

# Impact of using an evidence-based clinical guideline for the management of primary vesicoureteral reflux in children

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## ABSTRACT

**Objective:** To analyze changes in the therapeutic approach at a tertiary care hospital following the implementation of a clinical guideline for the treatment of primary vesicoureteral reflux (VUR) in children.

**Population and methods:** Retrospective study conducted in a cohort of patients with primary VUR (1989-2015) aged 0-15 years at a tertiary care hospital. The therapeutic approach before and after the development of the clinical guideline (2008) was compared.

**Results:** A total of 297 patients (49.8% boys, 50.2% girls) were included; their mean age at the time of diagnosis was 21.71 months. VUR grading was: VUR I-III 45.1%, VUR IV-V 54.9%; 124 were treated after the implementation of the clinical guideline (group 1), and 173, before (group 2). The mean follow-up period was 124.32 months. A conservative approach was the initial treatment in 70.3% of group 1 patients and 67.9% of group 2 patients. The number of surgeries remains constant (31.45% versus 31.79%), with an increase in the number of endoscopic surgeries ( $p < 0.005$ ). The profile of patients has changed based on the application of the algorithm proposed by the guideline. Fewer surgeries were done in patients with VUR IV-V (82.32% versus 59.9%,  $p = 0.000$ ) and there were fewer cases of kidney damage at diagnosis (49.4% versus 9.8%,  $p = 0.000$ ).

**Conclusions:** The implementation of the clinical guideline has favored an initially conservative approach in patients with severe grade VUR and nephropathy, for whom surgery was traditionally indicated initially. Using clinical guidelines favors a unanimous, evidence-based approach that reduces the performance of unnecessary invasive procedures.

**Key words:** vesicoureteral reflux, clinical practice guideline, nephropathy, pediatrics.

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## INTRODUCTION

Primary vesicoureteral reflux (VUR) is a heterogeneous process defined as retrograde, non-physiological flow of urine from the urinary bladder into the ureter, without an anatomic or neurological cause.<sup>1,2</sup> It is a common reason for consultation at the departments of Pediatric Nephrology, General Pediatrics, Pediatric Surgery or Pediatric Urology.

The traditional approach to VUR has been based on two fundamental alternatives: anatomic and functional correction with surgery or conservative management based on general hygiene measures and antibiotic prophylaxis while waiting for spontaneous resolution. In 2008, the first Clinical Practice Guideline (CPG) for primary VUR in children was developed through the Health Guideline (Guía Salud) project. The CPG lays the foundations for the management of VUR based on scientific evidence,<sup>3</sup> promotes patient sequential management (Figure 1), and assesses the effectiveness of different therapeutic strategies, their ability to reduce the number of urinary tract infections (UTIs) and, most importantly, their ability to protect the renal parenchyma and, secondarily, long-term kidney function. The CPG was updated in 2014 (Figure 2).<sup>4</sup>

Although most guidelines and consensus advocate a conservative management as the therapy of choice, and its modification based on the development of recurrent febrile UTI or risk factors, such as kidney injury or dilated VUR,<sup>5</sup> still some health care providers indicate a surgical

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approach as initial treatment for primary VUR.<sup>3</sup> Eight years after the publication of the CPG, not sufficient studies have been conducted to assess the impact of the guideline implementation so it was decided to analyze the therapeutic approach developed in a tertiary care hospital following the implementation of the CPG recommendations proposed in 2008 and reviewed in the 2014 update.<sup>4</sup>

