Available online at www.sciencerepository.org

Science Repository

Research Article

Clinical Significance of Antibiotic Prophylaxis in Children Diagnosed with Low-Grade (I-III) Vesicoureteral Reflux

Yalda Ravanshad[1], Mohadese Golsorkhi[2], Anoush Azarfar[2*], Azam Ghezi[2], Sahar Ravanshad[3], Gholamreza Sarvari[4] and Sepideh Seyedkaboli[4]

[1]*Department of Community Medicine, Mashhad Branch, Islamic Azad University, Mashhad, Iran*
[2]*Kidney Transplantation Complications Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*
[3]*Department of Internal Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[4]*Department of Pediatrics, Mashhad University of Medical Sciences, Mashhad, Iran*

ARTICLE INFO

Article history:
Received: 11 May, 2020
Accepted: 6 June, 2020
Published: 12 June, 2020

Keywords:
Vesicoureteral reflux
antibiotic prophylaxis
urinary tract infection

ABSTRACT

Objective: The benefit of continuing and low-dose antibiotic therapy in urinary tract infection (UTI) prevention and renal injury for children diagnosed with primary vesicoureteral reflux (VUR) is not obvious.
Materials and Methods: Patients aged between 2 to 71 months with VUR grade I–III with UTI proved microbiologically were randomly classified into two groups to receive either antibiotic prophylaxis (50 mg/kg cephalexin) daily or nothing at all for one year. The main outcome was symptomatic UTI confirmed by lab tests.
Results: A total of 60 children diagnosed with VUR grade I through III were enrolled in this study; At least five (17%) symptomatic UTI reported in 29 patients receiving antibiotic prophylaxis and four (12%) in 31 patients receiving no antibiotics at all. Results revealed that continuing and low-dose antibiotic prophylaxis does not significantly reduce the risk of symptomatic UTI in children with mild to moderate VUR.
Conclusion: The use of antibiotic prophylaxis in preventing recurrent infections and kidney scar formation in children with VUR grade I-III is not supported by this study.

Introduction

The backward flow of urine from the bladder to the ureters and kidneys during urination or storage is called vesicoureteral reflux (VUR). It is a predominant risk factor for renal scar formation in children presenting with urinary tract infection (UTI). Five years old children or younger with UTI have a high reflux probability with an approximate incidence of 25%–40% [1]. These patients are at risk of pyelonephritis or kidney scars, which may progress to reflux nephropathy and end-stage renal damage [2]. VUR increases the risk of pyelonephritis and kidney scar formation, which may progress to secondary complications such as chronic kidney disease, hypertension, and pregnancy side effects [3]. Abnormal ureteric bud development in the gestational period leads to abnormal ureterovesical junction valve formation and, therefore, primary VUR progression [3]. Secondary VUR is caused by functional or anatomical abnormalities such as bladder-bowel dysfunction, spastic bladder, and posterior urethral valve [4]. Voiding cystourethrography (VCUG) is the gold standard modality for diagnosis and grading of VUR and other bladder problems as parts of the evaluation of both lower and upper urinary tract. It is mainly used in small infants and children [5]. Contrast VCUG determines five grades of VUR, which are used to predict the disease prognosis and reflux resolution. In a study of 2,462 patients with VUR, the grade distribution was reported as follows: 6% grade I, 28% grade II, 51% grade III, 11% grade IV, and 4% grade V [6]. Many treatments for children with VUR have been used through years such as anti-reflux (endoscopic, laparoscopic) or open surgery and continuous antibiotic prophylaxis (CAP). CAP reduces the risk of retrograde upper UTI by keeping the urine sterile. Since most of the reflux cases will resolve by itself, many authors recommend conservative treatment, i.e., CAP as the primary management option in

