138:110384.

25. Anderson YC, Cave TL, Cunningham VJ, Pereira NM, Woolerton DM, Grant CC, et al. Effectiveness of current interventions in obese New Zealand children and adolescents. Obes Res Clin Pract. 2014;128:8.
26. Stanger JD, Oliveira C, Blackmore C, Avitzur Y, Wales PW. The impact of multi-disciplinary intestinal rehabilitation programs on the outcome of pediatric patients with intestinal failure: a systematic review and meta-analysis. J Pediatr Surg. 2013;48(5):983–92.
27. DeFoor W, Minevich E, Jackson E, Nehus E, Schulte M, Niehaus R, et al. Does a multidisciplinary pediatric stone center improve outcomes? Urol Pract. 2020;7(5):362–7.
28. Braun DA, Lawson JA, Gee HY, Halbritter J, Shril S, Tan W, et al. Prevalence of monogenic causes in pediatric patients with nephrolithiasis or nephrocalcinosis. Clin J Am Soc Nephrol. 2016;11(4):664–72.
29. Grivas N, Thomas K, Drake T, Donaldson J, Neisius A, Petrik A, et al. Imaging modalities and treatment of paediatric upper tract urolithiasis: a systematic review and update on behalf of the EAU urolithiasis guidelines panel. J Pediatr Urol. 2020;16(5):612–24.
30. Vance SR Jr, Deutsch MB, Rosenthal SM, Buckelew SM. Enhancing pediatric trainees' and students' knowledge in providing care to transgender youth. J Adolesc Health. 2017;60(4):425–30.
31. Burdalski CE, Ewachiw B, Lang M, Feliciano J. PS05.03 a multidisciplinary approach to a pharmacy-driven smoking cessation program: a pilot. J Thorac Oncol. 2017;12:11.
32. Callahan ST, Winitzer RF, Keenan P. Transition from pediatric to adult-oriented health care: a challenge for patients with chronic disease. Curr Opin Pediatr. 2001;13(4):310–6.

Chapter 14
Urinary Stone, Bone, and Cardiovascular Disease in Children

Kirsten Kusumi and Rupesh Raina

Introduction

Urinary stone disease (USD) is a common condition that affects approximately one in eleven adults [1]. Relapse rates in adults have been shown to be up to 50% within 5–10 years with as many as 75% of patients forming another stone within 20 years [1, 2]. Urinary stone morbidity is associated with the excruciating pain of acute stone episodes as well as urinary tract obstruction and infection. Data has linked USD with multiple systemic disease states including chronic kidney disease (CKD) [3]. In addition, adults with USD have higher rates of cardiovascular disease (CVD) including coronary artery disease, hypertension, myocardial infarction (MI), and stroke [4, 5]. Correlation has been found between USD and decreased bone mineral density (BMD) and increased skeletal fracture rates [6, 7]. The exact mechanisms behind the association of stone, bone, and vascular disease are unknown. Inflammation has indirectly been implicated by the association of common inflammatory metabolic conditions including diabetes, obesity, hypertension, and dyslipidemia with USD as well as CVD and bone disease [8]. The natural history of whether urinary stones

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precede cardiovascular or bone disease development is unclear; however, stone forming children and young adults have shown evidence of early atherosclerosis and suboptimal BMD with increased risk of skeletal fractures [9–11].

Clinical care for USD patients has not traditionally included preventative screening or treatment for CVD or bone disease. Research into the mechanism(s) driving bone disease and CVD development in urinary stone formers is paramount to identifying therapeutic targets and improved preventative care strategies. Furthermore, pediatric patients are a special population suited to early intervention in order to prevent CVD and bone disease development, with greater opportunity to improve long-term patient outcomes via supplements and lifestyle changes. In this chapter we will review both adult and pediatric USD literature specific to the kidney, bone, and vascular axis.

Cardiovascular and Urinary Stone Disease

CVD and USD in Adults

Westlund et al. were among the first to connect CVD with urinary stones when they observed increased myocardial infarctions in USD patients in the 1970s. They hypothesized that heart and stone disease were correlated due to shared risk factors including sedentary lifestyle and poor diet [12]. Over the following decades, evaluation of USD patients for CVD has continued and multiple studies have demonstrated increased risk for CVD endpoints in USD patients including AMI, coronary artery disease, and atherosclerosis. USD patients have also been studied for surrogate markers of CVD including carotid artery intima thickness and coronary artery calcification [13, 14] (Table 14.1).

The Olmsted County, Minnesota cohort has been collecting data since 1979 and was utilized by Rule et al. to demonstrate significantly increased MI risk in USD patients [2]. The increased risk for MI was independent of known risk factors including CKD, dyslipidemia, hypertension, and obesity. However, they also found that CKD, dyslipidemia, hypertension, and obesity were also independently associated with USD. When USD patients with these risk factors at baseline were excluded from the analysis, the elevated incidence of MI remained, but the association lost statistical significance. This is likely due to confounding by these comorbidities. This type of confounding variability has been a significant drawback in multiple adult case-control studies, and has complicated the study of USD. Liu et al. completed a meta-analysis totaling 106,103 USD patients with 3,531,610 controls, and demonstrated that USD is associated with increased CVD risk [5]. Specifically, there was a 19% increased risk of coronary heart disease (CHD) and 40% increased risk of stroke in USD patients. In addition, USD patients had a 29% higher adjusted hazard ratio for incident MI. Shortcomings of this study included heterogeneity between data sets including mixed prospective and retrospective cohorts as well as confounding risks for USD and CVD.

Table 14.1 Urinary stone and cardiovascular disease

	Controls	USD patients	Mean age (years)	Events for analysis	Outcome
Alexander et al. [117]	3,169,920	25,532	40.5	CHD, MI, PTCA/CABG, CVA	Increased risk of all events for USD patients, more pronounced for younger patients and women
Fabris et al. [94]	42	42	41.3	CR-PWV, CF-PWV, AI, BMD	Increased arterial stiffness and reduced BMD in USD
Ferraro et al. [48]	222,427	19,678	50.2	CHD	Increased risk for USD women but not men
Chung et al. [119]	125,905	25,181	44.3	CVA	Increased risk of CVA in USD (hazard ratio 1.43, 95% CI 1.35–1.50, $p < 0.001$)
Rule et al. [4]	14,144	5081	44.5	MI	31% increased risk for MI in USD
Reiner et al. [15]	4915	200	25	cIMT	USD significantly associated with carotid atherosclerosis (OR 1.6, 95% CI 1.1–2.3, $p = 0.01$)
Lin et al. [49]	214,107	53,659	47.9	CVA	Increased risk for CVA in USD, higher risk for younger patients and women. USD who underwent >4 surgeries had up to 42.5-fold higher risk of CVA
Hsi et al. [13]	2999	289	69.7	Coronary artery calcification by CT	Increased calcification in recurrent stone formers; no difference between non-USD and one-time stone formers.
Domingos et al. [47]	21,648	1701	58	HTN, DM, MI, CVA	USD higher prevalence of HTN and DM, higher rates of MI and CVA
Shavit et al. [14]	54	57	47 ± 13	Abdominal aortic calcification and BMD	USD similar prevalence but higher severity of AAC; USD had lower BMD; AAC did not correlate with hypercalciuria.

CHD coronary heart disease, *MI* myocardial infarction, *CVA* stroke, *CR-PWV* carotid-radial pulse-wave velocity, *CF-PWV* carotid-femoral pulse-wave velocity, *AI* augmentation index, *BMD* bone mineral density, *cIMT* carotid intima medial thickness, *PTCA* percutaneous transluminal coronary angioplasty, *CABG* coronary artery bypass grafting

In addition to linking USD to the CVD outcomes, multiple studies have linked USD to established predictors of CVD including subclinical carotid atherosclerosis and coronary artery calcification. The Coronary Artery Risk Development in Young Adults (CARDIA) study, a 20-year longitudinal cohort study evaluating the development of CVD risk factors, in 5115 participants between 18–30 years of age. They utilized ultrasound to measure carotid intima medial thickness (cIMT) to evaluate for subclinical atherosclerosis [15]. Arterial stiffness correlates with increasing cIMT measurements and cIMT has been shown to be a strong predictor of

cardiovascular outcomes such as left ventricular hypertrophy, ventricular failure, and atherosclerosis [16–19]. CARDIA followed participants over time and demonstrated that development of USD was associated with increased cIMT after 20 years. Utilizing a composite dichotomous end point of carotid stenosis and/or the upper quartile of internal carotid/bulb wall thickness, the association of urinary stones with carotid atherosclerosis was significant (OR 1.6, 95% CI 1.1–2.3, $p = 0.01$), even after adjusting for major atherosclerotic risk factors.

Hsi et al. utilized the Multi-Ethnic Study of Atherosclerosis (MESA) cohort to investigate history of USD and prevalent coronary artery calcification [13]. MESA is a multisite cohort study of participants 45–84 years old without known baseline CVD. They utilized computerized tomography (CT) to determine coronary artery calcification scores in 3282 participants approximately 10 years after initial enrollment; scores were graded as none, mild, moderate, or severe. Single episode urinary stone formers did not show any difference in coronary calcification compared to non-stone formers. However, participants with recurrent urinary stone episodes did show a significant association with moderate or severe calcification (OR 1.80, 95% CI 1.22–2.67). Furthermore, when comparing severity of coronary artery calcification, recurrent stone formation was associated with higher score categories on multivariable ordinal logistic regression (OR 1.44 per category, 95% CI 1.04–2.01). This has been one of the only studies to separate USD patients based on their history of stone recurrence and suggests that single stone episode formers may not have the same risk profile as those with recurrent stones.

Risk Factors for CVD and USD in Adults

Several studies have evaluated whether USD is associated with CVD risk factors including dyslipidemia, hyperinsulinemia, obesity, and metabolic syndrome (Table 14.2). Masterson et al. utilized a random retrospective cohort of 60,000 adults and demonstrated a significant association between dyslipidemia and USD with a hazard ratio (HR) of 2.2 [Confidence Interval (CI), 1.9–2.5; $p < 0.001$]; this relationship remained significant on multivariate analysis with a HR of 1.2 (1.0–1.5; $p = 0.033$) [20]. Kang et al. compared known USD patients with well-matched controls and adjusted for confounders including obesity, diabetes, and hypertension. USD associated with hypercholesterolemia has an odds ratio (OR) of 0.747($p = 0.003$), with hypertriglyceridemia (OR = 1.9, $p < 0.001$), with low high density lipoprotein (HDL) cholesterolemia (OR = 1.89, $p < 0.001$), and high low density lipoprotein (LDL) cholesterolemia (OR = 0.61, $p < 0.001$) [21]. Jeong et al. utilized a retrospective cohort of 34,895 patients; among these participants, 839 (2.4%) had radiologic evidence of USD [22]. They demonstrated that the OR for USD trends upward with an increasing quintile of waist circumference and systolic/diastolic blood pressure even after multivariable-adjustment for confounders. Moreover, metabolic syndrome had an OR of 1.25 (95% CI, 1.03–1.50) for USD prevalence. In participants with hypertension, the OR for USD was 1.47 (95% CI, 1.25–1.71). These studies support the conclusion of a strong association between

Table 14.2 Urinary stone disease and CVD risk factors

	Control	USD patients	Mean age (years)	Events for analysis	Outcome
Masterson et al. [20]	51,582	702	31.9	Dyslipidemia	USD significantly associated with dyslipidemia, HTN, tobacco abuse, and obesity
Kang et al. [21]	1965	655	46.8	Dyslipidemia	USD significantly associated with hypercholesterolemia, hypertriglyceridemia, low HDL, and high LDL
Jeong et al. [22]	34,056	839	40–59	Metabolic syndrome	OR for USD increased as waist circumference and systolic/diastolic blood pressure increased. Age, sex, hypertension, and metabolic syndrome were independent risk factors for USD.
Inci et al. [31]	50	49	48.7	BMI, cholesterol, triglyceride	BMI, hypercholesterolemia, and hyperlipidemia may be significantly associated with different types of urinary stones
Taylor et al. [25]	236,796	4827	34–75	Obesity and weight gain	Obesity and weight gain are associated with increased risk of USD; risk greater in women than men

OR odds ratio, *BMI* body mass index

risk factors for CVD with USD, particularly obesity, dyslipidemia, and metabolic syndrome. Multiple studies have demonstrated increased risk for USD in overweight and obese adults and further that obese adults have lithogenic risk factors in their urine chemistries [23–26]; however, other studies have questioned the link between increasing weight and USD risk [27–29].

