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Pediatric Nephrolithiasis: Trend, Evaluation and Management: A Systematic Review

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Abstract

Context: Pediatric nephrolithiasis is a noticeable cause of morbidity among children. Although, nephrolithiasis is a common disease in adults, its incidence has had a rising trend in children.
Objectives: Here in, we reviewed the current state regarding evaluation and management of children with nephrolithiasis in the last decade.
Data Sources: The current literature regarding incidence and trend, along with diagnostic evaluation and management of children aged less than 18 years old with nephrolithiasis was searched on MEDLINE and Google scholar from January 2005 to March 2016.
Study Selection and Data Extraction: The search terms included, "kidney stone OR nephrolithiasis OR urolithiasis and Pediatric OR children". English language and human studies were included. Expert opinions, editorials and case reports were excluded. Consequently, the authors independently reviewed the abstracts and the papers, which matched the inclusion criteria.
Results: From a total of 1050 studies identified through the database search, 71 articles were selected for the review. According to the results of this review, pediatric nephrolithiasis has an increasing rate worldwide. Recent studies in this regard indicated that the number of girls with nephrolithiasis has increased. The change of life style, diet, obesity and metabolic syndrome and popular imaging study along with referral of the patients to pediatric centers could be contributed to this trend.
Conclusions: Evaluation of patients, particularly young children, includes metabolic assessment. Stone analysis and 24-urine collection analysis are very helpful for determining underlying diseases. Medical as well as surgical approaches are used to prevent kidney injuries.

Keywords: Nephrolithiasis, Children, Incidence, Management

1. Context

Over the past decades, the prevalence of pediatric nephrolithiasis has increased by 70% in adults and has become the third top urinary tract disease, and the gender gap between males and females is narrowing in many countries, as about 10% and 5% of males and females, respectively, complain of this condition during their life (1-3). Sas et al. (4) reported in their study that during the last couple of decades, the incidence of pediatric nephrolithiasis has increased by approximately 6 to 10% annually and has actually reached 50 per 100000 in adolescents.

This situation may cause some complications and has subsequent health care and medical costs. Pearle et al. (5) estimated that more than two billion dollars is incurred annually for nephrolithiasis in the United States. This condition causes further chronic conditions requiring health care services in pediatric medicine. Moreover, recent studies revealed that this disorder has a gender-related distribution in this context by more inclination toward nephrolithiasis. In addition, race and geographic location may play a role in nephrolithiasis development. African countries have low prevalence and the Middle East, Pakistan and India have higher incidence of urolithiasis (6, 7).

2. Objectives

This review article tried to provide appropriate information about pediatric nephrolithiasis in different aspects such as epidemiology, risk factors and etiology, clinical presentation and management.

3. Data Sources

We reviewed the current literature regarding incidence and trend, diagnostic evaluation and management of children with nephrolithiasis. For this purpose, we searched MEDLINE and Google scholar from January 2005 to March 2016.

4. Study Selection and Data Extraction

The search terms or key worlds included "kidney stone OR nephrolithiasis OR urolithiasis and Pediatric OR children". The studies were included if their subjects were human aged less than 18 years and were written in English language. Also, expert opinions, editorials, and case reports

were excluded. Moreover, the bibliography of relevant review articles recognized in our search was read and appropriate articles were selected. Consequently, the authors independently reviewed the abstracts and the papers, which matched the inclusion criteria and selected more recent publications. The flow diagram of the study selection process is shown in Figure 1. Reviewed articles are summarized in Table 1.

5. Results

From the total of 1050 studies identified through database searching, 71 articles were selected for the review. Among 71 reviewed articles, 11 were cross-sectional, 23 retrospective cohort, 11 prospective studies, 20 review articles, three lab studies, and three were clinical trials. The qualitative results derived from the reviewed articles related to incidence and trend, risk factors and causes of nephrolithiasis, clinical presentation, evaluation of the patients including history taking and physical examination, urinalysis and other laboratory evaluations, imaging studies, therapeutic approaches such as acute management, surgical management, prevention of recurrence are summarized in Table 1, and discussed here.

6. Discussion

6.1. Incidence and Trend

The real incidence of nephrolithiasis in children remains non-conclusive. This fact is relatively secondary to multiple etiological factors and nonspecific clinical presentations. Multiple studies over the past decade have documented an increased incidence of nephrolithiasis in different countries (8). In the United States, the result of the national health and nutrition examination survey (NHANES), as a cross-sectional survey presented an increasing estimation of nephrolithiasis in adults of this country. Furthermore, recent studies revealed that the incidence of hospital admissions increased from 1 in 7600 to 1 in 685 admissions from 1999 to 2007 among children. The annual increase was 10.6% on average (9). These epidemiologic changes could be due to life style modifications, particularly in eastern countries, and increased diagnosis of nephrolithiasis by using ultrasonography evaluation in children with specific or nonspecific symptoms. Besides, adult urologists are now referring more patients to pediatric centers. Yasui et al. (10) from Japan displayed an incidence of 12.4/100000 to 17.7/100000 in female and male children aged 10 - 19 years old, respectively. Additionally, Edvardsson et al. (11) in Iceland reported an incidence of 5.6/100000 in patients younger than 18 years old. Furthermore, Routh et al. (12) in their study, by using national health information system database, declared an elevated incidence of nephrolithiasis in children. In an epidemiologic project in Minnesota from 1998 to 2008, the overall incidence of nephrolithiasis in adolescents was increased from 7 to 14 per 100000 patients aged 12 to 17 years old (13). Tasian et al. (14) in a large population study indicated that between 1997 and 2012, the rate of nephrolithiasis increases annually by one percent. On the other hand, there has been a change regarding the gender of patients. Previous reports demonstrated that nephrolithiasis was usually more common in boys than in girls, but recent studies have shown a noticeable rising incidence of nephrolithiasis in girls and some studies even substantiated that nephrolithiasis are more common among girls (4, 9, 10, 12, 15, 16). Usually girls in the second decade are more prone to hospital administration for kidney stone (12). The possible relationship between nephrolithiasis, obesity, and metabolic syndrome was demonstrated in previous reports but it is not conclusive (16, 17). As mentioned before, geographic location may affect nephrolithiasis development. Former studies revealed that nephrolithiasis is more common among non-Hispanic white individuals as compared with non-Hispanic black individuals in adults and pediatric populations (18-20). In addition, age of children may have a role in this setting as in some studies, it was demonstrated that the incidence of nephrolithiasis has increased from 0.6 per 100000 in children aged less than three years old to 34.9 per 100000 among adolescents aged less than 18. They indicated that the risk of nephrolithiasis in age group of 14 to 18 years is 10 times greater. The hospitalization rate also follows the same pattern (9, 12, 21, 22). In a Tasian study, the greatest change belonged to 15 to 19 year olds, and the incidence of nephrolithiasis increased by 26% per five years. The incidence increased by 15% per five years among females in general (14).

