

Predicting long-term renal damage in children with vesicoureteral reflux under conservative initial management: 205 cases in a tertiary referral center

Natalia Alvarez¹, Reyes Delgado Alvira², Yurema Gonzalez Ruiz², Rafael Fernandez Atuan², Alexander Siles Hinojosa², Miguel Angel Rihuete Heras², Marisa Justa Roldan², Jesus Gracia Romero^{2,3}

¹Universidad Autonoma De Barcelona, Parc Tauli, Pediatric Surgery, Sabadell, Spain

²Pediatric Surgical Department, Miguel Servet University Hospital, Zaragoza, Spain

³University of Zaragoza, Zaragoza, Spain

Citation: Alvarez N, Delgado Alvira R, Gonzalez Ruiz Y, et al. Predicting long-term renal damage in children with VUR under conservative initial management: 205 cases in a tertiary referral center. Cent European J Urol. 2018; 71: 142-147.

Article history

Submitted: July 12, 2017

Accepted: Jan. 28, 2018

Published online: Jan. 29, 2018

Corresponding author

Natalia Alvarez
Universidad Autonoma
De Barcelona
Pediatric Surgery
Parc Tauli
Xercavins 53
08202 Sabadell, Spain
phone: +34 635 875 482
alvarezgarcianatalia@gmail.com

Introduction Vesicoureteral reflux (VUR) is one of the most common ailments in children. Evidence-based guidelines recommend conservative treatment in children with VUR, followed by endoscopic surgery in those with breakthrough febrile urinary tract infections (UTIs). Despite this fact, the management of VUR is still controversial. Our objective is to evaluate the conservative strategy in children with primary VUR in terms of renal function and scarring, and identify factors associated with poor prognosis in those children.

Material and methods A retrospective study was carried out in a tertiary center in children with primary VUR under conservative strategy treatment from 1989 to 2015. Data extracted included age of presentation, family and prenatal backgrounds, radiographic evaluation including ultrasound (US), dimercaptosuccinic acid (DMSA) scans and voiding cystourethrogram (VCUG). The SPSS program was used for statistical analysis.

Results Two-hundred and five patients were diagnosed and followed a conservative therapy scheme (49.8% males, 50.2% females) after febrile UTI (73.17%) or prenatal diagnosis (26.83%). VCUG showed 53.20% of low-moderate VUR grade, 46.80% high VUR grade. Renal damage was present at diagnosis in 40.89%. Mean follow-up breakthrough recurrent febrile UTIs and underwent surgery. Conservative therapy was followed in 189 patients. Renal scarring or decreased kidney function were shown in 15.12% respectively. Renal damage was identified as a risk factor for poor prognosis (p-value <0.005) only for renal function deterioration. Patients with high-grade VUR required surgery in a significantly greater proportion (p <0.005) due to recurrent febrile UTIs.

Conclusions Conservative strategy is a feasible treatment for primary VUR in children. The majority of cases could be managed conservatively with good outcomes after long-term follow-up. Decreased renal function is more frequent in patients with high-grade VUR. Renal damage at diagnosis increases the risk for surgical treatment.

Key Words: evidence-based practice ↔ renal insufficiency ↔ children
↔ urinary tract infection ↔ vesicoureteral reflux

INTRODUCTION

Vesicoureteral reflux (VUR) is a heterogeneous ailment defined by the retrograde ascension of urine from the bladder to the urethra, in the absence of any anatomic abnormality or neurologic condi-

tion [1]. VUR is known to increase the risk of urinary tract infections (UTIs) and permanent renal damage. Traditionally, high-grade VUR is associated with a greater risk of febrile UTIs and severity of renal damage. Bilateral renal injury has also been related to hypertension and chronic renal

