

Pediatric vesicoureteral reflux approach and management

Review Article

Mohsen Akhavan Sepahi (MD)¹
Mostafa Sharifiain (MD)^{2*}

1. Pediatric Medicine Research Center,
Department of Pediatric Nephrology,
Faculty of Medicine, Qom University
of Medical Sciences and Health
Services, Qom, Iran.

2. Department of Pediatric Infectious
Disease, Faculty of Medicine, Qom
University of Medical Sciences and
Health Services, Qom, Iran.

* Correspondence:

Mostafa Sharifiain (MD), Pediatric
Infections Research Center and
Pediatric Nephrology Research Center
(PNRC), Faculty of Medicine, Shahid
Beheshti University of Medical
Sciences, Tehran, IR Iran.

E-mail: sharifiain.dorche@gmail.com

Tel: +98 2122227020

Fax: +98 2122220254

Received: 27 Dec 2016

Revised: 15 Jan 2017

Accepted: 7 Feb 2017

Abstract:

Vesicoureteral reflux (VUR), the retrograde flow of urine from the bladder toward the kidney, is congenital and often familial. VUR is common in childhood, but its precise prevalence is uncertain. It is about 10–20% in children with antenatal hydronephrosis, 30% in siblings of patient with VUR and 30–40% in children with a proved urinary tract infection (UTI). Ultrasonography is a useful initial revision but diagnosis of VUR requires a voiding cystourethrography (VCUG) or radionuclide cystogram (DRNC) and echo-enhanced voiding urosonography (VUS). Although for most, VUR will resolve spontaneously, the management of children with VUR remains controversial. We summarized the literature and paid attention to the studies whose quality is not adequate in the field of VUR management of children.

Key Words: Vesicoureteral Reflux, Urinary Tract Infection, Antenatal Hydronephrosis

Citation:

Akhavan Sepahi M, Sharifiain M. Pediatric Vesicoureteral Reflux Approach and Management. *Caspian J Pediatr* March 2017; 3(1): 209-14.

Introduction:

Vesicoureteral reflux (VUR) is described as the retrograde flow of urine from the bladder into the ureter and renal pelvis secondary to a dysfunctional vesicoureteral junction [1, 2, 3]. Reflux into parenchyma of renal is defined as the intrarenal reflux [4,5]. This junction who is oblique, between the bladder mucosa and detrusor muscle usually acts like a one-way valve that prevents VUR. VUR is caused by lateral or proximal dystopia of the orifice of ureter in bladder [6]. VUR is the most common congenital anomaly of the urinary tract. VUR predisposes to urinary tract infection (UTI) through facilitating the transport of pathogen bacteria from the bladder to the upper urinary tract. The inflammatory reaction caused by UTI can result in reflux nephropathy (RN). RN can lead to proteinuria, renin-mediated hypertension, renal insufficiency, impaired somatic growth and morbidity during pregnancy, too [7]. RN is a result of abnormal renal development leading to focal or extended renal dysplasia [7, 8]. In children with VUR and UTI, the incidence of renal scarring is higher at 30-56% [7]. The prevalence of primary VUR (PVUR) is 1%- 6% with dominant inheritance and variable penetrance [8-11], while this is likely an underestimate because of phenotypic heterogeneity and the lack of non-invasive and non-dangerous diagnostic tools. VUR is detected most commonly during voiding, when intravesical pressure rises, but may occur any time in the voiding cycle, particularly when bladder function is abnormal. VUR is common in childhood, whereas precise prevalence is uncertain since large-scale population screening using VCUG has not been done due to the dangers and cannot be justified [12-15]. Evaluation of children of parents with VUR showed that 66 % had VUR, indicating a significant parent-to-child transmission. A follow-up study showed that 75% of children identified with VUR by sibling screening were asymptomatic [7].

VUR does not usually cause renal injury in the absence of the risk factor. Severity is graded using the height of retrograde flow, and dilation and tortuosity of the ureters. This is important because VUR usually will spontaneously resolve with rise of age [12, 13]. Spontaneous resolution of VUR in children due to the natural elongation of the vesicoureteral junction is possible, especially in patients without risk factor [14]. Although the spontaneous resolution of VUR has been observed in many patients, the management of VUR remains multifactorial and individualized [15-18]. There are controversial issues about the treatment of renal abnormalities detected by VCUG [17].