6.2. Risk Factors and Causes of Nephrolithiasis

In general, nephrolithiasis in many cases is associated with a metabolic abnormality including hypercalciuria, hyperoxaluria, hypocitraturia, cystinuria, and hyperuricosuria, in which hypercalciuria or hypocitraturia are more frequent. However, we need to pay attention to some disorders such as cystic fibrosis (CF), spina bifida or inflammatory bowel disease, which may prone the patient to risk of stone recurrence or raise the possibility of stone formation such as oxalosis or Primary Hyperoxaluria (PH). This disorder has two types PH-1 and PH-2 (7, 23-25). Tubular disorders such as cystinuria increased the risk of stone formation, which accounted for 3% of renal stones (26). Some systemic diseases such as CF and inflammatory bowel diseases (IBD)

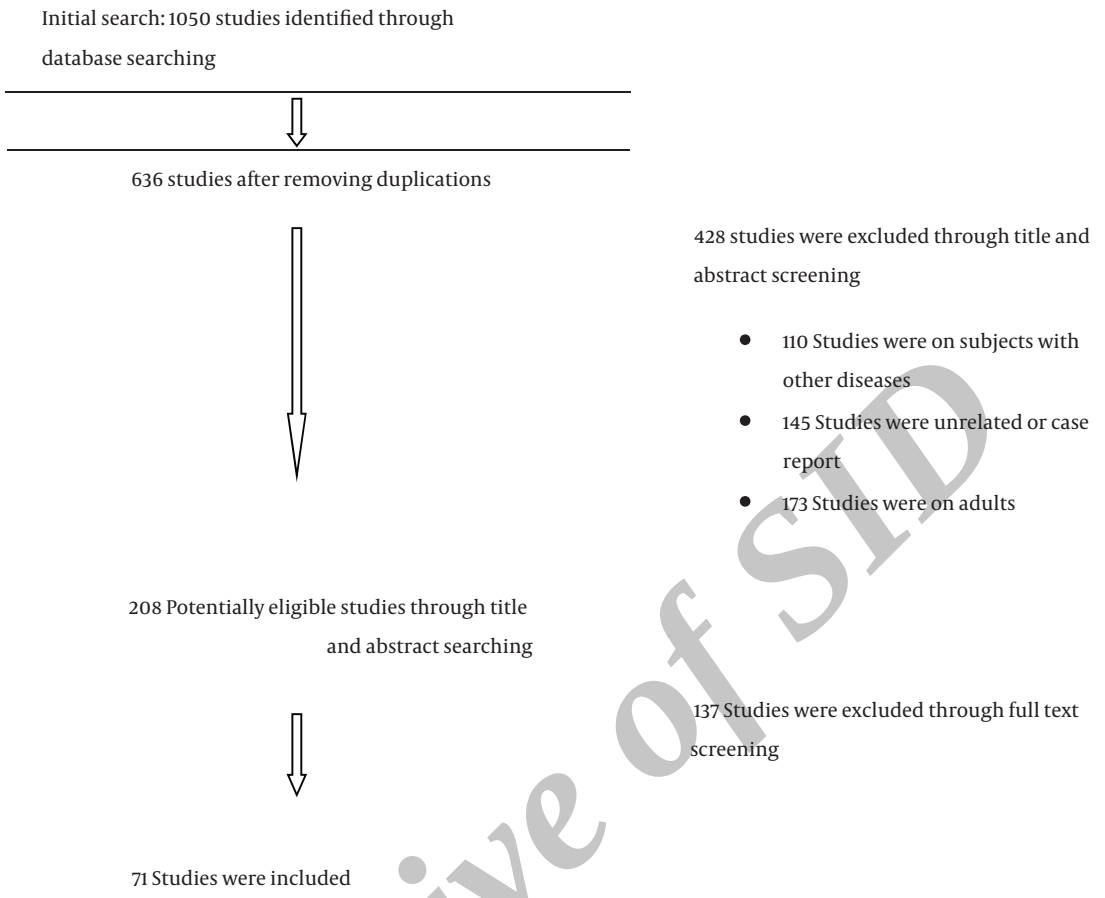

Figure 1. Flow Diagram of the Study Selection Process

may be associated with nephrolithiasis. These diseases usually affect the intestine and induce fat mal-absorption. Consequently, development of steatorrhea leads to chelating of calcium and absorption of oxalate from intestine and as a result leads to the development of calcium oxalate stones. Furthermore, renal tubular acidosis may be considered as an etiology of calcium phosphate stones. Struvite stones also in the setting of spinal cord injuries or neurogenic bladders might be considered. In patients with seizures, ketogenic diet and anti-seizer medications result in acidosis, hypercalciuria that need more attention (27-29).