[*]*Correspondence to: Anoush Azarfar, M.D., Kidney Transplantation Complications Research Center, Mashhad University of Medical Sciences, Mashhad, Iran; Tel: 989153017977; Fax: 05138709201; E-mail: azarfara@mums.ac.ir; ORCID: 0000-0002-2026-3495*

http://dx.doi.org/10.31487/j.CEI.2020.02.02

children, reserving invasive treatments for those patients resistant to CAP [7]. There is still controversy and treatment-related variability in VUR management among clinicians [8]. Despite the increasing application of antibiotic for the past forty years, its efficacy has been stayed unclear. Several prospective controlled trials from 2006 to 2008 were unable to show the role of CAP in UTI prevention compared to controls alone [9-11]. However, studies conducted by Craig *et al.* and Brandstrom *et al.* showed the efficacy of CAP, although its benefits were modest (absolute risk reduction of only 6%) and limited to girls less than two years with grades III and IV of the disease [12, 13].

Materials and Methods

This article is a prospective study of prophylactic cephalexin in children diagnosed with grade I-III VUR. Briefly, we registered 60 children aged 2 to 71 months with grade I through III unilateral or bilateral VUR after a first or second febrile or symptomatic UTI. They were selected from those admitted to or attending the Division of Pediatric Nephrology Clinic of Sheikh Hospital. The study protocol was approved by the Institute Ethical Committee of Mashhad University of Medical Sciences with registration number IR.MUMS.REC.1392.301, and informed consent form containing information about the disease, the trial drug, the protocol and duration of treatment was obtained from the parents or legal representatives of all children. Of them, 29 were under Cephalexin prophylaxis treatment, and 31 did not receive any antibiotics. Demographic information such as age, gender, and other findings like urinalysis, reflux grade, sonographic demonstrations, dimercaptosuccinic acid (DMSA) scan, and relapsing situations was recorded. Primary exclusion criteria included unwillingness to participate in the study, grade IV and V VUR, kidney scar in DMSA scan, significant hydronephrosis more than 15 mm, comorbid urologic anomalies (ureterocele, posterior urethral valve, solitary kidney, multicystic dysplastic kidney, spasmodic bladder, pelvic or fused kidney), contraindications for prescribing cephalexin, and other medical conditions. Patients were followed for one year, from September 2013 to October 2014, to ascertain recurrent febrile or symptomatic UTI and antibiotic prophylaxis failure measurement. Patients were categorized into two groups: 29 receiving prophylactic oral cephalexin, 50 mg/kg every night, as their usual regime, and 31 receiving no antibiotics at all. Urine specimens were collected monthly via catheterization among non-toilet-trained children and clean voided specimens in toilet-trained children. We required a urine culture producing a single micro-organism that was not lactobacillus or candida, at $\geq 5 \times 10^4$ /ml for catheterized urine specimens or $\geq 10^5$ /ml for clean voided specimens. Symptomatic UTI was diagnosed with abdominal or flank pain, urinary urgency, frequency or hesitancy, dysuria, and malodorous urine or in infants less than4 months of age, failure to thrive, dehydration, or hypothermia. Diagnostic criteria consist of positive evidence of pyuria on urinalysis, positive urine culture, and fever (≥38℃) or urinary tract symptoms within 24 hours before or after urine collection. The outcome was CAP efficacy in preventing UTI recurrence.

Results

Among the total of 60 children diagnosed with grade I through III VUR, 29 patients (48.3%) were categorized in group A (receiving antibiotics every night) and 31 (51.7%) in group B (receiving no antibiotics at all). Their mean age at diagnosis time was 3.35±2.04 years, and the male-to-female ratio was 38.3:61.7. The VUR grade at the time of diagnosis was I to III, in 15 (25%), 31 (51.7%), 14 (23.3%) cases, respectively (Table 1). Bilateral VUR in groups A and B were observed in 9 (31%) and 12 (38.7%) children, respectively (Table 2). The most frequent pathogens in urine culture were E.coli (56.0%), Enterococcus (17.5%), Klebsiella (11.6%), and Enterobacter (7.2%), Proteus (5.6%), and Pseudomonas (2.1%).

