

## Brief Reports

### Long-Term Clinical Follow up of Children with Primary Vesicoureteric Reflux

C.K. Abeysekara, B.M.C.D. Yasaratna and A.S. Abeyagunawardena

*From the Department of Pediatrics, Faculty of Medicine, University of Peradeniya, Sri Lanka.*

*Correspondence to: Dr. C.K. Abeysekara, Department of Pediatrics, Faculty of Medicine,*

*University of Peradeniya, Sri Lanka.*

*E-mail: chandrakum@hotmail.com*

*Manuscript received: May 4, 2005, Initial review completed: May 20, 2005;*

*Revision accepted: October 18, 2005.*

*Fifty-six children (35 boys and 21 girls) below the age of 12 years with primary Vesicoureteric reflux (VUR) detected by voiding cystourethrogram after an initial episode of documented urinary tract infection (UTI), were studied prospectively for a period of 6-12 years (Mean 8 years) with reference to scarring, grade of reflux, break-through infections, adverse effects to prophylactic drugs and clinical and laboratory evidence of renal failure. The mean age at presentation was 1.95 years. Grade I-V reflux occurred in 7.1%, 28.6%, 48.2%, 12.5%, 3.6% respectively. Thirty-one (55.3%) had detectable renal scars on dimercaptosuccinic acid (DMSA) scan. All of them were treated with low dose prophylactic antibiotics until the age of 5 years. None had any major adverse effects to the prophylactic antibiotics. Ten (17.9%) had breakthrough UTI while on prophylaxis and 3 (5.4%) had UTI after discontinuing prophylaxis at 5 years of age. Two patients underwent ureteric reimplantation. Clinical and laboratory evidence of renal failure was not observed during the follow up period. Systolic blood pressure of all patients was below the 90th percentile for age. One had significant proteinuria. Majority of this cohort of patients with varying degrees of reflux nephropathy were managed conservatively with regular monitoring and low-dose prophylactic antibiotic therapy.*

**Key words:** *Long-term outcome, Primary vesicoureteric reflux.*

**P**PRIMARY vesicoureteric reflux (VUR) is caused by a maturational abnormality of the vesicoureteric junction and passage of urine in a retrograde manner up the ureter. Although the exact prevalence in the general population is unknown, 30-40% of children with urinary tract infections (UTI) are found to have reflux and urinary tract infections occur approximately in 5-10% of children(1).

It is documented that VUR is a predisposing factor for UTI, which in turn may involve the kidney parenchyma and cause permanent renal scarring(1). Bailey first

introduced the term reflux nephropathy referring to the close relationship between reflux and scarring. The severity of VUR is graded using the International Study Classification from grade I-V, based on the appearance of the urinary tract on contrast Micturating cystourethrogram (MCU)(2). Children with high-grade reflux (grade IV-V) who acquire a UTI are at significant risk for pyelonephritis and renal scarring. This relationship between scarring and the grade of reflux is shown in several studies. With bladder growth and maturation, there is a tendency for

reflux to resolve or improve. Lower grades of reflux (grades I-III) are much more likely to resolve than higher grades IV-V(3,4).

Hypertension and uremia are the two most serious complications of scarring due to pyelonephritis. Proteinuria is an important predictor of progression to end stage renal disease. The incidence of hypertension in children with renal scarring has been reported in more than 10%(5). Although there are a few studies on the prevalence of VUR and renal scarring in Sri Lankan children presenting with a documented UTI, but none evaluate the long-term outcome(5,6). The aim of this study was to assess the long-term complications of primary VUR.

### Subjects and Methods

A prospective study was carried out on 808 children below the age of 12 years with the initial episode of UTI, registered from 1992 to 2004 in the renal clinic for children at Teaching Hospital, Peradeniya.

Two consecutive midstream or clean catch samples of urine were collected in children below the age of 12 years with a suspected UTI. In toxic, ill children suprapubic aspiration was performed before commencing on antibiotics. All the children with significant bacterial growth (colony count  $>10^5$  /mL) of a single organism in the urine were diagnosed as having UTI.

Ultrasonography (USG) of the urinary tract was performed in all children. A DMSA scan was performed 6 months after the initial episode of UTI in all children below 5 years. MCU was performed in all children less than two years with a confirmed UTI and in children who had abnormalities on USG or DMSA scan. Out of 333 MCU performed during the study period, 101 (30%) demonstrated VUR.

Children with primary VUR who had

completed more than six years of follow up were included for the present analysis. There were fifty-six children who fulfilled the criteria. VUR was graded according to the International Classification(2). All of them were treated with low-dose antibiotic prophylaxis until the age of five years. Repeat MCU was not routinely performed prior to discontinuation of prophylactic therapy but children who developed symptomatic breakthrough infections were re-evaluated with indirect radionuclide cystourethrogram. Ureteric reimplantation was done in 2 patients who had recurrent with grade V reflux.

