

Contrast-Enhanced Voiding Urosonography for the Diagnosis of Paediatric Vesicoureteral Reflux – A Single Centre Experience

A Urossonografia Miccional Seriada no Diagnóstico do Refluxo Vesicoureteral em Idade Pediátrica - A Experiência de um Centro Hospitalar

Rute Martins^{1,2}, Daniel Tiago^{3,2}, Filipa Garcês^{3,2}, Ana Marreiros^{4,2}, Patrícia Mendes^{3,2}, Henrique Patrício^{1,2}

¹Serviço de Radiologia de Faro, Centro Hospitalar Universitário do Algarve, Faro, Portugal

²Algarve Biomedical Center, Campus Gambelas, Faro, Portugal

³Serviço de Pediatria, Centro Hospitalar Universitário do Algarve, Faro, Portugal

⁴Departamento de Ciências Biomédicas e Medicina, Universidade do Algarve, Faro, Portugal

Address

Henrique Patrício
Serviço de Radiologia de Faro
Centro Hospitalar Universitário do Algarve
Rua Leão Penedo
8000-386 Faro, Portugal
email: henrique.miguel.patricio@gmail.com

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Abstract

Background: Contrast-enhanced voiding urosonography (ceVUS) has become, in recent years, an excellent alternative method to fluoroscopic voiding cystourethrogram for the diagnosis of vesicoureteral reflux in children, with comparable sensitivity and absence of ionizing radiation. In our country, this method has been implemented at the Serviço de Radiologia of the Centro Hospitalar Universitário do Algarve (CHUA) in 2017. The objective of this paper is to provide a detailed description of the technique and analyse its results since implementation.

Methods: Single-centre retrospective study of demographic characterization, clinical indications, imaging findings and safety assessment of urosonography exams, performed over a period of about 3 years.

Results: A total of 105 ceVUS have been performed in 98 children. The most frequent clinical indication for this exam was recurrent febrile urinary tract infection (29.5%) and the least frequent the follow-up of vesicoureteral reflux (10.5%). In 35.2% of exams, reflux was observed. The most frequent reflux grade was grade II (8.2%), and the least frequent was grade V (2.9%). Grade I reflux was not identified in any patient. No adverse events were found regarding the use of the contrast agent (SonoVue®).

Discussion: CeVUS is a safe technique, with excellent-quality images and good sensitivity to evaluate urinary tract disease.

Conclusion: It is expected an increase in the receptivity of the urosonography for the study of paediatric nephropathology, namely in what concerns the international consensus for the diagnosis of vesicoureteral reflux.

Keywords

Vesicoureteral reflux; Contrast-enhanced voiding urosonography; Children; Diagnosis.

Resumo

Introdução: A urossonografia tem vindo a ser considerada uma excelente alternativa à cistouretrografia miccional seriada para o diagnóstico do refluxo vesicoureteral (RVU) em crianças, com sensibilidade semelhante e sem exposição à radiação ionizante. Sendo um dos pioneiros no nosso país, este método foi implementado no Serviço de Radiologia no Centro Hospitalar Universitário do Algarve (CHUA) em 2017. O objetivo deste artigo é fornecer uma descrição técnica da urossonografia e analisar os seus resultados desde a sua implementação.

Métodos: Estudo unicêntrico retrospectivo de caracterização demográfica, indicações clínicas, achados imagiológicos e avaliação de segurança de exames de urossonografia, realizados num período de cerca de 3 anos.

Resultados: Foram realizadas um total de 105 urossonografias em 98 crianças. Relativamente à indicação clínica que motivou a sua realização, a mais frequente foi a presença de infeção urinária febril recorrente (29,5%) e a menos frequente o seguimento de RVU (10,5%). Em 35,2% dos exames verificámos a presença de RVU. O grau de refluxo mais frequentemente observado foi o grau II (8,2%) e o menos frequente o grau V (2,9%), não tendo sido identificado nenhum refluxo de grau I. Não foram registadas quaisquer intercorrências relativas ao uso do meio de contraste (SonoVue®).