The aim of this study was to describe VUR in children, to pay more attention to the studies whose quality is not adequate in the field of management, prognosis and complications of VUR in Iranian and global children and to focus on the need of research in this area.

Clinical Manifestations:

VUR as a genetic condition can facilitate the detection in other family members before clinical presentation [1, 19]. VUR can be an isolated finding and called primary reflux, or associated with others malformation. Primary VUR is often diagnosed via one of three ways: a) the follow-up period after UTI, b) through surveying the infants with previous history of antenatal hydronephrosis, c) by screening a sibling of a patient with VUR [7]. VUR usually is discovered during evaluation of UTI [2,3, 15]. Bladder and bowel dysfunction may be present in the management of more than half of children with VUR and recurrent UTI, which finally may lead to renal scarring and kidney failure [15,16, 17, 20].

Diagnosis:

The role of imaging is to evaluate for underlying urologic abnormalities for VUR and guide treatment. Detection of a condition before disease occurrence is justified when early intervention improves the outcomes for the patient. Ultrasonography is a useful initial revision to evaluate for renal and urinary system [21, 22]. Ultrasonography is the initial modality for the evaluation of postnatal hydronephrosis and UTI in children. Ultrasonography has been used to identify other urological abnormalities and has the benefit of being radiation free. Ultrasound is normal in lower grades of VUR, and overall, it is poor to identify the VUR. Ultrasound has also been utilized in the follow-

up evaluation of children after surgical correction of VUR and screening a sibling of a patient with VUR [6,7]. With the rapid improvement of ultrasound technology, the incidence of detection of renal anomalies is increased. Hydronephrosis is the most common congenital disorder, diagnosed by prenatal ultrasonography [23]. Some authors advise to perform all the diagnostic investigations for infants with prenatal hydronephrosis, but nowadays VCUG is recommended only in few selective cases [24-26]. According to previous studies, sonography cannot be a sensitive method to diagnose the UTI and VUR, while ultrasound study is helpful to detect the anatomical evaluation [27-30]. It is necessary to early diagnose the hydronephrosis and to reduce its complications. Diagnosis of VUR requires a VCUG or DRNC and echo-enhanced voiding urosonography (VUS) [31, 32]. However, the contrast VCUG provides more sensitive anatomic information but serves the radiation exposure [15, 16]. The bladder and if with VUR is present upper urinary tracts are imaged during bladder filling, voiding and post voiding. The gold standard for evaluation of children for VUR is VCUG, especially in male [7- 9]. The VCUG required catheterization and if with VUR presented an invasive diagnostic procedure that leads to significant stress among the children and their parents. The VCUG should be obtained as soon as the child has completed the course of antibiotic therapy for UTI. Evaluation with VCUG has been suggested after the first febrile infection in children younger than age 5. Radiation exposure is significantly less by using a DRNC than a contrast VCUG. So the former is preferred for follow-up evaluation [7].

VUS is an increasingly popular alternative for diagnosing and monitoring VUR [2, 22].

In one study, the correlation between the midline-to-orifice distances (MOD) measured by ultrasonography and VUS was compared to detect the VUR in children [31]. The VUR grading system is based on the appearance, dilation and tortuosity observed during the study [5].

Prognosis:

The voiding reflux is associated with a majority rate of spontaneous resolution and the filling reflux is more likely to need surgical intervention [33, 34]. The VUR is not the disease itself; it is maybe only one symptom of a syndrome so early diagnostic examination is mandatory for every child with suspicious event [35]. VUR grading in children is of high prognostic relevance [15, 16]. Although for most children, VUR will

spontaneously resolve in time, the management of children with VUR remains controversial, yet [15, 16].

