

## Special Report

J Ped. Nephrology 2015;3(4):174-177  
<http://journals.sbmu.ac.ir/jpn>

# Is D-penicillamine Safe in Management of Little Children with Kidney Cystine Stones? A Case Series

**How to Cite This Article:** Moghtaderi M, Malekzadeh I, Kajbafzadeh A, et al. Is D-penicillamine Safe in Management of Little Children with Kidney Cystine Stones? A Case Series. J Ped. Nephrology 2015;3(4):174-177.

**Mastaneh Moghtaderi,<sup>1\*</sup>**  
**Iran Malekzadeh,<sup>1</sup>**  
**Abdolmohamad Kajbafzadeh,<sup>2</sup>**  
**Hamid Arshadi,<sup>2</sup>**  
**Mohammad Ghohestani,<sup>2</sup>**  
**Amir Hossein Mahboobi,<sup>2</sup>**  
**Bahar Behzad Tahmuresi<sup>2</sup>**

1Department of Pediatric Nephrology, Chronic Kidney Disease Research Center, Children Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran.

2Pediatric Urology research Center, Children Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran.

### \*Corresponding Author

Mastaneh Moghtaderi, MD.  
Associate Professor of Pediatric Nephrology, Children Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran.  
Email: [drmoghtaderi@gmail.com](mailto:drmoghtaderi@gmail.com)

**Received:** July-2015

**Revised:** Agu-2015

**Accepted:** Sep-2015

Nephrolithiasis is quite common in children. It sometimes has a genetic basis and can lead to serious complications like urinary obstruction, multiple surgical interventions, or even renal insufficiency if left treated. Cystinic stones and cystinuria account for approximately 8% of the cases of nephrolithiasis in children. We studied seven pediatric patients, 1 to 3 years old (mean age: 20.5 months), with cystinic urinary stones receiving D-penicillamine plus other drugs to dissolve the stone. All of them tolerated the treatment very well and did not show any serious complication. All of our cases were managed with D-penicillamine that was initiated at a low dose and then increased progressively. We used low dose D-penicillamine, maximum 15 mg/kg/day, which was beneficial without any specific side effects. D-penicillamine can be used safely in little children. Gradual induction and close observation with CBC, urine analysis, BUN, creatinine, and liver function tests may be required. D-penicillamine can prevent new stone formation and resolve the present cystinic calculi. Low dose D-penicillamine may be sufficient in treating cystinic calculi in children. We suggest more evaluations on the advantage of low dose D-penicillamine in cystinuria.

**Keywords:** D-Penicillamine; Cystinuria; Nephrolithiasis; Complications

**Running Title:** D-penicillamine in Management of Kidney Cystine Stones

## Introduction

Kidney stones are quite common in little children. The incidence of kidney calculi in childhood increased 6%-10% annually in the last 25 years [1]. There are many predisposing factors including anatomical disorders, inborn error of metabolism, urinary tract obstruction, infections, and tubular dysfunctions such as hypercalciuria [2]. Cystinic nephrolithiasis accounts for approximately 8% of

uroolithiasis in children. Cystinuria is an autosomal recessive error in dibasic amino acids (lysine, cystine, ornithine, and arginine) transport in the intestinal and reno-tubular epithelium [3]. Cystinuria usually presents with renal colic, urinary tract obstruction, and renal function insufficiency due to multiple and recurrent urolithiasis. This lifelong urinary stone formation disease often starts in infancy. About 25-30% of

the patients experience their first urinary stone in the first decade of their lives. The global prevalence of cystinic nephrolithiasis is 1:7000 and is more frequent in developing countries because of consanguinity marriages [3,4]. This genetic-based nephrolithiasis, if left unattended, can lead to complications such as urinary obstruction, multiple surgical interventions, or even renal insufficiency. Cystinic kidney stones are usually treated with increasing the fluid intake and alkylating the urine, which requires a large amount of fluid and may be very difficult for young children. Therefore, unfortunately, this treatment is not sufficient; many new kidney stones may form and a urolithiasis crisis may happen during the treatment. Thiol-containing agents such as D-penicillamine are the common treatment of cystinuria in adults that resolve previous stones, as well. Due to its toxic side effects like bone marrow suppression, fever, proteinuria, loss of taste, liver dysfunction, arthropathy, and skin eruptions, the use of D-penicillamine in young children is limited [3] [5]. There are few reports on the treatment of cystinuria with d-penicillamine in young children. We studied seven children aged 1 to 3 years with cystinic kidney stones receiving D- penicillamine therapy plus other drugs to dissolve the stones.

