

## Medical management of primary vesicoureteric reflux: A changing trend: Single institute experience with 45 patients (77 renal units) over 2 years

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### ABSTRACT

**Background:** The management of vesicoureteric reflux (VUR) has undergone a radical change from initial ureteric reimplantation to a more conservative approach. Several studies have demonstrated the validity of this concept by evaluating the role of antibiotic prophylaxis. Recent randomized trials have shown no proven benefits of long-term antibiotic prophylaxis. **Objective:** The objective of this article is to review the outcome of conservative management of VUR with antibiotic prophylaxis over a period of 2-year. **Materials and Methods:** A prospective observational study for 2 years was performed in children with primary reflux. They were given continuous antibiotic prophylaxis and regularly followed up every 3 months. Relevant investigations were performed at every follow-up including monitoring of growth parameters. Outcome in terms of recurrent urinary tract infection (UTI) episodes, resolution of VUR, need for definitive surgery were analyzed. **Results:** Out of initial 48 patients enrolled in the study, three patients were lost for follow-up. Out of 45 patients (77 renal units), most of the patients had Grade III and IV reflux. Scarring was seen predominantly in Grade IV reflux (62.5%). At the end of 2 years, no units demonstrated Grade I reflux. Grade II reflux persisted in 16.67%. Grade III reflux persisted in 23.68%, while Grade IV reflux persisted in 62.5%. Most of the fresh UTI episodes occurred in Grade III and IV VUR patients. Fresh renal scars were seen mostly in Grade IV group. One patient underwent ureteric reimplantation due to fresh renal scar and persistent reflux. **Conclusions:** Conservative management of VUR with antibiotic prophylaxis appears to be a suitable option without adverse outcomes. In the current scenario, surgery has a minor role to play in the treatment of VUR..

**Key words:** Vesicoureteric reflux, Antibiotic prophylaxis, Urinary tract infection

Approximately, 3-5% of girls and 1-2% of boys experience urinary tract infection (UTI) before puberty. Vesicoureteric reflux (VUR) is associated with higher rates (57%) of febrile UTI [1,2]. VUR is present in one-third of children presenting with febrile UTI and has been associated with a heightened risk of renal scarring [3]. The complex nature of the interaction between VUR and UTIs and their effects on the kidneys make the identification of those patients at risk for recurrent UTI and subsequent renal damage the biggest challenge in managing VUR.

Prediction of reflux resolution varies from patient to patient and may involve other factors than anatomic one. Once VUR has been diagnosed, the basic premise in management is to prevent further ascending UTI which may, if left untreated, lead to pyelonephritis which in turn, would lead to potential renal damage [4]. The potentially serious consequences at long term include hypertension and renal failure. The patients with VUR demonstrate a wide range of severity and a majority of reflux patients do not develop renal scars and probably will not need any intervention [5].

However, the role of antibiotic prophylaxis alone in these patients is still debatable when considering their efficacy in preventing recurrent UTI and renal scarring. The basis for antibiotic prophylaxis in patients with VUR was the fact that,

ultimately, reflux in low Grades (I-III) was recognized to resolve over time and thus maintenance on low dose antibiotic would prevent or reduce the risk of UTI until such time that the reflux would disappear. Faster resolution of VUR is more likely in children who are aged <1 year at presentation, have a lower grade of reflux (Grades I-III), and have an asymptomatic presentation with prenatal hydronephrosis or sibling reflux [5].

Long-term requirement, questionable efficacy, potential side effects, allergic reactions, and antimicrobial resistance are few issues that make role of antibiotic prophylaxis in VUR questionable. Few trials have compared anti-reflux surgery with antimicrobial prophylaxis and showed no significant differences in the rates of recurrent UTI and renal scarring. Incidence of surgical management in these patients is showing a declining trend with more patients being managed conservatively. Here, we present our experience with conservative management of VUR with antibiotic prophylaxis over the last 2 years.

### MATERIALS AND METHODS

This prospective observational study was carried out from June 2014 to May 2016. Patients were enrolled in the study after

appropriate parental consent and ethical clearance was obtained from institutional ethics committee. Children from newborn period to 6-year of age, who were newly diagnosed with primary VUR between Grade I and IV VUR were included in the study. The patients who presented with UTI and whose ultrasound of kidney, ureter, and bladder (KUB) showing hydronephrosis or hydroureter were subjected to micturition cystourethrogram (MCU). Those patients with primary VUR were considered for the study. VUR was graded according to international classification [1].

