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Pediatric stone disease: Current management and future concepts

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ABSTRACT

Treatment of pediatric urolithiasis consists of medical and surgical approaches. The main goal of the treatment is to prevent stone recurrence by avoiding multiple surgical interventions. In recent years, many innovations have been reported in the medical diagnostic evaluation protocol and in surgical treatment. According to recent reports, single mutations could be responsible for a larger proportion of renal stones. This etiologic feature holds the potential to change the management in stone prevention from metabolically directed therapy to more specific approaches. In addition, miniaturized instruments have been adopted in clinical practice. In recent years, minimally invasive endoscopic surgery is the treatment of choice in pediatric urolithiasis. This review aims to assess the current literature on medical and surgical treatment options for pediatric urolithiasis. We also aim to provide an overview of potential future advances.

Keywords: Children, hypercalciuria, medical treatment, metabolic abnormality, minimally invasive surgery, nephrolithiasis, stone disease, urolithiasis

Introduction

The incidence of pediatric stone disease is significantly increasing worldwide. Pediatric stone disease differs from adult stone disease in many aspects. Reducing the rate of repetitive surgical intervention and protecting renal functions depend on medical planning based on the child's metabolic condition and surgical planning based on the child's anatomic structure (1). In the past 20 years, the most significant advances in pediatric stone disease includes the assessment of genetic infrastructure of the disease to better understand the etiological factors, development of instruments suitable to children's size, and classification of minimally invasive endoscopic approaches with a high success rate as preferred surgical methods (1-4). This review evaluates the current diagnosis and treatment algorithms for pediatric stone disease and the anticipated potential advances.

Methodoloy and Study Selection

A comprehensive search of the PubMed database and the Cochrane Library Central search facility was performed, focusing on the past 2 decades. In this nonsystematic review, we included original articles related to the medical and surgical management of stone disease in children. The European Association of Urology (EAU)/European Society of Pediatric Urology (ESPU) guidelines were also used for the review. Separate Medical Subject Headings keywords (MeSH) were used for the search term "medical treatment" (hypercalciuria, hypocitraturia, urolithiasis, diagnosis, medical treatment, metabolic risk factors) and the search term "surgical treatment" (shockwave lithotripsy [SWL], percutaneous nephrolithotomy [PNL], ureteroscopy, retrograde intrarenal surgery [RIRS], miniPERC, microPERC, laparoscopic and robotic stone surgery, cystolithotripsy), and priority was given to the evidence-based studies.

Epidemiology

The incidence of stone disease is affected by many factors, including race, geographical region, socioeconomic conditions, and dietary habits.

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As with the Middle/Near East and North Africa regions, stone disease is also endemic in Turkey. Although reasons such as hot climate and high consanguineous marriage rate have been associated with the disease being endemic, it is accepted that genetic and racial characteristics affect the epidemiology.

Whereas calcium oxalate or calcium phosphate stones localized in the kidney and ureter are common in economically developed countries, bladder stones containing uric acid and ammonium are common in developing countries.

Risk Factors

Environmental and metabolic risk factors

The most critical risk factor associated with the development of pediatric stone disease is metabolic problems. Hypercalciuria and hypocitraturia are the most detected metabolic problems (5, 6). Clinical conditions resulting in reduced urine output (insufficient fluid intake, dehydration, inflammatory disease, etc.) may lead to stone formation by causing an increase in the urinary solutes and formation of insoluble crystals.

Another risk factor for stone formation is urinary tract infection. Urinary tract infection may develop secondarily to congenital anomalies of the urinary system. Moreover, congenital obstructive anomalies (ureteropelvic junction stenosis, posterior urethral valve, duplication anomalies, and so on) may lead to stone formation due to urinary stasis even without infection (7).

Dietary habits are also known to affect stone formation. Increased dietary intake of sodium predisposes to stone formation by causing increased urinary excretion of calcium. A high-protein diet increases the urinary excretion of uric acid, oxalate, and calcium, causing lower urinary pH and calcium oxalate precipitation. Excessive protein intake reduces the urinary citrate level, the most potent inhibitor of crystallization (8, 9). In recent years, studies on a diet have focused on the effect of obesity on stone formation; however, there is no consensus (10, 11).

Another characteristic of childhood is that there are different risk factors for stone formation for different age groups. The risk factors identified during the neonatal period include a history of hospitalization in the neonatal intensive care unit, prematurity, and low birth weight (12). Other risk factors for this period include the use of nephrotoxic medications and diuretics. Later in life, chronic bowel diseases become a risk factor due to increased intestinal absorption of oxalate (3). Whereas anticonvulsant use (topiramate) during childhood and ketogenic diet in children who suffer seizures are effective in seizure control, it is known that they increase stone formation in the urinary tract after 2 years (9, 13).