Table 1: VUR grade.

Grade	Group A	Group B	Total
I	6 (20.7%)	9 (29%)	15 (25%)
II	15 (51.7%)	16 (51.6%)	31 (51%)
III	8 (27.6%)	6 (19.4%)	14 (24%)
Total	29 (48.3%)	31 (51.7%)	60 (100%)

Table 2: Bilateral and unilateral reflux.

Reflux	Group A	Group B	Total
Bilateral	20 (69%)	19 (61.3%)	39 (65%)
Unilateral	9 (31%)	12 (58.7%)	21 (35%)

Of 60 children, 12(20%) had abnormal sonography reports, and 11(18.3%) had abnormal DMSA scans (Table 3 and 4, respectively). Among all participants, 9 (15%) patients showed one or more relapse episodes, and 6 (10%) did not inform. The relapse rate in group A was 5 (17.2%), and group B was 4 (12.9%). Table 5 demonstrates the relapse rates in detail. In those who had grade I reflux, the recurrence rate in group A was one (50%) as well as in group B. No recurrence reported in four patients (40%) in group A and six (60%) in group B. one participant (33.3%) in group A and two (66.6%) in group B did not inform us about their disease status. Considering the equation of relapse in both groups, there were no significant differences between them (P-value=1.000). Table 6 shows the recurrence rate in patients with grade I reflux.

Table 3: Sonography report.

Sonography report	Group A	Group B	Total
Normal	24 (82.8%)	24 (77.4%)	48 (80%)
Abnormal	5 (17.2%)	7 (22.6%)	12 (20%)

Table 4: DMSA scan.

DMSA report	Group A	Group B	Total
Normal	24 (82.8%)	25 (80.6%)	49 (81%)
Abnormal	5 (17.2%)	6 (19.4%)	11 (19%)

Table 5: Relapse rate.

	Group A	Group B	Total
With relapse	5 (17.2%)	4 (12.9%)	9 (15%)
Without relapse	21 (72.4%)	24 (77.4%)	45 (75%)
Did not inform	3 (10.3%)	3 (9.7%)	6 (10%)

Table 6: Recurrence rate in grade I reflux.

Urinary tract infection	A	B	Total
Yes	1 (50%)	1 (50%)	2 (13%)
No	4 (40%)	6 (60%)	10 (66%)
Did not inform	1 (33.3%)	2(66.6%)	3 (20%)

In patients with grade II reflux, the recurrence rate in group A was three (60%) and two (40%) in group B. No recurrence reported in 10 patients (43.47%) in group A and 13 (56.52%) in group B. two participants (66.6%) in group A and one (33.3%) in group B did not inform us about their disease status. Regarding P-value=0.595, the difference between the two groups was not significant. Table 7 demonstrates the recurrence rate in grade II reflux.

Table 7: Recurrence rate in grade II reflux.

Urinary tract infection	A	B	Total
Yes	3 (60%)	2 (40%)	5 (16%)
No	10 (43.5%)	13 (56.5%)	23 (74%)
Did not inform	2 (66.6%)	1 (33.3%)	3 (10%)

Table 8: Recurrence rate in grade III reflux.

Urinary tract infection	A	B	Total
Yes	1 (50%)	1 (50%)	2 (14%)
No	7 (58.3%)	5 (41.7%)	12 (76%)

In patients with grade III reflux, as shown in (Table 8), the recurrence rate in group A was one (50%) as well as in group B. No recurrence reported in seven patients (58.3%) in group A and five (41.7%) in group B. All participants with grade III reflux informed us about their symptoms. Considering the equation of relapse in both groups, there were no significant differences between them (P-value=1.000).

