

Review

J Ped. Nephrology 2013 Oct;1(2):46-51
http://journals.sbmu.ac.ir/jpn

Evidence Based Practice in Pediatric Urolithiasis

How to Cite This Article: Otukesh H, Hoseini R. Evidence Based Practice in Pediatric Urolithiasis J Ped. Nephrology 2013 Oct;1(2):46-51.

Hasan Otukesh,
Rozita Hoseini*
Pediatric Nephrologist,
Iran University of
Medical Sciences

***Corresponding Author**
Rozita Hoseini.
Ali Asghar Hospital, Tehran-Iran
Email: rozitahoseini@yahoo.com

Received: July-2013
Revised: Aug -2013
Accepted: Sep-2013

Nephrolithiasis is an increasing problem in children. Due to the different presentations and etiology of this disease in children compared with adults, we decided to perform an extensive search to find trials and arrange an evidence based study in this regard

Keywords: Urolithiasis; Child; Evidence-Based Practice

Running Title: Evidence Based Practice in Urolithiasis

Introduction

Renal stone disease is an important problem and is being recognized more commonly in pediatric age group. In children, it has different characteristics in both presentation and treatment in comparison with this disease in adults. However, the randomized clinical trials, systematic reviews, evidence based information, and guidelines in pediatric patients are limited. In this article, a search was performed via the mesh and non mesh terms search system on the pubmed on the relevant articles. Additional searches were done in EMBASE, the Cochrane Central Register of Controlled Trials (The Cochrane Library), guideline websites, and reference lists of articles. The key words were urolithiasis, nephrolithiasis, renal stone, renal calculi, children, and pediatric.

Underlying causes of renal stone

Children with urolithiasis are high risk patients due to recurrent stone formation. On the other hand metabolic disorders are frequent associated disorders with urolithiasis in pediatric patients. Thereafter the investigations for both stone diagnosis and its underlying disorder especially metabolic disorders are necessary (level of evidence 2a, recommendation B). All pediatric patients with urolithiasis should be

evaluated for metabolic abnormalities based on stone analysis if available (recommendation A). Awareness of stone composition is helpful to direct metabolic evaluation. Additional serum and urine analysis may be required (level of evidence 2, A), notably in cases without available stone for analysis. Some authors believe that underlying metabolic disorders are not always reflected by the stone analysis. Thus, they suggest that the assessment of urine biochemistry is more useful than stone chemical composition analysis in children (1).

Depending on the geographic area, hypercalciuria, hyperoxaluria, hypocitraturia or their combinations can be the most frequent metabolic disorders in children with lithiasis. For example, hypercalciuria is the most common metabolic cause of renal stone disease in western children. In contrast, infection related stones are common in European children. The most common anatomical abnormalities which are associated with urolithiasis in children include vesicoureteral reflux, ureteropelvic junction stenosis, and neurogenic bladder (level 4).

Urinary tract infection is an important disease which can underlie renal stone disease. Thus, clinicians should take a precise history regarding urinary tract infection and suggest urinalysis and culture for all pediatric patients with urolithiasis

(level of evidence 2, recommendation A).

The metabolic evaluation of pediatric patients with renal stone disease depends on the size and laterality of the stone and associated manifestations. Every child with urolithiasis (not microlithiasis) should be assessed by following steps:

- Precise history, family history, and physical examination
- Stone analysis if available
- Measurement of serum potassium, sodium, BUN, creatinine, calcium, phosphorus, and uric acid
- Spot or 24 hours urine for calcium, cystine, uric acid, oxalate, and creatinine, Twenty four hour urine collection is preferable, but it is difficult in infants or children with incontinence. In these patients, assessment of random urine is recommended. The urine assessment should be done when the child is well, infection free, and on routine diet.
- Urinalysis and urine culture
- Parathyroid hormone (if there is hypercalcaemia)

Imaging procedures to diagnose renal stones in children.

Ultrasound is the first choice imaging modality to identify urinary tract stone (level 2a) and should include the kidney, filled bladder, and portions of the ureter (level 4, G: B). This imaging modality is the most suitable method for urolithiasis in children due to the lack of radiation and no requirement for anesthesia. Ultrasound provides information about the size and location of the stone in the urinary tract, the grade of hydronephrosis, the presence of obstruction due to stone, and associated anomalies. However, ultrasound sometimes fails to diagnose urinary tract stones (~40%) in children (2) (level 3).

