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Review Article

How to Detect Vesicoureteric Reflux in Children?

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Abstract

The development in detecting and follow-up of Vesico Ureteric Reflux (VUR) has gone in two directions: first, for whom and when it is important to detect VUR and, second, introducing new techniques for its detection.

In this review article, we first discuss bottom-up (looking for VUR in each child), and top-down (looking for VUR only in those in whom scars have been detected) approaches for VUR detection. We strongly believe that regardless of which approach one finds closer to one's opinion, there should nevertheless be a general agreement that the ongoing search for user-friendly investigations should be an imperative in taking care of the children in question.

In the second part of this review article we discuss various catheter-using methods for VUR detection. The grading of VUR by these different methods is shown. Catheter-free methods for VUR detection are also presented, where Color Flow Doppler ultrasonography and Ureteric jet Doppler Waveform measurement seems to be the most promising.

ABBREVIATIONS

VUR: Vesicoureteric Reflux; UTI: Urinary Tract Infection; VCUG: X-Ray Voiding Cystourethrography; RVC: Radionuclide-Voiding Cystography; VUS: Echo-Enhanced Voiding Urosonography; MRVCUG: Magnetic Resonance Voiding Cystourethrography; cfRVC: Noninvasive Radionuclide Voiding Cystography; cfVUS: Noninvasive Voiding Urosonography; MOD: Measurement Of Midline To Orifice Distance; CFDU: Color Flow Doppler Ultrasonography; UJDW: Ureteric Jet Doppler Waveform Measurement; 3DUSC: Three-Dimensional Ultrasonography-Based Virtual Cystoscopy; cfMRVCUG: Noninvasivemagnetic Resonance Voiding Cystourethrography; TIME: Thermal Imaging Using Microwave Energy; IVU: Intravenous Urography; MRU: Magnetic Resonance Urography; US: Ultrasound

INTRODUCTION

Significant progress in detecting and follow-up of Vesico Ureteric Reflux (VUR) in children has been made in past decades. The development has gone simultaneously in two directions: first, for whom and when it is important to detect VUR and, second, introducing new techniques for its detection. In this review article, this development is chronologically presented and discussed.

FOR WHOM AND WHEN IT IS IMPORTANT TO DETECT VESICOURETERIC REFLUX

The first direction in the development of detecting and follow-up of VUR in children was to find for whom and when it is important to detect VUR. A significant change in the algorithm for the evaluation of children after Urinary Tract Infection (UTI) has occurred in past decades. Currently, there are two approaches in the management of children after UTI - looking for VUR in each child (bottom-up), and looking for VUR only in those in whom scars have been detected (top-down) [1,2].

Regardless of which approach one finds closer to one's opinion, there should nevertheless be a general agreement that the ongoing search for user-friendly investigations should be an imperative in taking care of the children in question [1].

Management of Children after Urinary Tract Infection with Emphasis on the Detection of Vesicoureteric Reflux - Bottom-Up Approach

Initially, X-ray Voiding Cystourethrography (VCUG) was the only method used for VUR detection and, until recently, was considered a gold standard method. Thereafter, Radionuclide-Voiding Cystography (RVC) was introduced and diminished the radiation burden on patients. However, despite this fact and its acknowledged better sensitivity, it has not replaced VCUG in all justified cases. It was only with the development of echo-contrast agents that echo-enhanced Voiding Urosonography (VUS) was offered as an alternative. So far, numerous studies have confirmed that its sensitivity and specificity are high enough to allow it to be introduced as a routine method. This was largely owing to the

