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Renal Infection and Vesico-Ureteric Reflux

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Urinary tract infection (UTI) is a common disease of childhood. The investigation of UTI in children has been the subject of debate and controversy for many years. Most workers agree that the first imaging modality to be used should be an ultrasound examination to exclude obstruction, structural abnormalities, and renal calculi. The role of ^{99m}Tc dimercaptosuccinic acid scintigraphy (DMSA) in the diagnosis of acute pyelonephritis is becoming increasingly important. Many argue that if the DMSA study is normal at the time of acute UTI, no further investigation is required because the kidneys have not been involved and thus there will be no late sequelae. Others use the acute DMSA study to determine the intensity of antibiotic therapy. The importance of the role of vesico-ureteric reflux (VUR) is being debated. Some workers will only proceed to cystography to detect VUR if the DMSA study is abnormal, whereas others advocate a more aggressive approach. VUR can be identified by a variety of radiological and scintigraphic techniques. Although the radiological cystogram is the gold standard and is essential in the first UTI in a male patient, to exclude the presence of posterior urethral valves, radionuclide cystograms are advantageous in other situations. Suprapubic cystography techniques have been described to overcome the trauma of urethral catheterization but have not been widely accepted.
Semin Nucl Med 37:261-268

Urinary tract infection (UTI) is a common problem. In children, 3.5% of girls and 1.2% of boys have had a symptomatic UTI.[1] In Sweden, the cumulative incidence of symptomatic UTI at 7 years of age was 7.8% for girls and 1.6% for boys.[2] The investigation of UTI in children has been the subject of debate and controversy for many years.[3-8] It is generally agreed that the primary goal of investigating children with UTI is to identify patients at risk (such as those with renal tract malformation, vesico-ureteric reflux [VUR], and established renal damage), to prevent further infections and to prevent progressive renal damage.[9]

Clinical features that may identify a child at risk include recurrent UTI, bacteraemia, a sick infant requiring hospitalization, an unusual infective organism, ie, non-*Escherichia coli* in origin, clinical signs such as a poor urinary stream or palpable kidneys, slow response to treatment, prenatal ultrasound diagnosis of a renal/urinary tract abnormality, and recurrent cystitis in a girl usually older than 3 years of age.[10]

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Ultrasound Examination

Although much debate exists in the literature as to whether all children with UTI require imaging or whether only patients assessed to be at risk require evaluation, most workers agree that the first imaging modality to be used should be an ultrasound examination.[5,11-13] Ultrasound is undertaken to exclude the presence of hydronephrosis, hydroureteronephrosis or obstruction, to exclude structural abnormalities such as small kidneys and ureterocoeles, and to exclude the presence of renal calculi. However, one recent publication has questioned the need for US in the evaluation of infants and children with UTI.[8] These workers reported a 12% rate of sonographic abnormalities in a population of children with UTI. They argue that fetal US should be sufficient to detect all children with urinary tract malformation in developed countries. They concluded that, in a child with UTI and normal antenatal scans, US is not required.

There are a number of fallacies to this conclusion. Many would argue that a 12% abnormality rate is sufficiently high to justify routine ultrasound examination in the assessment of children presenting with urinary tract infection. It has been demonstrated that prenatal US alone should not be used to evaluate children at risk of VUR, because of poor diagnostic yield.[14] Pelvi-ureteric junction obstruction can be diagnosed at any age of life, even in patients with normal antenatal US, and can become complicated with severe infection. Even in

0001-2998/07/$-see front matter
doi:10.1053/j.semnuclmed.2007.02.006

developed countries, reliance on antenatal US can be problematic because of faults in communication between antenatal and postnatal medical teams.[15]

US is an efficient method to diagnose infectious emergencies such as renal abscess and pyohydronephrosis, with or without renal calculi. US may identify acute pyelonephritis, although it is acknowledged to be less sensitive than renal cortical scintigraphy.[16] At the very least, US is a noninvasive, inexpensive technique that can be performed at the bedside without the use of ionizing radiation and has the potential to provide useful information.