On the other hand, in recent studies, low fluid consumption, particularly water, has been considered as an etiological factor in kidney stone (20, 30, 31). In fact, super saturation of ions in urine such as calcium and oxalate directly depend on the volume of urine, hence an appropriate hydration could protect the stone formation. Furthermore, it has been demonstrated that high intake of salt (sodium) increases the excretion of urinary calcium and stone formation (32, 33). Although calcium in appropriate amounts may prevent oxalate absorption from the intestine, low intake of dietary calcium contributes to nephrolithiasis in adolescents (13). Therefore, an appropriate dietary calcium intake is advised.

We need to reemphasize that pediatric nephrolithiasis has a high risk of recurrence, and reaches 40% in different studies. It is particularly related to metabolic or genetic predisposing factors. The risk of recurrence is more common in patients aged less than ten years, for whom a metabolic disorder is common (34, 35). Among them, hypercalciuria, hyperuricosuria and cystinuria make 34 to 50%, 20% and 20% of metabolic abnormalities, respectively in pediatric nephrolithiasis (36-38). In the recurrence of nephrolithiasis, we need to evaluate the patients for inherited disorder such as PH, cystinuria, Dent disease and familial hypomagnesemia (20, 39). Moreover, mutations of CYP24A1, encoding the enzyme that influences conversion

of active forms of vitamin D to inactive metabolites, induce idiopathic infantile hypercalcemia (40). Moreover, mutation of SLC34A3 gene encoding sodium (Na+)-dependent phosphate cotransporter 2c (NPT2c) causes hereditary hypophosphatemic rickets with hypercalciuria that consequently may increase the risk of nephrolithiasis (41). There are not enough studies regarding obesity and pediatric nephrolithiasis. Obesity probably leads to a decreased urinary pH and increases the risk of uric acid stone. In a study in Turkey on 96 patients, the author concluded that overweight children with alteration of urine compositions, such as higher oxalate and uric acid and lower urine volume, are at the risk of forming of stone (42). Kieran et al. (43) also revealed that 41% of their patients were overweight or obese. Kurtz et al. (44), in a population-based study on 2871 patients aged 2 months to 18 years revealed that 420 (14.6%) were overweight and 440 (15.3%) were obese. They concluded that increased BMI in children was associated with increased overall complications. Generally, there is no consensus about obesity as a risk factor for nephrolithiasis and this association remains under question (15, 45).

In Iran there are limited reports regarding the etiology of nephrolithiasis, but to the best of our knowledge, the pattern of nephrolithiasis and its related factors follow other reports. However, we need to focus on the fact that the Middle East region, including Iran, is a warm region with a rapidly changing life style to western nations. In this setting, Safaei Asl et al. (46) in their report on 78 patients indicated that 52.6% had a metabolic risk factor including normocalcemic hypercalciuria (21.7%), hyperuricosuria (11.5%), cystinuria (3.8%), and hyperoxaluria (5.1%). In addition, Mohammadjafari in a 10-year prospective study on 217 children, two months to 16 years old revealed that 35.1%, 10% and 4.1% of patients had metabolic, infective and obstructive problems, respectively. In this study, 110 children had no recognized etiology; furthermore hypercalciuria hyperoxaluria and hypocitraturia were seen in 25.5%, 18.4% and 18.1% of patients (47), respectively. In addition, Sadeghi et al. (48) in a study in the south east of Iran on 100 patients reported that hypercalciuria and hypocitraturia were seen in 56% and 64% of patients, respectively, followed by anatomic malformation (32%) and Urinary Tract Infections (UTI) (9%). Alemzadeh-Ansari et al. (49) also in a study on 152 infants from southwest of Iran revealed that the most common metabolic risk factors were hypercalciuria (79.6%) and hypocitraturia (40.9%). In this study hyperoxaluria and hypomagnesuria were found in about 28% of patients.

6.3. Clinical Presentation

The presentations of nephrolithiasis in children are variable. The classic adult presentation with flank pain radiated to the groin is not common and almost age-dependent (33, 44, 50). Although, adolescents usually present colicky pain similarity to adults, younger children have nonspecific symptoms including abdominal pain, nausea and vomiting or irritability. Hematuria, microscopic or macroscopic can occur in up to 90% of cases. In addition, urinary infection (UTI) in children less than five years old could be the main presentation (36). Nonspecific and localized pain is typical of infants and young children with nephrolithiasis. Hematuria and uncharacteristic abdominal pain are common in only 10% to 14% of all pediatric cases (33, 37, 51). However, nephrolithiasis is discovered incidentally, during imaging evaluation for other reasons, and remains asymptomatic for a long time (24, 33). In our region, the symptoms generally follow the same pattern. Sadeghi et al. reported that the most common clinical presentations were irritability (62%), flank pain (33%) and gross hematuria (4%), while Sepahi et al. (48, 51) reported that of one hundred patients, 54% presented urinary tract infection (UTI), while in this study, fever, pain, irritability, dysuria and hematuria were the main clinical presentations. It seems that along with nonspecific abdominal pain, UTI may be an important sign of nephrolithiasis. Furthermore, in adolescents, hematuria may need greater evaluation to eliminate other serious problems (52). Moudi et al. (52-54) also demonstrated that long-term usage of aspirin might induce occult hematuria.