insufficiency [2]. On the other hand, VUR tends to disappear spontaneously during childhood, and in those children without UTIs, renal damage is uncommon. Currently, there is still a lack of consensus about the optimal treatment for primary VUR in order to prevent renal injury progression [3] and several strategies have been described with a huge variability between surgeons and paediatricians treating these patients. Classically, primary VUR treatment is based on two different pillars: surgical correction techniques or conservative treatment formed by hygienic habits recommendations and continuous antibiotic prophylaxis (CAP), looking forward to spontaneous resolution. The majority of evidence-based guidelines and consensus documents recommend the conservative strategy as the first-line therapy in all children with VUR, leaving surgery for those patients with breakthrough recurrent UTIs during follow-up [3, 4]. Several studies have demonstrated the lack of benefits in renal function in those pa-

tients who undergo surgery at diagnosis, in terms of appearance and progression of renal scars, hypertension or renal insufficiency [5]. Our objective was to identify prognostic factors in children under conservative initial treatment in terms of long-term renal function and damage outcomes, as well as to predict the need for surgical intervention, among the patients treated in a tertiary referral center during the last 25 years.

MATERIAL AND METHODS

A retrospective cohort study was carried out in patients between 0 and 15 years old, diagnosed with primary reflux after an urinary tract infection or prenatal ultrasound findings between 1989 and 2015 who underwent the non-operative strategy after diagnosis. Children with concomitant nephro-urologic diseases were excluded. Data included age of presentation, family and prenatal backgrounds,