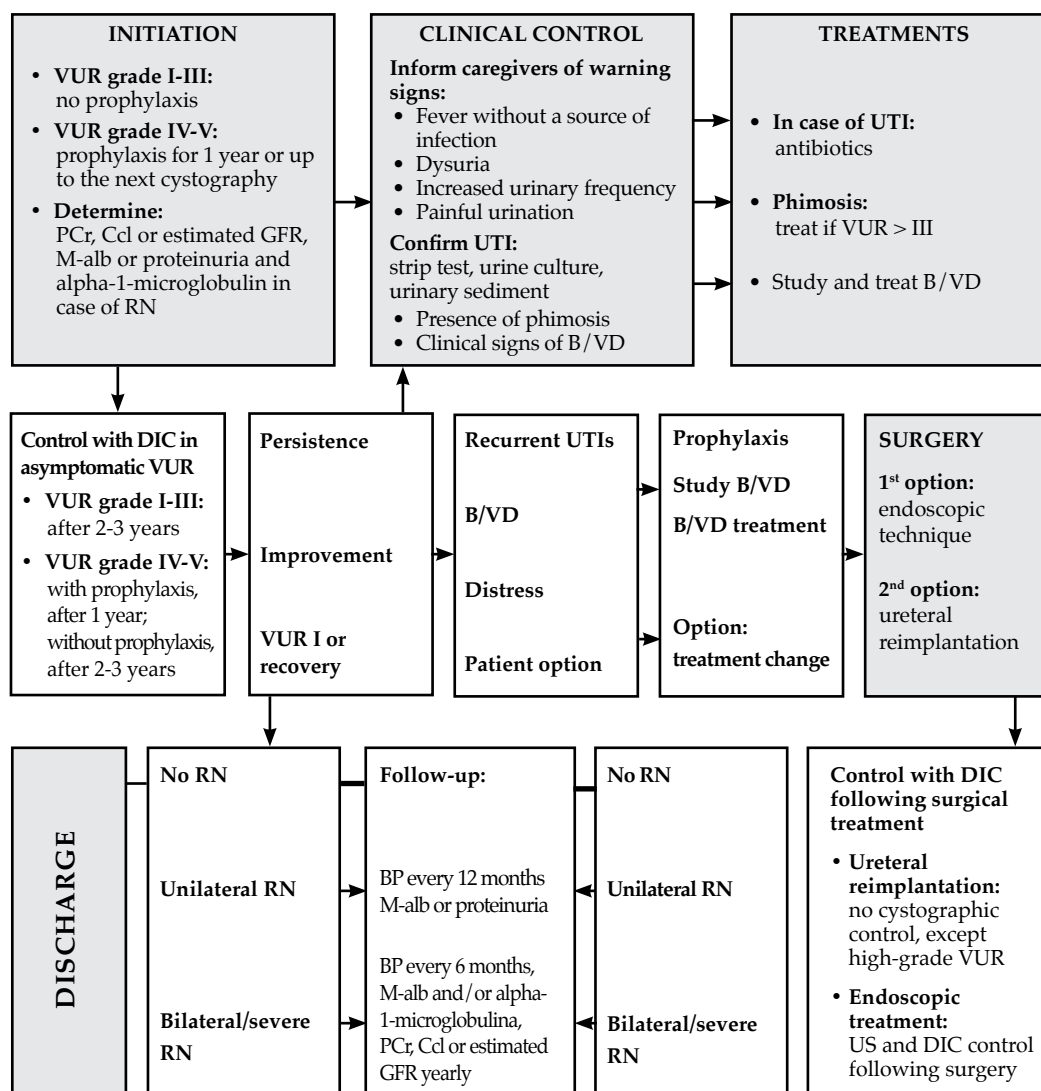
### MATERIAL AND METHODS

This was a retrospective study with patients

diagnosed with primary VUR, aged 0-15 years, following antenatal ultrasound findings or a UTI episode, seen at a referral pediatric urology facility in the Community of Aragón (Spain), between 1989 and 2015.

Patients were divided into group 1 (diagnosed as of 2008) and group 2 (diagnosed before 2008). Patients with concomitant kidney-urologic disease, including renoureteral duplication, urethral stricture, pyeloureteral junction stenosis, unilateral renal agenesis, neurogenic bladder, and bladder exstrophy, were excluded.

