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Discrepancy between power-Doppler voiding urosonography and voiding cystourethrography is not relevant for the management of primary vesicoureteric reflux

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Abstract

Aim: The aim of this study was to assess if discrepancy between power-Doppler voiding urosonography (PD-VUS) and voiding cystourethrography (VCUG) affects the management of patients with primary vesicoureteric reflux (VUR).

Materials and Methods: Fifty-six children with suspected or known VUR were assessed both by PD-VUS and VCUG. Two independent observers, both pediatric surgeons, each aware of the results of only one imaging modality, advised children's management according to present care standards. Agreement between diagnostic findings at the two imaging modalities and between therapeutic advice of the two observers was evaluated using κ statistics.

Results: PD-VUS diagnosed VUR in 3 patients and 6 ureteral units more than VCUG. VCUG showed VUR in 2 ureteral units, but in no patient more than PD-VUS. Accuracy of PD-VUS compared with VCUG was 92.8% and 94.6% considering ureteral units and patients, respectively. The two observers disagreed about the management of 4 (7%) of 56 cases. Agreement was significant ($P < .001$) both between findings at the two imaging modalities and between management options advised by the two independent observers.

Conclusion: Vesicoureteric reflux management based on PD-VUS findings is consistent with a management based on standard VCUG.

Primary vesicoureteric reflux (VUR) seldom requires surgery, but may often involve periodical assessments during conservative follow-up [1]. Such controls are classically accomplished by voiding cystourethrographies (VCUGs). However, owing to the potential adverse effects related to the use of ionizing radiation, the development of alternative imaging modalities has been claimed in recent years [1].

Ultrasonography (US) enhanced with contrast agents seems to be an ideal alternative to VCUG because it allows simultaneously to spare radiation and to achieve both a morphological and functional assessment of the urinary tract, the voiding urosonography (VUS) [2]. Effectiveness

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of this tool has already been evaluated in several studies comparing on the same child findings at VUS and at a reference imaging modality either VCUG or direct radionuclide voiding cystography (DRVC) [3-6]. Nevertheless, both VCUG and DRVC are partially unreliable reference standards presenting some limitation in the assessment of laterality and/or grading of VUR.

In practice, the key point is whether possible discrepancy between imaging modalities affects the final management of VUR. Indeed, every imaging modality is of value as long as it provides all the information that the physician considers necessary for patient's management based on local care standards. In a retrospective study, Darge et al [2] showed that VUS is effective in doing so whenever applied to selected indications.

To better clarify this aspect, we evaluated in a prospective study the agreement between therapeutic advice given to children assessed both by VUS and VCUG, by two independent observers each informed of the results of only one imaging modality.

1. Materials and methods

Fifty-six patients, for a total of 112 ureteral units (UUs), were enrolled in this study. There were 37 females and 19 males; average age was 4.1 ± 2.8 years (range, 28 days to 7.4 years).

Indications for investigation were urinary tract infections (UTIs), occasional detection of urinary tract dilatations, follow-up controls during conservative treatment, and screening in sibling of indexed children with VUR (Table 1).

Boys undergoing first examination for a suspected VUR and patients with anatomic anomalies (duplex kidney or ureterocele) or in whom visualization of the bladder or one of the kidneys on US was inadequate (ie, presence of severe scoliosis or obesity) were excluded. Children with galactosemia were excluded as well. None presented acute UTIs at the time of investigation.

All the sonographic examinations were performed with an ATL plus real-time scanner (ATL Ultrasound, Bothell, WA, USA) equipped with 3.5- to 7.5-MHz convex multiple frequency electronic transducers. VUS was performed with a power-Doppler technique (PD-VUS). Power setting of the US machine was turned to the lowest level (−9 dB), Doppler pulse repetition frequencies (PRF) were set at the highest level (6000 Hz), and a total color gain ranging from 50% to 75% was used.

