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ALARA

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Applying the ALARA concept to the evaluation of vesicoureteric reflux

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Abstract The voiding cystourethrogram (VCUG) is a widely used study to define lower urinary tract anatomy and to diagnose vesicoureteric reflux (VUR) in children. We examine the technical advances in the VCUG and other examinations for reflux that have reduced radiation exposure of children, and we give recommendations for the use of imaging studies in four groups of children: (1) children with urinary tract infection, (2) siblings of patients with VUR, (3) infants with antenatal hydronephrosis (ANH), and (4) children with a solitary functioning kidney. By performing examinations with little to no radiation, carefully selecting only the children who need imaging studies and judiciously timing follow-up examinations, we can reduce the radiation exposure of children being studied for reflux.

Keywords ALARA · Vesicoureteric reflux · Radiation

Introduction

The traditional method for diagnosing vesicoureteric reflux (VUR) is the fluoroscopic voiding cystourethrogram (VCUG). This study is primarily used to screen children who are at risk of VUR and to provide detailed anatomical information on the genitourinary system. Because this examination is mainly performed in children, who are at greatest risk of the harmful effects of ionizing radiation, we must find ways to achieve diagnostic accuracy while minimizing radiation dosage.

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In this article, we review the technical advances in the diagnosis of VUR and present recommendations for the evaluation of four groups of children widely studied for reflux: (1) children with urinary tract infection (UTI), (2) siblings of patients with VUR, (3) infants with antenatal hydronephrosis (ANH), and (4) children with a solitary functioning kidney. In addition, we discuss the timing and frequency of imaging studies to detect VUR resolution. By defining patients at risk of reflux and determining the differences between patient groups, we can utilize studies judiciously and minimize radiation exposure. Our recommendations are based on the imaging studies available at our hospital. The ultimate choice of imaging modality depends on diagnostic availability, the individual patient and the referring physician's preference.

Technical advances in voiding cystography

In the last two decades enormous strides have been made in reducing the radiation dosage in patients studied for VUR. The improvement has been a result of replacement of standard fluoroscopic machines with digital and pulsed fluoroscopy, judicious use of radionuclide cystograms (RNC), and the introduction and growing popularity of voiding urosonography (VUS).

A traditional VCUG exposes the patient to 100 times the radiation of an RNC. In the last 10 years, low-dose fluoroscopy techniques, including digital fluoroscopy and pulsed fluoroscopy, have led to a decrease in the radiation dose to the patient [1–5] while providing similar diagnostic quality images [6–10]. By changing from continuous to pulse fluoroscopy, the effective dose of radiation can be reduced by approximately 90% with minimal loss of resolution [10]. Pulsed fluoroscopy is now considered a requisite for optimal pediatric fluoroscopy [11].

Digital fluoroscopy offers the advantage of "image or screen save" so that the last image can be saved without additional radiation to the patient. Limiting the number of spot images and maximizing the number of image-save acquisitions decreases radiation [12]. Meticulous image

coning also significantly decreases patient radiation exposure. Thus low magnification, low-pulse-per-second fluoroscopy and image-save acquisition should be used when performing a VCUG.

In our department, the effective radiation dose of a VCUG using modern low-dose fluoroscopic methods is approximately 10 times that of RNC (mentioned below). For example, the average effective dose of a VCUG in a 3-year-old patient is 3 mrem, compared to 0.5 mrem for an RNC. For comparison, the average effective dose of an airplane ride from Boston to San Francisco is 5 mrem. The average effective dose of the VCUG is variable and depends on the patient size, operator and machinery.

The main advantage of RNC over fluoroscopic VCUG is decreased radiation exposure of the patient. The sensitivity of RNC for detecting reflux is equal to or greater than that of VCUG; however, the spatial resolution and anatomic detail seen on an RNC are inferior to those seen on a VCUG. To increase the sensitivity of either test, a cyclic study should be performed in children younger than 1 year [13].

In order to avoid instrumentation, methods of indirect cystography have been tested. Indirect cystography uses intravenously injected Tc 99m pentetate, which is cleared by the kidneys into the bladder to assess for reflux without bladder catheterization. Unfortunately, this method has a high percentage of false-negative studies, so it is not recommended.