The majority of USD studies do not stratify data by stone type, though few have restricted their analysis to a subgroup of stone formers. A prospective study by Hamano et al. compared 200 calcium oxalate stone formers to non-stone forming age and sex matched controls [30]. They demonstrated significantly higher rates of coronary heart disease in USD patients ($p = 0.007$). In addition, CVD risk factors including tobacco use, hypertension, hypercholesterolemia, and BMI were associated with USD on univariate analysis. On multivariate logistic regression analysis however, only tobacco use (OR 4.29, 95% CI 2.68–6.86, $p < 0.0001$), hypertension (OR 3.57, 95% CI 2.11–6.07, $p < 0.0001$), and hypercholesterolemia (OR 2.74, 95% CI 1.51–5.00, $p = 0.001$) held statistical significance, while BMI did not. To date there is only one study that evaluated CVD risk factors while stratifying for specific stone type. Inci et al. compared body mass index (BMI), total cholesterol levels (TC), and triglyceride levels (TG) in a cohort of 49 stone formers and 50 controls [31]. Stone subtypes included calcium oxalate monohydrate-calcium oxalate dihydrate (COM-COD), calcium oxalate monohydrate (COM), and uric acid. The study concluded that there was a significant association between USD and elevated BMI,

TC and TG levels for COM-COD and uric acid kidney stone formers. However, these relationships were not significant for COM stone formers; furthermore, TG levels in COM stone formers were much lower than those of COM-COD formers. This data suggests that CVD risk may be specific to stone phenotype, and may help explain the inconsistent findings of CVD risk and disease in general USD patients.

Pediatric CVD and USD

There is extremely limited data on USD and CVD in children and adolescents as it is relatively uncommon compared to its prevalence in adults. Kusumi et al. provided one of the first studies to evaluate adolescents with USD for subclinical CVD. A small 15 patient USD cohort was enrolled and compared to healthy matched controls 12–17 years of age [9]. Early CVD was evaluated for by cIMT measurement similar to the CARDIA study [15]. USD participants had significantly higher cIMT measurements for the right common carotid artery and overall median carotid wall measurements. Additional testing included urine enzyme-linked immunosorbent assay (ELISA) for atherosclerosis-associated biomarkers including fibronectin 1 (FN1), macrophage scavenger receptor 1 (MSR1), osteopontin (OPN), and vascular cell adhesion molecule 1 (VCAM1). They demonstrated that OPN significantly correlated with cIMT in both USD patients and controls. OPN is involved in the pathophysiology of multiple disease processes including as a scaffolding protein within urinary stones' matrix as well as inside atherosclerotic plaques; furthermore, OPN is a well-known inflammatory mediator [32–34]. Urine fibronectin was negatively correlated with cIMT in USD patients, but not controls. Fibronectin is also found within atherosclerotic lesions and is known to sustain endothelial inflammation. Furthermore, OPN and fibronectin assist in monocyte migration in vascular and stone disease [35, 36].

Kovacevic et al. evaluated dyslipidemia and development of USD in a pediatric cohort [37]. They utilized a case-control study of 58 USD formers and 351 controls; both groups had mean ages <10 years. In their comparison serum uric acid was higher, but serum calcium levels were lower in the USD group. When comparing lipids, USD participants demonstrated a higher non-high-density lipoprotein cholesterol (non-HDL-c) compared to controls. Other USD risk factors including age, sex, BMI, and blood sugar were similar between groups. Future studies evaluating subclinical CVD in young USD patients will hopefully expand on these preliminary findings and incorporate imaging as well as serum biomarkers.

Pediatric USD and CVD Risk Factors

Adult literature has made strong connections between well-established CVD risk factors and USD. However, CVD risk factors have not been well studied in pediatrics. The majority of data linking obesity, hypertension, and diabetes with USD in

children remains tenuous and is mostly reliant on database studies [24]. Matlaga et al. queried the Kids' Inpatient Database from 1997 to 2003 and demonstrated an overall increase in the number of children with USD [38]. Children with USD increased from 2040 patients in 1997 to 6764 patients in 2003; specifically, there was a 365% in pediatric female stone formers and 274% in pediatric male stone formers during this period. They also demonstrated that USD was significantly associated with hypertension and diabetes in children <6 years, but not obesity. Schaeffer et al. utilized the same database from 2003 to 2006 and found that USD was significantly associated with hypertension in children <10 years and diabetes in children <5 years; again, obesity was not significantly associated [39]. Alternatively, Kokorowski et al. utilized a different national database, the Pediatric Health Information Systems, from 2004 to 2009 and found that USD was associated with increased odds ratios of obesity and hypertension, but not diabetes [40].

In one of the few existing prospective studies, Kim et al. carried out a matched case-control study through a local pediatric primary care network [41]. Utilizing logistic regression analysis, they did not find an association between BMI Z-score, overweight status, or obese status with USD. Sarica et al. studied 94 non-stone forming children and compared them by body weight for urinary stone risk factors [42]. They demonstrated that overweight children had higher excretion rates of urinary oxalate and uric acid, higher supersaturation of CaOx, lower urine volume, and decreased urine citrate and magnesium. However, there are multiple shortcomings in this study such as normalizing urinary chemistries to body weight rather than normalizing to urine creatinine. Furthermore, these studies were carried out in non-stone forming children and it is difficult to say if these relationships can be generalized to USD patients [43].

Sex Differences

Traditionally men have been the most frequent stone formers, but the gender gap has been closing and stone prevalence in women has increased by 75% since 1994 [44, 45]. There are sex-specific characteristics for adult stone formers including a male predominance for calcium oxalate and uric acid vs a female preponderance for calcium phosphate and struvite stones; there is also an increasing prevalence of uric acid stones with age in both sexes [46]. While few studies have considered race when evaluating USD patients for CVD or bone disease, there is some evidence of sex-based differences. Multiple studies have found increased risk of CVD specifically for female USD patients as compared to male [14, 47, 48]. Lin et al. utilized a large Taiwanese database and found that the relative stroke risk for USD patients was 1.06-fold higher than that for the non-stone formers (95% confidence interval [CI] ¼ 1.01–1.11) [49]. Interestingly, the risk was greater in women and younger patients 20–34 years old. Another large cohort study by Alexander et al. utilized the Alberta Kidney Disease Network database found that USD patients had a higher risk of heart attack (HR 1.40; 95% CI 1.30–1.51), coronary revascularization (HR, 1.63; 95% CI, 1.51–1.76), and stroke (HR, 1.26; 95% CI, 1.12–1.42) [48]. Similar to Lin et al., they demonstrated that the excess risk associated with USD appeared

more pronounced in younger people ($p = 0.001$) and for women ($p = 0.01$). Two meta-analyses have also found greater risk for CVD outcomes in female USD patients compared to males [5, 50]. The mechanism behind greater CVD in female USD patients compared to male is unclear; however, it may be due to the influence of sex hormones, particularly estrogen, as they are known to influence CVD in non-stone formers.

Mechanism

The mechanisms linking urinary stone and CVD are unclear. Recurrent urinary stones are a systemic metabolic disorder affected by genetics and lifestyle. Cheungpasitporn et al. suggests that calcium precipitation in the coronary arteries and in the renal tubules might share the same pathophysiology, meaning stone formers could be lacking pyrophosphates (inhibitors of calcification) in both blood and urine leading to both stone formation and CVD [50]. Liu et al. also shared the same conclusion, explaining the potential link of CVD and kidney stones through a lack of calcification inhibition in the blood and urine for stone formers [5]. Further research is required to completely understand the underlying pathophysiology of kidney stones and CVD.

Urinary Stone and Bone Disease

Background

Adult bone density loss and orthopedic fractures result in significant burden to the healthcare system due to the resulting functional impairment, reduced quality of life, associated increase in mortality and cost of care [51]. Clinically physicians utilize areal bone mineral density (BMD), the amount of mineral per square centimeter of bone, as an indicator of bone strength and a predictor of skeletal fracture risk [52]. Per the World Health Organization (WHO) osteoporosis is a systemic skeletal disease of low bone mass as well as deterioration of bone microarchitecture culminating in increased bone fragility and elevated fracture risk [53]. Adult BMD is reported as a T-score which represent the number of standard deviations (SD) from peak BMD; T-score = (patient BMD – young normal mean BMD) / standard deviation of the young normal population [54]. Adult osteoporosis can be defined as a T-score < 2.5 or more than 2.5 SD below maximal peak BMD. Osteopenia describes low BMD with a T-score < 1. Since the T-score

fundamentally represents the decrease of BMD from physiologic peak in early adulthood, it is not applicable to children [54]. Pediatric definitions have been established by an international panel of bone experts comprising the Pediatric Consensus Development Conference on the Use and Interpretation of Bone Density Studies in Children. Their recommendations are a combination of evidence-based guideline as well as expert opinion due to the lack of data from dedicated pediatric research. Z-scores are utilized to define pediatric BMD and represent the SD from normative pediatric BMD based on a combination of age, sex, height, and body mass index. Pediatric osteoporosis has been defined BMD Z-score < -2 in combination with an either vertebral compression fractures or multiple non-traumatic long bone fractures [55]. Pediatric patients are becoming increasingly recognized as at risk for suboptimal BMD accrual due to multiple chronic diseases as well as genetic syndromes, medication side effects, immobility, and/or inadequate nutrition. Low BMD has been shown to increase risk for skeletal fracture in the pediatric age range and is also a predictor of future adult fractures [56, 57]. Urinary stone forming adults have BMD loss and increased skeletal fractures independent of other metabolic bone risk factors. Furthermore, children with USD have suboptimal BMD and adolescent boys have increased fracture rates [7, 10, 11].

Adult Bone and Urinary Stone Disease

Adult USD has been associated with osteoporosis and increased skeletal fractures. Melton et al. utilized a population-based retrospective cohort of 624 symptomatic USD patients and evaluated for vertebral fracture [6]. They demonstrated a four time increase in vertebral fracture rates in USD patients compared to the general population [standardized morbidity ratio (SMR), 4.3; 95% confidence interval, 3.4–5.3]. USD patients were then followed for 30 years and their fracture risk increased with a final rate of 45% for women and 28% for men. Lauderdale et al. utilized cross-sectional data from the Third National Health and Nutrition Examination Survey (NHANES III) to demonstrate that men with USD had significantly lower femoral neck BMD compared to controls even after adjusting for age, body mass index (BMI), and race/ethnicity [7]. Furthermore, urinary stone forming men were more likely to report prevalent wrist and spine fractures. Denburg et al. utilized data from British electronic medical records and compared 50,000 USD patients to 500,000 controls [10]. They demonstrated significantly increased skeletal fracture risk in USD patients with differences specified by sex and age. A major shortcoming of these studies is that they did not account for the type of urinary stone when evaluating for suboptimal BMD or fracture.

Pediatric Bone and Urinary Stone Disease

Retrospective data has also indicated an association between USD, hypercalciuria, and bone disease in children and adolescents [58] (Table 14.3). Garcia-Nieto et al. compared 73 children with hypercalciuric USD aged 3–18.4 years to 57 healthy controls and found that USD children had significantly lower lumbar BMD Z-scores (-0.70 ± 0.88 vs 0.26 ± 0.65, $p < 0.001$) [59]. Furthermore, thirty percent of the USD children had osteopenia (defined as a BMD Z-score < -1). Penido et al. utilized a cohort of children with idiopathic hypercalciuria (IHC), some of which also had urinary stones and were compared to controls. They also demonstrated a lower lumbar BMD Z-score in the IHC/USD cohort (-0.7 vs 0.0, $p < 0.001$) [60]. Similar to Garcia-Nieto et al., they found that 35% of IHC/USD patients had osteopenia at the time of diagnosis; however, this group included additional analysis comparing IHC patients with and without stones lumbar BMD and found no significant difference between the groups (0.67 g/cm^2 vs 0.64 g/cm^2, $p = 0.10$). Alternatively, Schwaderer et al. evaluated a 110 patient cohort of children with either USD or IHC for BMD and found 47% had a bone density Z-score < -1, and 26% had a bone density Z-score < -2 [11]. When they compared USD and IHC patients, they found that the urinary stone patients had lower BMD Z-scores than patients with hypercalciuria and no stones [11]. Whether hypercalciuria is driving BMD loss alone or if additional mechanisms are responsible remains a major question that has not been well addressed in the pediatric literature. The previously mentioned work by Denburg et al. has remained one of the only studies to demonstrate increased skeletal fracture risk in a pediatric USD cohort [10]. Specifically, they found a significantly increased hazard ratio for fracture in adolescent boys (HR 1.55; 95% confidence interval [95% CI], 1.07–2.25).

