Pediatric nephrolithiasis is an important kidney disorder encountered in clinical practice. Although nephrolithiasis is less common in children than in adults, its incidence in children is rising and can cause complications and lead to significant medical costs. Metabolic abnormalities associated with nephrolithiasis are more common in children than in adults and can result in frequent kidney stone recurrence. However, to our knowledge, there is a lag in quality data on nephrolithiasis in children compared with data on adults. This review examines the current state of evaluation and treatment of children with nephrolithiasis based on the relevant literature.

**Current Trends and Risk Factors**

Previously reported incidences of pediatric nephrolithiasis in the United States have ranged from 1 in 1000 to 1 in 7600 hospital admissions from 1970 to 1990. A recent study reported that the rate of hospitalization increased to 1 in 685 admissions from 2002 to 2007. Based on a published case series, nephrolithiasis is historically more common in boys than in girls. Population-based studies are showing an increasing incidence of kidney stones in children, with a significant rise now being demonstrated in girls. These observational studies have not yet been able, however, to establish the cause of these increases.

In a retrospective series from Schneider Children’s Hospital in New York, VanDervoort et al reported a 5-fold increase in the number of children diagnosed with nephrolithiasis from 1994 to 2005. Similarly, emergency department data from South Carolina demonstrated a dramatic increase in the incidence of nephrolithiasis in children between 1996 and 2007. The incidence in 1996 was approximately 8 per 100 000 children and increased to approximately 18 per 100 000 children in 2007. The ratio of boys to girls was 1:1.4, with the discrepancy in sex distribution becoming more obvious in the adolescent age group. An increased number of adolescents were diagnosed with kidney stones at age 14 to 18 years. Because the symptoms of nephrolithiasis in this age group are not subtle, the trends are not likely to be a result of reporting bias.

Routh et al conducted a study using the Pediatric Health Information System national database and demonstrated an increased incidence of nephrolithiasis in children. The data from 1999 to 2008 included all inpatient admissions, ambulatory short-stay...
areas, and emergency departments involving patients younger than 18 years with nephrolithiasis. Sex distribution was almost equal; however, with age stratification, more kidney stones were seen in younger boys but greater proportions of girls aged 12 to 18 years had kidney stones. After correcting for patient volume, the incidence of nephrolithiasis was 18 per 100 000 patients in 1999 and increased to 57 per 100 000 patients in 2008. The mean annual increase was 10.6%. This is an alarming increase and could be explained in part by practice pattern changes in that adult urologists are now more likely to refer patients to pediatric centers as opposed to treating the patients themselves. This shift would account for some of the increase observed in the children’s hospitals that were registered in the database but is unlikely to represent the complete explanation.

In the Rochester Epidemiology Project in Minnesota, children with nephrolithiasis were identified from 1984 to 2008, with increased incidence confined to the adolescent population aged 12 to 17 years. The overall incidence increased by an average of 4% annually. The age-adjusted incidence rate increased from 7 per 100 000 person-years between 1984 and 1990 to 14.5 per 100 000 person-years between 2003 and 2008. Girls in the second decade of life are admitted and hospitalized more frequently for kidney stones.4,5,7 This trend parallels the increasing number of adolescents with obesity observed in pediatric studies, suggesting a possible association with nephrolithiasis. Rising prevalence of female obesity has been linked to increasing risk of nephrolithiasis based on adult data. Abnormalities predisposing individuals to nephrolithiasis in adult studies include increased urinary sodium and uric acid excretion and low urine pH. However, evidence is not strong in pediatric patients, and there are limited data available linking obesity with nephrolithiasis in children. In the 25-year population-based study by Dwyer et al,9 for instance, no correlation was found between increased incidence of kidney stones and body mass index.