Diagnosis of Acute Pyelonephritis With DMSA Scintigraphy

Several recent publications have concluded that the diagnosis of upper tract involvement with UTI is critical in the planning of further investigations and treatment.[17-19] Acute pyelonephritis is most reliably diagnosed with ^{99m}Tc dimercaptosuccinic acid (DMSA) renal cortical scintigraphy.[20] Hansson and coworkers suggested that DMSA scintigraphy performed within 3 months of the acute infection may replace micturating cystourethrography (MCU) as part of the primary workup of children with UTI.[17] In their primary study, there were 7 of 80 children with a normal DMSA scan that had grade III VUR but whose follow-up was uneventful without recurrent UTI and with spontaneous regression of VUR, with only one developing a scarred kidney. On the basis of these results, it was argued that, with the use of a normal DMSA scintigraphy, MCU is not necessary. Moorthy and coworkers concluded that because only 16% of their children with VUR had an abnormal kidney, the presence of VUR did not identify a susceptible population with an abnormal kidney on DMSA.[18] In the context of a normal US, MCU contributed little to the management of children younger than the age of 1 with a UTI, because there was no correlation between VUR demonstrated on MCU and renal scarring identified on DMSA performed 3 to 6 months after UTI. In this context, a normal DMSA study reinforced the redundancy of cystography. On the basis of their data, their recommendation for children with UTI younger than the age of 1 year, when the US was normal was that DMSA should be the next imaging investigation. Where US is normal, MCU is only indicated if the DMSA is abnormal. The aim to reduce the number of MCU in children would be welcome because it is an unpleasant procedure requiring urethral catheterization and has a risk of introducing infection and a radiation burden associated with it.

Renal Cortical Imaging Using DMSA

DMSA is the radiopharmaceutical of choice because it is an excellent renal cortical imaging agent. Approximately 40% of the administered dose accumulates in the distal tubular cells, providing excellent visualization of the renal cortex, after background activity has cleared. Dynamic tracers with high excretion rates such as ^{99m}Tc-mercaptoacetyltriglycine (MAG3) give less accurate information on renal cortical abnormalities and constitute only second-choice tracers. Guidelines have been published for the performance of this investigation.[21,22] The recommended minimum dose is 0.4 to 0.5 mCi (15-20 MBq), with a maximum adult dose of 2.7 to 3.0 mCi (100-110 MBq). The administered dose should be scaled on a body surface basis. Images should be acquired 2 to 3 h after tracer injection, but if significant hydronephrosis exists, late images (4-24 h) or frusemide injection may be helpful. Images should include at least a posterior view acquired for a minimum of 200,000 counts or 5 min using a high-resolution parallel-hole collimator and both posterior oblique views. Many experts advocate the addition of pinhole images using a 2 to 4 mm aperture insert. Pinhole views are acquired for 100,000 to 150,000 counts or for 10 minutes.

Some workers add single-photon emission computed tomography (SPECT), which may provide useful information but can increase the number of false-positive results and is more technically demanding during both acquisition and analysis. Motion artifact constitutes a problem in SPECT related to the long acquisition time. Pinhole imaging is more easily repeated than is a SPECT study. Several workers recommend the addition of either pinhole or SPECT imaging to the planar studies to increase the level of certainty with which renal cortical scintigraphy is interpreted.

A normal DMSA study exhibits homogeneous cortical uptake throughout the kidneys except for a lower concentration in the region of the collecting system (Fig. 1). The consensus report confirmed the variety that can be found in normal images, including flattening of the superolateral aspect of the upper pole of the left kidney caused by splenic impression and prominent cortical columns of Bertin, resulting in heterogeneous uptake.[21] Differential function calculation can be undertaken on the posterior planar view. Depth correction using geometric mean data from the anterior view may also be obtained, although the need for depth correction has been questioned.[21] Renal length measurements also can be obtained and normal ranges have been established (Fig. 2).[23]

