

Vesicoureteral reflux in children with urinary tract infections caused by atypical pathogens: Diagnostic accuracy of renal ultrasound

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ABSTRACT

Introduction. The need to perform voiding cystourethrography (VCUG) in patients with a first episode of urinary tract infection (UTI) caused by atypical pathogens is controversial. The primary objective of this study was to evaluate the diagnostic accuracy of renal ultrasound for predicting vesicoureteral reflux (VUR) in these patients.

Population and methods. Retrospective study of diagnostic accuracy. We analyzed medical records of patients under 2 years of age with a first episode of UTI caused by an atypical pathogen, for whom ultrasound and voiding cystourethrography (VCUG) results were available. We calculated the ability of ultrasound to predict VUR, using the VCUG as the gold standard.

Results. A total of 166 patients were included (65.1% male, median age 2.36 months). The predominant uropathogen was *Klebsiella pneumoniae* (45.2%). Vesicoureteral reflux was diagnosed in 63 patients (prevalence: 38%, 95% CI 30.3-45.1); in 33 cases (52.3%), it was high-grade. Pathological ultrasound findings were significantly associated with VUR ($p < 0.001$; OR 4.3; 95% CI 2.2-8.5). The sensitivity, specificity, positive predictive value, and negative predictive value of ultrasound for predicting VUR of any grade were 55.6%, 77.7%, 60.3%, and 74.1%, respectively. For high-grade VUR, sensitivity was 100%, and specificity was 81.2%. No cases of high-grade VUR with normal ultrasound findings were observed.

Conclusion. In patients with the first episode of UTI caused by an atypical pathogen and normal ultrasound findings, no cases of high-grade VUR were observed, suggesting that these patients could be evaluated similarly to those with a first UTI caused by *Escherichia coli*.

Keywords: urinary tract infections; pediatrics; ultrasonography; urinary system; vesicoureteral reflux.

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INTRODUCTION

Urinary tract infections (UTIs) are one of the most common bacterial conditions in pediatrics; they affect 3% of prepubertal girls and 1% of prepubertal boys.^{1,2} *Enterobacteria* are the predominant causative agents in childhood. Among these, *Escherichia coli* causes 85-90% of cases, followed in frequency by *Klebsiella* spp., *Proteus* spp., *Enterococcus* spp., and *Enterobacter* spp.¹

When evaluating a patient with a urinary tract infection, it is important to rule out underlying nephro-urological malformations, as these determine the renal prognosis.³ Among these, the most common is vesicoureteral reflux (VUR), which—especially when severe—is associated with an increased risk of progression to chronic kidney disease.⁴ Although voiding cystourethrography (VCUG) is the gold standard for diagnosing and classifying VUR, it is an invasive procedure that carries a risk of infection and radiation exposure.⁵⁻⁷ In recent years, the indications for VCUG in children with UTIs have been significantly reduced; however, the management of patients with UTIs caused by atypical pathogens (defined as other than *E. coli*) remains controversial, and there is no consensus among the various guidelines on how these patients should be evaluated.^{1,2,8-16} Given that these uropathogens have a lower ability than *E. coli* to colonize and ascend the urinary tract, their isolation could suggest a urinary tract abnormality that facilitates infection,¹ which is why some guidelines recommend performing a VCUG on all children under 6 months of age with UTI caused by atypical pathogens, while others reserve it for patients with abnormal ultrasound findings, a family history of VUR, or recurrent UTI, and still others—such as the guidelines in Argentina—suggest an individualized evaluation.^{1,2,12} This issue arises because the evidence supporting current guidelines comes primarily from studies of patients with *E. coli* UTIs.^{17,18} Consequently, we conducted this study with the following objectives.

Primary objective

- To evaluate the diagnostic ability of renal and urinary tract ultrasound to predict VUR in patients with UTIs caused by atypical pathogens.

Secondary objectives

- Estimate the prevalence of VUR following the first episode of a urinary tract infection caused by an atypical pathogen.