Discussão: A urossonografia revelou ser uma técnica segura, com elevada qualidade das imagens e com uma boa sensibilidade para avaliar patologia do trato urinário.

Conclusão: É expectável o aumento da receptividade da urossonografia no estudo da patologia nefrológica pediátrica, nomeadamente no que diz respeito aos consensos internacionais para o diagnóstico do refluxo vesicoureteral.

Palavras-chave

Refluxo vesicoureteral; Urossonografia; Crianças; Diagnóstico.

Introduction

Vesicoureteral reflux (VUR) consists of the retrograde flow of urine from the bladder to the upper urinary tract. VUR is the most common urological disease in pediatric age, with an estimated prevalence of 1% in newborns.¹ This

prevalence increases to about 15% in newborns with prenatal hydronephrosis and to about 30-45% in children with febrile urinary tract infection (UTI).^{2,4} In addition to being a risk factor for febrile UTI, VUR can cause reflux nephropathy and renal scarring, with loss of renal parenchyma.^{4,5}

Early detection of VUR is essential to ensure adequate follow-up and treatment of these children, being the definitive diagnosis made through imaging tests. The clinical guidelines of the European Society of Pediatric Urology and the American Association of Urology recommend renovesical ultrasound in the initial approach of these children, being the voiding cystourethrogram (VCUG) the gold standard for the evaluation of VUR in children.^{6,7} This method, in addition to allowing the classification of VUR according to the system established by the International Reflux Study Committee, provides a precise anatomical detail.^{7,8}

In the 90's, with the main purpose of avoiding exposure to radiation, a new method for diagnosis of VUR was implemented. This method resorted to ultrasound using a contrast medium, serial voiding urosonography, hereinafter referred to as urosonography.^{9,10} This method is technically analogous to VCUG, and the diagnosis of VUR is defined by the presence of echogenic microbubbles (originating from the echographic contrast medium) moving through the upper urinary tract, using the same classification system as VCUG.^{8,11}

The urosonography can also be used, although less frequently, for the investigation of urinary tract malformations and in cases of suspected bladder rupture.^{11,12} In addition to avoiding exposure of the child to ionizing radiation, this method, when combined with a multicyclic study, presents greater sensitivity in the detection of VUR, allows the complete study of the male urethra and provides greater comfort and collaboration of the child when compared to the VCUG.¹³⁻¹⁵

The first commercially available ultrasound contrasts for urosonography had several limitations, such as a short conservation period and half-life, and a high amount of contrast required.¹⁶ As a consequence, since 2001, second generation contrasts have been developed and commercialized, containing lipid microspheres of sulfur hexafluoride (SonoVue®, Bracco, Milan, Italy in Europe and Lumason®, Bracco Diagnostics, Monroe Township, NJ in the United States of America). Although there are some contraindications for SonoVue® when administered intravenously, the safety of this contrast by intravesical route has already been widely studied, and there are no side effects attributed to its use.^{12,17-19} Thus, SonoVue® has been widely used in pediatric age urosonography in several centers, initially in an off-label context, and since 2017 with approval by the European Medicines Agency.²⁰ Published studies demonstrate a diagnostic accuracy of urosonography in the diagnosis of VUR comparable to VCUG in pediatric age, especially considering high-grade VUR in younger children.²¹⁻²³

Being one of the pioneers in our country, this method was implemented in the Radiology Service at the Centro Hospitalar Universitário do Algarve (CHUA) - Faro Unit in 2017. This implementation was authorized by the CHUA Ethics Committee, using echographic contrast in an off-label context (SonoVue®, Bracco, Milan, Italy).

The criteria for performing urosonography are not strict and should be individualized according to the child's clinical condition and ultrasound findings. In general, clinical indications considered are the presence of UTI, prenatal hydronephrosis, siblings with a history of VUR and among children where one parent has a history of VUR.^{6,7,11,24}

The purpose of this article is to provide a description of the urosonography's technical procedure and to analyze

the results of the urosonographies performed at the Radiology Service of CHUA - Faro Unit, from CHUA Pediatric Consultations, since its implementation. Thus, in addition to the demographic data of the subjects examined, it intends to describe the clinical indications conducting to the examination, the presence of reflux and the existence of complications resulting from the examination.

