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ARTICLE

Clinical Significance of Primary Vesicoureteral Reflux and Urinary Antibiotic Prophylaxis After Acute Pyelonephritis: A Multicenter, Randomized, Controlled Study

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ABSTRACT

OBJECTIVES. To evaluate the role of primary vesicoureteral reflux (VUR) in increasing the frequency and severity of urinary tract infections (UTIs) and renal parenchymal damage among patients with acute pyelonephritis and to determine whether urinary antibiotic prophylaxis reduces the frequency and/or severity of UTIs and/or prevents renal parenchymal damage among patients with mild/moderate VUR.

METHODS. Patients 3 months to 18 years of age with acute pyelonephritis, with or without VUR, were assigned randomly to receive urinary antibiotic prophylaxis or not. Patients were monitored every 3 months for 1 year. Dimercaptosuccinic acid renal scans were repeated at 6 months or if there was a recurrence of febrile UTI. Urinalysis and urine culture were performed at each clinic visit. Renal ultrasound scans and voiding cystourethrograms were repeated at the end of 1 year of follow-up monitoring.

RESULTS. Of the 236 patients enrolled in the study, 218 completed the 1-year follow-up monitoring. Groups were similar with respect to age, gender, and reflux grade distribution for those with VUR. No statistically significant differences were found among the groups with respect to rate of recurrent UTI, type of recurrence, rate of subsequent pyelonephritis, and development of renal parenchymal scars.

CONCLUSIONS. After 1 year of follow-up monitoring, mild/moderate VUR does not increase the incidence of UTI, pyelonephritis, or renal scarring after acute pyelonephritis. Moreover, a role for urinary antibiotic prophylaxis in preventing the recurrence of infection and the development of renal scars is not supported by this study.

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Key Words
vesicoureteral reflux, urinary antibiotic prophylaxis, acute pyelonephritis

Abbreviations
VUR—vesicoureteral reflux
UTI—urinary tract infection
DMSA—dimercaptosuccinic acid
VCUG—voiding cystourethrogram

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PRIMARY VESICOURETERAL REFLUX (VUR), defined as the retrograde flow of urine from the bladder to the ureter, is a common finding among patients with urinary tract infections (UTIs), compared with an incidence of <1% in healthy populations.[1,2] This association has led to the concept that VUR plays a role in the pathogenesis of UTIs by predisposing patients to recurrent UTIs, pyelonephritis, and renal scarring.

Currently, the therapeutic options considered for patients with VUR are either surgery to correct the reflux or the use of urinary antibiotic prophylaxis. The purpose of prolonged administration of antibiotics for patients with VUR is to keep the urinary tract sterile, preventing the development of acute pyelonephritis and the formation of renal scars. However, systematic review of the available data on the use of urinary antibiotic prophylaxis or surgery to correct VUR shows that "it is not clear whether any intervention" for these children "does more good than harm."[3]

The clinical significance of VUR has been questioned because there are no controlled studies among children that support the pathogenic role of VUR in UTI recurrence, pyelonephritis, and formation of renal scars.[4,5] There are no randomized, prospective trial reports comparing the use of urinary antibiotic prophylaxis with observation and prompt treatment of UTIs as they occur. The aims of this study were to evaluate the role of VUR in increasing the frequency and severity of UTIs and renal parenchymal damage among patients after an episode of acute pyelonephritis and to determine whether urinary antibiotic prophylaxis reduces the frequency and/or severity of UTIs and/or prevents renal parenchymal damage among patients with mild/moderate VUR.

METHODS

Study Groups

This investigator-initiated, randomized, controlled study was conducted at 4 centers (University of South Florida, Tampa Florida; Universidad Austral, Valdivia, Chile; Hospital de Nuestra Senora de la Candelaria, Tenerife, Spain; and Hospital Materno Infantil, Gran Canaria, Spain). The study was approved by the local medical ethics committees at all participating centers, and written informed consent was obtained before participation. Enrollment started on a different date at each site. Recruitment began in December 1998 and ended in December 2003.