- Describe the causative pathogens and the findings from imaging studies.
- To investigate the association between VUR and age at the time of UTI, sex, pathogen, and ultrasound findings.

POPULATION AND METHODS

Retrospective study of diagnostic accuracy. The study population consisted of medical records of patients under 2 years of age who were treated in the Nephrology Department of a tertiary-care hospital and presented with a first episode of febrile urinary tract infection (UTI) caused by an atypical pathogen, with documented results of VCUG and renal and urinary tract ultrasound. Patients who were immunosuppressed, had a neurogenic bladder, and/or had genetic syndromes associated with nephro-urological malformations were excluded. For sample selection, medical records from our Department were identified retrospectively from institutional records, and cases meeting the inclusion criteria were included consecutively in reverse chronological order, starting in January 2024, until the planned sample size was reached (May 2022). The following variables were collected: age at UTI diagnosis, sex, causative pathogen, and results of ultrasound, and VCUG. The imaging studies were performed by pediatric radiology specialists at our institution, who were aware of the results of the previous studies. The ultrasound was performed at least 15 days after resolution of the UTI, in accordance with current recommendations, as earlier testing may detect transient abnormalities.⁸ In our Department, it is standard practice to perform VCUG on all patients with atypical UTI after the acute inflammation has resolved (at least 4-6 weeks after the UTI).⁸ The procedure involves inserting a non-balloon catheter of an age-appropriate size. Prior to iodinated contrast infusion, a single anteroposterior view is obtained to cover the kidneys, ureters, and bladder. During bladder filling, and subsequently during voiding, multiple images are obtained in the anteroposterior, right oblique, and left oblique positions to detect possible anatomical abnormalities and/or passive or active reflux, respectively. Finally, the urethra is evaluated. The procedure is performed with a negative urine culture and under prophylactic antibiotic coverage.¹⁹

Operational definitions

ITU: signs and symptoms attributable to urinary

tract involvement associated with an inflammatory reaction and isolation of a single pathogen with a count of $\geq 10^5$ CFU in a spontaneous sample, $\geq 10^4$ CFU by bladder catheterization, or any count by suprapubic puncture.⁸

UTI caused by atypical pathogens: UTI caused by bacteria other than *E. coli*.⁸

Urological pathology: abnormalities detected on any imaging study of the kidneys and/or urinary tract.¹⁹

Normal renal and urinary tract ultrasound: both kidneys are orthotopic, with normal shape, size, and echostructure; normal bladder; and no hydronephrosis. The difference in renal longitudinal diameter is no greater than 10 mm.²⁰

VUR: retrograde flow of urine from the bladder to the upper urinary tract.²¹ Cases were classified (I-V) according to the International VUR Classification, with grades III through V considered high-grade; cases involving both sides were classified according to the grade of the more severe side.^{21,22}

Normal CUGM: absence of VUR with a normal bladder and urethra.²³

Statistical considerations

The sample size for evaluating the diagnostic performance of renal ultrasound in predicting VUR was estimated using a specificity of approximately 87% in patients with *E. coli* UTIs.²⁴ Assuming non-inferior performance, with a 95% confidence interval (95% CI), a margin of $\pm 10\%$, and an expected prevalence of VUR of 30%,⁴ 145 patients were required. Secondly, to estimate the prevalence of VUR in atypical UTIs, considering that 30% of UTIs are caused by atypical pathogens and that 40% present with VUR,^{17,18} with approximately 600 annual urine cultures for atypical pathogens in our hospital, and estimating that 50% would be excluded because they corresponded to recurrences, with a 95% confidence level and 80% power, 166 patients were required. Since this included the required sample size for the primary objective, the final sample size was 166 patients.

Quantitative variables were expressed as the median (interquartile range, IQR) because they did not follow a normal distribution (Shapiro-Wilk test), whereas categorical variables were reported as frequencies or percentages. They were then compared using the Wilcoxon test (quantitative variables) or the chi-square test or Fisher's exact test (categorical variables), with their respective odds ratios (ORs) and 95% CIs, as appropriate.