Sex Differences

Adult and pediatric urinary stone and bone disease studies have demonstrated conflicting data regarding the effect of sex. Melton et al. found increased vertebral fractures in female and male USD patients; however, Lauderdale et al. found that men were more likely to show significant BMD loss and increased fractures compared to women [6, 7]. Other adult studies including work by Vezzoli et al. demonstrated that women with hypercalciuric USD with high intestinal calcium absorption were predisposed to loss of BMD [61]. Similarly, Jaeger et al. demonstrated low tibial BMD in male calcium stone formers that correlated to dietary habits [62]. However, both of these studies were restricted to female and male participants respectively, and did not directly evaluate for sex-based differences. Kusumi et al. demonstrated a significantly lower BMD in adolescent boys with USD which is consistent with data by Denburg et al. who demonstrated higher skeletal fracture rates in adolescent males with USD compared to non-stone formers [10, 63]. Among

Table 14.3 Pediatric urinary stone and bone disease

Study	Population	Participants	Age	Site	Outcome	Conclusion
Kusumi et al. (2020) [63]	USD ± HC Controls	15 15	16.0 ± 1.69 15.87 ± 1.99	LS WB	• Male stone formers vs. controls BMD z-score − 1.3 ± 0.49 vs. − 0.7 ± 0.56, $p = 0.039$ • Females were not significantly different BMD Z-score − 0.92 ± 0.9 vs. − 0.58 ± 0.83, $p = 0.46$	• BMD z-score did not correlate with urine calcium, oxalate, citrate, or magnesium. • Higher urine IL-13 correlated with higher WB BMD Z-score $r = 0.677$, $p = 0.018$ • WB BMD Z-score did not correlate with BMI in the USD group $r = -0.1629$, $p = 0.5619$
Artemiuk et al. (2015) [120]	IHC ± USD	31	9.8 ± 4.0	LS	BMD • Z-score < −1 in 25.8% • Z-score − 1 to 1 in 64.5% • Z-score > 1 in 9.7%	• Majority had low 25OHD3 • Positive correlation between Z-score and 25OHD3 level
Escribano et al. (2014) [121]	Asymptomatic IHC 7-year-old children Controls	31 144	7 years	LS WB	BMD Z-score • IHC 0.09 ± 0.99 • Control 0.31 ± 0.88	• IHC BMD Z-score was significantly lower for WB but not LS • 22% of IHC had osteopenia
Penido et al. (2012) [122]	IHC ± USD	80	10.5 ± 3.5	LS	Treated with potassium citrate ± thiazide: • Decreased calcium excretion from 5.0 to 2.6 mg/kg/24 hours • BMD Z-score improved −0.763 ± 0.954 to −0.537 ± 0.898	• No control group • 0 of 80 patients decreased urine calcium with dietary changes alone and were then started on potassium citrate

(continued)

Table 14.3 (continued)

Study	Population	Participants	Age	Site	Outcome	Conclusion
Schwaderer et al. (2011) [123]	IHC ± USD Treated with: (1) Diet alone (2) Diet + citrate	12 7	9.2 ± 1.5 10.7 ± 1.5	LS	BMD Z-score change per year: (1) –0.11 ± 0.41 (2) 0.19 ± 0.38	• Improved (but not significant) BMD Z-score per year and lower percentage of patients with low BMD Z-score in IHC children treated with potassium citrate.
Schwaderer et al. (2008) [11]	IHC USD (±HC)	61 37	8.8 ± 3.1 10.2 ± 3.4	LS	BMD Z-score IHC: −0.6 ± 1.6 USD: −1.5 ± 1.9	47% Z-score < −1 26% Z-score < −2
Pendio et al. (2006) [124]	IHC ± USD (1) with hypocitraturia (2) w/o hypocitraturia (3) Controls	44 44 29	8.8* 8.4 9.8	LS	BMD Z-score (1) −0.8 (1.9–1.4) (2) −0.7 (2.2–1.7) (3) 0.0 (0.9–1.7)	Both group of IHC had significantly lower BMD than controls; comparison of 1 vs 2 just missed significance with $p = 0.055$
Penido et al. (2003) [60]	IHC ± USD Controls	88 29	9.8* 9.4	LS WB FN	LS Z-score • IHC: –0.7 (−2.2–1.7) • Control: 0.0 (−0.9–1.7) FN Z-score • IHC: 0.70 (0.39–1.23) • Control: 0.78 (0.47–1.56)	• WB Z-score was not significantly different • 35% of IHC patients had osteopenia at diagnosis
Skalova et al. (2005) [125]	IHC ± USD	15	12.4 ± 4.0	LS	BMD Z-score −1.41 ± 0.97	40%: BMD −1 to −2 SD 20%: BMD ≤ −2 SD
Garcia-Nieto et al. (2003) [126]	IHC girls (and their mothers) Controls	40 19	9.5 ± 3.0	LS	BMD Z-score −0.83 ± 0.84	• 42.5% of IHC LS Z-score < −1 • 47.5% mothers' LS and/or FN T-score < −1

Polito et al. (2003) [127]	IHC ± USD + hyperuricosuria No hyperuricosuria	9 17	12.5 ± 3.8	LS	BMD Z-score −0.68 ± 0.99 +0.21 ± 0.64	BMD significantly lower in IHC with hyperuricosuria
Freundlich et al. (2002) [128]	IHC ± USD (and their mothers)	21	9.6 ± 4.0	LS FN	BMD Z-score −0.1 ± 1.3 −0.32 ± 1.37	• Low BMD in 38% children and 33% of mothers • Children of mothers with osteopenia had significantly lower LS BMD than children of mothers with normal BMD
Reusz et al. (1998) [129]	IHC ± USD Treated with thiazide	18	9.6 (6–16)	Rad	IHC BMD Z-score • Initial: −1.3 ± 0.26 • After treatment: −0.8 + 0.22	IHC had lower Na+/K + -ATPase activity that improved with thiazide
Garcia-Nieto et al. (1997) [59]	IHC ± USD Controls	73 57	8.07 ± 3.65 7.90 + 2.21	LS	−0.70 ± 0.88 +0.26 ± 0.65	• 30.1% IHC had osteopenia, and low urine citrate and high urine uric acid vs those with normal BMD • Negative correlation between age and BMD in IHC

*denoting age reported as median

male USD patients the increased hazard ratio (HR) for fracture was greatest in adolescence (1.55; 95% confidence interval [95% CI], 1.07–2.25) with an overall male HR of 1.10 (95% CI, 1.05–1.16). Female USD patients had their greatest fracture HR in women aged 30–39 years (HR, 1.52; 95% CI, 1.23–1.87) compared to an overall female USD patients aged 30–79 years (HR, 1.17–1.52). Pediatric stone formers show sex prevalence which is age dependent [64, 65]. Children who make stones <10 years are more likely to be male and adolescents >10 years are more likely to be female [64, 65]. This break point is likely related to onset of puberty in American children [66]. The mechanism and influence of sex and puberty on kidney stone formation and BMD in USD patients is unclear.

Mechanism

The mechanisms driving bone disease in USD patients are unknown. General bone health is multifaceted and is influenced by genetics, diet, body habitus, activity level, and comorbid medical conditions [67]. Bone and stone disease is likely also driven by multiple processes and many have pointed to genetics, diet, renal calcium loss, and inflammation.

Osteoporosis has a heritable risk of 50–85% [68]; urinary stones also have significant heritable risk including that 79% of children with USD have a family history of urinary stones typically in a first degree relative [69]. Furthermore, specific genes have been independently tied to USD and low BMD including osteopontin (OPN) [70, 71]. OPN is an acidic phosphorylated glycoprotein that can act as both a cytokine and an extracellular matrix protein [72]. Ultrastructural observation of renal macrophages shows that OPN is required for macrophage phagocytosis of crystals *and* phagocytosis drives further macrophage release of OPN. In bone OPN drives increased bone resorption by upregulating osteoclast function both directly and indirectly via RANKL secretion from osteoblasts [33]. Claudin 14 has also been associated with low BMD and USD in humans as well as hypercalciuria in mice; it is a regulatory protein influencing paracellular permeability in nephrons [73, 74].

Nutrition and diet have been directly linked to urinary stone formation and are integral in the prevention of stone recurrence [45]. Specific to stone and bone disease the acid ash hypothesis may provide a bridge between the kidney and the skeleton [58]. In acid ash food metabolism can generate either acidic or alkaline ions; the overall effect on blood pH is dependent on the balance of food types [75]. If dietary choices consistently generates more acid than alkali, the body will utilize the skeleton for pH buffering, and subsequently drive bone demineralization with concomitant increases in urine calcium excretion [76]. Specific diets which alter blood pH such as the ketogenic diet have been utilized to treat neurologic disorders and seizures; ketogenic diet patients have been shown to be at increased risk for stone and bone disease potentially due to increased skeletal buffering and hypercalciuria [77]. Protein intake results in net acid production; specifically, high animal

protein intake is associated with increased urine acid and calcium secretion, and has been considered a risk factor for osteoporosis and bone fractures [75]. The typical modern Western diet does not provide a good balance between acid and alkali due to the relatively fewer fruits and vegetables vs higher quantities of acid-producing meat, dairy, and grains [78]. Increasing rates of obesity and the typical western diet have also been implicated in increasing urinary stone disease [25]. However, more recently multiple studies have questioned if dietary protein, even if from animal sources, is necessarily detrimental to bone health. Darling et al. completed a meta-analysis of studies evaluating protein intake and supplementation and found a positive association between protein and BMD; they also did not find an association of higher protein with skeletal fracture risk [79]. Additional studies have shown that long-term high protein intake is positively associated with increased BMD [80, 81].

While some experts consider plant protein to be better for bone health than animal sources, the data is not necessarily clear. Frassetto et al. demonstrated improved bone outcomes in geographic areas where diets contain higher amounts of plant protein compared to animal protein. A meta-analysis by Ho-Phan et al. demonstrates 4% lower BMD in vegetarians compared to omnivores [82, 83]. Sahni et al. utilized the Framingham cohort and found no association between hip fracture and dietary animal/plant protein ratio [84]. One potential explanation is that animal proteins also contain phosphorus, which has an overall hypocalciuric effect counteracting the hypercalciuric effect of protein [85]. When dietary protein and calcium intakes are constant, an increase in phosphorus will decrease urinary calcium. Lauderdale et al. demonstrated that men with USD had lower femoral neck BMD than men without stones, even after adjusting for potential confounders [7]. Interestingly, dietary calcium consumption, as estimated through milk consumption, was positively associated with BMD and ameliorated the deleterious effect of USD on BMD. Breslau et al. utilized healthy volunteers and prescribed three different diets including plant protein, plant and egg protein or animal protein. The content of each contained equivalent sodium, potassium, calcium, phosphorus, magnesium, and protein, but differed in that each had a progressively higher amount of sulfur which increases acid content. They found that as sulfur increased in the diet, there was a corresponding increase in urine calcium. Furthermore, as urine acid increased the urine cAMP, serum PTH and 1,25-OH vitamin D all decreased which is consistent with acid-induced bone resorption. However, when evaluating USD risk, they found that the animal protein diet had the greatest increase in uric acid excretion resulting in subsequent decrease in urine citrate and drop in urine pH. However, oxalate excretion was significantly lower in the animal protein group compared to the vegetarian diet group. Thus, when electrolyte composition and protein quantity were kept stable, an animal protein diet was associated with increased risk of uric acid stones, but not calcium oxalate or calcium phosphate. Thus, the effect of diet is incontrovertible in bone and stone disease; however, the multiple effects can make any simplistic guidelines difficult to design.