FIGURE 1. Therapeutic diagnostic algorithm for the management of primary vesicoureteral reflux in children based on the Clinical Practice Guideline from 2008<sup>3</sup>



DIC: direct isotope cystography. Ccl: creatinine clearance. B/V/D: bladder or voiding dysfunction. GFR: glomerular filtration rate. UTI: urinary tract infection. M-alb: microalbuminuria. RN: reflux nephropathy. PCr: plasma creatinine. VUR: vesicoureteral reflux. BP: blood pressure. US: ultrasound.

All patients were diagnosed with VUR by means of a serial voiding cystourethrography (VCUG) and classified according to the international VUR grading.<sup>6</sup> VUR grade I-III was considered low grade VUR and VUR grade IV-V, high grade VUR.

Kidney damage was assessed with a renal scintigraphy or scan with dimercaptosuccinic acid (DMSA) labeled with Tc99m and classified as per Goldraich's classification.<sup>7</sup> Renal impairment was defined as a reduction in differential renal function below 45%<sup>8</sup> in this test. Outcome measures were collected from the patients' medical records, including sex, age at diagnosis, VUR grade, nephropathy at diagnosis –understood as the presence of kidney scarring in the renal scintigraphy–,<sup>4</sup> bilaterality, voiding abnormalities, therapeutic sequence used, and type of intervention.

Statistical analysis: the software used for this study was PASW Statistic v.18.0.0 (SPSS Inc.). Pearson's  $\chi^2$  test was done for the study's qualitative outcome measures. Kruskal-Wallis non-parametric test was applied for the quantitative outcome measures. The level of confidence for the different tests was established at 95%.

## RESULTS

Three hundred and twenty-three patients were referred with a diagnosis of primary VUR; of these, 26 were excluded because of pyeloureteral duplication (21), pyeloureteral junction stenosis (4), and urethral stricture (1). A total of 297 patients were included in this study, with a proportion of 41.8% (124) of patients corresponding to the 2008-2015 period and 58.2% (173) of patients treated before 2008.

Seventy-one percent of patients had a diagnosis of primary VUR detected because of a UTI, whereas 29% were diagnosed because hydronephrosis was observed in the antenatal ultrasounds.

Patients' mean age at diagnosis was 21.71 months. The proportion of boys and girls in our overall sample was 49.8% and 50.2%,

respectively.

Also, 45.1% had mild-moderate VUR at the time of diagnosis (grade I-III) and 54.9%, severe VUR (grade IV-V). In terms of location, 50.2% of patients had unilateral VUR and 49.8%, bilateral VUR, which accounted for a total of 297 treated patients and 445 refluxing units.

Fifty percent of patients had some extent of renal damage (nephropathy at diagnosis).

The follow-up period of the overall sample was 124.32 months (~10.36 years). As for the therapeutic approach for each group (Table 1), no statistically significant differences were observed in the percentage of patients for whom the therapeutic diagnostic algorithm proposed by the CPG was applied, i.e., initially conservative treatment of VUR, with a proportion of 70.97% in group 1 and 67.63% in group 2 of patients managed with this strategy. In relation to the number of surgeries, a higher proportion of endoscopic surgery in group 1 was observed ( $p=0.000$ ).

Once the profile of patients treated in each group is analyzed (Table 2), and taking into account the clinical characteristics –age at diagnosis, reason for diagnosis, VUR grade, bilaterality, nephropathy at diagnosis–, it is observed that group 1 had a higher percentage of patients diagnosed with antenatal ultrasound, although most patients in both groups were diagnosed following one or several febrile UTI episodes. In relation to VUR grade at diagnosis, among patients with grade IV-V, the percentage of patients for whom conservative treatment was not indicated was significantly higher in group 2 compared to group 1 (82.32% versus 59.9%,  $p=0.000$ ). Likewise, the percentage of patients with nephropathy and initially conservative treatment was higher in group 1 than in group 2 (49.4% versus 39.8%,  $p=0.000$ ). In relation to age, although there were significant differences overall, given the trend towards antenatal diagnosis observed in group 1, no significant differences were identified between both groups in terms of bilaterality.