introduction of the second-generation echo-contrast agent, which further improved the sensitivity of VUS [3-8]. Recently, however, Magnetic Resonance Voiding Cystourethrography (MRVCUG) was also shown as a feasible and promising test for VUR detection without radiation exposure in children. It is however not feasible in toddlers due to the need for general anesthesia and it can only be performed in specialized MR units [9,10]. It should be noted that VUS was the first method with no radiation at all, while the fact that catheterization is still necessary, as in VCUG and RVC, posed a drawback to those who strongly opposed catheterization as such. It is therefore not surprising that various investigators were vigorously searching for a noninvasive (catheter-free) method that would still provide all the necessary information on VUR. Until now, a number of such methods for VUR detection have been described, i.e. Noninvasive Radionuclide Voiding Cystography (cfRVC) [11], Noninvasive Voiding Urosonography (cfVUS) [12-15], measurement of Midline to Orifice Distance (MOD) [16], Color Flow Doppler Ultrasonography (CFDU) [17-21], Ureteric Jet Doppler Waveform (UJDW) measurement [22-26], Three-Dimensional Ultrasonography-based Virtual Cystoscopy (3DUSC) [27], Noninvasive Magnetic Resonance Voiding Cystourethrography (cfMRVCUG) [9-10], and in experimental studies, Thermal Imaging using Microwave Energy (TIME) [28]. Some of the mentioned catheter-free methods were found to be good screening or follow-up methods for VUR detection. In addition to them, various biological markers (C reactive protein, beta-2-microglobulin, procalcitonin, interleukin-8 and 6, neutrophil gelatinase-associated lipocalin and some others) were also tested to detect VUR, however none of that turned out to be clinically validated [29-33].

The replacement of VCUG with RVC and finally with VUS represents a significant improvement in diminishing the radiation burden on patients, while the catheter-free procedures presented as a "screening methods" remain as yet to be validated on a larger number of patients.

Management of Children after Urinary Tract Infection with Emphasis on the Detection of Vesicoureteric Reflux through its Consequences (Renal Scarring) - Top-Down Approach

In the eighties, Intravenous Urography (IVU) was considered the gold standard for renal scar detection, and it was recommended that it be performed in every child together with VCUG after UTI [34]. Later on, it was almost completely substituted by DMSA, and nowadays IVU is recognized as an obsolete method for this purpose due to its low sensitivity, the radiation hazard and side effects caused by the contrast medium. In the last decade Magnetic Resonance Urography (MRU) has had a growing role in the evaluation of renal parenchymal defects. As compared to DMSA, it has superior anatomic and temporal resolution, and a superb soft tissue contrast. Functional MRU enables quantitative functional analysis (excretion curve, calculation of split renal function, different transit times). It can differentiate acquired renal scars (gained as a consequence of UTI) from inherited renal parenchymal defects (renal dysplastic parenchyma). The later being a great advantage of this method, since it allows a more precise identification of children at risk for renal parenchymal damage and progressive renal failure [9,10]. It could therefore be a very valuable tool to guide a follow up and treatment of children at risk.

Along with the development of new, less invasive and more sensitive methods for renal scars detection, many pediatric nephrologists have questioned the role of VUR as a predisposing factor for renal scarring. It was therefore suggested that VUR be looked for (mostly using VCUG) only in those cases where renal scars had been confirmed by DMSA. The latter was until recently recognized as the most sensitive method for renal scar detection [35-37]. In recent studies it has however been shown that MRU is at least equivalent to, or even superior to DMSA in the detection of renal scarring [38-41]. Despite high sensitivity of both mentioned methods for renal scar detection, DMSA unfortunately involves a relatively high radiation load for the patient, while MRU in small children in general needs to be done under general anesthesia, and both can only be performed in specialized nuclear medicine or magnetic resonance departments.

However, even when following this protocol, which differs significantly from the one described in the previous chapter, a less invasive and user-friendly approach can be achieved. There are reports confirming that ultrasound (US), a harmless and widely available method, can be used as a safe and efficient substitute for DMSA in the detection and follow-up of children with renal scars [42,43]. These papers are based on the assumption that although US is less sensitive than DMSA in detecting renal scars, it might well be the other way around, namely, that DMSA is too sensitive, not to mention MRU, and detects scars that are too small to be clinically significant, while US is sensitive enough to detect clinically significant scars. This assumption was proved by stratifying DMSA results according to the extent of renal scarring, and correlating them to clinical parameters suggestive of renal impairment in our latest studies [42,43]. Furthermore, when one follows this protocol, which suggests VCUG only in those children with proven scars, we believe there is enough evidence supporting the statement that the sensitivity and specificity of VUS is high enough for it to replace VCUG [3-8]. In other words, DMSA could be replaced by US and VCUG by VUS, while the role of new, catheter-free US techniques for VUR detection, as already described, has yet to be validated.

