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Review Article

The evaluation of vesicoureteral reflux among children using contrast-enhanced ultrasound: a literature review

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Summary

Introduction
Voiding cystourethrogram (VCUG) with fluoroscopy remains the gold standard for detection and evaluation of vesicoureteral reflux (VUR) among children. However, the ionizing radiation exposure remains a concern for this diagnostic modality. Recent studies have proposed using contrast-enhanced ultrasound as an alternative option for VUR screening and follow-up in children. The aim of the study was to review the literature of comparative studies that assessed the diagnostic accuracy of contrast-enhanced ultrasound compared with VCUG.

Methodology
A systematic literature search was performed on electronic medical literature databases in July 2017. Literature identification, screening, and assessment of eligibility were performed by five reviewers with a pediatric radiologist. Literature was summarized for the study population, contrast used, and ultrasound mode as well as the timing of comparative reference study being performed. The studies were clustered according to the kind of contrast used. Reported diagnostic accuracy was extracted from individual studies and summarized across the included studies using descriptive statistics of median and interquartile range (IQR).

Result
A total of 45 comparative studies were identified as eligible for the summary of the literature. Two generations of ultrasound contrast were identified in the available studies (first generation, Levovist and second generation, SonoVue). For the ultrasound studies using the first-generation contrast, the median sensitivity, regardless of the ultrasound mode, was 90.25 (IQR 83.25–97), and the median specificity was 93 (IQR 91.3–95.25). Among studies using the second-generation contrast, the median sensitivity was 86.26 (IQR 81.13–97), and the median specificity was 90.99 (IQR 84–98). No serious adverse events were reported in any of the studies.

Conclusion
Overall, this review highlights the application of contrast-enhanced ultrasound for its advantage of no exposure to ionizing radiation and diagnostic accuracy relatively comparable to VCUG in the evaluation of VUR. In addition to the functional evaluation of the VUR, it also provides an anatomic evaluation of the kidneys and bladder with ultrasound imaging. However, one should also note that this alternate procedure is highly operator dependent where diagnostic accuracy is excellent when the expertise is available.

Diagnostic parameters	First-generation contrast (Levovist), median (IQR)	Second-generation contrast (SonoVue), median (IQR)
Accuracy	93.7 (IQR 92.8–96; from 9 studies)	97 (IQR 96–98, from 2 studies)
Concordance with VCUG	90.6 (IQR 77.85–93.5; from 14 studies)	86.3 (IQR 81.5–88.625, from 7 studies)
Sensitivity	90.25 (IQR 83.25–97, from 20 studies)	86.26 (IQR 81.13–97, from 6 studies)
Specificity	93 (IQR 91.3–95.25, from 16 studies)	90.99 (IQR 84–98, from 5 studies)

IQR, interquartile range.

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Introduction

VUR is an anatomical and functional condition affecting over a third of children presenting with suspected urinary tract infections (UTIs) [1]. According to longitudinal studies, when VUR coexists with bladder bowel dysfunction, there is a higher risk of recurrent UTIs [2,3] which may lead to long-term sequelae such as renal scarring, hypertension, and renal failure [4—6]. Hence, preserving renal function in such a population requires timely identification for appropriate intervention [7,8].

Clinical practice guidelines from the European Society of Pediatric Urology and American Urological Association have both recommended ultrasound (US) as initial diagnostic imaging for upper tract assessment of patients with suspicion of UTI and VUR [8,9]. As US alone is not accurate for the diagnosis of VUR in children [10], the VCUG remains the gold standard because of its ability to allow a precise anatomical illustration [8]. However, owing to concerns of exposure to ionizing radiation, alternate imaging modalities, such as contrast-enhanced US, have been explored as a tool for assessment of VUR [11—13] in the place of VCUG.

Initial usage of contrast-enhanced US in VUR and its clinical applicability

In 1990, Hanbury et al. reported two cases of using US for assessing pediatric VUR by using microbubbles from agitated saline as contrast-enhanced media infused into the bladder. When compared with VCUG, there was 100% sensitivity with this method [14]. Atala et al. [15] (1993) subsequently assessed the usefulness of sonicated albumin (approximately 3 to 5 $\times$ 10^8 microspheres per milliliter) as an echogenic contrast in human and porcine urine. From this, they determined that 1:100 diluted sonicated albumin rendered diagnostic echogenicity in the bladder and refluxing ureters during US imaging. Furthermore, they also illustrated that the microsphere was stable for more than 40 min and allowed sonographic assessment of the entire urinary tract [15]. The same group from Boston Children's Hospital further applied the technology in 20 children and compared the diagnostic accuracy with radionuclide cystography and VCUG [16]. In this preliminary clinical application, they showed that the sonicated albumin-enhanced US did not cause any adverse events and identified six of seven (83%) refluxing ureters based on radionuclide cystography and 12 of 20 (60%) refluxing ureters based on VCUG [16]. The author group then concluded that the new technique can be useful as a follow-up study for the patient with previously documented VUR or as a primary study for sibling screening [16]. Similarly, Kaneko et al. (1994) reported a case of a 16-month-old girl whose reflux in the dilated renal pelvis was seen using sonicated albumin-enhanced US, which was equivalent to a VCUG diagnosis of grade 4 reflux [17]. Thereafter, several groups began comparing the diagnostic accuracy of contrast-enhanced US with standard VCUG and radionuclide cystogram, while commercialized contrast media has become available for use in clinical settings.