DMSA studies are used either early to make the diagnosis of acute pyelonephritis or late to detect the presence of renal cortical scarring. If the DMSA study is undertaken to assess for the presence of chronic damage after UTI, the study should not be performed less than 3 months from the time of UTI. There is much debate in the literature as to the time period between UTI and scanning. The minimum period is 3 months, although some workers have advocated waiting 6 months or 12 months to ensure that all reversible findings caused by resolving infection have occurred.[21] The accuracy of the DMSA study in the diagnosis of acute pyelonephritis and chronic renal cortical scarring has been established in the piglet model. Rushton and Majd from Washington Children's Hospital confirmed that the changes present on the DMSA study at the time of acute pyelonephritis do correspond to acute infective foci histologically using the piglet model.[24] Their findings were soon confirmed by Parkhouse and coworkers, who also validated the sensitivity of the DMSA

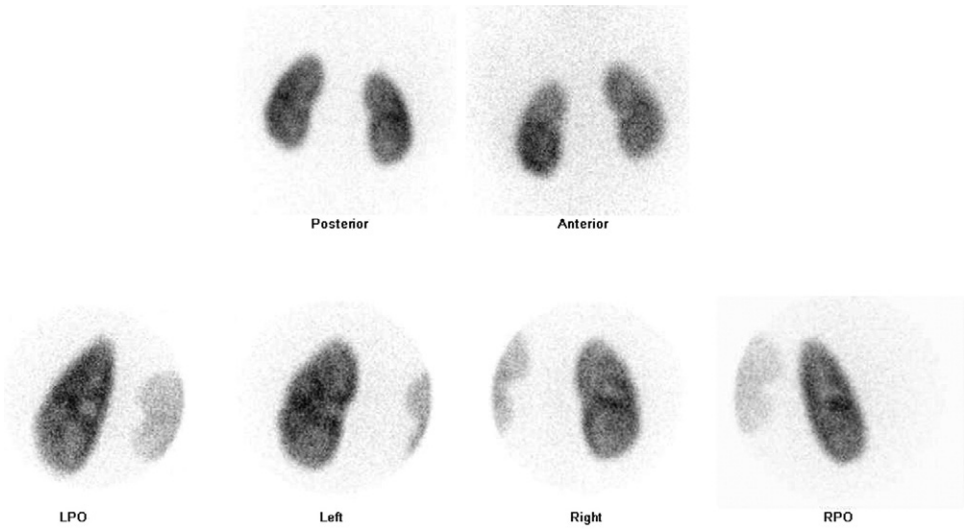

Figure 1 Normal DMSA study with anterior and posterior planar views in the upper row and posterior and posterior oblique pinhole views of both kidneys in the lower row. A normal DMSA study exhibits uniform uptake in the renal cortex with reduced uptake centrally in the medulla and collecting system.

study in the detection of acute pyelonephritis using the piglet model.[25]

There are 3 patterns of DMSA scan abnormality identified at the time of acute pyelonephritis, ie, unifocal or acute lobar nephronia (Fig. 3), multifocal, and diffuse. Scan features to suggest acute changes include focal decreased or absent cortical uptake without cortical or volume loss, in which the renal cortical contour remains intact.

Rosenberg and coworkers undertook a prospective study evaluating UTI in children by DMSA scintigraphy.[26] Clinicians were asked to assess whether children were likely to have upper tract involvement with infection on the basis of clinical findings or were considered to have lower tract infection. The children were classified into 2 groups. The septic group was systemically unwell and had persistent high fever of greater than 38.5°C. These children were considered to be likely to have acute pyelonephritis. The nonseptic group was those children with a lower fever who were only mildly ill. These children were thought to have lower tract infection only. A total of 15 of 20 children categorized as a septic presentation had an abnormal DMSA study; 5 had a normal scan ($P = 0.015$). However, of the 45 children with a nonseptic presentation, 19 had an abnormal DMSA study and 26 had a normal DMSA study, ie, no significant difference. It was concluded that when the child was assessed as having a septic presentation clinically, upper tract involvement with infection was likely. However, the converse was not true as a nonseptic presentation clinically could not reliably exclude upper tract involvement with infection.

