Primary vesicoureteral reflux: conservative therapy or surgical intervention

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Submitted on: 25/07/2013.
Approved on: 23/09/2013.

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Financial aid provided by CNPq (National Board for the Development of Science and Technology).

DOI: 10.5935/0101-2800.20140004

ABSTRACT

Introduction: The relationship between urinary tract infections and primary vesicoureteral reflux may lead to permanent renal damage. In the literature an increasing number of spontaneous cure of vesicoureteral reflux in children and the significant decrease in surgical therapy has been observed. **Objective:** To study the evolution of primary vesicoureteral reflux associated with recurring urinary tract infections settings in patients of the Pediatric Nephrology department of our institution, evaluating cases in which cure was achieved through conservative therapy only and those in which surgical intervention was required. **Methods:** We analyzed records and collected data refers to parameters: sex, age upon the diagnosis of primary urinary infection, age upon diagnosis of vesicoureteral reflux, number of urinary tract infections, vesicoureteral reflux grade; renal function, renal scaring, other malformation of urinary tract, and surgical or conservative intervention. Statistical analysis was descriptive and conducted with the SPSS program. **Results:** Within the subgroup of patients with grade IV and V, 63.6% of the cases evolved to surgical intervention and 36.4% to conservative intervention. In those with grades I, II, and III, 38.5% evolved to surgical treatment against 61.5% for conservative approach. Among those with bilateral vesicoureteral reflux, 72.7% had to undergo surgical intervention. No relationship was observed between the vesicoureteral reflux grade and the presence of renal scaring. **Conclusion:** Patients with low grade vesicoureteral reflux and recurring urinary tract infections tend to experience spontaneous reflux resolution with good renal evolution in the long term in a way that surgical intervention becomes limited to high grade reflux or when followed by other clinical issues.

Keywords: pediatrics, urinary tract infections, vesico-ureteral reflux.

INTRODUCTION

Retrograde flow of urine from the bladder into the upper urinary tract is an anomalous event in human beings known as vesicoureteral reflux (VUR). It results from intrinsic anatomic incompetence of the ureterovesical junction or abnormal bladder pressure elevation secondary to mechanical or dysfunctional vesicourethral orifice obstruction.[1] VUR is an autosomal dominant disorder. The reported prevalence of VUR in patients carrying urinary tract infections (UTI) ranges from 20% to 60%.[2] A number of studies were carried out between 1950 and 1970 with apparently disease-free children in an attempt to establish the prevalence of VUR, which was reported to have ranged between 0.4% and 1.8%.[3] In 2000, Sargent published the outcomes of a review comprising over 250 papers citing the results of voiding cystourethrograms (VCUG) performed with various indications.[4] Nine percent of the disease-free children were diagnosed with VUR, against 31% of the children with UTI. Vesicoureteral reflux disease has been categorized into grades, as defined by the International Reflux Study Committee:[5]

- Grade I: reflux into the ureter;
- Grade II: reflux into the ureter and renal pelvis without dilatation;
- Grade III: reflux with mild dilatation;

- Grade IV: reflux with moderate dilatation, rounded fornices;
- Grade V: gross dilatation of the ureter, ureter tortuosity, papillary obliteration.

Primary VUR is one of the most common malformations of the urinary tract. It is generally a congenital condition, by definition not associated with obstructive, neurologic, or vascular events.[2,6] During voiding, the intramural portion of the ureter is occluded as the detrusor muscle contracts. In subjects with VUR such occlusion fails and the anti-reflux valve mechanism cannot be established.[7] Two additional factors come into play: patients with higher grade VUR are less likely to see their condition resolved; and the younger the patient is, the less likely it is for VUR to persist due to the maturation and elongation of the ureterovesical junction as the individual grows.[3,8] The association of VUR and UTI in children may be indicative of permanent renal damage in a condition called reflux nephropathy (RN), in which bacteria ascend into the upper urinary tract to cause irreversible focal or diffuse renal parenchyma loss.[9] In addition to VUR, a few other factors increase the risk of kidney scarring in children with febrile UTI, such as: delays in antibiotic administration, first episode of febrile UTI at an early age, recurrent febrile UTI, urinary obstruction, and dysfunctional elimination syndrome (impaired bowel and bladder control).[10,11]

