Vesicoureteral Reflux

Abstract

Much research has been done regarding the diagnosis and treatment of vesicoureteral reflux (VUR). Predominantly, diagnosis of this disorder occurs in young children and infants, who are particularly susceptible to the effects of ionizing radiation. Options for diagnosis include direct radionuclide voiding cystography (RNC), voiding cystourethrography (VCUG), and renal ultrasonography. Patients have the option of managing the accompanying urinary tract infections (UTI) or treating the reflux directly. Management options include long-term antibiotic prophylaxis, long-term probiotic prophylaxis, or the treatment of each individual occurrence of UTI. Treatment options for VUR include invasive surgery, Deflux, and minimally invasive endoscopic injection of dextranomer/hyaluronic acid (Dx/HA). Recent research is beginning to look into the use of nonionizing means of diagnosis, such as ultrasound as well as less invasive forms of treatment.

Introduction

Vesicoureteral reflux (VUR) is an abnormal condition of the urinary system in which urine flows in the reverse direction, from the bladder to the kidney, through the ureter. It can affect either one or both ureters. VUR affects an estimated 2.2% of girls and 0.6% of boys who present for testing. However, that number may be higher due to patients who experience no adverse symptoms. One major symptom to indicate that testing may be needed is urinary tract infection. When urine waste is not expelled properly from the body, bacteria can grow, leading to infection. Children commonly present to the medical imaging department for a voiding cystourethrogram (VCUG) due to frequent urinary tract infections with or without fever. This test can aid in diagnosis of abnormal structures or function of the urinary system. Diagnosis of the underlying root of the UTI is very important for the renal health of the individual.

Vesicoureteral reflux can vary in severity and is classified from Grade I, being mild, to Grade V, being severe (see Figure 1). Regardless of severity, VUR can damage the renal system or can lead to complications due to the infections it causes. When bacteria grow in the kidneys, scarring can occur. Due to the young age of many of these individuals, it is critical that early detection and treatment are sought, as well as that treatment being as minimally invasive as
possible. It is unfortunate that so many of these patients must undergo ionizing radiation in order to detect VUR, and that the treatment is often an invasive procedure, such as vescostomy.\textsuperscript{2} Much is being done to find other means of diagnosis that does not utilize ionizing radiation, but demonstrates the same effectiveness. Renal ultrasound is one such tool used in the diagnosis of renal abnormality.\textsuperscript{3} There has also been research regarding less invasive treatment, such as minimally invasive endoscopic injection of dextranomer/hyaluronic acid (Dx/HA).\textsuperscript{4} All this leads to greater patient safety and improved prognosis of VUR.

Radiologic technologists (RTs) must be sensitive to the patients who present for testing, due to the young age of these individuals. Quite often, these children are afraid, in pain, or experiencing discomfort before the exams even begin. Unfortunately, the diagnosis of VUR most often requires catheterization, which can be quite frightening and uncomfortable for a small child. RTs should be able to show empathy to the individual while getting the best images possible for diagnosis. It is the physician’s moral obligation to choose a treatment plan that has the patient’s best interest in mind, whether that involves ultrasound instead of ionizing radiation or treating the patient non-invasively rather than performing an invasive surgery. However, the degree of VUR also affects the treatment plan, as invasive surgery may be the only way to achieve total resolution of VUR, and VCUG may be the most effective way to view the anatomy of the urinary system and its disorder. The patient and their biological disorder should always be the center of any treatment plan.

**Anatomy**

The urinary system is made up of two kidneys, each attached to a ureter that leads inferiorly to one urinary bladder. The urinary bladder is then connected inferiorly to one urethra. The two kidneys and their ureters lie in the retroperitoneal space of the abdomen. The kidneys lie to the left and right of the vertebral column, with the right kidney typically slightly lower than the left due to the space occupied by the liver. The ureters follow the curvature of the lumbar spine and then curve posteriorly at the pelvis where it meets the urinary bladder on the posterolateral surface. The bladder is then connected to one urethra on the inferior border of the bladder.\textsuperscript{5} The urethra leaves the body below the symphysis pubis by way of an opening in the female vulva or male penis.
The primary function of the urinary system is to produce and eliminate urine. During the production of urine, the kidneys perform a number of tasks. These tasks include regulating the water levels in the body, regulating the acid-base balance as well as the electrolyte levels within the blood, and removing nitrogenous waste, such as urea and creatinine, from the body. The ureters act as a transport system for urine from the kidneys, and the bladder functions as a holding tank, or reservoir for the urine until it can be expelled via the urethra. These waste products carry with them bacteria. When the elimination of urine is compromised, the bacteria has a suitable environment to grow and flourish, causing UTI.

