

Nuclear Medicine in Paediatric Nephro-Urology

An overview

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Introduction

Nuclear Medicine has been a well-established component of the diagnostic work up of several paediatric nephro-urological clinical conditions for at least 40 years. Despite vast technological advances in radiology over the last half century, the functional information provided by radionuclide studies remains a cornerstone for the management of many paediatric diseases.

Nephro-urology constitutes the bulk of the workload of a paediatric nuclear medicine unit. This is due to the relative frequency of urinary tract infections and the variety of congenital renal anomalies, such as hydro-ureteronephrosis, nowadays detectable with antenatal ultrasound, and the increasing incidence of acquired conditions, such as renal calculi, which sometimes may require further evaluation with a functional study.

A major advantage for the use of Nuclear Medicine in paediatric nephro-urology is that these techniques do not require sophisticated pieces of equipment, a single head gamma camera being sufficient for almost the entirety of paediatric examinations. Sedation or general anaesthesia is almost unnecessary and, in the case of dynamic renography, it can actually be detrimental due to its effect on diuresis. Central to successful paediatric radionuclide studies are human and environmental factors, in particular a team of child friendly radiographers / technicians (specially trained in paediatric nuclear medicine practice), who know how to interact with the child and family, winning their trust and confidence and ensuring that the child is relaxed and co-operative on the gamma camera couch during the test. Special skills in venepuncture are also essential, as is an appropriately decorated nuclear medicine unit that helps relieve fear and anxiety in the child, often associated with hospital visits.

Radionuclide renal scintigraphy encompasses several nuclear medicine investigations: dimercaptosuccinic acid (Tc-99m-DMSA) renal scintigraphy, mercaptoacetyltriglycine (Tc-99m-MAG3) or diethylenetriaminepentaacetic acid (Tc-99m-DTPA) dynamic renal scintigraphy and radionuclide micturating cystography (direct and indirect radionuclide cystography). These techniques, together with ultrasonography (US), fluoroscopic micturating cystogram (MCUG) or magnetic resonance imaging (MRI), and occasionally computerised tomography (CT), of the renal tract, provide functional data for the diagnosis and management of children with suspected genito-urinary tract problems, contributing to a holistic morpho-functional assessment of the paediatric urinary tract.

The framework for each of the renal scintigraphy procedures has been published and revised by both the European and North American (NA) societies (EANM and SNMMI, respectively) in their corresponding guidelines (1-7). Comprehensive highly informative reviews on different aspects of paediatric nuclear medicine have also been published in the last 10 years (8-10).

Nuclear medicine examinations play a well-established role in the diagnostic algorithm of the different paediatric nephro-urological conditions. However, long-term studies on their prognostic value are desperately required. For example, we still don't know the risk of long-term complications (hypertension, chronic renal failure, complications in pregnancy) of one, two, three, or multiple and bilateral renal scars. We can determine the function and drainage of a hydronephrotic kidney with a PUJ anomaly and we currently know that less than 40% of these need surgery to prevent deterioration of renal function; however, we still need to find a reliable way to identify those kidneys at risk of losing function if left untreated. We can accurately perform an acute DMSA study during a febrile UTI to determine whether the renal parenchyma is involved, but we don't know whether it is possible to avoid a catheter cystogram in a child with a normal acute DMSA.

This article reviews the practice of dynamic and static renal scintigraphy and its clinical applications in the paediatric population. In addition, a section on the different clinical conditions has been added to present the scintigraphic techniques in clinical context, in comparison to the other available radiological examinations. This demonstrates how combining these imaging modalities can contribute to the patient's overall management.

Patient Preparation

Preparation for the procedure starts during the clinic appointment where the reason for requesting the investigation and the examination itself are explained to the parents/child. Once a request form has been generated a nuclear medicine practitioner assesses the clinical data supplied by the referrer and justifies the medical exposure to radiation (in the UK under the Ionising Radiation (Medical Exposure) Regulations, - IR(ME)R - Employer's Procedures). As part of the justification process, the clinical history (including information related to the structural renal abnormalities that may result in the need for additional views), ultrasound data and previous radionuclide imaging should be reviewed. The importance of the justification process cannot be emphasized enough, as young children are much more sensitive to radiation than adults and all alternative diagnostic tests yielding equivalent information with less or no radiation burden should have been considered.

The parent/child should receive an appointment letter well in advance of the day of the examination containing detailed information on the procedure, including the waiting time between tracer injection and image acquisition, the probable duration of the scan and the need for adequate oral hydration of the child before getting to the department. Hydration should take into account that an increased oral intake of fluids might be needed in hot weather and this should also be briefly explained to the family in the clinic (11, 12).

A co-operative child should be encouraged to empty his/her bladder before the injection to reduce the need to void during the acquisition; this is essential for diuretic studies since a full bladder may delay upper tract emptying (11-13). If the test involves administration of furosemide or bladder catheterization these additional interventions should be fully explained as part of the informed consent process.

On the day of the test, as well as throughout and after completion of the examination, the parent(s) and child should feel that their emotional and physical needs have been considered in a friendly departmental environment and with the teamwork of trained staff, including booking staff, receptionists, nurses and technicians / radiographers. The injection room and the gamma camera room should be uncluttered, welcoming, and give the impression of a safe environment for both child and parent. This can be achieved by mural and gamma camera decorations, the availability of toys for different age groups, small rewards (stickers) for cooperative behaviour, books, warm lighting, music and video projection capabilities that can be successfully used to distract the child and ensure his/her cooperation (11). Departmental staff should have a positive and friendly attitude towards the child and parent, making them feel actively involved, reassured and part of the team. The child should remain the central focus throughout the entire procedure, but the parent should be made aware that he/she offers the best form of comfort and security for the child and his/her cooperation can greatly contribute to the success of the examination (11).

Anaesthetic cream can be applied to relieve the discomfort of the tracer injection, and the 60-minute wait for the cream to have its effect can be used to ensure good hydration. When necessary, an ultrasound can be performed during this interval time. Tracer injection can be performed either through a cannula (which also allows the administration of furosemide during dynamic renal scintigraphy) or a fine butterfly needle (gauge 23-25 according to child's age). Regardless of the chosen access method, great care should be taken when injecting the tracer to avoid extravasation. Administration of radioactivity beyond what is essential should be avoided and the amount of radiopharmaceutical to be injected should be optimized to give the desired diagnostic information at the cost of minimal radiation burden. Recommendations on administered activities for a number of paediatric nuclear medicine examinations have recently undergone harmonization by the European and NA societies. Calculation of the injected activity is now straightforward either through the EANM and/or SNMMI website or the EANM Dosage Card Calculator (14, 15).

Drug sedation is very rarely used, as adequate preparation, analgesia, environmental distractions and team communication with the parent(s) and child help reduce anxiety and assist in obtaining adequate immobilization of the child during the procedure (13, 16). Sandbags, Velcro straps on either side of the child or a vacuum cushion can also be used as external aids for comfortable, yet effective, immobilization. Many of the pitfalls and limitations encountered in paediatric radionuclide studies can be avoided by gaining the patient's and

family's cooperation, limiting the child's movements (by employing distraction techniques and immobilisation devices) and using an optimal technical setup for image acquisition (17).

These factors, combined with the full integration of the radionuclide study with complementary radiological investigations, will result in a complete morpho-functional assessment of the paediatric renal tract, thus aiding clinical management.

Static Cortical Renal Scintigraphy

The European procedure guidelines for Tc-99m-DMSA renal scintigraphy were initially published in 2001 and updated in 2011, while similar NA guidelines were initially published in 1997 and updated in 2003 (currently version 3.0) (5, 7). Tc-99m-DMSA scintigraphy is currently the investigation of choice in the assessment of renal parenchymal integrity, and provides the most reliable information on differential renal function. Tc-99m-DMSA is used for the detection of focal renal parenchymal abnormalities, acute pyelonephritis, post-infective renal sequelae, renal congenital anomalies (duplex kidney, hypoplastic or dysplastic kidney, horseshoe kidney and crossed-fused renal ectopia), and for confirmation of a non-functional kidney, such as the multicystic dysplastic kidney (5, 18, 19).

Tc-99m-DMSA is bound to plasma proteins, cleared from the blood stream by tubular absorption and retained by the renal cortex. Renal uptake is dependent on renal blood flow, glomerular filtration and megalin/cubilin-mediated endocytosis in the proximal tubule from the glomerular filtrate (20, 21). The NA and European dose harmonization process recommends a minimum administered activity of 18 MBq (0.49 mCi), gradually increasing it in older children according to body weight (EANM Dosage Card Calculator) (14, 15).

Optimum quality images are acquired at 2-3 hours after tracer injection, when the renal cortex has taken up 40%–65% of the injected radiopharmaceutical. Late images (between 4 to 24 hours) may be useful for quantitation of split renal function when some tracer still remains within a dysplastic renal collecting system, thus interfering with the evaluation of the split renal function. Images should be acquired with the child in a supine position, as close to the collimator surface as possible (ideally on a customized perspex table), to improve image quality. Posterior and posterior oblique views (additional anterior views for horseshoe or ectopic pelvic kidneys) should be acquired using a low energy, high-resolution or ultra-high-resolution (+/- pinhole) collimators. Pinhole collimators can improve image resolution and contribute to better detection of renal scarring; however they can distort anatomy and lengthen acquisition time, with the potential of image degradation by motion artefacts.

In an older and co-operative child, the European and NA guidelines recommend acquiring at least 300,000 - 500,000 counts (or a 600-second image) for the posterior view, and at least 350,000 counts (or a 600-second image) for the posterior oblique views. For younger and less co-operative children the count number can be reduced, with at least 250,000 counts (or a 600-second image) acquired for the posterior view and 200,000 counts (or a 600-second image) for the posterior oblique views. The acquisition matrix should be 128 × 128 or 256 × 256. If pinhole views are required, the guidelines advocate 100,000 - 150,000 counts for better detection of small cortical defects. In the majority of cases high-quality static planar images are sufficient for an accurate diagnostic assessment, but a SPECT acquisition, with the possible addition of a low dose CT (where such a scanner is available), can be useful in

complex cases, such as crossed-fused renal ectopia and complex renal stones (22, 23). Recent studies have suggested Tc-99m-DMSA scintigraphy for predicting dilating vesico-ureteral reflux (VUR) in young children with febrile urinary tract infection but so far only limited (and sometimes conflicting) data is available in the literature (24-29).

Data processing and reporting steps are generally straightforward, but can sometimes be challenging in duplex or horseshoe kidneys. Regions of interest (ROIs) are drawn around each kidney, with a further ROI defined for background subtraction. In children with normal kidney size and position, a reliable background-corrected differential renal function is calculated using the arithmetic mean from the posterior view, while in children with ectopic or very large kidneys the differential function has to be calculated with the geometric mean. Horseshoe kidneys are better defined when imaged anteriorly to detect the connecting bridge or isthmus of renal tissue anterior to the spine; however, a posterior view should also be acquired.

Image interpretation should consider several pitfalls, such as normal variants (pear-shaped kidney, foetal lobulation, kidney axis rotation), ectopic kidneys, crossed-fused ectopia, the influence of motion, high background activity, activity in the renal collecting system and tracer contamination (17). The DMSA images should ideally be assessed with the benefit of renal ultrasound images, if available.

Dynamic Renal Scintigraphy

Over its more than 40 year history, dynamic radionuclide renography has become an indispensable technique in the functional assessment of both adult and paediatric nephro-urological patients. Although initially suffering from significant local variability, the technique has been standardised and it has become increasingly popular in the clinical assessment of patients with hydronephrosis. The technique and interpretation have been summarized in recent guidelines and reviews (1, 30, 31). The most recent (2011) guideline gives recommendations for estimating two indicators of renal function: the relative renal clearance (differential renal function, DRF) and the renal excretion of the tracer (1). It recommends that DRF estimation should be undertaken between 1 and 2 min after tracer injection (with appropriate corrections for background and intra- and extra-renal vascular components), while renal excretion can simply be evaluated by inspecting the dynamic renal images and with tracer transit quantification techniques (32-34).

Dynamic radionuclide renography is performed using tubular extraction tracers (I-123-hippuran), Tc-99m- MAG3 and Tc-99m-ethylenedicycysteine (Tc-99m-EC), or Tc-99m-DTPA, the only glomerular filtration-dependent radiopharmaceutical. As tubular tracers have greater renal extraction than Tc-99m-DTPA (resulting in improved kidney-to-background ratio), they are preferred for DRF estimation and indirect cystography in children. Tc-99m-DTPA is preferred when glomerular filtration rate (GFR) estimation (with blood sample analysis) is required (1).

The most commonly used radiopharmaceutical is Tc-99m-MAG3, a highly protein-bound agent that is removed from the plasma by uptake in the proximal renal tubules (35-37). Its renal extraction fraction is 40%-50%, more than twice that of Tc-99m-DTPA, making it an

excellent clearance agent for patients with suspected obstruction and impaired renal function (21, 37). The clinical indications for the procedure include all uropathies that require evaluation of drainage (pelvi-ureteric and vesico-ureteric stenosis, bladder outlet obstruction, bladder dysfunction, complicated duplex kidneys, renal functional assessment post-trauma, asymmetrical renal function, chronic pyelonephritis – with an indirect cystogram performed at the end of the renogram - and renal transplantation) (1, 2). The recommended administered activities have not been fully harmonized – while the EANM Dosage Card Calculator recommends 15 MBq (0.41 mCi) minimum injected Tc-99m-MAG3, the NA guidelines suggest a minimum of 19 MBq (0.5 mCi) or, in some practices, 37 MBq (1 mCi) (2, 14). The effective dose to a 5-year-old child is < 1 mSv (0.54–0.82 mSv for Tc-99m-DTPA, 0.20 - 0.38 mSv for Tc-99m-MAG3 and 0.41 - 0.7 mSv for I-123-hippuran) and reduction of injected activity is advocated if renal function is impaired (38-40).

Good hydration is essentially for a good quality dynamic study. Some guidelines recommend intravenous hydration (2), whilst in other parts of the world oral hydration, starting a few hours prior to the renogram, is considered sufficient (1).

Image acquisition is performed with a constant 10 or 20 second frame rate (10 second frames for quantification), up-facing low energy general purpose collimator, 128 × 128 and word (or byte) mode, with zoom adjusted to patient size and including the heart for processing purposes. Post-micturition views (at the end of the study and 50-60 minutes post-tracer injection) are essential and they will help distinguish between a dilated non-obstructed and an obstructed renal tract. Although widely used in NA centres, bladder catheterization is not advocated by the European guidelines (2). The minimum recommended duration of the study is 20 minutes.

Evaluation of split renal function

The evaluation of split renal function has been standardised (32). In the processing step, the regions of interest (ROIs) should be generous, drawn on a summed image and encompassing the entire kidney to avoid excluding some renal activity (41-43). Background correction using rectangular, elliptical or peri-renal ROIs should be performed on all images / renogram curves, and the cardiac ROI, needed for quantification, should cover the hottest pixels over the heart on the very first two or three frames (1). A 2 – 3 minute summed image of all the frames during the clearance or uptake phase should be created and the DRF assessed visually on the images and uptake curves, as well as calculated using either the integral method or the Patlak-Rutland plot method (32, 41, 44-48).

The integral method calculates the mean value of the area under the background-subtracted renogram curves during a 1-2 minute period. This method has been shown reproducible and accurate in normal volunteers, with a difference of more than 5% representing a significant change (41).

The Rutland-Patlak plot is a graphic representation of the split renal function; the slope of the fit curve represents the relative function of each kidney. In theory, this method is more accurate than the integral method because of the added correction of the intrarenal vascular component. However, it is also more prone to statistical errors in conditions with increased background activity, such as infants with immature renal function and patients with chronic kidney disease.