Kidney ureter bladder imaging (KUB) in combination with ultrasound helps the clinicians to diagnose and follow renal stones.

Intravenous pyelography (IVP) is rarely indicated in patients with renal stone, but it can be helpful in some cases such as determining the anatomy of the calyces and pelvis before surgery.

Non contrast helical CT scan has an excellent visualization of all stones whether they are opaque or nonopaque and regardless of their size and location. It is rapid and has 97% sensitivity and 96% specificity (level 2, grade B). In children,

5% of the stones cannot be diagnosed by CT scan (level 4). Nowadays, the patients are less required to receive anesthesia and sedation and they are less exposed to radiation with modern high speed CT scans (level 4, grade C)

It is recommended to perform CT scan in children with persistent urolithiasis symptoms but without the evidence of stone in KUB and ultrasonography (level of evidence 3, recommendation C) (3).

Magnetic Resonance (MRU) is not able to detect stones in the urinary tract but shows an excellent view of the urinary tract anatomy.

Treatment

Spontaneous stone passage is more common in children when compared with adults (level 4, grade C). There are some medical and non medical treatments for urolithiasis in children.

Medical Treatment

Data on medical therapy of urolithiasis in pediatric patients are limited. There is a very limited number of trials focusing on the conservative treatment in children with varied metabolic types of renal stones. The aim of medical therapy is to prevent further growth of existing stones and formation of new stones.

A high fluid intake (well distributed over day and night time) is believed to be a key and universal treatment that is suggested for all types of stones. Other dietary considerations depend on the types of stones. There are no randomized double blind trials about the effect of diet alone on the outcome of pediatric patients with varied types of stones.

Hypercalciuria

Hypercalciuria is one of the most common metabolic disorders in children with urolithiasis in some studies. It is defined as urine calcium excretion more than 4/mg/kg/day in children and more than 5 mg/kg/day in infants younger than 3 months old. It can be primary or secondary to hypercalcemia. In all children without available stone for analysis, the urine calcium concentration should be measured. In infants, it can be measured in random urine as calcium/creatinine ratio while it is measured in 24-hour urine collection in older children. The treatment aim is to reduce urinary calcium concentration as follows.

Diet

Initial management is increased fluid intake. A short term period of low calcium diet can determine the contribution of calcium intake to high urinary calcium concentration. However,

calcium intake restriction should not be for a long time period (level of evidence 3, recommendation grade B) (15) due to the increased risk of osteopenia and hyperoxaluria, leading to renal stones containing oxalate compounds.

Studies on adult have shown that low sodium and protein diets are more effective than low calcium diets in reducing urinary calcium concentration. Thus, the optimal initial treatment of hypercalciuria is dietary changes including low sodium and high potassium diet, avoiding excess calcium and vitamin D supplements, and high fluid intake.

Hydrochlorothiazide

Thiazide diuretics can be administered (1-2 mg/kg/day) in patients with hypercalciuria (Level of evidence: 3; Grade of recommendation: C). Some observational studies have shown a reduction in the urine calcium concentration in the children treated with hydrochlorothiazide (3,15,16). However, this guideline believes that thiazides are not efficient in children with hypercalciuria to reduce renal stone recurrence (level 4, grade C).

Potassium Citrate

Potassium citrate therapy is suggested in patients with persistent hypercalciuria. It is also useful in patients who have hypocitraturia and hypercalciuria concurrently (Level of evidence: 4; Grade of recommendation: C). In this regard, the starting dose of potassium citrate is 1-2 meq/kg/day divided into two doses (Level of evidence: 4; Grade of recommendation: B). Draft 1 shows the evaluation and treatment of children with hypercalciuria. No study has compared citrate and thiazide diuretics in hypercalciuric patients.

However, no prospective studies have been performed on medical therapy for stone prevention in children with hypercalciuria.