Parents were educated regarding the illness, the importance of prophylaxis and follow up. They were advised to report to the pediatric unit with a urine culture if the child developed symptoms of a UTI or side effects to the drugs. All the children were seen monthly in the renal clinic under the supervision of the principal author.

All episodes of febrile and culture positive UTI were recorded. At each clinic visit, adverse effects to prophylactic drugs were recorded. Urine for protein excretion (dipstick method) was assessed once in three months and serum creatinine was checked annually. Blood pressure was measured every three months and values were compared with the age and sex specific percentiles for western children.

Prophylactic antibiotics were discontinued at the age of five years. After discontinuation of prophylaxis they were followed up periodically with assessment of the clinical status, blood pressure and proteinuria. They were advised to report immediately if they became symptomatic.

### Results

Fifty-six children with primary VUR were followed up for a period of 6-12 years (mean 8

years); 62.5% were boys with a male to female ratio of 1.7:1. Mean age at presentation was 1.95 years (range 1 month -12 years). Seventy six percent were below the age of two years. Thirty-three patients (58.9%) had unilateral reflux with 20 on the right side and 13 on the left; in 23 (41.1%) it was bilateral. Majority (48.2%) had grade III reflux while 28.6% had grade II and 8.9% had grade I reflux. Major grades of reflux were seen less frequently, grade IV in 12.5% and grade 5 in 1.8% of patients respectively.

Thirty-one (55.3%) had detectable renal scars on DMSA scan. Fourteen (45.2%) of them had upper pole scarring and 7 (22.6%) had lower pole scarring of a single kidney. Five (16.1%) had involvement of a single pole in both kidneys. Multiple scarring was noted in a single kidney in 2 (6.4%) and in both kidneys in 3 (9.7%).

Seventy five percent of children with higher grades (grades IV-V) of reflux and 49% children with lower grades of reflux had detectable renal scars on DMSA scan but, standard errors of difference between the two groups were not significant ( $P = 0.2$ ).

Prophylactic antibiotics were administered to all children until 5 years of age. Forty-eight (85.2%) received nitrofurantoin as the first prophylactic agent and in 5 (11.1%) it was changed to nalidixic acid due to vomiting. Four children (7.4%) received nalidixic acid as the first prophylactic agent and were well tolerated. Four children (7.4%) received cephalixin and co-trimoxazole. No major adverse effects to any of the antibiotics were observed.

Eight (14.3%) patients had breakthrough UTI while on prophylaxis and three (5.4%) had UTIs after discontinuing prophylaxis of which only one was symptomatic.

Reimplantation of ureters was done

in 2 (3.6%) patients who had recurrent symptomatic breakthrough infections at the ages of 3 and 10 yrs with a grade V VUR. Four patients underwent circumcision due to recurrent balanitis and one had corrective surgery for hypospadias.

Systolic blood pressure values in all patients were below 90th percentile for age (Table I). Only one patient (1.8%), with unilateral grade III reflux, had significant (1+ or above) proteinuria. Serum creatinine values of all children were within the normal range.

### Discussion

This study describes the long-term outcome of a group of Sri Lankan children with primary VUR detected following a documented UTI.

Sixty one percent with VUR in this study group were males. This is in accordance with reports describing a male preponderance of primary VUR in Indian children(3), although there are some studies from other countries that report a female preponderance(7).

Renal scarring was detected in 55.3% in the study group. The prevalence of renal scarring in children with VUR has been reported to vary

**TABLE I-** *Distribution of Blood Pressure Measurements.*

Percentile	Systolic (%)	Diastolic (%)
<5	17.3	3.8
5 - 10	17.3	-
10 - 25	5.8	3.8
25 - 50	32.7	17.3
50 - 75	23.1	30.8
75 - 90	3.8	38.5
90 - 95	-	1.9
>95	-	3.8

### Key Messages

- Children with primary vesicoureteric reflux had detectable renal scars in 55.3% cases.
- Majority of children with reflux nephropathy can be managed conservatively with regular monitoring and low-dose prophylactic antibiotic therapy without clinical or biochemical deterioration.

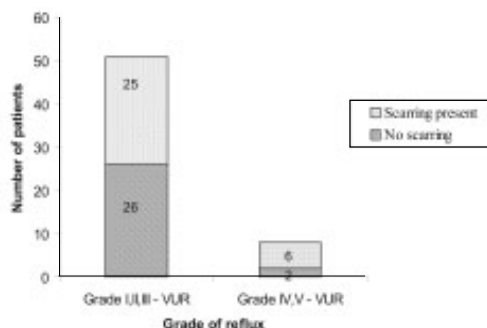


Fig. 1. Renal scarring in relation to grade of VUR

from 23-62%(7,8). The correlation between reflux and scarring has been demonstrated in other studies. The proportion of scarring in our study was higher in patients with higher grades (IV-V) VUR when compared with lower grades (I-III). This is in accordance with the finding that the risk of scarring is higher in patients with major degrees of reflux who develop UTI, when compared with lower degrees(7,8).

