

# Clinical management of vesicoureteral reflux with respect to EAU Guidelines: A multicenter study

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## Abstract

**Purpose:** We designed a multicenter, retrospective study to investigate the current trends in initial management of reflux with respect to EAU guidelines in Urology clinics of our country. **Materials and Methods:** The study group consisted of 1988 renal units (RU) of 1345 patients treated surgically due to VUR between years 2003-2017 in 9 different institutions. Patients were divided into 2 groups according to time of initial treatment and also grouped according to risk factors by “EAU guidelines on VUR”. **Results:** 1426 RUs were treated initially conservatively and 562 RUs were initially treated with surgery. In initially surgically treated group, success rates of surgery decreased significantly in low and moderate risk groups after 2013 ( $p=0.046$ ,  $p=0.0001$ , respectively), while success rates were not significantly different in high risk group ( $p=0.46$ ). While 26.6% of patients in low risk group were initially surgically treated before 2013, this rate has increased to 34.6% after 2013, but the difference was not statistically significant ( $p=0.096$ ). However, performing surgery as the initial treatment approach increased significantly in both moderate and high risk groups ( $p=0.000$  and  $p=0.0001$ , respectively) after 2013. Overall success rates of endoscopic and UNC operations were 65% and 92.9% before 2013, 60% and 78.5% after 2013, respectively. Thus the overall success rate for

surgery was 72.6%. There was significant difference between success rates of UNC operations before and after 2013( $p=0.000$ ), while the difference was not significant in the STING group ( $p=0.076$ ). Conclusion: Current trends in management of reflux in our country do not yet follow the EAU guidelines on VUR in low and moderate risk groups.

## **Title: Clinical management of vesicoureteral reflux with respect to EAU Guidelines:**

### **A multicenter study**

#### **Short title: Effect of EAU Guidelines on VUR management**

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#### **Clinical practice in vesicoureteral reflux with respect to EAU Guidelines: A multicenter study**

##### **Abstract**

**Purpose:** We designed a multicenter, retrospective study to investigate the current trends in initial management of reflux with respect to EAU guidelines in Urology clinics of our country.

**Materials and Methods:** The study group consisted of 1988 renal units (RU) of 1345 patients treated surgically due to VUR between years 2003-2017 in 9 different institutions. Patients were divided into 2 groups according to time of initial treatment and also grouped according to risk factors by “EAU guidelines on VUR”.

**Results:** 1426 RUs were treated initially conservatively and 562 RUs were initially treated with surgery. In initially surgically treated group, success rates of surgery decreased significantly in low and moderate risk groups after 2013 ( $p=0.046$ ,  $p=0.0001$ , respectively), while success rates were not significantly different in high risk group ( $p=0.46$ ). While 26.6% of patients in low risk group were initially surgically treated before 2013, this rate has increased to 34.6% after 2013, but the difference was not statistically significant ( $p=0.096$ ). However, performing surgery as the initial treatment approach increased significantly in both moderate and high risk groups ( $p=0.000$  and  $p=0.0001$ , respectively) after 2013. Overall success rates of endoscopic and UNC operations were 65% and 92.9% before 2013, 60% and 78.5% after 2013, respectively. Thus the overall success rate for surgery was 72.6%. There was significant difference between success rates of UNC operations before and after 2013( $p=0.000$ ), while the difference was not significant in the STING group ( $p=0.076$ ).

**Conclusion:** Current trends in management of reflux in our country do not yet follow the EAU guidelines on VUR in low and moderate risk groups.

**Keywords:** Vesicoureteral reflux; reflux risk grouping; reflux treatment management; EAU/ESPU guidelines on vesicoureteral reflux; pediatric urology