The prevalence of VUR was estimated as the percentage of patients with VUR in the total sample, along with its respective 95% CI.

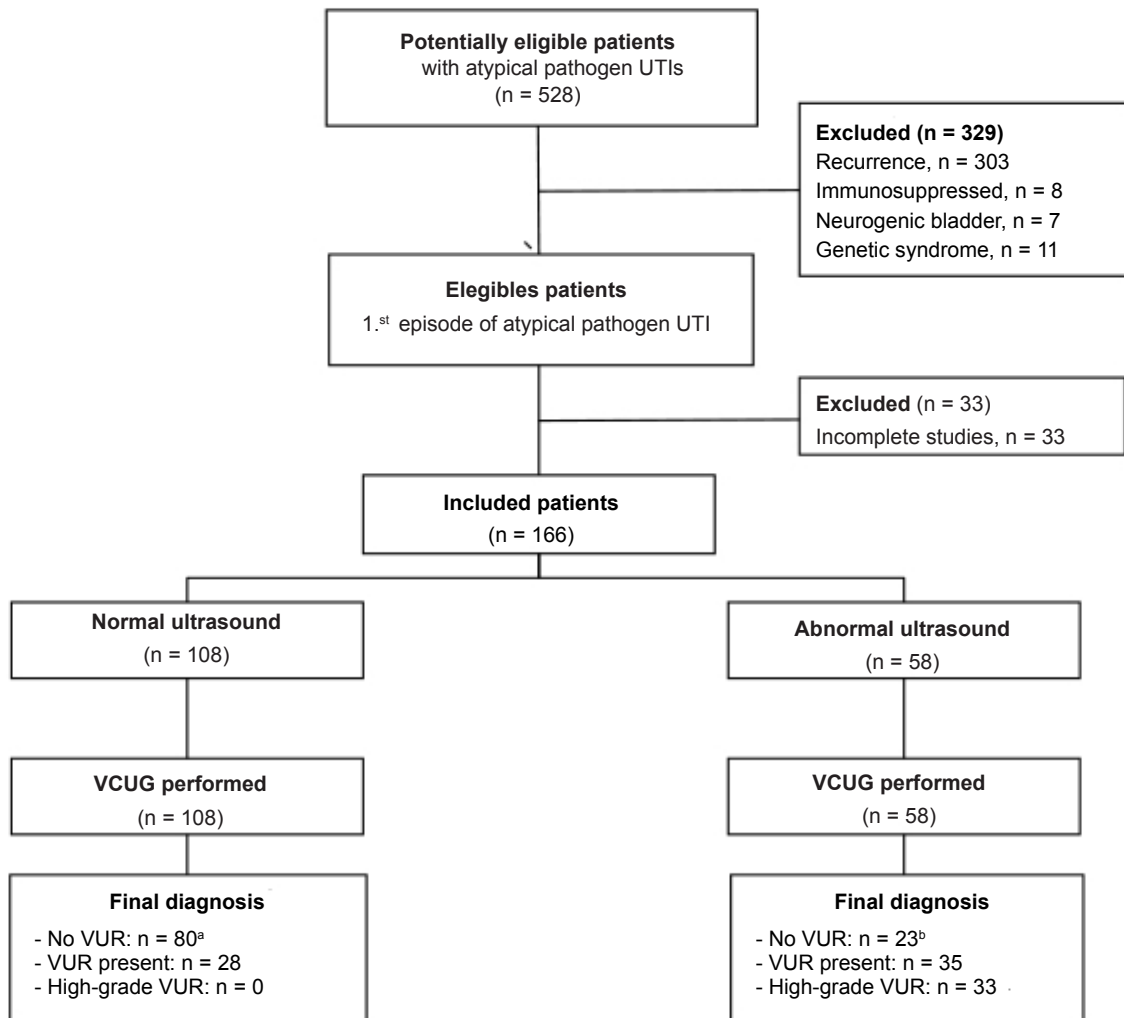
The diagnostic ability of renal ultrasound to predict VUR was assessed by calculating, in a two-way contingency table, the sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios, using the VCUG results as the gold standard. The post-test negative and positive probabilities were also calculated. The Statistix7™ software (Analytical Software, Tallahassee, FL) was used, with a p -value < 0.05 considered statistically significant. The study adhered to the ethical principles set forth in the Declaration of Helsinki and was approved by the Ethics Committee of the Hospital General de Niños Pedro de Elizalde. This article was written in accordance with the STARD guidelines for diagnostic studies.²⁵

