



Spontaneous resolution of vesicoureteral reflux (VUR) in Iranian children: A single center experience in 533 cases

Mostafa Sharifian ^{1*}, Hamed Zinsaz Boroujerdi ¹, Reza Dalirani ¹, Saeed Maham ¹, Mohsen Akhavan Sepahi ², Abdollah Karimi ¹, Maryam Ghaffari Shad ¹, Masoud Dadkhah Chymeh ¹, Maryam Sharifian ³

¹ Pediatric Infections Research Center (PIRC), Shahid Beheshti University of Medical Sciences, Tehran, IR Iran

² Department of Pediatrics, Qom University of Medical Sciences and Health Services, Qom, IR Iran

³ Department of Neurology, University of Medical Sciences Shiraz, Shiraz, IR Iran

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ABSTRACT

Background: Experience with vesicoureteral reflux (VUR) resolution differs in different centers.

Objective: The aim of this study was to evaluate the epidemiologic characteristics and outcome of VUR among Iranian children.

Patients and Methods: In this cohort study, 1278 children with urinary tract infection (UTI) who were visited at the pediatric nephrology clinic; Tehran, IR Iran during 1999 to 2007 were studied. Following the diagnosis, patients received prophylactic low-dose oral antibiotic and one to two yearly follow-ups with Radionuclide Cystography (RNC). Patients underwent surgery in case of breakthrough infection or new renal scar formation.

Results: Vesicoureteral reflux was found in 533 patients (42%) with a mean age of 6.3 ± 3.6 years (Range 2 days to 18 years), out of which 436 (82%) were females. During 3.3 ± 2.2 years follow-up, spontaneous resolution was observed in 109 (39%) of 279 patients with follow-up RNCs. Mean time to spontaneous resolution was 1.5 ± 1 years. Frequencies of VUR grades at initial investigation were 18%, 37%, 26%, 11% and 8% for grades I to V respectively, and 46% had bilateral VUR. Grades I to V resolved in 63%, 57%, 27%, 22% and 10%, respectively. Anti reflux surgery was performed in 27(10%) of patients. Two hundred forty nine patients proceeded to follow-up with Dimercaptosuccinic acid (DMSA) scan. There were 4 (4%) renal scars in patients with spontaneous resolution and 8 (5%) renal scars in patients without spontaneous resolution of VUR ($P > 0.05$).

Conclusions: According to the excellent results with medical therapy, it is recommended that VUR grades 1 to 4 be managed medically with low-dose antibiotic prophylaxis and close follow-ups.

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► Implication for health policy/practice/research/medical education:

Due to importance of VUR in children that it can be progressed to CKD, this article will focus on the benefit of medical treatment and close follow-up of these patients.

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* Corresponding author at: Mostafa Sharifian, Pediatric Infections Research Center (PIRC), Shahid Beheshti University of Medical Sciences, Mofid Children Hospital, Shariati Ave, Tehran, IR Iran. Tel: + 98-2122226941, Fax: + 98-2122220254.

E-mail: sharifian.dorche@gmail.com

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1. Background

Urinary tract infection (UTI) is a common health problem in pediatric age group; about 5% of girls and 1% of

boys develop UTI (1). Vesicoureteral reflux (VUR) is characterized by the retrograde flow of urine from the bladder to the kidneys. VUR is present in 1-2% of apparently normal children and more than 30-50% of children with UTI and 10% of neonates with hydronephrosis (2-4). Primary VUR is the most common heritable disorder of genitourinary tract with autosomal dominant inheritance (5, 6). Without appropriate treatment, between 30 and 60% of patients with UTI and VUR develop renal scar (7). The younger the patient in the time of UTI, the more probable is the incidence of VUR so that 70% of newborns with UTI and 15% of less than 12 years old patients have VUR (8). Renal scar (reflux nephropathy) is a risk factor for subsequent hypertension and renal failure (9). New scar formation in patients with primary VUR almost always develops following symptomatic UTI and pyelonephritis (10-13).