The inclusion criterion was a documented episode of acute pyelonephritis in a patient 3 months to 18 years of age. Patients with fever (38.5°C), pyuria (>10 white blood cells per high-power field; centrifuged specimen), and significant bacteriuria (>100 000 colonies per mL) underwent a dimercaptosuccinic acid (DMSA) renal scan. Urine samples were obtained through bladder catheterization for patients unable to void on command and with the midstream clean-catch technique for all others.

Patients with the typical findings of acute pyelonephritis on DMSA scintigraphic scans were included in the study. The DMSA scintigraphic scans were obtained 2 to 7 days after the diagnosis of UTI, with a high-resolution pinhole collimator. The interpretation was made at each participating center and was the result of consensus between a nuclear medicine consultant and a pediatric nephrologist.

Acute pyelonephritis was defined as focal or diffuse areas of decreased ^{99m}Tc-DMSA uptake without evidence of cortical loss. Renal scar was defined as decreased uptake associated with loss of the contours of the kidney or cortical thinning with decreased volume.[6] DMSA renal scanning has been shown to have high sensitivity (87%) and specificity (100%) as a diagnostic test for acute pyelonephritis,[7] as well as a high degree of interobserver reproducibility.[8]

Exclusion criteria were the presence of grade IV or V VUR, according to the International Classification of VUR,[9] neurogenic bladder, posterior urethral valves, urinary diversion, bladder diverticulum, ureterocele, renal failure, and pregnancy. Exit criteria included 2 episodes of pyelonephritis during the year of follow-up monitoring, failure to comply with urinary antibiotic prophylaxis through self-admission, and loss to follow-up monitoring.

Randomization

Patients with acute pyelonephritis underwent a voiding cystourethrogram (VCUG). At this point, patients were classified into those with VUR and those without VUR. Patients in each of these groups were assigned, through simple randomization (performed at the Tampa center), to receive or not to receive urinary antibiotic prophylaxis, in a 1:1 ratio. When a patient had bilateral VUR, the highest grade of reflux present was used for categorization.

Antibiotic Therapy

Treatment of acute pyelonephritis was at the discretion of the attending physician. Patients received gentamicin, cefadroxil, cefuroxime, ceftriaxone, or cefotaxime intravenously for 5 to 7 days (administered at standard doses). Subsequently, orally administered antibiotics (selected with the use of a bacterial antibiogram) were given to complete a total antibiotic course of 14 days.

Patients assigned to receive urinary antibiotic prophylaxis received either sulfamethoxazole/trimethoprim (1–2 mg/kg trimethoprim or 5–10 mg/kg sulfamethoxazole once daily) or nitrofurantoin (1.5 mg/kg once daily). The choice of antibiotic was left to each participating center. The total duration of treatment for patients who received urinary antibiotic prophylaxis was 1 year.

Study Design

At entry, patients underwent urinalysis, urine culture, and imaging studies, including VCUG, renal ultrasonography, and DMSA renal scanning. The VCUG and renal ultrasound scans were repeated after 1 year of follow-up monitoring. A DMSA renal scan was obtained 6 months after the initial episode of pyelonephritis or whenever the patient experienced a febrile UTI. If the patient experienced a recurrence of acute pyelonephritis (new photopenic defect on a DMSA scan), then the DMSA scan was repeated 6 months after the recurrence.

Patients were examined in the outpatient clinic at 3-month intervals for 1 year or at any time symptoms of UTI occurred. At each clinic visit, urinalysis and urine culture were performed. Primary end points were rates and types of recurrence of UTI and development of renal scars.

Statistical Analyses

The primary analysis was performed with patients who had completed 1 year of follow-up monitoring (on-treatment analysis). Patients who exited the trial were not counted in the final analysis. No attempt was made to enroll patients to compensate for those who did not complete the study.