Hyperoxaluria

Oxalate is a metabolite excreted in the urine. It is produced by metabolic pathways in the body or comes from diet. It appears that 10-15% of the urine oxalate comes from diet and restriction of diet oxalate affects this amount of urinary oxalate. Hyperoxaluria and consequently renal stones can be due to increased oxalate intake, increased intestinal absorption of oxalate, or inborn errors of metabolism. Inborn errors of metabolisms are the most severe causes of excessive urinary oxalate excretion named primary hyperoxaluria.

The aim of conservative treatment of hyperoxaluria is to reduce oxalate production and increase its urinary solubility. These treatments include high fluid intake, low oxalate diet, regular calcium intake and some medications such as calcium oxalate deposition inhibitors.

In hyperoxaluria type 1, “the most common type of primary hyperoxaluria”, the fluid intake should be 2-3 l/m² per day to reduce urinary oxalate concentration to less than 0.4mmol/l. It is believed that restriction of diet oxalate has a limited effect in these patients. Pyridoxine can reduce the urinary oxalate concentration and may be useful in 10-30% of the patients with primary hyperoxaluria who have some types of mutations. The response to an initial pyridoxine dose (5-10 mg/kg/day) as the test dose is defined as 30% reduction in urine oxalate after treatment and can predict its severity and progression to end stage renal failure (Level of evidence: 3; Grade of recommendation: B) (17). Patients who respond to pyridoxine have preserved renal function when they are under suitable medical treatment.

Potassium citrate can be used in patients who have hyperoxaluria (Level of evidence: 3; Grade of recommendation: B). Neutral phosphate compounds can also be administered in these patients (orthophosphate 20 mg/kg/day).

Cystinuria

Cystinuria is a recessive autosomal disease and accounts for 2-8% of the causes of renal stone in children. The aim of treatment in cystinuria is to decrease cystin saturation in the urine and to increase its solubility. Thus, high fluid intake, urine alkalization, and the use of chelators are suggested in these patients. Restriction of methionine intake is not suggested by most authors in the pediatric age group (15). A low salt diet is believed to reduce urine cystine concentration. It seems that a reduction in sodium intake to about 50 mmol/day (1mmol/kg/day) leads to a remarkable decrease in urine cystine levels; however, this low sodium diet achievement is difficult in the long term period (18). Alkali therapy is indicated in cystinuric children to maintain urine PH at about 7.5 but not in excess of 8 to prevent calcium containing stones. Potassium citrate is the preferred alkali therapy in these patients.

Cystine chelators such as mercaptopropionyl glycine or tiopronin (10-20 mg/kg/day up to 40 mg/kg/day in children given in divided doses), D-penicillamine (10-20 mg/kg/day) and/or captopril are suggested when preliminary

treatments such as citrate and high fluid therapy fail. With gradual initiation, penicillamine can be a useful and safe treatment in these patients. According to a recent cohort study, penicillamine can be initiated as the first line therapy in pediatric patients with cystinuria (level of evidence 3, recommendation B) (19,20,21).

It appears that mercaptopropionyl glycine or tiopronin is better tolerated than D penicillamine. The use of captopril as a thiol compound in some case series has shown to be able to reduce urinary cystine levels but with no proven effect on stone formation.

It is believed that the maximal urinary cystine concentration is found during night, thus night time treatment such as fluid intake and chelating therapy at bedtime is important.

There is no randomized clinical trial on the treatment of cystinuria. Therefore, it is not possible to arrange a guideline based on evidence levels 1 and 2 in these patients.

We can monitor cystinuric patients by measurement of urine PH, specific gravity, and the concentration of urine cystine concentration. The aim is to reach a urine PH of 7.5-8, specific gravity less than 1010, and urine cystine concentration less than 200-300 mg/l.

Hyperuricosuria

Hyperuricosuria is common in children, especially during infancy, and is the main cause of uric acid stones in children. Uric acid stone formation depends not only on hyperuricosuria but also on the acidic urine. Thus, the most important treatment in these patients is alkalization of the urine by citrate therapy.

Medical explosive therapy

This therapy includes the drugs that expel ureteral stones by relaxing its smooth muscle.

These drugs are calcium channel and alpha-1 receptor blockers. In some guidelines, this therapy is not recommended because of insufficient data in the pediatric age group (level 4). According to a recent small RCT, administration of doxazosin (an alpha blocker) was not effective in expelling distal ureteral stones smaller than 10 mm in children (level of evidence 1b)(22). However, some clinicians administer alpha blocker medications in children with distal ureteral stone.