Recent surveys of pediatric radiologists showed a high proportion of responders with a strong interest in the application, and pediatric radiologists welcomed the availability of contrast imaging US into their practice [18,19]. Moreover, this imaging option is becoming more familiar among pediatric urologists in recent years [10]. The aim of this literature review on comparative diagnostic assessment studies was to provide a concise synopsis on the diagnostic accuracy of contrast-enhanced US in diagnosis and follow-up of pediatric VUR.

Methods

The protocol of this review was registered in PROSPERO (CRD 42017073264), with reporting compliant with the PRISMA-DT statements [20]. The systematic literature search was performed with the assistance of a certified librarian in the medical electronic databases such as Medline, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trial (CENTRAL) on July 25, 2017. The search strategy for the Ovid platform used both Medical Subject Headings and free text in the retrieval of related records (Appendix). A further search for records of relevant literature was made in Scopus, World Health Organization International Clinical Trials Registry Platform, and Clinicaltrials.gov using the simplified and sensitive search strategy for retrieval of related records: (Urosonogram OR Urosonography) AND Ureterovesical reflux. There was no language restriction on any of the searches. In this study, all diagnostic studies assessing the accuracy of contrast-enhanced US as an index study compared with VCUG as the reference standard in the assessment of VUR among children were included. All studies that either reported summarized diagnostic parameters or raw 2 $\times$ 2 table data for extrapolation of the diagnostic parameters were considered. Excluded studies were those compared the contrast-enhanced US with other diagnostic modalities such as nuclear scan or single group series without reference study comparison. The literature screening process was performed by five reviewers (three pediatric urologists and two general physicians) who are adept in the systematic review and proficient in performing the critical appraisal of medical articles. The final eligibility assessment of the initially tagged articles was performed by a pediatric radiologist for inclusion in the literature review. All relevant surveys, reviews, and commentaries were cross-referenced for potentially relevant citations. An expert on the topic was e-mailed for any possible additional or unpublished studies that may be included.

The number of children involved for comparative assessment, the contrast and US setting used, and the timing of the comparative VCUG were extracted and summarized. The studies are summarized according to the generation of US contrast used. Owing to the heterogeneous reporting of diagnostic parameters and limited raw data for extrapolation of clinical parameters, the author group attempted to avoid false value conversions and adapted the reported diagnostic parameters of each study. Owing to severe interstudy heterogeneity and significant reported diverse parameters, meta-analysis was not recommended. The descriptive statistics summarized the median and interquartile range (IQR) of the following reported parameters: accuracy (of contrast-enhanced US in

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detecting VUR as determined by VCUG), concordance (of VUR grade as determined by both contrast-enhanced US and VCUG), sensitivity, specificity, positive predictive value, and negative predictive value.

Results

A total of 10,713 relevant records were retrieved from the literature search. After removal of duplicate records, 6336 were screened for potential eligibility. On initial and second screenings, 119 full-text articles were retrieved for the final assessment of inclusion eligibility. Forty-five publications were selected for this review.

Diagnostic accuracy of contrast-enhanced US VUR

First-generation contrast (Levovist)

Twenty-six publications (cited in Supplementary Table 1) assessed the diagnostic accuracy of contrast-enhanced US with Levovist (99.9% galactose and 0.1% palmitic). The reported overall median diagnostic accuracy was 93.7 (IQR 92.8—96; from nine studies); median concordance was 90.6 (IQR 77.85—93.5%, from 14 studies); median sensitivity was 90.25 (IQR 83.25—97, from 20 studies); median specificity was 93 (IQR 91.3—95.25, from 16 studies); median positive predictive value was 83.7 (IQR 75.25—87.85, from 11 studies); and median negative predictive value was 96.95 (IQR 90—98.68, from 12 studies). Some studies further used color Doppler or power Doppler settings to augment the diagnostic capability of contrast-enhanced US by detecting the microbubbles interaction with the Doppler imaging and generating artifacts. The median accuracy was 95.5 (IQR 94.6—96, from five studies); median concordance was 86.1% (IQR 77.85—95.55, from six studies); median sensitivity was 94 (IQR 91.7—100, from five studies); median specificity was 92.7 (IQR 92.05—94.15, from four studies); median positive predictive value was 86.7 (IQR 85.2—87.85, from three studies); and the median negative predictive value was 98.65 (IQR 96.28—100, from four studies). Supplementary Table 1 summarizes the study population, contrast with US setting, as well as a comparator reference which is cited from the original publication regarding diagnostic accuracy parameters. Almost all studies reported no contrast-related adverse reactions.