It is believed that medical and surgical management are equally effective in treating patients with VUR (7). Each form of treatment has advantages and disadvantages that must be discussed with parents before selecting the treatment strategy. If, on one hand, clinical treatment requires chronic antibiotic prophylaxis, periodic urine cultures and Radionuclide Cystography (RNC), which despite the low morbidity and radiation; may cause discomfort, on the other hand, surgery is has the risks of the surgical and anesthetic procedure. Several studies have established the rates of spontaneous resolution for patients with VUR undergoing medical management (14-20).

2. Objectives

Due to the lack of similar data in IR Iran, we analyzed our data and present our experience in this issue. The primary goal of this study was defining the rates of spontaneous resolution for patients with VUR in our center. These data are helpful to determine the indications for surgery and the proper follow-up in patients for medical management.

3. Patients and Methods

In this cohort study, 1278 children with urinary tract infection who were visited at pediatric nephrology clinic; Tehran, IR Iran during 1999 to 2007 were studied. VUR was found in 533 patients of whom 279 patients had follow-up RNCs and thus were analyzed for this study. Following the diagnosis patients received prophylactic low-dose oral antibiotic (1/3 therapeutic dose nightly) and yearly follow-up with RNC for low grade and every 1.5 years for high grade VUR. Patients underwent surgery in case of medical treatment failure (breakthrough infection) or new renal scar formation. Standard VCUG and RNC were performed using contrast medium and isotope material and the results were reported based on the international VUR classification as is reported by Lebowitz RL *et al.* (21). This classification is based on the extent of filling and dil-

atation of the ureter, the renal pelvis and the calyces by VUR (21). Radionuclide voiding cystography is a sensitive method for diagnosing VUR. This method allows detection of reflux during the study. It has a very low radiation burden to the patient and it is an ideal method for the diagnosis and follow-up of children with VUR (22). Data were analyzed by paired two tail student t test using Excel software and differences were considered significant if p value was found < 0.05.

4. Results

From 1278 patients with UTI, 1081 (85%) were female and (15%) male; mean age was 7.3 ± 3.9 years (Range 2 days to 21 years). Five hundred thirty three patients had VUR (42%), of these 436 (82%) were female and (18%) male, given a rate of 4.5/1. Mean age of patients with VUR was 6.3 ± 3.6 years (Range 2 days to 18 years). In 279 patients we

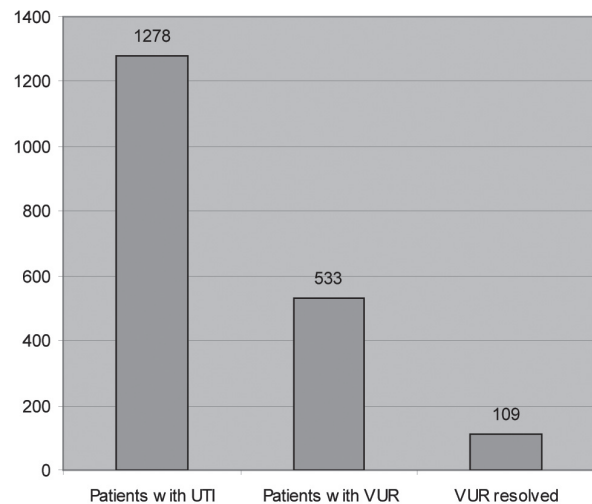


Figure 1. Distribution of patients with UTI, VUR and spontaneous resolution of VUR