ESWL

Currently, ESWL can be performed in children without long term kidney damage. The success of ESWL depends on some factors such as the type,

size, and location of the stone. ESWL may be less efficient in cases of cystine stone, calcium monohydrate stones, and the presence of anatomical abnormalities. It appears that the response to ESWL in children is higher than adults, even for large and staghorn stones. This can be due to differences in the body size, ureteral length, contractility, and elasticity (17). Although available data about ESWL in children are insufficient, it appears that percutaneous ESWL is safe and effective in this age group.

For all children, the indications of ESWL are identical to those in adults (level of evidence 1a). In this regard, renal stones with a diameter up to 20 mm are ideal for ESWL (level of evidence 1b). On the other hand, ESWL is more effective for upper ureteral calculi in comparison with ureteroscopy. Considering the better excretion of stone fragments in children post ESWL (18-21,23,24) as compared with adults, ESWL is sometimes suggested for staghorn stones in children. Although the data for pediatric patients with staghorn stones are limited, American Urology Association recommends ESWL for staghorn stones in children (grade C). In a randomized clinical trial, the authors suggested prophylactic ureteral stenting before ESWL of staghorn stones in pediatric patients because of lower complications and shorter hospitalization (level 1b, recommendation B) (14). Unlike American Urology Association, PCNL is suggested as the first choice modality to treat staghorn stones in children in the European Urology Guideline. It seems that the combination of PCNL and ESWL may be useful.

After ESWL, administration of potassium citrate is suggested to prevent stone regrowth and new stone formation in the long term period (level of evidence 2, recommendation grade B) (25).

Ureteroscopic lithotripsy

Both ureteroscopic lithotripsy and ESWL are effective modalities to treat ureteral stones. Selection of these modalities depends on the available equipment, expertise of the surgeon, child's size, urinary tract anatomy, and the location of the stone. It is better to perform ESWL in small sized children.

Ureteroscopy is useful for middle and distal ureter stones (level of evidence 1a, Grade A). According to two randomized clinical trials, ureteroscopy plus intracorporeal lithotripsy are recommended in children with distal ureteral stones although ESWL is also effective in these stones (15,16).

Ureterscopy plus lithotripsy is safe and effective in children (15,16) (level of evidence 1b, Grade A). The risk of ureteral stricture and reflux is not significant following this modality (Level of evidence: 1a; grade of recommendation: A).

Surgery Treatment

PCNL is a less invasive treatment compared to open surgery. Thus, this technique is a useful alternative to open surgery in children. The indications of PCNL are similar in children and adults (level of evidence 1a). PCNL is indicated in renal stones with a diameter more than 20 mm (level of evidence 1a, grade A)

Most pediatric urinary tract stones are removed by ESWL, ureteroscopy, and ultimately by PCNL and a low number of stones are removed by open surgery. The indication of open surgery is the presence of large stones, especially in small children. Recommended ESWL/surgical modalities in pediatric patients with urolithiasis are shown in Table 1.

Table 1: The preferred modalities in pediatric stone removal (26)

Stone size Or localization	Primary treatment option	LE	Secondary treatment option	
Staghorn stones	PCNL	2b	Open/SWL	Multiple sessions and accesses with PCNL may be needed. Combination with SWL may be useful.
Pelvis<10 mm	SWL	1a	RIRS/PCNI	
Pelvis 10-20 mm	SWL	2b	PCNI/Open	Multiple sessions with SWL may be needed. PCNI has similar recommendation grade.
Pelvis>20 mm	PCNL	2b	SWL/ Open	Multiple sessions with SWL may be needed.
Lower pole calix <10mm	SWL	2c	RIRS/PCNI	Anatomical variations are important for complete clearance after SWL.
Lower pole calix >10mm	PCNL	2b	SWL	Anatomical variations are important for complete clearance after SWL.
Upper ureteric stones	SWL	2b	RIRS/URS/ Open	
Lower ureteric stones	URS	1a	SWL/ Open	Additional intervention need is high with SWL.
Bladder stones	Endoscopic	2b	Open	Open is easier and with less operative time with large stones.