During the last two decades, in an effort to eliminate the radiation exposure intrinsic to RNC and VCUG, sonography has been used to evaluate reflux. Indirect US methods without the use of contrast agents avoid instrumentation but are significantly less sensitive [14–16]. A normal non-contrast US scan of the urinary tract without contrast agent does not exclude reflux [17]. The availability of a stable US contrast agent that can be administered intravesically is a great breakthrough that has popularized VUS [18]. During contrast sonocystography, the bladder is filled through a catheter with a US contrast agent, and reflux is assessed by the sonographic appearance of contrast agent within the kidneys and ureters. The grading system is similar to that for a VCUG [19]. This method is not as popular in North America as elsewhere in the world. In some German institutions, this method has led to a significantly reduced number of VCUGs and the associated ionizing radiation [20].

There is a 92% concordance in VUR diagnosis on VUS and VCUG/RNC [18, 21, 22]. In comparison to VCUG, the sensitivity and specificity of VUS range from 88% to 100% and 86% to 100%, respectively [18]. Although comparable to VCUG and RNC in sensitivity and accuracy in detecting VUR [23–30], VUS as compared to a VCUG does not provide comparable anatomic detail of the bladder, ureter, and urethra. Current recommendations for the use of VUS vary.

During MR cystography, images of the genitourinary tract are obtained before and after the intravesical administration of gadolinium and after voiding. The method is less sensitive than VCUG for detecting reflux and is experimental. The relative benefits of this examination are that it exposes the child to no additional radiation and can evaluate the kidneys for changes related to reflux nephropathy [31, 32]. However, the sedation or anesthesia often required in the young patients evaluated by MRI imposes medical risks and costs time and resources.

Children with urinary tract infection

Most UTIs in children are ascending and related to factors such as dysfunctional voiding or impaired lower tract defenses. The VCUG has been regarded as fundamental in evaluating the child with a well-documented UTI because it evaluates: (1) bladder and urethral anatomy, (2) bladder capacity, (3) ability of the bladder to empty, (4) presence of VUR, and (5) the grade of VUR.

Although cystitis alone does not pose a significant threat to the health of a child, a UTI combined with VUR can result in significant renal damage. VUR is present in 30–50% of children with a febrile UTI [33]. Studies demonstrate that on initial evaluation of children with a febrile UTI and VUR there is up to a 40% incidence of renal scarring [34]. Although the majority of VURs resolve spontaneously with time, the likelihood of resolution depends on age at diagnosis, laterality and VUR grade. In addition, as children get older, they are much less likely to have VUR, because if they had it, it has resolved (Fig. 1) [35]. The VCUG provides critical prognostic information by detecting and then defining the severity of VUR.

The VCUG is invasive in terms of instrumentation and radiation exposure; therefore, selectivity in its application is appropriate. The greatest reduction in radiation exposure occurs by avoiding the study altogether. Critical to determining which patients require a VCUG is the

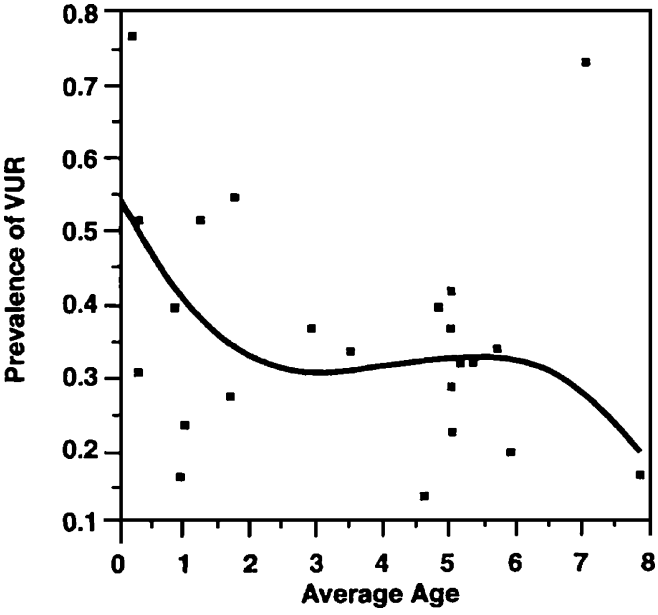

Fig. 1 Graphical representation of VUR prevalence determined from 54 studies weighted by sample size of children with UTI (reproduced with permission from *Pediatrics* vol. 103, pp 843–852, copyright 1999 by the AAP)

