



# Long-term Effectiveness of Amoxicillin Prophylaxis for Children with Primary Vesicoureteral Reflux

## Primer Vezikoüreteral Reflü Profilaksisinde Amoksisilinin Uzun Dönem Etkinliğinin Değerlendirilmesi

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### Abstract

**Aim:** The use of antibiotic prophylaxis in the conservative treatment of vesicoureteral reflux (VUR) has a long historical precedent. In this study, we investigated the long-term efficacy of amoxicillin as antibiotic prophylaxis.

**Material and Method:** A retrospective investigation was conducted to examine the clinical characteristics and follow-up results of patients with VUR who received amoxicillin prophylaxis for at least of six months.

**Results:** A total of 44 patients were included in the study, comprising 13 girls (29.5%) and 31 boys (70.5%), with a mean age of  $2.9\pm 1.3$  months. During a mean follow-up period of  $27.4\pm 19.4$  months, nine patients (20.5%) experienced one urinary tract infection (UTI), while two patients (4.5%) had a febrile UTI. Antibiotic revision was performed in a total of four patients (9%), including two patients with a febrile UTI and two patients with gastrointestinal side effects.

**Conclusion:** The long-term follow-up of patients with VUR who have been treated with amoxicillin prophylaxis has demonstrated that this is an effective and safe treatment option.

**Keywords:** Vesicoureteral reflux, urinary tract infection, amoxicillin

### Öz

**Amaç:** Vezikoüreteral reflü (VUR)'un konservatif tedavisinde antibiyotik profilaksisi uzun zamandan beri kullanılmaktadır. Bu çalışmada antibiyotik profilaksisi olarak amoksisilinin uzun dönem etkinliği araştırıldı.

**Gereç ve Yöntem:** VUR tanısı ile takip edilen ve en az 6 ay ve daha uzun süre amoksisilin profilaksisi alan hastaların klinik özellikleri ve izlem sonuçları retrospektif olarak araştırıldı.

**Bulgular:** Çalışmaya 13'ü kız (%29.5), 31'i erkek (%70.5) olmak üzere 44 hasta alındı ve yaş ortalaması  $2.9\pm 1.3$  aydı. Ortalama  $27.4\pm 19.4$  ay takipte 9 hastada (%20.5) bir kez idrar yolu enfeksiyonu (İYE) ve 2 hastada (%4.5) ateşli İYE tespit edildi. İki hasta ateşli İYE, 2 hastada ise gastrointestinal yan etkiler olmak üzere toplam 4 hastada (%9) antibiyotik revizyonu yapıldı.

**Sonuç:** VUR'lu hastaların amoksisilin profilaksisi ile uzun dönem takibi etkili ve güvenilir bir tedavi seçeneğidir.

**Anahtar Kelimeler:** vezikoüreteral reflü, idrar yolu enfeksiyonu, amoksisilin



## INTRODUCTION

Vesicoureteral reflux (VUR) is one of the most prevalent congenital urologic anomaly of the urinary tract, occurring in 1% of newborns and serving as a substantial risk factor for renal scarring. The prevalence of renal scarring has been documented to range from 36% to 56% in children with a history of urinary tract infection (UTI) and VUR.<sup>[1]</sup> VUR is present in 30 to 40 percent of children investigated for UTI.<sup>[2]</sup> The primary objective in the management of VUR is to prevent the patient from developing a febrile UTI and renal parenchymal scarring. Over the past 20 to 30 years, there has been a notable shift in approach from more aggressive surgical intervention to a more conservative management strategy. Studies have demonstrated that there is no notable discrepancy between the surgically and conservatively treated groups in terms of new renal scar formation or scar progression.<sup>[3,5]</sup> The initial preference for all degrees of reflux is to assess the potential for spontaneous resolution with conservative treatment. In the conservative approach, follow-up or antimicrobial prophylaxis is applied in accordance with the degree of VUR and the patient's clinical status.

The most commonly utilized agents in prophylaxis are trimethoprim-sulfamethoxazole, amoxicillin, and nitrofurantoin. Trimethoprim-sulfamethoxazole is the preferred antibiotic for prophylaxis, but its primary disadvantage is its high rate of antibiotic resistance and contraindication in infants under two months of age.<sup>[6]</sup> In infants under two months of age, amoxicillin is frequently the initial agent of choice for antibiotic prophylaxis. However, in the subsequent period, it is often replaced with trimethoprim-sulfamethoxazole, despite the absence of definitive clinical evidence to support this practice. The optimal duration of amoxicillin prophylaxis remains uncertain. Consequently, this study aimed to assess the efficacy of amoxicillin prophylaxis and to determine the safest duration for its use in patients with primary VUR.

## MATERIAL AND METHOD

In this study, the medical records of 285 patients with primary VUR who were followed up at pediatric nephrology clinic were retrospectively analyzed. The study included patients who had received amoxicillin prophylaxis for at least of six months. In order to be eligible for antibiotic prophylaxis, patients were required to have either dilated VUR or low-grade VUR, in addition to a history of UTI. Patients with other concomitant urologic abnormalities (obstructive uropathy, neurogenic bladder) and those receiving amoxicillin prophylaxis for less than six months were excluded from the study. The demographic characteristics, grade of VUR, scintigraphy findings, duration of follow-up, and UTIs during follow-up were recorded from the files. The diagnosis of UTI was made in cases with pyuria (>5 white blood cells per high power field) and/or nitrite positivity in urinalysis

by urine culture using the catheter or clean catch method. Positive urine culture was defined as 10.000 colonies in a catheterized sample or >50.000 colonies in a clean catch sample.<sup>[7,8]</sup>

The diagnosis of VUR was made via voiding cystourethrogram, and grading was conducted in accordance with the international reflux grading system. In cases where the reflux was bilateral, the grade was determined by averaging. A grade III or above was defined as dilated VUR. Renal parenchymal abnormalities were evaluated using dimercaptosuccinic acid (DMSA) scintigraphy. The study was approved by the local ethics committee (2023/11).