The likelihood of spontaneous resolution is affected by recurrent UTI, grade of VUR, age at diagnosis, male, low bladder volume in VUR and bladder dysfunction, and the presence of other urinary tract malformation [13, 33]. VUR does not usually cause renal injury in the absence of infection, but in situations with high-pressure VUR, sterile VUR can cause significant renal damage [12- 16]. History of VUR was not associated with accelerated ESKD [36].

In some studies, a significant association has been reported between VUR and nephrolithiasis by an increased prevalence of hypercalciuria in children and their family members [37- 39].

Treatment:

Major efforts have been made in the past to improve the detection and follow-up of VUR in children. Though the management of children with VUR still remains cryptic, the best way of therapy in children with VUR should be the prevention of complications caused by relapsing pyelonephritis and reflux nephropathy [12, 13, 34]. Available management options include close monitoring and early treatment of pyelonephritis, long-term antibiotic prophylaxis, follow-up renal imaging to assess the resolution of VUR and reflux nephropathy, appropriate management of voiding dysfunction and constipation and surgical correction on demand or need [20, 30]. The three main treatment modalities that have been practiced are long-term antimicrobial prophylaxis, surgical correction and no routine prophylaxis or surgical intervention. Many studies have raised serious doubts about the relevance of long-term antimicrobial prophylaxis in the prevention of recurrent UTI and secondary renal injury in patients with VUR.

In children older than 2 months with first episode of uncomplicated UTI, there is no need for prophylactic antibiotic and routine imaging as VUR, but the ultrasound is usually appropriate. In children with recurrent or complicated UTI, imaging of VUR is usually appropriate [20, 40]. Continuous antibiotic prophylaxis (CAP) is recommended as the initial treatment option in patients classified in less risk group without low urinary tract disorder and anomaly [41]. CAP is recommended in children at greatest risk for VUR-related renal injury, for evaluation of bladder and bowel dysfunction and in children with VUR, who have febrile UTI [8]. Some researchers believe that CAP should be recommended for patients with VUR

diagnosed after febrile UTI and with high grade VUR diagnosed through screening [7].

The antimicrobial agents most appropriate for prophylaxis include trimethoprim-sulfamethoxazole (TMP-SMZ), trimethoprim alone, nitrofurantoin, or cephalexin [7]. However, the decision to use antibiotic prophylaxis in children with VUR remains a clinical dilemma and uncertain question. Disadvantages of prophylactic antibiotic therapy are the side effects and development of resistant organisms in the host [7, 8, 42].

The authors concluded that there was no superiority of surgical treatment over medical management of VUR in children [7]. Surgical correction is recommended for VUR:

Patients with grade V after one year old, patients with progression of renal scarring while on antibiotic prophylaxis, patients with progression of VUR grade, patients with frequent relapsing pyelonephritis, particularly those who have breakthrough UTI or renal scarring and for the non-compliant patient [7, 43].

Endoscopic treatment (ET) which is the injection of bulking agents in the subureteral space has been suggested as a treatment modality for VUR. The indications for endoscopic injection are unclear at present. ET is the gold standard for symptomatic low-grade VUR in children [44]. ET is effective at eliminating VUR in children, even in patients with high-grade reflux or in patients with VUR and additional malformations and alternative to continuous prophylactic antibiotic administration. ET may reduce the incidence of UTIs and prevent long-term renal damage. The cure rate of VUR with this procedure is approximately 60–70% with first treatment [43, 45].

DRNC is very useful to determine the resolution of reflux during follow-up or after surgical correction. Though most practitioners do it yearly, the timing for follow-up is not well defined,. Some researchers recommended the VCUG from yearly to every 2 years in children with mild VUR (grades I and II) and every 3 years in children with moderate to severe VUR (grades III or higher) [7, 8].

Conclusion:

VUR is a common pediatric problem and predisposing factor for UTI and 25-40% of children with UTI have VUR [22, 46, 47]. The incidence of VUR in children is still unknown many studies have assessed whether the approach to diagnosis and medical or surgical interventions can decrease the recurrence of UTI in children with VUR. We reviewed the current literature on it, but the clinical trials needed to

determine the increasing prevalence, efficacy and effectiveness of approach, diagnosis and alternative treatments for children with VUR.