Table 1 Indications to investigation and VUR prevalence

Indication	No. of patients	No. of patients presenting VUR	
		On PD-VUS	On VCUG
UTIs	16	5	4
Urinary tract dilatation	13	4	3
Sibling of patients with VUR	10	3	3
Follow-up of VUR in conservative treatment	17	13	12
Total	56	25	22

PD-VUS and VCUG were performed consecutively (in this order) during the same diagnostic section in each child, on an outpatient basis, and after achievement of parental informed consent. A single transurethral catheterization was performed for both procedures using a 6F or 8F infant feeding tube in aseptic conditions. A single-dose antibiotic prophylaxis was given to all children not yet on prophylaxis. None of the children received sedative drugs. In infants, potentially more uncooperative and restless, the procedure was performed about half an hour after feeding.

In all patients, a preliminary urinary tract US was performed in supine and prone position including transverse and longitudinal scanning of both kidneys and bladder. During PD-VUS, the bladder was filled by means of gravity with normal saline solution prewarmed at 37°C until the estimated bladder capacity for patient's age was reached (mL = 30 × age + 30) [7] or until the patient complained initial urgency to micturate. The echo enhancer was then instilled very slowly to avoid sudden micturition. SH U 508A (Levovist, Shering, Berlin, Germany) was the utilized contrast. It was used at a concentration of 300 mg/mL and always prepared just before administration, as recommended by the manufacturer. Each kidney and the retrovesical space were scanned alternately approximately every 15 seconds. Micturition was obtained with the catheter in situ, no attempt was made to visualize the urethra. Reflux was diagnosed whenever colored Doppler-enhanced hyperechogenic microbubbles were detected in a ureter or in a renal pelvis. Refluxes were graded according to Darge and Troeger [8] as follows: grade 1: echocontrast detected only in the ureter; grade 2: echocontrast detected in the renal pelvis, but without any significant urinary tract dilatation; grade 3: echocontrast detected in the renal pelvis, significant renal pelvis dilatation, or mild calyceal dilatation; grade 4: echocontrast detected in renal pelvis, significant renal pelvis and calyceal dilatation; grade 5: as grade 4 plus loss of pelvic contour and dilated and tortuous ureter. The same ultrasonographer performed all PD-VUSs.

Standard VCUG was performed filling the bladder through the same catheter of VUS. A volume of prewarmed contrast medium (iodamide, Opacist ER 12.12 g, Bracco, Italy) similar in volume to that used for PD-VUS was instilled into the bladder by means of gravity with the bottle at the same height as the one of saline solution used during PD-VUS. Filling was checked with intermittent digital fluoroscopy. Spot films were taken at full bladder capacity, during voiding and post-voiding. Refluxes were graded according to the guidelines of the International Reflux Study

Table 2 Number of refluxing and nonrefluxing ureteral units and grade of reflux using the two different imaging modalities

VCUG grade	PD-VUS grade						
	Total	No VUR	I	II	III	IV	V
Total	112	75	4	9	15	6	3
No VUR	79	73		2	3	1	
I	6	1	4		1		
II	11	1		7	2	1	
III	12				9	2	1
IV	3					2	1
V	1						1

VUR was graded according the guidelines of the International Reflux Study in Children on VCUG [9] and according to Darge and Troeger [8] on PD-VUS.

in Children [9]. The same radiologist performed all fluoroscopies unaware of PD-VUS findings.

Two of the authors, both pediatric surgeons with more than 8 years of experience in the management of VUR, both provided with the same clinical notes including clinical history and standard US and DMSA scans, advised independently children's management each blindly to one imaging modality. Therapeutic options were in agreement with presently most accepted guidelines for the management of primary VUR [1] and were summarized as follows: (1) start chemoprophylaxis (newly detected VUR), (2) stop or do not start chemoprophylaxis (negative investigation in a child free from UTIs), (3) keep on chemoprophylaxis (persisting VUR), (4) formal ureteral reimplantation (breakthrough UTIs or worsening in DMSA scan and/or in US appearance of the kidneys).

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of PD-VUS were evaluated considering VCUG as the reference standard. Agreement between the two imaging techniques and between therapeutic advice of the two independent observers were evaluated by κ statistics. A $\kappa = 0$ was considered a random agreement and a $\kappa = 1$ a perfect agreement. A P value less than .05 considered significant.