Materials and Methods

Implementation of the urosonography

At the institution, these exams are performed based on the procedures proposed by Dr. Carmina Duran.^{11,25}

The team consists of a radiologist, who performs the exam, two nurses and an operational assistant who provides support in the room.

Prior to its performance, an information sheet is provided to parents with a description of the procedure and clarification of doubts. This also allows to obtain the informed written consent of the exam. Antibiotic prophylaxis is also performed.

In the room where the exam is performed, an attempt is made to create a child-friendly environment, adapted to the age group, with the presence of toys and often projecting videos of animations on the ceiling and walls of the room (Figure 1).

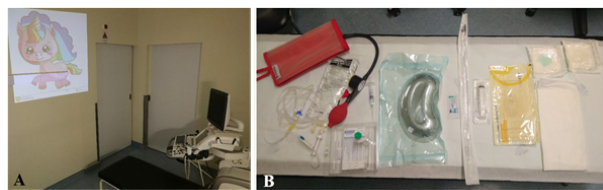


Figure 1 – Office and material used to perform urosonographies. **A.** Video projection of animation videos on the ceiling and walls of the room, adapted to the age group. **B.** Material used, from left to right: pressure sleeve, serum system, contrast product kit and catheter placing material.

GE Logiq E9 ultrasound equipment (General Electric Healthcare, Wauwatosa, WI, USA) is used, with a multi-frequency convex probe and dedicated software for contrast studies with pulse inversion harmonic image and a low mechanical index. This software also allows color coding and duplicated image with the conventional B mode (dual image).

Using a vesical probe, after emptying the bladder, it is retrograde replenished with a solution of 1 ml ultrasound contrast, prepared according to the manufacturer's instructions, diluted in 500 ml of 0.9% serum. A pressure of about 70 to 90 mmHg is applied to the serum bag, although a lower pressure may be convenient for newborns. Although it is possible to use an elevation of the bag of about 100 cm, the use of a pressure sleeve was preferable as it facilitates agitation to keep the solution homogeneous and it simplifies possible adjustments of pressure values. A progressive bladder repletion is obtained, which is evaluated by ultrasound, allowing the characterization of the bladder walls and lumen. When replenished, the urination phase begins. During the repletion and urination phases, the presence of contrast in the visible portions of the ureters and pyelocaliceal systems is evaluated.

The vesical probe has a diameter significantly smaller than the diameter of the urethra, varying according to the age group. For this reason, urination takes place

without resistance with the introduced probe, allowing cyclical studies to be carried out. Approximately 3 cycles are carried out per study; however, this number may vary depending on the need for better characterization of the demonstrated findings. In the last cycle, with a full bladder, the probe is removed and the urethra is evaluated, in girls suprapubically (or, rarely, interlabially), and in boys by interscrotal transperineal route, for evaluation of the posterior and anterior portions. The total examination time varies depending on the child's collaboration, taking approximately 20 to 30 minutes. The images obtained during the exam are digitally archived in the institution's PACS system. In the context of the authorization by the CHUA Ethics Committee to use the SonoVue® contrast (Bracco, Milan, Italy) in an off-label regime, an organized record of any side effects resulting from the procedure is made and kept after the approval of contrast use in these exams.

Study design, data collection and variables analyzed

This retrospective study was carried out at the Radiology Service, in collaboration with the Pediatric Service, both belonging to CHUA, Faro Unit, Portugal. All urosonographies performed since their implementation at this institution (May 2017 to March 2020) were included in this study. These exams were requested by CHUA's Pediatric Consultations. The data related to the image examinations were collected retrospectively using the RIS-Glantt® (version 16 R1.01.06) and Synapse softwares.

This project was approved by the CHUA Ethics Committee and was carried out in accordance with the Declaration of Helsinki.

The collected data were entered into an Excel database. The selected variables were the following: sex and age of the child; clinical indication for the examination; number of renal units analyzed; number of cycles performed; presence of reflux and its grade; other findings during the examination; and existence of complications (during the exam, immediately after and within 48 hours).