RESULTS

A total of 166 patients with UTIs caused by atypical pathogens were included (*Figure 1*). The median age at the time of the UTI was 2.36 months (IQR 1-5.4 months); 8 patients were older than 1 year (4.8%). The sample consisted of 108 males (65.1%). The most frequently isolated uropathogen was *Klebsiella pneumoniae* (45.2%) (*Table 1*).

Renal and urinary tract ultrasound findings were abnormal in 58 of 166 patients (35%), with hydronephrosis being the most common finding (28.3%; $n = 47$) (*Table 2*). On the other hand, 65 patients had abnormal CUGM findings; however, because findings in 2 cases were not VUR, the prevalence of VUR was 38% ($n = 63$; 95% CI, 30.3-45.1), of which 33 (52.3%) were high-grade VUR. There were no significant differences in age, sex, or causative pathogen between patients with and without VUR (*Table 3*). However, echographic abnormalities were significantly more frequent in patients with VUR ($p < 0.001$; OR 4.3; 95% CI 2.2-8.5); 91.6% ($n = 33$) of patients with abnormal ultrasound and abnormal VCUG findings had high-grade VUR; in contrast, all patients with normal ultrasound and abnormal VCUG findings had low-grade VUR (*Table 4*). Abnormal renal ultrasound showed a sensitivity of 100% (95% CI 89.4-100) and a specificity of 81.2% (95% CI 74.7-87.7) for predicting high-grade VUR (*Table 5*). In the presence of an abnormal renal ultrasound, the post-test probability of high-grade VUR was 56.9%, while a normal ultrasound was associated

FIGURE 1. Flowchart of patients



VCUG: voiding cystourethrography, VUR: vesicoureteral reflux.

a 1 case of bladder diverticulum.

b 1 case of ureterocele.

with the absence of high-grade VUR.

DISCUSSION

The prevalence of VUR in UTIs of any etiology is approximately 30%.^{1,2,17} In our series, which was limited to UTIs caused by atypical pathogens, the prevalence was 38%, consistent with other studies. Marcus *et al.* reported a higher frequency of ultrasound abnormalities in UTIs caused by atypical pathogens compared with those caused by *E. coli* (43.9% vs. 23%) and a higher prevalence of VUR, although not statistically significant (41.5% vs. 37%).¹⁸ In another study analyzing 139 patients with UTIs (107 caused by *E. coli* and 32 by atypical pathogens), the prevalence of urological anomalies was higher

in the latter group (43.8% vs. 5.6%).²⁶ Similarly, Honkinen *et al.* compared 92 patients with *E. coli* UTIs and 92 with UTIs caused by atypical pathogens, observing VUR in 33% and 42.4%, respectively. Furthermore, these authors found that when the causative agent was *Klebsiella* or *Enterococcus*, the VUR rate was nearly double (62%) that observed in cases caused by *E. coli*.¹⁷ In our series, the prevalence of VUR was similar among patients with UTIs caused by *Klebsiella* or other atypical organisms. However, the heterogeneity of the identified pathogens, which vary in virulence, could influence the results; therefore, these findings should be confirmed in studies with larger sample sizes that allow for the analysis of these subgroups. In a cohort of

TABLE 1. Microbiological findings in 166 patients with urinary tract infection caused by atypical pathogens