Several reports indicated that most nephrolithiasis in children are calcium based, in which calcium oxalate is the most common type of calculi with about 50% followed by calcium phosphate (10% - 20%). Mixed calcium oxalate and calcium phosphate are present in more than 10% and magnesium ammonium phosphate (infection related) stone is reported in more than 17% of patients (33, 36, 37).

6.4. Evaluation

6.4.1. History and Physical Examination

Obtaining an appropriate medical history and physical examination is a milestone for an accurate diagnosis and identification of those who are at risk and need treatment. In this regard, family history of urinary tract diseases may give a clue for metabolic and inherited conditions. The presence of a family history was reported in 23% - 75% of patients. In addition, focusing on diet by emphasizing on salt and fluid intake and having a special diet are important. Ketogenic diet increases the risk of uric acid stones. Furthermore, some medications, particularly corticosteroids, diuretics protease inhibitors, vitamins C and D or supplements are associated with nephrolithiasis; hence, there is a

need to clarify their usage. Patients with history of prematurity, IBD, CF, anatomical abnormalities or UTI are prone to nephrocalcinosis. Physical exam may be helpful to identify the dysmorphic shape of the body, rickets or other abnormalities of systemic diseases and genetics associated with nephrolithiasis (Table 2) (23).

6.4.2. Urinalysis

Urinalysis is the main part of initial assessment of nephrolithiasis. It provides good information of urine gravity as a marker of urine concentration and fluid intake, urine pH, hematuria and pyuria. Microscopic analysis may give good information regarding crystalluria that help clarify the origin of the problem. Tubular dysfunction is presented by glucosuria and proteinuria.

6.4.3. Other Laboratory Evaluations

To evaluate renal function, assessment of electrolyte levels including potassium, sodium, magnesium, calcium and phosphorus are highly recommended. In case of hypercalcemia, hyperparathyroidism may be considered. Hypervitaminose D can lead to hypercalciuria.

The second step is to determine the underlying diseases such as metabolic disorder. It has been demonstrated that in children, metabolic risk factors affect the majority of cases therefore a complete workup in this setting is required. On the other hand, the risk of recurrence is high and in line with metabolic abnormalities. Hence, stone analysis takes an important place and could canalize the physician to identify the risk factors of nephrolithiasis. In fact, in children due to rare spontaneous passage or surgical stone retrieval, stone analysis is not common. Furthermore, Aliramaji et al. (53) in a meta-analysis revealed that urine biomarkers may helpful in diagnosis of ureteropelvic junction obstruction, as a predicting factor. As an alternative, a 24-hour urine collection is a recommended workup. This test permits the screening of elements contributing to the stone-formation process. Due to variability of daily diet and fluid intake regimen, it is required to collect a 24-hour urine sample for evaluating creatinine, sodium, calcium, phosphorus, magnesium, oxalate, citrate, cysteine, uric acid and urine volume. Some authors recommend two 24-hour urine collections. Nevertheless, recent studies indicated the low volume of using this test. In case that the collection is not possible, the urine spot urine samples may be helpful but cannot replace 24-hour urine collection (33, 53-56). Normal urinary values in spot urine samples and 24-hour samples are shown in Tables 3 and 4.

6.5. Imaging

Imaging studies during or after the initial laboratory evaluation were required in pediatric nephrolithiasis. In adults, because of high sensitivity and specificity of computerized tomography (CT) scanning and regarding a good image of anatomy, taking a CT without contrast is usually recommended. In children, radiation of CT has been concerned in many recommendations, therefore ultrasonography is recommended by many pediatric associations as an initial imaging evaluation. Ultrasonography with low radiation and low cost simply identifies an echogenic mass and hydronephrosis as a consequence of stone in the kidney. Studies on adults demonstrated that there is no significant difference between CT and US as initial imaging evaluation. However, a pediatric study indicated that sensitivity and specificity of US compared with CT was 76% and 100%, respectively (33, 36, 57).

6.6. Management

6.6.1. Acute Management

The initial steps in therapeutic approach in nephrolithiasis are control of acute renal colic pain, recognition of the necessity of emergency intervention, and trying to pass the stone if possible. The second step is to prevent new stone formation.

The pain is usually controlled by analgesics such as non-steroidal anti-inflammatory drug (NSAID) or opium. Children may need hospitalization in case of initiation of parenteral analgesic or hydration. Usually, renal stone in children is not obstructing and emergency decompression is not indicated. However, the size and location of stone must be considered seriously as a stone less than 4 mm has a chance to pass spontaneously in all patients. In children, renal stones pass spontaneously in 50% of cases (36, 58). In this situation, conservative management may be enough. Besides, medical expulsive therapy such as alpha-blocker (tamsulosin, terazosin) or calcium channel blockers (nifedipine) may facilitate the passage of small stones by relaxing ureteral smooth muscle. Actually, tamsulosin is wildly prescribed for pediatric nephrolithiasis (59-62). The stone passage may take more than one month and in this period, the patients need appropriate care and follow-up.