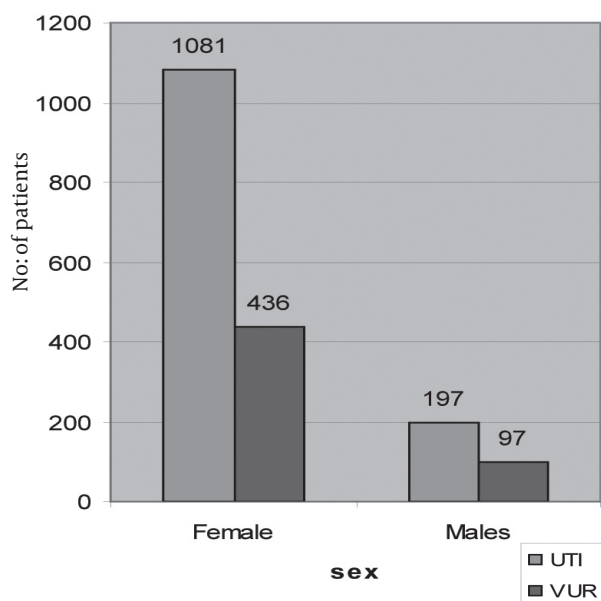


Figure 2. Distribution of patients with UTI and VUR according to sex

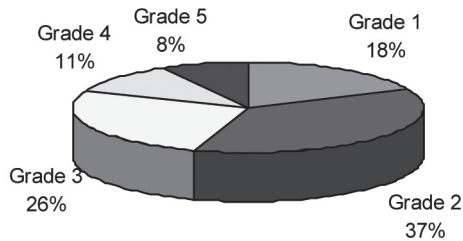


Figure 3. Distribution of patients with VUR according to grade

could do follow-up cystography; in 109 patients VUR resolved spontaneously (39%) (Figure 1), nine patients with recurrent UTI didn't show VUR in first contrast VCUG but showed it in RNC (2%). Among patients with spontaneous resolution, 78% were female. Twenty seven patients underwent antireflux surgery (10% of patients with regular follow-up). Mean follow-up time after VUR diagnosis was 3.3 ± 2.2 years (range 1 month to 9.1 years). Mean time to spontaneous resolution after VUR diagnosis was 1.5 ± 1 years (range 2 month to 6 years) and mean time from birth to spontaneous resolution of VUR was 2.4 ± 3.7 years (range 1 to 15 years).

Sixty two percent patients had unilateral and 38% bilateral VUR. Mean age of patients with spontaneous resolution of VUR was 6.5 ± 3.3 years (range 2 to 18 years), Distribution of patients with UTI and spontaneous resolution of VUR according to sex and grade of VUR are shown in figures 2- 4. From 51 patients with grade 5 VUR, spontaneous resolution occurred in 5 (10%), from 18 with grade 4 VUR, 4 (22%), from 63 with grade 3 VUR, 17 (27%), from 103 with grade 2 VUR, 59 (57%) and from 41 patients followed with grade 1 VUR, 26 (63%) resolved spontaneously. Eighty nine patients in spontaneous resolution group and 160 in patients without spontaneous resolution proceeded to follow-up Dimercaptosuccinic acid (DMSA) scan; there were 4 (4%) renal scars in patients with spontaneous resolution and 8 (5%) renal scars in patients without spontaneous resolution of VUR ($p > 0.05$).

5. Discussion

Vesicoureteral reflux is a common pediatric problem (1-3). The possibility of renal damage due to UTI especially when accompanied with VUR and consequently hypertension and renal failure mandate the diagnosis and appropriate management of these disorders. Sargent *et al.* (3) reported the prevalence of VUR in normal children to be 2.2 % of girls and 0.6 % of boys by the estimation. However, in children with urinary tract infection the prevalence was more than 30%. In present study prevalence of VUR in patients with UTI was 42 %; the relatively