Clarifying the contributions of hypercalciuria to low BMD in USD remains problematic in both adult and pediatric literature. In general, hypercalciuria due to an excessive dietary intake has been deemed absorptive hypercalciuria, whereas if hypercalciuria persists following normal or restricted calcium intake it is idiopathic or fasting hypercalciuria [86]. Bataille et al. compared adult calcium USD patients and evaluated lumbar BMD of absorptive hypercalciuric vs. idiopathic hypercalciuric patients [87]. They demonstrated normal vertebral BMD in absorptive hypercalciurics, but BMD was decreased in the idiopathic hypercalciurics. Pacifici et al. measured vertebral BMD in adults with absorptive hypercalciuria, fasting hypercalciuria, and non-hypercalciuric urinary stones; they demonstrated significantly lower BMD in the fasting hypercalciuric patients compared to the other two groups [88]. Sakhaee et al. succinctly summarized adult USD-bone data stating that while low BMD is present in both hypercalciuric and normocalciuric USD patients, hypercalciuric patients have demonstrated more significant reductions in BMD [89]. Furthermore, low BMD is not a unanimous finding in normocalciuric kidney stone formers. Pediatric data has been mired by the presence of idiopathic hypercalciuric patients mixed in with USD patients in the majority of studies. One study by Schwaderer et al. did separate and compare these groups and demonstrated that children with USD had lower BMD than IHC patients without stones [11]. Thus, while urine calcium must contribute to BMD loss in USD it is not sufficient to alone drive bone disease.

Urinary Stone, Bone, and Cardiovascular Disease

Adults with USD have been demonstrated to suffer from CVD and bone disease; children and adolescents with USD also suffer from bone disease and have preliminary evidence of subclinical CVD [4, 5, 7, 9, 58]. What is not known is the sequence of development of urinary stones, bone and vascular disease; also the molecular mechanisms driving these manifestations of systemic disease in the setting of urinary stones remain a mystery. Basic research has suggested that calcification of arterial tissue occurs in an organized, regulated process by mechanisms similar to the mineralization of bone [90]. Vascular smooth muscle cells can differentiate to osteoblastic phenotype and actively deposit bone matrix in the wall of blood vessels [91]. Animal studies have shown rats bred to be susceptible to the development of calcified atherosclerotic lesions have low BMD, whereas mice bred to be resistant atherosclerotic disease development have higher BMD [92, 93]. Studies of non-stone forming adults have demonstrated correlation between calcium loss from bones and arterial calcification. Schulz et al. evaluated BMD in >2000 postmenopausal women with fractures and found that aortic calcifications were inversely related to bone density [90]. When compared to women without aortic calcification, the OR for vertebral fractures in women with calcification was 4.8 (95% confidence interval, 3.6–6.5). However, this work and others relating bone and vascular disease is predicated on the commonality of both diseases in an aging population, which while suggestive of a relationship between bone and vasculature likely has different

pathophysiology than USD patients who have demonstrated pediatric origins for both diseases.

Few studies have considered vascular and bone disease simultaneously in USD patients, and it is difficult to ascertain if similar mechanisms are responsible. Fabris et al. evaluated BMD and ultrasound measures of arterial stiffness in a small cohort of adult USD patients; they demonstrated increased arterial stiffness and reduced BMD in USD patients compared to controls [94]. However, analysis found that arterial stiffness was independent of reduced BMD. Shavit et al. utilized a small cohort of adult USD patients and measured abdominal aortic calcification (AAC) scores and BMD. They demonstrated the prevalence of AAC was similar between USD patients and controls; however, AAC severity score was significantly higher in the USD group and BMD was significantly lower. Multivariate analysis adjusted for comorbidities and confirmed significantly higher AAC scores and lower BMD in USD patients compared to controls; furthermore, when AAC was correlated with hypercalciuria the relationship was not statistically significant. However, Shavit et al. did not correlate AAC to BMD.

Inflammation has been shown to affect all three disease states independently and may be the link tying USD to the inception of vascular and bone disease. Urinary stone research has shown that crystal deposition results in renal inflammation in both animal and human models [34]. IL-6 is an inflammatory cytokine whose secretion from renal epithelial cells increases as a result of urinary oxalate deposition in renal tissue [95]. In addition, binding and phagocytosis of calcium oxalate crystal by macrophages cause them to release of TNFα and IL-6 [96]. Kusumi et al. published data demonstrating elevated urine levels of cytokines involved in chronic inflammation and fibrosis in adolescent USD patients outside of acute stone episodes. Osteopontin and fibronectin link cardiovascular and stone disease as they are stone matrix proteins and also are found in atherosclerotic plaques [97]. Cardiovascular research has built a large body of evidence that inflammatory proteins and cytokines, including IL-6, are involved in the evolution of vessel thickening from adaptive response to pathological event [98]. The American Heart Association along with the Center for Disease Control published a statement calling for use of inflammatory markers in risk stratification of cardiac patients [98]. Bone metabolism research also has a rich body of evidence involving inflammation as a molecular mechanism for bone resorption. One of the main pathways involves activation of receptor activator of NF-kappa β ligand (RANKL) that promotes osteoclast maturation and increased bone resorption. IL-1 and IL-6 have also been linked to bone resorption by their ability to increase osteoclastogenesis as well as osteoclast survival [99–101].

Treatment

There is no standard of care in adult or pediatric USD management, nor any specific treatments to address extrarenal diseases including cardiovascular and bone disease. Traditional adult dietary treatment strategies aimed at reducing stone recurrence,

such as protein restriction, are not appropriate in pediatric patients given the need to protect bone health and linear growth [102]. Similarly, children should not have calcium restricted from their diet as it is necessary for BMD accrual and bone growth. Additional considerations could include vitamin D surveillance and replacement. Data has been mixed on whether vitamin D supplementation may increase intestinal calcium resorption and thus hypercalciuria [103, 104]. However, given the importance of vitamin D to bone mineralization, cardiovascular health and immune function replacement with conservative dosing with ongoing monitoring is likely warranted, especially in children [105, 106].

Pharmacologic treatment for urinary stones typically includes two medications: thiazides and citrate salts. Both of these may have some effect on bone health. Thiazides, while originally used in the treatment of hypertension, have the additional effect of lowering urine calcium. Thiazide may influence BMD by increasing renal calcium reabsorption as well as directly stimulating osteoblastic bone formation and mineralization [107]. Adult USD studies have demonstrated decreased urinary stone recurrence and increased BMD with thiazide treatment [108, 109]. However, data concerning thiazide's effects on pediatric patients' BMD is conflicting. While Garcia-Nieto et al. demonstrated a negligible effect of thiazide on BMD in children, Reusz et al. demonstrated improved BMD with thiazide; however, these studies were carried out in IHC patients [58, 59, 110]. Citrate salts were historically thought to prevent urinary stone recurrence by complexing with calcium and thus decreasing urine supersaturation. Additional effects are likely due to its ability to buffer acid and anti-inflammatory properties [58]. In adults with and without USD citrate supplementation has been demonstrated to improve BMD and bone microarchitecture [111–113]. Citrate also appears to have beneficial effects on BMD for children with IHC [114].

Adult USD literature has demonstrated a strong association with CVD; however, the potential for CVD prevention and/or treatment in urinary stone patients has yet to be addressed. USD has the potential to be included in CVD risk assessment similar to traditional scoring systems use of diabetes and smoking history [115]. General health advice can include making families aware of the known association of CVD with USD, and that having USD is one more reason to follow a heart healthy lifestyle. Heart healthy diets including The Dietary Approaches to Stop Hypertension (DASH) diet are high in fruits and vegetables, moderate in low-fat dairy products, and low in animal protein and sodium; these dietary habits are advantageous in decreasing urinary stone recurrence as well as reducing hypertension and CVD risk [116].

Conclusion

The morbidity of urinary stones extends beyond pain, and includes increased risk of low BMD, skeletal fractures, and CVD; this increased risk is independent of established cardiovascular and bone risk factors [4, 9, 10, 117]. Approximately ~50% of adults will have recurrent urinary stones, and 10% of adults will have ≥3 lifetime

stone episodes [2]. Children's urinary stone recurrence rates may be even higher due to their greater prevalence of lithogenic urinary metabolic anomalies [118]. Thus, children may be at higher risk for bone and cardiovascular disease given their greater lifetime exposure to USD vs. adults. Furthermore, how the pathology of cardiovascular and bone disease development may affect the growing bodies of children who have yet to attain optimal BMD accrual is unclear. Whether stone composition or number of stone episodes influence vascular and bone disease development or severity is also unknown. Future studies are necessary to help implement evidenced-based improvements in patient care aimed at reducing the morbidity/mortality of cardiovascular and bone diseases in urinary stone formers.

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References

1. Scales CD, Smith AC, Hanley JM, Saigal CS, Project UDiA. Prevalence of kidney stones in the United States. Eur Urol. 2012;62(1):160–5.
2. Moe OW. Kidney stones: pathophysiology and medical management. Lancet. 2006;367(9507):333–44.
3. Rule AD, Bergstralh EJ, Melton LJ 3rd, Li X, Weaver AL, Lieske JC. Kidney stones and the risk for chronic kidney disease. Clin J Am Soc Nephrol. 2009;4(4):804–11.
4. Rule AD, Roger VL, Melton LJ, Bergstralh EJ, Li X, Peyser PA, et al. Kidney stones associate with increased risk for myocardial infarction. J Am Soc Nephrol. 2010;21(10):1641–4.
5. Liu Y, Li S, Zeng Z, Wang J, Xie L, Li T, et al. Kidney stones and cardiovascular risk: a meta-analysis of cohort studies. Am J Kidney Dis. 2014;64(3):402–10.
6. Melton LJ 3rd, Crowson CS, Khosla S, Wilson DM, O'Fallon WM. Fracture risk among patients with urolithiasis: a population-based cohort study. Kidney Int. 1998;53(2):459–64.
7. Lauderdale DS, Thisted RA, Wen M, Favus MJ. Bone mineral density and fracture among prevalent kidney stone cases in the Third National Health and Nutrition Examination Survey. J Bone Miner Res. 2001;16(10):1893–8.
8. Sakhaee K. Nephrolithiasis as a systemic disorder. Curr Opin Nephrol Hypertens. 2008;17(3):304–9.
9. Kusumi K, Smith S, Barr-Beare E, Saxena V, Schober MS, Moore-Clingenpeel M, et al. Pediatric origins of nephrolithiasis-associated atherosclerosis. J Pediatr. 2015;167(5):1074–80.e2.
10. Denburg MR, Leonard MB, Haynes K, Tuchman S, Tasian G, Shults J, et al. Risk of fracture in urolithiasis: a population-based cohort study using the health improvement network. Clin J Am Soc Nephrol. 2014;9(12):2133–40.
11. Schwaderer AL, Cronin R, Mahan JD, Bates CM. Low bone density in children with hypercalciuria and/or nephrolithiasis. Pediatr Nephrol. 2008;23(12):2209–14.
12. Westlund K. Urolithiasis and coronary heart disease: a note on association. Am J Epidemiol. 1973;97(3):167–72.
13. Hsi RS, Spieker AJ, Stoller ML, Jacobs DR, Reiner AP, McClelland RL, et al. Coronary artery calcium score and association with recurrent nephrolithiasis: the multi-ethnic study of atherosclerosis. J Urol. 2016;195(4 Pt 1):971–6.
14. Shavit L, Girfoglio D, Vijay V, Goldsmith D, Ferraro PM, Moochhala SH, et al. Vascular calcification and bone mineral density in recurrent kidney stone formers. Clin J Am Soc Nephrol. 2015;10(2):278–85.