6.6.2. Surgical Management

In case of obstructing or large stones, acute intervention and decompression may be required. In this context, urethral stent, nephrostomy, Shock Wave Lithotripsy (SWL) or even removal of stone via ureteroscopy is advised. Previous studies demonstrated that in children, the stone with

a size more than 5 mm rarely passes spontaneously. Different studies revealed that about 22% of patients would need surgical therapeutic approach during the next six months after initiation of disease (36, 61, 63). The choice of each procedure depends on patient's characteristic. While SWL and ureteroscopy are considered for small stones, percutaneous nephrolithotomy and pyelolithotomy are reserved for large calculi (> 1.5 cm) (36, 63). Generally, by the improvement of endourological techniques, interventions have shifted to minimally invasive procedures. In this setting, ureteroscopy is used commonly and is becoming the therapeutic approach of choice in lower and also upper tract stones (64-66). Tejwani et al. (67) in a large study to compare SWL and ureteroscopy demonstrated that patients, who benefit from ureteroscopy, had less stone-related procedures in the next 12 months after the procedure, but a higher rate of readmissions within subsequent month after the initial intervention. Comparison of treatment modalities for surgical management of pediatric nephrolithiasis is summarized in Table 5 (36).

6.7. Prevention of Recurrence

Prevention of nephrolithiasis recurrence in children is an effort to determine the potential risk factors of stone formation and their modification. Previous reports indicated that children with known underling metabolic disorder have a 50% risk of recurrence of nephrolithiasis, compared to 10% in patients without these risk factors (58, 66, 68). Appropriate fluid intake, about 1.5 l/ m^2/d, and limited dietary intake should be advised to help decrease supersaturation of urinary elements such as calcium, oxalate and uric acid. The fluid intake could be enough to provide urine volume more than 750 mL/d in infants and more than 1000 mL/d for children less than five years old, 1500 mL/d for children 5 to 10 years, and 2000 mL/d in children more than 10 years. Children need appropriate dietary calcium and calcium restriction is not recommended. Excessive protein intake can lead to hypercalciuria and hypocitraturia; hence a sufficient protein intake is recommended (20, 30, 31, 36). Furthermore, avoidance of medication that may cause nephrolithiasis should be considered. Medication may be a part of management of children with recurrent nephrolithiasis, solitary kidney, or metabolic disorders. In this context, the result of stone analysis or a 24-hour urine collection analysis plays an important role (33, 39, 69, 70). Thiazides and potassium-sparing diuretics are on top of the list. In a case with hypocitraturia, potassium and citrate can increase the urinary Ph and prevent uric acid crystallization. Patients with hypercalciuria benefit from thiazide diuretics, which decreases urinary calcium excretion. In this condition, a low sodium diet and adequate fluid intake must be encouraged. However, in presence of hypercalcemia, the prescription of thiazide is forbidden and combination of thiazide and potassium-sparing diuretics can increase calcium absorption (36, 66). The treatment of hyperoxaluria includes prevention of oxalate absorption by reducing the intake of oxalate –rich foods and preventing crystallization of calcium oxalate in the urine. Usually, pyridoxine can be empirically prescribed. In fact, hyperoxaluria, secondary to malabsorption syndromes, requires treatment of underlying disease (15, 31, 33). Moreover, magnesium and pyrophosphate may prevent calcium oxalate crystallization. In case of citric acid stones, the increase of excretion of citric acid by urinary alkalization is a helpful modality. Allopurinol can be used in patients with purine metabolism disorders. Furthermore, alkalization can be used for the treatment of cyctine stone. The aim is to reach a urinary pH of 7 - 7.5. Potassium citrate is recommended. Similarly, D-penicillamine and Tiopronin (Alpha-mercaptopropionylglycine) can be used in cystinuria. However, generally speaking, conservative management remains the first line of management of patients with nephrolithiasis.

6.8. Conclusions

Pediatric nephrolithiasis, because of changing trend and underlying risk factors is different in adults. The aim of the treatment is to preserve the function of kidney and prevent the recurrence of disease. Metabolic disorders are important in this setting and work up is recommended. Despite advances in technology and medication, the risk factor modifications remain the basis for the treatment of nephrolithiasis.

Table 2. Systemic Diseases and Genetic Associated With Nephrolithiasis

Disease	Stone Characteristic
Hyperoxaluria type 1	Calcium oxalate
Hyperoxaluria type 2	Calcium oxalate
Cystinuria	Cystine
Dent disease	Calcium oxalate/calcium phosphate
2, 8-dihydroxyadeninuria disease	2, 8-hydroxyadenine crystalluria
Crohn disease	Calcium oxalate/uric acid
Cystic fibrosis	Calcium oxalate
Myelomeningocele	Struvite/calcium phosphate and oxalate
Seizures (treated with ketogenic diet)	Calcium oxalate/uric acid
Renal tubular acidosis	Calcium phosphate
Lesch-Nyhan disease/Partial HGPRT deficiency	Uric acid

Abbreviation: HGPRT, hypoxanthine phosphoribosyl transferase.

Table 3. Normal Urinary Values in Spot Urine Samples[a]

Urine Constituent	Age	Value, mg/mg Creatinine
Calcium	< 7 months	< 0.86
	7 - 18 months	< 0.6
	19 months - 6 years	< 0.42
	> 6 years	< 0.2
Oxalate	< 6 months	< 0.29
	6 months - 2 years	< 0.20
	>2 - 5 years	< 0.11
	6 - 12 years	< 0.06
Citrate	< 5 years	> 0.42
	> 5 years	> 0.25
Cystine	All ages	< 0.07
Uric acid	All ages	< 0.56 per GFRa

Abbreviation: GFR, glomerular filtration rate.
[a]Calculated by multiplying the ratio of uric acid to creatinine (mg/mg) with serum creatinine (mg/dL) (71).

