AUDIT OF PAEDIATRIC RENOGRAMS PERFORMED AT THE CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Yetunde Ajoke Onimode

A research report submitted to the Faculty of the Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Medicine in the branch of Nuclear Medicine.

Johannesburg 2011

Declaration

I, Yetunde Ajoke Onimode, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Nuclear medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

10th day of November 2011

Dedication

To those who believed in me, they cheered me onwards

To those who didn't, they spurred me forward nevertheless

Abstract

Paediatric Nuclear Medicine is associated with a high preponderance of nephro-urological investigations. This preponderance has been attributed to the relatively higher occurrence of urinary tract infections and their sequelae in children, as well as to improved antenatal detection of anomalies of the genitor-urinary tract. Nuclear Medicine is involved in the management of these children to assist with diagnosis, clinical decision-making and follow-up of global and relative renal function. As such, these scans need to be carried out as efficiently as possible.

International protocols established by the European and American societies of Nuclear Medicine have been formulated to aid the Nuclear Medicine technologist and physician in performing these procedures and interpreting them correctly.

Audits of Nuclear Medicine practice are performed in order to assess compliance with these guidelines. A clinical audit has been defined as "a systematic and critical analysis of the quality of medical care, including procedures for diagnosis and treatment."

An audit of the renal paediatric procedures carried out in the Division of Nuclear Medicine at the Charlotte Maxeke Johannesburg Academic Hospital was performed retrospectively on studies carried out from January 2006 - December 2009, as well as a prospective study of procedures from February – July 2010. Results showed overall conformity to most of the recommended practices of the EANM guidelines. As occurs in most institutions, each institution may adapt guidelines to comply with local circumstances.

Acknowledgements

The author would like to appreciate the immense contribution of the following individuals toward the realization of this project;

- God Almighty, my constant Source of strength
- The Onimodes, my perpetual cheering team, who have withstood all the storms and drama of my medical training
- My Uncle; Dr BN Olorunfemi
- Prof B.O.A. Osifo
- Dr F Osaisai
- Prof A.O. Ilesanmi
- Prof MDTWH Vangu, my supervisor, for his patience and dedication to research and all things academic
- Prof Mike Mann for his invaluable counsel and willingness to teach at all times
- Dr Elena Libhaber, faculty statistician, for being available at short notice to perform statistical analysis

Table of Contents

List of tables

List of abbreviations

- ACE: Angiotensin converting enzyme
- ADPKD: Autosomal dominant polycystic kidney disease
- ARPKD: Autosomal recessive polycystic kidney disease
- CAKUT: Congenital Acquired Kidney and Urinary Tract abnormalities
- CME : Continuing Medical Education
- DMSA: Dimercaptosuccinic acid
- DRF: Differential renal function
- DTPA: Diethylenetriaminepentaacetic acid
- EANM: European Association of Nuclear Medicine
- ECF: Extracellular fluid
- EDTA: Ethylenediaminetriacetic acid
- ERPF: Effective renal plasma flow
- GFR: Glomerular filtration rate
- IRC: Indirect radionuclide cystography
- IVI: intravenous injection
- LEAP: Low-energy all-purpose collimator

- LEHR: Low-energy high-resolution collimator
- MAG3: mercaptoacetyltriglycine
- MCKD: Multicystic kidney disease
- MCUG: Micturating cystourethrogram
- NORA: Normalized residual activity
- OIH: Ortho-iodohippuric acid
- PAH: Para-amino hippuric acid
- PUJ: Pelvi-ureteric junction
- ROI: Region of interest
- TAC: Time-activity curve
- VUJ: Vesico-ureteric junction
- VUR: Vesico-uretric reflux

Chapter 1: Introduction

1.1 Renal embryology

The urogenital membrane is the first indicator of the development of the urinary system. It develops in the embryo from the intermediate layer of mesoderm. This layer lies along the dorsal wall of the embryo and is carried forward ventrally when embryonic folding occurs. Thereafter mesodermal elevations termed urogenital ridges appear on either side of the dorsal aorta. The part of the urogenital ridge that is the primordium for the urinary system (kidneys, ureters, bladder and urethra) is termed the nephrogenic ridge.[1-2]