Kidney damage prevention may be attained with the use of antimicrobial agents or surgery. Prophylaxis with antibiotics is designed so that drug dosage is high enough to prevent bacteria in the bladder from multiplying into the urinary tract. The inconveniences of prolonged antibiotic therapy include low compliance rates and side effects. Eight to ten percent of the patients will suffer from side effects, most of which not severe and include nausea, vomiting, and cutaneous manifestations; however, drug therapy increases the possibility of the intestinal and oropharyngeal flora developing antimicrobial agent resistance.[12] The Brazilian Society of Pediatrics dictates that drug therapy be offered to all children with VUR until the condition is resolved - spontaneously or with the aid of surgery - or until the child reaches the age of five years. Regardless of the chosen surgical approach, current success rates are as high as 98%. UTI may occur after surgery despite the resolution of VUR, but patients need to be followed up to rule out the possibility of contralateral reflux, seen in up to 18% of the cases.[13,14] Surgery is indicated in a limited number of cases, depending on the grade of VUR, presence of recurrent pyelonephritis due to poor compliance with chemoprophylaxis; associated ureterovesical anomalies - pyeloureteral duplication, ureteral ectopia or paraureteral diverticula; and persistent reflux in females after puberty (increased risk of pyelonephritis during pregnancy).[15]

Many authors have shown that a great deal of VUR cases do not require surgery. A study performed with 214 children aged 15 and under revealed that 13% of the grade I to III and 5% of the grade IV and V reflux cases resolve within a year.[16] Other authors reported progressive resolution in grade III and IV reflux cases and significant decreases in the intensity of VUR in patients submitted to conservative treatment.[17] Approximately 40% of the cases of reflux resolve spontaneously or in the long term. Conservative treatment or surgery do not alter the natural history of the renal injury inflicted upon the involved site, but may prevent future injury.[18] Therefore, surgery is recommended only for children with repeated UTI episodes despite drug therapy and individuals who cannot be followed up in an outpatient basis.

This paper aimed to study the outcomes of primary vesicoureteral reflux in patients with urinary tract infections seen at the UNIFESP/EPM Pediatric Nephrology Service. Cases were analyzed for occurrences of spontaneous resolution and prescription of surgery or conservative treatment, along with the events potentially related to each scenario.

Methods

The charts of the patients diagnosed with urinary tract infection and primary vesicoureteral reflux seen at the Pediatric Nephrology Service of the

Department of Pediatrics of the Paulista School of Medicine of the Federal University of São Paulo, Brazil, from 1998 to 2009 were analyzed. After checking patient information and screening charts based on the study's pre-requisites, the selected cases were analyzed based on their outcomes (spontaneous resolution during antibiotic therapy or need for surgery) and the factors potentially associated with each chosen approach.

Enrollment criteria

Patients with primary vesicoureteral reflux diagnosed based on VCUG and recurrent urinary tract infections.

Exclusion criteria

Patients with symptoms of urinary tract infection not confirmed by urine culture, subjects on drug therapy inadequately followed up, individuals with specific causes for secondary reflux, and patients with voiding dysfunction related to elimination syndrome.

Analyzed parameters

The following indicators were observed for the group of 35 patients selected:

- Pattern of incidence of VUR per gender;
- Mean age at the first episode of UTI;
- Mean age when diagnosed with VUR;
- Correlation between VUR grade and number of episodes of UTI confirmed by positive urine culture;
- Correlation between VUR grade and chosen approach;
- Factors connected to the appearance of kidney scars and its correlation with the chosen approach;
- Correlations between number of UTI episodes, duration of antibiotic therapy, and outcome;
- Correlation between presence of other urinary tract malformations and patient outcome;
- Causes related to the chosen approaches.

The patients included in this study had urinary tract infections confirmed by midstream urine culture.

Statistical method

The data sets included in this study were loaded into a database and treated with MS-Excel. Descriptive statistical analysis was carried out with the aid of software package SPSS. Qualitative variables were analyzed considering the observed and relative frequencies of interest. In some cases, frequency distributions were represented using bar charts. Descriptive statistics was used to explain quantitative variables in the form of mean and median values, scatter and standard error.

This study was approved by the Ethics Committee of our institution.

Results

The charts of pediatric patients with vesicoureteral reflux and recurrent urinary tract infections seen at the UNIFESP Pediatric Nephrology Ward were selected for analysis. A total of 39 patients were enrolled, but two were excluded due to poor compliance with antibiotic therapy and two for not having records of urine culture confirming some of their UTI episodes. None of the patients had grade I VUR.