definition of a UTI. Urine specimens obtained by catheterization or suprapubic aspiration are the gold standard. Any significant pure growth from a catheterized specimen or suprapubic aspiration is regarded as positive. A bacterial count of $>10^5$ cfu/ml from a clean midstream collection has an 80% (and two such collections a 90%) likelihood of representing a true infection [35]. Specimens that are obtained by adhering a plastic bag to the perineum are useful only if no organisms grow, as any bacterial growth usually reflects perineal flora. Contamination rates range from 60% to 70% [36]. Results from catheterization through a phimotic foreskin can also be misleading.

In addition, clinical presentation, age, race and social factors contribute to selecting which patients should have a VCUG. The combined presence of fever (>38.5°C) [37] and UTI are important clinical findings, as they might indicate a pyelonephritis as opposed to cystitis, which typically does not produce fever. Pyelonephritis can result in significant kidney damage unless prompt antimicrobial therapy is instituted. Children with repetitive febrile UTI are at further increased risk of renal damage. Therefore, in the young child with a febrile UTI, cystographic evaluation to rule out VUR is most strongly warranted.

Recently, attempts to link biomarkers of inflammation such as procalcitonin, known to be associated with renal scarring, have shown promise in attempting to stratify patients by risk of renal damage [38]. Further investigation is needed to accurately stratify patients by their risk of renal damage.

The greatest risk of renal damage is during the first 2 years of life. Therefore, we recommend aggressive screening of children <2 years of age, because of their increased risk and inability to describe symptoms. For prepubertal boys with a well-documented UTI, the VCUG is the preferred diagnostic study so that the urethral anatomy might be defined. In less well-documented cases, an initial renal bladder US is reasonable. For prepubertal girls with pyelonephritis, the VCUG is recommended, whereas for prepubertal girls with recurrent lower UTI and the ability to describe symptoms (>5 years of age) an RNC is recommended. If the veracity of the diagnosis of UTI in a girl is questioned, a US is a proper initial study.

Postpubertal children are at minimal risk of renal scarring and do not require diagnostic imaging when presenting with cystitis. Similarly, because of the low incidence of reflux in black children, the black child between the age of 5 years and puberty presenting without fever but with infection do not require a VCUG [39]. In settings where parental vigilance is questionable, an aggressive approach should be considered.

Sibling vesicoureteric reflux

VUR is the most common heritable disorder of the genitourinary tract, but has not been linked to a particular chromosome or genetic defect. A recent research synthesis of 1,768 siblings of various ages showed a mean VUR incidence of 32% [40]. The research demonstrated that certain factors help predict the risk of sibling VUR. When stratified by sibling age, 44% of children <2 years of age have VUR, as opposed to 9% of children >6 years [40]. If the sex of the sibling or index patient is considered individually there is no statistically significant difference in VUR risk; however, if the sex of both patients is considered, female siblings of female index patients are at higher risk of VUR than their male counterparts [41]. Twins are at particularly increased risk, and monozygotic twins are at higher risk than dizygotic twins [42, 43]. Approximately two-thirds of sibling VURs are low-grade (I/II) and half are unilateral [40]. Sibling VUR shows an inverse relationship between age and grade of reflux [44]. Although the data are limited, siblings might have a higher resolution rate as compared to children discovered after a febrile UTI [40].

Although the incidence of VUR in siblings is significantly higher than in the general population, the majority of sibling VUR is asymptomatic (no history of UTI) and might be innocuous. Hollowell and Greenfield [40] determined from the literature an 11% incidence of renal damage documented by various radiographic modalities in which the majority of patients were asymptomatic [40]. Furthermore, Puri et al. [45] demonstrated that symptomatic siblings (history of febrile UTI) not only have higher grades of VUR but also an increased rate of reflux nephropathy (25%) as compared to reported data on asymptomatic siblings. Therefore, the early detection of VUR in asymptomatic siblings might decrease the incidence of renal damage [46].

Although the goal of screening for sibling VUR is the prevention of renal damage, no current genetic tests can determine who is at risk of renal damage, let alone which siblings will have VUR. Based on the literature, we have divided children into four groups for potential screening: (1) newborns to the age of toilet training, (2) prepubertal children older than toilet-training age, (3) postpubertal children, and (4) any symptomatic sibling. The age of toilet training is chosen because typically at this age children can describe their symptoms and parents can detect signs of UTI such as frequency.