Initially, three sets of kidneys develop. The initial kidneys (pronephroi) degenerate while their ducts persist. Remnants of the second set of kidneys (mesophroi) form parts of the male reproductive system. Definitive kidneys (metanephroi) appear in the 5th week of intrauterine life. They develop from the ureteric bud and the metanephric mass of intermediate mesoderm.[1-2]

The ureteric bud is the primordium of the collecting system; it develops as an outgrowth from the mesonephric duct. It derivatives constitute the renal collecting system.[1-2]Nephrons are derived from the metanephric mass of mesoderm. Uriniferous tubules (draining urine) form; they comprise nephrons and collecting tubules. Nephron formation continues until birth. At term, each kidney has 800 000 – 1 000 000 nephrons.[1-2]

Renal function begins in the 9th week of life, and urine production continues throughout life. The fetal kidney has a lobulated appearance that disappears during infancy due to growth of nephrons.

The kidneys ascend from the pelvis into the abdomen between the 6th and 9th weeks of life due to caudal lengthening of the embryo. Contact with adrenal glands signifies the termination of renal ascent. In addition, the kidneys undergo medial rotation of almost 90°. Furthermore, there is a change of blood supply from arteries in the vicinity, from the common iliac arteries to the abdominal aorta.[2]

Glomerular filtration begins in the 9th week of life. The normal range of glomerular filtration is 5-12 ml/min/1.73 m^2.[3] Adult levels of glomerular filtration are achieved by the 2nd year of postnatal life.

1.2 Brief renal anatomy

The kidneys are bean-shaped, reddish-brown organs measuring 10 x 5 x 2.5 cm. Each is located between vertebral levels T12-L3. A thin renal fascia covers each kidney, underneath which is a thin renal capsule. Each kidney has a pelvis and a hilum. The hilum is the medial opening that leads to the renal sinus. The renal sinus is the space in the kidney through which blood vessels, nerves and ureters enter and leave the kidneys. The renal pelvis is the funnel-shaped proximal part of the ureter. A cut section of the kidneys shows a division into a medulla and a relatively thinner cortex. Triangular renal pyramids are seen, which empty into renal papillae at their tips. The papillae in turn empty into minor calyces. There are two to three major calyces per kidney, each of which receives drainage from two to three minor calyces.[4]

Looking at the histology of the kidneys, one can notice on cut section that each kidney comprises a paler outer cortex and a reddish medulla. The cortex is better vascularized than the medulla, receiving 90% of renal blood supply. Hence, the medulla is more susceptible to ischaemia than the cortex. Cortical tissue extends between pyramids as columns of Bertin. The functional unit of the kidney is the nephron. Each nephron comprises a renal corpuscle and a tubule. The glomerulus is a tuft of capillaries enclosed in a cup-like structure (Bowman's capsule) at the proximal end of each nephron. It continues distally as the renal tubule. As each kidney has a million nephrons, it follows that each has a million glomeruli.[5]

Ureters are expansile, muscular, tubular retroperitoneal structures about 25-30cm long that drain urine from the renal pelvis into the urinary bladder. Peristaltic contractions move urine down into the bladder at intervals of 12-20 seconds. Each ureter enters the urinary bladder at an oblique angle that forms a one-way valve-like mechanism. Both ureteric orifices are enclosed by loops of

detrusor muscle in the wall of the bladder; as the bladder is fills with urine, increased intravesical pressure causes the intravesical part of the ureters to collapse. A physiologic sphincter is also created by vesical contraction during micturition.[4]