Female patients accounted for 65.7% of the cases (23/35), and males for 34.3% (12/35). Males were diagnosed earlier with VUR and had their first episode of UTI at a younger age than female subjects, although the difference was not statistically significant (chi square = 0.26), as seen on Table 1. Male and female patients had a mean age of 23.3 months and 42.4 months respectively when they were first diagnosed with UTI, and 64.7 months and 101.9 months at the time they were diagnosed with VUR, respectively.

Unlike female patients, most male individuals were eventually referred to surgery, although the difference was not statistically significant (chi square = 0.47).

The charts revealed that 28.6% (10/35) of the subjects had VUR on the right side and 40% (14/35) on the left side. Eleven (31.4%) children had bilateral VUR. Forty-six ureters (24 from unilateral and 22 from bilateral cases) were considered in the assessment of VUR grade.

Table 1 Mean age at the diagnosis of VUR and first UTI episode

		VUR diagnosis		First UTI episode	
	n	Mean (months)	SD	Mean (months)	SD
Females	23	101.9	78.1	42.4	52.4
Males	12	64.7	113.6	23.3	46.8
Total	35	89.2	91.9	35.8	50.7

SD: Standard deviation.

For purposes of clinical assessment, the more severely affected side was considered in patients with bilateral involvement.

Despite the lack of statistical significance (chi square = 0.18), higher grade VUR and surgery were directly correlated, as seen on Graph 1. Three of the 19 patients managed through surgery underwent nephrectomies and 16 had ureteral reimplantation procedures. The frequency of occurrence of the various grades of VUR seen in this study are presented in Table 2. None of our patients had grade I VUR.

Graph 1. Correlation between VUR grade and management mode.

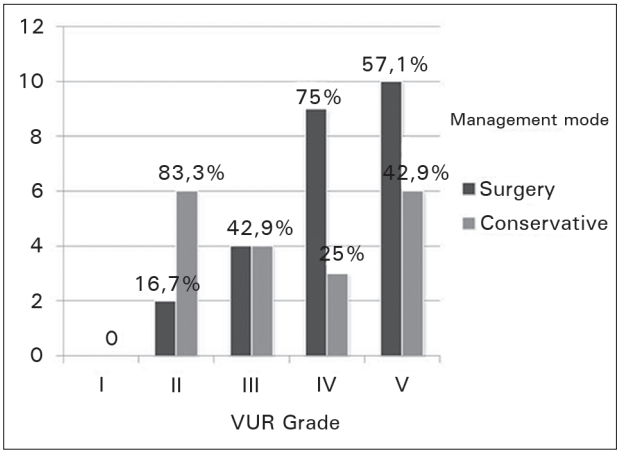


Table 2 Frequencies of different VUR grades seen in the study

	Frequency	Percentage
Grade 2	8	17.4
Grade 3	9	19.6
Grade 4	12	26.1
Grade 5	16	34.8
Total	46	100

Infection by E. coli was described in 77% of the patients. Other pathogens included *Proteus*, *Klebsiella*, *Enterobacter*, *Pseudomonas*, *Acinetobacter*, and *Morganella*. Additionally, the incidence of positive urine cultures was higher in cases of higher grade VUR, as seen in Table 3, despite the lack of statistical significance (chi square = 0.62). This data was obtained from the urine cultures done during the last UTI episode the patients had before they were diagnosed with VUR, i.e., at a time when patients had not been given antibiotics yet.

Table 3 Correlation between VUR grade and positive urine culture results

Grade	Positive urine culture	Negative urine culture	Total
2	4	2	6
3	3	4	7
4	6	2	8
5	9	5	14
Total	22	12	35

Patients with grades IV and V VUR took antibiotics for a mean time of 13 months (390.18 days), while individuals with disease grades I, II, and III were given antibiotics for a mean time of 17.38 months (521.53 days). The correlation between time on antibiotics and management mode was not statistically significant (chi square = 0.17). In the first subgroup (grades IV and V), 67.9% of the subjects were offered surgery, while 32.1% were administered conservative therapy. In the second subgroup (grades I, II, and III), 41.2% underwent surgery and 58.8% were managed conservatively. The correlation between VUR grade and management mode is shown in Graph 1.