Uropathogen	Number of patients	%
<i>Klebsiella pneumoniae</i>	75	45.2
<i>Enterobacter cloacae</i>	18	10.9
<i>Proteus mirabilis</i>	18	10.9
<i>Enterococcus faecalis</i>	16	9.6
<i>Klebsiella oxytoca</i>	12	7.2
<i>Serratia marcescens</i>	6	3.6
<i>Klebsiella</i> spp.	4	2.4
<i>Candida albicans</i>	3	1.8
<i>Pseudomonas aeruginosa</i>	3	1.8
<i>Citrobacter braakii</i>	2	1.2
<i>Streptococcus agalactiae</i>	2	1.2
Other pathogens	7	4.2

TABLE 2. Ultrasound findings in 166 patients with atypical urinary tract infection

Ultrasound finding	Patients (n, %)
Normal ultrasound	108 (65.1)
Abnormal ultrasound	58 (34.9)
Hydronephrosis	47 (28.3)
Double excretory system	3 (1.8)
Anatomical solitary kidney	3 (1.8)
Hydronephrosis + renal asymmetry	2 (1.2)
Ureterocele	1 (0.6)
Asymmetry in kidney size	1 (0.6)
Hydronephrosis + anatomical solitary kidney	1 (0.6)

TABLE 3. Comparison between patients with and without vesicoureteral reflux

Variable	VUR (n = 63)	No (n = 103)	p-value	Odds ratio (CI 95%)
Age (months), median (IQR)	2.1 (1.03-4.2)	2.5 (0.9-5.6)	0.8	N/A
Age (categorical), n (%)				
<3 months	37 (58.7)	56 (54.4)	0.58	1.19 (0.6-2.2)
3-6 months	14 (22.2)	23 (22.3)	0.98	0.99 (0.4-2.1)
6 months-1 year	9 (14.3)	19 (18.5)	0.48	1.35 (0.7-3.2)
>1 year	3 (94.8)	5 (4.8)	1.00	1.02 (0.2-4.4)
Sex (M/F), n (%)	42/21 (66.7/33.3)	66/37 (64/36)	0.73	1.12 (0.5-2.1)
Causative pathogen, n (%)				
<i>Klebsiella pneumoniae</i>	34 (54)	41 (39.8)	0.13	1.77 (0.9-3.3)
Others	29 (46)	62 (60.2)		
Abnormal ultrasound, n (%)	35 (55.5)	23 (22.3)	<0.001	4.3 (2.2-8.5)

VUR: vesicoureteral reflux, IQR: interquartile range, M/F: male/female, N/A: not applicable.

769 children (699 with *E. coli* UTIs and 70 with other microorganisms), they observed a higher incidence of high-grade VUR in infections caused by atypical pathogens.²⁷

The evaluation of the urinary tract in children with UTIs is based on renal ultrasound. In this context, a normal ultrasound has a negative

predictive value of 86% for ruling out VUR of any degree.²⁸ However, its greatest value lies in the low prevalence of high-grade VUR (6%) among these patients, supporting its role as an initial risk stratification tool.²⁸

Pennesi *et al.* observed that UTIs caused by atypical pathogens presented pathological

TABLE 4. Findings on voiding cystourethrography in relation to the results of renal and urinary tract ultrasound

Variable	Normal VCUG	Pathological VCUG	VUR (all grades)	Low-grade VUR (I-II)	High-grade VUR (III-IV)
Normal ultrasound (n = 108)	79	29 ^a	28	28	0
Pathological ultrasound (n = 58)	22	36 ^b	35	2	33
Total (n = 156)	101	65	63	30	33

VCUG: voiding cystourethrography, VUR: vesicoureteral reflux.

^a 1 case of bladder diverticulum.

^b 1 case of ureterocele.