TABLE 1. Therapeutic procedures done in groups 1 and 2 (N: 297)

Therapeutic approach	Group 1 (2008-2015) (N: 124)	Group 2 (1989-2008) (N: 173)	p (95% CI $\chi^2$ )
Sequential therapy	88 (70.97%)	117 (67.63%)	$p=0.627$
Anti-reflux surgery	39 (31.45%)	55 (31.79%)	$p=1.000$
Open surgery	4 (3.23%)	31 (17.92%)	$p=0.000$
Endoscopic surgery	31 (25.83%)	24 (13.87%)	$p=0.000$

VUR: vesicoureteral reflux; CI: confidence interval.

## DISCUSSION

The first national guideline for the management of primary VUR in children was developed by the Health Guideline project, whose objective was to standardize treatment guidelines and, through their dissemination, help to harmonize therapeutic-diagnostic criteria and promote evidence-based practice.<sup>3</sup> Once results obtained as of 2008 are compared, it is observed that a high percentage of patients had undergone sequential therapy before the guideline implementation. This evidences that physicians and surgeons working in our hospital followed, based on available evidence and the accumulated experience, a conservative approach to VUR in their everyday practice and that, as of 2008, the number of patients treated conservatively has remained practically consistent. Bias is easily identified because the guideline's authors are mostly health care professionals from our field of work; therefore, this analysis would have greater validity if carried out in facilities not related to the development of this area.

In relation to the number of surgeries, the percentage of patients who were operated has not changed significantly. This is the result of a previous eminently conservative approach, so no reduction was expected in the number of surgeries. It has also been observed that the surgical technique of choice shifted to a greater percentage of endoscopic surgery at present. However, authors consider that the CPG itself has not encouraged the performance of endoscopic surgeries but the improvement in several factors, such as the technique itself, the materials used, and hospital accessibility, among

others. Undoubtedly a longitudinal analysis of the study involves time as a factor in this phenomenon, and it is considered that outcomes are the consequence of said bias.

The analysis of the profile of patients treated in each group showed significant differences in multiple outcome measures, which were considered relevant.

The first change was the higher proportion of patients with antenatal diagnosis observed in group 1 compared to group 2. However, although such difference is significant, it cannot be attributed to the CPG itself; it should be interpreted as the result of better antenatal diagnoses, which increase the percentage of congenital hydronephrosis and, as a result, the number of children diagnosed with VUR referred to the Department of Pediatric Urology, and most likely subjected to screenings.

In spite of the notably conservative approach applied in group 2, this study reveals that the traditional concept of surgery as the therapy of choice to prevent kidney damage in patients with increased risk for unfavorable clinical course, high-grade VUR, and nephropathy at diagnosis<sup>8-11</sup> is, and still is for some health care professionals, the cause for the selection of surgery as the initial therapeutic option for these patients. It has been observed how, in spite of a trend towards conservative treatment in the pre-guideline era, patients with VUR IV-V and nephropathy at diagnosis tended to be excluded from the sequential treatment algorithm. Little by little, the proportion of children with these characteristics treated with sequential treatment has increased from 34.48% among patients in group 2 with

TABLE 2. Treatment received by each type of patient according to their clinical profile (N: 297)

Clinical outcome measures	Group 1 (2008-2015) N= 124		Group 2 (1989-2008) N= 173		p (95% CI $\chi^2$ )
	CT (N= 88)	ST (N= 36)	CT (N= 117)	ST (N= 56)	
Reason for diagnosis					
Antenatal dx	38.64%	44.44%	17.95%	26.79%	p = 0.002
Febrile UTI	61.36%	55.56%	82.05%	73.21%	
VUR grade					
I-III	54.65%	41.67%	52.14%	17.86%	p = 0.000
IV-V	45.35%	58.33%	47.86%	82.14%	
Age at diagnosis	23.1 months	34.6 months	33.5 months	24.3 months	p = 0.027
Nephropathy at diagnosis	49.43%	63.64%	35%	75%	p = 0.000
Bilaterality	51.14%	47.22%	43.59%	62.5%	p = 0.134

CT: conservative treatment; ST: surgical treatment; dx: diagnosis; UTI: urinary tract infection; VUR: vesicoureteral reflux.

nephropathy at diagnosis and sequential therapy to 49.43% in group 1.