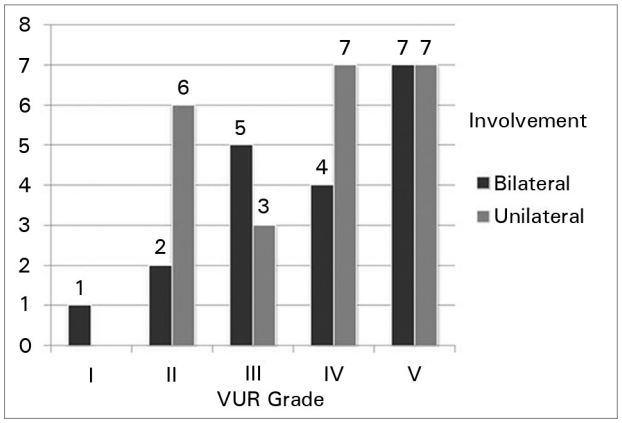
The most frequently prescribed prophylactic drugs were cefalexin and sulfamethoxazole-trimethoprim, followed by nitrofurantoin and nalidixic acid. Additionally, 51.42% of the subjects made non-concurrent use of more than one drug.

Concerning the side of involvement, 28.6% of the patients had VUR on the right side, 40% on the left, and 31.4% on both sides. Higher prevalences of bilateral involvement were observed in patients with higher grade reflux, as seen in Graph 2. In patients with bilateral VUR

(11/39), 72.7% (8/11) were referred to surgery and 27.3% (3/11) were managed conservatively.

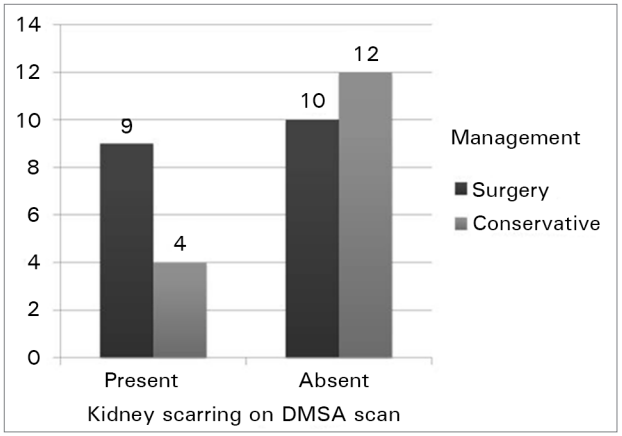
Despite the lack of statistical significance, 68.86% of the patients with VUR had other malformations of the genitourinary tract, the most common being ureterocele and duplicated pyelocaliceal systems. A direct correlation was also observed between higher grade VUR and lower incidence of urinary tract infections, although without statistical significance (chi square = 0.17).

Graph 2. Correlation between VUR grade and unilateral or bilateral involvement.



No correlation was found between VUR grade alone and presence or absence of kidney scarring, or number of infection episodes and formation of kidney scars. However, patients with kidney scarring were predominantly referred to surgery (Graph 3), although this finding was not statistically significant (chi square = 0.3). Additionally, 43.5% of the female and 27.3% of the male patients had kidney scars.

Graph 3. Correlation between kidney scarring and VUR patient outcomes.



Discussion

This study described the follow-up of patients with UTI subsequently diagnosed with VUR referred to the department of Pediatric Nephrology at UNIFESP/EPM. Given this was a retrospective study based on information retrieved from patient charts, some limitations were observed, such as the loss of continuity in the follow-up of some patients and absence of complete data, to name a few, which significantly reduced the number of patients eligible for analysis. Thus, considering the small size of our sample, statistical significance was not attained in the tests applied herein. Nonetheless, some of the trends described in the literature on the topic were reproduced in our population.

The higher incidence of disease in females reported in our study is in agreement with the literature, as is the earlier detection of VUR in male subjects. Approximately 80% of the neonates with VUR are males. However, the literature shows that after the first few months of life incidence increases among females to a point in which they surpass males by a ratio of 4:12.[19,20] This change indicates VUR has a multifactorial pathogenesis, as although it is considered congenital in newborns, it can also be acquired, particularly by girls, probably as a consequence of bladder dysfunction.[21-23]

The study of VUR in experimental and clinical trials has gained relevance in the last three decades. As a result, some progress has been made in the description of the natural history of the disease and the well-established tendency toward spontaneous resolution of the condition, as seen in 45.7% of the subjects in our series.[24] In patients with prenatally diagnosed VUR, the trend toward spontaneous resolution is even stronger depending on the severity of the involvement.[25]