In some centers, the acute DMSA study is undertaken to determine antibiotic therapy for UTI. An abnormal DMSA study will require the child to have more intensive antibiotic therapy. This approach has not been adequately validated in the literature, although there is some evidence to support it. Levtchenko assessed the efficiency of 7 days of intravenous anitbiotics compared with 3 days of intravenous antibiotics, both followed by an oral agent in children with acute pyelonephritis.[27] In children treated for 7 days with intravenous antibiotics, the percentage of patients with chronic renal cortical scarring on the delayed DMSA study was the same whether the children presented early or the diagnosis and treatment was delayed for more than 1 week. However, in the group treated for 3 days with intravenous antibiotics, there was a significantly greater incidence of sequelae, with renal cortical scarring on the delayed DMSA study in the group of children with a delay in diagnosis and treatment of more than 1 week.

In approximately 10% of children of any age with a clinical diagnosis of acute pyelonephritis, urine cultures are found to be either equivocal or negative.[28] In this group of children, the acute DMSA study can be undertaken to confirm the clinical diagnosis and result in an appropriate management plan. Without the DMSA study, the child would remain with the diagnosis of a fever of unknown origin. Some workers use DMSA studies to assess for chronic sequelae once acute infective changes have resolved in the kidney. The utility of DMSA scintigraphy in the detection of chronic renal cortical scarring has been validated.[29]

Using the pig model, the DMSA findings of chronic scarring were confirmed histologically. The features that suggest chronic scarring on a DMSA study are defects in uptake associated with cortical thinning and volume loss resulting in a localized deformity of the renal outline (Fig. 4).

Vesico-Ureteric Reflux

The importance of the role of VUR in children presenting with UTI is currently being debated vigorously.[30-34] The final report of the International Reflux Study in children showed no significant difference in the long term outcome of children during a 10-year period managed medically with antibiotic prophylaxis compared with children managed surgically