In developing countries, diagnosis of bladder stone containing ammonium acid urate is common. It is associated with reduced consumption of animal protein and phosphor and vitamin A deficiency. In developed countries, urinary tract stones are detected more frequently in children with congenital spinal cord anomalies or spinal cord trauma history. Bladder augmentation is also a known risk factor for bladder stone formation. In these patients, urinary stasis, bacterial colonization, mucous retention, and foreign bodies lead to the formation of mostly struvite stones in the bladder (13-15).

Genetic risk factors

Recent studies have pointed out the role of genetics in epidemiology. It was found that pediatric stone disease is frequently seen secondarily to monogenetic causes (4). Today, however, as long as no findings suggest the presence of significant genetic predisposing factors, guidelines do not recommend genetic research. The most important reason for this is the high cost (1, 4). The most significant sign associated with genetic stone disease is nephrocalcinosis or the recurrence of stone within a year (14). Delays in the diagnosis and treatment of patients with stone disease with detected genetic predisposing factors pose a high risk of chronic renal failure. It is therefore important for clinicians to know the genetic epidemiological factors and make a diagnosis. Table 1 summarizes the genetic causes associated with pediatric stone disease (4, 16).

Clinical Symptoms

Clinical symptoms differ by age. Nonspecific symptoms such as irritability and crying attacks are common first symptoms in infants. In preschool children, the most commonly expressed symptoms are nonspecific, such as nonlocalized abdominal pain and nausea. School children and adolescents usually seek medical advice due to renal colic (1, 14, 17).

Gross hematuria is not common in childhood. Microhematuria and signs of urinary system infection may sometimes be the only positive signs. In addition, possible lower urinary tract irritation during the stone passage may cause dysuria or problems associated with urination. Urinary retention or acute renal failure may be seen when the tract is obstructed with the stone; however, it is rare in children (7).

Diagnosis

Metabolic assessment

A complete systemic and metabolic assessment should be done in every child being evaluated for stone disease. The medical history of the children and their families should be questioned for predisposing genetic factors to determine the risk factor. Anatomical conditions with congenital urinary tract anomalies in the first place, followed by dietary habits, urinary tract infection, and possible history of previous stone passage should be assessed/noted. Examination of the passed stone sample is essential for diagnosis and treatment (7, 14).

Laboratory examinations include blood, spot urine, and/or 24-hour urine analyses. Levels of blood electrolytes (sodium, potassium, and chlorine), blood urea nitrogen, calcium, creatinine, phosphor, alkaline phosphatase, uric acid, total protein, bicarbonate, albumin, and parathormone (when hypercalcemia is suspected) are assessed (1). Calcium/creatinine ratio can be calculated in the spot urine analysis. In children, this ratio being below 0.2 is normal. When it is above 0.2, the test needs to be repeated. If it is still high in the repeated test, 24-hour urine analysis is necessary for hypercalciuria work-up. The diagnosis protocol also involves a urine culture. Levels of calcium, phosphor, magnesium oxalate, uric acid, citrate, protein, and creatinine clearance are assessed in the 24-hour urine analysis. Urine pH is recommended to be measured in fresh urine (1). If cystinuria is suspected (positive sodium nitroprusside test, presence of