Surgery and conservative management rates are closely matched, although preferences seem to lean slightly toward the first. This can be explained by the fact that this study included only patients from a tertiary reference center, who generally have other aggravating conditions

which may turn them better candidates for surgery. Other factors play a role in the choice for surgery, such as age, compliance with the treatment, or presence of other anatomical anomalies that hamper spontaneous healing, such as ureteral duplication and paraureteral diverticula,[26,27] all of which frequently seen in our population. In our service, all patients diagnosed with VUR were offered antibiotic therapy and followed up. Patients with persistent recurrent UTI, signs of kidney scarring, or deteriorated renal function despite treatment were referred to surgery to minimize the chances of onset of chronic kidney disease.[28]

According to Edwards *et al.*,[29] there is an inverse correlation between VUR spontaneous resolution and reflux severity, as evidenced in our study. A study carried out in the University of Texas[30] reported that 80% of the patients with VUR grade I or II (low grade disease) had spontaneous resolution of the condition within five years. A revision comprising 26 studies and 1,987 patients found a correlation between VUR grades and spontaneous resolution, also supporting the idea that higher grade patients generally need surgery.[31] Thus, patients with low grade reflux are followed conservatively, hoping their condition will evolve favorably, while subjects with higher grade disease are offered surgery, as done in our cases.

Our study failed to show the currently established correlation[32] between higher grade VUR and renal scarring. This may have occurred because of the limited size of our sample or because of early diagnosis and prompt surgical intervention offered to patients with high grade VUR before kidney scars had a chance to develop.

In the group of children with VUR, 37.2% of the individuals had renal injury, which underscored the need to carefully monitor and follow up the subjects with UTI. Patients with kidney scars were more referred to surgery than subjects without renal scarring. Chronic kidney failure and systemic hypertension - neither targeted by this study - may occur consequently to severe renal injury, and may be prevented with early diagnosis and treatment.[33]

Our study revealed a correlation between higher grade VUR and higher incidence of UTI. However, no correlation was observed between the number of UTI episodes and kidney scarring. The literature is rather contradictory when it comes to defining the role of ITU in the pathogenesis of kidney injury. Some authors advocate reflux as the only factor in the formation of cortical and capillary injuries, while others consider that the reflux of infected urine alone is harmful.[34] Despite the looming controversy, chemoprophylaxis is offered to all patients with or suspected for VUR.

It is assumed that patients referred to surgery are kept on antibiotics for shorter periods of time due to early indication for surgery or other factors such as age at diagnosis, presence of kidney scars, and poor clinical outcome.

Much has been discussed about this topic. The American Academy of Pediatrics has recently introduced a new guideline for the diagnosis and management of children aged between two months to two years with repeat UTI and VUR, based on a meta-analysis that found no statistically significant benefits in antibiotic therapy as a means to prevent recurrent febrile UTI in children with VUR grades I to IV; more data is still required to assess the effects of such treatment in patients with grade V VUR.[35] Recently, the NICE (National Institute for Health and Care Excellence) reinforced, in its guidelines for urinary tract infections in children, the need for better designed double-blind randomized placebo controlled studies, in order to determine both the effectiveness of antibiotic therapy and surgery for patients with VUR in preventing recurrent UTI and kidney scarring.[36]

Although this was not covered in our study and patients with this type of voiding disorder were excluded, it is worth mentioning cases of vesicoureteral reflux and recurrent urinary tract infection secondary to dysfunctional elimination syndrome, in which patients have urinary symptoms along with defecation difficulties (stool leakage, fecal incontinence). For these patients, in addition to prophylactic care, treatment also includes dietary (higher fiber and fluid intake)

and behavioral measures to address constipation, in addition to psychosocial support, biofeedback techniques and electrostimulation.[37]

Conclusion

This study showed that patients with lower grade VUR and recurrent UTI tend to spontaneously resolve their condition, in addition to presenting good long-term renal evolution. Surgery was reserved for patients with high grade VUR or other clinical complications.

Male patients were diagnosed earlier with VUR and had their first episode of UTI at a younger age than their female counterparts ($x^2 = 0.26$).

None of the patients enrolled in this study had grade I VUR. A greater portion of the individuals enrolled in the study had higher grade VUR.

A higher prevalence of positive urine cultures was observed in patients with higher grade VUR, as shown in Table 3 ($x^2 = 0.62$).

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