VUR resolution based on grade

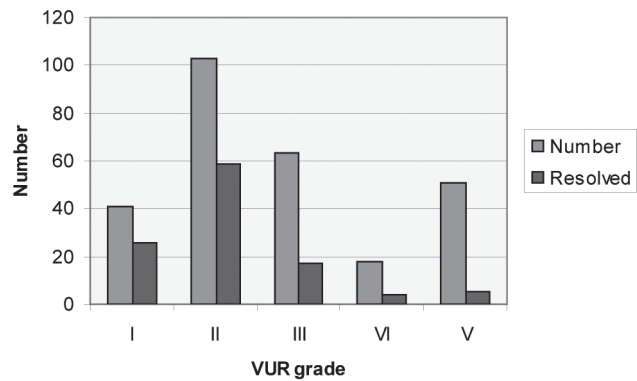


Figure 4. Distribution of patients with spontaneous resolution of VUR according to grade in patients with regular follow-up

higher rate of VUR in our patients was because of the fact that our clinic is a referral center for children with renal diseases. Of 213 patients more than 3 years old with recurrent urinary tract infections reported by Huland H, *et al.* (11), new pyelonephritic scars occurred in patients with UTI that superimposed to VUR. Of 61 patients with that combination renal scars developed in 7 (11.48%) and severe clubbing of calyces in two patients. In a review of 105 children with UTI Shah KJ, *et al.* (13) showed an increased prevalence of grades II-III VUR with younger age. During infancy reflux was almost always severe, and affected boys equal to girls. Kidneys with scar had reflux in 98% of cases. The prevalence of scars was also related significantly with severe reflux. Deterioration of scars or development of new scar was seen in 15 children; 18 out of 20 affected kidneys (90%) had grade III VUR. Two of 5 children developed new scars after 5 years of age.

In a study by Tamminen-Möbius T *et al.* (16) 401 children with severe vesicoureteral reflux (97 with grade III and 304 with grade IV) were entered the European branch of the International Reflux Study in Children. Of these patients 37 with grade III and 43 with grade IV reflux enrolled for medical treatment as the reflux grade III or IV had improved to grade II or I or resolved in 2 to 6 months (median 4). Of 321 patients with grade III or IV reflux, 158 were selected for medical treatment of which 3 ended up in surgery. Resolution of VUR was observed significantly more often in children with unilateral than with bilateral reflux. No significant difference was noted between grades III and IV reflux. Vesicoureteral reflux resolved in 25 of 153 children (16%) from the medical group and in 32 of 75 children (43%) in the sideline group. Of 194 children with VUR detected for the first time, reflux resolved in 55 (28%). Only 2 of 34 children (6%) in whom VUR was detected more than 1 year before study, reflux resolved after 5 years. Recurrence of urinary tract infection in children in whom VUR disappeared, or remained unchanged was almost similar. In Fallahzadeh *et al.* report in 2007 from Shiraz IR Iran, the spontaneous resolution rate of VUR was 55% in a 4.5 years follow-up (18). These results are compatible with the worldwide trend of medical man-

agement of primary VUR and avoidance of invasive surgical methods. Predictive factors of early spontaneous resolution in children with primary VUR were reported by Knudson *et al.* (19). In this study, medical records and cystograms of 324 children (257 girls and 67 boys) with primary vesicoureteral reflux were reviewed. Resolution of reflux was related with its grade. In their study, multivariate analysis demonstrated that age younger than 2 years at diagnosis ($p = 0.003$) and history of prenatal hydronephrosis ($p < 0.001$) were significant predicting factors for the resolution within 2 years. They concluded that initial reflux grade, bladder volume at reflux onset, age at diagnosis and history of prenatal hydronephrosis were independent factors for the resolution of reflux.

In a report of the International Reflux Study in Children by Weiss *et al.* (20), results of a randomized clinical trial of medical versus surgical management of grades III and IV reflux were analyzed. In this study, 132 infants and children with grades III and IV primary VUR were entered into a prospective investigation to compare medical with surgical treatment. Medical therapy consisted of continuous low dose antibiotic prophylaxis until VUR resolved. Sixty eight patients were allocated to the medical group and 64 to the surgical group. New renal scarring developed in 22% of medical and 31% of surgical patients ($p < 0.4$). There was no significant change in glomerular filtration rate in each group and no difference in glomerular filtration rate between groups. Hypertension was not detected during the follow-up period. The resolution rate of VUR in patients with grade IV reflux was approximately 8% per year. Of patients on medical management, 75% had VUR after 3 years of follow-up (20).