All children should be initially screened by an extensive history including voiding habits and any unexplained febrile events. We recommend elective screening with RNC for both girls and boys, because RNC is a sensitive examination for VUR and confers a very low dose of radiation. In the future, VUS might be a viable alternative to the RNC.

Because the prevalence of VUR drops considerably with increasing age (Fig. 1) for prepubertal children older than toilet training age (group 2), we recommend an initial screening US scan. If the renal US scan demonstrates abnormalities, such as size discrepancy, renal malformation or scarring, dilated ureter, hydronephrosis or change in renal pelvis or ureteral caliber during the examination, we recommend an RNC. If VUR is discovered, the follow-up study at 1 year should be a VCUG to more clearly define the genitourinary anatomy.

We accept that ultrasonography is not as sensitive as DMSA for the detection of renal scars in patients with a history of acute pyelonephritis; however, the role of evaluating the asymptomatic patient sonographically as compared to DMSA has not been defined [47–49]. If the sibling population has remained asymptomatic during the most vulnerable period for renal damage secondary to infection and reflux, the value of conducting a DMSA scan as the initial screening test is low.

Vulnerability to renal damage is thought to persist until puberty [50, 51]. Taking this into consideration, with the decreasing incidence of reflux with age and the possible higher resolution rate of reflux in siblings, we recommend that asymptomatic postpubertal boys and girls be screened with a renal US scan only (group 3). We especially recommend screening of girls because of the increased risk of UTI during their reproductive years and the deleterious effects of an upper UTI during pregnancy. If there are no renal abnormalities, we recommend no further investigation unless symptoms develop. If abnormalities are found on sonography, we recommend a VCUG or RNC. Symptomatic siblings (group 4) need to be studied aggressively and treated as any other child with a UTI.

Antenatal hydronephrosis and vesicoureteric reflux

ANH affects 1–5% of all pregnancies and is one of the most common prenatally detected abnormalities; however, the clinical relevance of varying degrees of ANH is unclear [52–61]. Although the prenatal US scan is noninvasive and without ionizing radiation, postnatal assessment can be invasive and expose the child to radiation. To date there are no large comprehensive prospective studies that have determined the risk of VUR with varying degrees of ANH. Similarly, there are no large studies that have examined both ANH and postnatal US (PNUS) findings to predict postnatal risk of VUR or kidney damage. There is general agreement that the postnatal evaluation of children with moderate to severe ANH that persists postnatally should include a VCUG. However, the postnatal management of children with mild ANH, any degree of ANH that resolves soon after birth, or a nonspecific history of ANH is controversial.

Numerous small series demonstrate that children with ANH have an increased risk of VUR as compared to the general population [62–64]. Overall, boys are thought to be at greater risk of bilateral high-grade reflux than girls [65]. The largest single series that documented mild ANH and its relationship to VUR established a 15% incidence of VUR; however, this series only had 40 patients [63].

Attempts to stratify risk based on PNUS findings have not been successful [62–64, 66, 67]. Many studies have shown that a normal postnatal US scan is not a reliable indicator or predictor for the exclusion of VUR [68–70]. In one study, hydronephrosis on PNUS had a sensitivity of 63% and specificity of 66% for VUR on VCUG [63]. Although the data are limited, children with ANH and VUR seemingly have a more benign course with a higher resolution rate of VUR than children discovered to have VUR after a febrile infection [71–73].

We provide the following recommendations for the evaluation of children with ANH with the understanding that the current literature is controversial and that the care of each child is individual. Children with bilateral severe ANH or a solitary kidney with any grade of ANH should undergo a PNUS shortly after birth, keeping in mind that physiologic dehydration within the first 5 days might decrease the degree of hydronephrosis. Those with any other grade of ANH should undergo a PNUS within the first month of life. Male and female children with moderate or severe ANH should undergo a VCUG. Children with mild ANH that persists after birth might be followed by US with or without a VCUG or RNC. Management of mild ANH that resolves is controversial and might require further imaging.

The solitary kidney

The incidence of VUR in patients with a multicystic dysplastic kidney (MCDK) or renal agenesis has been examined in a number of studies. It is logical to do so because the child's renal function is entirely dependent upon the integrity of the solitary kidney such that reflux nephropathy would have devastating consequences.