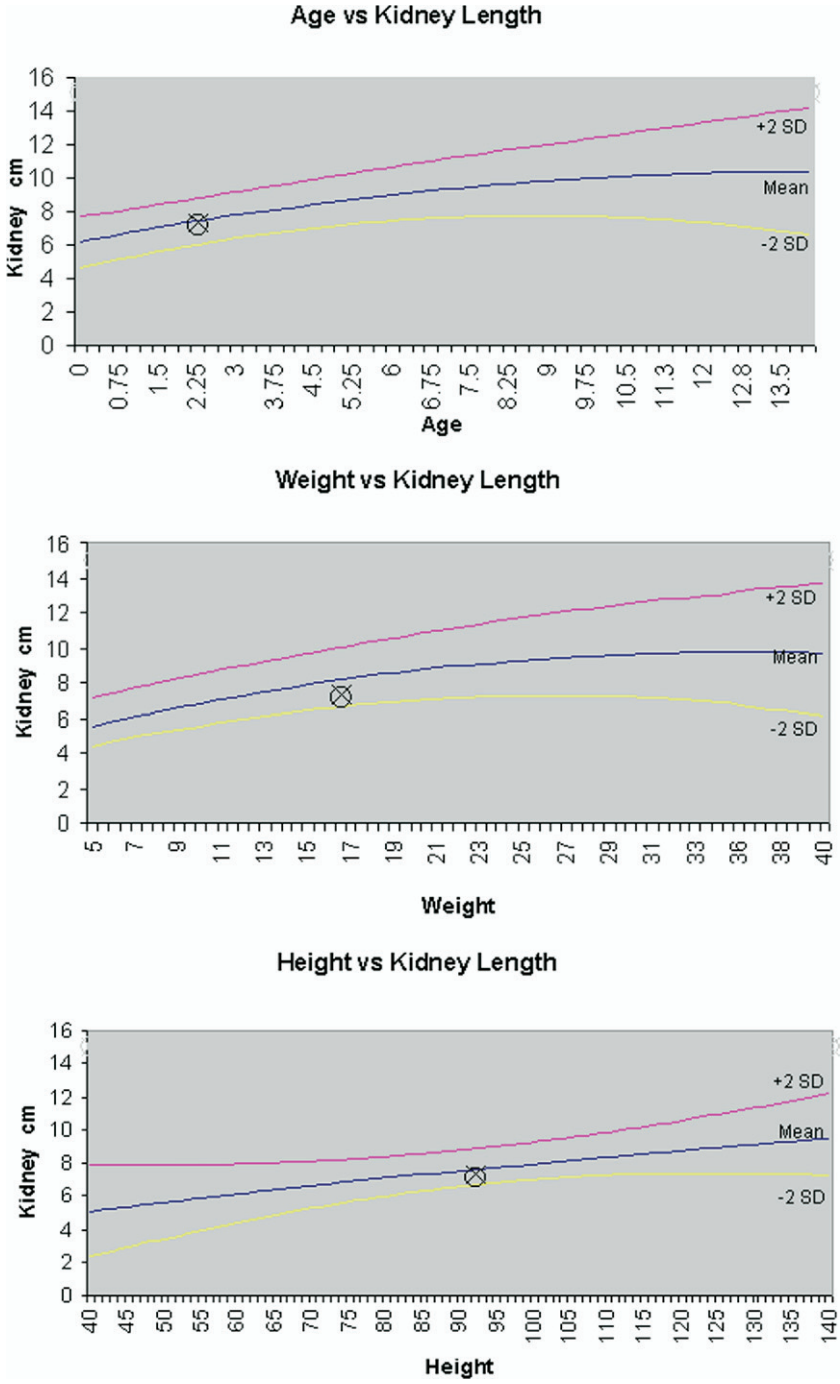

Figure 2 Nomograms of renal lengths for age, height, and weight have been established.

with ureteric reimplantation.[30] Criticism of this study includes the poor surgical results in 17% of patients, as compared with the usual surgical success rates of 94% to 99% reported in the literature.[31] Wheeler and coworkers undertook a meta-analysis of randomized controlled trials evaluating antibiotics and surgery for VUR.[32] They were unable to demonstrate any clinically important benefit in the identification and treatment of children with VUR, with no reduction in the number of children developing UTI or renal damage. Recently, a further multicenter, randomized, controlled study questioned the role of antibiotic prophylaxis as it was not able to demonstrate any prevention in the recurrence of infection and the development of renal scars.[33] Children with high-grade dilating reflux were not included in this study. Nevertheless, an editorial on this article concluded that, despite the data, there should be continuation of the recommendation to perform MCU to determine the presence of VUR and a search for strategies to keep the urine free of infection in children with high grades of VUR.[34]

It is well documented that approximately 30% of children with UTI have VUR and that VUR may predispose to upper tract involvement with infection. However, it has been con-