Changing patterns of fluid consumption in children, specifically a decrease in water intake, may be an important contributing factor to the increase in pediatric nephrolithiasis.11 It is well established that increased supersaturation of urinary calcium, oxalate, and phosphate related to low urine volume and inadequate hydration are important risk factors for nephrolithiasis. Intake of dietary sodium has also increased above the recommended dietary allowance in US children. The higher intake of sodium is coupled with increased excretion of urinary calcium. Decreased intake of dietary calcium also has been proposed as another factor contributing to nephrolithiasis in older children, with increased consumption of sugary drinks replacing intake of milk.6 Adequate intake of calcium prevents increased intestinal absorption of oxalate, limiting its urinary excretion. Last, the increased use of computed tomography (CT) for diagnosing nephrolithiasis in children has been cited as a possible reason for the increased incidence of nephrolithiasis.9 Because of the high specificity and sensitivity of CT scanning for detecting kidney stones, the perceived increase in incidence may be related to the decrease in the number of diagnoses that would have been missed if other imaging modalities were used.

The increasing incidence of pediatric nephrolithiasis is concerning. The level of concern is raised by findings that children with kidney stones represent a group with high risk of recurrence, which ranges from 16% to 44%.11,17 Recurrence is usually more common in children with metabolic, genetic, and urinary tract abnormalities. Increased risk of recurrence is linked to metabolic factors such as hyperparicalciuria, hypocitraturia, hyperoxaluria, hyperuricosuria, cystinuria, and changes in urine pH that, together with low urine volume, contribute to nephrolithiasis. This risk is more significant in younger patients (<10 years) because 50% of patients with nephrolithiasis in this age group also have metabolic abnormalities.18-20 Hypercalciuria is the most common, accounting for 34% to 50% of metabolic abnormalities, while hyperuricosuria, cystinuria, hypocitraturia, and hyperoxaluria make up 2% to 20%, 5% to 20%, 10%, and 10% to 20%, respectively, of the abnormalities in pediatric series of nephrolithiasis.16,18,22,24 The ability of these factors to predict recurrence, however, is yet to be characterized and may be affected by the fact that the commonly used definitions for these metabolic abnormalities are based on statistical cutoffs (>95th percentile for the study population) and not on clinical outcome (nephrolithiasis).21 In children with recurrent nephrolithiasis, there is also a need to consider inherited monogenic disorders such as adenine phosphoribosyltransferase deficiency, cystinuria, Dent disease, familial hypomagnesemia with hypercalciuria and nephrocalcinosis, and primary hyperoxaluria. Development of chronic kidney disease can be associated with these rare inherited disorders and the delay in diagnosis related to underrecognition compounds the risk of developing chronic kidney disease.

Although recurrence of nephrolithiasis is common in children, the recurrence rate is lower than that in adults.26 However, Tasian and Copelovitch27 argued in a recent review that studies of recurrence rates in children were conducted in the past, when reported incidence rates were much lower, and that contemporary recurrence rates may now be different given the changing incidence of nephrolithiasis. The increasing incidence in children could translate into increasing disease burden and the rising cost of medical evaluation and treatment. Lack of studies and guidelines in children compound the problems in evaluation and management. The annual cost of kidney stone treatment in the adult population was estimated to be almost $2 billion in 2000.28 In South Carolina alone, where increased incidence of nephrolithiasis in children has been reported, the health care dollars spent for kidney stone management in children nearly quadrupled from $3.4 million in 1996 to $12.6 million in 2007.5

**Clinical Presentation**

The presentation of nephrolithiasis in children is variable, depending on the age of the patient.23 Severe colicky abdominal pain is common in adolescents and school-aged children. Nonspecific symp-
toms of abdominal pain, nausea, vomiting, and irritability, rather than the typical renal colic, are seen in younger children. Gross hematuria is a common presenting sign. In patients younger than 5 years, kidney stones are frequently discovered following a urinary tract infection or as an incidental finding. Patients also may be asymptomatic, with nephrolithiasis incidentally discovered in an imaging study conducted for other indications. In North American children, stones are mostly located in the kidneys and upper urinary tract.

As reported in several pediatric series, most kidney stones in children are calcium based. Calcium oxalate is most common and accounts for 40% to 60% of cases of pediatric nephrolithiasis while calcium phosphate accounts for 10% to 20%. Mixed stones composed of both calcium oxalate and calcium phosphate constitute 10% to 25% of cases of pediatric nephrolithiasis. Magnesium ammonium phosphate (struvite or infection-related) stones are seen in 17% to 30% of cases. Infection-related stones are less common today because of improvements in antenatal screening and management of congenital anomalies of the urinary tract. Cystine stones are found in 6% to 10% of cases of pediatric nephrolithiasis while uric acid stones make up 2% to 10% of cases. Rare stones to consider include those composed of xanthine and dihydroxyadenine.