15. Reiner AP, Kahn A, Eisner BH, Pletcher MJ, Sadetsky N, Williams OD, et al. Kidney stones and subclinical atherosclerosis in young adults: the CARDIA study. J Urol. 2011;185(3): 920–5.
16. Dalla Pozza R, Beyerlein A, Thilmany C, Weissenbacher C, Netz H, Schmidt H, et al. The effect of cardiovascular risk factors on the longitudinal evolution of the carotid intima medial thickness in children with type 1 diabetes mellitus. Cardiovasc Diabetol. 2011;10:53.
17. Barra S, Gaeta G, Cuomo S, Guarini P, Foglia MC, Capozzi G, et al. Early increase of carotid intima-media thickness in children with parental history of premature myocardial infarction. Heart. 2009;95(8):642–5.
18. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr. 2008;21(2):93–111. quiz 89-90
19. Urbina EM, Williams RV, Alpert BS, Collins RT, Daniels SR, Hayman L, et al. Noninvasive assessment of subclinical atherosclerosis in children and adolescents: recommendations for standard assessment for clinical research: a scientific statement from the American Heart Association. Hypertension. 2009;54(5):919–50.
20. Masterson JH, Woo JR, Chang DC, Chi T, L'Esperance JO, Stoller ML, et al. Dyslipidemia is associated with an increased risk of nephrolithiasis. Urolithiasis. 2015;43(1):49–53.
21. Kang HW, Lee SK, Kim WT, Kim YJ, Yun SJ, Lee SC, et al. Hypertriglyceridemia and low high-density lipoprotein cholesterolemia are associated with increased hazard for urolithiasis. J Endourol. 2014;28(8):1001–5.
22. Jeong IG, Kang T, Bang JK, Park J, Kim W, Hwang SS, et al. Association between metabolic syndrome and the presence of kidney stones in a screened population. Am J Kidney Dis. 2011;58(3):383–8.
23. Maalouf NM, Sakhaee K, Parks JH, Coe FL, Adams-Huet B, Pak CY. Association of urinary pH with body weight in nephrolithiasis. Kidney Int. 2004;65(4):1422–5.
24. Siener R, Glatz S, Nicolay C, Hesse A. The role of overweight and obesity in calcium oxalate stone formation. Obes Res. 2004;12(1):106–13.
25. Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. JAMA. 2005;293(4):455–62.
26. West B, Luke A, Durazo-Arvizu RA, Cao G, Shoham D, Kramer H. Metabolic syndrome and self-reported history of kidney stones: the National Health and Nutrition Examination Survey (NHANES III) 1988-1994. Am J Kidney Dis. 2008;51(5):741–7.
27. Daudon M, Lacour B, Jungers P. Influence of body size on urinary stone composition in men and women. Urol Res. 2006;34(3):193–9.
28. Negri AL, Spivacow FR, Del Valle EE, Forrester M, Rosende G, Pinduli I. Role of overweight and obesity on the urinary excretion of promoters and inhibitors of stone formation in stone formers. Urol Res. 2008;36(6):303–7.
29. Powell CR, Stoller ML, Schwartz BF, Kane C, Gentle DL, Bruce JE, et al. Impact of body weight on urinary electrolytes in urinary stone formers. Urology. 2000;55(6):825–30.
30. Hamano S, Nakatsu H, Suzuki N, Tomioka S, Tanaka M, Murakami S. Kidney stone disease and risk factors for coronary heart disease. Int J Urol. 2005;12(10):859–63.
31. Inci M, Demirtas A, Sarli B, Akinsal E, Baydilli N. Association between body mass index, lipid profiles, and types of urinary stones. Ren Fail. 2012;34(9):1140–3.
32. Dhore CR, Cleutjens JP, Lutgens E, Cleutjens KB, Geusens PP, Kitslaar PJ, et al. Differential expression of bone matrix regulatory proteins in human atherosclerotic plaques. Arterioscler Thromb Vasc Biol. 2001;21(12):1998–2003.
33. Giachelli CM, Steitz S. Osteopontin: a versatile regulator of inflammation and biomineralization. Matrix Biol. 2000;19(7):615–22.
34. Khan SR. Crystal-induced inflammation of the kidneys: results from human studies, animal models, and tissue-culture studies. Clin Exp Nephrol. 2004;8(2):75–88.
35. Okada A, Yasui T, Fujii Y, Niimi K, Hamamoto S, Hirose M, et al. Renal macrophage migration and crystal phagocytosis via inflammatory-related gene expression during kidney stone

formation and elimination in mice: detection by association analysis of stone-related gene expression and microstructural observation. J Bone Miner Res. 2010;25(12):2701–11.
36. Liaw L, Almeida M, Hart CE, Schwartz SM, Giachelli CM. Osteopontin promotes vascular cell adhesion and spreading and is chemotactic for smooth muscle cells in vitro. Circ Res. 1994;74(2):214–24.
37. Kovacevic L, Lu H, Caruso JA, Kovacevic N, Lakshmanan Y. Urinary proteomics reveals association between pediatric nephrolithiasis and cardiovascular disease. Int Urol Nephrol. 2018;50(11):1949–54.
38. Matlaga BR, Schaeffer AJ, Novak TE, Trock BJ. Epidemiologic insights into pediatric kidney stone disease. Urol Res. 2010;38(6):453–7.
39. Schaeffer AJ, Feng Z, Trock BJ, Mathews RI, Neu AM, Gearhart JP, et al. Medical comorbidities associated with pediatric kidney stone disease. Urology. 2011;77(1):195–9.
40. Kokorowski PJ, Routh JC, Hubert KC, Graham DA, Nelson CP. Association of urolithiasis with systemic conditions among pediatric patients at children's hospitals. J Urol. 2012;188(4 Suppl):1618–22.
41. Kim SS, Luan X, Canning DA, Landis JR, Keren R. Association between body mass index and urolithiasis in children. J Urol. 2011;186(4 Suppl):1734–9.
42. Sarica K, Eryildirim B, Yencilek F, Kuyumcuoglu U. Role of overweight status on stone-forming risk factors in children: a prospective study. Urology. 2009;73(5):1003–7.
43. Sas DJ. An update on the changing epidemiology and metabolic risk factors in pediatric kidney stone disease. Clin J Am Soc Nephrol. 2011;6(8):2062–8.
44. Scales CD, Curtis LH, Norris RD, Springhart WP, Sur RL, Schulman KA, et al. Changing gender prevalence of stone disease. J Urol. 2007;177(3):979–82.
45. Scales CD, Tasian GE, Schwaderer AL, Goldfarb DS, Star RA, Kirkali Z. Urinary stone disease: advancing knowledge, patient care, and population health. Clin J Am Soc Nephrol. 2016;11(7):1305–12.
46. Daudon M, Doré JC, Jungers P, Lacour B. Changes in stone composition according to age and gender of patients: a multivariate epidemiological approach. Urol Res. 2004;32(3):241–7.
47. Domingos F, Serra A. Nephrolithiasis is associated with an increased prevalence of cardiovascular disease. Nephrol Dial Transplant. 2011;26(3):864–8.
48. Ferraro PM, Taylor EN, Eisner BH, Gambaro G, Rimm EB, Mukamal KJ, et al. History of kidney stones and the risk of coronary heart disease. JAMA. 2013;310(4):408–15.
49. Lin SY, Lin CL, Chang YJ, Hsu WH, Lin CC, Wang IK, et al. Association between kidney stones and risk of stroke: a nationwide population-based cohort study. Medicine (Baltimore). 2016;95(8):e2847.
50. Cheungpasitporn W, Thongprayoon C, Mao MA, O'Corragain OA, Edmonds PJ, Erickson SB. The risk of coronary heart disease in patients with kidney stones: a systematic review and meta-analysis. N Am J Med Sci. 2014;6(11):580–5.
51. Cauley JA. Public health impact of osteoporosis. J Gerontol A Biol Sci Med Sci. 2013;68(10):1243–51.
52. Johnell O, Kanis JA, Oden A, Johansson H, De Laet C, Delmas P, et al. Predictive value of BMD for hip and other fractures. J Bone Miner Res. 2005;20(7):1185–94.
53. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. Am J Med. 1993;94(6):646–50.
54. Khan AA, Bachrach L, Brown JP, Hanley DA, Josse RG, Kendler DL, et al. Standards and guidelines for performing central dual-energy x-ray absorptiometry in premenopausal women, men, and children. J Clin Densitom. 2004;7(1):51–64.
55. Lewiecki EM, Gordon CM, Baim S, Leonard MB, Bishop NJ, Bianchi ML, et al. International Society for Clinical Densitometry 2007 Adult and Pediatric Official Positions. Bone. 2008;43(6):1115–21.
56. Boot AM, de Ridder MA, van der Sluis IM, van Slobbe I, Krenning EP, Keizer-Schrama SM. Peak bone mineral density, lean body mass and fractures. Bone. 2010;46(2):336–41.
57. Ferrari SL, Chevalley T, Bonjour JP, Rizzoli R. Childhood fractures are associated with decreased bone mass gain during puberty: an early marker of persistent bone fragility? J Bone Miner Res. 2006;21(4):501–7.

58. Schwaderer AL, Kusumi K, Ayoob RM. Pediatric nephrolithiasis and the link to bone metabolism. Curr Opin Pediatr. 2014;26(2):207–14.
59. García-Nieto V, Ferrández C, Monge M, de Sequera M, Rodrigo MD. Bone mineral density in pediatric patients with idiopathic hypercalciuria. Pediatr Nephrol. 1997;11(5):578–83.
60. Penido MG, Lima EM, Marino VS, Tupinambá AL, França A, Souto MF. Bone alterations in children with idiopathic hypercalciuria at the time of diagnosis. Pediatr Nephrol. 2003;18(2):133–9.
61. Vezzoli G, Rubinacci A, Bianchin C, Arcidiacono T, Giambona S, Mignogna G, et al. Intestinal calcium absorption is associated with bone mass in stone-forming women with idiopathic hypercalciuria. Am J Kidney Dis. 2003;42(6):1177–83.
62. Jaeger P, Lippuner K, Casez JP, Hess B, Ackermann D, Hug C. Low bone mass in idiopathic renal stone formers: magnitude and significance. J Bone Miner Res. 1994;9(10):1525–32.
63. Kusumi K, Schwaderer AL, Clark C, Budge K, Hussein N, Raina R, et al. Bone mineral density in adolescent urinary stone formers: is sex important? Urolithiasis. 2020;48:329.
64. Kusumi K, Becknell B, Schwaderer A. Trends in pediatric urolithiasis: patient characteristics, associated diagnoses, and financial burden. Pediatr Nephrol. 2014;30:805.
65. Novak TE, Lakshmanan Y, Trock BJ, Gearhart JP, Matlaga BR. Sex prevalence of pediatric kidney stone disease in the United States: an epidemiologic investigation. Urology. 2009;74(1):104–7.
66. Rosenfield RL, Bachrach LK, Chernausek SD, Gertner JM, Gottschalk M, Hardin DS, et al. Current age of onset of puberty. Pediatrics. 2000;106(3):622–3.
67. (US) OotSG. Bone health and osteoporosis: a report of the surgeon general. 2004.
68. Richards JB, Zheng HF, Spector TD. Genetics of osteoporosis from genome-wide association studies: advances and challenges. Nat Rev Genet. 2012;13(8):576–88.
69. Spivacow FR, Negri AL, del Valle EE, Calviño I, Fradinger E, Zanchetta JR. Metabolic risk factors in children with kidney stone disease. Pediatr Nephrol. 2008;23(7):1129–33.
70. Gao B, Yasui T, Itoh Y, Li Z, Okada A, Tozawa K, et al. Association of osteopontin gene haplotypes with nephrolithiasis. Kidney Int. 2007;72(5):592–8.
71. Richards JB, Kavvoura FK, Rivadeneira F, Styrkársdóttir U, Estrada K, Halldórsson BV, et al. Collaborative meta-analysis: associations of 150 candidate genes with osteoporosis and osteoporotic fracture. Ann Intern Med. 2009;151(8):528–37.
72. Barry ST, Ludbrook SB, Murrison E, Horgan CM. Analysis of the alpha4beta1 integrin-osteopontin interaction. Exp Cell Res. 2000;258(2):342–51.
73. Thorleifsson G, Holm H, Edvardsson V, Walters GB, Styrkarsdottir U, Gudbjartsson DF, et al. Sequence variants in the CLDN14 gene associate with kidney stones and bone mineral density. Nat Genet. 2009;41(8):926–30.
74. Elkouby-Naor L, Abassi Z, Lagziel A, Gow A, Ben-Yosef T. Double gene deletion reveals lack of cooperation between claudin 11 and claudin 14 tight junction proteins. Cell Tissue Res. 2008;333(3):427–38.
75. Nicoll R, McLaren HJ. The acid-ash hypothesis revisited: a reassessment of the impact of dietary acidity on bone. J Bone Miner Metab. 2014;32(5):469–75.
76. Hanley DA, Whiting SJ. Does a high dietary acid content cause bone loss, and can bone loss be prevented with an alkaline diet? J Clin Densitom. 2013;16(4):420–5.
77. Sampath A, Kossoff EH, Furth SL, Pyzik PL, Vining EP. Kidney stones and the ketogenic diet: risk factors and prevention. J Child Neurol. 2007;22(4):375–8.
78. Schwalfenberg GK. The alkaline diet: is there evidence that an alkaline pH diet benefits health? J Environ Public Health. 2012;2012:727630.
79. Darling AL, Millward DJ, Torgerson DJ, Hewitt CE, Lanham-New SA. Dietary protein and bone health: a systematic review and meta-analysis. Am J Clin Nutr. 2009;90(6):1674–92.
80. Meng X, Zhu K, Devine A, Kerr DA, Binns CW, Prince RL. A 5-year cohort study of the effects of high protein intake on lean mass and BMC in elderly postmenopausal women. J Bone Miner Res. 2009;24(11):1827–34.
81. Kerstetter JE, Kenny AM, Insogna KL. Dietary protein and skeletal health: a review of recent human research. Curr Opin Lipidol. 2011;22(1):16–20.