Renal blood supply follows lobar divisions and subdivisions. Renal arteries originate from the abdominal aorta at the vertebral level of L1. Each artery divides into five segmental arteries at the hilum. The anterior branch gives off the superior segmental/lobar artery which supplies the apex, the anterior superior and anterior inferior arteries supply the anterior superior and anterior inferior segments, while the inferior segmental artery supplies the inferior segment. The posterior branch of the artery continues as the posterior segmental artery that supplies the posterior segment of the kidney. Segmental arteries give rise to interlobar arteries which continue around pyramids as arcuate arteries. Arcuate arteries divide to form the interlobular arteries that culminate in the glomerular arterioles. Each afferent arteriole divides into many capillaries which form a glomerulus. Post-glomerular capillaries merge to form the efferent glomerular arterioles. These in turn break up into the peritubular capillaries and then drain into the interlobular veins, lobular veins and finally form the renal veins. Glomerular capillaries are thus unique in being the only capillaries that drain into arterioles. Renal veins are tributaries of the inferior vena cava, which receives them also at the level of L1. The veins lie anterior to the arteries.[4,6]

For cortical nephrons, capillaries draining their tubules form a peritubular network as above. In juxtamedullary glomeruli, efferent glomerular arterioles form both peritubular capillaries as well as vasa recta; the latter are capillaries that form loops into the medullary pyramids alongside the loops of Henle. Ascending vasa recta are fenestrated, in keeping with their solute-conserving function. Descending vasa recta are non-fenestrated and possess a urea transporter that aids their capacity as urea-excreters. The total surface area of renal tubules is approximately $12m^2$.[4,6]

1.3 Renal pathology

The scope of renal pathology covered includes abnormalities of renal morphology and function, as well as infection. A third of fetal abnormalities detected by prenatal ultrasonography are due to congenital anomalies of the kidney and urinary tract.[7] Up to 10% of pregnancy terminations are due to fatal renal anomalies.[8] Congenital anomalies of the urinary tract are also the main cause of childhood end-stage renal disease especially in males; renal dysplasia and obstructive uropathy are the principal culprits in North America and Europe.[9,10,11]

1.3.1 Congenital abnormalities of morphology

Regarding live births, 3-4% of neonates are born with *structural* abnormalities of the kidneys and the ureters. The commonest renal disorders are those of shape and position.[2] Examples of such are renal agenesis (unilateral and bilateral), ectopic kidneys, and multicystic kidneys. Others are anomalies of number and rotation such as duplex and horseshoe kidneys.

a. Renal agenesis may be unilateral or bilateral. It occurs due to the failure of development of the ureteric bud, or its degeneration, or failure of the ureteric bud to penetrate the mass of intermediate mesoderm. Bilateral agenesis of the kidneys is a fatal abnormality which is incompatible with life. It is a component of Potter sequence (renal agenesis, anuria, oligohydramnios, and hypoplastic lungs). Its main presentation *in utero* is of unexplainable oligohydramnios. Fortunately, it is rarer than the unilateral type (1:3000-1:10000 births vs. 1:1000-1:1500, respectively.) Unilateral renal agenesis results in compensatory hypertrophy of the one functioning kidney, which is usually the left kidney. This kidney is then at risk of renal failure later in life. It is frequently discovered incidental finding whilst investigating the patient for other

pathology. The presence of a single umbilical artery should alert the clinician to the presence of this anomaly.[1-2]

b. Ectopic kidneys result from complete/partial failed "ascent" of the kidneys. Ectopic kidneys derive their blood supply from adjacent blood vessels. The commonest variety is the pelvic kidney, with the kidney lying just above the pelvic brim or within the pelvis. Patients are prone to urinary obstruction of their ureters and thus to repeated episodes of urinary tract infections. Ectopic kidneys are also associated with disorders of fusion as kidneys come into contact during their development:

i. Pelvic kidneys may fuse together to form a "pancake" kidney.

ii. Crossed renal ectopia refers to the condition in which the ectopic kidney crosses to the other side of the abdomen and fuses with its other normal counterpart.