TABLE 5. Diagnostic accuracy of renal and urinary tract ultrasound for detecting vesicoureteral reflux in patients with urinary tract infection caused by atypical pathogens

VUR grade	Sensitivity % (95% CI)	Specificity % (CI 95%)	PPV % (CI 95%)	NPV % (CI 95%)	PLR % (CI 95%)	NLR % (CI 95%)
Grade I-II	55.6 (43.5-67.3)	77.7 (69.9-85.4)	60.3 (48.3-72.3)	74.1 (66.0-82.2)	2.5 (1.6-3.8)	0.5 (0.4-0.7)
Grade III-IV	100 (89.4-100)	81.2 (74.7-87.7)	56.9 (44.1-69.7)	100 (96.6-100)	5.3 (3.7-7.6)	0 (0-0)

VUR: vesicoureteral reflux; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value;

PLR: positive likelihood ratio; NLR: negative likelihood ratio.

ultrasound findings 5.5 times more frequently than those caused by *E. coli* (27.7% vs. 6.3%, respectively).²⁹ Consistently, in our series, abnormal ultrasound findings were also common and were associated with a significant increase in the frequency of VUR; 91.6% of patients with abnormal ultrasound and VCUG findings had high-grade VUR (III-V), whereas only low-grade VUR was observed in patients with normal ultrasound. Furthermore, in our cohort, a normal ultrasound was associated with the absence of high-grade VUR, suggesting a very low risk in this subgroup. Consistent with our findings, a study of 40 patients with UTI caused by atypical pathogens found no evidence of high-grade VUR in those with normal ultrasound results.²⁹

The results of this study could provide useful information for the discussion on imaging follow-up after a urinary tract infection (UTI) caused by an atypical pathogen,¹⁰⁻¹⁶ which helps avoid invasive procedures and ionizing radiation, which are often unnecessary. Of particular interest, the guidelines of the Sociedad Argentina de Pediatría leave the decision to perform a VCUG to the specialist's discretion,⁸ whereas the American Academy of Pediatrics recommends performing it in all cases of UTI caused by atypical pathogens.¹ Given an 80% rate of spontaneous resolution of VUR in grades I and II, with a low

risk of developing pyelonephritic scars and minimal clinical implications,^{6,7} our findings suggest that patients with a first UTI caused by atypical pathogens and a normal ultrasound may not require additional testing. Taken together, these findings suggest that the imaging evaluation following a first UTI caused by an atypical pathogen may reasonably mirror that recommended for patients with a first UTI caused by *Escherichia coli*.

This study has several limitations that should be noted. First, it was conducted in a nephrology department, which may have overestimated the prevalence and severity of VUR; however, this is expected, since the recommendation in such cases is evaluation by a specialist. Furthermore, although VCUG was routinely performed at our center in patients with UTIs caused by atypical pathogens, selection bias cannot be completely ruled out; therefore, these results should be extrapolated with caution to settings where its use is more selective. Consequently, the higher prevalence and severity of VUR in this cohort may have led to an overestimation of ultrasound's diagnostic yield. Furthermore, male patients predominated in our series. Although this is to be expected, given that at the age of the patients included in this study, UTIs are more common in males,¹ these findings should be

generalized to females with caution. Additionally, the presence of phimosis, a factor that may predispose patients to UTIs caused by atypical pathogens,³⁰ was inconsistently documented in the medical records, preventing its inclusion in the analysis. Furthermore, the lack of blinding among diagnostic imaging professionals and the fact that ultrasounds were performed by pediatric specialists may have introduced diagnostic bias, leading to an overestimation of the tests' accuracy. Finally, the absence of false negatives in our sample resulted in a sensitivity of 100% and a post-test probability of 0% for normal ultrasound scans; however, these findings should be considered empirical estimates rather than absolute values. Given these limitations, it would be advisable to confirm these findings with prospective studies.

CONCLUSION

VUR was found in 38% of patients with a first episode of UTI caused by an atypical pathogen. In our cohort, no cases of high-grade VUR were observed among patients with normal renal ultrasound findings, suggesting that these patients could be evaluated similarly to those with a first UTI caused by *Escherichia coli*. ■

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