Table 1. Hereditary causes of renal stones

Disease	Type	Inheritance	Gene and gene location	Metabolic Features
Cystinuria				
	Type A	AR	*SLC3A1*	Elevated urine cystine, cystine stone ± calcium stone
	Type B	AR-ID	*SLC7A9*	
Hyperoxaluria				
	Type 1	AR	*AGXT*	Elevated urine oxalate, Ca oxalate monohydrate stones
	Type 2	AR	*GRHPR*	
	Type 3	AR	*HOGA1*	
DENT Disease				
	DENT 1	X-LR	*CLCN5, Xp11.23*	Fanconi syndrome, hypercalciuria, glycosuria, aminoaciduria, phosphaturia, nephrocalcinosis
	DENT 2	X-LR	*OCRL, Xq26.1*	Additionally, cataracts, mental retardation, muscular hypotonia, nephrotic proteinuria, metabolic acidosis
Batter Syndrome				
	Type 1	AR	*SLC12A1, 15q21.1*	Classical presentation; hypokalemic metabolic alkalosis, renal salt wasting, hypercalciuria, increased renin, secondary hyperaldosteronism, nephrocalcinosis
Antenatal presentation; polyhydramnios, renal salt wasting, prematurity, hypercalciuria, nephrocalcinosis				
	Type 2	AR	*KCLJ1, 11q24.3*	
	Type 3	AR	*CLCNKB, 1p36.13*	
	Type 4a	AR	*BSND, 1p32.3*	
	Type 5	X-LR	*MAGED2, Xp11.21*	
Xanthinuria	AR	XDH	*Xanthine stones, hypouricemia*	
Renal hypouricemia		AD or AR	*URAT1, SLC22A12, GLUT9, SLC2A9*	Hypouricemia, hypercalciuria, uric acid or calcium stone
Infantile idiopathic hypercalcemia		AR-ID	*CYP24A1*	Hypercalcemia, hypercalciuria, nephrocalcinosis, reduced calcitiriol metabolism, increased 1.25(OH)2D3 levels
Infantile hypercalcemia 2		AR	*SLC34A1, 5q35.3*	Hyperkalemia, hypercalciuria with nephrocalcinosis, hypophosphatemia, low PTH and increased 1.25(OH)2D3 levels
Autosomal dominant hypocalcemia hypercalciuria		AD	*CASR, 3q21.1*	Hypocalcemia, hypercalciuria, normal PTH level, calcium stone
Familial hypocalciuric hypercalcemia		AD	*CASR*	Hypocalcemia, hypercalsuria normal to high PTH level
Autosomal dominant absorptive hypercalciuria		AD	*ADCY 10*	Hypercalsuria
Hereditary hypophosphatemic rickets with hypercalciuria		AR-ID	*NPT2c, SLC34A3*	Hypophosphatemia, elevated 1,25(OH)2D3 level
Primary distal renal tubular acidosis				
		AR	*ATP6V1B1, ATP6V0A4*	Impaired urine acidification, ± metabolic acidosis, calcium phosphate stones
		AD	*AE1*	
Primary proximal and distal renal tubular acidosis		AR	*CA2*	Impaired urine acidification, ± metabolic acidosis, calcium phosphate stones
Adenine phosohoribosyltransferase deficiency		AR	*APRT*	2,8-dihydroxyadenine stones
Familiar hypomagnesemia with hypercalcuria and nephrocalsinosis		AR-ID	*CLDN16, 3q28, CLDN19, 1p34.2*	Hypercalciuria, hypomagnesemia, hyperkalcemia, nephrocalsinosis
Calcium oxalate nephrolithiasis		Unknown	*SLC26A1*	Calcium oxalate nephrolithiasis
Phosphoribosyl pyrophosphate synthetase superactivity		X-LR	*PRPS1*	Hyperuricemia, uric acid stones
Hypophosphatemic nephrolithiasis/ osteoporosis		AD	*NHERF1, SLC9A3R1*	Calcium stones, low bone density
Pseudohyperaldosteronism type two (PHA2 PHA2B)		AD	*WNK4, 17q21.2*	Hyperkalemia, metabolic acidosis, ammonium excretion, hypertension

AR, autosomal recessive; AR-ID, autosomal recessive incomplete dominance; AD, autosomal dominant; X-LR, X-linked recessive [modified from Policastro et al and Hoppe et al. (4, 16)].

Table 2. Normal ranges of metabolites in urine analysis (1, 3, 14)

Parameter	Age	Solute/creatinine in spot urine sample		Solute in 24-hour urine sample
		mg/mg	mmol/mmol	
Calcium				
	0-6 months	<0.8	<2	≤4 mg/kg (<0.1 mmol)
	7-12 months	<0.6	<1.5	
	1-3 years	<0.53	<1.5	
	3-5 years	<0.39	<1.1	
	5-7 years	<0.28	<0.8	
	>7 years	<0.21	<0.6	
Oxalate				
	0-6 months	<0.26	<0.36	<45 mg/1.73m2 (<0.5mmol)
	7-24 years	<0.11	<0.17	
	2-5 years	<0.08	<0.09	
	5-14 years	<0.06	<0.08	
	>16 years	<0.03	<0.04	
Citrate				
	0-5 years	<0.42	<0.25	>365 mg/1.73m2 (>1.9 mmol) males
	>5 years	<0.25	<0.15	>310 mg/1.73m2 (>1.6 mmol) females
Uric Acid				
	<1 years	<2.2	<1.5	<13 mg/kg (<486 mmol)
	1-3 years	<1.9	<1.3	<11 mg/kg
	3-5 years	<1.5	<1	
	5-10 years	<0.9	<0.6	<9 mg/kg
	>10 years	<0.6	<0.4	
Magnesium				
	>2 years	>0.13	>0.63	>0.8 mg/kg (>0.04 mmol)
Cystine				
	<10 years	<0.07		<13 mg/1.73m2 (<55 µmol)
	>10 years			<48 mg/1.73m2 (<200 µmol)
Xanthine				
	All ages	N/A	N/A	20-60 µmol