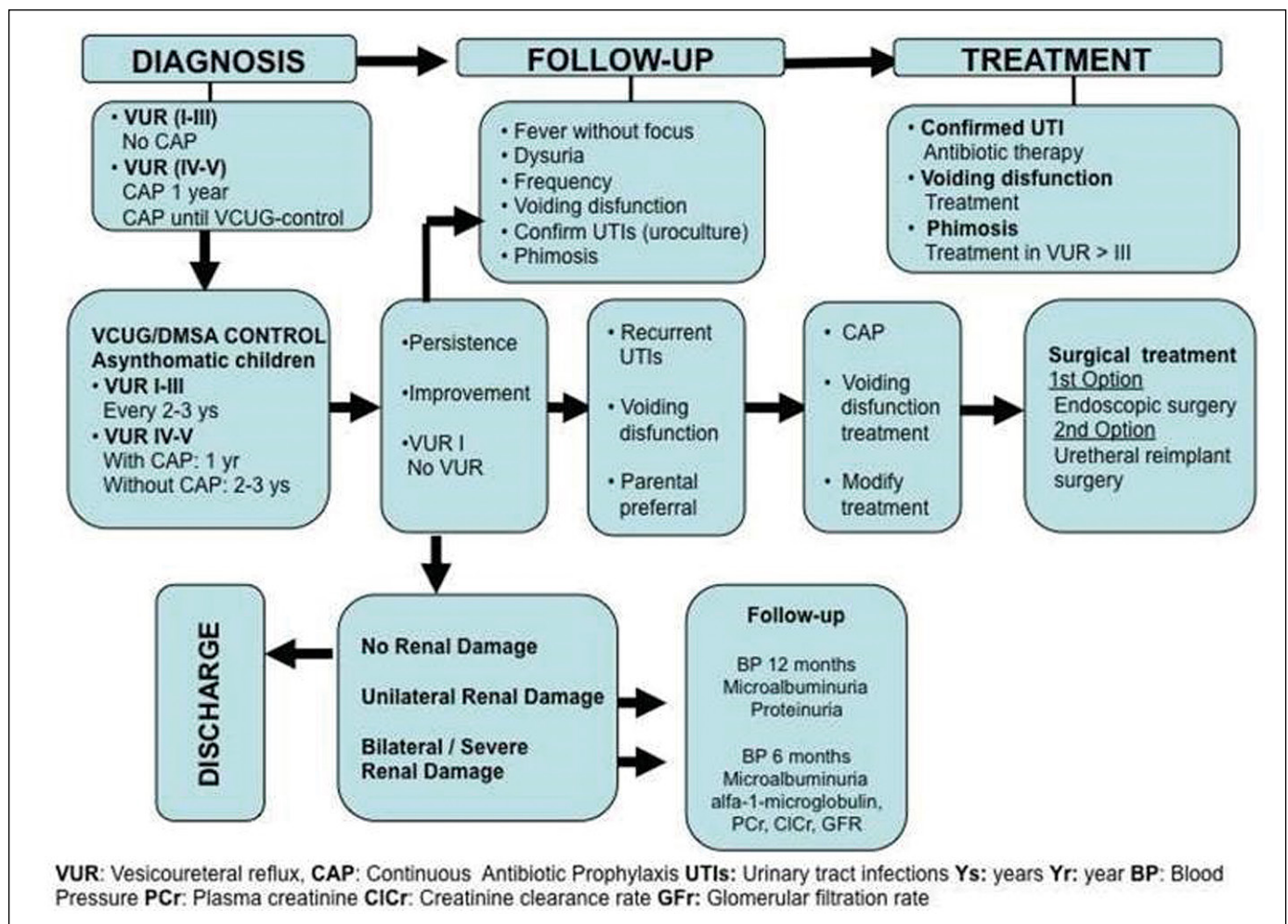


Figure 1. Current evidence-based guidelines standard algorithm for vesicoureteral reflux management in children. The figure has been created based on a figure published in the Spanish National Guidelines for VUR (source [4]).

radiographic evaluation including ultrasounds (US), dimercaptosuccinic acid (DMSA) scans and voiding cystourethrograms (VCUG), extracted from electronic medical records. All patients were diagnosed with VCUG and classified using the International VUR Classification [6]. Renal damage was evaluated with DMSA scan and classified using the Goldraich Classification [7, 8]. Febrile UTIs were defined by the presence of fever, alterations in urinary sediment and confirmation by urine culture. Conservative strategy includes clinical observation, hygienic habits recommendations and CAP, indicating surgery in those with breakthrough febrile UTIs following an evidence-based algorithm (Figure 1). Analysis of poor prognostic factors was based on current literature and included gender, type of diagnosis, age of first UTI, VUR grade, bilaterality, renal damage at diagnosis and voiding dysfunction. All statistical analysis was performed using SPSS v.18.0.

RESULTS

A total of 297 patients were diagnosed with primary VUR from 1989 to 2015. Of these, 205 patients were managed with conservative treatment and were included in the study. Epidemiological variables were: 49.8% males and 50.2% females were included, with a mean age at diagnosis of 21.71 months (0–144). Clinical variables were: primary VUR was diagnosed after a febrile UTI in 73.17% of children and 26.83% with prenatal ultrasound diagnosis of hydronephrosis. First VCUG showed 53.2% of low-moderate grade VUR (I–III grades) and 46.80% presented high-grade VUR (IV–V grades). Bilateral reflux was present in 46.83% of children. Renal damage at diagnosis was present in 40.89% of patients. During the clinical course,

mean follow-up period was 115 months (107–124). Among the 205 patients included in the study, control DMSA scan were performed in 172, showing renal function deterioration and renal scarring worsening in 15.12% of patients, respectively (n = 26). Fifty-two patients had suffered at least one UTI, but only 16 presented with recurrent episodes. The percentage of patients with high-grade VUR who underwent surgery was higher (81.25%) than those with low-intermediate grade VUR (18.75%) (OR = 5.60, IC 95% 1.54–0.31). Among the potential renal damage risk factors analyzed, we have only found statistically significant differences in renal damage at diagnosis (p = 0.005 χ^2 Pearson test) for renal function worsening (Table 1). In relation to renal scarring worsening, the risk factors analyzed did not show statistically significant differences (Table 2). Age of diagnosis in patients diagnosed after febrile UTIs has not been identified as a risk factor for neither decrease in renal function (p = 0.142, Mann-Whitney test) nor scarring (p = 0.0117, Mann-Whitney test) In terms of risk factors for surgery, among the 205 patients who followed the initial non-operative treatment scheme, 16 underwent surgery because of recurrent febrile UTIs. In those patients, risk factor analysis showed statistical difference only in patients with high-grade VUR (IV–V) at diagnosis (p = 0.009, OR = 5.6 IC 95%) (Table 3). Age of diagnosis was not identified as a risk factor (p = 0.223, Mann-Whitney test) for requiring surgery in those patients diagnosed after a febrile UTI.