The evaluation of the split renal function using two independent methods constitutes a good quality control; both methods should give the same result (within 5% difference).

Evaluation of drainage

The furosemide test was introduced in the late 1970s to help in differentiating between urinary outflow obstruction and urinary stasis due to a baggy collecting system (49). Furosemide is injected at 20 minutes if the dynamic images show slow drainage: a dilated non-obstructed renal pelvis usually shows response with significant drainage, whilst an obstructed renal pelvis shows poor response to the diuretic. More recently, the “F0” technique has been introduced, with the diuretic injected together with the radiotracer: this shortens the time of acquisition and results in better drainage at the end of the renogram. Administration of furosemide 15 minutes prior to tracer injection is another possible technique, which allows starting the renogram under the full effect of furosemide (50-54). Recommended furosemide doses are 1mg/kg i.v. in infants and 0.5 mg/kg in children above the age of 1 year (20 mg maximum dose). One of the pitfalls related to drainage is the presence of a full bladder at the end of the renogram. Therefore, the insertion of a bladder catheter during the test has been recommended, especially in North America (55). The European guidelines recommend instead the acquisition of a post-micturition view, after the child has been in upright position for at least 15 minutes and has emptied the bladder, acquired in the same way as the dynamic renography, so that it can be compared with it (1).

The evaluation of drainage has been standardised, with several functional parameters being proposed. The Output Efficiency (OE) represents the amount of activity that has left the kidney, expressed in a percentage of what has entered the kidney (56). The Normalised Residual Activity (NORA) is a parameter inversely correlated with OE and describes the amount of activity remaining in the kidney at the end of the renogram (57). These parameters are independent on the level of differential function and can be calculated at the end of the renogram as well as on the delayed post-micturition views.

For a long time, drainage has been estimated on the basis of the slope of the furosemide curve, a long T-half reflecting obstruction and a short T-half indicating good urinary outflow. This method is accurate only when drainage is good, but fails to differentiate poor drainage due to obstruction from poor drainage due to a dilated non-obstructed collecting system.

Lack of protocol standardization (especially for post-micturition images), tracer extravasation, motion, high background activity, bladder status, poor renal function, degree of renal pelvic dilatation, can all pose interpretation challenges (17).

Renal Immaturity

When evaluating newborns and infants, nuclear medicine practitioners should recognize normal renal immaturity and its effect on the renal handling of radiotracers (58). The glomerular filtration rate (GFR) per unit of surface area in the newborn is approximately 30% of the adult rate. Depending on renal maturation, renal uptake of tracers may be lower in newborns than in older children and adults. In addition, intrarenal transit time and excretion of these tracers may be slow at this age. Background may be high throughout the study, reflecting slow plasma clearance of the tracer.

Radionuclide Micturating Cystography

Direct radionuclide cystography (DRC) is a catheter cystogram that entails administration of a small amount of Tc-99m-pertechnetate together with saline into the bladder. It is indicated in non-toilet trained boys (usually less than 3 years of age), when a reassessment to look for persistent VUR after endoscopic or surgical treatment is required, once a baseline radiological MCUG has excluded posterior urethral valves. In girls, less than 3 years of age, it is utilised when the DMSA scan is abnormal and an US shows a dilated ureter and/or pelvis. It can also be used in the diagnosis of familial reflux, or in the serial evaluation of bladder dysfunction (neuropathic bladder) for VUR (3, 4, 6).

As VUR is an intermittent phenomenon and it may only occur in the filling phase of the bladder, the advantage of DRC is that both the filling and micturition phases can be studied, increasing the chances of detecting VUR (59-61). DRC may be undertaken in any child, but it has a limited role in low lying or ectopic kidneys with ureteric dilatation. The main disadvantage is that it requires bladder catheterisation (with all its associated risks / discomforts): this should be performed by an experienced operator under strict aseptic conditions and antibiotic prophylaxis (3).

Imaging acquisition requires the administration of 20 – 40 MBq of Tc-99m-pertechnetate in 500 ml saline through the catheter over 10 minutes until full bladder capacity is reached and then the child is allowed to void. Dynamic posterior view frames are acquired at maximum 5 seconds per frame using a general-purpose collimator and 64 x 64 or 128 x 128 matrix. The radiation burden from the procedure is favourable compared to MCUG, although a recent publication has reported a lower radiation exposure from the fluoroscopic procedure when using state-of-the-art equipment and frame grab techniques (62).

Indirect isotope cystography (IRC) is a completely physiological test in toilet trained children used for the detection and follow-up of VUR and the assessment of the effect of a full and empty bladder on the drainage from dilated upper tracts (4). The advantage of this technique is that it allows a complete functional assessment of the urinary tract (including renal parenchymal integrity, split renal function, drainage, timing and completeness of bladder emptying), it has a low radiation burden and it does not require bladder catheterization, which can be physically and emotionally traumatic for the patient.

The patient sits on a commode with the gamma camera centred posteriorly over the region of the bladder and kidneys. The patient voids into a urinal, a bedpan, or a jug. Precautions to reduce contamination of the equipment and the room must be taken. Recording is begun when the patient is ready to void and continues until the end of voiding. If the child has failed to void on the first attempt, or has voided incompletely, another cystogram can be acquired later on, until the bladder is empty, or VUR has been demonstrated. Repeated acquisitions increase the sensitivity for VUR.

The most common pitfalls in radionuclide micturating cystography are too early micturition, before the radiographer has commenced images acquisition (often because the child is not really toilet trained), and a dilated renal collecting system with persisting urinary stasis from the immediately previous dynamic renography (17). These can be mitigated by performing

IRC in children who are continent and by furosemide administration before the start of the first IRC to clear the upper tracts (17). Knowledge of the expected functional bladder capacity is useful for evaluation of VUR in children.

In the absence of bladder pathology such as bladder exstrophy-epispadias complex, the expected bladder capacity for age can be estimated by the formula $30 + (30 \times \text{age in years})$ for children above 2 years of age (63) and $38 + (2.5 \times \text{age in months})$ for children less than 2 years (64).

CLINICAL APPLICATIONS OF NUCLEAR MEDICINE IN PAEDIATRIC NEPHRO-UROLOGY

URINARY TRACT INFECTIONS AND VESICO-URETERIC REFLUX

Background

Approximately 2% of males and 8% of females will develop a urinary tract infection (UTI) at some point. Most UTIs in males occur at <3 months of age with prevalence 10 times less in circumcised males versus uncircumcised males in this age group. After one year of age, most UTIs occur in females.

Symptomatic UTI must be differentiated into upper tract infections, with lesions of the kidneys (acute pyelonephritis and pyelitis), and lower tract infections (acute cystitis). Upper UTI usually presents with high fever, flank pain or tenderness, malaise, irritability, leukocytosis, and bacteriuria, but there may be no clear indication that there is renal parenchymal infection. Lower UTI presents with voiding symptoms. However, it is often impossible to differentiate them or even to diagnose UTI, particularly in babies (65).

Primary goal in the diagnosis of UTI and in the subsequent evaluation of the predisposing factors is to reduce the incidence of recurrent UTI and prevent acquired renal damage.

Imaging in UTI

The purpose of imaging is to detect pathological malformations and/or risk factors that, if not diagnosed and managed appropriately, might lead to additional infections and on-going parenchymal damage. Ultrasound, MCUG and Tc-99m-DMSA scan are the core imaging examinations utilised. However, the use of these imaging techniques is variable with different approaches.

Ultrasound

Renal ultrasound can define kidney shape, length, echogenicity, and the presence of dilatations. Ultrasonography can also describe the bladder volume, bladder wall thickness and renal and bladder calculi, ureteric abnormalities and adjacent pathology (such as collections). The disadvantages are the poor detection rate of parenchymal defects and

VUR. In one series of children with their first febrile UTI (66), 88% of patients had normal US findings (11.5% had dilated urinary tract and 0.3% renal calculi).

Renal cortical scintigraphy

“Acute” DMSA: A DMSA scan performed during the acute phase of a UTI can confirm the presence of acute pyelonephritis. The diminished uptake of Tc-99m-DMSA in areas of acute inflammation probably reflects both focal tubular cell dysfunction and ischaemia (67). DMSA scanning does not differentiate old from new lesions unless a previous examination exists. Acute DMSA imaging will confirm the diagnosis of acute pyelonephritis in patients with equivocal symptoms. The advantage of this approach is that in patients with normal acute DMSA there is no probability of developing renal scarring. The sensitivity of Tc-99m-DMSA scintigraphy for the early diagnosis and localization of acute pyelonephritis reaches over 90% (68).

“Late” DMSA: If treated appropriately within 48 hours, acute pyelonephritis may resolve completely and scintigraphic images typically would become normal within 4–6 months. Alternatively, without adequate and early antibiotic treatment, a permanent cortical scar may develop. A mature cortical scar is usually associated with contraction and apparent loss of volume of the involved cortex. This may manifest as cortical thinning on ultrasound, flattening of the renal contour, or a wedge-shaped defect. The scintigraphic pattern of a maturing scar on DMSA varies according to the severity of the UTI, the location of the lesion, the age of the patient, as well as the rate of growth of the surrounding normal renal tissue. The guidelines issued by the National Institute for Health and Clinical Excellence (NICE) recommend a DMSA scan in children with recurrent or atypical UTIs, 4–6 months after the infection (69). Some investigators recommend renal scintigraphy 6–12 months after the first febrile UTI to detect the formation of scarring, which would require follow up (70, 71).

The prognostic value of renal scars needs to be further evaluated. A study from Sweden showed that a cohort of children with renal scarring followed up for 1—26 years had no increased likelihood of developing hypertension in comparison to the general population (72). However, a recent study showed increased blood pressure in a cohort of patients with normal renal function and UTI associated renal damage (73). Other studies have reported a significantly increased risk of hypertension and chronic kidney disease in children with bilateral scarring (73–75).

Although ultrasound is the favoured imaging method in children, MRI, and occasionally CT, may have a role when intrarenal abscesses are suspected or when there is a delayed response to antibiotic treatment (76, 77).

Vesico-Ureteric Reflux

Vesico-ureteric reflux (VUR) refers to the retrograde flow of urine from the bladder into the ureter and, usually, into the collecting system of the kidney. In most individuals, VUR results from a congenital anomaly of the vesico-ureteric junction, whereas in others it results from high-pressure voiding secondary to posterior urethral valves, neuropathic bladder or voiding dysfunction. Its management is one of the most controversial topics in paediatric urology.

The clinical importance of VUR consists in its association with pyelonephritis and its contribution to reflux-related renal scarring. Vesico-ureteric reflux is a not an uncommon urological anomaly in children, with an incidence of nearly 1%. However, the incidence of VUR is much higher among children with UTIs (30-50%, depending on age). Among all children with UTIs, boys are more likely to have VUR than girls (29% vs. 14%); boys also tend to have higher grades of VUR diagnosed at younger ages, although their VUR is more likely to resolve (78).

Grading of reflux is based on the work of the International Reflux Study Group and includes VUR from grade I–V (Fig.1). Not all types of VUR carry the same risk of contributing to renal scarring. For example, dilating VUR will increase the risk of developing acute pyelonephritis and renal scarring. A significant percentage (10 – 40%) of children with symptomatic VUR have evidence of renal scarring, resulting from either congenital dysplasia and/or acquired post-infectious damage, which may have a negative impact on growth and general wellbeing (79).

High grade VUR is associated with a higher risk of renal scarring and recurrent UTIs (80). Lower grade VUR is associated with a lower risk of renal scarring and may vary from examination to examination. VUR varies also with bladder volume, voiding or filling, patient position, and level of anxiety. Renal scarring occurs in approximately 10% of children with prenatal hydronephrosis and VUR (81, 82), whereas in patients with lower urinary tract dysfunction scar rate may increase up to 30% (83). Renal scarring may adversely affect renal growth and function, with bilateral scarring increasing the risk of chronic kidney disease. Follow-up studies have shown that 10-20% of children with chronic pyelonephritis and VUR develop hypertension or end-stage renal disease (84).

The spontaneous resolution of VUR is dependent on age at presentation, sex, grade, laterality, mode of clinical presentation and renal tract anatomy (85). In several Scandinavian studies, the complete resolution rate for high-grade VUR has been reported in excess of 25%, which is higher than the resolution rate for VUR detected after infancy (86).

High grade VUR, age at diagnosis and male gender have been shown to be risk factors for renal parenchymal damage. In this group of patients it is mandatory to discover reflux early to prevent renal damage (87).

Management of a Patient with VUR

Controversy persists over the optimal management of VUR, particularly the choice of treatment (observational, medical, endoscopic or open/laparoscopic surgical), and the timing of treatment. The main goal in management is the preservation of kidney function, by minimising the risk of pyelonephritis. By defining and analysing the risk factors for each patient (i.e. age, sex, reflux grade, lower urinary tract dysfunction, anatomical abnormalities, and kidney status), it is possible to identify those patients with a potential risk of UTIs and renal scarring.

There are two main approaches to the management of VUR: conservative and surgical. In all patients with secondary VUR, management of the underlying anomaly should be considered before treating the VUR (88, 89).

Conservative approach

The conservative approach includes watchful waiting, intermittent or continuous antibiotic prophylaxis, and bladder rehabilitation in those with lower urinary tract dysfunction. The objective of conservative therapy is prevention of febrile UTI and it is based on the understanding that VUR resolves spontaneously, mostly in young patients with low-grade reflux. Resolution is nearly 80% in VUR grades I and II and 30-50% in VUR grades III-V within 4-5 years of follow-up (85). Furthermore, VUR does not damage the kidney when patients are free of infection and have normal lower urinary tract function. There is no evidence that small scars can cause hypertension, renal insufficiency or problems during pregnancy (72). Circumcision during early infancy may be considered as part of the conservative approach, as it is effective in reducing the risk of infection in normal children (90).

Regular follow-up with ultrasound imaging is part of the conservative management. In all cases of febrile breakthrough infections despite prophylaxis, intervention should be considered.

Recent prospective randomised controlled trials have shown that the role of prophylaxis in children with no VUR or with grade I or II VUR is questionable, as the rate of recurrent symptomatic UTIs was similar in the group with prophylaxis and in the group with no therapy (80, 91-93). For children with VUR grade III to V, who have a much higher rate of recurrent UTI (80, 94-96) prophylaxis would be appropriate, particularly in girls. There is no data on the optimal duration of prophylaxis.

Surgical correction of VUR

Endoscopic treatment: VUR can be corrected by endoscopic injection of a bulking agent at the VUJ or by surgical re-implantation.

The sub-ureteric injection of bulking materials is currently the first therapeutic option in children with VUR and recurrent infections. The injected agent elevates the ureteral orifice and the distal ureter, so that coaptation is increased. This results in narrowing of the lumen, which prevents reflux of urine into the ureter, while still allowing its antegrade flow. With the availability of biodegradable substances, endoscopic sub-ureteric injection has become an alternative to long-term antibiotic prophylaxis and surgical intervention.

The reported resolution rate is 83% for endoscopic therapy after a single injection (American Urological Association guidelines (97)). Imaging with a MAG3 dynamic renogram and an indirect cystogram is helpful at follow up, usually 6-9 months after the procedure, to demonstrate the resolution of VUR and to show possible complications (most commonly obstruction at the VUJ).