Our study was designed to detect a possible difference in the occurrence of UTI, pyelonephritis, and renal scars of 20 points between groups, with a 95% confidence level and a power of 80%, on the assumption of a baseline rate of 10% for the occurrence of end points in the study population. The calculation meant that 60 patients per group, for a total of 240 patients, were needed. Data were analyzed with Fisher's exact test.

RESULTS

Demographic Data

Demographic data are shown in Table 1. Although 236 patients were enrolled in the study, groups included only patients who completed the first 1 year of follow-up monitoring. The groups receiving urinary antibiotic prophylaxis were smaller in size, reflecting, in addition to patients who were lost to follow-up monitoring, a higher dropout rate because of poor compliance with prophylactic antibiotic therapy.

Baseline characteristics were similar between the groups. No statistical differences were found in the median age or the gender ratios of patients in the groups. The group with VUR receiving urinary antibiotic prophylaxis had a median age 1 year older, compared with the other groups, but this difference was not statistically significant. Among patients with VUR, there were no significant differences in the grade of reflux between the group that received antibiotic prophylaxis and the one that did not.

The rates of resolution of VUR after 1 year of follow-up monitoring were 37.5% (grade I reflux), 12.5% (grade II reflux), and 10.3% (grade III reflux). The resolution rates did not differ significantly in the groups with or without the use of urinary antibiotic prophylaxis.

Recurrence of UTIs

Most of the patients did not experience UTI recurrence. The overall incidence of UTI after pyelonephritis, including all groups, was 20.1%. Among patients not receiving urinary antibiotic prophylaxis, the incidence of 22.4% for those with VUR was not significantly different from the 23.3% for those without VUR ($P = .9999$). Among children receiving urinary antibiotic prophylaxis, the recurrence rate of 8.8% for patients without VUR was not significantly different from the recurrence rate of 23.6% for those with VUR ($P = .0633$).

Timing of Recurrence

A total of 17.5% of recurrences occurred in the first 3 months after the initial episode of acute pyelonephritis, 17.5% between 3 and 6 months, 12.0% between 6 and 9 months, and 53.0% between 9 and 12 months.

Type of Recurrence

Most of the recurrent UTIs were diagnosed as cystitis, 9 among patients without VUR (8.6%) and 15 among patients with VUR (13.3%) (Table 2). The overall rate of recurrence of pyelonephritis was small (12 of 218 pa-

TABLE 1 **Distribution of Demographic Characteristics in the Different Groups**

Characteristic	Patients With VUR		Patients Without VUR	
	Prophylaxis	No Prophylaxis	Prophylaxis	No Prophylaxis
No.	55	58	45	60
Female/male	46/9	45/13	36/9	51/9
Age				
Median	3 y	2 y	2 y	2 y
Range	3 mo to 12 y	3 mo to 9 y	3 mo to 15 y	6 mo to 17 y
Degree of VUR, *n* (%)				
Grade I	9 (16.2)	10 (17.2)		
Grade II	28 (51.1)	29 (50.0)		
Grade III	18 (32.5)	19 (32.7)		

TABLE 2 **Rate and Type of UTI Recurrence in the Different Groups**

Type	*n* (%)			
	Patients With VUR		Patients Without VUR	
	Prophylaxis	No Prophylaxis	Prophylaxis	No Prophylaxis
Asymptomatic	0 (0.0)	3 (5.1)	1 (2.2)	4 (6.6)
Cystitis	6 (9.2)	9 (15.5)	1 (2.2)	8 (13.8)
Acute pyelonephritis	7 (12.9)	1 (1.7)	2 (4.5)	2 (3.3)
None	42 (79.6)	45 (75.6)	41 (91.1)	46 (76.7)

TABLE 3 **Rate of Renal Scars After Acute Pyelonephritis in the Different Groups**

	Patients With VUR		Patients Without VUR	
	Prophylaxis	No Prophylaxis	Prophylaxis	No Prophylaxis
Renal scars, *n* (%)	5/55 (9.0)	2/58 (3.4)	2/45 (4.5)	4/60 (6.6)

tients, 5.5%). Although the number of patients with repeat pyelonephritis was greater among patients with VUR, compared with those without VUR (8 patients with VUR versus 4 patients without VUR), there was no significant evidence that VUR increased the chances of recurrence of acute pyelonephritis ($P = .3781$).