## Main Text

### Introduction

Vesicoureteral reflux(VUR) is the non-physiologic retrograde flow of urine from the bladder to the kidneys in children which can lead to pyelonephritis and secondary renal injury due to renal scarring [1]. Though it is a common urogenital abnormality in children with the prevalence of 0.4-1.8%, every stage of management of VUR is still under debate [2]. The clinical management of reflux includes observational, medical and surgical therapies. The surgical correction of reflux has been the mainstay approach in high grade reflux but generally it is not the sole objective of management considering the aims of treatment: to avoid the occurrence of urinary tract infections (UTI) and to avoid development of new renal scars [3]. Also the benefit and necessity of antibiotic prophylaxis in low grade reflux are under debate. Thus, management should be individualized and based on each patient’s age, gender, grade of reflux, presence of renal scar, clinical course, bilaterality, ipsilateral renal function, bladder dysfunction (related lower urinary tract symptoms (LUTS) such as urgency, urge incontinence, weak stream, hesitancy, frequency) and parental preference [4]. Patients who have both VUR and lower urinary tract dysfunction (LUTD) may have elevated risk of kidney damage and worse outcome after treatment [5]. If LUTD is detected in a reflux patient, it should be treated initially regardless choice of treatment method.

The “European Association of Urology (EAU) Guidelines on Vesicoureteral Reflux in Children (September 2012)” created a modified risk classification by analyzing and defining risk factors such as age, sex, reflux grade, LUTD, anatomic abnormalities, and kidney status for each patient. They grouped patients into three groups according to the risk classification and made recommendations for each group based on early risk assessment. The authors aimed to identify cases requiring immediate intervention or to avoid overtreatment in the spontaneous resolution expected patients or only requiring conservative therapy [6]. We hypothesized that the publication of guidelines altered the initial management approach to patients with VUR. Therefore, we designed a multicenter retrospective study to investigate the current trends in initial management of reflux with respect to EAU guidelines and their effect on results of treatments in our country. As a secondary outcome, this study tried to highlight the preoperative determinants of postoperative success rates of VUR correction techniques; either endoscopic treatment or open reimplantation.

### Material and Methods

The study group consisted of 1988 renal units (RU) of 1345 consecutive patients who were referred to 9 different urology clinics in all across our country and treated surgically due to VUR between years 2003-2017. The institutions that agreed to send their data for this study are composed of mostly members of European Society for Pediatric Urology (ESPU) and also members of Turkish Pediatric Urology Society and are in collaboration with each other and reference centers for treatment of pediatric urology patients in our country. Accordingly, the protocols for initial evaluation, treatment decisions and follow up were basically the same. The study was based on clinical registry and a data extraction form (Appendix 1) including parameters agreed by the board of Turkish Pediatric Urology Society was sent to all centers included in this study and gathered back for analysis. Thus all of the consecutive cases with available data and follow up were included. The main intention of the study was whether we followed the new guidelines for reflux and how did it affect our success.

Among all the referred 1345 consecutive patients 1426 (71.7%) RUs were treated initially conservatively and 562 (28.2%) RUs were initially treated with surgery. Mean time elapsed between initial treatment and operation was 16.67 months (1-192).

Diagnostic evaluation included medical history (age, sex, history of urinary tract infection, presence of LUTS), physical examination, urine culture, renal ultrasonography (USG) and voiding cystourethrography (VCUG). Demarcaptosuccinic acid scanning (DMSA) was used to affirm the parenchymal changes detected by USG or in patients with high grade reflux or history of acute pyelonephritis. Patients were treated regarding the institutional preference and categorized retrospectively according to the risk classification of EAU guidelines on VUR. Surgical indications were presence of additional ureteral anomaly, high grade reflux, gender, age beyond resolution-persistent reflux, breakthrough infections, renal scarring and noncompliance with medical management (especially for rural patients). Conservative treatment consisted of continuous antibiotic prophylaxis (CAP) and/or anticholinergic drugs. Dosages of antibiotics were 50-100 mg/kg/day for Ampicillin (<2 months old patients) and 2 mg/kg/day for Trimethoprim-Sulfamethoxazole (>2 months). All the patients beyond toilet training age were evaluated for LUTS and treated if needed prior to the choice of treatment method. LUTS of patients were treated with urotherapy (timed voiding, dietary manipulation for fluid intake and constipation and anticholinergics (mainly oxybutynin hydrochloride). In all patients endoscopic subureteric transurethral injection and/or open ureteral reimplantation were carried out to correct the reflux. Patients were divided into two groups according to time of initial treatment being before or after 2013 and also grouped according to risk factors under guidance of "EAU guidelines on Vesicoureteral Reflux in Children". Preoperative and postoperative data of patients with VUR were retrospectively reviewed. Preoperative clinical parameters such as age and gender of the patient, grade and laterality of reflux, presence of renal scar and lower urinary tract symptoms, initial and follow-up treatments and durations, outcomes of medical treatment and surgical procedures and postoperative data of patients were analyzed retrospectively. After treatment modalities patients were followed clinically by presence of symptoms, regular urine culture, USG and DMSA scan. Breakthrough infections, new renal scars on DMSA, reflux on VCUG (if performed) or additional complications like increase in hydronephrosis were accepted as surgical treatment failure. Postoperative VCUG was not routinely performed in all patients. The main indications for postoperative VCUG were new renal scar formation on DMSA scan and having breakthrough urinary tract infection. Statistical analysis was performed by SPSS ver. 15.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were compared using the chi-square test and regression analysis was carried out. Statistical significance was considered as  $p \leq 0.05$ .