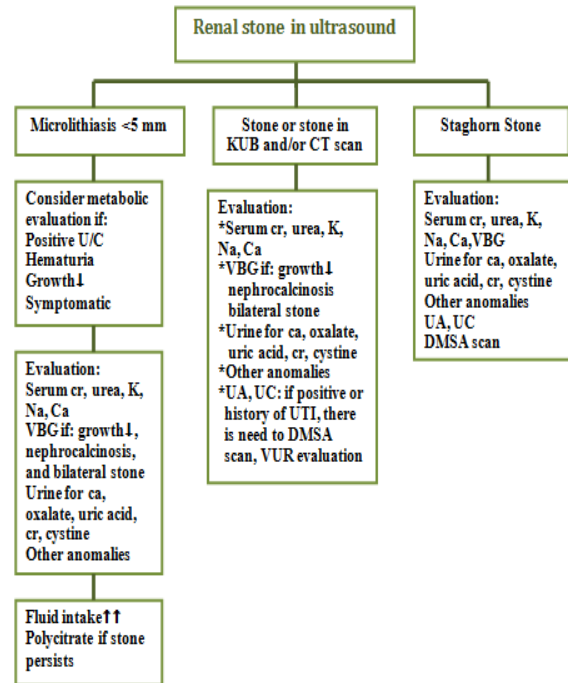


Figure 1. The approach to children with urolithiasis based on the stone size

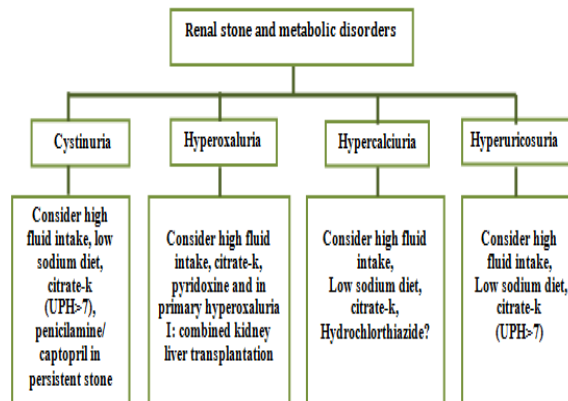


Figure 2. Therapeutic suggestions in children with diverse metabolic etiologies of urolithiasis

Conflict of Interest

None declared

Financial Support

None declared

References

- 1- Duffy P, Thomas FM D, Flett EM. Stone disease in children, chapter 11, Essential of pediatric urology, second edition, united kingdom, 2008, P 143-149.
- 2- Palmer JS, Donaher ER, O’Riordan MA, Dell KM.