In relation to VUR grade, it has been observed how, despite the highly similar percentage of patients with severe VUR in both groups, there is a marked trend in the group where surgery is selected as the initial treatment. Thanks to the recommendations made in the clinical guideline, VUR grade itself does not appear to be the reason for performing a surgery on a patient; however, other factors are assessed, such as recurrent UTIs. At present, a higher percentage of children with these characteristics are treated with an initially conservative approach.

In the last decade, conservative treatment, based on hygiene measures and nocturnal antibiotic prophylaxis,<sup>12-14</sup> has definitely positioned as the initial treatment of choice. The effectiveness of this therapeutic strategy and, most importantly, its ability to protect the renal parenchyma and, secondarily, long-term kidney function, have been repeatedly weighed up and analyzed.

The systematic reviews by Wheeler et al.<sup>14</sup> and Nagler et al.<sup>15</sup> highlight three clinical assays that attempted to elucidate the effectiveness of surgical and conservative treatment and the advantages of one over the other in terms of permanent kidney damage. These are the International Reflux Study in Children (IRSC),<sup>16</sup> the Birmingham Reflux Study (Great Britain), and the Swedish Reflux Trial in Children.<sup>9,13</sup> Results showed no differences in the total number of recurrent UTIs between both treatment strategies at 2, 5 or 10 years of follow-up and in the risk of developing new renal parenchymal injuries, the

progression of existing parenchymal defects, and overall kidney growth. The incidence of arterial hypertension (AHT) or end-stage renal disease (ESRD) in the follow-up of both types of patients was similar.

The evidence obtained from studies like the ones mentioned above has led, at present, to treat primary VUR based on a conservative approach and, consecutively, advance to surgical treatment –with endoscopic technique as the first choice– in the case of recurrent UTIs, always maintaining an individualized approach, treating bladder dysfunction, and using complementary, non-invasive tests for the follow-up of asymptomatic patients.<sup>9</sup>

Following 2008, the CPG was updated in 2014 (*Figure 2*);<sup>4</sup> its drafting included an analysis of the CPG by the National Institute for Health and Care Excellence (NICE) from 2013,<sup>17</sup> the CPG for the management of VUR by the American Urological Association (AUA)<sup>18</sup> from 2010, the CPG for the management of UTI by the Spanish Association for Pediatric Nephrology (Asociación Española de Nefrología Pediátrica, AENP) from 2011,<sup>19</sup> the CPG by the American Academy of Pediatrics from 2011,<sup>20</sup> and the CPG by the European Association of Urology (EAU) from 2012.<sup>21</sup>

Based on the bibliography available at that time and, fundamentally, the publication of the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) project,<sup>22-24</sup> some of the initial guidelines have been modified, especially in relation to nocturnal antibiotic prophylaxis. Compared to the algorithm proposed in 2008,<sup>3</sup> the universal indication has been

TABLE 3. Antibiotic prophylaxis recommendations proposed in the clinical guideline based on scientific evidence

Antibiotic prophylaxis is recommended for girls with VUR grade III-V during 1 year or until a new cystographic control is done to determine VUR grade again.	B
Antibiotic prophylaxis is recommended for boys with VUR grade IV-V during 1 year or until a new cystographic control is done to determine VUR grade again.	√
As a general rule, the group would recommend to assess antibiotic prophylaxis individually, considering any factor that may influence the development of new UTIs and once parents or caregivers are informed of its risks and benefits.	√

**B recommendation:** evidence made up of studies classified as 2 ++, directly applicable to the guideline's target population and showing a high level of inter-study consistency; or evidence extrapolated from studies classified as 1 ++ or 1 +.