82. Ho-Pham LT, Nguyen ND, Nguyen TV. Effect of vegetarian diets on bone mineral density: a Bayesian meta-analysis. Am J Clin Nutr. 2009;90(4):943–50.
83. Frassetto LA, Todd KM, Morris RC, Sebastian A. Worldwide incidence of hip fracture in elderly women: relation to consumption of animal and vegetable foods. J Gerontol A Biol Sci Med Sci. 2000;55(10):M585-92.
84. Sahni S, Cupples LA, McLean RR, Tucker KL, Broe KE, Kiel DP, et al. Protective effect of high protein and calcium intake on the risk of hip fracture in the Framingham offspring cohort. J Bone Miner Res. 2010;25(12):2770–6.
85. Calvez J, Poupin N, Chesneau C, Lassale C, Tomé D. Protein intake, calcium balance and health consequences. Eur J Clin Nutr. 2012;66(3):281–95.
86. Pak CY, Britton F, Peterson R, Ward D, Northcutt C, Breslau NA, et al. Ambulatory evaluation of nephrolithiasis. Classification, clinical presentation and diagnostic criteria. Am J Med. 1980;69(1):19–30.
87. Bataille P, Achard JM, Fournier A, Boudailliez B, Westeel PF, el Esper N, et al. Diet, vitamin D and vertebral mineral density in hypercalciuric calcium stone formers. Kidney Int. 1991;39(6):1193–205.
88. Pacifici R, Rothstein M, Rifas L, Lau KH, Baylink DJ, Avioli LV, et al. Increased monocyte interleukin-1 activity and decreased vertebral bone density in patients with fasting idiopathic hypercalciuria. J Clin Endocrinol Metab. 1990;71(1):138–45.
89. Sakhaee K, Maalouf NM, Kumar R, Pasch A, Moe OW. Nephrolithiasis-associated bone disease: pathogenesis and treatment options. Kidney Int. 2011;79(4):393–403.
90. Schulz E, Arfai K, Liu X, Sayre J, Gilsanz V. Aortic calcification and the risk of osteoporosis and fractures. J Clin Endocrinol Metab. 2004;89(9):4246–53.
91. Leopold JA. Vascular calcification: mechanisms of vascular smooth muscle cell calcification. Trends Cardiovasc Med. 2015;25(4):267–74.
92. Parhami F, Tintut Y, Beamer WG, Gharavi N, Goodman W, Demer LL. Atherogenic high-fat diet reduces bone mineralization in mice. J Bone Miner Res. 2001;16(1):182–8.
93. Naito S, Ito M, Sekine I, Hirano T, Iwasaki K, Niwa M. Femoral head necrosis and osteopenia in stroke-prone spontaneously hypertensive rats (SHRSPs). Bone. 1993;14(5):745–53.
94. Fabris A, Ferraro PM, Comellato G, Caletti C, Fantin F, Zaza G, et al. The relationship between calcium kidney stones, arterial stiffness and bone density: unraveling the stone-bone-vessel liaison. J Nephrol. 2015;28(5):549–55.
95. Huang MY, Chaturvedi LS, Koul S, Koul HK. Oxalate stimulates IL-6 production in HK-2 cells, a line of human renal proximal tubular epithelial cells. Kidney Int. 2005;68(2):497–503.
96. de Water R, Leenen PJ, Noordermeer C, Nigg AL, Houtsmuller AB, Kok DJ, et al. Cytokine production induced by binding and processing of calcium oxalate crystals in cultured macrophages. Am J Kidney Dis. 2001;38(2):331–8.
97. Canales BK, Anderson L, Higgins L, Slaton J, Roberts KP, Liu N, et al. Second prize: comprehensive proteomic analysis of human calcium oxalate monohydrate kidney stone matrix. J Endourol. 2008;22(6):1161–7.
98. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003;107(3):499–511.
99. Jimi E, Nakamura I, Ikebe T, Akiyama S, Takahashi N, Suda T. Activation of NF-kappaB is involved in the survival of osteoclasts promoted by interleukin-1. J Biol Chem. 1998;273(15):8799–805.
100. Kotake S, Sato K, Kim KJ, Takahashi N, Udagawa N, Nakamura I, et al. Interleukin-6 and soluble interleukin-6 receptors in the synovial fluids from rheumatoid arthritis patients are responsible for osteoclast-like cell formation. J Bone Miner Res. 1996;11(1):88–95.
101. Kurihara N, Bertolini D, Suda T, Akiyama Y, Roodman GD. IL-6 stimulates osteoclast-like multinucleated cell formation in long term human marrow cultures by inducing IL-1 release. J Immunol. 1990;144(11):4226–30.

102. Chu DI, Tasian GE, Copelovitch L. Pediatric kidney stones—avoidance and treatment. Curr Treat Options Pediatr. 2016;2(2):104–11.
103. Tang J, McFann KK, Chonchol MB. Association between serum 25-hydroxyvitamin D and nephrolithiasis: the National Health and nutrition examination survey III, 1988-94. Nephrol Dial Transplant. 2012;27(12):4385–9.
104. Letavernier E, Daudon M, Vitamin D. Hypercalciuria and kidney stones. Nutrients. 2018;10:3.
105. Ferraro PM, Taylor EN, Gambaro G, Curhan GC. Vitamin D intake and the risk of incident kidney stones. J Urol. 2017;197(2):405–10.
106. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357(3):266–81.
107. Lajeunesse D, Delalandre A, Guggino SE. Thiazide diuretics affect osteocalcin production in human osteoblasts at the transcription level without affecting vitamin D3 receptors. J Bone Miner Res. 2000;15(5):894–901.
108. Fernández-Rodríguez A, Arrabal-Martín M, García-Ruiz MJ, Arrabal-Polo MA, Pichardo-Pichardo S, Zuluaga-Gómez A. The role of thiazides in the prophylaxis of recurrent calcium lithiasis. Actas Urol Esp. 2006;30(3):305–9.
109. Legroux-Gerot I, Catanzariti L, Marchandise X, Duquesnoy B, Cortet B. Bone mineral density changes in hypercalciuretic osteoporotic men treated with thiazide diuretics. Joint Bone Spine. 2004;71(1):51–5.
110. Reusz GS, Dobos M, Vásárhelyi B, Sallay P, Szabó A, Horváth C, et al. Sodium transport and bone mineral density in hypercalciuria with thiazide treatment. Pediatr Nephrol. 1998;12(1):30–4.
111. Jehle S, Zanetti A, Muser J, Hulter HN, Krapf R. Partial neutralization of the acidogenic Western diet with potassium citrate increases bone mass in postmenopausal women with osteopenia. J Am Soc Nephrol. 2006;17(11):3213–22.
112. Jehle S, Hulter HN, Krapf R. Effect of potassium citrate on bone density, microarchitecture, and fracture risk in healthy older adults without osteoporosis: a randomized controlled trial. J Clin Endocrinol Metab. 2013;98(1):207–17.
113. Pak CY, Peterson RD, Poindexter J. Prevention of spinal bone loss by potassium citrate in cases of calcium urolithiasis. J Urol. 2002;168(1):31–4.
114. Moreira Guimarães Penido MG, de Sousa Tavares M, Campos Linhares M, Silva Barbosa AC, Cunha M. Longitudinal study of bone mineral density in children with idiopathic hypercalciuria. Pediatr Nephrol. 2012;27(1):123–30.
115. Lloyd-Jones DM, Wilson PW, Larson MG, Beiser A, Leip EP, D'Agostino RB, et al. Framingham risk score and prediction of lifetime risk for coronary heart disease. Am J Cardiol. 2004;94(1):20–4.
116. Taylor EN, Fung TT, Curhan GC. DASH-style diet associates with reduced risk for kidney stones. J Am Soc Nephrol. 2009;20(10):2253–9.
117. Alexander RT, Hemmelgarn BR, Wiebe N, Bello A, Samuel S, Klarenbach SW, et al. Kidney stones and cardiovascular events: a cohort study. Clin J Am Soc Nephrol. 2014;9(3):506–12.
118. Pietrow PK, Pope JC, Adams MC, Shyr Y, Brock JW. Clinical outcome of pediatric stone disease. J Urol. 2002;167(2 Pt 1):670–3.
119. Chung SD, Liu SP, Keller JJ, Lin HC. Urinary calculi and an increased risk of stroke: a population-based follow-up study. BJU Int. 2012;110(11 Pt C):E1053-9.
120. Artemiuk I, Pańczyk-Tomaszewska M, Adamczuk D, Przedlacki J, Roszkowska-Blaim M. Bone mineral density in children with idiopathic hypercalciuria. Dev Period Med. 2015;19(3 Pt 2):356–61.
121. Escribano J, Rubio-Torrents C, Ferré N, Luque V, Grote V, Zaragoza-Jordana M, et al. Reduced bone mass in 7-year-old children with asymptomatic idiopathic hypercalciuria. Ann Nutr Metab. 2014;64(3–4, 304):–13.
122. Moreira Guimarães Penido MG, de Sousa TM. Bone disease in pediatric idiopathic hypercalciuria. World J Nephrol. 2012;1(2):54–62.
123. Schwaderer AL, Srivastava T, Schueller L, Cronin R, Mahan JD, Hains D. Dietary modifications alone do not improve bone mineral density in children with idiopathic hypercalciuria. Clin Nephrol. 2011;76(5):341–7.

124. Penido MG, Lima EM, Souto MF, Marino VS, Tupinambá AL, França A. Hypocitraturia: a risk factor for reduced bone mineral density in idiopathic hypercalciuria? Pediatr Nephrol. 2006;21(1):74–8.
125. Skalova S, Palicka V, Kutilek S. Bone mineral density and urinary N-acetyl-beta-D-glucosaminidase activity in paediatric patients with idiopathic hypercalciuria. Nephrology (Carlton). 2005;10(2):99–102.
126. García-Nieto V, Navarro JF, Monge M, García-Rodríguez VE. Bone mineral density in girls and their mothers with idiopathic hypercalciuria. Nephron Clin Pract. 2003;94(4):c89–93.
127. Polito C, Iolascon G, Nappi B, Andreoli S, La Manna A. Growth and bone mineral density in long-lasting idiopathic hypercalciuria. Pediatr Nephrol. 2003;18(6):545–7.
128. Freundlich M, Alonzo E, Bellorin-Font E, Weisinger JR. Reduced bone mass in children with idiopathic hypercalciuria and in their asymptomatic mothers. Nephrol Dial Transplant. 2002;17(8):1396–401.
129. Reusz G. Idiopathic hypercalciuria in childhood. Orv Hetil. 1998;139(49):2957–62.

Chapter 15
Obesity and Pediatric Nephrolithiasis

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Introduction

There is an ongoing obesity epidemic in the United States and in many other parts of the Western World. This involves not only adults, but it extends to children. In 1975, the childhood obesity prevalence was 4%. In 2016, this same statistic was 18% [1]. In parallel, there has been an increase in both the incidence and prevalence of pediatric nephrolithiasis. [2]. The purpose of this book chapter is to examine the current association between obesity and kidney stones in children.

Epidemiology

Once considered relatively rare, pediatric nephrolithiasis has become exceedingly more common. Between 1984 and 2008, the incidence of pediatric nephrolithiasis increased 4% per year [2]. Similarly, the proportion of patients with pediatric kidney stones in a freestanding hospital increased 10.6% in 2008 alone [3]. There have been many proposed theories for these increases including climate change, dietary habits, and obesity [4]. For example, when looking at the incidence of pediatric

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kidney stones from 1997 to 2012 in South Carolina in 15–19-year-olds, there was a 26% increase over 5 years (incidence rate ratio, 1.26; 95% confidence interval, 1.22–1.29). These increases in incidence were most prominent in females (relative to males) and in blacks (relative to whites) [5]. Other studies have looked at the same database of South Carolina patients and reported an increased prevalence of pediatric nephrolithiasis [6]. However, they did not report the same trends with race and gender.

Interestingly, female adolescents have a higher rate of stone formation compared to male adolescents, inverse to what is seen in the adult population [7]. Even in the adult population, trends from 1997 to 2002 showed the ratio of prevalence of kidney stones between genders has shifted from 1.7:1 to 1.3:1 male-to-female [8]. In addition, a study from 2002–2007 showed that adolescent females were 1.5 times more likely to be hospitalized for kidney stones [9]. In that same study, 88% of pediatric patients hospitalized for kidney stones were white and hospitalizations were more common in the North Central region compared to the Southern United States. These trends suggest that perhaps other factors, outside of obesity, may contribute to kidney stone risk in children as compared to adults.