Recurrence of Pyelonephritis and Urinary Antibiotic Prophylaxis

Among patients with VUR, there was no clinical advantage to the use of urinary antibiotic prophylaxis to prevent acute pyelonephritis (Table 2). Recurrent acute pyelonephritis was observed for 7 patients receiving urinary antibiotic prophylaxis, compared with only 1 of the patients with no prophylaxis ($P = .0291$). In all of the 7 cases, the offending bacteria showed resistance to the antibiotic used for prophylaxis.

Recurrent Pyelonephritis and Degree of Reflux

Six of the 8 patients with recurrent pyelonephritis and VUR had grade III reflux. For the other 2 patients, the reflux was grade II. Four of the patients without reflux had a recurrent episode of pyelonephritis. In the case of cystitis and VUR, 46% of the patients had grade III reflux, 40% grade II, and 14% grade I.

Renal Scars

Only 13 (5.9%) of the 218 patients developed renal scars, identified with DMSA renal scans, during the 1 year of follow-up monitoring, including 7 of the patients with VUR (6.2%) and 6 of the patients without VUR (5.7%) (Table 3). Similar rates of scarring were found for patients who received prophylaxis and those who did not. One of the 19 patients with grade I VUR (5.3%), 3 (5.2%) of the 57 with grade II VUR, and 5 (13.5%) of the 37 with grade III VUR showed parenchymal defects consistent with scars on subsequent DMSA renal scans. There was no significant evidence that VUR increased the chances of developing renal scars after pyelonephritis ($P = .9999$). There were no reported side effects associated with the use of urinary antibiotic prophylaxis.

DISCUSSION

The well-known association between VUR and UTI has led to the concept that VUR plays a pathogenetic role in the development of UTI, acute pyelonephritis, and renal scars. This pathogenetic role has become the basis for the current therapeutic modalities designed to avoid renal parenchymal damage.[3] Despite a plethora of reports on the subject, none of the pathogenetic considerations or therapeutic modalities has been validated rigorously. Therapeutic recommendations have been based on expert opinion rather than objective data.[10]

In this study, patient groups were similar regarding gender distributions, age, and, in the case of VUR, distributions of the different grades. The distribution of the different grades of VUR is also similar to those in previous reports, which suggests that results are not biased by a disproportionate number of patients with a particular reflux grade.[6,11] In addition, the rate of resolution of reflux among our patients is similar to published rates.[12]

It is difficult to compare UTI recurrence rate, type of infection after recurrence, and scar formation observed in this study with those reported previously, for several reasons. (1) Earlier studies included, at entry, patients with cystitis and pyelonephritis.[13–15] In the same reports, the diagnosis of acute pyelonephritis and cystitis was made on the basis of clinical and laboratory findings. Both have been shown to be unreliable as diagnostic tools for pyelonephritis among patients <2 years of age.[16–18] Because the natural courses of cystitis and pyelonephritis may differ, the inclusion of these 2 types of UTIs in the initial selection may influence the rate and type of recurrence seen during follow-up monitoring. (2) In the International Reflux Study, only patients with grade III and IV reflux were studied.[13,14] Hoberman et al[6] included patients with grade IV VUR in addition to those with grade I to III reflux. (3) The duration of intravenous

therapy was longer in our studies than in the majority of published reports. Although it was not tested systematically, the length of treatment could be a factor influencing the formation of renal scars.