Ureteric re-implantation: Surgical treatment of VUR in the form of open or laparoscopic/robot assisted ureteric re-implantation is considered whenever endoscopic treatment has been unsuccessful or is inappropriate. It is an alternative in children older than 1 year of age, or in patients with persistent VUR after 2–3 years of follow-up, in patients in whom decreasing renal function is observed, or in patients presenting with recurrent UTI despite adequate antibiotic therapy.

Imaging VUR

Imaging is the basis of diagnosis and management of VUR. The aim in detecting VUR and initiating a prophylactic treatment is to prevent long-term complications (98-101).

Micturating Cystogram (MCUG) is the most widely used radiological examination for the study of the lower urinary tract and especially of VUR. It is the only method that allows precise grading of VUR and the detection of intrarenal reflux (102-106). MCUG should always be performed in infant boys, to exclude posterior urethral valves, but less so in girls. The main disadvantages of the technique are the risk of infection, the need for retrograde filling of the bladder and the possible deleterious effect of radiation on children. In recent years, tailored low-dose fluoroscopic MCUG has been used for the evaluation of VUR in girls in order to minimize radiological exposure.

Direct Radionuclide Cystogram (DRC) is a sensitive technique to diagnose VUR. The advantages of DRC are the extremely low radiation dose and the ability to continually screen for VUR during both the bladder filling and emptying. This unique ability of the DRC is the reason for its high sensitivity in picking up reflux, with higher sensitivity and higher temporal resolution than MCUG (107). The disadvantages include the insertion of a bladder catheter and poor anatomical detail. As mentioned previously, this technique is used in the follow up of non-toilet trained boys who have already had a MCUG to exclude posterior urethral valves, and in non-toilet trained girls when detailed anatomy of the bladder and ureters is not required.

The **Indirect Radionuclide Cystogram (IRC)** represents an attractive alternative to conventional cystography, as previously noted, especially when following patients with reflux, because of its lower dose of radiation and lack of catheterisation. Disadvantages are poor image resolution and difficulty in detecting lower urinary tract abnormalities (108).

Imaging strategies in children with UTI and VUR

The use of diagnostic imaging tests in a child with UTI is still a matter of controversy. In much of the literature considerable attention has been placed on the diagnosis of VUR, with the conclusion that the only useful examination after a first febrile UTI is a MCUG (66). Most researchers would agree that detecting VUR with associated dilatation is important, given the increased risk of scarring and the ability to intervene medically and surgically in this condition (94, 95). Because the presence and the severity of VUR can be reliably determined only by MCUG, these groups advocate performing MCUG in all children after a first febrile UTI (66).

Alternatively, the so-called “top down” approach is adopted in many countries. This imaging strategy aims to reduce the number of MCUGs. A DMSA scan is performed during the acute phase of the UTI. If this is positive, the chance of dilating VUR is high and a MCUG will be performed. If the acute DMSA is negative, a MCUG is not performed. Some studies have shown a strong correlation between clinically relevant VUR with dilatation and abnormal scintigraphic scans (24, 109-113); however, other studies have disputed this approach (28, 114).

Other groups feel reluctant to adopt the “top down” approach, because the result of an acute DMSA would not change the duration and the form of delivery of antibiotic therapy. Previous studies have shown that longer courses (7 to 14 days) of intravenous antibiotic therapy, compared to shorter courses (3 to 4 days) followed by oral treatment (115-117), resulted in no difference in rates of subsequent renal damage, irrespective of the duration of therapy. Oral antibiotics have been compared to a regimen including three days of intravenous cefotaxime followed by 11 days of oral cefixime alone, with no difference in outcome (118).

In 2007 the National Institute for Health and Clinical Excellence (NICE) in the UK published a set of guidelines on urinary tract infections (69). The main philosophy of these guidelines is to concentrate imaging studies in the child clinically at risk of developing renal damage following an episode of infection. Children with a non-febrile UTI do not need any initial imaging of their urinary tract. Children with recurrent attacks of lower UTI might need imaging that focuses on bladder function. Children with febrile UTI can be divided into two groups: children at high risk and at low risk of developing renal damage. If the UTI is atypical or they have recurrent UTI, the children fall in the high risk category and need an US 6 weeks after the UTI and a DMSA scan at 4-6 months. High-risk children under 6 months of age require a renal tract ultrasound during the acute infection followed by a DMSA 4-6 months after infection and a MCUG. Children between 6 months and 3 years of age do not require any imaging if they respond to antibiotic treatment within 48 hours and are classified as low risk. Low risk children need no imaging if they do not develop a second infection (which brings them into the high risk group). A MCUG is not routinely performed unless there is evidence of dilatation on US, poor urine flow, non-E. Coli UTI, or family history of VUR. In children older than 3 years of age, a DMSA scan is performed at 4-6 months only if the child has had recurrent UTI (69).

The NICE guidelines have been criticised by studies that show that a significant number of abnormalities, especially high grade VUR, may be missed if the guidelines are followed (119-121); the authors state that the NICE guidelines should be used with full awareness of their limitations.

The Italian Renal Infection Study Group has proposed an alternative imaging approach in young children with a first febrile UTI (71). Their results in a group of 300 children aged <2 years with a first febrile UTI suggest that the benefit of performing US at diagnosis and acute DMSA is minimal. They recommend a specific role for US, namely for children in whom it was not performed ante-natally, those with poor response to antibiotics, and those with complicated or recurrent infections. A good quality US during the prenatal screening will detect the small proportion of congenital abnormalities. In their study, the MCUG yielded positive results for VUR in only 22% of children, with only 4 children showing grade IV or V VUR. They concluded that the use of MCUG in 300 children to detect 4 cases of severe VUR, which could be diagnosed after a second UTI, is not justified. The acute DMSA was positive in 54% of cases and showed changes compatible with acute pyelonephritis. However, this did not change management as no significant difference has been demonstrated between administering antibiotics intravenously or orally (122). Therefore, the authors question the value of routinely performing acute DMSA scans in children with a febrile UTI. This study emphasises the importance of renal scarring, rather than VUR, as the main prognostic factor for a patient's outcome after a UTI. The detection of VUR was poorly correlated with subsequent renal scarring in children with a first febrile UTI, with no evidence

that its diagnosis improved outcomes or warranted alteration in management. Those patients with scarring on late DMSA (done at 12 months after the UTI) and those with recurrent febrile UTI should be considered for further investigation. The impact of such renal scars on the development of long-term complications has yet to be determined.

Conclusion: Controversy still exists in imaging and management of UTI. Long-term cohort studies with sufficient statistical power that establish the prognostic significance of renal scarring are needed. Ultrasound of the kidneys and bladder is always the first line investigation to assess dilatation and secondary signs of reflux such as intermittent collecting system dilatation, uroepithelial thickening in the collecting system and ureters and evidence of scarring.

ANTE-NATALLY DIAGNOSED HYDRONEPHROSIS

Ante-natally diagnosed hydronephrosis may have several causes, of which the most common is the pelvic-ureteric junction anomaly (PUJA) (123).

PUJ ANOMALY

Dilatation of the upper urinary tract still presents a significant clinical challenge in determining which patient may gain benefit from therapy. Due to the widespread use of ultrasonography during pregnancy, antenatal hydronephrosis is often found. The challenge in the management of dilated upper urinary tracts is to decide which child can be observed, which one should be managed medically and which one requires surgical intervention.

Diagnostic Imaging – Definition of Obstruction

An ante-natally diagnosed hydronephrosis is normally monitored with ultrasound after birth. On ultrasound, the antero-posterior diameter of the renal pelvis, calyceal dilatation, kidney size, thickness of the parenchyma, cortical echogenicity, ureters, bladder wall and residual urine are assessed. The sonographic diagnosis of a PUJ anomaly depends on the demonstration of a dilated renal pelvis in the absence of any dilation of ureter or bladder. It should particularly be suspected when moderate (10-15 mm) or severe (>15 mm) dilation is seen (124). Hydronephrosis has been classified in different grades (Fig.2).

The pathological basis of the PUJA is an abnormal muscle arrangement with an anomalous collagen collar at the level of the PUJ. In vast majority of cases an ante-natally diagnosed hydronephrosis resolves spontaneously, as a manifestation of physiologic change during development (125, 126).

Not all children with antenatally diagnosed hydronephrosis require assessment with dynamic renography. This is reserved for children with a moderately to very dilated renal pelvis (>12mm in AP diameter) and with calyceal dilatation. For an infant, 6 weeks of age is generally accepted as a reasonable time to undergo first renal scintigraphy. As mentioned earlier, Tc-99m-MAG3 provides superior diagnostic images and is the agent of choice for renal scintigraphy in children (127).

It has been noted that the vast majority of cases of ante-natally diagnosed hydronephrosis resolve spontaneously (125, 128). In approximately 25% - 30% of cases the PUJ anomaly in an asymptomatic patient causes a significant resistance to urinary outflow, with backward pressure on the renal tubules. This causes stretching of the parenchyma and, in the long run, loss of kidney function if the condition is left untreated (128). These are the kidneys that get obstructed.

Unfortunately this definition of obstruction is retrospective and unhelpful. Contrary to the adult practice where an obstructed kidney declares itself with symptoms, the vast majority of children with ante-natally diagnosed hydronephrosis are asymptomatic, including the majority of those who will develop obstruction to urinary outflow. Therefore, it is difficult to clinically identify the kidney at risk.

Slow drainage and urinary stasis at the level of the PUJ does not necessarily mean obstruction (129). It may signify a condition of equilibrium, thereby there is a degree of resistance to urinary outflow, but not sufficient to cause a fall of renal function; with time and with maturation and growth of the excretory system, the PUJ stenosis may resolve. Therefore, it is important to consider that the previously widely accepted classification of the diuretic renogram curve patterns as no obstruction, indeterminate or obstruction (49, 130) has been superseded by a better understanding of the urodynamics. A large renal pelvis without significant urinary flow impairment may cause very slow drainage, with no significant deterioration in renal function and eventually spontaneous improvement.

In a young child with hydronephrosis, one should not arrive at the diagnosis of obstruction based on a single examination. A single study provides only a "snapshot" of a changing situation. Serial studies over time provide a better indication of the natural progression of renal dilatation and help determine the presence of an obstruction. Future deterioration of renal function cannot be predicted solely based on findings of increasing dilatation on ultrasound, or a rising curve and/or a low differential function on diuretic scan.

The function of the hydronephrotic kidney will be affected by the severity of the PUJ stenosis. High pressure in the pelvi-calyceal system can result in reduced renal blood flow and decreased cortical function. In the young, this can be reversed after relief of the urinary obstruction. Renal blood flow decreases rapidly with increased pressure in the pelvi-calyceal system. This can be reversible for a period of time, but if increased pressure is long-standing, reduction in blood flow and function can become permanent.

It is usually possible to identify a single site of obstruction at the VUJ or the PUJ, but obstruction at both the PU and VU junctions may be difficult to detect. Detection of the level of urinary stasis depends on adequate renal function and the presence or absence of dilatation of the pelvi-calyceal system and ureter (124).

In studies of hydronephrosis due to a severe PUJ stenosis, the affected kidney paradoxically may take up more tracer than the contralateral side (supra-normal kidney). It is thought that the kidney with a tight PUJ stenosis develops transiently increased blood flow. Over time, renal function in an obstructed kidney will reduce.

Symptomatic obstruction (recurrent flank pain, urinary tract infection) and decreased split renal function at initial assessment are often used as absolute indications for surgery. The recommendation is to perform an open, laparoscopic or robotic assisted pyeloplasty, according to the standardised technique of Anderson and Hynes (131). Open surgery remains the management of choice in neonate and young infants compared with a minimally invasive approach. In older children, the choice is more controversial but the laparoscopic approach continues to gain increasing acceptance.

Renal scintigraphy may help physicians in the follow up of patients after surgery. Scintigraphy is usually performed 6-9 months after pyeloplasty. Young patients with moderately impaired differential renal function and patients diagnosed because of symptoms may have the greatest likelihood of a functional improvement (132).

The Hydronephrotic Kidney at Risk

The identification of the hydronephrotic kidney at risk of losing function is still controversial, with different approaches to the management of the child (133).

The degree of hydronephrosis in the post-natal period is important. Spontaneous resolution takes place in approximately 50% of the cases with mild hydronephrosis, whereas it is much less frequent in cases with more pronounced dilatation (134). No intervention is required in the majority of cases. It is more likely that the child will need surgery if the renal pelvis diameter is greater; however, a convincing demonstration that pyeloplasty is mandatory is missing. Some urologists have shown that a dilated renal pelvis may have a protective role on the kidney (135).

Decreased split function at initial assessment is often used as an absolute indication for surgery, but this has been questioned in a prospective study with conservative follow-up (136, 137). Moreover, the overall impression is that improvement does not occur when surgery is performed because of initial decreased function. Very different is the sudden increase of hydronephrosis during follow up, which indicates imbalance of a urodynamic equilibrium and the risk of renal deterioration.

A parameter thought to be diagnostically helpful is the renal cortical transit of the tracer, in other words the passage of tracer from the outer cortex to the medulla and collecting system. In a normal kidney, a rapid cortical transit is expected in the first minutes of the acquisition. It has been suggested that impaired cortical transit of tracer, with absence of activity in the subcortical structures of the kidney within 3 minutes of tracer injection, might be predictive of a significant improvement of function after pyeloplasty, or might represent a high risk of deterioration if surgery is delayed (138-140) (Fig.3a,b).

Conclusion: The identification of the ante-natally diagnosed asymptomatic hydronephrotic kidney at risk of losing function is still the main clinical challenge. Slow cortical transit of tracer may be a helpful sign but larger studies are necessary to confirm this finding.

MEGAURETERS AND VUJ ANOMALY

Foetal ultrasonography has identified a greater prevalence of megaureter (ureteric diameter greater than 7mm), in the general paediatric population than previously thought.

Megaureters are reported to occur in approximately 23% of neonates noted to have antenatal hydro-ureteronephrosis. They occur more often in males and more likely on the left side (141).

Dynamic renography with Tc-99m-MAG3 is indicated to assess the cortical renal function and confirm the level of urinary hold up with a full and an empty bladder. It is worth noticing that in the case of VUJ anomalies with a dilated renal pelvis, the MAG3 renogram may show predominant or exclusive urinary stasis within the renal pelvis, with little or no significant urinary stasis within the dilated ureter. In this case, if the ultrasound shows a dilated ureter down to the level of the VUJ (and possibly more dilated at the distal end), the diagnosis of a megaureter is still likely, even if the dynamic renography has not demonstrated this. This is a well-recognized pitfall of renography in this condition (Fig. 4a,b,c).

Only 10-20% of megaureters require surgical treatment, whilst the remainder may be monitored conservatively. The characteristic adynamic segment of the distal ureter just prior to its insertion into the bladder can either be cut using balloons at cystoscopy, or excised with subsequent re-implantation of the ureter.

Non-obstructed megaureters

Children with asymptomatic megaureters associated with a DRF in excess of 40% may be managed conservatively. If a functional study reveals adequate ureteral drainage, low-dose prophylactic antibiotics within the first year of life are recommended for prevention of urinary tract infections, although there are no prospective randomised trials to evaluate this regimen (142). Close follow-up every 3-4 months with ultrasound and antibiotic prophylaxis are warranted, especially in cases with significant dilatation (>1cm ureteral diameter) (143, 144). Megaureters with grades 0 - 2 hydronephrosis at diagnosis are likely to resolve between 12 and 36 months of age. Grades 3 - 4 hydronephrosis may take longer to resolve, up to 72 months (144, 145).

Obstructed megaureters

In some clinical scenarios surgical management is necessary: increasing hydro-ureteronephrosis, deteriorating renal function on scintigraphy, recurrent urinary tract infections despite antibiotics, or presence of pain, pyonephrosis or stones.