There is compelling epidemiologic evidence demonstrating the association between obesity and incident kidney stones in adult cohorts [10–12]. However, this association is not as clearly demonstrated in children. In a multivariate analysis of the Kid's Inpatient Database ("KID"), Schaeffer and associates found that obesity did not influence the need for inpatient hospitalization for kidney stones [13]. In contrast, Kokorowski and colleagues, in a multivariable conditional logistic regression analysis of the Pediatric Health Information System Database, found a significantly higher odds ratio for kidney stones in obese subjects. Both groups also reported positive correlations with kidney stones and hypertension, a condition associated with kidney stone risk.

With the rise in both obesity and kidney stones in children, one might expect a tangible relationship [14]. However, when examining trends from 1999–2010 in pediatric obesity, there was an increase in BMI among boys age 12–19 ($p = 0.04$), but no such increase in any other age group or in girls [15]. In contrast, the increase in pediatric kidney stones seems to be predominantly adolescent girls [16]. Another study found no significant relationship between BMI and urolithiasis, but did find a significant decrease in the odds of urolithiasis in black race and Medicaid payer status [17]. While the aforementioned studies collectively do not identify a relationship between obesity and kidney stones in children, pediatric kidney stone formers may just be in a prodrome state marching towards obesity. Thus, longitudinal studies of this cohort are warranted [2, 18–22].

Diet and Nutrition

If we hypothesize that kidney stone formers are in a march towards obesity, nutritional habits of children in general need to be taken into consideration. Two dietary habits in children, low fluid intake and increased sodium consumption, can both

lead to an increase in the supersaturation of stone forming salts, a surrogate for kidney stone risk [23, 24]. Children, on average, spend more time exercising and playing outdoors than adults, and therefore require more water on average per body weight. To compound this, children often do not meet their daily water intake requirements [25, 26]. A univariate and multivariate analysis demonstrated that overweight and obese children have lower urinary volumes than their normal-weight counterparts [27].

Two-thirds of water intake in the pediatric population occurs at mealtimes, perhaps indicating that during non-mealtimes many children are not adequately hydrating. Additionally, the same study found all age groups had a mean water intake that was less than the suggested adequate water intake. The aforementioned fluid consumption patterns may serve as a major contributing factor to stone disease [28]. In addition, water intake has been shown to be inversely associated with the consumption of energy dense foods, suggesting the unhealthier a child's diet, the less water intake they will have. It is well established that obese children eat a poorly energy dense diet, thus suggesting this cohort may be more susceptible to stone formation based on dietary and water intake factors.

In regard to sodium, an analysis of NHANES data has demonstrated that the average sodium consumption for the pediatric population was close to 3400 mg/day, when the recommended daily allowance is less than 2300 mg/day [29]. Sodium intake is positively correlated to urinary calcium excretion and the latter is correlated to kidney stone risk (Table 15.1).

It is well described that high sodium diets predispose to stone formation. These same high salt diets typically go hand-in-hand with high fat, high carbohydrate diets, potentially resulting in obesity [20]. BMI directly correlated with increases in urinary sodium, calcium, uric acid, magnesium, and oxalate, while also decreasing the urinary pH. In addition to higher urinary volumes and low dietary sodium, weight reduction would be useful when counseling stone formers [30].

In a mouse model, feeding mice a diet rich in both sodium and fructose yielded both an increase in uric acid in the urine and a decrease in "stone inhibitors," such as magnesium and citrate [31]. Not only did increasing intake of sodium result in more sodium in the urine, effectively concentrating the urine output, but the decrease in protective factors such as magnesium and citrate further increase the risk of stone formation. It is important to note that adolescents, aged 12–18, have the greatest consumption of fructose (73 g/day) than any other age group [32].

The association between sugar-sweetened beverages and obesity and Type II diabetes in children and adolescents has been demonstrated by several epidemiological

Table 15.1 Risk factors for pediatric stone forming patients [7]

Risk factors in pediatric stone formers	Note
Decreased fluid intake	<3 L/day
Increased salt intake	>2300 mg/day
Metabolic abnormalities	Hypercalciuria, hypocitraturia
Environmental	Temperature, relative humidity
Medications	Topiramate, calcitriol, steroids

trials [33]. The intake of sugar-sweetened beverages, such as soda and juice, has been on the climb in the United States [34]. Providing children and adolescents with proper knowledge of nutrition may be a necessary primary preventative measure, thereby reducing obesity and any downstream disease, such as pediatric kidney stone disease [35].

Obesity may lead to a plethora of other acute and chronic renal conditions, including an increased risk of urinary tract infections (UTIs). UTIs can increase risk of certain types of kidney stones. At all data stratifications, obese patients were significantly more likely to be diagnosed with a UTI or pyelonephritis than non-obese patients. The data remains inadequate to draw such conclusions in children, thus necessitating the requirement for more studies to be conducted analyzing obesity, UTIs, and infection-related stones [36].

24-Hour Urine

24-hour urine has widely been considered the gold standard in the workup of pediatric urolithiasis. Normal values can vary based on a child's age, gender, growth status, and race. Given the wide range of a child's diet, environment, and genetics, two 24-hour urine collections are now becoming a common component of clinical workup. While there are no studies yet suggesting how many 24-hour urine samples are adequate for children, adult studies support two collections on initial presentation [37–39]. Spot 24-hour urine testing has been utilized to assess stone risk but due to its shortcomings is mainly used in situations where accurate 24-hour urine specimens cannot be collected.

One study retrospectively analyzed 110 stone forming pediatric patients and sorted these patients into two groups: BMI below 85th percentile and BMI above 85th percentile. When analyzing the 24-h urine parameters of these patients, the study found that overweight and obese patients (BMI >85th percentile) had lower body surface area adjusted citrate ($p = 0.03$), lower urine phosphate ($p = 0.04$), lower urine magnesium ($p = 0.01$), and an increased incidence of hypercalciuria ($p = 0.02$). While this study did not find an association between BMI and urine pH, it may help describe the causal pathway of obesity, to changes in 24-h urinary parameters, to eventual stone formation in obese pediatric patients [40]. Despite some studies showing 24-h urine differences, other studies have determined that BMI itself could not be considered a separate and definite risk factor for urolithiasis in pediatric patients [41]. The lack of consistent findings further warrant larger studies to investigate pediatric BMI and its effects on 24-h urinary parameters.

There have been attempts to associate pediatric stone formation with metabolic disorders, such as hypocitraturia [42]. These disease states, including metabolic syndrome, affect urinary parameters, thereby theoretically increasing the risk of pediatric stone formation. When measuring BMI, urinary pH, and other parameters in obese adolescents, it appears those diagnosed with metabolic syndrome have specific urine findings: decreased urinary pH and increased relative saturation ratio

Table 15.2 Abnormal 24-h urinary findings in pediatric stone formers [68, 69].

	Abnormal Values
Calcium	>4.0 mg/kg/day
Uric acid	>10.7 mg/kg/day
Oxalate	>40 mg/1.73 m^2/day
Citrate	<320 mg/1.73m^2/day
Magnesium	<1.2 mg/kg/day
Calcium/citrate	>0.33 mg/mg

of calcium oxalate [43]. 24-h urine studies have also demonstrated that pediatric kidney stone formers have lower urine volume, higher calcium excretion, and increases in the relative supersaturation of calcium phosphate and calcium oxalate [44] (Table 15.2). One single-institution study looked closer at the urinary mineral profile and showed that obese pediatric patients do have lower levels of citrate, potassium, and urine pH compared to their normal-weight counterparts [22].

While poor nutrition may lead to obesity and predispose to pediatric stone disease, proper nutrition may be the key to stone prevention for the patient. Newer nutritional guidelines have been published that suggest increasing fluid intake to 3 L, trying to maintain 2 L of daily urine output to prevent supersaturation of calcium, and increasing urinary citrate with lemon and orange juices [45]. Additionally, limiting sodium intake per child age group (to less than <2 g of sodium per day) and increasing intake of fruits and vegetables to alkalinize the urine all help prevent stone formation in pediatric patients [46]. Other guidelines broadly suggest low-protein (<20 g daily), low-salt (<2 g daily), and adequate hydration (3 L daily) [47].

Stone Composition

In children, most stones are a composition consisting of calcium oxalate and/or calcium phosphate, with mixed uric acid stones having a relatively higher prevalence compared to the adult population [48]. This differs slightly from adults where mixed uric acid stones are much less common. A study showed that as pediatric BMI increased, urine oxalate excretion decreased, and supersaturation of calcium phosphate increased [49]. Another study hypothesized is that the pediatric population may have different renal handling of solutes compared to adults and may have more pronounced effects of diet on the renal handling of uric acid.

The western diet, rich in animal protein, refined carbohydrates, processed foods, and added sugar, act as an acid load on the body, which may explain the uric acid found in pediatric kidney stones. It is possible that obesity may not directly lead to stone formation, instead that the dietary indiscretions seen in obese children may predispose to increased calcium phosphate, calcium oxalate, and/or uric acid in the renal tubules. The complexity of stone composition changes in the pediatric population over time makes it difficult to determine any one cause for the changes [50, 51].

A composition analysis of 5245 pediatric urinary stones between the years of 2000 and 2009 determined that calcium was seen in 89% of all stones and that ammonium-containing stones decreased with age [52]. Additionally, a 24-h urine analysis in the pediatric stone population showed that calcium oxalate stones have a stronger association with calciuria and a moderate association with oxaluria, magnesuria, and acidification of urine, whereas calcium phosphate stones had lower associations with urinary risk factors, suggesting calcium oxalate stones may be more closely linked to traditional risk factors [53].

Medical Management

Should a pediatric patient, obese or not, experience severe or recurrent stone disease, treatment may progress from dietary to medical.

Interestingly, medications alone are typically not the most beneficial treatment. Following general guidelines, such as increasing or decreasing certain dietary parameters, adding or removing specific food groups, or adjusting fluid intake, play an additive or synergistic role with the aforementioned medications [54]. Eighty five percent of patients could significantly decrease their risk of stone recurrence by taking primary precautions such as adjusting their lifestyle and dietary habits. In the remaining 15% in which stones continued to recur, the combination therapy of thiazides and citrate therapy were sufficient as medical treatment [55] (Table 15.3).

Surgical Management and Techniques

Should non-surgical management of acute pediatric stone disease fail, there are more immediate and invasive approaches to treating the stone [48]. If medical expulsion therapy or other non-invasive treatments fail, surgical interventions such as extracorporeal shockwave lithotripsy, ureteroscopy (URS), and percutaneous nephrolithotomy may be indicated [56] (Table 15.4).

Table 15.3 Associated urinary findings with possible medical management [70]

Urinary metabolic findings	Suggested medical treatment(s)	Suggested dietary treatment(s)
Hypercalciuria	Thiazide diuretics	Decreased salt intake
Hypocitraturia	Potassium citrate	Increased fruit and veggies
Hyperuricosuria	Allopurinol	Decreased protein intake
Hypernatriuria	None	Decreased salt intake
Hyperoxaluria	Pyridoxine	Reduction of oxalate-rich foods (e.g., spinach)
Low pH	Alkalinization therapy	Decreased protein intake

Table 15.4 Pros and cons of main surgical approaches in pediatric patients [7]

Type of Surgical Approach	Pros	Cons
Shockwave lithotripsy	Non-invasive	Lower success rate, post-operative HTN
Ureteroscopy	Better stone clearance, advancing technology	Ureteral stenting, dependent on available technology
Percutaneous nephrolithotomy	High success rate	Invasive, increased surgical complications

Historically, extracorporeal shockwave lithotripsy was considered the preferred management, particularly for stones <20 mm [57]. Recent analyses of surgical techniques at major institutions across the United States have shown ureteroscopy is quickly gaining traction as arguably a better surgical approach, particularly in children [58]. Advances in endoscopy, including scope size and improved optics, has allowed for the adoption of ureteroscopy in the pediatric population, particularly in obese patients that present with more challenging anatomy.

While ureteroscopy is gaining traction and may overtake shockwave lithotripsy as the first-line surgical intervention in pediatric patients, it is important to note the challenges and limitations with this modality. A child's ureters are still developing and are both fragile and smaller than adult ureters, occasionally necessitating pre-stenting. Rarely, a ureteral stricture may occur, requiring ureteral reimplantation [59, 60]. With advancements in both optics and in the size of the ureteroscope, these complications are likely to decrease with time, cementing this as a safe and efficacious first-line surgical intervention in the pediatric population [61].