iii. "Helicopter ascent" describes the ascent of the normal kidney whilst bearing the other ectopic kidney fused to it.

iv. The horseshoe kidney refers to the fusion of the medial poles of two kidneys; usually the lower poles are affected. Normal ascent of the kidneys is obstructed by the bridge of connected tissue catching in the root of the inferior mesenteric aorta. A relatively common anomaly, it is found in 1:500-1:600 people. Impedance of urinary drainage may lead to obstruction and then to infections.[1-2]

c. Renal hypoplasia refers to renal underdevelopment, which is usually unilateral. The affected kidney has a reduced number of pyramids and lobes. No scarring is present, thus distinguishing it from a secondarily atrophic kidney.[12]

d. Multicystic dysplastic kidney disease (MCKD) is a relatively common non-hereditary renal disorder mostly subsequent to urinary tract obstruction during development of the kidneys. MCKD was previously ascribed to failure of the ureteric bud to attach to tubules from the metanephric mass of intermediate mesoderm.[1, 12] However, an opposing view is that its cysts are "wide dilations of parts of otherwise continuous nephrons, especially those in the loops of Henle."[13] The affected kidney has cysts of various sizes and the ureter is atretic. A male predominance exists, as well as a propensity for involution of the kidney. However, larger kidneys might not.[3]

e. Congenital polycystic kidney disease: There are two types; the autosomal dominant variety (ADPKD) and its autosomal recessive variant (ARPKD). ADPKD is the commoner of the two, occurring in 1:400-500 to 1 000-4000 births. Cysts are formed from all parts of the nephron. Other pathologies associated with the disease are polycystic liver disease (40%), cerebral berry aneurysms (10-20%) as well as mitral valve prolapse (20-25%). It pursues a more benign course than ARPKD; renal failure usually does not set in until the patient is an adult. ARPKD has a worse prognosis; patients develop renal failure whilst still infants or in their childhood. Presentation may be perinatal, neonatal, infantile, or juvenile. Cysts are formed from the collecting ducts, causing renal enlargement. Polycystic liver disease is almost always present; as such, children may develop congenital hepatic fibrosis in infantile and juvenile ARPKD.[1,12]

f. Malrotation of the kidneys may complicate their development, with abnormal rotation causing the hilum to face posterior, lateral or anterior.[2]

g. Duplex kidneys: These may be accompanied by duplex ureters which may drain separately into the bladder, or may fuse together before draining into it. The upper moiety of the kidney is prone to obstruction, while its lower moiety is prone to vesicoureteric reflux.[2]

h. Posterior urethral valves (PUV) result in congenital damage from long-standing high-pressure obstructive uropathy which occurs *in utero*. Postnatally, renal damage occurs following UTIs, obstructive uropathy and transmitted pressure from the lower to the upper urinary tract.[14]

1.3.2 Functional uropathy

The incidence of *functional* foetal uropathy, as revealed by routine ultrasonography, ranges from 1:154 in the UK to 1:1200 in Sweden, and is purportedly influenced by differences in detection and intervention. Upper urinary tract obstruction accounts for 40-60% of all clinically significant antenatally detected uropathy. A study of prenatally detected uropathy in 426 live births identified pelviureteric junction (PUJ) obstruction as the commonest anomaly (35%), followed by vesicoureteric reflux (VUR, 19.5%) and MCKD (15%), respectively. Infants with PUJ obstruction accounted for up to 35% of referrals to the author's urology unit.[8]

Unilateral or bilateral hydronephrosis is a feature of 1:100-200 pregnancies.[15] Hydronephrosis refers to pathological dilatation of the renal pelvis, while hydroureter refers to pathological ureteric dilatation. An anteroposterior renal pelvic diameter of 10mm is accepted as the upper limit for normal kidneys. However, a more holistic approach involving the incorporation of other aspects of renal ultrasonography has been recommended when assessing kidneys for hydronephrosis.[8] Furthermore, a more conservative approach has been adopted over the years in the management of moderate hydronephrosis. Such an approach has been validated because spontaneous resolution occurs in most cases, and needless pyeloplasty is avoided.[14] Vesicoureteric junction (VUJ) obstruction also tends to run a benign course of spontaneous resolution. In a study of 40 megaureters managed conservatively for almost 7 years, Shukla et al[16] showed that 21 of

these had complete resolution of pathology, while 19 showed some improvement or remained stable.