Acknowledgment:

The authors wish to thank of Pediatrics Medicine Research Center of Qom University of Medical Sciences.

Funding: This study was self-funded.

Conflict of interest: No conflict of interest in declared by the authors.

References:

1. Sharifian M, Dalirani R, Mohkam S, et al. Spontaneous resolution of vesicoureteral reflux (VUR) in Iranian children: A single center experience in 533 cases. *Nephro-Urol Mon* 2011; 3(3): 191-5.
2. Sorkhi H, Nooreddini H, Amiri M, et al. Prediction of Vesicoureteral Reflux in Children with First Urinary Tract Infection by Dimercaptosuccinic Acid and Ultrasonography. *Iran J Pediatr* 2012; 22(1): 57-62. PMID: PMC3448216.
3. Fallahzadeh M, Ghane F, Hashemi G, Derakhshan A. Primary Vesicoureteral Reflux in Children in Southern Iran. *Iran J Med Sci* 2015; 27(3): 110-3.
4. Kim SW, Im YJ, Hong CH, Han SW. The clinical significance of intrarenal reflux in voiding cystourethrography (VCUG). *Korean J Urol* 2010; 51(1): 60-3. doi: 10.4111/kju.2010.51.1.60. PMID: PMC2855467.
5. Fukui S, Watanabe M, Yoshino K. Intrarenal reflux in primary vesicoureteral reflux. *Inter J Urol* 2013; 20(6): 631-6.
6. Hickling DR, Sun TT, Wu XR. Anatomy and Physiology of the Urinary Tract: Relation to Host Defense and Microbial Infection. *Microbiol spect* 2015; 3(4): 10.1128/microbiolspec.UTI-0016-2012. doi: 10.1128/microbiolspec.UTI-0016-2012.
7. Mattoo TK, Mathews R, Gupta IR. Vesicoureteral Reflux and Renal Scarring in Children. In: Avner ED, Harmon WE, Niaudet P, et al. *Pediatric nephrology*. 7th Ed. Baltimore: Lippincott Williams & Wilkins; 2016: 1716-35.
8. Elder JS, Vesicoureteral Reflux. In: Elder J, Behrman RE, Kliegman RM, Jenson HB. *Nelson textbook of Pediatrics*. 17th Ed. Philadelphia: W.B Saunders company; 2016: 2562-4.
9. Sharifian M, Shiva MR, Akhavan Sepahi M, et al. Urinary Ghrelin Concentration in Children With Urinary Tract Infections Before and After Treatment. *Arch Pediatr Infect Dis* 2016; 4(2): e34096.
10. Ghane Sharbaf F, Hosein Fallahzadeh M, Modarresi A, Esmaeili M. Primary vesicoureteral reflux in Iranian children: a follow-up of 330 cases. *Med J Islamic Repub Iran* 2006; 20(1): 29-32.
11. Hains DS, Schwaderer AL. Genetic variations in vesicoureteral reflux sequelae. *Pathogens* 2016; 5(1): 14.
12. Brakeman P. Vesicoureteral reflux, reflux nephropathy, and end-stage renal disease. *Advanc Urol* 2008; (2008): Article ID 508949. <http://dx.doi.org/10.1155/2008/508949>.
13. Nickavar A, Hajizadeh N, Harahdashti AL. Clinical course and effective factors of primary vesicoureteral reflux. *Acta Medica Iranica* 2015; 53(6): 376-9.
14. Costers M, Van Damme-Lombaerts R, Levtschenko E, Bogaert G. Antibiotic prophylaxis for children with primary vesicoureteral reflux: where do we stand today? *Advanc Urol* 2008; (2008): Article ID 217805. <http://dx.doi.org/10.1155/2008/217805>.
15. Esposito C, Escolino M, Lopez M, et al. Surgical management of pediatric vesicoureteral reflux: a comparative study between endoscopic, laparoscopic, and open surgery. *J Laparoendosc Adv Surg Tech* 2016; 26(7): 574-80. doi: 10.1089/lap.2016.0055.
16. Blais A-S, Bolduc S, Moore K. Vesicoureteral reflux: From prophylaxis to surgery. *Can Urol Assoc J* 2017; 11(1-2Suppl1): S13-8. doi: 10.5489/cuaj.4342 PMID: PMC5332225.
17. Koyle MA, Elder JS, Skoog SJ, et al. Febrile urinary tract infection, vesicoureteral reflux, and renal scarring: current controversies in approach to evaluation. *Pediatr surg int* 2011; 27(4): 337-46. doi: 10.1007/s00383-011-2863-y. Epub 2011 Feb 9.
18. Schwab CW, Wu H-Y, Selman H, et al. Spontaneous resolution of vesicoureteral reflux: a 15-year perspective. *J Urol* 2002; 168(6): 2594-9.
19. Elahi S, Homstad A, Vaidya H, et al. Rare variants in tenascin genes in a cohort of children with primary vesicoureteric reflux. *Pediatr Nephrol* 2016; 31(2): 247-53. DOI 10.1007/s00467-015-3203-6.
20. Dos Santos J, Lopes RI, Koyle MA. Bladder and bowel dysfunction in children: An update on the diagnosis and treatment of a common, but underdiagnosed pediatric problem. *Canadian Urol Asso J* 2017; 11(1-2Suppl1): S64-72. doi: 10.5489/cuaj.4411.
21. Wongbencharat K, Tongpenyai Y, Na-Rungsri K. Renal ultrasound and DMSA screening for high-grade vesicoureteral reflux. *Pediatr Int* 2016; 58(3): 214-8.
22. Sharifian M, Sharifian S. Diagnostic challenges in urinary tract infections in children. *Arch Pediatr Infect*