DISCUSSION

Primary VUR is a classical common topic for debate between paediatricians and paediatric urological

Table 1. Risk factors for renal function worsening in children with primary vesicoureteral reflux under conservative treatment

Risk factors		RF Stable (n)	RF Worsening (n)	p-value
Gender	Male	66	14	p = 0.336
	Female	80	11	
Diagnosis	UTIs	114	18	p = 0.464
	Prenatal US	32	8	
VUR Grade	I–III	78	9	p = 0.120
	IV–V	68	17	
Bilateral VUR	Yes	65	15	p = 0.304
	No	81	11	
Voiding Dysfunction	Yes	26	8	p = 0.207
	No	120	18	
Renal damage at diagnosis	Yes	55	18	p = 0.005
	No	91	8	
Total patients		146	26	

RF – renal function; UTIs – urinary tract infections; US – ultrasound; VUR – vesicoureteral reflux

Table 2. Risk factors for renal scarring Worsening in children with primary vesicoureteral reflux under conservative treatment

Risk factors		RF Stable (n)	RF Worsening (n)	p-value
Sex	Male	68	13	p = 0.913
	Female	78	13	
Diagnosis	UTIs	113	19	p = 0.819
	Prenatal US	32	7	
VUR Grade	I–III	77	10	p = 0.259
	IV–V	10	16	
Bilateral VUR	Yes	82	10	p = 0.304
	No	64	16	
Voiding Dysfunction	Yes	27	7	p = 0.207
	No	119	19	
Renal damage at diagnosis	Yes	59	14	p = 0.005
	No	87	12	
Total patients		146	26	

RS – renal scarring; UTIs – urinary tract infections; US – ultrasound; VUR – vesicoureteral reflux

Table 3. Prognostic factors for surgery in children with primary vesicoureteral reflux under conservative treatment

Risk factors		No Surgery (n)	Surgery (n)	p-value
Sex	Male	93	6	p = 0.523
	Female	96	10	
Diagnosis	UTIs	137	13	p = 0.566
	Prenatal US	52	3	
VUR Grade	I–III	105	3	p = 0.009
	IV–V	82	13	
Bilateral VUR	Yes	85	11	p = 0.117
	No	104	5	
Voiding Dysfunction	Yes	29	5	p = 0.151
	No	160	11	
Renal damage at diagnosis	Yes	73	10	p = 0.117
	No	114	6	
Total patients		189	16	

UTIs – urinary tract infections; US – ultrasound; VUR – vesicoureteral reflux

surgeons. Despite the high incidence of this ailment and the increasing number of publications about its management, there is still a high variability in opinions among professionals. The majority of the evidence-based guidelines promote a non-operative therapy for primary VUR in children. In our country, the first National Guideline was published in 2008 [4] in order to improve clinical practice. Those recommendations included not only algorithms for the diagnosis and management of those children, but also indications for non-invasive follow-up avoiding unnecessary complementary testing in asymptomatic children, which should be performed every 2 or 3 years. Because of that, we have not performed DMSA-control nor VCUG-control tests in all patients, only in 172 of 205 patients. Both renal function decrease and worsening of renal scarring have

been observed in 15.12% of our sample group. Comparing our results to current literature, our rates are very similar to those published by the RIVUR study [9, 10, 11] in which 11.9% of patients under prophylaxis and 10.2% with placebo showed progression of renal scarring. Systematic reviews performed by Nagler et al. [5] and Wheeler et al. [12] comparing conservative treatment to surgery include three studies – IRS EUR [13], IRS USA [14] and Smellie 2001 [15] – where renal scarring was evaluated after 5 years of follow-up. The 43.3% of patients operated and the 41.39% with CAP showed progression of renal damage (RR 1.05, 0.95–1.29). Attending to a comparative period of follow-up with our cohort, the IRS EUR 1981–2003 study [16] performs the evaluation after 10 years but the outcomes only include the appearance of new renal scars and their