Children with secondary reflux with congenital anomalies of urinary tract such as ureterocele, solitary kidney, ectopic or fused kidney, multicystic dysplastic kidney, and with renal insufficiency were excluded from the study. Furthermore, children more than 6 years of age or with Grade V reflux and where parents refused to participate were excluded from the study. Patients' demographic data including height/length, weight, and blood pressure were documented at diagnosis. Bowel and bladder habits were noted. Urine microscopy, renal function tests, ultrasound of KUB, and Technetium 99 dimercaptosuccinic acid (DMSA) scan were done as a baseline.

All patients received cephalexin prophylaxis single dose in the night daily as per the weight. Patients allergic to cephalexin received amoxicillin or trimethoprim-sulfamethoxazole as an alternative. Antibiotics were changed every 6 months to prevent the development of resistance and side effects (cephalexin to amoxicillin; amoxicillin to trimethoprim-sulfamethoxazole).

Patients were followed up every 3 months over the next 2-year period. At each follow-up, patients' symptoms, if any, were recorded, and investigations such as urine routine/culture, renal function tests (urea, creatinine), and ultrasonography of KUB were performed. At the end of each year, MCU and Technetium 99 DMSA scan were also performed for evaluation of reflux and scar status, respectively. Patients with culture-proven UTI were treated according to the sensitivity report. Primary outcome analysis on the number of UTI episodes, resolution of reflux, scar status, and the need for surgery was performed.

Statistical analysis for the study was performed using SPSS software (version 16.0, SPSS Inc, Chicago, IL). Kruskal-Wallis one-way analysis of variance was used to compare the categorical variables between groups. Unpaired t-test was used to analyze continuous variables between groups. All the values were expressed as mean±SD.

**RESULTS**

A total of 48 patients were included in the study, but three patients were lost to follow-up; hence, 45 patients were included in the analysis. Of these, 84.44% (n=38) were males and 15.56% (n=7) were females with male to female ratio of 5:1. Bilateral VUR was seen in 32 patients (71.11%) and was a more common in boys. The age of the youngest patient was 17 days, and the oldest patient was aged 42 months at diagnosis with a mean of 10.3±2.8 months. These patients were diagnosed most commonly after an episode of UTI (n=33; 73.33%) followed by workup for

antenatally detected hydronephrosis/hydroureter (n=11; 24.44%). Most UTIs were febrile at presentation (n=29) and more common in boys (n=21) than girls (n=8). There was no prior history of UTI in patients who were worked up for antenatally detected hydronephrosis/hydroureter. There was no evidence of growth impairment or hypertension in these patients to begin with.

The frequency of different grades of VUR according to International classification of reflux on MCU were: Grade I – 3 units, Grade II – 12 units, Grade III – 38 units, and Grade IV – 24 units. Baseline DMSA scans showed scarring in 12 patients (18 renal units) and all had a history of febrile UTI. The comparison between grade of VUR and incidence of scarring is depicted in Table 1. The highest incidence of scarring was noted in children with Grade IV reflux – 15 units (62.5%). No scarring was seen in Grade I or Grade II reflux groups.

Follow-up results at the end of 1 year and 2 years are summarized in Tables 2 and 3, respectively. No units demonstrated Grade I reflux at the end of 2 years. Grade II reflux persisted in two of 12 units (16.67%), Grade III in 23.68%, and Grade IV reflux persisted in 62.5% units. Most of the fresh UTI episodes occurred in Grade III and IV VUR patients. Fresh renal scars were seen mostly in Grade IV group. In one patient belonging to Grade IV group with fresh renal scar, surgery was considered due to persistent bilateral reflux (right Grade III and left Grade IV), same as that of the previous grade. None of the patients experienced growth retardation, deterioration in renal function or developed

**Table 1: Comparison between grade of MCU and scarring (baseline)**

Grade on MCU	Number of units	Number of units showing scarring on DMSA scan	%
I	3	0	0
II	12	0	0
III	38	3 units	7.9
IV	24	15 units	62.5

MCU: Micturition cystourethrogram, DMSA: Dimercaptosuccinic acid

**Table 2: Comparison at the end of 1-year follow-up**

Grade on MCU	Number of units (old+new*)	Number of breakthrough UTI episodes	Number of units showing fresh scars
I	0	0	0
II	6+7	1	0
III	19+3	4	1 unit
IV	19	3	3 units

\*Previously higher grade reflux which decreased in grade. MCU: Micturition cystourethrogram, UTI: Urinary tract infection

**Table 3: Comparison at the end of 2-year follow-up**

Grade on MCU	Number of units (old+new*)	Number of breakthrough UTI episodes	Number of units showing fresh scars
I	0	0	0
II	2+9	0	0
III	9+5	2	0
IV	15	3	2 units

\*Previously higher grade reflux which decreased in grade. MCU: Micturition cystourethrogram, UTI: Urinary tract infection

hypertension. None of our patients had constipation or bladder dysfunction. Circumcision was done in four boys due to recurrent UTI following which no further infections occurred.