- Dis 2015; 3(2): e21386. DOI: 10.5812/pedinfect.21386.
23. Zee RS, Herbst KW, Kim C, et al. Urinary tract infections in children with prenatal hydronephrosis: a risk assessment from the society for fetal urology hydronephrosis registry. *J pediatr Urol* 2016; 12(4): 261 (e1-7).
 24. Gordon ZN, McLeod DJ, Ching CB, et al. Uroepithelial thickening improves detection of vesicoureteral reflux in infants with prenatal hydronephrosis. *J Pediatr Urol* 2016; 12(4): 257 (e1-7).
 25. Sidhu G, Beyene J, Rosenblum ND. Outcome of isolated antenatal hydronephrosis: a systematic review and meta-analysis. *Pediatr Nephrol* 2006; 21(2): 218-24.
 26. Mallik M, Watson AR. Antenatally detected urinary tract abnormalities: more detection but less action. *Pediatr Nephrol* 2008; 23(6): 897-904.
 27. Moorthy I, Wheat D, Gordon I. Ultrasonography in the evaluation of renal scarring using DMSA scan as the gold standard. *Pediatr nephrol* 2004; 19(2): 153-6.
 28. Bhatnagar V, Mitra D, Agarwala S, et al. The role of DMSA scans in evaluation of the correlation between urinary tract infection, vesicoureteric reflux, and renal scarring. *Pediatr Surg Inter* 2002; 18(2): 128-34.
 29. Temiz Y, Tarcan T, Onol F, et al. The efficacy of Tc-99m dimercaptosuccinic acid (Tc-DMSA) scintigraphy and ultrasonography in detecting renal scars in children with primary vesicoureteral reflux (VUR). *Inter Urol Nephrol* 2006; 38(1): 149-52.
 30. Sinha MD, Gibson P, Kane T, Lewis MA. Accuracy of ultrasonic detection of renal scarring in different centres using DMSA as the gold standard. *Nephrol Dialysis Transplant* 2007; 22(8): 2213-6.
 31. Battelino N, Kljucevsek D, Tomazic M, Levart TK. Vesicoureteral reflux detection in children: a comparison of the midline-to-orifice distance measurement by ultrasound and voiding urosonography. *Pediatr Nephrol* 2016; 31(6): 957-64. DOI 10.1007/s00467-015-3301-5.
 32. Mir S, Ertan P, Ozkayin N. Risk factors for renal scarring in children with primary vesicoureteral reflux disease. *Saudi J Kidney Dis Transplant* 2013; 24(1): 54-9.
 33. Lee JN, Lee SM, Ha Y-S, et al. VUR timing on VCUg as a predictive factor of VUR resolution after endoscopic therapy. *J Pediatr Urol* 2016; 12(4): 255 (e1-6). DOI: 10.1016/j.jpuro.2016.04.002.
 34. Celik O, Ipekci T, Aydogdu O, Yucel S. Current medical diagnosis and management of vesicoureteral reflux in children. *Nephro-Urol Month* 2014; 6(1): e13534. DOI: 10.5812/numonthly.13534.
 35. Nakaya T, Hyuga T, Tanaka Y, et al. Renal dysplasia characterized by prominent cartilaginous metaplasia lesions in VACTERL association: A case report. *Med* 2017; 96(15): e6499. DOI: 10.1097/MD.0000000000006499.