Evaluation
Evaluation includes a complete medical history and physical examination complemented by appropriate laboratory and imaging studies. The goal of evaluation is to identify modifiable risk factors and abnormalities for which targeted therapy can be prescribed to decrease recurrence and complications of nephrolithiasis. Screening for rare hereditary causes of kidney stones should be considered in the appropriate clinical setting to prevent missed diagnosis. Prompt evaluation is needed to rule out urinary tract obstruction and urinary tract infection.

Medical History and Physical Examination
The medical history should focus on diet, fluid intake, medications, family history, and presence or absence of specific disorders that can lead to nephrolithiasis. A detailed dietary history should be obtained, including information regarding the amount of fluid and dietary sodium intake. The ketogenic diet is a risk factor for formation of uric acid stones and may be associated with hyperuricemia, hypocitraturia, and low urine pH. Excessive animal protein intake has been associated with increased urinary excretion of calcium and uric acid and decreased urinary excretion of citrate, resulting in calcium oxalate and uric acid stones.

Medications and supplements associated with nephrolithiasis include vitamin D, calcium supplements, vitamin C, diuretics (furosemide and acetazolamide), seizure medications (felbamate, topiramate, and zonisamide), steroids, uricosuric drugs, and antibiotics (indinavir sulfate and ceftriaxone sodium). Information should be obtained on all supplements or herbal preparations a patient is taking.

A positive family history is present in 22% to 75% of cases of nephrolithiasis. In one case series in the United Kingdom, 16% of children had a first-degree relative and 33% had both first- and second-degree relatives with kidney stones. Familial recurrence of nephrolithiasis, however, does not necessarily indicate a genetic cause, as shared environmental factors and dietary habits can contribute to a familial predisposition. Features in a patient’s history suggestive of a possible hereditary etiology would include infantile or early childhood presentation; parental consanguinity; positive family history with unexplained renal insufficiency; recurrent kidney stones; signs and symptoms of tubular dysfunction with associated polypoikulia, acidosis, rickets, growth retardation, or renal insufficiency; nephrocalcinosis; and dysmorphism. Specific disorders or conditions predisposing a patient to nephrolithiasis would include urinary tract obstruction, vesicoureteral reflux, inflammatory bowel disease, short gut syndrome, cystic fibrosis, seizure disorder, and immobilization. Key elements of the physical examination include documentation of blood pressure, growth parameters, bony deformities, abnormal calcifications, rickets, abnormal genitalia, and immobility.

Laboratory Evaluation
Results of urinalysis provide information regarding specific gravity, urine pH, and the presence of hematuria or pyuria. Tubular dysfunction may be present if the results of urinalysis show glucosuria and proteinuria. A diagnosis of infection accompanying acute kidney stone episodes may be supported by the presence of pyuria. Urine should be obtained for culture as part of the evaluation for nephrolithiasis. Microscopic analysis can demonstrate the presence of cystine crystals in cystinuria. Xanthine and dihydroxyadenine crystals can be seen by microscopic examination of the urine, providing the initial indication of adenine phosphoribosyltransferase deficiency. Low-molecular-weight proteinuria in boys with kidney stones or nephrocalcinosis can establish the diagnosis of Dent disease.

It is essential that kidney stone material be retrieved and analyzed whenever possible. Kidney stone composition can narrow the differential diagnosis and help tailor evaluation and management. For instance, identification of a uric acid stone should prompt investigation for inborn errors of purine metabolism, given the rarity of this stone in children.

Metabolic evaluation should incorporate measurement of electrolyte levels, including calcium, magnesium, and phosphorous. Creatinine levels should be measured to assess overall renal function. If hypercalcemia is present, measuring the parathyroid hormone level can help diagnose hyperparathyroidism. High levels of vitamin D can cause hypercalciuria, requiring measurement of the 25-hydroxyvitamin D level. Presence of vitamin D deficiency should be determined and corrected.