## Results

The mean follow-up duration of the 1345 patients (1988 RUs) with the mean age of  $5.18 \pm 3.6$  (0-18) years, was 32 (1-184) months. 70% (941) percentage of patients was female and 30% (404) were male. 118 (8.8%) patients were known to have anatomic abnormalities like ureterocele, solitary kidney, ectopic ureter, Hutch or paraureteral diverticulum and most commonly duplications (3.7%). 35.8% (482) of patients were treated due to LUTD prior to the treatment of reflux. Renal scar was detected on preoperative DMSA scintigraphy in 64.2% (864) percentage of patients (defining at least a moderate risk according to guidelines.) The percentages

of patients with right, left sided and bilateral reflux were 18.7%, 33.4% and 47.8% respectively. 54.1 % of the renal units were presented with low grade reflux (grade 1-3), while 45.9% were high (grade 4-5). 811 (60.3%) patients initially referred with breakthrough urinary tract infection (Table 1).

Among the preoperative parameters, only the presence of renal scar on DMSA and treating lower urinary tract symptoms were found to determine the postoperative success rates significantly ( $p=0.002$ ,  $p=0.000$ ); while age, sex, grade of reflux, risk groups had no effect. (regression analysis results)

65 (3.3%) RUs were excluded in analysis of surgical treatment success due to lost to follow-up or insufficient data. Accordingly, 1238 (62.3%) RUs were treated with subureteric injection (STING) (533 unilateral; 705 bilateral) and 685 (34.4%) RUs with Cohen type ureteroneocystostomy (UNC) (199 unilateral; 486 bilateral). The percentages of both endoscopic and open reimplantations were 63.1%, 36.1% before 2013 and 61.2%, 32.3% after 2013, respectively. 353 (17.7%) children had urinary tract infection and 275 (13.8%) children had new renal scar formation on DMSA postoperatively. Also 83 children with new renal scar had postoperative urinary tract infection additionally. 67 (3.4%) patients had increasing hydronephrosis while persistent reflux was detected in 541 (27.2%) patients among ones who had postoperative VCUG. Success rates of endoscopic and UNC operations were 65% and 92.9% before 2013, 60% and 78.5% after 2013, respectively. Thus the overall success rate for surgery was 72.6%. There was significant difference between success rates of UNC operations before and after 2013( $p=0.000$ ), while the difference was not significant in the STING group ( $p=0.076$ ).

Then, the patients were grouped into three risk groups according to EAU VUR risk classification and percentages of the low, moderate and high risk groups were 18.9%, 52.6% and 28.5% respectively. The data were analyzed due to risk groups, time of diagnosis and initial treatment modalities. As stated before among all the referred 1345 consecutive patients 1426(71.7%) RUs were treated initially conservatively prior to surgery and 562(28.2%) RUs were initially treated with surgery on referral. Mean time elapsed between initial treatment and operation was 16.67 months (1-192). In initially surgically treated group, success rates of surgery decreased significantly in low and moderate risk groups after 2013 ( $p=0.046$ ,  $p=0.0001$ , respectively), while success rates were not significantly different in high risk group ( $p=0.46$ ) (Table 2). The overall success rate in initially surgically treated group before 2013 was 80.9%. That was decreased to 70.5% after 2013 ( $p=0.004$ ).