Traditionally, the surgical management of an obstructing megaureter has been via ureteric re-implantation with or without ureteral remodelling. Ureteral re-implantation has good results, with a success rate of 90 - 96% (146, 147).

In general, follow-up investigations using ultrasonography and radionuclide imaging are carried out between 6 and 9 months after surgery. After the first follow up, prophylactic antibiotics are usually stopped if the child is toilet-trained.

RENOVASCULAR HYPERTENSION

Renal disease associated with hypertension can be caused by conditions that involve the renal arteries or the renal parenchyma. Renovascular disease (RVD) is an important but

uncommon cause of hypertension in children, accounting for about 10% of cases (148-150). Renal pathology is the cause of hypertension in over 90% of children after 1 year of age. Less frequently, secondary hypertension may be caused by disorders of the endocrine, cardiovascular, or nervous systems. Radionuclide renal studies play an important role in the evaluation of hypertension in infants and children.

Fibromuscular dysplasia is the commonest cause of RVD in childhood, but other associations include neurofibromatosis type 1, Williams' syndrome, idiopathic hypercalcemia of infancy, and vasculitis, especially Takayasu disease. Middle aortic syndrome is a morphological pattern in which the abdominal aorta and one or more of its major branches are stenosed. This pattern may arise from most of the major causes of RVD in childhood.

In children, especially those with an identifiable underlying cause such as neurofibromatosis type 1, arterial involvement tends to be more extensive than in adults. Bilateral disease and involvement of the intra-renal vasculature occur in 50% or more of children with RVD (149, 151).

Imaging

Non-invasive imaging alone cannot reliably exclude RVD as the cause of paediatric hypertension (152, 153), but may confirm or exclude an alternative pathology. Ultrasound is a simple first imaging test in a child found to have high blood pressure. It may detect small and/or scarred kidneys, renal and adrenal tumors, or hydronephrosis. Doppler studies are most useful for the diagnosis of RVD because direct visualization of renal artery stenosis is difficult. A normal ultrasound study does not exclude a single renal scar, renovascular pathology (especially within smaller intrarenal branches), or a small pheochromocytoma (especially if it is extra-adrenal). If ultrasound has demonstrated Doppler abnormalities clearly suggesting RVD, it is most appropriate to proceed directly to angiography. If this is not the case then further investigations are focused on confirming or excluding an alternative renal cause for the hypertension.

Some of the renal causes of hypertension, such as infarction, scarring, and post-traumatic lesions, are readily diagnosed by DMSA scintigraphy. If the ultrasound is normal a DMSA scan may reveal focal scarring as an underlying pathology. If both the ultrasound and the DMSA are normal, RVD should still be considered and a diagnostic angiogram may still be indicated.

Dynamic renal scintigraphy has been utilised in the diagnostic work up of renovascular hypertension (154), especially before and after administration of an angiotensin-converting enzyme (ACE) inhibitor such as captopril (155-157). Although pre- and post-captopril scintigraphy has been suggested in the investigation of secondary causes of hypertension (158), this technique is weak in bilateral or segmental disease, and its use in the diagnostic algorithm of renovascular hypertension is not routinely advocated (159). The sensitivity and specificity of captopril renal scintigraphy for RVD are reported to be 59%–73% and 68%–88% (160, 161). Although detection of segmental abnormalities is sometimes possible with this technique (162), the high prevalence of bilateral and/or branch artery RVD limit its utility in children.

For the time being digital subtraction angiography (DSA) is the cardinal investigation in the

assessment of paediatric RVD, due to its superior spatial resolution. In addition, DSA is the basis of endovascular intervention (163). Renal DMSA scanning has a role in monitoring the cortical function of a kidney supplied by a functionally significant artery stenosis before and after revascularization procedures such as angioplasty (158). A kidney supplied by a very stenotic renal artery can gain significant function after arterial dilatation with possible stenting at angiography.

Renal Vein Thrombosis

In neonates, renal vein thrombosis (RVT) is usually related to venous stasis secondary to shock, septicaemia, or dehydration. The diagnosis may be suggested by the presence of oliguria, macroscopic haematuria, and proteinuria, with a clinically enlarged and hard kidney. RVT is also seen in infants of diabetic mothers and children with congenital heart disease. Nephrotic syndrome is a very frequent cause of large-vessel thrombosis because of urinary losses of antithrombin III, protein C, protein S, and other factors. The venous obstruction then leads to infarction and haemorrhage.

Although RVT is associated with low mortality, the outcome of renal function is not always good, so these patients require close clinical follow up with serial sonography and a baseline DMSA scan at between six months and a year of age (164). In severe cases, there may be apparent function of the involved side. A follow up study may be useful to demonstrate the residual renal function after recovery. Radionuclide studies may reveal information of prognostic significance, with a normal study predicting a rapid and complete recovery. Dynamic renography is not indicated unless there are issues of impaired drainage (127).

Renal Infarction

Renal infarction can occur in patients with cyanotic congenital heart disease, polycythaemia, atrial fibrillation, dehydration, or trauma. Aortic thrombosis and renal infarction are also well-recognized complications of prolonged umbilical artery catheterization. Treatment with thrombolytic agents may allow resolution of the clot and recovery of renal function in some cases. DMSA scintigraphy demonstrates focal perfusion defect(s) in the affected kidney(s).

UROLITHIASIS AND NEPHROCALCINOSIS

Urolithiasis and nephrocalcinosis (NC) are two patterns of calcification associated with the urinary tract. Urolithiasis is macroscopic calcification in the urinary tract causing renal calculi. Urinary calculi are composed of crystal aggregates, sometimes mixed with proteins. Nephrocalcinosis represents increased calcium content in the kidney, in the form of microscopic calcification in the tubules, tubular epithelium, or interstitial tissue of the kidney. Nephrocalcinosis is not a uniform entity, but rather a complication of various renal disorders, metabolic disturbances or pharmacotherapy. Hypercalciuria appears to be the most common abnormality associated with NC (165).

Urolithiasis in children is an increasingly common cause of morbidity and hospital admissions. Recent studies have shown that the incidence of urolithiasis in children has

increased 6-10% annually during the past 25 years (166, 167). No one factor accounts for this dramatic increase; this is likely due to a combination of genetic predisposition, socioeconomic conditions and dietary intake. Metabolic risk factors in paediatric urolithiasis can be identified in 75-84% of evaluated children (168, 169).

Urolithiasis may be related to hypercalciuria, hyperoxaluria, hypocitraturia, cystinuria or hyperuricosuria. Additional risk factors for lithiasis include prematurity, urinary tract infection, urinary tract abnormalities, immobilization, chronic bowel disease and neurological disorders. Medications may be associated with an increased risk of nephrolithiasis, such as furosemide, vitamin D excess, vitamin C excess, topiramate and zonisamide.

The most common symptoms of calculi are abdominal pain, sometimes clearly identifiable as colicky pain, vomiting, urinary tract infection, gross or microscopic non-glomerular haematuria and, more rarely, flank/loin tenderness or urinary retention. However, one in six children do not complain of any of these symptoms and their stones are detected unexpectedly on imaging (170).

Renal calculi in children are treated by Extracorporeal Shock Wave Lithotripsy (ESWL), Percutaneous Nephro-Lithotomy (PCNL), ureterorenoscopic retrograde intrarenal surgery and, less frequently, by open surgery or laparoscopy.

With PCNL, stones are removed directly from the renal collecting system using keyhole access into the pelvi-calyceal system. PCNL is favoured in cases of renal stones of high density (Hounsfield Unit > 1000 on CT kidneys ureters bladder - KUB), stones situated in a dilated renal pelvis or a calyx from which fragments are unlikely to clear after ESWL, or when the calculus is stuck in a calyceal infundibulum causing obstruction to urinary outflow.

ESWL is the preferred surgical technique in cases of less dense (Hounsfield Unit <500), renal stones up to 2cm in size, or in the presence of other comorbidities that preclude PCNL. This technique uses high energy sound waves to break a stone into small pieces that can more easily travel through the urinary tract and pass urethrally.

Imaging

Urinary tract calcification and stones are usually easily diagnosed by US, abdominal radiographs and low dose CT KUB, although small stones may not be detectable even when their presence is strongly suggested. Urolithiasis and NC can coexist in the same patient and NC may be permanent even after eliminating the cause.

Most urinary tract calculi are visible on abdominal x-ray as a result of their calcium content, although fecal loading within the large bowel may obscure detail of the urinary tract and thus miss small calculi. A good quality ultrasound and an abdominal radiograph are therefore complementary techniques (171). CT is still commonly used to investigate suspected urolithiasis in children, as the majority of institutions involved in acute paediatric care are adult-centred and thus influenced by adult-centred practices (172). CT should be reserved for problem solving or treatment planning, as it is more accurate in determining stone size and it also helps with the identification of ureteric stones.

Functional imaging plays a role in selected patients. DMSA scan or MAG3 renogram

contribute little to the management of a patient with a sub-centimetre parenchymal renal stone, with normal surrounding parenchyma visible on ultrasound. However, a DMSA scan is important in a child with renal stones complicated by UTI, particularly if recurrent, as it will show possible renal scarring of the surrounding renal parenchyma. A MAG3 with diuretic will demonstrate function and drainage of a kidney with a stone obstructing the infundibulum of a calyx or partially obstructing the renal pelvis.

A DMSA scan with planar and tomographic images, with SPECT images co-registered to a contemporaneous CT scan (acquired either on a SPECT CT scanner or on a standalone CT scanner, with the images subsequently co-registered to the SPECT images) can be a helpful imaging technique to define the anatomy, determine the number and density of the stone(s), precisely localize the calculus in the renal collecting system, and to provide information on the function of the renal parenchyma adjacent to the stone, thereby guiding surgical decision making (Fig.5a,b,c). It will also help differentiate NC from calculi and identify any possible ureteric stones with their associated risk of obstruction.

The latest CT scanners with paediatric friendly protocols, minimise radiation levels to a fraction of that of a plain abdominal radiograph (0.056mSv versus 0.7mSv) as well as allowing a very short acquisition time (only approximately 1.5 seconds), thereby avoiding the need for sedation or general anaesthesia.

CONGENITAL RENAL ANOMALIES

Duplex

A duplex collecting system refers to a kidney with two pelvicalyceal systems, generally defined as the upper and lower moieties. If the kidney has two ureters that connect separately into the bladder (double ureters), it is considered a complete duplication. In contrast, in a partial or incomplete duplication (Y duplication), a common single ureter enters the bladder. A bifid system is a form of duplication with two pelvicalyceal systems joining before or at the PUJ (bifid pelvis) (173). The upper moiety ureter tends to insert more caudally and medially into the bladder than the normally inserting lower moiety ureter. The lower moiety ureter is often affected by VUR, whereas the upper moiety ureter is associated with a ureterocele and therefore may obstruct.

Ureteroceles are cystic dilatations of the distal segment of the ureter. This obstruction may lead to partial or complete loss of function of the upper moiety. The upper moiety ureter may also insert ectopically, such as in the vagina in a girl or below the bladder neck. If it is obstructed and thus atrophic and almost invisible on ultrasound, a girl may present with constant wetting. A careful high quality ultrasound may find the cryptic upper moiety, or an MRI urogram may show the ureter and its ectopic insertion.

Functional imaging is very important. A MAG3 renogram may confirm the diagnosis of a duplex kidney, clarifying the ultrasound findings. The diagnosis of a duplex on MAG3 may be suspected by differential tracer uptake in the upper and in the lower moiety; the tracer distribution in the collecting system during the drainage phase of the renogram can also suggest the presence of a duplex if tracer is seen in two complete separate collecting systems not merging into a common pelvis.

If the upper moiety of a duplex is obstructed by a ureterocele, it may show very poor or no function on DMSA or MAG3. It may not be visible on functional imaging and therefore the ultrasound should be scrutinized for the presence of a duplex (Fig.6a,b).

Vesico-ureteric reflux is the most common anomaly associated with renal duplex systems. VUR may occur in both moieties, but it is much more frequent into the lower moiety. The ureter draining the lower moiety of a duplex kidney opens more laterally in the bladder. This type of VUR may be associated with renal damage of the corresponding lower pole. A MAG3 renogram with an indirect cystogram can provide accurate information on the cortical function of each moiety of the duplex kidney, as well as show the presence of VUR. Vesico-ureteric reflux into a lower pole still has a potential of spontaneous resolution just as VUR into a single collecting system can spontaneously resolve (174-176). If the child is not toilet-trained, reflux may be seen during the dynamic renography itself, if the child voids in the nappy (Fig.7). In this case, a catheter cystogram may be avoided. Reflux in an obstructed upper moiety, draining via a dilated and tortuous ureter due to the presence of a ureterocele is very uncommon; however, it is demonstrated in approximately 30% of duplex kidneys following puncture of the ureterocele.

The treatment depends on the function of the affected moiety and the presence of symptoms, and it varies from conservative management with or without prophylactic antibiotics, to surgery. Management of a refluxing duplicated ureter depends on the function of the lower pole. Lower grades of reflux with good function may resolve spontaneously as the child grows. Higher grades of reflux may benefit from re-implantation of the ureter, if the refluxing lower moiety shows maintained parenchymal function, or lower pole heminephrectomy if the lower moiety functions poorly. A poorly functioning upper moiety of a duplex is usually treated with upper pole heminephrectomy.

Ectopic Kidney

Single renal ectopia refers to a kidney that remains in the ipsilateral retroperitoneal space, the most common position being the pelvis. Ultrasonography can make the diagnosis in the majority of cases. One or both kidneys may be ectopic in association with, or independent of, other renal malformations. Scintigraphy with DMSA is very useful to estimate the contribution of the ectopic kidney to total renal function: an anterior view is required in all cases, with the split renal function calculated using the geometric mean, in view of the asymmetric position compared to the contralateral kidney and the attenuation artefact from the renal pelvic bones in the posterior view. A MAG3 can be helpful to evaluate drainage, as this can be slow due to the possible high insertion of the ureter in the renal pelvis.

Horseshoe Kidney and crossed renal ectopia

Horseshoe kidneys are characterised by fusion of the lower poles across the midline by an isthmus lying anteriorly to the aorta and inferior vena cava. Radionuclide studies are useful to confirm the diagnosis (which may be unsuspected on ultrasound in view of the overlying bowel gas) and to look for possible functional abnormalities such as infection, hypertension, and haematuria. DMSA imaging (including anterior views or SPECT imaging) shows the function of the renal parenchyma and whether the kidneys are joined by functioning renal tissue or by a fibrous band.

Pelvic-ureteric junction obstruction in one of the moieties of a horseshoe kidney is common, due to high insertion of the ureter or to an anomalous crossing renal vessel. A MAG3 renogram will confirm the diagnosis and assess the drainage, confirming the level of possible urinary stasis. Renal calculi develop in 20% of patients with horseshoe kidneys (177).

Crossed renal ectopia is the second most common fusion anomaly after the horseshoe kidney. Crossed renal ectopia with fusion is much more common than without fusion. There are many possible combinations of crossed renal ectopia. The crossed ectopic side lies on the opposite side to the ureteral insertion in the bladder. It may be difficult to differentiate a crossed fused kidney from a crossed kidney without fusion on ultrasound. A functional assessment with DMSA (better if supplemented with SPECT imaging) is often required to evaluate renal parenchymal integrity and confirm the diagnosis. If further anatomical details are required, especially with regard to vascular supply, ultrasound and MRI urography are the imaging methods of choice in children.