Regarding the variable clinical indication for the exam, it was divided into 5 categories: presence of moderate or severe hydronephrosis in the prenatal diagnosis (pelvis diameter greater than 10 mm); recurrent feverish urinary tract infection; feverish urinary tract infection with associated ultrasound changes; other changes in the urinary tract (cystic renal dysplasia; single kidney; megaureter; suspicion of urethral stenosis, etc.) and follow-up of vesicoureteral reflux (children with already known reflux).

Grading the reflux is based on its appearance on urosonography according to the system defined for VCUG by the International Reflux Study Committee,¹¹ classified from grade I (microbubbles only in the ureter) to grade V (microbubbles in the pyelocaliceal system with significant pyelic and calyceal dilation, associated to loss of contour of the renal pelvis and a tortuous and dilated ureter).

The variable "other findings during the exam" refers to intermittent reflux, intrarenal reflux and other events potentially seen during the exam. Intermittent reflux refers to reflux seen only in some of the cycles performed, while intrarenal reflux, or pyelotubular reflux, consists of the contrast reflux from the renal pelvis to the collecting tubules.

The variable "complications during the exam, immediately after and within the following 48 hours" is related to the

use of contrast (allergic character) and to the procedure itself, namely with catheterization. For this variable, the organized records described in the previous section were used.

Statistical Analysis

The statistical treatment of the results was analyzed using the IBM SPSS Statistics® software (version 25). The continuous variables were summarized as mean and standard deviation, while the discrete variables were in median and interquartile range. Categorical variables were described in frequency and percentage. The association between the variables "clinical indication for the examination" and "presence of reflux" was analyzed using Pearson's chi-square test. The statistical significance level defined was 5%.

Results

Demographic data

In the period covered in this study, between May 2017 and March 2020, a total of 105 urosonographies were performed. As it was not possible to perform two exams requested, one due to an unknown pregnancy and the other due to agitation and refusal, they were not included in this study.

The demographic data of the children studied are summarized in Table 1. Children had a mean age of 24.3 ± 27.1 months of age (mean $\pm$ standard deviation), the majority of children being female ($n = 58$; 55.2%). The age range varied from the first day of life in a male infant who was examined due to bilateral prenatal hydronephrosis and diffuse bladder wall thickening, so he was suspected of having posterior urethral valves; and a 9-year-old child, whose clinical indication for the exam was the presence of urinary tract infection associated with bilateral pyelocaliceal dilation.

Table 1 – Children's demographic data

Characteristics	
Examinations performed, n	105
Age, mean (+/- DP), months	24,3 $\pm$ 27,1
Age range, months	0 – 113
Male/Female, n (%)	47 (44,8%) / 58 (55,2%)
Clinical indication, n (%)	
Prenatal hydronephrosis	24 (22,9%)
Recurrent UTI	31 (29,5%)
UTI with ultrasound changes	26 (24,8%)
Other changes in the urinary tract	13 (12,4%)
VUR follow-up	11 (10,5%)
Children studied, n	98
Renal units analyzed, n	208
Cycles performed, median ($\pm$ IR)	3 $\pm$ 1
Urination not visualized, n (%)	7 (6,7%)
Children repeating the exam, n	7

IR, interquartile range; SD, standard deviation; UTI, urinary tract infection; VUR, vesicoureteral reflux

This study comprised a total of 98 children, 91 of whom were submitted to the exam only once, while 7 children were twice. A total of 208 kidney units were analyzed, as there were two children with a single kidney. The median of cycles performed was 3 ± 1 (median $\pm$ interquartile range).

In 7 urosonographies, due to the absence of urination during the entire exam, it was not possible to carry out the urination study and a directed study of the urethra. Regarding the clinical indication that motivated the examination, the most frequent was the presence of recurrent febrile urinary infection (n = 31; 29.5%) and the least frequent was the follow-up of known vesicoureteral reflux (n = 11; 10.5%). With regard to other changes in the urinary tract, the changes were as follows (n = 13 tests): 3 cases with unilateral renal cystic dysplasia, 2 with neurogenic bladder, 2 with chronic kidney disease, 1 with suspected urethral stenosis undergoing the examination twice, 1 with a single kidney, 1 with an atrophic kidney, 1 with unilateral pyeloureteral duplication and 1 with a megaureter.