### Case Report

Over 3 years (2011–2014), 7 patients with cystinic urinary tract calculi were studied in detail using D-penicillamine plus other drugs such as potassium citrate. The children, 6 boys and one girl, were 1-3 years old (mean age: 20.5 months). All of them had multiple cystinic stones in the urinary tract (mean: 4.3+<sub>1</sub>). Two patients were referred with obstruction of the urinary tract leading to acute kidney injury (failure phase) and underwent peritoneal dialysis. After removing cystinic stones by surgery, the renal function returned to baseline. An 11-month boy underwent 6 operations to remove renal and ureteral stones because of recurrent urinary tract obstruction. Three patients underwent open surgery. There was no anatomical abnormality causing narrowing in the urinary tract in the cases. The diameter of the stones was 5-30 mm. Five patients had a positive family history of recurrent nephrolithiasis. All patients received general advice on renal stones such as increasing the use of water and fluids, and reducing dietary sodium intake. They received potassium citrate for urine alkalization and captopril. Also, for all patients, we

prescribed low dose D-penicillamine (8mg/kg). One week later, all of them were visited and evaluated for probable complications and complete blood count (CBC), erythrocyte sedimentation rate (ESR), and kidney and liver function tests were checked again. If the test results were normal, the dose of D-penicillamine was increased slightly up to 10 mg/kg. The patients were evaluated periodically and continued taking the drugs. The dose of D-penicillamine was increased up to 15 mg/kg/day. This management and follow-up evaluations were continued for 6-24 months. There were no complications such as lupus like syndrome, cytopenia, skin rash, or arthropathy. All patients showed a good response to the treatment; some of them became stone free and others showed a significant decrease in stone size. New stone formation was stopped. Renal function became stable in all patients. Since our patients were very young and the D-penicillamine dose was very low and increased gradually, we did not have any significant complications.

### Discussion

As mentioned earlier, the prevalence of cystinuria, as a genetic disorder in the transport of dibasic amino acids in the proximal tube, is 1:7000 [3]. Cystinic stones, without appropriate treatment, can lead to renal failure in very young children. Our patients' clinical manifestations were as follow:

- Abdominal pain: 69%
- Gross hematuria: 42%
- Urinary tract infection: 31%
- Urinary tract obstruction: 28%
- Acute kidney injury: 28%

In 2006, Seyedzadeh et al. reported 22 cases of cystinic calculi with a mean age of 34.2 months of whom 59% had bilateral and 41% had unilateral kidney calculi. The size of the calculi was 2-20 mm. Nine patients (41%) had renal atrophic changes and 1 (4.5%) had obstructive acute renal failure [6]. Recurrent nephrolithiasis and renal crisis due to cystinic calculi usually requires multiple urological interventions. Four of our patients experienced open surgery and 2 experienced ESWL which was unsuccessful. In the study by Seyedzadeh, researchers reported 5 cases of successful extracorporeal shockwave lithotripsy and 13 (59.1%) surgical interventions, whereas 6 (27.2%) patients required more than 1 surgical operation [6]. Asanuma et al. reported 15 cases of cystinuria with a mean age of 3 years and

**Table 1.** Clinical presentation of study group

Case	Gender	Age (month)	Family history of renal calculi	Clinical Presentation	Renal Failure according to RIFEL criteria
1	Male	18	+	AKI <sup>1</sup> + Bilateral UPJO <sup>2</sup> + Abdominal Pain	+
2	Male	12	-	Abdominal Pain	-
3	Female	13	+	AKI + UVJO <sup>3</sup>	+
4	Male	22	+	Abdominal Pain + UTI + Gross Hematuria	-
5	Male	30	-	UTI	-
6	Male	33	+	Gross Hematuria	-
7	Male	16	-	Abdominal Pain	-