Renal Hypoplasia

This condition originates from disturbed differentiation of metanephrogenic tissue or problems with the induction of tissue differentiation. Histologically, it is defined by reduction in the number and/or size of nephrons, mostly in combination with dysplastic elements. Many children are otherwise healthy, and renal hypoplasia is detected by chance; others with more severe and bilateral disease may suffer from renal failure, urinary tract infection, and hypertension.

Imaging usually starts with US. Volume calculations show a small kidney with otherwise often normal sonographic appearance. Additional work up is performed with MCUG to rule out VUR as a possible cause for a radiologically small kidney. A DMSA scan is very useful to confirm the diagnosis: this shows homogeneously reduced tracer uptake, with no evidence of focal cortical defects.

Multicystic Dysplastic Kidney

Multicystic dysplasia of the kidney (MCDK) is the most common cystic disorder of infants and children with an incidence of about 1 in 4,000 births and is more common in males (2.4:1). By definition, the affected kidney is non-functioning and is usually associated with an atretic ureter.

The aim of imaging in MCDK is to establish the diagnosis, confirm a normal contralateral renal unit, and to rule out associated anomalies. Imaging is initially performed with US (178). Associated urinary tract anomalies are present in one third of patients (PUJ urinary stasis in 12%, VUR in 20%). Scintigraphy with DMSA shows no tracer uptake in the MCDK, confirming absence of cortical function, and dynamic renography will confirm normality of the contralateral kidney. MCDK may involve a portion of a duplex (usually the upper moiety) or of a horseshoe kidney.

The majority of MCDKs involute during the first decade of life. Previously, MCDK was managed with nephrectomy to prevent potential development of proteinuria, hypertension,

and degeneration into Wilms' tumor. Several large studies have since shown these risks to be extremely low if present at all (179, 180).

Conservative management with serial ultrasounds is now standard practice for MCDK (181). While exact imaging protocols vary, renal US is often performed every 3 to 6 months in the first 2 years and annually thereafter. Cystograms are unnecessary in isolated MCDK with a normal contralateral kidney.

Nephrectomy is only reserved for cases where the large size of the kidney is causing abdominal distension, discomfort, pain, difficult feeding or respiratory compromise in the first few months of life, where the cysts continue to increase in size and in case of hypertension. Failure to regress is considered by some as a relative indication for surgery.

Cystic Renal Disease

Cystic renal disease includes a variety of entities. Inherited diseases as well as a disturbed renal embryogenesis and renal development create a wide spectrum of manifestations that spans diffuse, severe, bilateral congenital disease to simple, single renal cysts occurring in the adult.

Imaging in cystic kidneys always starts with ultrasound. Functional imaging is occasionally requested to evaluate the amount of cortical function present, especially if the condition is unilateral. Occasionally it may be difficult to distinguish a single cyst from a dilated calyx. A MAG3 renogram with delayed images can be helpful: a cyst will remain photopaenic on delayed images, whereas a dilated calyx will fill with tracer.

LOWER URINARY TRACT DYSFUNCTION (LUTD)

Voiding Dysfunction

Non-neurogenic bladder-sphincter dysfunction ("voiding dysfunction") is a very common childhood disorder that all paediatric urologists, paediatricians and paediatric radiologists encounter in their daily practice. The most common clinical presentations are recurrent UTIs, VUR, and daytime and night-time urinary incontinence.

Two main entities have been identified: overactive bladder (or unstable bladder, urge syndrome) and dysfunctional voiding. The common denominator of lower urinary tract dysfunction is bladder sphincter disco-ordination leading to chronic high intravesical pressure, with resulting negative consequences for the urinary tract.

Nuclear Medicine may have a potential role in the screening for LUTD, through the use of the indirect cystogram supplemented by a non-invasive urodynamic bladder assessment with a flow meter.

Overactive bladder (unstable bladder)

The primary abnormality is the failure to suppress involuntary detrusor contractions due to the inability to exert complete voluntary control over the micturition reflex. The child, attempting to maintain continence during such contractions, must voluntarily and tightly

constrict the external urethral sphincter to stay dry. This results in simultaneous and non-physiological contraction of both the bladder and external urethral sphincter and leads to symptoms such as urgency, frequency and urge incontinence (overactive bladder syndrome) (182). The IRC study may show episodes of VUR with no micturition, in keeping with ineffective bladder contractions.

Detrusor-sphincter dysfunction during micturition (dysfunctional voiding)

The primary abnormality of this dysfunction is overactivity of the sphincter mechanism during voiding.

Dysfunctional voiding can be subdivided into the following types:

- *Staccato voiding* is caused by bursts of pelvic floor activity during micturition resulting in peaks in bladder pressure together with interruption in urinary flow;
- *Interrupted voiding* is caused by hypoactivity of the detrusor muscle, with voiding consisting of several unsustained detrusor contractions each with its own flow. Voiding frequency tends to be low; bladder capacity is large;
- *Lazy bladder syndrome* is the consequence of long-standing dysfunctional voiding. It results from detrusor decompensation. Abdominal pressure is mostly responsible for voiding. Large volumes of urine can be observed (183).

High intravesical pressure is the main mediator that leads to morphologic changes of the urinary bladder in terms of trabeculation and formation of diverticula, and this may lead to VUR.

There is a clear co-prevalence between LUTD and VUR. Lower urinary tract dysfunction refers to the presence of lower urinary tract symptoms, including urgency, urge-incontinence, weak stream, hesitancy, frequency and UTIs, which reflect the filling and/or emptying dysfunction. The development of VUR may be caused by the anatomical distortion of the vesico-ureteric junction as a consequence of chronic high pressure; high pressure itself does not cause VUR. In cases of borderline competent ureteric orifices, chronic high pressure itself may directly induce and perpetuate VUR.

A modified IRC with the addition of a flow meter may be a possible screening test for bladder function, while at the same time looking for VUR and assessing the function and drainage of the upper tracts (Fig.8a-e). The child sits on the commode and voids in a jug placed on the flow meter platform, with wireless connection to a computer. The platform is sensitive to the pressure of the jet of urine. This non-invasive urodynamic assessment informs on voiding time, time to maximum urine flow, maximum urine flow in ml/sec, and average flow. The shape of the bladder contraction curve gives some insight into bladder function. A normal bladder contraction curve typically has a bell shape, reflecting a harmonious synchronous and efficient contraction. Fractionated voiding is reflected by a bladder contraction curve with multiple spikes. Lazy bladder syndrome will show as incomplete bladder emptying over a prolonged period of time, with an elongated bladder contraction curve and multiple small spikes on the flow meter study. It is important to take note of the voided volume of urine: a large voided volume, in excess of that expected for a child of that particular age (see previous formula to calculate the expected voided volume for age), raises the possibility of a decompensated bladder. Conversely, if the child passes very little urine, this may mean that they were not well hydrated and therefore the IRC may be suboptimal.

The IRC supplemented with a flow meter study may potentially be a screening tool for bladder dysfunction and direct patients to a comprehensive urodynamic bladder assessment. This approach needs proper evaluation. If VUR is detected, the initial goal of management is the normalisation (or improvement) of bladder function.

Neuropathic Bladder

Children with neuropathic bladder-sphincter dysfunction may be unable to retain urine normally, to evacuate normally, or both. Most neurological conditions in children leading to a neuropathic bladder dysfunction include myelo-meningocele, lipomeningocele, sacral agenesis, and occult lesions such as congenital neurospinal dysraphisms (184). Children after sacrococcygeal teratoma resection may also develop a neuropathic bladder (185). The neuro-urological changes may arise from the tumor itself due to spinal compression and/or from the surgery. Therapeutic goals in children with neuropathic bladder are the preservation of renal function, avoidance of urinary tract infection, and achievement of appliance-free and social continence.

Neuropathic bladder occurs also in 80%–90% of patients who suffer from myelodysplasia. Myelomeningocele is the most common defect. Neonatal assessment consists of an ultrasound of the bladder and kidneys and, in most centres, a MCUG as well.

Although continence is readily appreciable by history, there is an insidious risk of renal damage. Therefore, regular assessment of the upper tracts with ultrasound is required to detect changes before irreversible damage has occurred. In these patients, renal scintigraphy with DMSA is used to monitor renal cortical function and to identify scars secondary to recurrent infections as well as congenital renal dysplasia (186).

RENAL TRAUMA

Radionuclide imaging is used infrequently in these patients. In the case of minor injuries, such as renal contusion, intra-renal and sub-renal haematoma, minor laceration without extension to the renal collecting system, or small subcortical infarcts, nuclear medicine investigations are usually not necessary, as management is conservative. CT is the imaging modality of choice in the initial trauma staging.

In the case of major injuries, for example major renal laceration extending through the cortex to the medulla and collecting system, patient's management can vary. If the patient is haemodynamically stable, management can still be conservative. If the patient is unstable, surgical exploration is required. In this case, DMSA scintigraphy (if feasible, in view of the patient's clinical conditions) may be helpful prior to surgery to assess viability of renal parenchyma. Renal scintigraphy with DMSA can be also used to assess recovery or residual damage several months after trauma. Studies using Tc-99m-MAG3 or Tc-99m-DTPA can effectively detect urinary leaks following trauma.

RECIPIENTS OF RENAL TRANSPLANTS

It is possible to assess perfusion of the transplant with scintigraphic methods during the early and late post-operative periods, and assist in the differential diagnosis of diminished graft function, which includes rejection, obstruction, and urinary leak (187). In practice, Doppler ultrasound is commonly used to assess renal perfusion; the ultrasound examination can also raise the suspicion of obstruction to outflow by showing increasing renal pelvic or ureteric dilatation in comparison to the baseline ultrasound. When rejection is suspected, a renal biopsy is usually performed, making scintigraphy assessment almost always unnecessary.

Renal transplant recipients have a high incidence of UTIs. A DMSA scan is useful to assess the degree of renal damage after a UTI. A DMSA in renal transplant recipients a few weeks after transplantation may be a helpful baseline, particularly in those young renal transplant recipients with a previously unused of “hostile” bladder (such as in posterior urethral valves or augmented bladders). The acquisition of six views (anterior, posterior, right and left posterior obliques, right and left anterior obliques) is highly recommended for better visualisation of the transplanted kidney. A SPECT dataset is helpful where the transplant may be unusually positioned.

Obstruction

Urinary obstruction is a possible complication following renal transplantation. Obstruction soon after surgery may be due to oedema and/or inflammation in the region of the vesico-ureteric junction, which may be temporary. Later, obstruction may be due to external compression, which may be caused by a lymphocele or surgical scars or by stenosis at the ureteral anastomosis site. Because the transplant ureter obtains its blood supply only from the graft, the distal ureter may be poorly perfused, which may result in distal ureteral scarring and obstruction. Partial or even total obstruction of a transplant kidney may be relatively asymptomatic, as the graft is not innervated. Diagnosis of partial obstruction is sometimes difficult, and radionuclide dynamic renography with furosemide may be helpful.

Urinary Leak

Urinary leak usually occurs in the first few months following transplantation. It can occur at the site of anastomosis of the transplant ureter or through necrosis of the distal transplant ureter related to diminished perfusion. In cases of suspected urinary leak following transplantation, multiple serial images, usually as part of a MAG3 renogram, can effectively detect the presence of urinary leak and urinoma (188). Renal scintigraphy with Tc-99m-MAG3 can also be used to differentiate urinoma from lymphocele or seroma. On the series of scintigrams, the leakage appears as a focal or diffuse area of increasing tracer accumulation outside the confines of the transplant, the ureter, or the bladder. Urinoma usually appears as a photo-deficient area on early images (5–10 min), due to the presence of non-radioactive urine, with subsequent accumulation of tracer on later images. If the initially photopenic area does not concentrate radiotracer on later images, this region may represent a haematoma or a lymphocele.

NUCLEAR MEDICINE IN SOME PAEDIATRIC NEPHRO-UROLOGICAL TUMOURS

Wilms' Tumours

Wilms' tumour (WT) is the most common renal tumour in children. It accounts for 6% of all paediatric malignancies; the overall survival at 5 years exceeds 90% (189). Most WTs

contain a mixture of blastemal, stromal, and epithelial cell components in varying proportions. Up to 10% will demonstrate anaplasia, which is associated with a poorer prognosis (190). Prognosis depends mostly on stage at diagnosis and histologic components of the lesion (intermediate versus anaplastic histology).

Treatment of WT is based on histopathology and the stage of the disease. Staging is based on surgical and imaging findings. The primary goals of surgery are tumour resection, resection of involved lymph nodes, and avoidance of tumour spillage. Adjuvant chemotherapy and radiation therapy depend on the extent of the disease (191, 192).

Local tumour staging requires information on tumour location, size, local extension, vascular compression or invasion, and local lymph node metastases. Initial staging requires ultrasound, CT, MRI. Bone scan is used if there is suspicion of skeletal metastases; however, skeletal metastases in WT are rare. The most common site for metastases is the lungs, which are typically evaluated with chest CT.

The use of FDG PET CT in WTs has not been fully tested. The studies available are preliminary and include few patients. Possible applications for FDG PET CT in WTs are evaluation of response to neo-adjuvant chemotherapy and recurrent or metastatic disease.

Wilms' tumours show intense FDG uptake (193, 194), in particular anaplastic tumours. Misch D et al. (194) found PET advantageous in ruling out residual disease after completion of first-line treatment and in pre-therapeutic staging of relapsed patients. There was also a good correlation of standardised uptake value (SUV) and histological differentiation. Begent (193) showed that PET/CT findings following initial chemotherapy correlated with histologically confirmed viable tumour, presence of lung metastases and areas of anaplasia. Another study showed no significant correlation between FDG uptake and histopathology (192). FDG PET CT may have the potential of predicting WT response to chemotherapy, with a significant correlation between pathologic response and reduction of SUV before and after induction chemotherapy (195); however, in view of conflicting reports, further evaluation is needed.

No systematic studies exist on the use of FDG PET CT in nephroblastomatosis, clear cell sarcoma, genito-urinary rhabdoid tumour, and renal cell carcinoma. A study to compare FDG uptake in WT and nephroblastomatosis would be particularly useful.

DMSA SPECT CT studies are becoming increasingly useful in specialised centres where stage V bilateral WTs are managed. The bilateral disease most often occurs in children with a genetic mutation leading to a WT1 gene alteration (for example in Denys Drash syndrome) or in other syndromes associated with the development of WT such as Beckwith-Wiedemann syndrome. Nephron sparing surgery is being performed for bilateral disease in these high risk children, who may develop metachronous tumours. DMSA SPECT CT, with or without fusion of three dimensional contemporaneous MRI datasets, aids in attempting innovative preservation of renal tissue in those children who were previously rendered anephric (Fig 9).

Rhabdomyosarcoma

Most studies that evaluate FDG PET/CT in soft tissue sarcomas of childhood include small numbers and heterogeneous series of patients. Within this group of tumours, rhabdomyosarcomas of the genito-urinary tract constitute a small portion of paediatric rhabdomyosarcomas (10% in some series, Casey et al (196).

For the majority of these tumours, MRI and/or CT are used to define the primary tumour, and CT of the lungs is used to exclude pulmonary metastases. Reports of using 18 F-FDG PET are becoming more common in staging, assessing response to treatment, and detecting residual, recurrent, or metastatic disease. Several studies on heterogeneous groups of patients with soft tissue sarcomas showed that the sensitivity and accuracy of FDG PET in the detection of bony lesions was higher than Tc-99m-methylene-diphosphonate bone scans (197, 198) and cross-sectional imaging with CT and MRI (199).

The presence of regional lymph node metastases is a strong prognostic factor in rhabdomyosarcoma patients (200). FDG PET/CT has been shown to be more accurate than conventional imaging for detection of lymph node metastases (201, 202). FDG PET-CT can also predict survival in paediatric sarcoma patients based on the metabolic activity of the primary tumour at diagnosis (203, 204).