We also evaluated the recurrence rate in different age groups and concluded that there is no significant difference between them (P-value=0.230). Table 9 demonstrates this evaluation in detail. Besides, we evaluated the recurrence rate of different genders. We found out there is no significant difference between males and females (P-value=0.286), which is probably because of the small number of samples. Table 10 demonstrates this evaluation in detail. Furthermore, participants with abnormal kidney sonography were checked out, and the recurrence rates in both groups were evaluated. There were no significant differences between the two groups (P-value=1.000). More information is given in (Table 11). Patients with abnormal DMSA scans were assessed, and the recurrence rates in both groups were evaluated. As one can see in (Table 12), there were no significant differences between the two groups (P-value=0.455).

Table 9: Recurrence rate in different age groups*.

Reflux grade	Recurrence rate	Age			Standard deviation
		minimum	maximum	mean	
I	2	1	1	1	0
II	5	1	6	2.2	2.16
III	2	2	3	2.5	0.70

*Kruskal-Wallis test.

Table 10: Recurrence rate in different gender.

gender	Reflux grade			total
	I	II	III	
Male	2	2	2	6
Female	0	3	0	3
Total	2	5	2	9

Table 11: Recurrence rate in participants according to sonographic findings.

Recurrence	Reflux grade		Total
	II	III	
Yes	2	1	3
No	5	4	9

Table 12: Recurrence rate in participants according to DMSA scan.

Recurrence	Reflux grade		Total
	II	III	
Yes	1	0	1
No	5	6	10

Discussion

CAP therapy in patients with VUR is controversial. Physicians prescribe CAPs due to different criteria because of the lack of high-quality information and conflicting outcomes from articles. In one-year-old children or younger with VUR and a past medical history of UTI with fever or with high-grade VUR (III–V) diagnosed by screening, CAP is suggested by the 2010 American Urological Association guidelines. In patients, less than one-year-old with asymptomatic VUR grade I–II and no past medical history of UTI and fever, CAP may be offered [14]. After the initial evaluation of the articles, the CAP was suggested to be beneficial only in patients with VUR grade III/IV. Nevertheless, by adding the data from the 2014 Randomized Intervention for Children with Vesicoureteral Reflux study, the new data supported CAP therapy in all children diagnosed with VUR in order to reduce recurrent UTIs in all reflux grades. Four RCTs suggested that CAP therapy in VUR patients reduced UTI in about 37% of cases, which was in contrast with our study. Another RCT on 225 patients (156 girls and 69 boys, aged between one to 36 months) with low-grade VUR (I–III) randomly categorized them to receive either co-trimoxazole every day or nothing for 18 months [11].

They reported no significant differences in the UTI recurrence rate between the two groups (17% with CAP vs. 26% without; p=0.2). Though, the subsequent analysis demonstrated that CAP could reduce the UTI recurrence rate in boys (p=0.013), particularly in patients with higher-grades (III) (p=0.042). Monthly urinalysis was also performed in children with no clinical symptoms to diagnose UTI, which may have overestimated the UTI recurrences rates. In another study, 203 children (128 girls and 75 boys, aged between one to two years) with moderate to severe VUR (grade III-IV) were randomly classified into three groups: CAP, endoscopic intervention, or surveillance [13]. They reported that febrile UTI was reduced in girls followed by CAP and endoscopic therapy: 19% (8/43) on CAP, 23% (10/43) on endoscopic therapy, and 57% (24/42) on surveillance (p=0.0002). Renal scar formation was more prevalent in patients with febrile UTIs than those without (22% vs. 3%; p<0.0001).

While CAP and endoscopic treatment were supposed to reduce UTI and renal scar formation in girls, in boys, non-significant event rates between the treatment groups were observed. In contrast to Roussey-Kessler, that evaluated low grades VUR children (I–III,) the Swedish study entered patients with higher grades of VUR (III-IV). The two excellent placebo-

controlled RCTs evaluating the role of CAP in VUR treatment are "the Prevention of Recurrent Urinary Tract Infection in Children with Vesicoureteral Reflux and Normal Renal Tracts" (PRIVENT) and "Randomized Intervention for the Management of Vesicoureteral Reflux" (RIVUR). PRIVENT trial results were published in 2009 [12]. In that RCT, 576 patients with a mean age of 14 months (369 girls and 207 boys) have participated. In 42% of them, VUR of all types has been observed, with at least grade III in 53%. Symptomatic UTIs that were confirmed by laboratory tests developed in 13% of patients under co-trimoxazole therapy versus19% in the control arm over 12 months (HR 0.61; p=0.02).