Since children with kidney stones have a high risk of recurrence associated with metabolic abnormalities, 24-hour urine collection is the mainstay of the workup for pediatric nephrolithiasis, as it is in adults. Because of significant intra-individual variability related to diet and environment, two 24-hour urine collections are recommended. There are no studies regarding the appropriate number of urine collections in children, but adult studies support 2 urine collections on initial evaluation. Urinary excretion of calcium, oxalate, uric acid, citrate, magnesium, phosphorus, sodium, and potassium should be assessed. Valuable information that can be obtained from the urine collection also includes pH, volume, creatinine, sulfate, and urea nitrogen levels, and supersaturation. When patients are unable to give 24-hour urine samples, spot urine samples can be collected, especially in young patients who are not toilet trained. Normal values for spot urine samples and 24-hour urine collection are given in Table 4 and Table 2.

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Table 1:...

Table 2:...
Imaging

In adults, CT without contrast is the criterion standard for diagnosing nephrolithiasis and urinary tract calculi because of its high sensitivity and specificity. The ability of CT scanning to localize kidney stones and its characteristic high spatial resolution provide anatomical detail that can be useful for surgical planning. In children, radiation exposure has been a major concern, resulting in recommendations supporting the initial use of renal ultrasound (US) with or without radiographs to limit radiation exposure. However, in centers with the capability to adjust CT radiation dose based on the patient’s size and weight, low-dose CT without contrast continues to be the initial imaging study in children with suspected renal colic. The concern regarding radiation exposure is starting to be recognized in the adult population. In a recent study by Smith-Bindman et al. no difference in serious outcome arising from a missed or delayed diagnosis was demonstrated between the use of US and CT as the initial imaging studies in adults with suspected nephrolithiasis. This finding, together with the lower cumulative radiation exposure over 6 months from multiple imaging tests that followed the initial use of US, supports the conclusion that US can be considered as an initial imaging study of choice.

Acute Management

The first step in the management of acute renal colic is determining the need for emergency urinary decompression. Renal calculi are generally nonobstructing and acute decompression is not indicated. Obstructed ureteral calculi require acute decompression with either a ureteral stent or percutaneous nephrostomy tube in obstructed pyelonephritis, acute kidney injury, or intractable pain. Both methods are equally effective, although size and location of the calculus, the patient’s hemodynamics, and availability of interventional radiology procedures may influence the choice of decompression. Even in the setting of well-controlled pain and nausea, the combination of infection and an obstructing kidney stone constitutes an emergency necessitating prompt urologic evaluation and intervention.

Most patients with acute renal colic can be managed without hospital admission, with an emphasis on presentation on the importance of adequate analgesia. While literature specific to children is lacking, studies of pain control in acute renal colic in adults have shown acetaminophen, nonsteroidal anti-inflammatory drugs, and narcotics to be equally effective analgesics, with combination therapy being superior to single agents. Medical expulsive therapy is a well-established treatment for ureteral calculi in adults that uses α-blockers (tamsulosin, terazosin, doxazosin, prazosin) or calcium channel blockers (nifedipine) to relax ureteral smooth muscle, resulting in increased rates of stone passage, decreased time to stone passage, and improved analgesia. Although limited data exist in children, tamsulosin use for nephrolithiasis has increased in pediatric hospitals. Two recent studies demonstrated the benefit of tamsulosin in children with ureteral calculi, with tamsulosin reported to have up to a 3-fold increase in rate of stone passage. Health care professionals should be aware that the use of medical expulsive therapy is off-label and beneficial only for ureteral calculi. Stone passage may take 4 to 6 weeks and confirmation of passage by either repeated imaging or visualization of the passed calculus is mandatory.