√: consensus by the drafting team.

**Antibiotic prophylaxis:** nitrofurantoin or trimethoprim-sulfamethoxazole, unless it is specifically contraindicated or in case of resistance observed in urine cultures and sensitivity tests. Dosage: 1/3 of the daily dose by mg/kg.

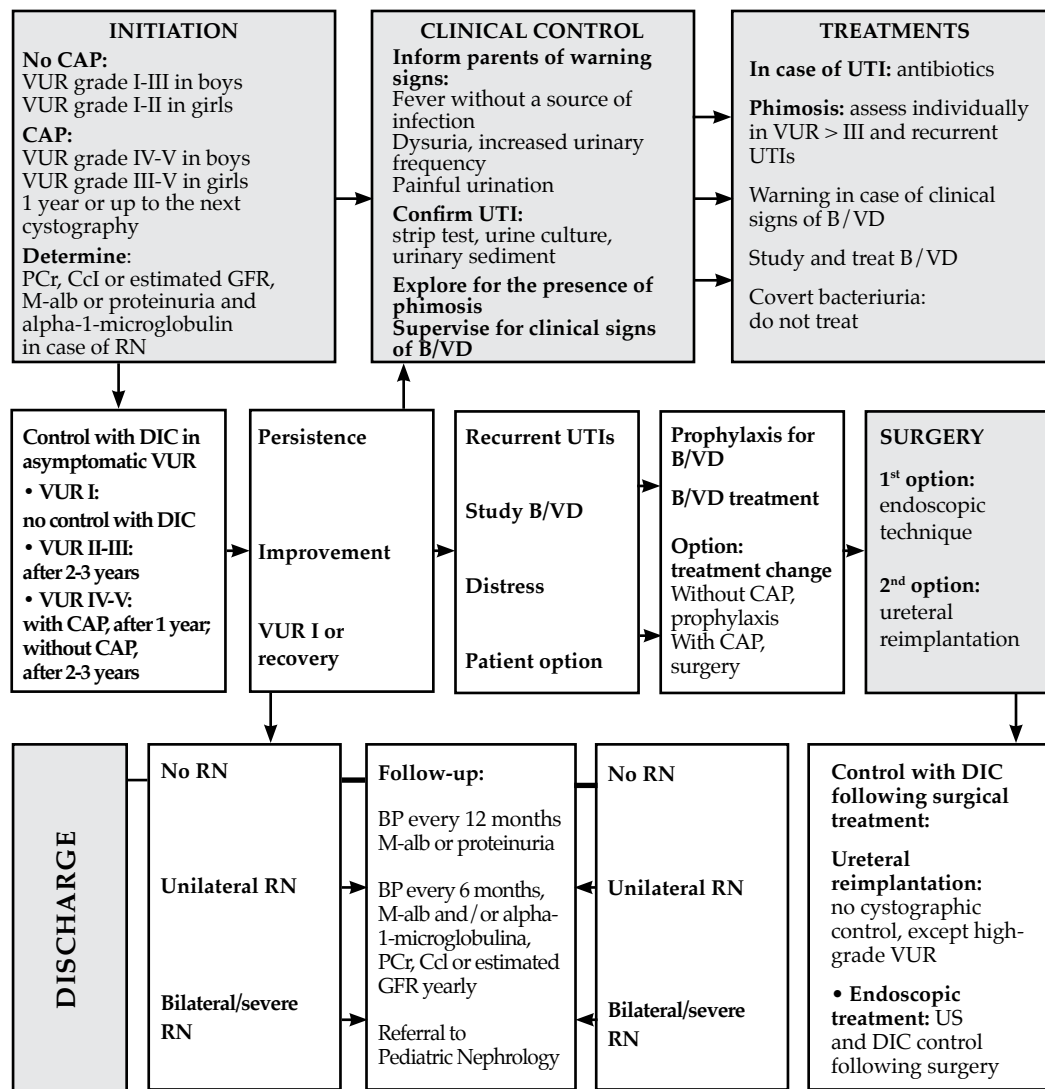
UTI: urinary tract infection; VUR: vesicoureteral reflux.