Our study also indicated that lower grades VUR had higher rates of spontaneous resolution. But in contrast to this report, our study revealed that spontaneous resolution in patients with grade 5 VUR occurred more than VUR grade 4 of this study. Spontaneous resolution rate of VUR in Brazilian children in 30 years was reported by Filho *et al.* (23). In this study 417 girls (81.6%) and 94 boys (18.4%) with all grades of reflux were reviewed retrospectively. Significant difference was found in rate of VUR resolution based on grade. These results are nearly similar to ours. The prevalence of VUR in our study was higher in girls, this was the case in most reported series (1, 18, 19, 23). However in Snodgrass report it was equal in both sexes (24).

Jodal *et al.* in 2007 retrospectively studied the relationship between UTI, VUR and renal damage in children. They studied 303 children younger than 2 years with first time, urinary tract infection (25). Vesicoureteral reflux was found in 36 of 163 boys (22%) and in 44 of 140 girls (31%). Of the 303 patients, 80 (26%) had renal scar in dimercapto-succinic acid (DMSA) scan. The rate of abnormality increased significantly with grade of VUR in boys and girls. They concluded that there was a significant relationship between grade II VUR and higher and permanent renal damage in boys and girls. Their findings support the idea that renal damage is associated with

vesicoureteral reflux which is often congenital in boys; however, in girls it is more related to urinary tract infection with vesicoureteral reflux (25).

Elder *et al.* (26) reported the VUR Guidelines of the American Urological Association on the management of primary VUR in children. They searched the Medline data base for all articles from 1965 to 1994 on VUR and systematically analyzed outcomes for 7 treatment alternatives: 1) intermittent antibiotic therapy, 2) bladder training, 3) continuous antibiotic prophylaxis, 4) antibiotic prophylaxis and bladder training, 5) antibiotic prophylaxis, anticholinergics and bladder training, 6) open surgery and 7) endoscopic repair. Outcomes identified were probability of resolution of reflux, and developing pyelonephritic scarring. In conclusion, for most children they recommended continuous antibiotic prophylaxis as initial treatment and surgery was recommended for persistent reflux and other indications as is our treatment strategy as well. Nasrallah *et al.* used nuclear cystography as a sensitive test for detection of VUR in 1982. In 15 out of 86 patients (17%) reflux was demonstrated only by the isotope cystography (27). In our study this condition occurred in 9 out of 533 patients (2%) which are far less than this report. In the International Reflux Study in Children reported by Weiss *et al.*, in 532 children of whom 401 were from Europe and 131 from the United States compared the results of medical and surgical treatment of children with grade III or IV vesicoureteral reflux and UTI. Of the European and United States children 48% and 54% had renal scarring, and 17% and 14% had scar, respectively (28). In a prospective study from Netherlands, results of 3 years treatment of VUR were reported by Scholtmeijer. In his study, the results of medical treatment of reflux grade I to III were excellent, but for grades IV and V reflux, he suggested that surgery should be the treatment of choice if detrusor instability is normal (29). Final report of the International Reflux Study in Children was presented by Jodal *et al.* and in this study 306 patients were randomly allocated to receive antimicrobial prophylaxis or reimplantation. They conclude that, children entering the study with GFR ≥ 70 ml/min per 1.73 m² remained normal under either medical or surgical management, with continued follow-up (30). Only 52% of our patients had regular follow-up and control RNCs which we could analyze their data and this is our limitation in this study because the patients can change their physician easily in our area.