While 26.6% of patients in low risk group were surgically treated before 2013, this rate has increased to 34.6% after 2013, but the difference was not statistically significant ( $p=0.096$ ). However, performing surgery as the initial treatment approach increased significantly in both moderate and high risk groups ( $p=0.000$  and  $p=0.0001$ , respectively) after 2013. Thus, we can say that there was increased preference for surgical treatment initially in moderate and high risk groups after 2013 (Table 3).

Among the patients with low grade 1-2 reflux (Grade 1-2), only one patient had UNC and 71 patients had subureteric injection initially. During follow up, the total number of patients who had subureteric injection had risen to 206 while 20 patients had UNC. The mean time between the initial treatment and surgical intervention was 14.2 months and the mean follow-up duration of this group was 24.8 months. 69.5 % percentage of these low grade VURs had successful clinical outcomes after surgery.

## Discussion

Despite the optimal management of reflux has been discussed over more than thirty years several times in the literature, it is still contradictory which type of treatment, medical or surgical is superior [1]. The main two aims of treating reflux is to avoid the development of new renal scars and to avoid the urinary tract infections in attempt to preserve kidney function [3]. From past to present treatment management has been based on age, sex, presence of renal scar, grade of reflux, laterality of reflux, presence of bladder dysfunction and toilet training. Starting from this contradiction about treatment of reflux, EAU published guidelines on VUR in second half of 2012 [6]. In the guidelines patients are grouped into three groups, according to being symptomatic/asymptomatic, gender, before or after toilet training (age), grade of reflux, presence of LUTD and kidney status. As well, initial and follow up treatment methods are suggested for each group.

According to EAU guidelines the hallmarks of low risk disease are normal kidneys, low grade reflux (grade 1-3) and absence of LUTD. In the low risk group, there are two options of initial treatment: either no treatment or CAP, similar to the AUA guidelines [6, 7]. In the classical and new guidelines, surgery is not offered to patients with grades 1-2 reflux, in the absence of breakthrough infections or new renal scars. With a minor difference in classical view, grade 3 reflux was not accepted as low grade and surgery was an option if persistent after 5 years of age [8]. Although it is not recommended to do surgery initially in low risk group, use of CAP in every reflux patient or observational management in primary reflux is still controversial. There are several studies declaring the efficacy of CAP, such as the well-known randomized studies; the PRIVENT study, the RIVUR study and Swedish Reflux Trial [9-14]. Nevertheless, a large number of studies supporting the insignificant difference between CAP and observational management in VUR were also carried out [15-18]. In our study, CAP was preferred in the initially conservatively treated group rather than no treatment. However, despite the guidelines there might be increased tendency to surgical interventions in the low risk group after 2013 but not significant.

In the moderate risk group, CAP is the offered initial treatment method and intervention may be considered in case of breakthrough infections and persistent reflux. Also LUTD treatment should be given if needed. In all groups treatment for LUTD was given initially and it was seen to be effective on clinical success of reflux treatment. In our study, performing surgery as initial treatment approach increased significantly in the moderate group after 2013 that might be partially related to the parental incompliance.

Increased surgical preference (UNC/endoscopic) as an initial treatment method in low (it was not significant though) and moderate risk groups might seem controversial but considered to reflect our cultural attitude towards definitive treatment. Initial preference of surgical treatments in these low grade refluxes (72 patients) representing incompatibility with the EAU guidelines, could be attributed to parental preference and patients coming from rural areas because of difficult follow up. The centers included in the study are referral centers and the patients usually come from distant regions. Thus the follow up could be problematic. The increase could also be attributed to increased surgical expertise and confidence in pediatric urology practice over the years in our country. In addition, our study has a retrospective design and nine clinics were included from different parts of the country. Due to the fact that pediatric urologists from different centers might have different treatment tendencies for the patient with similar clinical variables, this could be another reasonable explanation for the increased preference for surgical treatment modalities. In the study by Prisca et al. parental incompliance was a negative predictive factor in VUR resolution and these patients had a worsening tendency because of being un-followed. The authors proposed that parental compliance should be considered in EAU guidelines application[19].