In 2007, Darge [21] reviewed and summarized the diagnostic importance of contrast-enhanced US and the procedural technique, with a further review updated in 2010. However, in 2005, Levovist (Bayer Schering AG, Germany) production became unavailable with complete cessation of production around 2010 [21].

Second-generation contrast (SonoVue)

In 2001, the second-generation contrast SonoVue (sulfur hexafluoride with a phospholipid shell) Bracco SpA, Milan, Italy, was introduced in Europe and later in the United States [12,21]. SonoVue has since become the most studied US contrast for intravesical instillation and diagnosis of VUR. There were 14 studies (cited in Supplementary Table 2) using SonoVue for intravesical instillation and detection of VUR in children. The second-generation contrast has 6-h stability compared with 2 h for the first-generation contrast [12,21]. The median accuracy of the second-generation contrast was 97 (IQR 96—98, from two studies); median concordance was 86.3 (IQR 81.5—88.625, from seven studies); median sensitivity was 86.26 (IQR 81.13—97, from six studies); median specificity was 90.99 (IQR 84—98, from five studies); median positive predictive value was 85.71 (IQR 61.61—92.86, from three studies); and median negative predictive value was 90.17 (IQR 80.59—93.59, from three studies). Supplementary Table 2 summarizes the studies that used the SonoVue.

Advances were also made in the US equipment and software with a new 'contrast-specific US mode' based on pulse-inversion harmonic imaging. This allows for subtraction imaging and greatly increases the contrast conspicuity. The harmonic imaging's application provides additional armamentarium in diagnosing VUR and seems to be augmenting the accuracy of upper to lower urinary tract US while being comparative to VCUG investigation.

Supplementary Figs. 1—5 illustrate cases from the senior author's personal experience on the utilization of contrast-enhanced US in assessing VUR. Some investigators have applied special software to incorporate real-time reconstruction of the urinary tract using a three-dimensional plane [22,23]. In 2017, Duran et al. [12] summarized the diagnostic utility of SonoVue for diagnosis of VUR in children with a detailed description of procedural technique and quality assurance criteria to ensure high accuracy.

Current status of contrast-enhanced US

Duran et al. [12] recently described the optimal technique and setting for contrast-enhanced US in VUR assessment. Ultrasound equipment with contrast-specific software is required, preferably one based on pulse-inversion harmonic imaging. Mechanical index, which grossly corresponds to power output, should be kept low (0.04—0.10) to reduce early microbubble bursting. As in all US examinations, the use of appropriate transducers is essential with the higher frequency usually more appropriate for younger patients. Before the procedure begins, a 500-mL saline bag is connected to intravenous tubing after removal of air so as to prevent it from entering the bladder. No sedation is required for the procedure. With the patient placed in a supine position, a 5F to 8F catheter is inserted to empty the bladder and is then connected to the saline bag. There are two main methods for administering the contrast: one in which a dilution of contrast is prepared and then infused into the bladder and a second one in which the bladder is first filled with saline and afterward contrast is injected directly into the full bladder.

In the first method, 1 ml of the contrast agent is injected into the saline bag, the circuit is opened, and contrast solution begins filling the bladder until capacity is reached ([age +2] * 30 in mL). During this filling phase, the bladder, ureters, and kidneys are scanned to identify passive reflux. After filling is complete, the patient is asked to begin voiding if it has not already begun. During voiding, the urinary tract is imaged as before to identify active reflux. Multiple voiding and filling cycles can be performed during the same examination which takes about 15—30 min.

The international system for VUR grading can be applied, but grade 1 reflux is rarely characterized, because of (1) difficult visualization of the non-dilated ureter and (2)

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visualization of microbubbles in the renal pelvis of a dilated urinary tract with grade 1 VUR due to the inherent high contrast in the background. It is also worth mentioning that Darge and Troeger [24] proposed a modified grading system in which each of the five grades is further subdivided into two groups based on whether the reflux is primarily in a dilated or non-dilated urinary tract. Specifically, grade 2 is defined as visualization of the ureter, pelvis, and calyces without dilatation and normal calyceal fornices; grade 3 is the ureter with mild to moderate dilatation and/or tortuosity with mild to moderate dilatation of the pelvis, no blunting or slight blunting of fornices; grade 4 is the ureters demonstrating moderate dilatation with tortuosity and renal pelvis showing moderate dilation with preservation of papillary impressions; grade 5 is the papillary impressions being no longer identifiable in most calyceal system [12].