Table 4. Normal Urinary Values in 24-Hour Urine Collection

Urine Constituent Age Timed Collection	Urine Constituent Age Timed Collection	Urine Constituent Age Timed Collection
Calcium	All ages	< 4 mg/kg
Oxalate	> 2 y	< 0.45 mg/1.73 m^2
Citrate	All ages, male	> 365 mg/1.73 m^2
	All ages, female	> 310 mg/1.73 m^2
Cystine	All ages	< 60 mg/1.73 m^2
Uric acid	All ages	< 815 mg/1.73 m^2
Creatinine[a]	3 - 5 y	12 - 20 mg
	6 - 13	15 - 25
	14 - 18 male	18 - 27
	14 - 18 female	17 - 24

[a]Adequacy of urine collection can be assessed by checking urinary creatinine. Excretion based on age and gender (55, 56).

Table 5. Comparison of Treatment Modalities for Surgical Management of Pediatric Nephrolithiasis

Treatment	Indication Stone	Stone Free Rate (%)	Limitation	Complications
Extracorporeal shock wave lithotripsy	Smaller stones, ureter and kidney	80 - 83	Lacks direct visualization of stone, high bretreatment rate	Steinstrasse, perirenal hematoma
Ureteroscopy	Smaller stones, ureter and kidney	85 - 88	Adult-sized instruments, surgical expertise needed	Infection, ureteral obstruction, ureteral stricture
Percutaneous nephrolithotomy	Larger stones, abnormal anatomy	70 - 97	Adult-sized instruments, surgical expertise needed, higher complication rate, inpatient procedure	Bleeding (8%-16% require blood transfusion), urine leak, urinary obstruction, sepsis
Open pyelolithotomy	Larger stones	79 - 98	Invasive, long postoperative convalescence	As for any open surgery
Minimally invasive pyelolithotomy	Larger stones	No data	Surgical expertise needed, learning curve	As for any minimally invasive surgery

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Table 1. The Summary of Articles Used in This Work

Author and Year	Subject	Type of Study	Location	Finding
Kasaeeyan A A et al. 2015 (1)	TUL	Cross-sectional	Iran	The total success rate of TUL in the treatment of upper urethral calculi was 93.6%
Sas DJ 2010 et al. (4)	Epidemiology	Retrospective cohort	USA	The incidence of kidney stone disease has risen dramatically in the state of South Carolina since 1996
Pearle MSet al. 2005 (5)	Urolithiasis epidemiology in USA	Prospective cohort study	USA	The increasing trend of renal stone disease
Palmer JS et al. 2005 (6)	Clinical diagnosis	Retrospective cohort	USA	Ultrasound failed to detect calculi in 41% of the children with urolithiasis symptoms, whereas CT was highly accurate in all situations
Romero V et al. 2010 (8)	Prevalence and incidence of urolithiasis	Review	USA	The evidence suggests that the incidence and prevalence of kidney stones is increasing globally. Changes in dietary practices may be a key driving force.
Bush NC et al. 2010 (9)	Epidemiology	Retrospective cohort	USA	Urolithiasis of children now account for 1 in 685 pediatric, more than half of the patients are younger than 13 years at hospitalization. Gender and location did not risk factor S.
Edvardsson V et al. 2005 (11)	Incidence of urolithiasis	Retrospective cohort	Iceland	The incidence of kidney stones in Icelandic children is high compared with other Western populations, affecting females more than male
Routh JC et al. 2010 (12)	Urolithiasis Epidemiology	Retrospective cohort	USA	There has been a significant increase in the number of children diagnosed with and treated for urolithiasis
Dawer M et al. 2012 (13)	Epidemiology	Prospective cohort	USA	The incidence of kidney stones increased dramatically among adolescents in the general population. Although the incidence of spontaneous stone passage in adolescents did not increase significantly.
Tasian GE et al. 2016 (14)	Epidemiology	Retrospective cohort	USA	From 1997, the incidence of kidney stones has increased among young patients, particularly females and African Americans.
Tasian GE et al. 2014 (15)	Treatment of urolithiasis	Prospective cohort study	USA	Spontaneous passages of ureteral stones were greater in children prescribed tamsulosin vs. analgesics alone.
Kirejczyk JK 2015 (16)	Dyslipidemia in overweight	Cross-sectional	Poland	Urinary citrate excretion was related to both Body Mass Index (BMI) Z-scores and all lipid fraction abnormalities. Hypercholesterolaemia and low-density lipoprotein hypercholesterolemia may play a major role.
Taylor EN et al. 2005 (17)	Obesity	Prospective cohort	USA	Obesity and weight gain increase the risk of kidney stone formation
Novak TE et al. 2009 (18)	Epidemiology; gender	Retrospective cohort	USA	Pediatric urolithiasis varied with age, with boys more commonly affected in the first decade of life and girls in the second decade.
Matlaga BR et al. 2010 (19)	Urolithiasis epidemiology	Retrospective cohort	USA	Age and gender had an influence on renal stone formation. The risk of kidney stone diagnosis in children younger than six years of age was significantly associated with hypertension and diabetes mellitus.
Sas Dj et al. 2011 (20)	Incidence of childhood nephrolithiasis	Cross-sectional	USA	The kidney stone disease rate has risen dramatically among children