## DISCUSSION

VUR refers to retrograde flow of urine from the bladder into the ureter and collecting system of the kidney. It can be primary or secondary. The management of secondary VUR is directed at the cause rather than the reflux itself. Primary reflux is known to resolve over a period, and this fact forms the foundation for the basis of conservative management of primary VUR. VUR with UTI is known to produce renal damage. Identification of the patients at risk for recurrent UTI and subsequent renal damage remains a gray area in the management of VUR. VUR is present in one-third of children presenting with febrile UTI and has been associated with a heightened risk of renal scarring [1-3].

The somatic growth curve is one of the best global parameters of renal health in children and children with VUR and UTI, who fall below the third percentile, have shown catch up growth with successful suppression of pyelonephritis with continuous antibiotic prophylaxis or surgical correction of reflux. Hence, height and weight evaluation of these patients is necessary [2]. Patients with VUR demonstrate a wide range of severity, and a majority of reflux patients do not develop renal scars and probably will not need any intervention as shown in this study. Furthermore, the time bound factor associated with reflux resolution makes regular follow-up an essential part of management.

Antibiotic prophylaxis alone in these patients is still debated when considering their efficacy in preventing recurrent UTI and renal scarring. Faster resolution of VUR is more likely in children who are aged <1 year at presentation, have a lower grade of reflux (Grade I-III), and have an asymptomatic presentation with prenatal hydronephrosis or sibling reflux. Antibiotic prophylaxis is recommended regardless of VUR grade, renal scarring or symptoms in all children diagnosed within the first year of life [5]. Opponents of prophylaxis quote long-term requirement, questionable efficacy, side effects, allergic reactions and emergence of antimicrobial resistance as the criteria for not using antibiotics [6]. Few trials have compared anti-reflux surgery with antimicrobial prophylaxis and showed no significant differences in the rates of recurrent UTI and renal scarring.

Although the efficacy of antibiotic prophylaxis remains unproven, we have adopted to this measure mainly to assure regular follow-up and pacify the parents' anxiety. Studies have shown that parents of children with VUR generally prefer antibiotic prophylaxis as the initial treatment modality [7,8]. The incidence of infection appears to be high in the groups with Grade III and IV reflux. Considering this fact studies have preferentially avoided prophylaxis in Grade I and II reflux with no detrimental effects [6,9,11]. This is also supported by the fact that low-grade reflux has higher and faster rates of resolution.

Another important factor, frequently associated with VUR and most frequently neglected also, is the presence of constipation and dysfunctional voiding. Constipation is proven to increase the

incidence of symptomatic UTI and bacteriuria in patients with VUR. Females are more commonly affected by constipation and dysfunctional voiding. Constipation is also known to prolong the duration of resolution and reduce the resolution rates of reflux [12]. Lower urinary tract dysfunction (LUTD) was seen in 34% of children with VUR, and recurrent UTI was found in 33% children with LUTD according to the Swedish Reflux Trial [13]. Hence, bladder training and constipation treatment remain an integral part of VUR management. In our study, none of our patients had constipation as per history and X-ray abdomen done during MCU.

Incidence of surgical management in these patients is showing a declining trend with more patients being managed conservatively. In this study, only one patient required ureteric reimplantation for definitive management of VUR accounting for 2.22% of cases. Further, boys with recurrent UTI and high-grade VUR have been managed with circumcision with no further UTI episodes in our study. Circumcision is effective in reducing the risk of UTI as per meta-analysis of 12 studies by Singh-Grewal et al. by decreasing preputial colonization [14]. Endoscopic subureteric injection therapy (STING) has become popular over the recent years as another alternative to conventional surgery. In a meta-analysis of endoscopic therapy, the reflux resolution rate after a single endoscopic treatment was 72% for Grade III, 63% for Grade IV, and 51% for Grade V [15]. It has inherent disadvantages of high cost, unknown long-term efficacy and lower resolution rates compared to open surgery. We have not employed STING in any of these patients owing to the cost and more, so we wanted to evaluate the role of conservative management in these patients. Hence, STING therapy was not considered.

## CONCLUSION

Conservative management of VUR with antibiotic prophylaxis appears to be a suitable option without adverse outcomes. Prophylaxis may not be beneficial in low-grade reflux but it may help in allaying parents' anxiety from the fact that something is being done for the child. In the current scenario, surgery has a minor role to play provided that the reflux is resolving with no fresh renal scars or growth impairment.

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