In terms of relative outcomes, ureteroscopy complications are not significantly different from shockwave lithotripsy. The success rates of the two types of operations were around 90% and not significantly different [62]. The challenging component of applying adult ureteroscopy techniques towards a pediatric population are surgeon training, ability, experience, and available technology [63]. It may be in the urologist's best interest to consider utilizing the latest ureteroscopy technology, with semi-rigid or flexible scopes, given a pediatric patient's fragile anatomy [64]. Should a stone's burden exceed 20 mm, progression to percutaneous nephrolithomy is typically the next best indication [65].

In the case of failure of progression from nephrolithiasis to urolithiasis, retrograde intrarenal surgery (RIRS) may be the next step. The RIRS approach has risen to the first rank in the preference of pediatric urologists, partly due to the method's reliability and efficacy. It may serve as a replacement for shockwave lithotripsy in small renal calculi and percutaneous nephrolithotomy in larger renal calculi [66]. The RIRS approach has been shown to be similar in overweight or obese pediatric patients when compared to normal weight, making it a useful surgical technique in this population as well [67].

Conclusion

Despite the existing evidence that obesity is linked to stones in adults, the evidence remains unclear if obesity plays a role in children. Further research into this area is needed.

References

1. Greydanus DE, et al. Pediatric obesity: current concepts. Dis Mon. 2018;64(4):98–156.
2. Dwyer ME, et al. Temporal trends in incidence of kidney stones among children: a 25-year population based study. J Urol. 2012;188(1):247–52.
3. Routh JC, Graham DA, Nelson CP. Epidemiological trends in pediatric urolithiasis at United States freestanding pediatric hospitals. J Urol. 2010;184(3):1100–4.
4. Clayton DB, Pope JC. The increasing pediatric stone disease problem. Ther Adv Urol. 2011;3(1):3–12.
5. Tasian GE, et al. Annual incidence of nephrolithiasis among children and adults in South Carolina from 1997 to 2012. Clin J Am Soc Nephrol. 2016;11(3):488–96.
6. Vicedo-Cabrera AM, et al. Sex differences in the temperature dependence of kidney stone presentations: a population-based aggregated case-crossover study. Urolithiasis. 2020;48(1):37–46.
7. Bowen DK, Tasian GE. Pediatric stone disease. Urol Clin North Am. 2018;45(4):539–50.
8. Scales CD Jr, et al. Changing gender prevalence of stone disease. J Urol. 2007;177(3):979–82.
9. Bush NC, et al. Hospitalizations for pediatric stone disease in United States, 2002–2007. J Urol. 2010;183(3):1151–6.
10. Antonelli JA, et al. Use of the National Health and Nutrition Examination Survey to calculate the impact of obesity and diabetes on cost and prevalence of urolithiasis in 2030. Eur Urol. 2014;66(4):724–9.
11. Sorensen MD, et al. Activity, energy intake, obesity, and the risk of incident kidney stones in postmenopausal women: a report from the Women's Health Initiative. J Am Soc Nephrol. 2014;25(2):362–9.
12. Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. JAMA. 2005;293(4):455–62.
13. Schaeffer AJ, et al. Medical comorbidities associated with pediatric kidney stone disease. Urology. 2011;77(1):195–9.
14. Prevention, C.f.D.C.a., *Prevalence of childhood obesity in the United States*, in *CDC Official Statistics*. 2019, CDC: Division of Nutrition, Physical Activity, and Obesity, National Center for Chronic Disease Prevention and Health Promotion.
15. Ogden CL, et al. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. JAMA. 2012;307(5):483–90.
16. Saadeh SA. Pediatric nephrolithiasis: risk factors, evaluation, and prevention. Pediatr Ann. 2020;49(6):e262–7.
17. Kim SS, et al. Association between body mass index and urolithiasis in children. J Urol. 2011;186(4 Suppl):1734–9.
18. Roddy JT, et al. Metabolic evaluation of urolithiasis and obesity in a midwestern pediatric population. J Urol. 2014;191(3):771–6.
19. Ogden CL, et al. Trends in obesity prevalence among children and adolescents in the United States, 1988-1994 through 2013–2014. JAMA. 2016;315(21):2292–9.
20. Kieran K, et al. Pediatric urolithiasis—does body mass index influence stone presentation and treatment? J Urol. 2010;184(4 Suppl):1810–5.

21. Ogden CL, Carroll MD, Flegal KM. High body mass index for age among US children and adolescents, 2003–2006. JAMA. 2008;299(20):2401–5.
22. Murphy MO, et al. Influence of BMI in nephrolithiasis in an Appalachian pediatric population: a single-center experience. J Pediatr Urol. 2018;14(4):330 e1–8.
23. Sorensen MD, et al. Impact of nutritional factors on incident kidney stone formation: a report from the WHI OS. J Urol. 2012;187(5):1645–9.
24. Ferraro PM, et al. Dietary and lifestyle risk factors associated with incident kidney stones in men and women. J Urol. 2017;198(4):858–63.
25. Leung CW, et al. Sugar-sweetened beverage and water intake in relation to diet quality in U.S. children. Am J Prev Med. 2018;54(3):394–402.
26. Suh H, Kavouras SA. Water intake and hydration state in children. Eur J Nutr. 2019;58(2):475–96.
27. Cambareri GM, et al. Do overweight and obese pediatric stone formers have differences in metabolic abnormalities compared with normal-weight stone formers? Urology. 2017;101:26–30.
28. Kant AK, Graubard BI. Contributors of water intake in US children and adolescents: associations with dietary and meal characteristics—National Health and Nutrition Examination Survey 2005–2006. Am J Clin Nutr. 2010;92(4):887–96.
29. Yang Q, et al. Sodium intake and blood pressure among US children and adolescents. Pediatrics. 2012;130(4):611–9.
30. Eisner BH, Eisenberg ML, Stoller ML. Relationship between body mass index and quantitative 24-hour urine chemistries in patients with nephrolithiasis. Urology. 2010;75(6):1289–93.
31. Ross SS, et al. The effect of dietary sodium and fructose intake on urine and serum parameters of stone formation in a pediatric mouse model: a pilot study. J Urol. 2013;190(4 Suppl):1484–9.
32. Vos MB, et al. Dietary fructose consumption among US children and adults: the Third National Health and Nutrition Examination Survey. Medscape J Med. 2008;10(7):160.
33. Yoshida Y, Simoes EJ. Sugar-sweetened beverage, obesity, and type 2 diabetes in children and adolescents: policies, taxation, and programs. Curr Diab Rep. 2018;18(6):31.
34. Tahmassebi JF, BaniHani A. Impact of soft drinks to health and economy: a critical review. Eur Arch Paediatr Dent. 2020;21(1):109–17.
35. van Westing AC, Kupers LK, Geleijnse JM. Diet and kidney function: a literature review. Curr Hypertens Rep. 2020;22(2):14.
36. Semins MJ, et al. The impact of obesity on urinary tract infection risk. Urology. 2012;79(2):266–9.
37. Nayan M, Elkoushy MA, Andonian S. Variations between two 24-hour urine collections in patients presenting to a tertiary stone clinic. Can Urol Assoc J. 2012;6(1):30–3.
38. Parks JH, et al. A single 24-hour urine collection is inadequate for the medical evaluation of nephrolithiasis. J Urol. 2002;167(4):1607–12.
39. Yagisawa T, Chandhoke PS, Fan J. Comparison of comprehensive and limited metabolic evaluations in the treatment of patients with recurrent calcium urolithiasis. J Urol. 1999;161(5):1449–52.
40. Bandari J, et al. 24-hour urinary parameters in overweight and obese children with urolithiasis. J Urol. 2016;196(2):526–30.
41. Caltik Yilmaz A, et al. Influence of body mass index on pediatric urolithiasis. J Pediatr Urol. 2015;11(6):350 e1-6.
42. Vieira MS, et al. Association between dietary pattern and metabolic disorders in children and adolescents with urolithiasis. J Pediatr. 2020;96(3):333–40.
43. Tiwari R, et al. Metabolic syndrome in obese adolescents is associated with risk for nephrolithiasis. J Pediatr. 2012;160(4):615–620 e2.
44. Sas DJ, et al. Clinical, demographic, and laboratory characteristics of children with nephrolithiasis. Urolithiasis. 2016;44(3):241–6.
45. Carvalho-Salemi J, Moreno L, Michael M. Medical nutrition therapy for Pediatric kidney stone prevention, part one. J Ren Nutr. 2017;27(1):e5–8.

46. Carvalho-Salemi J, Moreno L, Michael M. Medical nutrition therapy for pediatric kidney stone prevention, part two. J Ren Nutr. 2017;27(2):e11–4.
47. Prezioso D, et al. Dietary treatment of urinary risk factors for renal stone formation. A review of CLU working group. Arch Ital Urol Androl. 2015;87(2):105–20.
48. Miah T, Kamat D. Pediatric nephrolithiasis: a review. Pediatr Ann. 2017;46(6):e242–4.
49. Eisner BH, Eisenberg ML, Stoller ML. Influence of body mass index on quantitative 24-hour urine chemistry studies in children with nephrolithiasis. J Urol. 2009;182(3):1142–5.
50. Wood KD, et al. Changing stone composition profile of children with nephrolithiasis. Urology. 2013;82(1):210–3.
51. Alaya A, Nouri A, Najjar MF. Urinary stone composition in pediatric patients: a retrospective study of 205 cases. Clin Chem Lab Med. 2011;49(2):243–8.
52. Gabrielsen JS, et al. Pediatric urinary stone composition in the United States. J Urol. 2012;187(6):2182–7.
53. Kirejczyk JK, et al. An association between kidney stone composition and urinary metabolic disturbances in children. J Pediatr Urol. 2014;10(1):130–5.
54. D'Alessandro C, et al. Which diet for calcium stone patients: a real-world approach to preventive care. Nutrients. 2019;11:5.
55. Straub M, Hautmann RE. Developments in stone prevention. Curr Opin Urol. 2005;15(2):119–26.
56. Van Batavia JP, Tasian GE. Clinical effectiveness in the diagnosis and acute management of pediatric nephrolithiasis. Int J Surg. 2016;36(Pt D):698–704.
57. Alsagheer G, et al. Extracorporeal shock wave lithotripsy (ESWL) monotherapy in children: predictors of successful outcome. J Pediatr Urol. 2017;13(5):515 e1–5.
58. Ost MC, Fox PJ Jr. Pediatric ureteroscopy. J Endourol. 2018;32(S1):S117–8.
59. Singh A, et al. Ureteral access sheath for the management of pediatric renal and ureteral stones: a single center experience. J Urol. 2006;175(3 Pt 1):1080–2. discussion 1082
60. Smaldone MC, et al. Is ureteroscopy first line treatment for pediatric stone disease? J Urol. 2007;178(5):2128–31. discussion 2131
61. Utangac MM, Sancaktutar AA, Tepeler A. Micro-ureteroscopy for the treatment of distal ureteral calculi in children. J Pediatr Surg. 2017;52(3):512–6.
62. Galal EM, Fath El-Bab TK, Abdelhamid AM. Outcome of ureteroscopy for treatment of pediatric ureteral stones. J Pediatr Urol. 2013;9(4):476–8.
63. Satar N, et al. Rigid ureteroscopy for the treatment of ureteral calculi in children. J Urol. 2004;172(1):298–300.
64. Tan AH, et al. Ureteroscopy for pediatric urolithiasis: an evolving first-line therapy. Urology. 2005;65(1):153–6.
65. Assimos D, et al. Surgical Management of Stones: American Urological Association/ Endourological Society Guideline, PART I. J Urol. 2016;196(4):1153–60.
66. Ozgur BC, et al. Pediatric extracorporeal shock wave lithotripsy: multi-institutional results. Urologia. 2016;83(2):83–6.
67. Caskurlu T, et al. The impact of body mass index on the outcomes of retrograde intrarenal stone surgery. Urology. 2013;81(3):517–21.
68. Bak M, et al. The metabolic etiology of urolithiasis in Turkish children. Int Urol Nephrol. 2009;41(3):453–60.
69. Cameron MA, Sakhaee K, Moe OW. Nephrolithiasis in children. Pediatr Nephrol. 2005;20(11):1587–92.
70. Gul Z, Monga M. Medical and dietary therapy for kidney stone prevention. Korean J Urol. 2014;55(12):775–9.

Index

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