Seitz C et al. 2013 (21)	Role of gender	Cohort	Austria	Female gender was associated with significantly different risk ratio of stone development in different variables. Lifestyle must be considered.
Prezioso D et al. 2015 (22)	Diet and urolithiasis	Systematic review	Italy	Moderate dietary salt restriction and implementation of potassium intake are useful in limiting urinary calcium excretion whereas dietary calcium restriction is not recommended for children with nephrolithiasis
Schissel BL et al. 2011 (2)	Urolithiasis epidemiology	Review	USA	Changing epidemiology and etiology of renal stone in children as well as providing a framework for appropriate clinical evaluation
Penido 2015 (15)	Pediatric primary urolithiasis	Review	Brazil	Most children with idiopathic stone disease have an underlying metabolic abnormality
Copelovitch L et al. 2012 (7)	Medical treatment of urolithiasis	Review	USA	Metabolic diseases are common and metabolic evaluation is essential for all children with renal calculi
Yasui T et al. 2008 (10)	Incidence of urolithiasis	Retrospective cohort study	Japan	Increasing incidence of urolithiasis
Valentini et al. RP 2011 (23)	Epidemiology of nephrolithiasis	Review	USA	Aggressive fluid intake is the mainstay of prevention for all forms of stone disease, but specific therapy targeted to the most likely underlying metabolic abnormality is often used.
VanDervoort K et al. 2007 (24)	Clinical presentation	Cross-sectional	USA	The primary diagnostic test could be a 24-hour urine collection. The most common metabolic abnormality was hypocitraturia, followed by hypercalciuria. Recurrence of stones is common
Seyedzadeh A et al. 2006 (25)	Cystine urolithiasis	Cross-sectional	Iran	Metabolic workup of childhood urolithiasis and appropriate medical management of its underlying disease.
Bernd Hoppe et al. 2013 (26)	Diagnostic examination	Review	UK	The stone is not the disease itself; it is only one serious sign, so it needs a complete evaluation including physical exam, history taking and lab evaluations.
Matlaga BR et al. 2006 (27)	Composition of calculi	Retrospective cohort	USA	Patients with neurogenic bladder experience urolithiasis secondary to infection and metabolic diseases.
Sampath A et al. 2007 (28)	Ketogenic diet and renal stone	Retrospective cohort study	USA	There is no association between these two items.
McNally MA et al. 2009 (29)	Ketogenic diet	Cross-sectional	USA	Oral potassium citrate is an effective preventive supplement against kidney stones in children who receive KD
Saez-Torres C et al. 2013 (30)	Risk factors for urinary stones in children	Prospective cohort study	Spain	Family history and no adequate fluid intake are important for lithiasis formation
Prezioso D et al. 2015 (31)	Diet and urolithiasis	Review	Italy	Adequate fluid intake in children as well as moderate dietary salt restriction and implementation of potassium intake are useful in limiting urinary calcium excretion whereas dietary calcium restriction is not recommended for children
Cogswell ME et al. (32)	Sodium intake in urolithiasis	Prospective cohort study	USA	Sodium intake among school-aged children is much higher than recommended, which requires reduction based on New national nutrition standards
Sas DJ et al. 2016 (33)	Clinic and laboratory characteristics	Review	USA	Low urine volume and high level of urinary calcium was associated with lithiasis although BMI was not. More girls presented their first stone during adolescence.

Penido MG et al. 2015 (34)	Medical management	Review	Brazil	Most children with idiopathic stone disease had an underlying metabolic abnormality substantiating the importance of metabolic evaluation already following initial diagnosis of urolithiasis.
Tasian GE 2014 (35)	Medical management of urolithiasis	Review	USA	Dietary or pharmacological interventions decrease the recurrence of kidney stones in children
Hernandez DJ et al. 2015 (36)	Trend and management of renal stone	Review	USA	A multidisciplinary clinic can help provide the medical and surgical support needed for patients
Penido MG et al. 2013 (37)	Clinical and etiology of urolithiasis	Cross-sectional	Brazil	Oliguria and hypercalciuria continue to be the most common etiologies of pediatric primary urolithiasis, followed by hypocitraturia
Kovacevic L et al. 2014 (38)	Hypercalciuria & hypocitraturia	Cross-sectional	USA	The majority of children had an identifiable metabolic risk factor for urolithiasis, with hypocitraturia being the most common. Diet must be considered in this setting.
Braun DA et al. 2016 (39)	Genes as etiology	Lab test	USA	Nephrolithiasis may result from mutational analysis in individuals with early manifestation of nephrolithiasis or nephrocalcinosis.
Figueres et al. 2015 (40)	Mutation of CYP24A1	Lab test	France	CYP24A1, the enzyme that converts the major circulating and active forms of vitamin D to inactive metabolites, recently has been implicated in idiopathic infantile hypercalcemia
Dasgupta D et al. 2014 (41)	Mutation of SLC34A3/NPT2	Lab test	Australia	Mutation in SLC34A3 alleles had a significantly increased risk of kidney stone formation or medullary nephrocalcinosis
Sarica K et al. 2009 (42)	Obesity	Cross-sectional	Turkey	Overweight status in children might be associated with an elevated risk of stone formation in both genders with change in their urine composition.
Kieran K et al. 2010 (43)	BMI and urolithiasis	Retrospective cohort	USA	Upper percentile body weight was not associated with earlier stone development, larger stones or the need for multiple surgical procedures.
Kurtz MP et al. 2015 (44)	BMI & postoperative status	Prospective cohort	USA	High BMI may be associated with higher post-operative complications.
Kuroczycka-Saniutycz E et al. 2015 (45)	Obesity	Prospective cohort	USA	Obesity and overweightness had no direct influence on the lithogenic risk profile in urinary stone formers. Higher serum uric acid may be associated with impairment in renal function
Safaei Asl A et al. 2011 (46)	Clinical manifestation	Retrospective cohort	Iran	Family history of urolithiasis, urologic abnormalities, especially under the age of five years, metabolic disorders, and urinary tract infections tend to be associated with childhood urolithiasis.
Sadeghi S. et al. 2015 (48)	Metabolic factors	Retrospective cohort	Iran	Most patients were symptomatic and hypocitraturia was the most common risk factor
Alemzadeh-Ansari MH et al. 2014 (49)	Risk factors evaluation	Retrospective cohort	Iran	Urinary metabolic abnormalities are very common among Iranian infants with urolithiasis
Mohammadjafari H et al. 2015 (47)	Pattern of urolithiasis in north Iran	Review	Iran	Metabolic derangement plays a significant role in stone formation in Iran.
Cambareri GM et al. 2015 (50)	Age and urolithiasis	Review	USA	Children $\leq$ 10 years of age were more likely to have a metabolic disorder