2. Results

Vesicoureteric reflux was detected in 37 (33%) of 112 UUs by PD-VUS and in 33 (29.4%) of 112 by standard VCUG. Vesicoureteric reflux was detected by both techniques in 31 UUs; grade was the same in 23 (74%) UUs, whereas in 8 (26%), PD-VUS upgraded VUR. Vesicoureteric reflux was diagnosed by one of the two imaging modalities in 8 UUs; in 6, it was present only on PD-VUS, and in 2, only on VCUG. Reflux grading is reported in Table 2. Accordingly, sensitivity of PD-VUS compared with VCUG considering UUs was 94%, specificity 92.4%, PPV 83.7%, NPV 97.3%, and diagnostic accuracy 92.8%. The agreement between the two technique was significant (κ score = 0.78, $P < .001$) (Table 3).

Table 3 VUS sensitivity, specificity, PPV, NPV, and accuracy compared with VCUG considering the ureteral units

Results of VCUG	Results of PD-VUS		Total	
	PD-VUS−	PD-VUS+		
VCUG−	73	6	79	Specificity 92.4%
VCUG+	2	31	33	Sensitivity 94%
Total	75	37	112	
	NPV 97.3%	PPV 83.7%		Accuracy 92.8%

Table 4 VUS sensitivity, specificity, PPV, NPV, and accuracy compared with VCUG considering the number of patients detected with VUR

Results of VCUG	Results of PD-VUS		Total	
	PD-VUS−	PD-VUS+		
VCUG−	31	3	34	Specificity 88%
VCUG+	0	22	22	Sensitivity 100%
Total	31	25	56	
	NPV 100%	PPV 88%		Accuracy 94.6%

PD-VUS detected VUR in 3 patients more than VCUG. All had unilateral refluxes. One was grade IV and 2 were grade II. In the remaining 22 patients, VUR was detected by both techniques (Table 1). Accordingly, considering the number of patients, sensitivity of VUS was 100%, specificity 88%, PPV 88%, NPV 100%, and accuracy 94.6%. Agreement between the two techniques was significant (κ score = 0.87, $P < .001$) (Table 4).

Management options advised by the two independent observers are summarized in Table 5. Agreement was high and the advice differed in only 4 (7%) of 56 cases differed (κ score = 0.81, $P < .001$). In 3 cases, the observer relying upon PD-VUS suggested to keep on (n = 1) or start (n = 2) prophylaxis because of the presence of VUR; no VUR instead was observed on VCUG prompting therapeutic abstention. In another case, the observer relying upon VCUG indicated reimplantation. Vesicoureteric reflux was observed on both imaging modalities and the indication was rather because of an apparent progressive reduction in kidney diameter on US and a worsening in renal DMSA uptake on successive investigations.

Table 5 Treatment advice based on each of the two diagnostic modalities

Treatment	No. of patients	
	PD-VUS group	VCUG group
Start prophylaxis	12	10
Stop or do not start prophylaxis	31	34
Keep on prophylaxis	8	6
Formal reimplantation	5	6

3. Discussion

The present study did not aim primarily to evaluate the accuracy of PD-VUS in the assessment of VUR. We adopted a procedure already standardized and validated [10,11]; hence, not surprisingly, sensitivity, specificity, PPV, NPV, and accuracy of PD-VUS comparing with VCGU were consistent with previous reports [3].

We rather focused on the reliability of PD-VUS in determining the management of primary VUR. In a large proportion of our patients, results at the two imaging modalities were consistent, and thus, it is not surprising that also the management advice was so. However, in 8 cases, PD-VUS upgraded VUR and VUR was present only on PD-VUS in 6 UUs and 3 children. These are the most problematic cases.