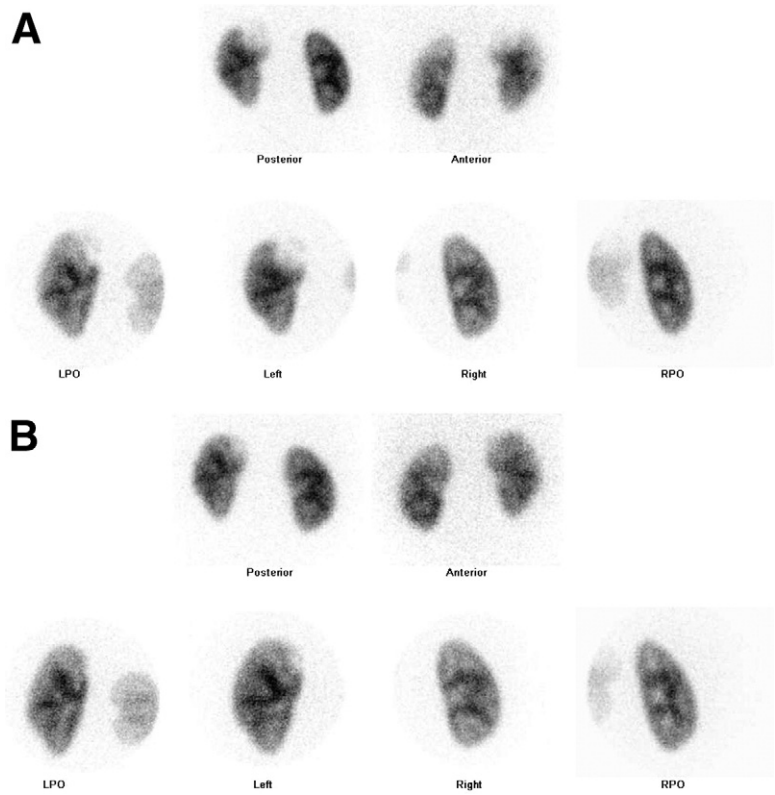

Figure 3 (A) Unifocal pyelonephritis or acute lobar nephronia involving the upper pole of the left kidney identified on a DMSA study performed to investigate an infant with a 7-day history of high fevers with no localizing signs. (B) Follow-up DMSA study performed 6 months after the treated UTI revealed a small residual scar at the apex of the upper pole of the left kidney.

firmed by a number of workers that acute pyelonephritis frequently occurs in the absence of demonstrable reflux.[26,35,36] Rosenberg found VUR in only 24% of children with DMSA scan evidence of acute pyelonephritis.[26] Majd found VUR in only 37% of patients with acute pyelonephritis.[35] Ditchfield found VUR in 39% of children with acute pyelonephritis demonstrated on acute renal cortical scintigraphy.[36] Conversely, 53% of children with VUR did not have upper-tract involvement with the acute UTI. The correlation between the incidence of renal cortical scarring and the grade of VUR has been debated. Farnsworth evaluated 113 infants younger than 1 year of age at risk of renal scarring.[37] He demonstrated that there was a markedly significant increase in the incidence of renal cortical scarring detected on the DMSA study in children with high-grade VUR when compared with lower grades. Conversely, there was also a statistically significant absence of renal cortical abnormalities on the DMSA study in children with low grade VUR when compared with the higher grades.

Stockland investigated 303 children younger than 2 years of age with UTI and found that there was a significantly increased risk of renal damage on the DMSA scan in children

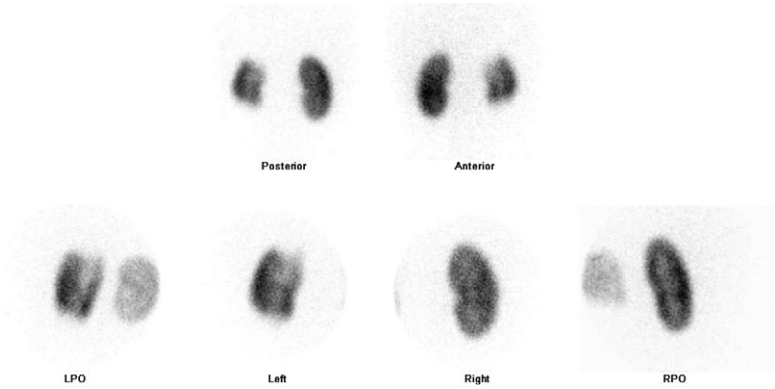

Figure 4 Chronic renal scarring identified on a DMSA study with loss of the normal renal outline in the upper and lower poles of the left kidney. The right kidney appears normal.

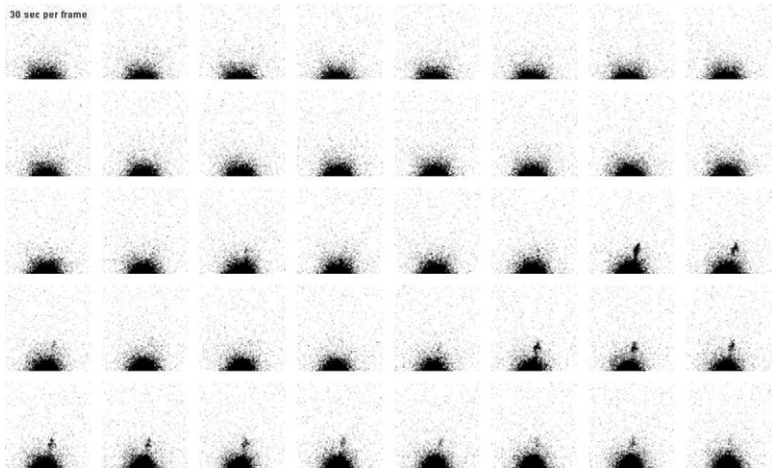

Figure 5 A direct radionuclide cystogram that revealed right-sided dilating VUR.