The overall UTI recurrence rate is similar to that reported by Hoberman et al[6] (after 6 months, 6.3% in our group and 8.5% in their study) and the International Reflux Study group.[13] The Southwest Pediatric Nephrology Study Group (which also included only patients with grade I–III reflux), reported that an overall 17.6% of patients experienced a breakthrough infection.[15]

The recurrence rate seen among our patients with VUR not receiving prophylaxis was similar to that observed among patients without VUR. This finding, if confirmed by others, will be clinically significant, because the aim of urinary antibiotic prophylaxis has been to prevent a postulated increased risk of UTI recurrence among patients with VUR. Studies before the time when it became customary to use urinary antibiotic prophylaxis for patients with reflux demonstrated that the rates of recurrence of UTI among patients with reflux did not differ significantly from the rates for the group of children with UTI who did not have VUR.[19,20]

At least 80% of our patients experienced no recurrence of UTI during the 1-year period of observation. Those who presented with an infection had cystitis as the most common type of UTI. Moreover, no differences in recurrence patterns between patients with VUR and those without VUR were apparent. After 1 year of follow-up monitoring, the rate of recurrence of acute pyelonephritis was low. Govan and Palmer,[21] working before DMSA scanning was available and defining the site of infection through bacteriologic evaluation, reported that, after acute pyelonephritis, most patients' recurrences were cystitis. These data contrast with those of Jodal et al,[13] representing the European branch of the International Reflux Study, in which most patients receiving prophylaxis developed pyelonephritis as recurrence. However, not all of their patients presented initially with acute pyelonephritis, and their study population included patients with grade IV reflux. In addition, the recurrence rate was highest in the group <1 year of age and the diagnosis was made on clinical grounds. As mentioned previously, the diagnosis of pyelonephritis among <2-year-old children is difficult to make solely with clinical data.

Currently it is thought that VUR of grade II and above increases the incidence of acute pyelonephritis because infected urine is allowed to reach the kidney. This would be particularly important for patients with intrarenal reflux.[22] Studies of piglets and adult pigs demonstrated that only infected animals with VUR developed renal parenchymal infection.[23,24] We did not observe an overall effect of VUR on the development of acute pyelonephritis. However, the *P* value ($P = .3781$) observed when the role of VUR as a factor predisposing patients to develop acute pyelonephritis was evaluated might be indicative of a relationship that was simply not detected in this study; therefore, additional studies with larger number of patients are warranted.

A review of the reports that used DMSA scans to define the pathogenetic role of reflux in acute pyelonephritis yields conflicting data. Some studies support the role of VUR in the development of acute pyelonephritis, whereas others do not.[25–30] Moreover, patient selection is biased toward the association between reflux and pyelonephritis, because in many instances patients underwent a VCUG only because of abnormal DMSA scan results.[28]

In their studies of piglets with bilateral pyelonephritis, Ransley and Risdon[23] reported the presence of scars only in kidneys with refluxing ureters. We did not identify a role for mild/moderate VUR as a predisposing factor in the development of renal scars. The incidence of renal scars after acute pyelonephritis was low, but scars were observed with the same frequency among patients without reflux.

The decreased rate of renal scars in this study cannot be explained by the age of our population, because most of our patients were <5 years of age and thus the effect of acute pyelonephritis on renal scarring should have been more apparent. It was suggested that older children have the same or increased rates of renal scars after acute pyelonephritis.[11,31] In both studies, however, repeat DMSA renal scans were obtained 3 months after the acute episode. This time interval could be too short to differentiate between parenchymal inflammatory changes and renal scars, as shown by others.[32]

Previous studies that used DMSA scans to assess for renal scars did not support the concept that VUR predisposes patients with acute pyelonephritis to renal scarring.[33–35] A recent systematic review and meta-analysis showed that primary VUR was a weak predictor of renal damage among patients hospitalized because of an UTI. The authors also emphasized that renal damage often occurs among patients with UTIs but no demonstrable VUR.[36]

A relationship between VUR grade and scarring after acute pyelonephritis has been postulated. With DMSA renal scintigraphy, renal scars after acute pyelonephritis are seen more frequently among patients with higher grades of reflux.[37] This finding is consistent with those seen in animal studies, because intrarenal reflux, which in theory may occur even with low grades of reflux, has been documented only with higher grades of reflux. In this study, most of the patients who developed recurrence of pyelonephritis had grade III VUR.