N/A, not available.

hexagonal cystine crystal in urine, or previous cystine stone history), cystine analysis should be performed in 24-hour urine (1). The normative values of assessed metabolites differ by age in childhood. This should be kept in mind during the assessment (Table 2) (12, 14).

The excretion rate of the urinary creatinine informs us whether the urine is collected correctly. This value is approximately between 15 and 20 mg/kg. In values above or below this range, it is considered that the urine is collected incorrectly (18).

Imaging methods

Ultrasonography (USG) is the first-line imaging method in pediatric stone disease. Direct urinary system X-ray is successful in showing opaque stones, such as calcium stones; however, it may be insufficient to show nonopaque stones, such as uric acid stones, and semiopaque stones, such as cystine stones. Today, low-dose nonenhanced helical computed tomography (CT) is a fast and safe assessment method in detecting urinary system stones. CT is also valuable for revealing the urinary tract anatomy in patients who will undergo surgical intervention. Intravenous pyelography is no longer preferred as a diagnostic method (19-21).

Approaches

In children, preventing the recurrence of stones is as important as removing them from the system. Therefore, it is essential to determine the metabolic condition causing the stone formation. The first step in the treatment is to increase fluid intake. Upon diagnosis, the pain can be reduced using analgesic and antispasmodic treatments. In general, asymptomatic small stones (<4-5 mm) pass spontaneously. Medical expulsive treatment has been reported to increase the rate of stone passage. Therefore, as with adults, medical expulsive treatments promoting stone passage (α-blockers) may be used in children (22, 23). Table 3 summarizes the metabolic assessment, diagnosis, and treatment algorithm for pediatric stone disease.

Medical theraupetic interventions

Calcium oxalate stones are formed due to supersaturation of calcium (hypercalciuria) and oxalate (hyperoxaluria) or reduced levels of inhibiting citrate or magnesium. Supersaturation of calcium oxalate is also associated with multiple stone formation. In general, stones containing calcium oxalate are common in children (70%) (1).

Table 3. Algorithm for metabolic investigations and treatment protocols in urinary stone disease in children

Stone Composition	Metabolic Phenotype	Diagnosis	Treatment
Calcium stone	Differs depending on the type of metabolic abnormality	Hypercalciuria	K-citrate (2-3 mEq/kg/d), diet (normal Ca, low Na), HCTZ diuretic (0.5-1 mg/kg/d)
		Hyperoxaluria	High fluid intake, regular Ca intake, low oxalate intake, K-citrate/Ca-citrate, pyridoxine
		Hyperuricosuria	K-citrate, allopurinol (10mg/kg)
		Hypocitraturia	K-citrate
Cystine Stone	Elevated urine cystine level	Cystinuria	High fluid intake
			K-citrate (3-4 mEq/kg/day)
			Mercaptopropionylglycine (10-15 mg/kg/d)
			Penicillamine (30 mg/kg/d)
			Captopril (1-4 mg/kg/d)
Struvite Stone	Positive urine culture		Antibiotics
			Acidification of urine (urine pH <6.2)
			Total elimination of stone (surgery or SWL)
Uric acid Stone	Acid urine		Low purine diet
	Hyperuricosuria		K-citrate (3-4 mEq/kg/d)
	Hyperuricemia		Allopurinol (10 mg/kg)

RTA, renal tubular acidosis; K-Citrate, potassium citrate; Ca, calcium; Na, Sodium; HCTZ, hidroclorothiazid,
[Modified from European Association Urology/European Association of Pediatric Urology Guideline 2020, Radmayr et al. (1)].

Hypercalciuria: Hypercalciuria is the most common problem associated with stone formation (1). In idiopathic hypercalciuria, an underlying cause cannot usually be detected. Although 45% of patients have a family history of stones, specific genetic mutations are rarely detected. The other type is hypercalcemic hypercalciuria (secondary). In hypercalcemic hypercalciuria, serum calcium levels are increased due to increased bone resorption (hyperparathyroidism, hyperthyroidism, immobilization, acidosis, metastatic disease) or gastrointestinal hyperabsorption (hypervitaminosis) (5). Renal tubulopathies associated with Bartter syndrome and Fanconi syndrome may also lead to hypercalcemia (14).