CONCLUSION

Much ground has been covered since the introduction of nuclear medicine examinations in paediatric nephro-urology; however, scintigraphy still has a significant role to play. High quality examinations that address a specific clinical question, complemented by a fully informative report that takes into account all the previous imaging and clinical details, are essential. Detailed guidelines on the acquisition and interpretation of the different radionuclide techniques have been published and are widely available on-line, leaving no room for unapproved and untested protocols.

It is important to be aware of the already available applications of radionuclide imaging in congenital renal anomalies, renal calculi, and renovascular disorders with hypertension. The availability of SPECT supplemented by low dose child friendly CT acquisition parameters has significantly improved the diagnostic yield of DMSA scanning in urolithiasis.

Research that can answer some important clinical questions is needed. Long-term appropriately powered cohort studies need to fully inform on the clinical significance of different degrees of renal scarring in children with UTIs and the associated risk of hypertension, chronic kidney disease and, in females, complications in pregnancy. In the context of an ante-natally diagnosed hydronephrosis, only a fraction of patients are at risk of losing renal function if left untreated; in the others the renal pelvic dilatation undergoes spontaneous resolution with time. Currently, we still struggle to reliably identify the hydronephrotic kidney at risk. It is essential to further evaluate in large paediatric studies promising parameters, such as the cortical tracer transit time, for the identification of the kidney at risk.

Finally, in recent years new promising possible applications of FDG PET CT in sarcomas of the genito-urinary tract have been proposed; these need proper testing. The advent of MR/PET imaging will likely benefit the management of paediatric patients with urogenital tumours, opening up new exciting developments.

REFERENCES

1. Gordon I, Piepsz A, Sixt R, Auspices of Paediatric Committee of European Association of Nuclear M. Guidelines for standard and diuretic renogram in children. *Eur J Nucl Med Mol Imaging*. 2011;38(6):1175-88.
2. Shulkin BL, Mandell GA, Cooper JA, Leonard JC, Majd M, Parisi MT, et al. Procedure guideline for diuretic renography in children 3.0. *J Nucl Med Technol*. 2008;36(3):162-8.
3. Fettich J, Colarinha P, Fischer S, Frokier J, Gordon I, Hahn K, et al. Guidelines for direct radionuclide cystography in children. *Eur J Nucl Med Mol Imaging*. 2003;30(5):B39-44.
4. Gordon I, Colarinha P, Fettich J, Fischer S, Frokier J, Hahn K, et al. Guidelines for indirect radionuclide cystography. *Eur J Nucl Med*. 2001;28(3):BP16-20.
5. Piepsz A, Colarinha P, Gordon I, Hahn K, Olivier P, Roca I, et al. Guidelines for 99mTc-DMSA scintigraphy in children. *Eur J Nucl Med*. 2001;28(3):BP37-41.
6. Mandell GA, Eggli DF, Gilday DL, Heyman S, Leonard JC, Miller JH, et al. Procedure guideline for radionuclide cystography in children. Society of Nuclear Medicine. *J Nucl Med*. 1997;38(10):1650-4.
7. Mandell GA, Eggli DF, Gilday DL, Heyman S, Leonard JC, Miller JH, et al. Procedure guideline for renal cortical scintigraphy in children. Society of Nuclear Medicine. *J Nucl Med*. 1997;38(10):1644-6.
8. Piepsz A, Ham HR. Pediatric applications of renal nuclear medicine. *Semin Nucl Med*. 2006;36(1):16-35.
9. Piepsz A. Antenatally detected hydronephrosis. *Semin Nucl Med*. 2007;37(4):249-60.
10. Ismaili K, Piepsz A. The antenatally detected pelvi-ureteric junction stenosis: advances in renography and strategy of management. *Pediatr Radiol*. 2013;43(4):428-35.
11. Gordon I. Issues surrounding preparation, information and handling the child and parent in nuclear medicine. *J Nucl Med*. 1998;39(3):490-4.
12. Mandell GA, Cooper JA, Majd M, Shalaby-Rana EI, Gordon I. Procedure guideline for pediatric sedation in nuclear medicine. Society of Nuclear Medicine. *J Nucl Med*. 1997;38(10):1640-3.
13. Pintelon H, Jonckheer MH, Piepsz A. Paediatric nuclear medicine procedures: routine sedation or management of anxiety? *Nucl Med Commun*. 1994;15(8):664-6.
14. Grant FD, Gelfand MJ, Drubach LA, Treves ST, Fahey FH. Radiation doses for pediatric nuclear medicine studies: comparing the North American consensus guidelines and the pediatric dosage card of the European Association of Nuclear Medicine. *Pediatr Radiol*. 2015;45(5):706-13.
15. Lassmann M, Treves ST, Group ESPDHW. Paediatric radiopharmaceutical administration: harmonization of the 2007 EANM paediatric dosage card (version

- 1.5.2008) and the 2010 North American consensus guidelines. *Eur J Nucl Med Mol Imaging*. 2014;41(5):1036-41.
16. Pintelon H, Dejonckheere M, Piepsz A. Pediatric nuclear medicine: a practical approach. *Q J Nucl Med*. 1997;41(4):263-8.
17. Biassoni L. Pitfalls and Limitations of Radionuclide Renal Imaging in Pediatrics. *Semin Nucl Med*. 2015;45(5):411-27.
18. Familiari D, Di Franco D, Cacciaguerra S, Ruggeri A, Russo S, Fornito MC. Potential Usefulness of 99mTc-DMSA for Radio-Guided Surgery in Pediatric Renal Dysplasia. *Clin Nucl Med*. 2016;41(2):e107-10.
19. Tsalkidis A, Gardikis S, Kambouri K, Zissimopoulos A, Boussios N, Deftereos S, et al. (99m)Tc-DMSA scintigraphy diagnosing crossed renal ectopia with fusion in a three years old boy. *Hell J Nucl Med*. 2011;14(3):300-3.
20. Weyer K, Nielsen R, Petersen SV, Christensen EI, Rehling M, Birn H. Renal uptake of 99mTc-dimercaptosuccinic acid is dependent on normal proximal tubule receptor-mediated endocytosis. *J Nucl Med*. 2013;54(1):159-65.
21. Taylor AT. Radionuclides in nephrourology, part 1: Radiopharmaceuticals, quality control, and quantitative indices. *J Nucl Med*. 2014;55(4):608-15.
22. Cao X, Xu X, Grant FD, Treves ST. Estimation of Split Renal Function With 99mTc-DMSA SPECT: Comparison Between 3D Volumetric Assessment and 2D Coronal Projection Imaging. *AJR Am J Roentgenol*. 2016:1-5.
23. Sheehy N, Tetrault TA, Zurakowski D, Vija AH, Fahey FH, Treves ST. Pediatric 99mTc-DMSA SPECT performed by using iterative reconstruction with isotropic resolution recovery: improved image quality and reduced radiopharmaceutical activity. *Radiology*. 2009;251(2):511-6.
24. Zhang X, Xu H, Zhou L, Cao Q, Shen Q, Sun L, et al. Accuracy of early DMSA scan for VUR in young children with febrile UTI. *Pediatrics*. 2014;133(1):e30-8.
25. Shih BF, Tsai JD, Tsao CH, Huang FY. Reappraisal of the effectiveness of (9)(9)mTc-dimercaptosuccinic acid scans for selective voiding cystourethrography in children with a first febrile urinary tract infection. *Kaohsiung J Med Sci*. 2014;30(12):608-12.
26. Sheu JN, Wu KH, Chen SM, Tsai JD, Chao YH, Lue KH. Acute 99mTc DMSA scan predicts dilating vesicoureteral reflux in young children with a first febrile urinary tract infection: a population-based cohort study. *Clin Nucl Med*. 2013;38(3):163-8.
27. Printza N, Farmaki E, Piretzi K, Arsos G, Kollios K, Papachristou F. Acute phase 99mTc-dimercaptosuccinic acid scan in infants with first episode of febrile urinary tract infection. *World J Pediatr*. 2012;8(1):52-6.
28. Mantadakis E, Vouloumanou EK, Georgantzi GG, Tsalkidis A, Chatzimichael A, Falagas ME. Acute Tc-99m DMSA scan for identifying dilating vesicoureteral reflux in children: a meta-analysis. *Pediatrics*. 2011;128(1):e169-79.
29. Shaikh N, Spingarn RB, Hum SW. Dimercaptosuccinic acid scan or ultrasound in screening for vesicoureteral reflux among children with urinary tract infections. *Cochrane Database Syst Rev*. 2016;7:CD010657.
30. Piepsz A. Antenatal detection of pelviureteric junction stenosis: main controversies. *Semin Nucl Med*. 2011;41(1):11-9.
31. Taylor AT, Blafox MD, De Palma D, Dubovsky EV, Erbas B, Eskild-Jensen A, et al. Guidance document for structured reporting of diuresis renography. *Semin Nucl Med*. 2012;42(1):41-8.
32. Prigent A, Cosgriff P, Gates GF, Granerus G, Fine EJ, Itoh K, et al. Consensus report on quality control of quantitative measurements of renal function

- obtained from the renogram: International Consensus Committee from the Scientific Committee of Radionuclides in Nephrourology. *Semin Nucl Med.* 1999;29(2):146-59.
33. Rutland MD. A comprehensive analysis of renal DTPA studies. I. Theory and normal values. *Nucl Med Commun.* 1985;6(1):11-20.
 34. Durand E, Blaufox MD, Britton KE, Carlsen O, Cosgriff P, Fine E, et al. International Scientific Committee of Radionuclides in Nephrourology (ISCORN) consensus on renal transit time measurements. *Semin Nucl Med.* 2008;38(1):82-102.
 35. Shikano N, Kanai Y, Kawai K, Ishikawa N, Endou H. Transport of ^{99m}Tc-MAG3 via rat renal organic anion transporter 1. *J Nucl Med.* 2004;45(1):80-5.
 36. Eshima D, Taylor A, Jr. Technetium-99m (^{99m}Tc) mercaptoacetyltriglycine: update on the new ^{99m}Tc renal tubular function agent. *Semin Nucl Med.* 1992;22(2):61-73.
 37. Bubeck B, Brandau W, Weber E, Kalble T, Parekh N, Georgi P. Pharmacokinetics of technetium-99m-MAG3 in humans. *J Nucl Med.* 1990;31(8):1285-93.
 38. Lassmann M, Biassoni L, Monsieurs M, Franzius C, Jacobs F, Dosimetry E, et al. The new EANM paediatric dosage card. *Eur J Nucl Med Mol Imaging.* 2007;34(5):796-8.
 39. Stabin MG, Gelfand MJ. Dosimetry of pediatric nuclear medicine procedures. *Q J Nucl Med.* 1998;42(2):93-112.
 40. Smith T, Gordon I. An update of radiopharmaceutical schedules in children. *Nucl Med Commun.* 1998;19(11):1023-36.
 41. Piepsz A, Tondeur M, Ham H. Relative ^{99m}Tc-MAG3 renal uptake: reproducibility and accuracy. *J Nucl Med.* 1999;40(6):972-6.
 42. Lythgoe MF, Gordon I, Khader Z, Smith T, Anderson PJ. Assessment of various parameters in the estimation of differential renal function using technetium-99m mercaptoacetyltriglycine. *Eur J Nucl Med.* 1999;26(2):155-62.
 43. Tomaru Y, Inoue T, Oriuchi N, Takahashi K, Endo K. Semi-automated renal region of interest selection method using the double-threshold technique: inter-operator variability in quantitating ^{99m}Tc-MAG3 renal uptake. *Eur J Nucl Med.* 1998;25(1):55-9.
 44. Moonen M, Jacobsson L, Granerus G, Friberg P, Volkmann R. Determination of split renal function from gamma camera renography: a study of three methods. *Nucl Med Commun.* 1994;15(9):704-11.
 45. Piepsz A, Kinthaert J, Tondeur M, Ham HR. The robustness of the Patlak-Rutland slope for the determination of split renal function. *Nucl Med Commun.* 1996;17(9):817-21.
 46. Groothedde RT. The individual kidney function. A comparison between frame summation and deconvolution. *Nucl Med Commun.* 1985;6(9):513-8.
 47. Sennewald K, Taylor A, Jr. A pitfall in calculating differential renal function in patients with renal failure. *Clin Nucl Med.* 1993;18(5):377-81.
 48. Samal M, Nimmon CC, Britton KE, Bergmann H. Relative renal uptake and transit time measurements using functional factor images and fuzzy regions of interest. *Eur J Nucl Med.* 1998;25(1):48-54.
 49. O'Reilly PH, Testa HJ, Lawson RS, Farrar DJ, Edwards EC. Diuresis renography in equivocal urinary tract obstruction. *Br J Urol.* 1978;50(2):76-80.
 50. Liu Y, Ghesani NV, Skurnick JH, Zuckier LS. The F + 0 protocol for diuretic renography results in fewer interrupted studies due to voiding than the F - 15 protocol. *J Nucl Med.* 2005;46(8):1317-20.

51. Kuyvenhoven J, Piepsz A, Ham H. When could the administration of furosemide be avoided? *Clin Nucl Med*. 2003;28(9):732-7.
52. Adeyolu AA, Burke D, Atkinson C, McKie C, Pollard AJ, O'Reilly PH. The choice of timing for diuresis renography: the F + 0 method. *BJU Int*. 2001;88(1):1-5.
53. Wong DC, Rossleigh MA, Farnsworth RH. Diuretic renography with the addition of quantitative gravity-assisted drainage in infants and children. *J Nucl Med*. 2000;41(6):1030-6.
54. Sfakianaki E, Sfakianakis GN, Georgiou M, Hsiao B. Renal scintigraphy in the acute care setting. *Semin Nucl Med*. 2013;43(2):114-28.
55. Conway JJ, Maizels M. The "well tempered" diuretic renogram: a standard method to examine the asymptomatic neonate with hydronephrosis or hydroureteronephrosis. A report from combined meetings of The Society for Fetal Urology and members of The Pediatric Nuclear Medicine Council--The Society of Nuclear Medicine. *J Nucl Med*. 1992;33(11):2047-51.
56. Chaiwatanarat T, Padhy AK, Bomanji JB, Nimmon CC, Sonmezoglu K, Britton KE. Validation of renal output efficiency as an objective quantitative parameter in the evaluation of upper urinary tract obstruction. *J Nucl Med*. 1993;34(5):845-8.
57. Piepsz A, Tondeur M, Ham H. NORA: a simple and reliable parameter for estimating renal output with or without frusemide challenge. *Nucl Med Commun*. 2000;21(4):317-23.
58. Treves ST, Baker A, Fahey FH, Cao X, Davis RT, Drubach LA, et al. Nuclear medicine in the first year of life. *J Nucl Med*. 2011;52(6):905-25.
59. Peters AM, Morony S, Gordon I. Indirect radionuclide cystography demonstrates reflux under physiological conditions. *Clin Radiol*. 1990;41(1):44-7.
60. Gordon I, Peters AM, Morony S. Indirect radionuclide cystography: a sensitive technique for the detection of vesico-ureteral reflux. *Pediatr Nephrol*. 1990;4(6):604-6.
61. Gordon I. Indirect radionuclide cystography--the coming of age. *Nucl Med Commun*. 1989;10(7):457-8.
62. Haid B, Becker T, Koen M, Berger C, Langsteger W, Gruy B, et al. Lower radiation burden in state of the art fluoroscopic cystography compared to direct isotope cystography in children. *J Pediatr Urol*. 2015;11(1):35 e1-6.
63. Hjalmas K. Urodynamics in normal infants and children. *Scand J Urol Nephrol Suppl*. 1988;114:20-7.
64. Holmdahl G, Hanson E, Hanson M, Hellstrom AL, Hjalmas K, Sillen U. Four-hour voiding observation in healthy infants. *J Urol*. 1996;156(5):1809-12.
65. Majd M, Rushton HG, Jantusch B, Wiedermann BL. Relationship among vesicoureteral reflux, P-fimbriated Escherichia coli, and acute pyelonephritis in children with febrile urinary tract infection. *J Pediatr*. 1991;119(4):578-85.
66. Hoberman A, Charron M, Hickey RW, Baskin M, Kearney DH, Wald ER. Imaging studies after a first febrile urinary tract infection in young children. *N Engl J Med*. 2003;348(3):195-202.
67. Majd M, Rushton HG. Renal cortical scintigraphy in the diagnosis of acute pyelonephritis. *Semin Nucl Med*. 1992;22(2):98-111.
68. Verboven M, Ingels M, Delree M, Piepsz A. 99mTc-DMSA scintigraphy in acute urinary tract infection in children. *Pediatr Radiol*. 1990;20(7):540-2.
69. National Institute for Health and Care Excellence. Urinary tract infection in under 16s: diagnosis and management. August 2007; Accessed 2016 (November); <https://www.nice.org.uk/guidance/cg54>.