Statistical Method; Descriptive analyses included means and standard deviations (SD) of continuous variables and distributions of categorical variables. Chi-square test was used to compare categorical variables. The overall level of significance was set at 0.05. Statistical analyses were done using the SPSS 24.0 (IBM Inc.) statistical package.

## RESULTS

A total of 44 patients who met the established criteria were included in the study. The cohort consisted of 13 female (29.5%) and 31 male (70.5%) patients, with a mean age of  $2.9 \pm 1.3$  months (**Table 1**). A history of previous UTI was present in 24 patients (54.5%), while 20 patients (45.5%) had a history of febrile UTI. Among the patients with a history of UTI, 10 were female (76.9%) and 14 were male (45.2%), and no statistically significant difference was observed between the two groups ( $p=0.053$ ). The prevalence of dilated VUR was 77.3% ( $n=34$ ), with a statistically significant higher incidence in males ( $p=0.025$ ). Among these patients, 7 (53.8%) were female and 27 (87.1%) were male. During the follow-up period, nine patients (20.5%) experienced one episode of UTI, and two patients (4.5%) had a febrile UTI. A total of four patients (9%) underwent antibiotic revision, including two patients with febrile UTI and two patients with diarrhea. The mean duration of amoxicillin use was  $15.9 \pm 10.1$  months (range: 6-48 months), with a mean follow-up period of  $27.4 \pm 19.4$  months (range: 6-69 months).

**Table 1. Clinical and demographic characteristics of the patients**

Age (month)	2.9±1.3
Gender (Male:Female)	13:31
Antenatal Hydronephrosis	22 (50%)
Dilated VUR	34 (77.3%)
Bilateral VUR	25 (56.8%)
Renal Scarring	7 (7.3%)

## DISCUSSION

A review of recent studies indicates that there is no significant difference between conservative and surgical treatment of VUR in terms of the formation of scar tissue. In all cases of reflux, the initial approach should be to assess the potential

for spontaneous resolution through conservative treatment.<sup>[2]</sup> In the conservative approach, follow-up or antimicrobial prophylaxis is applied according to the degree of VUR and the patient's clinical status. In the European Urological Association guidelines, follow-up with prophylaxis is recommended as the initial treatment for children aged 1-5 years with grade III-V VUR.<sup>[5,7]</sup> In our study, 77% of the patients had dilated VUR and were followed up with antibiotic prophylaxis from the outset.

The randomized intervention for children with VUR (RIVUR) study demonstrated that the incidence of recurrent UTIs was 50% lower in the group that received prophylaxis compared to the placebo group.<sup>[8]</sup> In the Swedish Reflux study, antibiotic prophylaxis was compared with endoscopic injection and observation in children with VUR, and it was found that the incidence of recurrent UTI was significantly lower in girls who received antibiotic prophylaxis than in those who received observation.<sup>[9]</sup> Furthermore, these studies demonstrated that delayed treatment of UTIs was associated with an increased risk of renal scarring. In our study, 45.5% of patients had a history of febrile UTI prior to prophylaxis, whereas only 4.5% had febrile UTI at follow-up.

Advantage of antibiotics used in prophylaxis is that their active form or metabolites are excreted in the urine, thus keeping the urine free of bacteria. Trimethoprim-sulfamethoxazole is contraindicated in infants under 2 months of age and in newborns due to liver toxicity. Amino penicillins are the drugs of choice for the treatment of enterococcal urinary tract infection and can be used for prophylaxis in infants younger than 2 months of age. The bioavailability of amoxicillin is better than ampicillin.<sup>[12]</sup> There is insufficient information in the literature about the long-term use of amoxicillin prophylaxis and its effects. In our study, prophylactic amoxicillin use for a mean of 15.9 months was largely successful in preventing UTI and was generally well tolerated. During follow-up, amoxicillin was discontinued and trimethoprim-sulfamethoxazole was switched to amoxicillin in a total of 4 patients (9%), including 2 patients with febrile UTI and 2 patients with gastrointestinal side effects. Based on these results, long-term amoxicillin prophylaxis seems to be an effective and safe treatment option. In addition, it is an advantage to start treatment with a narrower spectrum agent in terms of possible resistance development.

There are some limitations in our study. First, there may be bias due to the retrospective nature of the study. Second, the number of patients is relatively small. Nevertheless, considering the mean follow-up and treatment times, it can be considered that the study may make a significant contribution to the treatment of VUR.

## CONCLUSION

In patients diagnosed with VUR in the infantile period who have been initiated on prophylaxis with amoxicillin, the continuation of this treatment option in the future has been demonstrated to be effective and safe.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was obtained from Karamanoğlu Mehmetbey University Clinical Researches Ethics Committee (Date: 27.02.2023, Decision No: 01-2023/11).

**Informed Consent:** All patients signed the free and informed consent form.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

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**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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