Although CAP demonstrated a moderate advantage in VUR treatment, the UTI risk reduction was reported to be 6%. Lately, the RIVUR trial was published in 2014, including 607 children with a mean age of 12 months (558 girls and 49 boys) and a wide variety of VUR grades (Grade I–IV), divided into co-trimoxazole and placebo [15]. They concluded that recurrent febrile UTI in the CAP group was significantly diminished (13%) compared to the control group (25%). CAP therapy advantage was more predominant in patients with underlying conditions such as bladder and bowel dysfunction (BBD) and in those who presented with a febrile UTI for the first time. Although the number of new renal scar formation was reported to be low and approximately similar in both groups (the CAP 12%, and control groups 10%). Pennesi *et al.* published an RCT on 100 children aged between one day to 30 months (52 girls and 48 boys) with VUR grade II-IV after their first episode of acute pyelonephritis [10]. They followed up patients for two years and reported no statistically significant differences concerning recurrent pyelonephritis between the CAP (36%) and control (30%) groups, as well as no differences in the rate of subsequent UTIs and renal scar formation.

Montini *et al.* categorized 338 patients aged between two months to seven years (234 girls and 104 boys) to either CAP therapy (co-trimoxazole or co-amoxiclav) for 12 months or placebo after their first febrile UTI [9]. The analysis revealed no significant difference in the recurrence of febrile UTI between the two groups (CAP 7%and control 9%). The multicenter RCT conducted by Garin *et al.* randomized 218 children (aged between three months to 18 years) with a medical history of pyelonephritis and grade I–III VUR to CAP (nitrofurantoin or co-trimoxazole) and control groups [16]. A year later, they reported that VUR did not significantly increase the UTI recurrence rate or renal scar formation on DMSA scan. Hari *et al*. classified 93 children aged between one to 12 years (31 girls and 62 boys) with VUR Grade I–IV to either receive co-trimoxazole or no antibiotic at all for one year [17]. Like what Garin *et al.* reported, they concluded that CAP might be damaging due to its increased risk of symptomatic UTIs (21%) in the CAP group compared to control (7%; HR 3.9; p=0.02). Renal scans at 12 months revealed the same rates of developing new scars or worsening of existing ones for both groups (CAP 16% vs. placebo 16%). Therefore, they reported that long-term CAP therapy could increase the risk of symptomatic UTI compared to placebo.

Conclusion

Although researches showed that CAP could reduce UTI risk in some patients, not all of them will benefit. Attempts to recognize children at risk of recurrent UTIs who are the best options for CAP therapy have been made and will generate the evidence to guide clinical practice. In our study, after one year of follow-up, grade I-III VUR did not increase UTI recurrence rate, or renal scar formation after acute pyelonephritis. In conclusion, urinary antibiotic prophylaxis in lowering the incidence of UTI and the development of renal scar formations is not supported by this study.

Main Points

The authors finally indicated that continuous antibiotic prophylaxis in children diagnosed with vesicoureteral reflux disease grade I to III did not reduce infection recurrent rate and renal scar development.

Conflicts of Interest

None.

Acknowledgment

This study was supported by a grant from the Vice Chancellor of Research at Mashhad University of Medical Sciences.