Currently, there are several US contrasts available mainly in the European and North American countries. These include Definity/Luminity (octafluoropropane [perflutren] with a lipid shell), Sonazoid (perfluorobutane with a phospholipid shell: hydrogenated egg phosphatidylserine), and Optison (perflutren protein—type A microspheres). A recent publication by Ntoulia et al. (2018) has reported Optison providing a high concordance with VCUG in the detection of VUR and grading, 84.3% and 81.8%, respectively. Considering VCUG as the standard, the sensitivity was 91.7% (95% confidence interval [CI] 61.5%—99.8%), and the specificity was 98% (95% CI 89.4—99.9%) [13]. Furthermore, a recent review of over 1000 cases revealed no adverse events, ensuring its good safety profile for children [25].

Discussion

From this systematic literature search, comparative studies assessing the diagnostic accuracy of contrast-enhanced US in the detection and evaluation of VUR among children was identified. The diagnostic parameters at the moment mainly used VCUG as the standard reference. Nakamura et al. [26] used the operational definition of true positive cases when VUR was diagnosed in either approach using the first-generation contrast, while true negative being defined as VUR undetected by both diagnostic approaches. Their assessment revealed a slightly higher sensitivity for VCUG than contrast-enhanced US (96% versus 85%, respectively), although they found that among younger patients with lesser bladder capacity, a higher proportion of contrast can increase the sensitivity to 94% (38). Similarly, using the same definition of true positive and negative VUR, recent studies using second-generation contrast with contrast-specific settings have reported a better sensitivity reaching approximately 88—100% for the contrast-enhanced US [27—29].

From this literature review, it can be inferred that the diagnostic accuracy of contrast-enhanced US in diagnosing VUR among children is comparable to VCUG, specifically for high-grade VUR and in younger children. Although both diagnostic procedures require catheterization, contrast-enhanced US has an excellent safety profile and lack of radiation [25]. However, when using contrast-enhanced US, considerations must be taken into account for the technical expertise and operator dependence required of the procedure. Finally, owing to the limited the availability of the contrast, its related cost, and the expertise needed of the radiologist, implementing it as the global standard for VUR detection is still debatable. Nonetheless, this diagnostic parameter can be used in developed countries with high-volume centers and readily available technical expertise. A recent commentary from Adeb and Darge (2013) suggests that US may still be a more economically viable alternative to VCUG in centers that do not already have fluoroscopy equipment, especially because US equipment is more widely available (and the most modern equipment have contrast-specific capabilities) than having a fluoroscopy equipment [30]. Moreover, although contrast-enhanced US remains inferior in terms of accurately diagnosing low-grade VUR, it has comparable accuracy in detecting high-grade VUR, which is the clinically significant condition that requires surgical management. Thus, contrast-enhanced US may have value in the subsequent follow-up of VUR patients and high-risk patients for upper tract compromise.

Despite the sensitive search strategy used, a major limitation of this review is the small number of studies available for quantitative assessment. Similarly, another limitation is the heterogeneity of the available literature with significant variations of diagnostic techniques, small study size, and inconsistency of reporting. Hence, a meta-analysis with study quality assessment is not pragmatic to generate meaningful recommendations. This review was able to highlight the clinical applicability of such new technology in VUR management among children using simple statistics as a fundamental basis to summarize the reported diagnostic accuracy of the available studies.

Although the majority of the retrieved studies used the currently unavailable Levovist, the literature on the diagnostic accuracy of SonoVue was included. Similarly, the authors believe this comprehensive summary will stimulate awareness to promote future studies to further assess the clinical utility of this new alternative diagnostic modality for children. Currently, newer generation US contrast agents Perflutren Protein—Type A Microspheres *Optison; GE Healthcare, Chicago, IL) and Definity® (perflutren lipid microsphere) are also being evaluated with the use of the advanced contrast-specific mode as an adjunctive approach [11—13]. With these advanced technologies and availability of better contrast agents, the authors recommend future studies to further determine the utilization of these new generation contrasts with more advanced US settings.

Conclusion

This review of the currently available literature on contrast-enhanced US and its clinical applicability for diagnosis and follow-up of pediatric VUR highlights its potential to be an alternative to the current gold standard, VCUG. Contrast-enhanced US eliminates of ionizing radiation while maintaining the same diagnostic accuracy as VCUG. Despite its limitation of high operator dependence, its diagnostic accuracy is excellent in large-volume centers with readily available expertise.

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Author statements

Ethical approval

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Competing interests

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpurol.2018.11.006.

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