Vesicoureteral reflux

Regarding the presence of reflux, the data obtained are summarized in Table 2. In the 105 tests performed, we verified the presence of vesicoureteral reflux in 37, corresponding to 35.2% of the tests performed. With regard to renal units, 51 showed reflux, totaling 24.5% of all units studied.

Grade II was the most frequently reflux grade observed, comprising 17 renal units (n = 17; 8.2%) and the least frequent grade V (n = 6; 2.9%), and there no images identifying grade I reflux. Figure 2 shows the various grades of reflux seen.

Table 2 – Vesicoureteral reflux data.

Characteristics	n
Presence of reflux* (per exam), n (%)	37 (35,2%)
Presence of bilateral reflux* (per exam), n (%)	13 (12,4%)
Presence of reflux (per renal unit), n (%)	51 (24,5%)
Reflux grade, n (%)	
II	17 (8,2%)
III	13 (6,3%)
IV	15 (7,2%)
V	6 (2,9%)

* In these variables, the percentage calculation was performed using the total number of tests performed. In the remainder, the percentage was calculated using the total number of kidney units studied (n=208).

There was no association between the presence of reflux and the clinical indication for the exam (p = 0.150). The lack of variability in VUR follow-up, as it is almost always associated with the presence of reflux, justified the extraction of this option in the variable indicated for the exam.

Other imaging findings

In 10 renal units (4.8%) there was an intermittent reflux, that is, reflux seen in only some of the cycles performed. In 6 renal units (2.9%), the presence of intrarenal reflux was seen (Figure 3). As in the presence of intrarenal reflux, this technique also made it possible to identify other changes that are of diagnostic importance, such as pyeloureteral duplication, ureterocele and renal scars (Figure 3).