- Diagnosis of pediatric urolithiasis: role of ultrasound and computerized tomography. *J Urol* 2005; 174(4 Pt 1):1413-1416.
- 3- S. Oner1, A. Oto2, S. Tekgul1, M. Koroglu3, M. Hascicek1, A. Sahin1*, O. Akhan2, COMPARISON OF SPIRAL CT AND US IN THE EVALUATION OF PEDIATRIC UROLITHIASIS, *JBR-BTR*, 2004, 87: 219-223.
 - 4- Naseri M, Sadeghi R, Role of high dose hydrochlorothiazide in idiopathic hypercalciuric urolithiasis of childhood, *Iran J kid Dis*, 2011, 5 (3), 162-168.
 - 5- Bartosh SM. Medical management of pediatric stone disease. *Urol Clin North Am* 2004;31(3):575-87.
 - 6- Preminger GM, Pak CY. Eventual attenuation of hypocalciuric response to hydrochlorothiazide in absorptive hypercalciuria. *J Urol* 1987;137(6):1104-8.
 - 7- Carla G. Monico, Sandro Rossetti, Julie B. Olson, Dawn S. Milliner, Pyridoxine effect in type I primary hyperoxaluria is associated with the most common mutant allele, *Kidney international*, Vol: 67, (2005), 1704-1709.
 - 8- Cochat P, Pichault V, Bacchetta J, et al. Nephrolithiasis related to inborn metabolic diseases, *Pediatr Nephrol*, 2010; 25 (30):415-425.
 - 9- Shakaee K, Sutton RAL, Cystinuria In: Coe FL, Favus MJ, Pak Cys, Park S JH, Preminger GM, *Kidney stones: medical and surgical management*. 1996 Lippincott-Raven, Philadelphia.
 - 10- Rodriguez R, Sanchez L, Gorostidi M, Alvarez J. Effects of variation in sodium intake on cystinuria, *Nephron* 1991; 57: 416-418.
 - 11- Balph J. Deberardinis, Curtis R. Coughlin, Paige Kaplan, Penicillamine therapy in pediatric cystinuria: experience from cohort of American children, *J Urol*, 2008;18(6): 2620-2623.
 - 12- Combe C, Deforges Lasseur C, Chehab Z, de precigout V, Aparicio M, Cystine lithiasis and its treatment with d-penicillamine. The experience in nephrology service in a 23 year period. Apropos of 26 patients. *An Urol (Paris)* 1993;27(2), 79-83.
 - 13- Ralph J. De Berardinis,, Curtis R. Coughlin, Paige Kaplan, Penicillamine therapy in pediatric cystinuria: experience from a cohort of American children, *J Urol*. 2008; 180(6): 2620-2623.
 - 14- Al-Busaidy SS, Prem AR, Medhat M., Pediatric staghorn calculi: the role of extracorporeal shock wave lithotripsy monotherapy with special reference to ureteral stenting. *J Urol*. 2003 Feb;169(2):629-33.
 - 15- Basiri A, Zare S, Shakhssalim N, Hosseini moghadam SM, Ureteral calculi in children what is best as minimally invasive modality, *Urol J* 2008, spring 5(2), 67-73.
 - 16- De Dominicis M, Matarazzo E, Capozza N, Collura G, Caione P., Retrograde ureteroscopy for distal ureteric stone removal in children, *BJU Int*. 2005 May;95(7):1049-52.
 - 17- Gofrit O.N, Pode D., Meretyk S, Katz G, Shapiro A, Goljijanin D, Is the pediatric ureter as efficient as the adult ureter in transporting fragments following extracorporeal shock wave lithotripsy for renal calculi larger than 10 mm, *J Urol*, 166: 1862, 2001.
 - 18- Lahme S: Shockwave lithotripsy and endourological stone treatment in children. *Urol Res* 2006; 34: 112.
 - 19- Desai M: Endoscopic management of stones in children. *Curr Opin Urol* 2005; 15: 107.
 - 20- Van Savage JG, Palanca LG, Andersen RD, Rao GS and Slaughenhaupt BL: Treatment of distal ureteral stones in children: similarities to the American Urological Association guidelines in adults. *J Urol* 2000; 164: 1089.
 - 21- Slavkovic A, Radovanovic M, Vlajkovic M, Novakovic D, Djordjevic N and Stefanovic V: Extracorporeal shock wave lithotripsy in the management of pediatric urolithiasis. *Urol Res* 2006; 34: 315.
 - 22- Aydogdu O, Burgu B, Gucuk A, Suer E, Soygur T., *J Urol*. Effectiveness of doxazosin in treatment of distal ureteral stones in children. 2009 Dec;182(6):2880-4. Epub 2009 Oct 28.
 - 23- Kuvezdić H, Tucak A, Perić N, Prlić D, Zorić I and Galić, R: ESWL treatment of urinary stones in children – the overview of 14 years of experience. *Coll Antropol* 2003; 27: 71.
 - 24- Tan AH, Al-Omar M, Watterson JD, Nott L, Denstedt JD and Razvi H: Results of shockwave lithotripsy for pediatric urolithiasis. *J Endourol* 2004; 18: 527.
 - 25- Sarica K, Erturhan S, Yurtseven C, Yagci F. Effect of potassium citrate therapy on stone recurrence and regrowth after extracorporeal shockwave lithotripsy in children. *J Endourol*. 2006 Nov;20(11):875-9.
 - 26- S. Tekgül, H. Riedmiller, E. Gerharz, P. Hoebeke, R. Kocvara, R. Nijman, Chr. Radmayr, R. Stein, *Guidelines on pediatric Urology*, European Society for Paediatric Urology, European Association of Urology 2011.