Polat H et al. 2016 (52)	Neoplasm	Retrospective cohort	Turkey	Bladder tumors in children are usually rare and not considered with good prognosis. Ultrasonography is sufficient in follow-up.
Moudi E et al. 2016 (54)	Hematuria and asprine	Cohort study	Iran	Taking regular doses of aspirin may be accompanied with higher rate of microscopic hematuria
Alipour A et al. 2016 (55)	Urine Biomarker	Meta-analysis	Iran	The assessment of urinary biomarkers is a helpful tool to assess the presence and severity of UPJO, but there is little published data on each of the studied biomarkers.
Chen W et al. 2016 (56)	Urine sample Evaluation	Prospective cohort study	China	The 24-hour UIC was more accurate and reproducible than the MUIC
Ellison JS et al. 2014 (57)	The role of 24-h urine collection	Retrospective cohort	USA	24-hour urine collection appears to be underused among children. More common among younger patients and those who visited urologists or nephrologists.
Aliramaji et al. 2015 (53)	Incidence of cancer in childhood	Cross-sectional	Iran	Smoking and opium consumption associated with bladder cancer
Passeroti c et al. 2009 (59)	US vs. CT scanning	Review cohort study	USA	Computerized tomography is more sensitive for detecting urolithiasis than ultrasound. Ultrasound should be considered the first imaging test in children
Azili MN et al. (60)	Management of Urolithiasis	Retrospective cohort	Turkey	The cutoff value of stone size for open surgery was 10 mm. There was a significant relationship between the conversion to open procedures and stone size, stone location and symptom presentation
Tisian Ge et al. 2014 (61)	Medical management	Review	USA	There is no effective randomized trial on urolithiasis among children. Thiazide diuretics may be helpful in the treatment of children with calcium-based stones and persistent hypercalciuria refractory to reductions in salt intake.
Mokhless et al. 2012 (62)	Tamsulosin in pediatrics	Clinical trial	Egypt	Tamsulosin demonstrated no clinically significant adverse effect, while proving to be a safe and effective treatment option in children.
McClinton S et al. 2014 (63)	Expulsive therapy	Clinical trial	Scotland	Spontaneous passage of stone was seen by using nifedipine or tamsulosin versus placebo, in four weeks
Pickard R et al. 2015 (64)	Expulsive therapy	Clinical trial	UK	Tamsulosin 400 μg and nifedipine 30 mg were not effective at decreasing the need for further treatment to achieve stone clearance in four weeks for patients with expectantly managed ureteric colic.
Long CJ et al. 2014 (65)	Percutaneous nephrolithotomy	Review	USA	Percutaneous nephrolithotomy in children and its applicability to current surgical management of pediatric stone disease are discussed.
Smaldone MC et al. 2010 (66)	Surgical management	Review	USA	Large series demonstrate comparable stone-free and complication rates with SWL, URS, and PCNL, although there remains controversy regarding children
Raza A et al. 2006 (72)	Endourological management	Review	UK	For most renal stones smaller than 20 mm, SWL was the most effective primary treatment modality

Wang HH et al. 2012 (68)	SWL	Retrospective cohort	USA	3377 children with renal stones, of whom 538 (16%) underwent surgery (shock wave lithotripsy in 48%, ureteroscopy in 52%). Treatment choice depends significantly on the hospital at which a patient undergoes treatment
Tejwani R et al. 2016 (67)	SWL vs. Ureteroscopy	Retrospective cohort study	USA	Ureteroscopy is now used more commonly than shock wave lithotripsy for initial pediatric stone intervention. However, recurrence during the next 30 days was high.
Schwarz RD et al. 2006 (69)	Long term outcome of Urolithiasis	Prospective cohort	Canada	Extensive metabolic screening of children with upper tract urinary stones is not necessary
Elmaci AM et al. 2014 (70)	Metabolic risk factors	Retrospective cohort study	Turkey	Metabolic abnormalities were found in 79.2% of patients, including hypercalciuria in 31.5%, hypocitraturia in 24.2%, hyperoxaluria in 11.4%, hyperuricosuria in 9.1%, hypomagnesuria in 3.9%, and cystinuria in 3.1% of patients.
Akhavan-Sepahi M,2012 (73)	Biochemical risk factors	Cross sectional	Iran	The prevalence of hypercalciuria is significantly higher compared to other countries, it may be associated with excessive intake of sodium
Dauw CA et al. 2015 (74)	Metabolic management	Retrospective cohort study	USA	Follow up testing is an important issue that is usually missed by non-urologist or nephrologists medicines.