70. Marks SD, Gordon I, Tullus K. Imaging in childhood urinary tract infections: time to reduce investigations. *Pediatr Nephrol.* 2008;23(1):9-17.
71. Montini G, Zucchetta P, Tomasi L, Talenti E, Rigamonti W, Picco G, et al. Value of imaging studies after a first febrile urinary tract infection in young children: data from Italian renal infection study 1. *Pediatrics.* 2009;123(2):e239-46.
72. Wennerstrom M, Hansson S, Hedner T, Himmelmann A, Jodal U. Ambulatory blood pressure 16-26 years after the first urinary tract infection in childhood. *J Hypertens.* 2000;18(4):485-91.
73. Geback C, Hansson S, Himmelmann A, Sandberg T, Sixt R, Jodal U. Twenty-four-hour ambulatory blood pressure in adult women with urinary tract infection in childhood. *J Hypertens.* 2014;32(8):1658-64; discussion 64.
74. Jacobson SH, Hansson S, Jakobsson B. Vesico-ureteric reflux: occurrence and long-term risks. *Acta Paediatr Suppl.* 1999;88(431):22-30.
75. Smellie JM, Katz G, Gruneberg RN. Controlled trial of prophylactic treatment in childhood urinary-tract infection. *Lancet.* 1978;2(8082):175-8.
76. Lim R. Vesicoureteral reflux and urinary tract infection: evolving practices and current controversies in pediatric imaging. *AJR Am J Roentgenol.* 2009;192(5):1197-208.
77. Grattan-Smith JD, Little SB, Jones RA. Evaluation of reflux nephropathy, pyelonephritis and renal dysplasia. *Pediatr Radiol.* 2008;38 Suppl 1:S83-105.
78. Hannula A, Venhola M, Renko M, Pokka T, Huttunen NP, Uhari M. Vesicoureteral reflux in children with suspected and proven urinary tract infection. *Pediatr Nephrol.* 2010;25(8):1463-9.
79. Peters C, Rushton HG. Vesicoureteral reflux associated renal damage: congenital reflux nephropathy and acquired renal scarring. *J Urol.* 2010;184(1):265-73.
80. Montini G, Hewitt I. Urinary tract infections: to prophylaxis or not to prophylaxis? *Pediatr Nephrol.* 2009;24(9):1605-9.
81. Estrada CR, Peters CA, Retik AB, Nguyen HT. Vesicoureteral reflux and urinary tract infection in children with a history of prenatal hydronephrosis--should voiding cystourethrography be performed in cases of postnatally persistent grade II hydronephrosis? *J Urol.* 2009;181(2):801-6; discussion 6-7.
82. Ylinen E, Ala-Houhala M, Wikstrom S. Risk of renal scarring in vesicoureteral reflux detected either antenatally or during the neonatal period. *Urology.* 2003;61(6):1238-42; discussion 42-3.
83. Leonardo CR, Filgueiras MF, Vasconcelos MM, Vasconcelos R, Marino VP, Pires C, et al. Risk factors for renal scarring in children and adolescents with lower urinary tract dysfunction. *Pediatr Nephrol.* 2007;22(11):1891-6.
84. Blumenthal I. Vesicoureteric reflux and urinary tract infection in children. *Postgrad Med J.* 2006;82(963):31-5.
85. Estrada CR, Jr., Passerotti CC, Graham DA, Peters CA, Bauer SB, Diamond DA, et al. Nomograms for predicting annual resolution rate of primary vesicoureteral reflux: results from 2,462 children. *J Urol.* 2009;182(4):1535-41.
86. Sjostrom S, Sillen U, Bachelard M, Hansson S, Stokland E. Spontaneous resolution of high grade infantile vesicoureteral reflux. *J Urol.* 2004;172(2):694-8; discussion 9.
87. Silva JM, Diniz JS, Lima EM, Pinheiro SV, Marino VP, Cardoso LS, et al. Independent risk factors for renal damage in a series of primary vesicoureteral reflux: a multivariate analysis. *Nephrology (Carlton).* 2009;14(2):198-204.

88. Jodal U, Hansson S, Hjalmas K. Medical or surgical management for children with vesico-ureteric reflux? *Acta Paediatr Suppl.* 1999;88(431):53-61.
89. Jodal U, Lindberg U. Guidelines for management of children with urinary tract infection and vesico-ureteric reflux. Recommendations from a Swedish state-of-the-art conference. Swedish Medical Research Council. *Acta Paediatr Suppl.* 1999;88(431):87-9.
90. Singh-Grewal D, Macdessi J, Craig J. Circumcision for the prevention of urinary tract infection in boys: a systematic review of randomised trials and observational studies. *Arch Dis Child.* 2005;90(8):853-8.
91. Garin EH, Olavarria F, Garcia Nieto V, Valenciano B, Campos A, Young L. Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. *Pediatrics.* 2006;117(3):626-32.
92. Pennesi M, Travan L, Peratoner L, Bordugo A, Cattaneo A, Ronfani L, et al. Is antibiotic prophylaxis in children with vesicoureteral reflux effective in preventing pyelonephritis and renal scars? A randomized, controlled trial. *Pediatrics.* 2008;121(6):e1489-94.
93. Montini G, Rigon L, Zucchetta P, Fregonese F, Toffolo A, Gobber D, et al. Prophylaxis after first febrile urinary tract infection in children? A multicenter, randomized, controlled, noninferiority trial. *Pediatrics.* 2008;122(5):1064-71.
94. Brandstrom P, Neveus T, Sixt R, Stokland E, Jodal U, Hansson S. The Swedish reflux trial in children: IV. Renal damage. *J Urol.* 2010;184(1):292-7.
95. Brandstrom P, Esbjorner E, Herthelius M, Swerkersson S, Jodal U, Hansson S. The Swedish reflux trial in children: III. Urinary tract infection pattern. *J Urol.* 2010;184(1):286-91.
96. Brandstrom P, Esbjorner E, Herthelius M, Holmdahl G, Lackgren G, Neveus T, et al. The Swedish reflux trial in children: I. Study design and study population characteristics. *J Urol.* 2010;184(1):274-9.
97. American Urological Association; Accessed 2016 (November); <https://www.auanet.org>.
98. Jakobsson B, Jacobson SH, Hjalmas K. Vesico-ureteric reflux and other risk factors for renal damage: identification of high- and low-risk children. *Acta Paediatr Suppl.* 1999;88(431):31-9.
99. Gordon I. Vesico-ureteric reflux, urinary-tract infection, and renal damage in children. *Lancet.* 1995;346(8973):489-90.
100. Caione P, Villa M, Capozza N, De Gennaro M, Rizzoni G. Predictive risk factors for chronic renal failure in primary high-grade vesico-ureteric reflux. *BJU Int.* 2004;93(9):1309-12.
101. Polito C, Rambaldi PF, Signoriello G, Mansi L, La Manna A. Permanent renal parenchymal defects after febrile UTI are closely associated with vesicoureteric reflux. *Pediatr Nephrol.* 2006;21(4):521-6.
102. Lebowitz RL, Olbing H, Parkkulainen KV, Smellie JM, Tamminen-Mobius TE. International system of radiographic grading of vesicoureteric reflux. International Reflux Study in Children. *Pediatr Radiol.* 1985;15(2):105-9.
103. Lebowitz RL. The detection of vesicoureteral reflux in the child. *Invest Radiol.* 1986;21(7):519-31.
104. Lebowitz RL. The detection and characterization of vesicoureteral reflux in the child. *J Urol.* 1992;148(5 Pt 2):1640-2.

105. Blickman JG, Taylor GA, Lebowitz RL. Voiding cystourethrography: the initial radiologic study in children with urinary tract infection. *Radiology*. 1985;156(3):659-62.
106. Fernbach SK, Feinstein KA, Schmidt MB. Pediatric voiding cystourethrography: a pictorial guide. *Radiographics*. 2000;20(1):155-68; discussion 68-71.
107. Dalirani R, Mahyar A, Sharifian M, Mohkam M, Esfandiar N, Ghehsareh Ardestani A. The value of direct radionuclide cystography in the detection of vesicoureteral reflux in children with normal voiding cystourethrography. *Pediatr Nephrol*. 2014;29(12):2341-5.
108. Piaggio G, Degl' Innocenti ML, Toma P, Calevo MG, Perfumo F. Cystosonography and voiding cystourethrography in the diagnosis of vesicoureteral reflux. *Pediatr Nephrol*. 2003;18(1):18-22.
109. Hansson S, Dhamey M, Sigstrom O, Sixt R, Stokland E, Wennerstrom M, et al. Dimercapto-succinic acid scintigraphy instead of voiding cystourethrography for infants with urinary tract infection. *J Urol*. 2004;172(3):1071-3; discussion 3-4.
110. Preda I, Jodal U, Sixt R, Stokland E, Hansson S. Normal dimercaptosuccinic acid scintigraphy makes voiding cystourethrography unnecessary after urinary tract infection. *J Pediatr*. 2007;151(6):581-4, 4 e1.
111. Herz DB. The top-down approach: an expanded methodology. *J Urol*. 2010;183(3):856-7.
112. Herz D, Merguerian P, McQuiston L, Danielson C, Gheen M, Brenfleck L. 5-year prospective results of dimercapto-succinic acid imaging in children with febrile urinary tract infection: proof that the top-down approach works. *J Urol*. 2010;184(4 Suppl):1703-9.
113. Awais M, Rehman A, Zaman MU, Nadeem N. Recurrent urinary tract infections in young children: role of DMSA scintigraphy in detecting vesicoureteric reflux. *Pediatr Radiol*. 2015;45(1):62-8.
114. Fouzas S, Krikelli E, Vassilakos P, Gkentzi D, Papanastasiou DA, Salakos C. DMSA scan for revealing vesicoureteral reflux in young children with urinary tract infection. *Pediatrics*. 2010;126(3):e513-9.
115. Benador D, Neuhaus TJ, Papazyan JP, Willi UV, Engel-Bicik I, Nadal D, et al. Randomised controlled trial of three day versus 10 day intravenous antibiotics in acute pyelonephritis: effect on renal scarring. *Arch Dis Child*. 2001;84(3):241-6.
116. Levtchenko EN, Lahy C, Levy J, Ham HR, Piepsz A. Role of Tc-99m DMSA scintigraphy in the diagnosis of culture negative pyelonephritis. *Pediatr Nephrol*. 2001;16(6):503-6.
117. Levtchenko E, Lahy C, Levy J, Ham H, Piepsz A. Treatment of children with acute pyelonephritis: a prospective randomized study. *Pediatr Nephrol*. 2001;16(11):878-84.
118. Hoberman A, Wald ER, Hickey RW, Baskin M, Charron M, Majd M, et al. Oral versus initial intravenous therapy for urinary tract infections in young febrile children. *Pediatrics*. 1999;104(1 Pt 1):79-86.
119. Narchi H, Marah M, Khan AA, Al-Amri A, Al-Shibli A. Renal tract abnormalities missed in a historical cohort of young children with UTI if the NICE and AAP imaging guidelines were applied. *J Pediatr Urol*. 2015;11(5):252 e1-7.
120. Ristola MT, Hurme T. NICE Guidelines Cannot Be Recommended for Imaging Studies in Children Younger Than 3 Years with Urinary Tract Infection. *Eur J Pediatr Surg*. 2015;25(5):414-20.

121. Ristola MT, Hurme T. NICE guidelines for imaging studies in children with UTI adequate only in boys under the age of 6 months. *Pediatr Surg Int*. 2013;29(3):215-22.
122. Montini G, Toffolo A, Zucchetta P, Dall'Amico R, Gobber D, Calderan A, et al. Antibiotic treatment for pyelonephritis in children: multicentre randomised controlled non-inferiority trial. *BMJ*. 2007;335(7616):386.
123. Lebowitz RL, Griscom NT. Neonatal hydronephrosis: 146 cases. *Radiol Clin North Am*. 1977;15(1):49-59.
124. Ismaili K, Hall M, Piepsz A, Alexander M, Schulman C, Avni FE. Insights into the pathogenesis and natural history of fetuses with renal pelvis dilatation. *Eur Urol*. 2005;48(2):207-14.
125. Gordon I, Dhillon HK, Peters AM. Antenatal diagnosis of renal pelvic dilatation--the natural history of conservative management. *Pediatr Radiol*. 1991;21(4):272-3.
126. Homsy YL, Saad F, Laberge I, Williot P, Pison C. Transitional hydronephrosis of the newborn and infant. *J Urol*. 1990;144(2 Pt 2):579-83; discussion 93-4.
127. Jang SJ. Nuclear Medicine in Pediatric Urology. *Childhood Kidney Diseases*. 2015;19(1):14-22.
128. Koff SA. Postnatal management of antenatal hydronephrosis using an observational approach. *Urology*. 2000;55(5):609-11.
129. Amarante J, Anderson PJ, Gordon I. Impaired drainage on diuretic renography using half-time or pelvic excretion efficiency is not a sign of obstruction in children with a prenatal diagnosis of unilateral renal pelvic dilatation. *J Urol*. 2003;169(5):1828-31.
130. O'Reilly PH, Lawson RS, Shields RA, Testa HJ, Edwards EC, Carroll RN. A radioisotope method of assessing uretero-ureteric reflux. *Br J Urol*. 1978;50(3):164-8.
131. Tan BJ, Smith AD. Ureteropelvic junction obstruction repair: when, how, what? *Curr Opin Urol*. 2004;14(2):55-9.
132. Castagnetti M, Novara G, Beniamin F, Vezzu B, Rigamonti W, Artibani W. Scintigraphic renal function after unilateral pyeloplasty in children: a systematic review. *BJU Int*. 2008;102(7):862-8.
133. Ismaili K, Avni FE, Piepsz A, Wissing KM, Cochat P, Aubert D, et al. Current management of infants with fetal renal pelvis dilation: a survey by French-speaking pediatric nephrologists and urologists. *Pediatr Nephrol*. 2004;19(9):966-71.
134. Feldman DM, DeCambre M, Kong E, Borgida A, Jamil M, McKenna P, et al. Evaluation and follow-up of fetal hydronephrosis. *J Ultrasound Med*. 2001;20(10):1065-9.
135. Koff SA. "The beneficial and protective effects of hydronephrosis". *APMIS Suppl*. 2003(109):7-12.
136. Ulman I, Jayanthi VR, Koff SA. The long-term followup of newborns with severe unilateral hydronephrosis initially treated nonoperatively. *J Urol*. 2000;164(3 Pt 2):1101-5.
137. Eskild-Jensen A, Gordon I, Piepsz A, Frokiaer J. Congenital unilateral hydronephrosis: a review of the impact of diuretic renography on clinical treatment. *J Urol*. 2005;173(5):1471-6.
138. Schlotmann A, Clorius JH, Clorius SN. Diuretic renography in hydronephrosis: renal tissue tracer transit predicts functional course and thereby need for surgery. *Eur J Nucl Med Mol Imaging*. 2009;36(10):1665-73.