The treatment includes restricted sodium intake by keeping the daily calcium amount within the normal range. Low calcium consumption is considered to be a risk factor for stone formation (1, 14). Hydrochlorothiazide and other thiazide diuretics may be initiated. However, the hypocalciuric effect may be reduced in long-term use. Furthermore, it may lead to hypokalemia, hypocitraturia, hyperuricemia, and hypomagnesemia. Blood and serum levels should be monitored at regular intervals. Citrate treatment may be initiated when citrate levels are reduced or in conditions where hypercalciuria persists despite other treatment protocols (1).

Hyperoxaluria: Only 10% of oxalate is taken through diet. Hyperoxaluria can be caused by genetic disorders (primary hyperoxaluria), intestinal disease (enteric hyperoxaluria) or excessive consumption of foods high in oxalate (dietary hyperoxaluria). Primary hyperoxaluria is a rare and life-threatining genetic disorder caused by autosomal recessive enzymatic defects in glyoxylate metabolism in the liver due to mutations in the genes of AGXT, GRHPR, and HOGA1. Increase in calcium oxalate crystals may supersaturate in urine and kidney, leading to stone formation and chronic kidney disease (1, 3, 14). Enteric hyperoxaluria is a distinct entity that usually occurs in the conditions of fat malabsorbtion, such as short bowel syndrome, inflammatory bowel disease, pancreatitis, and cystic fibrosis (1, 3, 14). Treatment includes restricted dietary intake of oxalate. Other diatary recommendations are low fat diet, maintaining an adequate calcium intake (RDA), and large fluid intake. Pyridoxine helps to reduce urinary oxalate levels, especially in primary hyperoxaluria. The addition of citrate to the treatment is beneficial for increasing the inhibitory activity (1, 3, 14).

Hypocitraturia: Citrate exerts its inhibitory effect by directly binding to calcium or inhibiting the growth and/or aggregation of the calcium oxalate and calcium phosphate crystals. Low urinary citrate level is one of the main reasons for the formation of calcium stones in children (30%-60%) (24). Hypocitraturia is asymptomatic and not associated with a metabolic problem. It may accompany metabolic acidosis, distal tubular acidosis, or diarrhea syndromes. Excessive protein and salt consumption cause a reduction in citrate levels.

Potassium citrate is used in hypocitraturia treatment. The side effects of potassium citrate include nonspecific gastrointestinal symptoms. Dosing should be performed with caution in patients with hyperkalemia and chronic renal failure (1).

Cystinuria: This is an autosomal recessive disease characterized by cystinuria due to defective tubular absorption of dibasic amino acids, namely, cystine, lysine, arginine, and ornithine. Cystinuria is seen in 2%-6% of all children with urinary tract stone disease. The solubility of cystine in urine is low and pH dependent (pH<7). It may accompany hypercalciuria, hypocitraturia, and hyperuricosuria, leading to the formation of mixed-type stones. Imaging of the cystine stones in plain X-rays is difficult due to its semiopaque structure, and SWL treatment is difficult due to its hard structure (1). These children have a high risk of stone recurrence (25).

Treatment includes increasing fluid intake to increase the solubility of cystine by reducing its saturation and urine alkalinization. The goal is to maintain the pH level above 7.0-7.5 using potassium citrate. In case of treatment failure, second-line agents include α-mercaptopropionyl glycine and D-penicillamine. The medications' side effects include mild gastrointes-