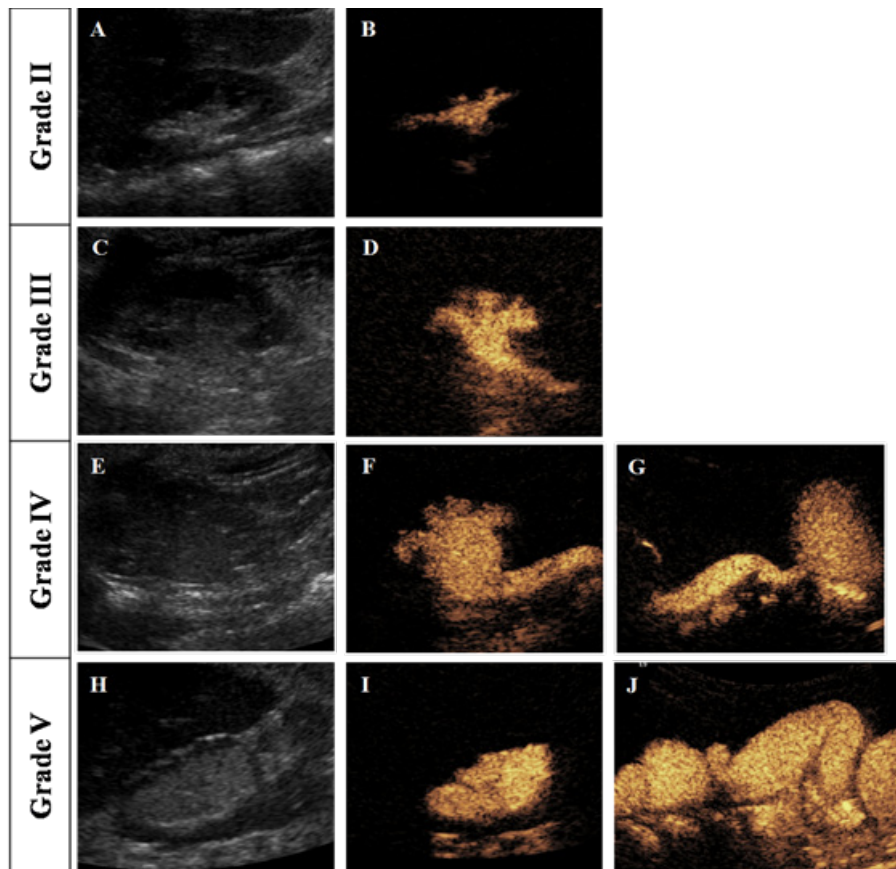


Figure 2 – Vesicoureteral reflux grades. Dual image, with B-mode image (left) and with contrast color coding (right). **Grade II.** **A and B.** Presence of contrast at the level of the renal pelvis, without dilation. **Grade III.** **C and D.** Presence of contrast in the pyelocaliceal system, with slight ureteral and pyelocaliceal dilation, and calyces of normal morphology. **Grade IV.** **E and F.** Presence of contrast in the pyelocaliceal system, with pyelocaliceal dilation, flattening of the calices, but without eversion of the calyceal fornices. **G.** Ureter with moderate dilation and tortuous. **Grade V.** **H and I.** Presence of contrast and marked pyelocaliceal dilation, with eversion of the calyx fornices. **J.** Marked dilation and tortuosity of the ureter.

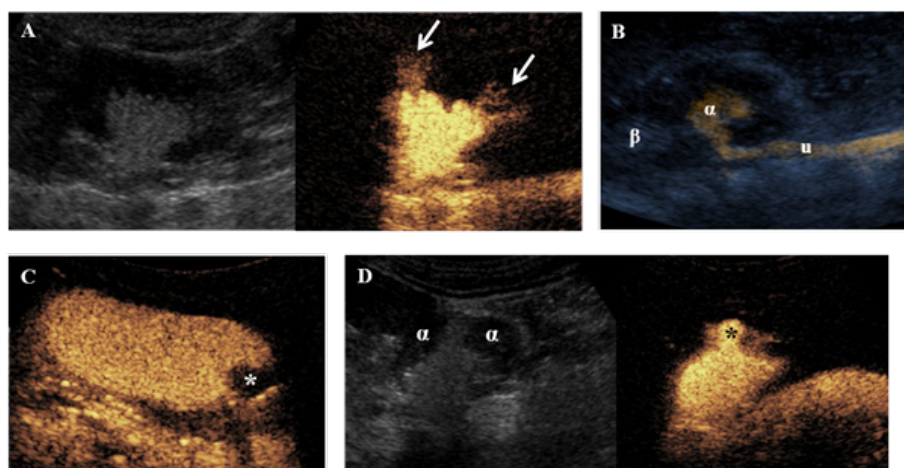


Figure 3 – Pathological findings detected by urosonography. **A.** Intrarenal or pyelotubular reflux. (Dual image) Presence of reflux to the renal parenchyma (arrows). **B.** Pyeloureteral duplication. Composite image of B-mode and color coding of contrast, showing vesicoureteral reflux with the presence of contrast only in the lower renal pelvis (α) and absence in the upper renal pelvis (β). u, ureter. **C.** Ureterocele. Subtraction image (*) at the ureterovesical junction. **D.** Renal scar. (Dual image) Area of focal decrease in the thickness of the renal parenchyma (x), with protuberance of the adjacent calyx(*).

In 4 urosonographies performed on female children, vaginal reflux was observed during micturition (Figure 4). In the 44 studies of the male urethra via interscrotal transperineal performed, no changes were identified (Figure 4).