with dilating, ie, high-grade VUR.[38] However, in 2 systematic reviews and meta-analyses, it was difficult to convincingly show a relationship between VUR and renal damage in children with UTI.[32,39] What are possible explanations for these opposing findings? It appears clear that on an acute DMSA study performed at the time of UTI, there appears to be no relationship between the presence of VUR and acute pyelonephritis and that on a late scan performed at least 3 months from a UTI, the incidence of renal cortical scarring is related to the grade of VUR. In the reviews and meta-analysis of the literature, a clear distinction may not have been made between data obtained from acute studies and information obtained from late scans obtained distant from the UTI. Another possible source of error is that in a significant number of publications, DMSA findings are correlated with the presence of VUR, without taking into account the grade of VUR.

Micturating Cystourethrography

The radiological cystogram remains the gold standard examination for the detection of VUR. It gives excellent anatomical definition and the grade of reflux can be determined using the international classification for VUR.[40] It is essential in the first UTI in a male to assess the urethra and to exclude the presence of posterior urethral valves. However, the radiation dose from a radiological cystogram is in general higher than the radiation dose from a radionuclide cystogram. Radionuclide cystograms can be performed in 3 ways: direct, indirect, and suprapubic.

Direct Radionuclide Cystogram

Bladder catheterization is required as with a radiological cystogram. A small amount of radioactivity, eg, 20MBq ^{99m}Tc sulfur colloid, diethylene triamine pentaacetic acid, or pertechnetate, is instilled into the urinary bladder via a bladder catheter and normal saline gently heated to body temperature is infused into the bladder until voiding occurs. Ten-second dynamic images are obtained during filling and voiding and the sequence can be repeated while the bladder catheter remains in situ (Fig. 5). The advantage of the direct radionuclide cystogram over a contrast cystogram is not only the lower radiation dose associated but the ability for a longer observation time when compared with the radiological cystogram. It should be noted that VUR is an intermittent and variable phenomenon and that repeat filling of the bladder may demonstrate VUR, which is not evident on the first fill.[41]

Indirect Radionuclide Cystogram

The advantage of this technique is that a bladder catheter is not required, but the disadvantage of this technique is that the child must be toilet trained. The target group for the detection of VUR and the subsequent prevention of reflux nephropathy is children younger than 3 years of age.[42] The indirect radionuclide cystogram cannot be applied in this group because of their inability to void on demand. With this technique, VUR can only be detected in the older age group in which reflux nephropathy is most likely already established or excluded. This technique requires the intravenous administration of ^{99m}Tc MAG 3. Dynamic renal imaging can be obtained. When the child is ready to void, approximately 30 to 60 min after injection, the child sits with his or her back to the gamma camera and 5-s frame dynamic imaging is acquired commencing 30 s before voiding until micturation is complete.

Suprapubic Cystography

This has recently been described using both the radiological approach with the instillation of contrast or by the instillation of radionuclide. Oswald and coworkers described the use of the instillation of contrast into the bladder by a suprapubic puncture.[43] They reported that the mean pain score was lower in the suprapubic group compared with children examined using the transurethral route. In the group of children who underwent transurethral cystography, the pain score increased with age whereas in the group in whom a suprapubic puncture was used, the pain score decreased with age. Their conclusions were that, in children older than 24 months, the suprapubic approach was preferred. Wilkinson described the application of percutaneous direct radionu-

clide cystography in children.[44] He applied this technique to 103 toilet-trained children aged between 2.1 and 15.6 years of age. Most children preferred the percutaneous suprapubic injection when compared with an intravenous injection. He found the images easy to interpret and the detection of reflux more reliable as it avoided the doubt as to whether the activity in the renal areas was due to reflux or excretion when comparing this technique to the indirect radionuclide cystogram. Despite these 2 papers encouraging the use of this technique, this method of the detection of VUR has not been widely accepted.

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