The incidence of reflux to the contralateral kidney in a child with MCDK ranges from 13% to 28% [74–77]. Reflux in the majority of children is mild to moderate in degree, and the spontaneous resolution rate is high. Renal agenesis has been evaluated in fewer studies, but the incidence of VUR appears comparable to that in MCDK (5–24%) [74–76]. Without doubt, some of these cases might represent undetectable MCDK. For both MCDK and renal agenesis, RNC and VUS seem advisable as screening studies for VUR because the stakes in this group of patients with a solitary functioning kidney are particularly high.

Timing and frequency of radiologic intervention for the detection of VUR resolution

The majority of patients with primary VUR are managed medically with prophylactic antibiotics until either resolution of VUR or an indication for surgical intervention. The rate of VUR resolution by grade and laterality has been well-documented. Nonetheless, guidelines vary considerably regarding the frequency or type of diagnostic imaging needed to follow VUR until resolution [78–81]. Although most pediatric urologists and pediatric radiologists recommend annual follow-up studies, this has not been rigorously tested.

The dilemma has recently been analyzed by modeling, in both a theoretical and retrospective cohort of children younger than 10 years with a diagnosis of primary VUR and febrile UTI, different strategies of VCUG follow-up and its effects on antibiotic exposure and cost [82]. Based on their analysis, the authors recommended that patients

with mild VUR undergo a VCUG every 2 years during follow-up and every 3 years if reflux was moderate to severe. The authors made these recommendations by determining which timing strategy would most effectively decrease the number of VCUGs and cost per patient while minimizing increase in antibiotic exposure. Using a small retrospective cohort of patients with low-grade reflux and a resolution rate similar to that of published rates they applied their clinical algorithm and predicted that the number of VCUGs performed per patient would be reduced by 19% (P=0.001), the costs reduced by 6% (P=0.17), and the antibiotic exposure increased by 26% (P=0.001).

With less frequent VCUG follow-up, long-term antibiotic exposure will increase significantly in patients who are compliant. However, it is well-documented that adherence to medication regimens in children with chronic diseases is about 50% [83]. The longer they require medication, the less likely they are to adhere to the regimen [83]. Although it is difficult to quantify, it is possible that voiding cystography would serve as a reminder of VUR, which in turn would improve medication compliance before VUR resolution.

Without doubt, if we could stratify VUR patients by their risk of renal damage, we would significantly decrease the amount of diagnostic imaging performed during medical management. Some authors have recently questioned the conventional management of children with low-grade reflux who might be at a low risk of renal injury; however, it is still difficult to determine which children are at risk of damage [84–86].

We recommend that patients with low-grade (I, II) primary VUR, regardless of laterality, be followed annually because of the higher resolution rate with lower grades of VUR. If the initial study to document VUR was an RNC, we recommend the first follow-up examination be a VCUG in order to detect any occult bladder or urethral abnormalities that would decrease the likelihood of VUR resolution (e.g. hutch diverticulum, posterior urethral valves). All subsequent follow-up studies should be an RNC, keeping in mind that grade I reflux is sometimes difficult to discern on RNC. For patients with moderate to severe VUR (≥III), a more prolonged resolution period is anticipated. Initially, anatomical abnormalities need to be ruled out with a VCUG. At the discretion of the urologist and taking into consideration family compliance, patient age, and the logistics of follow-up, an RNC might be performed every 18 months to 2 years until resolution or surgical intervention. For patients with bilateral disease, the higher grade of VUR is the rate-limiting step to resolution and, therefore, dictates the frequency of follow-up.

For children who undergo antireflux surgery, postoperative imaging should be an RNC. A VCUG is rarely indicated, and many pediatric urologists [87] no longer perform postoperative voiding studies at all. For those who are committed to documenting the success of surgery, the VUS might prove to be the ideal study in the future.

Conclusion

Significant technical innovations, such as digital pulsed fluoroscopy and VUS, and the judicious use of the studies emitting ionizing radiation have led to the overall decrease in radiation exposure in children being evaluated for VUR. In the future, advances in basic science such as genetic screening and biomarker discovery might help determine which children are at risk of reflux and renal damage, potentially replacing our current invasive and radiation-emitting examinations for reflux.

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