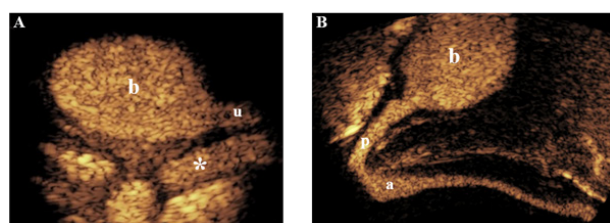


Figure 4 – **A.** Vaginal reflux during micturition. Filling of the vaginal lumen (*) by contrast during urination. b, bladder. u, urethra. **B.** Male urethra (anatomical orientation). Lumen filling by contrast of the male urethra in the interscrotal transperineal urination assessment. b, bladder. p, posterior urethra. a, anterior urethra

Complications

No complications relating to the use of the SonoVue® contrast medium, either during, immediately after, or within 48 hours after the exam were registered. Only in one urosonography, a complication related to the exam, terminal hematuria with the removal of the catheter, was observed in a 3-year-old female child, with spontaneous resolution in less than 12 hours.

Discussion

With the main objective of reducing radiation exposure, urosonography has increasingly been used to replace VCUG, with sensitivity rates of VUR detection comparable in both techniques in the various studies carried out.^{22,23,26} One of the main limitations described in the urosonography is related to its learning curve, as it is clearly an operator-dependent procedure. At our Center, there was no difficulty in acquiring experience, emphasizing team's stability, avoiding disruptions in the learning process. A recent study by Velasquez et al. 2019, demonstrated that, even in a Center without previous experience in urosonography, it is possible to acquire, in a short period of time, a good correlation between urosonography and VCUG (Cohen kappa of 0.72), as already described in other articles.²⁷⁻²⁹ That way, as it is a recent diagnostic technique, sharing the experience can be fundamental in its implementation and dissemination.

A disadvantage of performing urosonography is the cost per exam, namely regarding the cost of ultrasound contrast. Due to the stability of the microbubbles for a period of about 6 hours, if possible, costs can be optimized by examining several children in the same session (ideally 4 to 5), in order to use the entire ampoule completely. Additionally, in our institution, these children, prior to the implementation of the urosonography, underwent cystoscintigraphy in Lisbon, so this examination has brought several benefits, not only from an economic point of view, but also logistical and socially, regarding parents' transportation and their absenteeism at work.

There was absence of urination in 7 exams, preventing the direct study of the urethra. Nevertheless, some studies suggest that it does not significantly decrease the diagnostic acuity of vesicoureteral reflux.³⁰

With regard to the safety of the second-generation contrast SonoVue®, in this study there were no complications, which agrees with several studies published.^{12,19,31} There was only one complication - terminal hematuria, after removal of the catheter, in a 3-year-old child, with spontaneous resolution in less than 12 hours.

Of the 7 children who repeated the urosonography, in 6 of them the reason for the second exam was the reevaluation of reflux, and in all these reevaluations, the time interval between exams was about 2 years. The other child had a suspicion of urethral stenosis as clinical indication and repeated the exam due to the absence of urination in the first exam, making it impossible to evaluate the urethra. Urosonography has been increasingly used to evaluate the urethra in both sexes, namely posterior urethral valves, the most frequent urethral pathology in these age groups.^{11,15,32} The performance of these exams and the results obtained over these three years took place with a good reception by the professionals involved in monitoring these children, namely the clinicians, and by the parents as well. The examination was well tolerated by the children, given the possibility of maintaining some movements and the distractions created by the team.

Conclusion

Urosonography has proven to be an excellent technique to evaluate VUR. Its main advantage is the absence of radiation, especially considering the study of reflux that occurs mainly in the first years of life, when the susceptibility is greater. In addition, it is a safe technique,

with high quality of images and with a good sensitivity to assess pathology of the urinary tract.

It is expected that the use of urosonography will gain more and more acceptance in the study of pediatric nephrological pathology, namely with regard to international consensus for the diagnosis of vesicoureteral reflux.

Divulgações Éticas / Ethical disclosures

Conflitos de interesse: Os autores declaram não possuir conflitos de interesse.

Conflicts of interest: The authors have no conflicts of interest to declare.

Suporte financeiro: O presente trabalho não foi suportado por nenhum subsídio ou bolsa.

Financing Support: This work has not received any contribution, grant or scholarship.

Confidencialidade dos dados: Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação dos dados de doentes.

Confidentiality of data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Proteção de pessoas e animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.

Protection of human and animal subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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