Wheeler *et al.* in a meta-analysis of randomized controlled trials of antibiotics and surgery for VUR evaluated different treatment options of these patients. In their search eight trials which involved 859 children comparing long term antibiotics with surgical correction of VUR and antibiotics (seven trials) and antibiotics compared with no treatment (one trial) were identified. Risk of UTI by 1-2 and 5 years was not significantly different between surgical and medical groups. Combined treatment resulted in a 60% reduction in febrile UTI by 5 years (RR 0.43) but no significant reduction in risk of

new or progressive renal damage at 5 years were noted. They concluded that treatment of children with VUR may not have clinically important benefit and the benefit of surgery over antibiotics alone is small. They concluded that in five years, nine reimplantations are required to prevent one febrile UTI (31). As in our study, all of these reports emphasize the benefit of medical therapy and careful follow-up of these patients and we also had excellent results with spontaneous resolution of 63 to 10%, in grades 1 to 5 VUR. According to the excellent results obtained with medical therapy using low dose antibiotic prophylaxis, it is recommended that VUR grades 1 to 4 be managed medically with low-dose oral antibiotic prophylaxis and close follow-ups and surgery be considered only for breakthrough UTIs and high grade VUR which persists and causes formation of renal scar.

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Conflict of interest

None declared.

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References

- Kaplan BS, Meyers KEC. *Pediatric nephrology and urology: the requisites in pediatrics*. Elsevier Mosby; 2004.
- Lebowitz RL. The detection and characterization of vesicoureteral reflux in the child. *J Urol*. 1992;**148**(5 Pt 2):1640-2.
- Sargent MA. What is the normal prevalence of vesicoureteral reflux? *Pediatr Radiol*. 2000;**30**(9):587-93.
- Woodward M, Frank D. Postnatal management of antenatal hydronephrosis. *BJU Int*. 2002;**89**(2):149-56.
- Jacobson SH, Hansson S, Jakobsson B. Vesico-ureteric reflux: occurrence and long-term risks. *Acta Paediatr Suppl*. 1999;**88**(431):22-30.
- Riccabona M. Management of recurrent urinary tract infection and vesicoureteral reflux in children. *Curr Opin Urol*. 2000;**10**(1):25-8.
- Avner ED, Harmon WE, Niaudet P. Vesicoureteral Reflux and Scarring. In: Rushton HG, Jr., editors. *Pediatric Nephrology*. 5th ed. Berlin: Lippincott Williams & Wilkins; 2009. p. 1311-36.
- Baker R, Maxted W, Maylath J, Shuman I. Relation of age, sex, and infection to reflux: Data indicating high spontaneous cure rate in pediatric patients. *J Urol*. 1966;**95**(1):27-32.
- Bailey RR, Mailing T.M.J, C.P S. Vesicoureteric reflux and reflux nephropathy. In: Scherier R.W, C.W G, editors. *Disease of the Kidney*. 5th ed. Boston: Little, Brown & Co; 1993. pp. 689-727.
- Smellie JM, Ransley PG, Normand IC, Prescod N, Edwards D. Development of new renal scars: a collaborative study. *Br Med J (Clin Res Ed)*. 1985;**290**(6486):1957-60.
- Huland H, Busch R. Pyelonephritic scarring in 213 patients with upper and lower urinary tract infections: long-term followup. *J Urol*. 1984;**132**(5):936-9.
- Winberg J, Bollgren I, Kallenius G, Mollby R, Svenson SB. Clinical pyelonephritis and focal renal scarring. A selected review of pathogenesis, prevention, and prognosis. *Pediatr Clin North Am*. 1982;**29**(4):801-14.
- Shah KJ, Robins DG, White RH. Renal scarring and vesicoureteric reflux. *Arch Dis Child*. 1978;**53**(3):210-7.