1.3.3 Urinary tract infections (UTIs) are defined as infections of the kidneys, the bladder, or of both. Up to 5% of children suffer from UTIs, with the highest incidence in the first year of life.[12] The commonest causative organism is *E.coli*. Most patients who are at high-risk for UTIs have abnormalities of the urinary tract. [17]

1.3.4 Renal scarring is associated with underlying blunted, deformed or dilated calyces, and is caused by reflux nephropathy or chronic obstruction. It has been cited as an aetiological factor in up to 10-20% of patients with chronic renal failure.[10,12]

1.3.5 Vesicoureteric reflux (VUR) occurs due to the failure of the valve mechanism of the ureterovesical junction[18], which normally would close passively with bladder filling in order to prevent reflux of urine into the ureters. Some evidence suggests that a deficiency of the ureterovesical junction is contributory.[19,20] An incidence of 1-3% has been quoted in the paediatric population, 80% of whom fortunately tend to outgrow it, and by the age of two or three years, 40-60% of cases of congenital reflux would have resolved.[21,22] Resolution is commoner in the lower grades of reflux.[23] Reflux-associated dilatation of the urinary system and that which causes PUJ obstruction are more likely to cause parenchymal damage.[24] Fortunately most cases of VUR are said to be non-dilating in nature.

A school of thought opines that it is the reflux of *infected* urine that produces the subsequent renal damage. Therefore, it is important to detect VUR early enough in order to prevent the development of renal scarring and other complications.[25,26] On the other hand, other opinions differ as to the origin of renal scarring as being pyelonephritic in nature.[27,28] The detection of VUR

on a micturating cystourethrogram (MCUG) was not predictive of renal damage on a Tc-99m DMSA scan performed later on. Likewise, renal damage often occurred in hospitalized children with UTI without its being demonstrated on MCUG. As such, the authors hold that VUR is not essential for the development of renal damage in children with UTIs.

Reflux nephropathy may be congenital in origin, acquired, or may be experienced as a combination of both aetiologies. Congenital reflux nephropathy results in ipsilateral hypoplasia or renal dysplasia, while acquired reflux is a component of chronic pyelonephritis and results in renal scarring.[8] Fortunately, as has been mentioned, congenital reflux resolves spontaneously in most infants. Reflux-induced renal damage, in turn, may result in complications such as hypertension, pre-eclampsia and renal failure. Acquired reflux nephropathy is a sequel of pyelonephritis.[10]

Chapter 2: Brief renal physiology

The main function of the kidney is the regulation of homeostasis of ECF as it forms urine. It is also involved in the regulation of acid-base balance, calcium metabolism, erythropoietin production as well as the excretion of waste products of metabolic processes.

2.1 Glomerular function

Urine formation involves glomerular filtration and tubular secretion/reabsorption. The glomerular filtration rate (GFR) is defined as the volume of plasma cleared of a certain substance, x, over a certain period of time. The formula is given below:

$$GFR = U_x \times V / P_x$$

where: U_x = urine concentration of substance

V= rate of urine flow in ml/min

P_x= plasma concentration of substance x

The normal GFR in an adult man is approximately 125 ml/min/1.73m^2. The normal volume of urine produced daily is approximately 1.5 litres; thus of 180 litres of glomerular filtrate generated daily, 99% of it is conserved by the kidneys.[6]

2.1.1 Factors affecting glomerular filtration

a. Substances eligible for glomerular filtration should first of all possess the following characteristics; molecular size ≤ 8nm, molecular charge (cations > neutral molecules > anions), and should exhibit minimal/no protein-binding.