Signs and Symptoms of Vesicoureteral Reflux

Vesicoureteral reflux is often associated with urinary tract infection, most commonly in children. Urinary tract infections in infants can be caused by a number of factors and therefore, determining the cause may be difficult. Some sources of UTIs among the infant population include bacterial infection, a congenital anomaly of the kidney and urinary tract (CAKUT), and an obstructed or neurogenic bladder. Infants with a UTI may present with failure to thrive, irritability, vomiting, diarrhea, lethargy, jaundice, or fever, although only about half of neonates have a high fever. Prolonged jaundice may be the only presenting symptom as well, which is why proper testing is critical. Common practice is to perform a urinalysis for babies presenting with any of these symptoms in order to determine if there is a presence of bacteria and what type of bacteria it is. These infants are often given an antibiotic as well, and the responsiveness to the infection is monitored.

Diagnosis

There are two classifications of vesicoureteral reflux. Primary reflux is diagnosed after the presence of a UTI or during follow up for an antenatally diagnosed CAKUT. Secondary reflux can occur as a result of a bladder outlet obstruction or a neurogenic bladder. Patients with VUR are also at increased risk of renal scarring. This renal scarring is called reflux nephropathy and increases a person’s risk of developing proteinuria, hypertension, and renal disease later in life. This is why it is so critical to get early, accurate diagnosis of VUR, followed by successful treatment of the cause. VCUG and direct radionuclide voiding cystography have been the
conventional means of testing following UTI in children, but the ionizing radiation to the young individual is a concern.

VCUG is an x-ray examination involving the kidneys, bladder, ureters, and urethra.¹ The patient is catheterized and a radiopaque contrast agent is injected into the urethra and bladder. Several images or video are taken with the fluoroscope (see Figure 2). When the bladder has filled, the patient is instructed to void and images or video are again obtained. This exam may be quite uncomfortable for patients. When patients are young and not yet potty-trained, it may be easier for them to void. However, young children who have recently potty-trained may find it very hard to urinate on the radiographic table with the Radiologist and Radiologic Technologist present. It can make the child feel that they are doing something wrong and against what they’ve recently learned. This experience can even be quite traumatizing for a young child; from the catheter, to filling of the bladder, to voiding on the table. VCUG also requires exposing the patient to significant amounts of radiation.

Radionuclide cystography (RNC) is a nuclear medicine study in which a radioactive material is injected into the bladder through a catheter, and then the abdomen and pelvis are scanned as the patient voids, or immediately after voiding.¹ This procedure can have similar implications to the child, with fear and discomfort from the catheter, full bladder, and voiding on the table. There can also be negative consequences due to the use of the radioactive material. “RNC is more sensitive than VCUG but does not provide as much detail of the bladder anatomy.”¹(p.3) These images are more difficult to interpret, as this is a functional study, rather than an anatomical study (see Figure 3).

Renal ultrasound is another method used in the diagnosis of VUR. There are a number of different techniques used during ultrasound of the urinary system, with each giving differing results in the detection of VUR (see Figure 4). Voiding urosonography (VUS) is done without the use of ionizing radiation to the patient, but an echo-enhancing agent may be used in order to maximize visualization of the anatomy. With standard VUS, the patient must be catheterized and the bladder filled mechanically in order to monitor the filling phase. The patient must also void as directed to monitor the voiding phase and check for reflux. These disadvantages are similar to those in VCUG and RNC. However, there have been advancements in the use of Doppler ultrasound to detect VUR without the need for catheterization. This exam would require the patient to come to the imaging department with a full bladder. Ultrasound would be
performed on the full bladder to evaluate the flow or possible backflow of urine, and then the patient would void while still being scanned. The images would appear in a certain color, depending on the direction of flow. Unfortunately, this exam can only be done on a patient who is toilet trained, as it requires bladder control. Since there is a wide range of methods within ultrasound, the effectiveness as a whole varies greatly.