results are not feasible for comparison with ours. The high percentage of patients with renal injury progression is noticeable in these studies, as well as similar rates in our cohort to the RIVUR study. These results should be taken with caution, as multiple epidemiological and clinical variables make VUR cohorts very heterogeneous, hindering the extrapolation of results. Despite this fact, we consider the non-operative therapy a feasible treatment for all children with VUR. In our cohort, the majority of patients were managed conservatively and our results are comparable to other strategies already published. In relation to the analysis of risk factors, renal function worsening is associated with the renal damage at diagnosis. This association has already been reported by several authors [2, 17, 18]. Currently, some authors consider congenital VUR a different entity from the diagnosis of reflux after a febrile UTI, as congenital hydronephrosis due to vesicoureteral reflux is usually accompanied by a variable degree of renal dysplasia, which is considered an independent factor for renal injury progression itself, in absence of pyelonephritis [19]. Risk factors for surgical treatment are in direct relationship to recurrent febrile UTIs as shown in the non-operative management algorithm (Figure 1). A small proportion of children under conservative treatment presented with recurrent UTI episodes. According to our data, 52 children suffered isolated episodes of febrile UTIs, but only 16 presented with recurrent infections which led to the indication of surgery. The percentage of patients with high-grade VUR who underwent surgery was higher (81.25%) than those with low-intermediate grade VUR (18.75%)

(OR = 5.60, IC 95% 1.54–20.31). The relation between VUR grades and recurrent UTIs has been widely reported in the literature [17, 20–24]. Hertz et al. [25] did not find this association in patients with congenital renal damage. Despite this finding, we would like to highlight that the majority of children with VUR followed a conservative treatment, despite their initial VUR grade, renal damage, gender, age or type of VUR. These results should be taken into account, as surgery persists as the elective therapy for some colleagues even though surgical treatment has not demonstrated any benefit in this group of patients. Our study supports the evidence-based recommendations and could help to stamp out the stigma of VUR as a primarily surgical disease.

CONCLUSIONS

The presence of renal damage at diagnosis is considered an independent risk factor for poor renal function prognosis. Patients with high-grade VUR are most at risk of surgery, despite the minority of patients requiring surgical treatment during follow-up. Conservative initial therapy for primary VUR in children shows similar results in terms of renal function progression and worsening of scarring to other strategies reported in the literature. Evidence-based algorithms should be promoted in order to avoid unnecessary aggressive therapies in these children. VUR should not be considered a surgical entity any longer.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

References

1. Khoury A, Bägli DJ. Reflujo y megaureter. In: Wein AJ, Kavoussi LR, Parlin AW, Novick AC. Campbell-Walsh Urology. Ed. Panamericana 2007; pp. 3423-3481.
2. Fidan K, Kandur Y, Buyukkaragoz B, Akdemir UO, Soylemezoglu O. Hypertension in pediatric patients with renal scarring in association with vesicoureteral reflux. *Urology*. 2013; 81: 173-177.
3. Arlen AM, Cooper CS. Controversies in the management of vesicoureteral reflux. *Curr Urol Rep*. 2015; 16: 64.
4. Grupo de trabajo de la Guía de Práctica Clínica sobre Manejo del Paciente con Reflujo Vesicoureteral primario o esencial. Guía de Práctica Clínica. Manejo del Paciente con Reflujo Vesicoureteral primario o esencial. Actualización. Asociación Española de Nefrología Pediátrica. 2014. <http://www.guiasalud.es/egpc/reflujo/completa/apartado01/introduccion.html> accessed 05.07.17
5. Nagler EV, Williams G, Hodson EM, Craig JC. Interventions for primary vesicoureteric reflux. *Cochrane Database Syst Rev*. 2011; 6: CD001532.
6. 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: 105-109.
7. Goldraich NP, Goldraich IH, Anselmi OE, Ludwig EB, Ramos OL. Assessment of individual renal function with DMSA renal scan in children with primary vesicoureteric reflux. *Eur J Pediatr*. 1983; 140: 212.
8. Christian MT, McColl JH, MacKenzie JR, Beattie TJ. Risk assessment of renal cortical scarring with urinary tract infection by clinical features and ultrasonography. *Arch Dis Child*. 2000; 82: 376-380.
9. Hoenig DM, Diamond DA, Rabinowitz R, Caldamone AA. Contralateral reflux after unilateral ureteral reimplantation. *J Urol*. 1996; 156: 196-197.
10. Kumar R, Puri P. Newly diagnosed contralateral reflux after successful unilateral endoscopic correction: is it due to the pop-off mechanism. *J Urol*. 1997; 158: 1213-1215.