1 Acute kidney injury    2 Ureteroplvic junction obstruction    3 Ureterovesical junction obstruction

4 months at diagnosis. Surgical interventions were performed in 13 patients (lithotomy: 17 calculi, endourology: 7 calculi, and ESWL: 7 calculi). The stone free rate was 100% with lithotomy, 80-100% with endourology, and 43% with ESWL at an average of 5.9 procedures [7]. Appropriate hydration and diluting and alkylating the urine along with D-penicillamine treatment can stop this awful process [3,5]. Tangnararatchakit et al. reported a 4.5-year-old child with recurrent nephrolithiasis due to cystinuria. After the first episode of pyelolithotomy, despite a high fluid intake and potassium citrate therapy, recurrent cystinic stones were formed. Therefore, she was treated with D-penicillamine, which slowed down the rate of kidney stone formation [8]. In 2008, DeBerardinis et al. evaluated the treatment of cystinuria with D-penicillamine in 11 children aged 1.2-12 years old. They started with low dose D-penicillamine and increased the dosage gradually. The results of their study showed no calculi formation or stone crisis during the treatment and follow-up [3]. In this regards, Seyedzadeh et al reported no favorable results in response to D-penicillamine [6]. As mentioned earlier, all of our patients were treated with D-penicillamine that initiated at a low dose and then increased gradually. There observed no significant drug side effects in our study. Asanuma reported tiopronin nephrotic syndrome in 1 case [7]. In the cohort study conducted by DeBerardinis, after many months of follow-up, only 2 severe side effects were noted: drug eruptions and generalized aminoaciduria [3]. We used D-penicillamine at a low dose of 15 mg/kg/day, which was beneficial without any specific side effects, while the usual dose is 20-30 mg/kg/day. In the cohort study by DeBerardinis, six patients were maintained on 20 mg/kg/day D-

penicillamine while increased doses (up to 40 mg/kg/day) were used in five others to reduce the urinary concentration of cystine [3]. We studied only seven children suffering from cystinic calculi, which was the most important limitation of this study. Therefore, we believe more studies are required to evaluate the advantage of low dose D-penicillamine in cystinuria. D-penicillamine can be used for treating cystinuria in young children in addition to high fluid intake and urinary alkalization. Gradual induction and close observation along with the evaluation of CBC, urinalysis, BUN, creatinine, and liver function tests may be required. D-penicillamine can prevent new stone formation and resolve the present cystinic nephrolithiasis. Low dose D-penicillamine may be adequate in treating cystinic calculi in children.

**Conflict of Interest**

None declared

**Financial Support**

None declared

**References**

1. Tasian GE, Copelovitch L. Evaluation and medical management of kidney stones in children. *J Urol.* 2014 Nov; 192(5):1329-36.
2. Balestracci A, Battaglia LM, Toledo I, Idiopathic hypercalciuria in children with urinary tract infection. *Arch Argent Pediatr.* 2014 Oct; 112(5):428-33..
3. DeBerardinis RJ, Coughlin CR 2nd, Kaplan P. Penicillamine therapy for pediatric cystinuria: experience from a cohort of American children. *J Urol.* 2008 Dec; 180(6):2620-3.
4. Aydogdu SD, Kirel B, Coskun T, Kose S. Prevalence of cystinuria among elementary schoolchildren in

- Eskisehir, Turkey. *Scand J Urol Nephrol.* 2009; 43(2):138-41.
5. Halperin EC, Thier SO, Rosenberg LE. The use of D-penicillamine in cystinuria: efficacy and untoward reactions. *Yale J Biol Med.* 1981 Nov-Dec; 54(6): 439-446.
  6. Seyedzadeh A, Momtaz HE, Moradi MR, Moradi A. Pediatric cystine calculi in west of Iran: a study of 22 cases. *Urol J.* 2006 Summer;3(3):134-7; discussion 138..
  7. Asanuma H, Nakai H, Takeda M, et al. [Clinical study on cystinuria in children--the stone management and the prevention of calculi recurrence]. *Nihon Hinyokika Gakkai Zasshi.* 1998 Sep;89(9):758-65..
  8. Tangnaratchakit K, Ariyaprakai W, Tapaneya-Olarn W, et al. Cystinuria: cause of recurrent renal stones in a 4-year-old girl. *J Med Assoc Thai.* 2002 Nov;85 Suppl 4:S1281-6.