Fallah et al³ conducted a study of 66 pediatric patients ranging in age from three months through 11 years and compared the detection and grading of vesicoureteral reflux using direct radionuclide voiding cystography and Doppler voiding urosonography. They did not focus their study on VCUG because “comparative studies have shown that direct radionuclide voiding cystography in experienced hands is more sensitive for the detection of vesicoureteric reflux than x-ray voiding cystourethrography.”³(p.56) The purpose of their study was to determine if ultrasound could compare in diagnostic effectiveness to the best tests done with ionizing radiation. Their findings confirmed that ultrasound can be equally as effective as ionizing radiation when diagnosing and grading vesicoureteral reflux. This was especially true for patients under one year of age, and patients with severe reflux. However, their study did not produce any significant information as to whether echo contrast agents benefitted the diagnosis or grading of vesicoureteral reflux, although echo-enhancing agents were tolerated well among the patients.

**Treatment**

Proper treatment of any disease or disorder is critical in order for a patient to obtain the best possible outcome. One cause of VUR may be a complete duplex collecting system, which means that the patient has a kidney that is divided into two separate moieties. This condition is the most common anomaly found in the upper urinary system of children.⁴ The effected kidney has two ureters emptying the kidney and entering the bladder, with the upper ureter often associated with a ureterocele. A ureterocele is a balloon-like malformation in the area of the bladder where the ureter enters.⁹ That upper ureter enters the bladder in a lower position than the second ureter, leaving it susceptible to reflux of the urine and higher risk of UTIs. In order to manage vesicoureteral reflux, there are options to manage the UTI and renal scarring, or correct the VUR itself. Options for UTI management include long-term antibiotic treatment, long-term probiotic treatment, or simply treating UTIs as they manifest themselves. Options for the
correction of VUR include open surgery, Deflux, and minimally invasive endoscopic injection of dextranomer/hyaluronic acid (Dx/HA).^{4,7}

Ethically, the treatment plan designed by the doctor would be one that is minimally invasive, won’t cause complications with other organs or organ systems, won’t cause future problems, and will be successful in treating the target concern. However, Lee et al^{10} performed a study in which physician preference was found to be a major factor in designing a treatment plan. This study only included treatment via surgery, Deflux, or no surgery. It is unfortunate that this study did not show that the patients’ needs were the first consideration when deciding on a treatment approach.

Hunziker et al^{4} performed a study of 123 pediatric patients diagnosed with intermediate and high grade vesicoureteral reflux by means of a Dimercapto-succinic acid scan. These patients were treated with endoscopic injection of dextranomer/hyaluronic acid (Dx/HA). This procedure involves the patient being under a general anesthetic and a catheter being inserted by means of a cystoscope. Through the catheter, a needle is introduced and inserted into the bladder wall just below the entrance area of both the duplicate ureters. The Dx/HA is injected in the form of a paste, which causes a bulge under the tissue. This, in turn, results in minimizing the opening of the ureter at the border of the bladder. Depending on the proximity of the duplicate ureters and the degree of dilation, more or less of the paste may be injected. If the ureteral opening is extremely dilated, such as the case in grade IV or V VUR, the Dx/HA may be injected directly into the ureteral orifice.

In all, 110 patients experienced unilateral duplex systems while 13 experienced bilateral duplex systems. Of the 136 refluxing ureters, each case was ultimately resolved after endoscopic injection, with 35 ureters requiring two injections and only eight needing three injections. These results are very exciting for the patient, as it shows a high success rate. The need for patients to require successive injections was discovered to be age-related, with the younger children requiring a second or third injection. Follow up was performed for all patients after three months with ultrasound and VCUG, and then every 2 years by means of renal ultrasound. Patients continued their prescribed antibiotic prophylaxis until their initial three month follow-up. No patients in this study required surgery or ureteral reimplantation, or experienced any major complications. This method of treatment was a minimally invasive outpatient procedure, which
took approximately 15 minutes each treatment and proved to be a viable option and success in the treatment of VUR.

This treatment minimized the need for redundant radiation exposure, recurrent administration of antibiotics, and invasive open surgery, which can all be disadvantageous to a pediatric patient. Urinary tract infection alone can be very frightening for a young child. If vesicoureteral reflux is not resolved quickly and effectively, not only can these patients experience frequent UTIs, but they are also at risk for pyelonephritis and ultimately kidney failure.