REFERENCES

1. Kjell Tullus (2015) Vesicoureteric reflux in children. *Lancet* 385: 371-379. [Crossref]
2. Valentina Pastore, Fabio Bartoli (2017) Urinary excretion of EGF and MCP-1 in children with vesico-ureteral reflux. *Int Braz J Urol* 43: 549-555. [Crossref]
3. Ted Lee, John M Park (2017) Vesicoureteral reflux and continuous prophylactic antibiotics. *Investig Clin Urol* 58: S32-S37. [Crossref]
4. Khoury A, Bagli D, Wein A, Kavoussi L, Novick A et al. (2012) Contributors. In: Campbell-Walsh Urology.
5. Anahita Alizadeh, Maryam Naseri, Yalda Ravanshad, Shahabaddin Sorouri, Malihe Banihassan et al. (2017) Use of sedative drugs at reducing the side effects of voiding cystourethrography in children. *J Res Med Sci* 22: 42. [Crossref]
6. Carlos R Estrada Jr, Carlo C Passerotti, Dionne A Graham, Craig A Peters, Stuart B Bauer et al. (2009) Nomograms for predicting annual resolution rate of primary vesicoureteral reflux: results from 2,462 children. *J Urol* 182: 1535-1541. [Crossref]
7. Hsin-Hsiao S Wang, Rasheed A Gbadegesin, John W Foreman, Shashi K Nagaraj, Delbert R Wigfall et al. (2015) Efficacy of antibiotic prophylaxis in children with vesicoureteral reflux: systematic review and meta-analysis. *J Urol* 193: 963-969. [Crossref]
8. Jonathan C Routh, Caleb P Nelson, Dionne A Graham, Tracy A Lieu (2010) Variation in surgical management of vesicoureteral reflux: influence of hospital and patient factors. *Pediatrics* 125: e446-e451. [Crossref]
9. Giovanni Montini, Luca Rigon, Pietro Zucchetta, Federica Fregonese, Antonella Toffolo et al. (2008) Prophylaxis after first febrile urinary tract infection in children? A multicenter, randomized, controlled, noninferiority trial. *Pediatrics* 122: 1064-1071. [Crossref]
10. Marco Pennesi, Laura Travan, Leopoldo Peratoner, Andrea Bordugo, Adriano Cattaneo et al. (2008) Is antibiotic prophylaxis in children with

vesicoureteral reflux effective in preventing pyelonephritis and renal scars? A randomized, controlled trial. *Pediatrics* 121: e1489-e1494. [Crossref]

11. G Roussey-Kesler, V Gadjos, N Idres, B Horen, L Ichay et al. (2008) Antibiotic prophylaxis for the prevention of recurrent urinary tract infection in children with low grade vesicoureteral reflux: results from a prospective randomized study. *J Urol* 179: 674-679. [Crossref]
12. Jonathan C Craig, Judy M Simpson, Gabrielle J Williams, Alison Lowe, Graham J et al. (2009) Antibiotic prophylaxis and recurrent urinary tract infection in children. *New Engl J Med* 361: 1748-1759. [Crossref]
13. Per Brandström, Ulf Jodal, Ulla Sillén, Sverker Hansson (2011) The Swedish reflux trial: review of a randomized, controlled trial in children with dilating vesicoureteral reflux. *J Pediatr Urol* 7: 594-600. [Crossref]
14. Craig A Peters, Steven J Skoog, Billy S Arant Jr, Hillary L Copp, Jack S Elder et al. (2010) Summary of the AUA guideline on management of primary vesicoureteral reflux in children. *J Urol* 184: 1134-1144. [Crossref]
15. Alejandro Hoberman, Russell W Chesney, RIVUR Trial Investigators (2014) Antimicrobial prophylaxis for children with vesicoureteral reflux. *New Engl J Med* 371: 1072-1073. [Crossref]
16. Eduardo H Garin, Fernando Olavarria, Victor Garcia Nieto, Blanca Valenciano, Alfonso Campos et al. (2006) Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. *Pediatrics* 117: 626-632. [Crossref]
17. Pankaj Hari, Smriti Hari, Aditi Sinha, Rakesh Kumar, Arti Kapil et al. (2015) Antibiotic prophylaxis in the management of vesicoureteric reflux: a randomized double-blind placebo-controlled trial. *Pediatric Nephrol* 30: 479-486. [Crossref]