Surgical Management

Up to 22% of children with nephrolithiasis will require surgical intervention within 6 months of presentation, with 25% requiring more than 1 procedure. Surgical options for pediatric nephrolithiasis include extracorporeal shock wave lithotripsy, ureteroscopy with lithotripsy and/or kidney stone extraction, percutaneous nephrolithotomy, and minimally invasive or open pyelolithotomy. The choice of specific surgical procedure depends on multiple factors. Ureteroscopy and extracorporeal shock wave lithotripsy are classically used for smaller calculi within the ureter or kidney and, in most cases, they are considered to be relatively equivalent in the rate of success. While the choice of ureteroscopy or extracorporeal shock wave lithotripsy may be determined in part by kidney stone characteristics, the availability of equipment and surgeon preference also play significant roles in the choice of surgical treatment.
endoscopic techniques, open pyelolithotomy in the management of patients with kidney stones has been minimized.53,65 Laparoscopic and robotic-assisted kidney stone removal may prove to be the future of kidney stone surgery in children, if indeed these procedures can improve on kidney stone-free rates seen in endoscopic techniques while providing equal convalescence and pain control postoperatively.66,67 Recent advances in instrumentation and robotic-assisted kidney stone removal may prove to be beneficial in preventing kidney stone recurrences with medical interventions.59,62 Surgical options for children with kidney stones, including indications and complications, are summarized in Table 3.63,68-74

### Prevention and Medical Management

Preventive measures for kidney stone recurrence should focus on modifying risk factors. Limiting dietary sodium intake can decrease hypercalciuria. Patients should be encouraged to maintain adequate fluid intake to help decrease urinary supersaturation of calcium, oxalate, and uric acid and maintain urine flow rate. A minimum fluid intake of 1.5 to 2 L/m²/d is recommended. The volume of fluid intake should be adjusted to maintain urine volume greater than 750 mL/d in infants, greater than 1000 mL/d in children younger than 5 years, greater than 1500 mL/d in children between 5 and 10 years, and more than 2000 mL/d in children older than 10 years.54 Discontinuation or weaning of medications that can cause kidney stones should be part of treatment. Dietary calcium restriction is not recommended since it can increase intestinal oxalate absorption and risk of nephrolithiasis.79 Children should consume the recommended dietary allowance of calcium. A low vitamin D level would need correction to maintain bone health. Excessive protein intake should be avoided since the acid load from protein metabolism can cause hypercalciuria and hypocitraturia. Protein restriction is also not recommended because of concerns regarding its effects on growth. Children should be encouraged to increase their intake of vegetables and fruits, which are excellent sources of citrate and potassium. Both citrate and potassium in the urine act as kidney stone inhibitors.

Medications should be considered in children with recurrent kidney stones, obstruction in a solitary kidney, and genetic kidney stone diseases. The primary medications used in children with nephrolithiasis include potassium citrate and thiazide and potassium-sparing diuretics. Potassium citrate can be used to treat hypocitraturia and increase urine pH to prevent uric acid crystallization in hyperuricosuria. Thiazides, which work by reducing urinary calcium excretion, should be considered in patients with persistent hypercalciuria and recurrent kidney stones. Potassium-sparing diuretics, such as amiloride, may enhance calcium reabsorption when combined with thiazides. Treatment of hyperoxaluria should focus on limiting oxalate absorption and preventing calcium oxalate crystallization in the urine. Pyridoxine can be given empirically if primary hyperoxaluria is suspected. Tiopronin and penicillamine can be used in cystinuria to increase cystine solubility. Allopurinol can be prescribed to help treat patients with a de-
fect in purine metabolism. Conservative management should be the first-line treatment for patients with kidney stones and is composed of altering diet and fluid intake. Table 4 provides a summary of medical treatment strategies.

The need for a multidisciplinary approach to prevent and treat kidney stones has resulted in an increasing number of dedicated kidney stone clinics for children. The combined expertise of a pediatric nephrologist, urologist, dietitian, and clinical nurse aims to provide comprehensive and coordinated care to children with kidney stones. Outcome studies supporting the benefits of a dedicated center are lacking in children but have been published in the adult literature.76

Conclusions

The changing current trends, rising medical costs, and limited studies in children with nephrolithiasis highlight the need for evidence-based research in this population. Meticulous medical management together with less invasive surgery are essential in eliminating kidney stone burden and recurrence in children. Although technologies to treat nephrolithiasis are becoming more focused on pediatric patients, our primary efforts should be directed toward modifying the risk factors that led to nephrolithiasis in the first place.

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