139. Piepsz A, Tondeur M, Nogarede C, Collier F, Ismaili K, Hall M, et al. Can severely impaired cortical transit predict which children with pelvi-ureteric junction stenosis detected antenatally might benefit from pyeloplasty? *Nucl Med Commun.* 2011;32(3):199-205.
140. Harper L, Bourquard D, Grosos C, Abbo O, Ferdynus C, Michel JL, et al. Cortical transit time as a predictive marker of the need for surgery in children with pelvi-ureteric junction stenosis: preliminary study. *J Pediatr Urol.* 2013;9(6 Pt B):1054-8.
141. Brown T, Mandell J, Lebowitz RL. Neonatal hydronephrosis in the era of sonography. *AJR Am J Roentgenol.* 1987;148(5):959-63.
142. Arena F, Baldari S, Proietto F, Centorrino A, Scalfari G, Romeo G. Conservative treatment in primary neonatal megaureter. *Eur J Pediatr Surg.* 1998;8(6):347-51.
143. Liu HY, Dhillon HK, Yeung CK, Diamond DA, Duffy PG, Ransley PG. Clinical outcome and management of prenatally diagnosed primary megaureters. *J Urol.* 1994;152(2 Pt 2):614-7.
144. McLellan DL, Retik AB, Bauer SB, Diamond DA, Atala A, Mandell J, et al. Rate and predictors of spontaneous resolution of prenatally diagnosed primary nonrefluxing megaureter. *J Urol.* 2002;168(5):2177-80; discussion 80.
145. Baskin LS, Zderic SA, Snyder HM, Duckett JW. Primary dilated megaureter: long-term followup. *J Urol.* 1994;152(2 Pt 2):618-21.
146. McLorie GA, Jayanthi VR, Kinahan TJ, Khoury AE, Churchill BM. A modified extravesical technique for megaureter repair. *Br J Urol.* 1994;74(6):715-9.
147. Mollard P, Foray P, De Godoy JL, Valignat C. Management of primary obstructive megaureter without reflux in neonates. *Eur Urol.* 1993;24(4):505-10.
148. Gill DG, Mendes de Costa B, Cameron JS, Joseph MC, Ogg CS, Chantler C. Analysis of 100 children with severe and persistent hypertension. *Arch Dis Child.* 1976;51(12):951-6.
149. Deal JE, Snell MF, Barratt TM, Dillon MJ. Renovascular disease in childhood. *J Pediatr.* 1992;121(3):378-84.
150. Wyszynska T, Cichocka E, Wieteska-Klimczak A, Jobs K, Januszewicz P. A single pediatric center experience with 1025 children with hypertension. *Acta Paediatr.* 1992;81(3):244-6.
151. Shroff R, Roebuck DJ, Gordon I, Davies R, Stephens S, Marks S, et al. Angioplasty for renovascular hypertension in children: 20-year experience. *Pediatrics.* 2006;118(1):268-75.
152. Tullus K, Brennan E. Blood pressure charts in UK children. *Arch Dis Child.* 2007;92(11):1045-6.
153. Vo NJ, Hammelman BD, Racadio JM, Strife CF, Johnson ND, Racadio JM. Anatomic distribution of renal artery stenosis in children: implications for imaging. *Pediatr Radiol.* 2006;36(10):1032-6.
154. Rosen PR, Treves S, Ingelfinger J. Hypertension in children. Increased efficacy of technetium Tc 99m succimer in screening for renal disease. *Am J Dis Child.* 1985;139(2):173-7.
155. Geyskes GG, Oei HY, Faber JA. Renography: prediction of blood pressure after dilatation of renal artery stenosis. *Nephron.* 1986;44 Suppl 1:54-9.
156. Geyskes GG, Oei HY, Puylaert CB, Dorhout Mees EJ. Renography with captopril. Changes in a patient with hypertension and unilateral renal artery stenosis. *Arch Intern Med.* 1986;146(9):1705-8.

157. Siegel MJ, St Amour TE, Siegel BA. Imaging techniques in the evaluation of pediatric hypertension. *Pediatr Nephrol*. 1987;1(1):76-88.
158. Tullus K, Brennan E, Hamilton G, Lord R, McLaren CA, Marks SD, et al. Renovascular hypertension in children. *Lancet*. 2008;371(9622):1453-63.
159. Abdulsamea S, Anderson P, Biassoni L, Brennan E, McLaren CA, Marks SD, et al. Pre- and postcaptopril renal scintigraphy as a screening test for renovascular hypertension in children. *Pediatr Nephrol*. 2010;25(2):317-22.
160. Ng CS, de Bruyn R, Gordon I. The investigation of renovascular hypertension in children: the accuracy of radio-isotopes in detecting renovascular disease. *Nucl Med Commun*. 1997;18(11):1017-28.
161. Minty I, Lythgoe MF, Gordon I. Hypertension in paediatrics: can pre- and post-captopril technetium-99m dimercaptosuccinic acid renal scans exclude renovascular disease? *Eur J Nucl Med*. 1993;20(8):699-702.
162. Cheung WS, Wong KN, Wong YC, Ma KM. Segmental renal artery stenosis diagnosed with captopril renography in a child. *Pediatr Radiol*. 2004;34(8):636-9.
163. Flynn JT, Tullus K. Severe hypertension in children and adolescents: pathophysiology and treatment. *Pediatr Nephrol*. 2009;24(6):1101-12.
164. Piscitelli A, Galiano R, Piccolo V, Concolino D, Strisciuglio P. Successful management of neonatal renal venous thrombosis. *Pediatr Int*. 2014;56(5):e65-7.
165. Stapleton FB. Idiopathic hypercalciuria: association with isolated hematuria and risk for urolithiasis in children. The Southwest Pediatric Nephrology Study Group. *Kidney Int*. 1990;37(2):807-11.
166. Dwyer ME, Krambeck AE, Bergstralh EJ, Milliner DS, Lieske JC, Rule AD. Temporal trends in incidence of kidney stones among children: a 25-year population based study. *J Urol*. 2012;188(1):247-52.
167. Routh JC, Graham DA, Nelson CP. Epidemiological trends in pediatric urolithiasis at United States freestanding pediatric hospitals. *J Urol*. 2010;184(3):1100-4.
168. Hoppe B, Kemper MJ. Diagnostic examination of the child with urolithiasis or nephrocalcinosis. *Pediatr Nephrol*. 2010;25(3):403-13.
169. Spivacow FR, Negri AL, del Valle EE, Calvino I, Fradinger E, Zanchetta JR. Metabolic risk factors in children with kidney stone disease. *Pediatr Nephrol*. 2008;23(7):1129-33.
170. Coward RJ, Peters CJ, Duffy PG, Corry D, Kellett MJ, Choong S, et al. Epidemiology of paediatric renal stone disease in the UK. *Arch Dis Child*. 2003;88(11):962-5.
171. Riccabona M, Avni FE, Blickman JG, Dacher JN, Darge K, Lobo ML, et al. Imaging recommendations in paediatric uro-radiology. Minutes of the ESPR uro-radiology task force session on childhood obstructive uropathy, high-grade fetal hydronephrosis, childhood haematuria, and urolithiasis in childhood. ESPR Annual Congress, Edinburgh, UK, June 2008. *Pediatr Radiol*. 2009;39(8):891-8.
172. Passerotti C, Chow JS, Silva A, Schoettler CL, Rosoklija I, Perez-Rossello J, et al. Ultrasound versus computerized tomography for evaluating urolithiasis. *J Urol*. 2009;182(4 Suppl):1829-34.
173. Glassberg KI, Braren V, Duckett JW, Jacobs EC, King LR, Lebowitz RL, et al. Suggested terminology for duplex systems, ectopic ureters and ureterocele. *J Urol*. 1984;132(6):1153-4.
174. Ben-Ami T, Gayer G, Hertz M, Lotan D, Boichis H. The natural history of reflux in the lower pole of duplicated collecting systems: a controlled study. *Pediatr Radiol*. 1989;19(5):308-10.

175. Bisset GS, 3rd, Strife JL. The duplex collecting system in girls with urinary tract infection: prevalence and significance. *AJR Am J Roentgenol.* 1987;148(3):497-500.
176. Claudon M, Ben-Sira L, Lebowitz RL. Lower pole reflux in children: urologic appearances and pitfalls. *AJR Am J Roentgenol.* 1999;172(3):795-801.
177. Evans WP, Resnick MI. Horseshoe kidney and urolithiasis. *J Urol.* 1981;125(5):620-1.
178. Dewan PA, Goh DW. A study of the radiological anatomy of the multicystic kidney. *Pediatric Surgery International.* 1994;9(5):368-72.
179. Aslam M, Watson AR, Trent, Anglia MSG. Unilateral multicystic dysplastic kidney: long term outcomes. *Arch Dis Child.* 2006;91(10):820-3.
180. Homsy YL, Anderson JH, Oudjhane K, Russo P. Wilms tumor and multicystic dysplastic kidney disease. *The Journal of urology.* 1997;158(6):2256-60.
181. Cambio AJ, Evans CP, Kurzrock EA. Non-surgical management of multicystic dysplastic kidney. *BJU international.* 2008;101(7):804-8.
182. Staskin DR, Dmochowski RR. Future studies of overactive bladder: the need for standardization. *Urology.* 2002;60(5 Suppl 1):90-3.
183. Norgaard JP, van Gool JD, Hjalmas K, Djurhuus JC, Hellstrom AL. Standardization and definitions in lower urinary tract dysfunction in children. *International Children's Continence Society. Br J Urol.* 1998;81 Suppl 3:1-16.
184. Goepel M, Kregge S, Portgys P, Rubben H. [Urological diagnosis in children with myelomeningocele]. *Urologe A.* 1999;38(1):10-3.
185. Ozkan KU, Bauer SB, Khoshbin S, Borer JG. Neurogenic bladder dysfunction after sacrococcygeal teratoma resection. *J Urol.* 2006;175(1):292-6; discussion 6.
186. Koh CJ, DeFilippo RE, Borer JG, Khoshbin S, Bauer SB. Bladder and external urethral sphincter function after prenatal closure of myelomeningocele. *J Urol.* 2006;176(5):2232-6.
187. Stanescu AL, Hryhorczuk AL, Chang PT, Lee EY, Phillips GS. Pediatric Abdominal Organ Transplantation: Current Indications, Techniques, and Imaging Findings. *Radiol Clin North Am.* 2016;54(2):281-302.
188. Son H, Heiba S, Kostakoglu L, Machac J. Extraperitoneal urine leak after renal transplantation: the role of radionuclide imaging and the value of accompanying SPECT/CT - a case report. *BMC Med Imaging.* 2010;10:23.
189. Smith MA, Seibel NL, Altekruse SF, Ries LA, Melbert DL, O'Leary M, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. *J Clin Oncol.* 2010;28(15):2625-34.
190. Faria P, Beckwith JB, Mishra K, Zuppan C, Weeks DA, Breslow N, et al. Focal versus diffuse anaplasia in Wilms tumor--new definitions with prognostic significance: a report from the National Wilms Tumor Study Group. *Am J Surg Pathol.* 1996;20(8):909-20.
191. Hamilton TE, Shamberger RC. Wilms tumor: recent advances in clinical care and biology. *Semin Pediatr Surg.* 2012;21(1):15-20.
192. Hossain AM, Shulkin BL, Gelfand MJ, Bashir H, Daw NC, Sharp SE, et al. FDG positron emission tomography/computed tomography studies of Wilms' tumor. *European journal of nuclear medicine and molecular imaging.* 2010;37(7):1300-8.
193. Begent J, Sebire NJ, Levitt G, Brock P, Jones KP, Ell P, et al. Pilot study of F(18)-Fluorodeoxyglucose Positron Emission Tomography/computerised tomography in Wilms' tumour: correlation with conventional imaging, pathology and immunohistochemistry. *Eur J Cancer.* 2011;47(3):389-96.

194. Misch D, Steffen IG, Schonberger S, Voelker T, Furth C, Stover B, et al. Use of positron emission tomography for staging, preoperative response assessment and posttherapeutic evaluation in children with Wilms tumour. *Eur J Nucl Med Mol Imaging*. 2008;35(9):1642-50.
195. Qin Z, Tang Y, Wang H, Cai W, Fu H, Li J, et al. Use of 18F-FDG-PET-CT for Assessment of Response to Neoadjuvant Chemotherapy in Children With Wilms Tumor. *J Pediatr Hematol Oncol*. 2015;37(5):396-401.
196. Casey DL, Wexler LH, Fox JJ, Dharmarajan KV, Schoder H, Price AN, et al. Predicting outcome in patients with rhabdomyosarcoma: role of [(18)f]fluorodeoxyglucose positron emission tomography. *Int J Radiat Oncol Biol Phys*. 2014;90(5):1136-42.
197. Walter F, Czernin J, Hall T, Allen-Auerbach M, Walter MA, Dunkelmann S, et al. Is there a need for dedicated bone imaging in addition to 18F-FDG PET/CT imaging in pediatric sarcoma patients? *J Pediatr Hematol Oncol*. 2012;34(2):131-6.
198. Franzius C, Sciuk J, Daldrop-Link HE, Jurgens H, Schober O. FDG-PET for detection of osseous metastases from malignant primary bone tumours: comparison with bone scintigraphy. *Eur J Nucl Med*. 2000;27(9):1305-11.
199. Volker T, Denecke T, Steffen I, Misch D, Schonberger S, Plotkin M, et al. Positron emission tomography for staging of pediatric sarcoma patients: results of a prospective multicenter trial. *J Clin Oncol*. 2007;25(34):5435-41.
200. Wharam MD, Meza J, Anderson J, Breneman JC, Donaldson SS, Fitzgerald TJ, et al. Failure pattern and factors predictive of local failure in rhabdomyosarcoma: a report of group III patients on the third Intergroup Rhabdomyosarcoma Study. *J Clin Oncol*. 2004;22(10):1902-8.
201. Federico SM, Spunt SL, Krasin MJ, Billup CA, Wu J, Shulkin B, et al. Comparison of PET-CT and conventional imaging in staging pediatric rhabdomyosarcoma. *Pediatr Blood Cancer*. 2013;60(7):1128-34.
202. Eugene T, Corradini N, Carlier T, Dupas B, Leux C, Bodet-Milin C. (1)(8)F-FDG-PET/CT in initial staging and assessment of early response to chemotherapy of pediatric rhabdomyosarcomas. *Nucl Med Commun*. 2012;33(10):1089-95.
203. Baum SH, Fruhwald M, Rahbar K, Wessling J, Schober O, Weckesser M. Contribution of PET/CT to prediction of outcome in children and young adults with rhabdomyosarcoma. *J Nucl Med*. 2011;52(10):1535-40.
204. Brenner W, Conrad EU, Eary JF. FDG PET imaging for grading and prediction of outcome in chondrosarcoma patients. *Eur J Nucl Med Mol Imaging*. 2004;31(2):189-95.