 36. Ishikura K, Uemura O, Hamasaki Y, et al. Insignificant impact of VUR on the progression of CKD in children with CAKUT. *Pediatr Nephrol* 2016; 31(1): 105-12.
 37. Akhavan Sepahi M, Eftekhari SS, Shahmoradi S, et al. Metabolic and anatomic abnormalities associated with pediatric nephrolithiasis: a cross-sectional study. *Inter J Pediatr* 2017; 5(5): 4833-8. DOI: 10.22038/ijp.2017.22705.1896.
 38. Akhavan Sepahi M, Eftekhari SS, Rashidinia S, et al. Relationship between urinary reflux and nephrolithiasis in children-a cross-sectional study. *Inter J Pediatr* 2017; 5(5): 4965-73. DOI: 10.22038/ijp.2017.22728.1898.
 39. Akhavan Sepahi M, Heidari A, Shajari A. Clinical manifestations and etiology of renal stones in children less than 14 years age. *Saudi J Kidney Dis Transplant* 2010; 21(1): 181-4. PMID: 20061721.
 40. Karmazyn BK, Alazraki AL, Anupindi SA, et al. ACR Appropriateness Criteria Urinary Tract Infection-Child. *J American College Radiol* 2017; 14(5): S362-71. DOI: 10.1016/j.jacr.2017.02.028.
 41. Prisca RA, Gozar H, Prisca AM, et al. Parent compliance: a bad predictor of resolution and a problem in the application of EAU guidelines on vesicoureteral reflux in children. *Inter Urol Nephrol* 2017; 49(5): 741-5. DOI: 10.1007/s11255-017-1551-9.
 42. Ingelfinger JR, Stapleton FB. Antibiotic prophylaxis for vesicoureteral reflux-answers, yet questions. *Mass Med Soc* 2014; 370(25): 2440-2. DOI: 10.1056/NEJMe1404774.
 43. Esposito C, Escolino M, Lopez M, et al. Surgical management of pediatric vesicoureteral reflux: a comparative study between endoscopic, laparoscopic, and open surgery. *J Laparoendoscop Advanc Surg Techniq* 2016; 26(7): 574-80. DOI: 10.1089/lap.2016.0055.
 44. Boudaoud N, Line A, Pons M, et al. Secondary mega ureter: A rare complication of Deflux, endoscopic management of vesicoureteral reflux in children. *Arch Pediatr: Organ Offic Soc Franc Pediatr* 2017; 24(3): 249-53. DOI: 10.1016/j.arcped.2016.12.005.
 45. Hacker F-M, Frech-Dorfler M, von Rotz M, Rudin C. Endoscopic hyaluronic acid/dextranomer gel implantation is effective as first-line treatment of vesicoureteral reflux (VUR) in children: a single centre experience. *Euro J Pediatr Surg* 2011; 21(5): 299-303. DOI: 10.1055/s-0031-1279700.

46. Mattoo TK. Vesicoureteral reflux and reflux nephropathy. *Advanc chron kidney dis* 2011; 18(5): 348-54. DOI:10.1053/j.ackd.2011.07.006.

47. Williams G, Fletcher JT, Alexander SI, Craig JC. Vesicoureteral reflux. *J American Soc Nephrol* 2008; 19(5): 847-62.