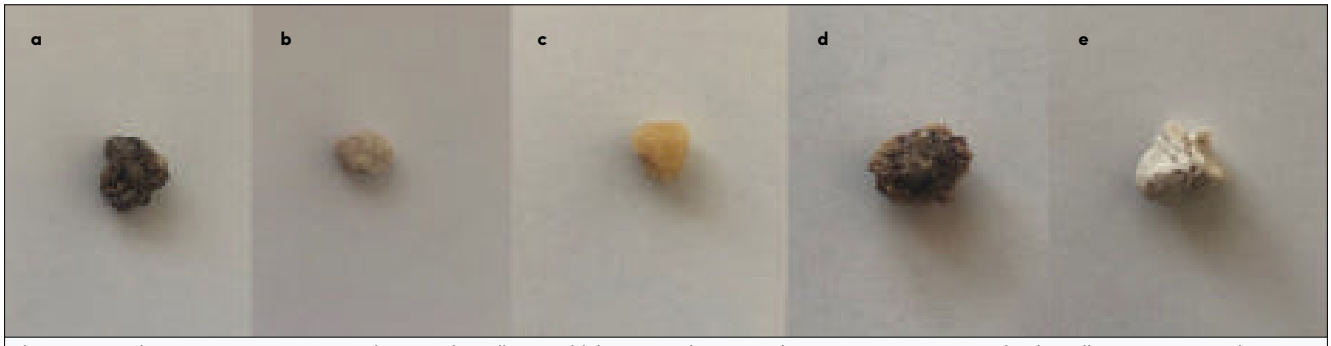

Figure 1. a-e. The urinary tract stone samples. (a) Whewellite/Weddelite stone, (b) uric acid stone, (c) cystine stone, (d) Whewellite stone, (e) Brushit stone (photos are from the archive of Bülent Önal, MD, Professor)

Table 4. Recommendations for the EAU/ESPU guidelines for interventional management in pediatric urolithiasis* (1)

Stone Size &Localization	Treatment option		Comment
	Primary	Secondary	
Staghorn stones	PNL	Open/SWL	Multiple sessions/accesses with PNL may be needed. Combination with SWL may be useful
Pelvis <10 mm	SWL	RIRS/PNL/micro-PNL	
Pelvis 10-20 mm	SWL	PNL/RIRS/micro-PNL/open	Multiple sessions with SWL may be needed. PNL has a similar recommendation grade
Pelvis >20 mm	PNL	SWL/open	Multiple sessions with SWL may be needed
Lower pole calyx <10 mm	SWL	RIRS/PNL/micro-PNL	Anatomic variations are important for complete clearance after SWL
Lower pole calyx >10 mm	PNL	SWL/micro-PNL	Anatomic variations are important for complete clearance after SWL
Upper ureteric stones	SWL	PNL/URS/ open	
Lower ureteric stones	URS	SWL/open	Additional intervention need is high with SWL
Bladder stones	Endoscopic		Open is easier and with less operative time with larger stones

*Cystine and uric acid stones excluded; EAU, European Association of Urology; ESPU, European Society of Pediatric Urology (1); PNL, percutaneous nephrolithotomy; SWL, shockwave lithotripsy; RIRS, intrarenal surgery using flexible ureterorenoscopy; URS, ureterorenoscopy

tinal complaints (reduced taste and smell), fever, and rash. However, caution should be exercised for serious side effects, including bone marrow suppression, nephrotic syndrome, and epidermolysis (1).

Uric acid stones: Uric acid is the end-product of purine metabolism. Uric acid is not soluble in acidic urine (pH<5.8); therefore, it precipitates, leading to uric acid stone formation. Serum uric acid levels are usually normal in familial or idiopathic hyperuricosuria. However, pathologies characterized by excessive uric acid production (e.g., myeloproliferative diseases and pathologies associated with cell destruction) are accompanied by hyperuricemia. Hyperuricosuria is also associated with a high-protein diet and purine intake. Uric acid stones are non-opaque. USG and/or low-dose, nonenhanced CT examination is used for diagnosis and treatment planning (1).

Citrate preparations are used for the treatment. The goal is to maintain the urinary pH at 6-6.5. In case of treatment failure or in myeloproliferative diseases, allopurinol is initiated. Rash, diarrhea, and eosinophilia may develop during allopurinol use (26).

Infection stones: These account for 5% of the pediatric urinary tract stone diseases. Urinary tract obstruction or functional anomalies may lead to the development of *Proteus*, *Klebsiella*, and *Pseudomonas* (known as urease enzyme-producing bacteria) infections. These microorganisms increase urinary pH, causing struvite (magnesium ammonium phosphate) and calcium phosphate apatite supersaturation and leading to the formation of infection stone (15). The main principle of the treatment is treating the urinary tract infection and removing the stone from the system. The anatomic or functional reason causing urinary tract infection should be eliminated (1). Figure 1 shows the macroscopic appearance of the urinary tract stones.