The high risk disease is defined as high grade reflux (grade 4-5) and abnormal kidneys and the initial treatment is mostly suggested surgical in the EAU guidelines (greater possibility or may be considered) and definitely surgical in classical management strategies. In the high risk groups, the priority of open surgery, after the treatment of LUTD if needed (in symptomatic cases after toilet training with high grade reflux and abnormal kidney) [6]. In our study we determined increased preference of surgical treatments as initial method in the high risk group after 2013. This is usual and in concordance with the guidelines. The result was in compliance with the recommendations of the guidelines. Consequently, there was preference of surgical methods in all groups after 2013. Before 2013 we were classically treating patients surgically according to age (being <1, 1-5 or >5), gender (female), grade of reflux, presence of additional ureteral anomaly and renal functions-renal scar on DMSA scan [8]. In the meantime, we accepted persistent reflux-hydronephrosis and new renal scar formation or breakthrough infections while the patient is under antibiotic prophylaxis as surgical indications in low-moderate risk groups.

Success rates of treatment in high risk group were not different after 2013, because of the same attitude towards the more successful UNC before and after 2013. In low and moderate risk groups guidelines prefer conservative methods first and if necessary surgery as the next step. However, performing surgery as the initial treatment approach increased in all groups after 2013 as patients were increasingly referred from rural areas (risk of lost to follow up and parental preference). The decreased success rate after 2013 in

initially surgically treated group could be attributed to multiple factors. Pediatric urology is still evolving in our country within time and all the institutions included in this study are training centers. Thus there is increasing variability and divergence in treatment attitudes among regions effecting success rates throughout the country. There is surely increasing population and immigration in our country and easy transportation facilities have been causing increased referral. This decrease in success rate should alert us about more serious consideration and concordance with the new EAU guidelines on VUR. These factors might be also related to our overall surgical success rate for reflux surgery (both endoscopic and UNC) that was 72.6%. Success rates of endoscopic and UNC operations were 65% and 92.9% before 2013, 60% and 78.5% after 2013, respectively. Thus the overall success rate for surgery was 72.6%. There was significant difference between success rates of UNC operations before and after 2013( $p=0.000$ ), while the difference was not significant in the STING group ( $p=0.076$ ). This could be partly due to increased preference of surgical treatments as initial method in the high risk group after 2013. The high risk disease is high grade reflux (grade 4-5) that is usually treated with UNC and more technically demanding compared to UNC's done for lower grades of reflux. Also the centers included in the study were referral (complicated cases) and teaching institutions.

The main limitations of the study are being retrospective and multi-central. Thus, institutional preferences and success achievements could be variable. However, the study represents large number of patients and a wide and scattered spectrum of treatment attitude towards reflux treatment in our country. All the centers included known to be experienced in pediatric urology in our country and patients were accepted from pediatric nephrologists when the medical treatment fails thus the study reflects a selection bias for surgery. Pediatric nephrologists follow-up successful patients with medical therapy and refers urologists unsuccessful patients for the surgical option so this results in uneven distribution of the sample.

## Conclusions

As a conclusion current trends in management of reflux in our country do not yet follow the EAU guidelines on VUR in low and moderate risk groups. This might be due to several factors including parental preference, cultural attitudes, surgical expertise and approach of different pediatric urology clinics. As expected there is an increased tendency for initial surgical treatment in high risk groups in accordance with the EAU guidelines. The overall success rate could be low due to variability between clinics and reference of complex cases to the tertiary centers as well as inclusion of endoscopic surgery and increased preference of surgical treatments as initial method in the high risk group after 2013 as high risk disease is high grade reflux (grade 4-5) that is usually treated with UNC and more technically demanding compared to UNC's done for lower grades of reflux.

## Conflicts of Interest:

All authors disclose any potential conflict of interest.

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**Availability of data and materials:** All the data supporting our findings is contained in the manuscript. The datasets used and/or analysed in the current study is available from the corresponding author on reasonable request

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