From a practical standpoint, an imaging modality is clinically valuable when it provides all the information that the physician considers necessary for patients' management according to local practice regarding care of VUR. Over the last two decades, pediatric urologists have learned to be more and more conservative in treating VUR [12]. Evidence suggests that low-grade VURs usually cease spontaneously over time, whereas renal damage is mostly congenital in children with high-grade VUR undergoing renal function deterioration while on conservative treatment [13]. Hence, outcome is largely independent from surgery [14] and a nonoperative treatment has become the first-line approach to VUR, no matter what grade or laterality [1,12-15]. Surgery seems indicated only on a clinical ground, potential indications for reimplantation being breakthrough UTIs, appearance of new renal scars or worsening in renal function during follow-up, and parents' noncompliance with long-term prophylaxis [1,12]. Accordingly, accuracy of the imaging modality in grading VUR seems no longer paramount. Reflux grading may still be considered relevant only whether lack of improvement or progression of VUR grade, in a patient otherwise asymptomatic, is considered an indication for surgery too. However, actual association among VUR degree, renal damage, and need for surgery remains controversial as well as the real need to treat persistent VUR [12,16]. Furthermore, with a routine use of PD-VUS, comparison would be done among multiple PD-VUSs, increasing consistency.

Besides, also the reliability of VCUG in assessing VUR is questionable. Indeed, it has been shown that both number of refluxing units and grade of refluxes change with multiple cycles of bladder filling/emptying [4,5]. In the series by Papadopoulou et al [4], a second voiding cycle at VCUG enabled detection of VUR in 50 (19.5%) of 257 children not presenting any reflux on first cycle. Discrepancy in presence, side, or degree of reflux between two cycles was noted in 63 (23%) of the 257 patients. Jequier and Jequier [5] reported that an additional 4% of patients can show VUR after a third cycle. Greenfield and Wan [12] reported a reappearance of reflux after a negative VCUG in 27% of patients followed on prophylaxis suggesting that probably VCUG overlooked an intermittent VUR in one fourth of their patients. Similar data were reported for DRVC [17].

In our opinion, nowadays, the only crucial aspect of an ideal diagnostic test for VUR is a high sensibility in order not to miss any reflux even if intermittent. Indeed, PD-VUS seems to be superior to VCUG [3], and also to DRVC [6,18], in this respect. The prolonged duration of PD-VUS could allow detection of short-lasting refluxes possibly overlooked by VCUG. We wonder whether the 3 patients who would have been treated based on PD-VUS findings, but not on VCUG, should actually be considered false negatives of VCUG rather than false positives of PD-VUS.

Agreement between the two independent observers advising treatment in the present series was probably so high also because we did not consider endoscopic treatment among the therapeutic options. Although large international series have shown its effectiveness in the treatment of VUR [19,20], this treatment modality is not considered in the American Urological Association guidelines [1]. Hence, indications are still not generally agreed upon and its use is mostly based on single institution experience and local care policy [19,20] or on parents' preference [21]. Nevertheless, also for endoscopic treatment, grade of VUR does not seem to be a crucial factor any longer [19,20].

Finally, only cases of primary VUR were included in this study. PD-VUS was never used if a morphological anomaly of the urinary tract, other than dilatation, was evident at standard US. It was seldom the primary imaging modality in our patients and never in boys, in whom presence of posterior urethral valves always has to be ruled out. According to present knowledge, VCUG is superior to VUS in demarking the urethral profile [2,3,10,11]. However, Bosio and Manzoni showed that infravesical obstruction can be detected also by VUS [22], whereas de Kort et al [23] reported that VCUG could be unreliable in detecting urethral obstruction, including minor degree of posterior urethral valves, beyond the neonatal period.

The discussed data form published studies suggest that most of the drawbacks generally attributed to PD-VUS applies to VCUG as well. The latter is probably a fairly less accurate imaging modality than usually thought. More than being caused by intrinsic limitations of PD-VUS, reluctance of pediatric surgeons to use this tool could be easily caused by a lack of familiarity with its images, a low diagnostic confidence. Accordingly, Darge [24] maintained that the key step to make PD-VUS accepted is not the improvement of its accuracy, rather the possibility to print out images, which stand up to comparison with images of fluoroscopic examination.

In conclusion, the present study shows that PD-VUS is a reliable imaging modality to select the management of primary VUR not leading to substantial different therapeutic choices with respect to VCUG.

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