TECHNIQUES FOR VESICOURETERIC REFLUX DETECTION

The second direction in the development of detecting and follow-up of VUR in children was to introduce new techniques for VUR detection. The objective of this development has been to diminish the radiation burden on the patient and to avoid bladder catheterization without losing important data. Decades ago, VCUG was not only the golden standard, but rather the only method for the detection of VUR. It was followed by RVC, which diminished the radiation burden on the patient. Later on, VUS, the first method with no radiation at all, became a routine procedure in an increasing number of centers [3-8]. A drawback of all the mentioned methods, however, continues to be the need for urinary bladder catheterization. To avoid this inconvenience, various catheter-free methods for VUR detection have been developed.

It appears that with the increasing number of new techniques

for VUR detection, there is a need for the currently used terminology to be thoroughly scrutinized, and for the introduction of new terminology based on the actual characteristics of various procedures (direct/indirect, catheter-using/catheter-free, radiation-giving/radiation-free) rather than on commonly accepted, though inaccurate denomination. In our recent paper about catheter-free methods for VUR detection this has already been proposed and is described in detail [44]. Following this new terminology, characteristics of various methods for VUR detection are presented in (Table 1) [44].

Catheter-Using Methods for Vesicoureteric Reflux Detection

All catheter-using methods for VUR detection require catheterization of the urinary bladder in order to fill it with a contrast medium or radiotracer. These methods differ among themselves by the kind of medium that the bladder is filled with (iodinated contrast medium, radiotracer (^{99m}Tc-colloid or ^{99m}TC-DTPA (diethylenetriaminepentaacetic acid)), and echo enhancing agent in VCUG, RVC, and VUS, respectively), and by the mode of its detection in the collecting system of the urinary tract (intermittent pulsed fluoroscopy, Gamma camera, and ultrasound in VCUG, RVC, and VUS, respectively). The sensitivity of RVC and VUS can be increased without additional radiation to the patient by repeated fillings of the bladder and micturition (*cyclic RVC and cyclic VUS, respectively*) through the same urinary catheter that is not removed after each filling [45,46].

The grading of VUR by various catheter-using methods is presented in (Table 2). It should be noted that the three-grade VUS system of VUR by Kenda et al [47] was based on the use of the first generation echo-contrast agent Levovist®. The second generation echo-contrast agent SonoVue® is more conspicuous than Levovist, and can thus more reliably differentiate the extent of dilatation [48,49]. It therefore seems reasonable that a three-grade scale be used for the first generation echo-contrast medium, and a five-grade scale for the second-generation echo-contrast medium.

Catheter-Free Methods for Vesicoureteric Reflux Detection

As noted in the previous chapter, all catheter-using methods for VUR detection require catheterization of the urinary bladder, which is an invasive, unpleasant, painful, and even potentially dangerous procedure. It is therefore not surprising that ongoing efforts were aimed at finding a noninvasive, radiation-free procedure that would be sufficiently reliable to detect VUR.

Table 1: Methods for vesicoureteric reflux detection categorized in terms of their characteristics (direct/indirect, catheter-using/catheter-free, radiation-giving/radiation-free) [44].

Methods Characteristics	VCUG	RVC	VUS	cfRVC	cfVUS	MOD	CFDU	UJDW	3DUSC	cfMRVCUG	TIME
Direct	+	+	+	+	-	-	+	-	-	+	-
Catheter-Using	+	+	+	-	-	-	-	-	-	-	-
Radiation	+	+	-	+	-	-	-	-	-	-	-

Abbreviations: VCUG - X-ray Voiding Cystourethrography, RVC - Radionuclide Voiding Cystography, VUS - Echo-enhanced Voiding Urosonography, cfRVC - Catheter-Free Radionuclide Voiding Cystography, cfVUS - Catheter-Free Voiding Urosonography, MOD - Ultrasound Measurement of Midline to Orifice Distance, CFDU - Colour Flow Doppler Ultrasonography, UJDW - Ureteric jet Doppler Waveform Measurement, 3DUSC - Three-Dimensional Ultrasonography-Based Virtual Cystoscopy, cfMRVCUG - Catheter-Free Magnetic Resonance Voiding Cystourethrography, TIME - Thermal Imaging Using Microwave Energy

Table 2: Grading of vesicoureteric reflux by various catheter-using methods.