replaced by a prudent, individualized approach, with the recommendation of prophylaxis for girls with VUR III-V and boys with VUR IV-V for 1 year or until a new cystographic control is done to determine VUR grade, as well as among patients with bladder dysfunction and recurrent UTIs, always with an individualized assessment of the risks and benefits of this strategy (Table 3).

The use of generalized prophylaxis has become increasingly restricted in the different recommendations made by scientific societies;

however, its indications are still controversial. In the latest update of the Argentine Society of Pediatrics,<sup>25</sup> chemoprophylaxis is indicated for infants younger than 1 year with the first UTI episode if no imaging studies have been done yet and with any grade VUR, older children with VUR grade III or higher, regardless of sex, children with scarring and VUR, in the presence of bladder dysfunction and VUR, and patients who undergo screening tests because of, e.g., antenatal hydronephrosis, in whom VUR is detected.

FIGURE 2. Therapeutic diagnostic algorithm for the management of primary vesicoureteral reflux in children based on the updated Clinical Practice Guideline from 2014<sup>4</sup>



DIC: direct isotope cystography. Ccl: creatinine clearance. B/VD: bladder or voiding dysfunction. GFR: glomerular filtration rate. UTI: urinary tract infection. M-alb: microalbuminuria. RN: reflux nephropathy. BP: blood pressure. CAP: continuous antibiotic prophylaxis. PCr: plasma creatinine. VUR: vesicoureteral reflux. US: ultrasonography.

Another controversial aspect observed in the latest updates refers to the different methods used for VUR diagnosis and follow-up. The 2014 update still advocates the serial VCUG is the method of choice for VUR diagnosis because of its optimal anatomic definition,<sup>4</sup> highlighting the role of indirect cystography as the method of choice for control given its lower level of radiation compared to the serial VCUG, its lower reliance on technical equipment and observers, and its lower cost compared to cystosonography.<sup>26</sup>

However, other scientific societies, such as the Argentine Society of Pediatrics<sup>25</sup> or the AUA in 2011,<sup>18</sup> have proposed to initiate the diagnostic algorithm with an ultrasound.

These indications are not considered contradictory because most patients seen in our outpatient offices have generally had an ultrasound, either antenatally or following the first febrile UTI, as recommended by the CPG for the management of UTI in the pediatric population by the AENP.<sup>19</sup> An ultrasound should be the test of choice for those patients referred without one because, in spite of its low sensitivity to detect VUR<sup>20</sup> and scarce cost-effectiveness published by some authors,<sup>27</sup> its sensitivity is much higher to detect urinary tract dilation and anatomic abnormalities, and poses the advantage of not using radiation and being a fast, inexpensive method for VUR screening.<sup>28</sup>

Although the implementation of these guidelines may be complicated because of the different public health settings where they are used –e.g., according to the AGREE analysis, reviewers of the CPG subject of our study considered that the applicability of the CPG proposed by the AUA was only 25%–<sup>3</sup> therefore, restricting its dissemination, their development is encouraged because, as observed in our study, the therapeutic approach becomes more uniform, gains greater scientific soundness, and improves health care quality.

In our case, adherence to the CPG has made it possible for us to maintain these patients' management updated, has favored the selection of a conservative treatment for patients with severe and congenital VUR, which resulted in a reduction in the number of aggressive procedures in these patients, and has promoted the gradual implementation of necessary measures based on scientific evidence. ■

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