The management strategy for children with VUR has been the avoidance of UTI induced damage by surgical correction of VUR or long-term antibiotic prophylaxis or both. Most patients are managed on long-term antibiotic prophylaxis until spontaneous resolution of VUR. Almost all children except two in the study group were managed conservatively on long-term antibiotic prophylaxis. The main drugs used were nitrofurantoin, nalidixic acid, cephalexin and cotrimoxazole. No patients in

the study group had any major adverse reactions to drugs *e.g.*, hypersensitivity, peripheral neuropathy or benign intracranial hypertension, but a few experienced minor side effects like anorexia, nausea, vomiting and diarrhea. A systematic review of trials comparing long-term prophylactic antibiotic use with placebo does not show any major side effects of commonly used drugs except intolerance to nitrofurantoin(10). Our observations are similar to findings of trials in the published literature.

In this study, 15.3% had breakthrough UTI during antibiotic prophylaxis. The frequency of febrile UTI reported by the antibiotic-only arm of the International reflux study group after 5 years was 22% and combined surgery and antibiotic arm was 8-10%(11). Inclusion of children with bilateral higher grades of VUR (grades IV-V) may explain the higher percentage of breakthrough infections in their study group in comparison to this study.

Studies have shown that reflux disappears without any permanent renal impairment in a vast number of children on prophylaxis(3,4) and therefore the management programmes for children with VUR should take into account the self-resolving nature of reflux.

Although 55.3% of children had detectable scarring in this cohort it is interesting to note that none of them had clinical or biochemical evidence of deterioration of renal parameters during the study period.

### Acknowledgements

Authors acknowledge the help of C.K. Abeysinghe and T.D. Manuwickrama in collecting data and providing care for the study patients.

*Contributors:* CKA did drafting of manuscript, analysis of data, overall supervision and contributed to patient management. BMCDY contributed to collection and analysis of data and literature search, ASA revised the article critically and contributed to patient management.

*Funding:* None.

*Competing interests:* None.

### REFERENCES

1. Rushton HG. Urinary tract infections in children: Epidemiology, evaluation and management. *Pediatr Clin N Am* 1997; 44: 1133-1169.
2. International Reflux Study in Children. International system of radiographic grading of vesicoureteric reflux. *Pediatr Radio* 1985; 15: 105-109.
3. Menon P, Rao KLN, Bhattacharya A, Mahajan JK, Samujh R. Primary vesicoureteric reflux: Progress of disease, somatic growth and renal parameters. *Indian Pediatr* 2004; 41: 1025-1030.
4. Smellie JM, Jodal U, Lax H, Mobius TT, Hirche H, Obling H. Outcome at 10 years of severe vesicoureteric reflux managed medically: Report of the International Reflux Study in Children. *J Pediatr* 2001; 139: 656-663.
5. Lamabadusuriya SP. A prospective study of urinary tract infections in children. *Sri Lanka Child Health* 2001; 30: 31-37.
6. Abeysekera CK. Renal scarring in children with urinary tract infections. *Sri Lanka Child Health* 2000; 29: 85-87.
7. Macedo CS, Riyuzo MC, Bastos HD. Renal scars in children with primary vesicoureteric reflux. *J Pediatr (Rio J)* 2003; 79: 355-362.
8. Olbing H, Smellie JM, Jodal U, Lax H. New renal scars in children with severe VUR: a 10-year study of randomised treatment. *Pediatr Nephrol* 2003; 18: 1128-1131.
9. Sally A Feather, Sue Malcolm, Adrian Woolf, Victoria Wright, *et al.* Vesicoureteric reflux and its nephropathy is genetically heterogenous, with a locus on chromosome 1. *Am J Hum Genet* 2000; 66: 1420-1425.
10. Williams GJ, Lee A, Craig JC. Long term antibiotics for preventing recurrent urinary tract infection in children. *The Cochrane Library*, Issue 2, 2003. Available from: URL: <http://www.update-software.com/abstracts/ab001534.htm>.
11. Smellie J, Barratt TM, Chantler C, Gordon I, Prescod NP, Ransley PG, *et al.* Medical versus surgical treatment in children with severe bilateral vesicoureteric reflux and bilateral nephropathy: A randomised trial. *Lancet* 2001; 357: 1329-1333.
12. Gordon I, Barkovics M, Pindoria S, Cole TJ, Woolf AS. Primary vesicoureteric reflux as a predictor of renal damage in children hospitalized with urinary tract infections: A systematic review and meta-analysis. *J American Soc Nephrol* 2003; 14: 739-744.