Surgical Intervention

Shock wave lithotripsy

According to the EAU/ESPU guidelines, SWL is the first-line treatment protocol for the majority of the renal and proximal ureteral stones (1). The success rate is between 59% and 94% (2). Although the success of SWL is affected by many factors, the most known factor is the stone size. The larger the stone, the lower the success rate and the higher the rate of retreatment. A general opinion on the effect of stone localization on stone-free rate is that SWL is more effective in stones localized in the renal pelvis and proximal ureter than the calyceal stones (27, 28). Our clinical experience indicates that the success rate is the same in all localizations within the kidney for the stones of <2 cm; however, the success rate of SWL is reduced in distal ureteral stones (29, 30). Many factors affecting success are evaluated together using nomograms. In their nomogram, Onal et al. (31) reported the factors increasing the success rate as being under 5 years of age, stone load being <1 cm, localization of the stone (pelvic or upper calyceal stone; only in females), absence of a

history of stone treatment in the same side and having a single stone. Other than the factors included in this nomogram, a history of open stone surgery has been reported to reduce the success rate of SWL, especially in lower calyceal stones (32). In a similar nomogram developed by Dogan et al. (33), the size of the stone, age, sex, localization, and history of stone treatment in the same side have been reported as factors determining the stone-free success rate. Subsequent studies demonstrated that both nomograms are useful in determining the stone-free rate of SWL in the population in which they are developed and in other endemic populations (33, 34).

The complication rate after SWL is between 1.5% and 35% (2). The most frequent complications are renal colic and steinstrasse. Steinstrasse is usually seen in children with a high stone load, and the treatment is performed using SWL (35). Stent placement before SWL reduces the formation of steinstrasse. Other than this, urinary tract infection, subcapsular hematoma, and renal parenchymal injury are rarely seen. The information on the long-term effect of SWL on the kidneys in children is lacking. A small number of studies indicate that overall, it does not affect renal development; there is a study reporting that longitudinal kidney growth is affected negatively (36).

Minimally invasive surgical options that are highly effective in providing stone-free status reduced the interest in SWL; however, minimally invasive techniques and SWL have comparable stone-free rates. Moreover, the advantages of SWL include shorter post-procedural hospitalization, detection of less post-procedural readmission rates and is cheaper (Table 4) (1).

Ureterorenoscopy

The success rate of semirigid ureterorenoscopy (URS) in ureteral stones is 90%. Factors associated with complication development include age, surgeon's experience, orifice dilation, stone load, and prolonged operative time (37). Flexible URS is a suitable treatment method in stones localized in the proximal ureter and kidney (38).

Reaching to the stone or the calyceal system during the flexible URS procedure might be difficult in stenosis of ureterovesical junction or ureteral trace. It is recommended that a stent is placed, and the procedure is delayed until the next session. Using a ureteral sheath during the procedure provides convenience for re-entries and also helps preserve ureterovesical junction.

Intrarenal surgery using flexible ureterorenoscopy

It has been reported that intrarenal surgery using flexible URS (RIRS) might provide success in fewer sessions compared with SWL. Factors determining the success rate of RIRS include stone load and localization, younger age, and stone composition. Success rates in procedures performed on an appropriate indication are between 87% and 100%. The complication rate is 10%. They are usually seen in younger children with a spinal anomaly and a history of neurogenic bladder (2).

The first step in preventing complications is performing the flexible or semirigid URS using instruments chosen based on the child's age and anatomical structure. For safety, the guidewire must be placed into the ureter before the procedure, and direct vision must be used for proceeding and placement (1). Because hydrodilation is a well-accepted method, no significant risk has been reported for ureteral stenosis formation and reflux development (39). The most important complication associated with URS is ureteral injuries. Hydronephrosis developed after the operation suggests a possible ureteral injury during the procedure. These injuries might be limited to mucosal ruptures, or perforation may occur. The most serious complication is ureter avulsion. In mucosal injuries, ruptures, and injuries with urine extravasation, it is recommended that a stent be placed and the procedure is terminated (1, 2, 15).

Percutaneous nephrolithotomy

Miniaturization of the instruments for PNL has facilitated its use in the pediatric population. There is no standard sheath size reported in the literature, but the general opinion is that sheath size above 24 Fr is defined as classic PNL (2). PNL remains the standard treatment option for larger stone (>2 cm) (1). When administered as monotherapy and in a single session, the stone-free success rate is between 86% and 98%. Increasing the sessions or treatments combined with RIRS/SWL increases the success rate (28, 40). The most frequently seen PNL complication is hemorrhage, and blood transfusion becomes necessary in 10% of the patients. Other PNL complications include fever and persistent urine leaks from the nephrostomy area (41). In our multicenter study, we observed a PNL complication rate of 27% in children. Operative time, sheath size, mid-calyceal puncture, and partial staghorn stone formation were the statistically significant parameters affecting complication rates (42).