**Alternative Treatment**

One treatment plan for UTI and the management of VUR is prolonged, low-dose administration of antibiotics. Brandström and Hansson\(^1^1\) collected data from several studies regarding treatment for UTI caused by VUR. Their data focused on prophylaxis of a low-dose antibiotic. The data they collected showed mixed results, but few were truly randomized and controlled. The overall result showed that young children, particularly girls, with dilating VUR benefited from the prophylaxis treatment. However, Brandström and Hansson\(^1^1\) concluded that the underlying cause of the dilating VUR should be the primary concern and other treatment should focus on correcting this cause. However, in the meantime, prophylaxis can be used to minimize damage caused by recurring UTIs.

There is fairly new research regarding the use of probiotic prophylaxis in order to minimize the recurrence of UTI and the damage to the kidney through renal scarring. Lee and Lee\(^1^2\) performed a study comparing the effectiveness of antibiotic prophylaxis and probiotic prophylaxis. This study was a non-controlled study because there was not a “no prophylaxis” group. The authors of this study used a group of infants within one year of age at the first febrile UTI and diagnosis of primary VUR. Each individual in the study was diagnosed and graded via renal ultrasound, Technetium-dimercaptosuccinic acid scan, and VCUG. There were 128 infants chosen for this study and randomly separated into the two groups. The probiotic group was given *Lactobacillus acidophilus*, 1.0×108 CFU/g while the antibiotic group was given trimethoprim/sulfamethoxazole, 2/10 mg/kg. The probiotic group was instructed to take their dose twice daily and the antibiotic group was instructed to take their dose once daily, with both groups participating in the study for one year. Their findings suggest that the use of the probiotic
prophylaxis was as effective as the antibiotic prophylaxis, with the difference in bacteria the
generated UTI, the rate of VUR resolution, and the development of renal scarring being statistically
insignificant. However, one aspect of the study did find a statistically significant difference
between the two groups. The bacterial resistance was greater with the antibiotic group than the
probiotic group. This showed that the bacteria causing UTIs was becoming resistant to the
antibiotics more than the probiotic, and therefore long-term prophylaxis may become ineffective.
This study showed that there is a need to further research the use of probiotics, as they show
some encouraging results in the management of UTI and VUR.

Conclusion

Urinary tract infections can be both frightening and painful for a young child to
experience. It is very important to get a proper diagnosis when dealing with UTIs, especially in
infants due to the complications these infections, or the roots of these infections, can create later
in life. Vesicoureteral reflux may spontaneously resolve itself, or it may require further
management in the form of antibiotic treatment, monitoring, or invasive surgery. In order for
these infants to have the best renal health, it is critical that there is speedy diagnosis and
treatment of any UTI and then proper diagnosis and treatment of the underlying root to the UTI.

Patients with this condition are often times quite young and will require follow-up imaging
so minimizing their exposure to radiation is crucial. Considering that many patients who have
suspected cases of reflux are found to not have this condition, it is even more critical that the
initial imaging be done without ionizing radiation. With the findings from Fallah et al, ultrasound should be seriously considered for the diagnosis, grading, and follow-up of pediatric
patients with vesicoureteric reflux.

Once diagnosed, treatment should be planned with the patient’s best interests in mind.
Patients and their family should play a key role as the center of any treatment plan. Although the
use of antibiotics or probiotics can reduce the occurrence of renal scarring due to UTIs, it does
not correct the underlying cause which is VUR. Treatment by means of a minimally invasive
procedure, such as endoscopic injection of Dxt/HA have been proven to have a very high rate of
success. With these patients being so young, they have a long life ahead of them to deal with
any complications from VUR or subsequent treatments. The effects of ionizing radiation are
cumulative, so young patients have a much longer time to deal with any negative side effects
from the use of x-ray or nuclear medicine imaging. Lastly, it would be unfortunate if any patient experienced further kidney problems as a result of inappropriate diagnosis or treatment.
References


Figures and Captions

Vesicoureteric reflux


Figure 2. Unilateral grade 4 vesicoureteral reflux seen with VCUG. Image reprinted with permission from http://radiopaedia.org/cases/unilateral-vesicoureteric-reflux. Accessed November 8, 2014.
Figure 3. Radionuclide cystogram showing moderate VUR bilaterally. Image reprinted with permission from Reddy PP. Recent advances in pediatric uroradiology. Indian J Urol. 2007 Oct;23(4):390-402. doi: 10.4103/0970-1591.36713.