VCUG	RVC	VUS	
		Kenda et al [47]	Darge et al [53]
I	I	I	I
II	II	II	II
III			III
IV	III	III	IV
V			V

VCUG - X-ray Voiding Cystourethrography; Vesicoureteric Reflux (VUR) [50]: Grade I - contrast in ureter; Grade II - contrast in ureter and renal pelvis without dilatation; Grade III - contrast in mildly/moderately dilated ureter and renal pelvis + no or slightly blunting calyces; Grade IV - contrast in moderately dilated and/or tortuous ureter with moderate dilatation of renal pelvis and calyces and complete obliteration of sharp angels of calyces, but maintenance of papillary impressions in most calyces; Grade V - contrast in grossly dilated and tortuous ureter, gross dilatation of renal pelvis and calyces; papillary impressions not visible in most calyces.

RVC - Radionuclide-voiding Cystography [51,52]: Grade I - radiotracer reaching the ureter only; Grade II - radiotracer reaching the pelvis; Grade III - radiotracer reaching the pelvis, which seems dilated.

VUS - Echo-enhanced Voiding Urosonography; VUR is graded by two different grading systems into three and five grades, respectively.

• The three-grade system by Kenda et al [47]: Grade I - contrast in the ureter only; Grade II - contrast in the pelvis; Grade III - contrast in the pelvis, which seems dilated.

• The five-grade system by Darge at al. [53]: Grade I - contrast only in the ureter; Grade II - contrast in the renal pelvis, no significant renal pelvic dilatation; Grade III - contrast in the renal pelvis + significant renal pelvic dilatation + moderate calyceal dilatation; Grade IV - contrast in the renal pelvis + significant renal pelvis dilatation + significant calyceal dilatation; Grade V - contrast in the renal pelvis + significant calyceal dilatation + loss of renal pelvis contour + dilated tortuous ureter.

Currently available evidence appears to be promising as regards the use of various catheter-free methods for VUR detection. All catheter-free methods for VUR detection are performed without catheterization of the urinary bladder, and they are all, except for cfRVC, based on the use of ultrasound, and are therefore also radiation-free. These methods differ among themselves by the signs of VUR that are detected, and the mode (by gamma camera or ultrasound) of their detection. Signs of VUR that are detected by catheter-free methods can be direct as in cfRVC (radiotracer appearing in the kidney) [11], CFDU (a change in color on the monitor suggests a reversal flow from the bladder into the distal ureter) [17-21], and cfMRVCUG (contrast appearing in the kidney) [9,10], or indirect as in cfVUS (an increase in the antero-posterior diameter of the collecting system during and/or after voiding) [12-15], MOD (ureters with more laterally placed ureteric orifices are more likely to be affected by VUR) [16], UJDW (the shape of UJDW) [22-26], 3DUSC (gapping ostium configuration, an asymmetrical ureteral inflow jet, a lateralized position of the ostium, and dilatation of the distal retrovesical ureter) [27], and TIME (localized heating) [28].

Among all the mentioned catheter-free methods, CFDU and UJDW were shown to be the most promising. CFDU happened to have a relatively high overall sensitivity especially in high grade VUR [17-20], while UJDW seems to be the most promising of the above-mentioned methods, especially as a screening method in a two-stage protocol in detecting VUR. If one were to proceed from UJDW measurement to VUS only in those cases where UJDW measurement was indicative for VUR, a considerable number of children over 3 years of age would be spared from one of the invasive micturition cystographies [22-25]. In addition, in a recent study by D'Souza et al, UJDW was shown to have a uniformly high specificity regardless of age or etiological groups, making it a good tool for follow-up [26].

CONCLUSION

Searching for patients at risk for renal scarring and searching for new "patient-friendly" techniques for the detection of VUR, as well as for the detection of renal scarring, should be an ongoing process. The replacement of VCUG with RVC and ultimately with VUS represents a significant improvement in diminishing the radiation burden on patients, while the catheter-free procedures presenting a "final solution" remain as yet to be validated on a larger number of patients. Hopefully, radiation and catheter-free methods are only one of the steps along this line. It seems that in the future the genetics will play an important role in decision making, help us to determine those patients who are genetically at risk for renal scarring, and to perform investigations only on them, while all others will be spared any investigations at all, even though these may be "patient-friendly".

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