- Skoog SJ, Belman AB, Majd M. A nonsurgical approach to the management of primary vesicoureteral reflux. *J Urol*. 1987;**138**(4 Pt 2):941-6.
- Smellie JM, I.C.S N. Reflux nephropathy in childhood. In: Hodson J, P.K-S, editors. *Reflux Nephropathy*. 1st ed. New York: Masson; 1979. p.14-20.
- Tamminen-Mobius T, Brunier E, Ebel KD, Lebowitz R, Olbing H, Seppanen U, et al. Cessation of vesicoureteral reflux for 5 years in infants and children allocated to medical treatment. The International Reflux Study in Children. *J Urol*. 1992;**148**(5 Pt 2):1662-6.
- Garin EH, Olavarria F, Garcia Nieto V, Valenciano B, Campos A, Young L. Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. *Pediatrics*. 2006;**117**(3):626-32.
- Sharbat FG, Fallahzadeh MH, Modarresi AR, Esmaeili M. Primary vesicoureteral reflux in Iranian children. *Indian Pediatr*. 2007;**44**(2):128-30.
- Knudson MJ, Austin JC, McMillan ZM, Hawtrey CE, Cooper CS. Predictive factors of early spontaneous resolution in children with primary vesicoureteral reflux. *J Urol*. 2007;**178**(4 Pt 2):1684-8.
- Weiss R, Duckett J, Spitzer A. Results of a randomized clinical trial of medical versus surgical management of infants and children with grades III and IV primary vesicoureteral reflux (United States). The International Reflux Study in Children. *J Urol*. 1992;**148**(5 Pt 2):1667-73.
- Lebowitz RL, Olbing H, Parkkulainen KV, Smellie JM, Tamminen-Mobius TE. International system of radiographic grading of vesicoureteric reflux. International Reflux Study in Children. *Pediatr Radiol*. 1985;**15**(2):105-9.
- Willi U, Treves S. Radionuclide voiding cystography. *Urol Radiol*. 1983;**5**(3):161-73, 75.
- Zerati Filho M, Calado AA, Barroso U, Jr., Amaro JL. Spontaneous resolution rates of vesicoureteral reflux in Brazilian children: a 30-year experience. *Int Braz J Urol*. 2007;**33**(2):204-12; discussion 13-5.
- Snodgrass W. Relationship of voiding dysfunction to urinary tract infection and vesicoureteral reflux in children. *Urology*. 1991;**38**(4):341-4.
- Swerkersson S, Jodal U, Sixt R, Stokland E, Hansson S. Relationship among vesicoureteral reflux, urinary tract infection and renal damage in children. *J Urol*. 2007;**178**(2):647-51; discussion 50-1.
- Elder JS, Peters CA, Arant BS, Jr., Ewalt DH, Hawtrey CE, Hurwitz RS, et al. Pediatric Vesicoureteral Reflux Guidelines Panel summary report on the management of primary vesicoureteral reflux in children. *J Urol*. 1997;**157**(5):1846-51.
- Nasrallah PF, Nara S, Crawford J. Clinical applications of nuclear cystography. *J Urol*. 1982;**128**(3):550-3.
- Weiss R, Tamminen-Mobius T, Koskimies O, Olbing H, Smellie JM, Hirche H, et al. Characteristics at entry of children with severe primary vesicoureteral reflux recruited for a multicenter, international therapeutic trial comparing medical and surgical management. The International Reflux Study in Children. *J Urol*. 1992;**148**(5 Pt 2):1644-9.
- Scholtmeijer RJ. Treatment of vesicoureteric reflux: results after 3 years in a prospective study. *Child Nephrol Urol*. 1991;**11**(1):29-32.
- Jodal U, Smellie JM, Lax H, Hoyer PF. Ten-year results of randomized treatment of children with severe vesicoureteral reflux. Final report of the International Reflux Study in Children. *Pediatr Nephrol*. 2006;**21**(6):785-92.
- Wheeler D, Vimalachandra D, Hodson EM, Roy LP, Smith G, Craig JC. Antibiotics and surgery for vesicoureteric reflux: a meta-analysis of randomised controlled trials. *Arch Dis Child*. 2003;**88**(8):688-94.