Moreover, multiple punctures are necessary for cystine and infection stones, but stone composition does not affect the success rate (43). PNL is also an effective treatment method in children who have a previous history of open stone surgery. However, because the risk of colon injury is increased in this group, it is recommended that the anatomic structure before the procedure be evaluated using CT (44). Clinical classifications can be used to evaluate many factors before PNL. One of these is the Guy's stone scoring system. This system is useful in estimating the success rate in children. Our experience shows that an increased Guy's stone score is associated with a reduced success rate (45).

PNL should not be performed during anticoagulant use. PNL is contraindicated in untreated urinary tract infection and mass in the kidney (15).

Cystolithotripsy

In bladder stones <2 cm, transurethral lithotripsy provides success with minimum complication rate in children. In bladder stones >2 cm, it is not preferred because urethra calibration does not allow an effective treatment. Percutaneous cystolithotripsy might be preferred for bladder stones of all sizes. It is mostly the first choice in bladder stones >2 cm. It can be easily performed in an augmented bladder for stones of all sizes. Urethral entry and instrument control might be difficult in the transurethral approach, which may prolong the operative time and increase the risk of urethral injury. Percutaneous approaches are advantageous because urethra-associated problems are not observed (15, 46).

Future Concepts

Medical aspect

A 10-year recurrence rate has been reported to be 12%-56% in the literature. From a medical point of view, prevention of

stone recurrence is possible by a sound analysis of the metabolic problems. Recent studies have shown that monogenic reasons are higher than known in stones defined as idiopathic. These studies have indicated that the effective use of genetic tests will facilitate diagnosis in many children. In this way, treatment protocols classified by metabolic assessment might also be classified by genetic diagnoses (protein defects). Such classifications may provide benefits in improving the treatment protocols (4).

Surgical aspect

Thin instruments designed in recent years allowed PNL to be performed using a thinner nephroscope. Mini-PNL (15-24 Fr), ultramini PNL (11-15 Fr), and micro-PNL (<11Fr) are believed to minimize the blood loss and increase the maneuver ability of the nephroscope in the small kidney (47). The fact that micro-PNL has similar stone-free rates to those of mini-PNL in stones of sizes between 10 mm and 20 mm with lower hemorrhage rates and allows fewer sessions compared with those of RIRS drew attention. Consequently, the fact that these methods provide high stone-free rates with acceptable complication rates showed that they could be a good alternative to SWL and other minimally invasive interventions. Furthermore, surgeries using tubeless PNL method without a nephrostomy tube or a double-J stent placement or catheter into the ureter primarily in patients with uncomplicated stones of <2 cm were included practice (48, 49). Indeed, the advances in high-power laser devices allowed us to work with these thin instruments. High-power laser devices allow working with miniaturized PNL even in cystine stones (2).

In these techniques, the stone is completely fragmented, and fragments are expected to be cleared spontaneously from the urinary tract (28). Complete fragmentation without removing might be expressed as a disadvantage of this technique. However, even if calibration is thin, instrument sizes can still be considered as long for children. We hope that complete optimization will be provided for children with technological advances in the upcoming years.

The use of laparoscopy and robot-assisted laparoscopic surgical methods in children is now a part of current protocols. They are used for the treatment of kidney and ureter stones in special patient groups. Laparoscopic or robot-assisted laparoscopic surgery can be performed after failed endoscopic interventions, in case of accompanying ureteropelvic joint stenosis and in children with large impacted stones accompanying complex kidney anomalies. Laparoscopic and robot-assisted laparoscopic surgeries have been reported to be performed safely even in infants (1, 15).

Our clinical experience showed that the surgical success rate in pediatric stone disease is associated with determining the suitable surgical treatment method. Therefore, we believe that knowing the success and complication rates associated with the individual patients before the treatment is essential in planning the method and the number of sessions. The Guy's scoring system is useful in anticipating the success of PNL (45). However, it is not sufficient for the evaluation of complications. We think that establishing scoring systems for children in future clinical studies will facilitate surgical planning.

Conclusion

The most critical risk factor associated with the development of pediatric stone disease is metabolic conditions. Therefore, a complete systemic and metabolic assessment should be performed in every child. Appropriate medical treatment is required for the prevention of recurrent stone formation and surgical interventions. Today, SWL is still an effective method of treatment with low complication rates. Moreover, minimally invasive methods provide success. The main steps in preventing the complications are performing the planned surgery using instruments chosen based on the stone and anatomical structure. In the future, demonstration of the genetic etiology might improve diagnosis and treatment protocols of pediatric stone disease, leading to a reduction in the possibility of stone recurrence.

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