11. Hjalmas K, Lohr G, Tamminen-Mobius T, Seppanen J, Olbing H, Wikstrom S. Surgical results in the International Reflux Study in Children (Europe). *J Urol.* 1992; 148: 1657-1661.
12. 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: 688-694.
13. Hjalmas K, Löhr G, Tamminen-Möbius T, Seppänen J, Olbing H, Wikström S. Surgical results in the International Reflux Study in Children (Europe). *J Urol.* 1992; 148: 1657-1661.
14. 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: 1667-1673.
15. Smellie JM, Barratt TM, Chantler C, et al. Medical versus surgical treatment in children with severe bilateral vesicoureteral reflux and bilateral nephropathy: a randomised trial. *Lancet.* 2001; 357: 1329-1333.
16. Smellie JM, Jodal U, Lax U, et al. Writing Committee, International Reflux Study in Children (European Branch). Outcome at 10 years of severe vesicoureteral reflux managed medically: Report of the International Reflux Study in Children. *J Pediatr.* 2001; 139: 656-663.
17. Kang M, Lee JK, Im YJ, Choi H, Park K. Predictive factors of chronic kidney disease in patients with vesicoureteral reflux who were treated by surgery and followed until post-puberty. *J Urol.* 2016; 195: 1100-1106.
18. Smellie JM, Prescod NP, Shaw PJ, Risdon RA, Bryant TN. Childhood reflux and urinary infection: a follow-up of 10-41 years in 226 adults. *Pediatr Nephrol.* 1998; 12: 727-736.
19. Duckett JW, Walker RD, Weiss R. Surgical results: International Reflux Study in Children- United States branch. *J Urol.* 1992; 148: 1674-1675.
20. Brandstrom P, Neveus T, Sixt R, Stokland E, Jodal U, Hansson S. The Swedish reflux trial in children: IV. Renal damage. *J Urol.* 2010; 184: 292-297.
21. Garin EH, Campos A, Homsey Y. Primary vesicoureteral reflux: review of current concepts. *Pediatr Nephrol.* 1998; 12: 249-256.
22. Melhem RE, Harpen MD. Ethnic factors in the variability of primary vesicoureteral reflux with age. *Pediatr Radiol.* 1997; 27: 750-751.
23. Anderson P, Rickwood A. Features of primary vesicoureteric reflux detected by prenatal sonography. *Br J Urol.* 1991; 67: 267-271.
24. Ochoa C, Perez C, Solias G, et al. Recomendaciones de la Conferencia de Consenso "Manejo Diagnóstico y Terapéutico de las Infecciones del Tracto Urinario en la Infancia". *An Pediatr (Barc).* 2007; 67:517-525
25. Herz D, Merguerian P, McQuiston L. Continuous antibiotic prophylaxis reduces the risk of febrile UTI in children with asymptomatic antenatal hydronephrosis with either ureteral dilation, high-grade vesicoureteral reflux, or ureterovesical junction obstruction. *J Pediatr Urol.* 2014; 10: 650-654. ■