Chapter 1
Epidemiology of Pediatric Nephrolithiasis

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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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N. J. Paloian, K. L. Penniston (eds.), *Diagnosis and Management of Pediatric Nephrolithiasis*, https://doi.org/10.1007/978-3-031-07594-0_1

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 non-specific 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.