In contrast, the relationship between reflux grade and renal scars after acute pyelonephritis has been challenged by Winberg et al.[38] Those authors, using intravenous pyelograms to detect renal scars during follow-up monitoring of children with "usually febrile" UTIs, found

that 23 kidneys developed scars; no kidneys with grade IV reflux had renal scarring, whereas 15 with grade 0 to II reflux did.[38]

The incidence of renal scars in this study is low, compared with previous publications.[10,11,31] In this study, DMSA scans to assess for scars were repeated 6 months after the acute episode. The highest incidence rates of scars were reported in series that repeated DMSA scans 3 months after the acute episode.[11,31] Hoberman et al,[6] studying patients 6 months after the initial UTI, reported rates of renal scars between 16.9% and 13.6% (with oral and intravenous therapy, respectively).

It was demonstrated in piglets that antibiotic therapy decreased the incidence of renal scars among animals with VUR.[23] Our patients received 5 to 7 days of intravenous antibiotic therapy, in contrast to previous studies in which the duration of intravenous antibiotic therapy was shorter. It is not known, however, whether longer courses of intravenous therapy could decrease the incidence of renal scars after acute pyelonephritis.

The purpose of the long-term use of urinary antibiotic prophylaxis among patients with VUR is to keep the urinary tract sterile, preventing the development of acute pyelonephritis and the formation of renal scars. Our data indicate that urinary antibiotic prophylaxis among patients with grade I to III VUR does not decrease the overall incidence of recurrent UTI, the rate of pyelonephritis, or the formation of renal scars. Among our patients, prophylaxis increased the chance of developing pyelonephritis. In addition, because most of the patients experienced cystitis during the follow-up period and the rates of pyelonephritis and cystitis were not different between the prophylaxis group and the no-prophylaxis group, the prolonged use of antibiotics does not seem to be indicated.

Previously, the use of urinary antibiotic prophylaxis among patients with VUR had not been tested in randomized studies that included a no-treatment group. In contrast to initial studies in which patients with VUR who received prophylaxis had almost no recurrence of infections,[39] subsequent studies of patients who received urinary antibiotic prophylaxis demonstrated that the rate of breakthrough infections among patients with VUR was as high as that observed for our group of patients without prophylaxis.[12,40] Moreover, systematic reviews of randomized, controlled trials of antibiotic treatment for the prevention of UTIs among children showed considerable uncertainty regarding whether long-term, low-dose, antibiotic administration prevents UTIs among children,[41,42] especially because no-treatment groups were not included.[39]

The aim of urinary antibiotic prophylaxis is to reduce the incidence of renal scars by reducing the episodes of acute pyelonephritis. Our data showed that the rate of recurrence of acute pyelonephritis was rather low and that, at the end of the 1-year follow-up period, there was no significant difference in the rates of renal scars, regardless of the use of antibiotic prophylaxis. Finally, the rates of renal scarring are similar for patients who receive urinary antibiotic prophylaxis and those who do not but are treated for each episode of acute UTI.[13,43,44]

This is the first report that addresses the discussed issues in a controlled, randomized study. The size of our sample was powered to detect a clinically significant difference of 20% with respect to the effect of VUR on recurrence of infection, acute pyelonephritis, renal scarring, and use of urinary antibiotic prophylaxis. The sample size was calculated as 60 patients per group. During the trial, it was clear from the beginning that the dropout rate for the group receiving prophylaxis was higher than planned. The analysis based on treatment is biased toward finding a significant difference between the groups. The fact that we did not observe a significant difference and that the end point results among the groups were similar suggests that either using an intent-to-treat approach or specifically recruiting patients in the prophylaxis groups to complete the number of patients to be allocated would not have changed the conclusions of this study.

CONCLUSIONS

After 1 year of follow-up monitoring, our study suggests that mild/moderate VUR does not increase the incidence of UTI, pyelonephritis, or renal scarring after an acute episode of pyelonephritis. Moreover, a role for urinary antibiotic prophylaxis in preventing recurrence of infection and development of renal scars is not supported by this study.

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