b. Factors affecting glomerular filtration are similar to those that affect capillary filtration elsewhere in the body. They are: hydrostatic and osmotic pressures across the walls of the capillaries, size of the glomerular capillary bed, permeability of glomerular capillaries and the filtration coefficient. Each of these factors will now be examined in turn.

i. Hydrostatic capillary pressure: This denotes pressure in the glomerular capillary that forces fluid across the capillary wall into Bowman's space. This pressure is opposed by hydrostatic pressure in Bowman's capsule, which attempts to push fluid out of Bowman's capsule into the glomerular capillary. It is also opposed by the osmotic gradient across the wall of the capillary which attempts to pull and retain fluid in the glomerular capillary.

ii. Osmotic capillary pressure refers to the oncotic force generated by plasma proteins that attracts fluid into the capillary by osmosis. Osmotic pressure in the capillary increases from the arteriolar to the venular end as fluid is reabsorbed into the capillary. In Bowman's capsule this force is essentially non-existent, because usually plasma proteins are not retained in glomerular filtrate.

iii. Size of glomerular capillary bed: A reduction in the size of the capillary bed reduces the rate of filtration, as the surface area available for filtration is reduced.

iv. Permeability of glomerular capillaries: Capillary permeability is increased in inflammatory conditions such as glomerulonephritis, and reduced in pathologies which thicken the wall of the glomerular membrane, such as hypertensive and diabetic nephropathy.

v. The filtration coefficient, κ_f, represents the product of the surface area of available capillaries for filtration and the permeability of the glomerular capillary wall. Changes in the filtration coefficient would also affect GFR secondary to changes in capillary permeability and the filtration area.[29]

The formula for calculating GFR incorporates these factors as follows:

$$GFR = \kappa_f \{(H_{GC} - H_{BC}) - (O_{GC})\}^{29}$$

2.1.2 Agents for measurement of GFR

a. Inulin: Previously, inulin was regarded as the gold standard for determining GFR owing to its favourable characteristics; solely excreted by glomerular filtration, neither reabsorbed nor secreted by renal tubules, not influencing GFR, not metabolized by the body. However, GFR measurement with inulin is labourious, requiring a loading dose followed by constant infusion of the substance (330mg/min). Inulin is also no longer available in certain regions of the world.

b. Serum urea: Serum urea is another clinical indicator of glomerular function. It underestimates GFR owing to falsely elevated levels following its reabsorption.

c. Serum creatinine: Its clearance overestimates GFR.[29] It produces errors in estimated clearance as high as 10-15%.[30] Creatinine is secreted by renal tubules, and it may also be reabsorbed.[6] It is not very sensitive to nephron loss; values may remain normal with nephron loss as high as 50%.

c. Cr-51 EDTA: Because of its similarity to inulin, Cr-51 ethylenediaminetetraacetic acid (EDTA) has been validated as an excellent substitute.[30]

d. Tc-99m DTPA: Its measurement also gives satisfactory GFR measurements in clinical practice. Although the latter exhibits lower (5% difference) GFR results than for Cr-51 EDTA, it has the advantage of possessing favourable energy characteristics such that dynamic scintigraphy can be performed. Then, when relative renal function is derived from the Tc-99m DTPA renogram, split GFR can in turn be calculated from the absolute values of GFR.[30]

2.2 Renal tubular function

Following glomerular filtration, substances filtered into peritubular capillaries undergo secretion into tubules, reabsorption into tubules or both. Thus, the net amount of the substance that is excreted is the sum of the amount filtered by the glomerulus and the amount secreted by the tubules, excluding that reabsorbed by the tubules.

2.2.1 Tubular function along the nephron

The different parts of the renal tubule perform different functions, but all work in synchrony to complete the process of urine formation.[6,29]

a. The proximal convoluted tubule: About 65% of sodium, and secondarily, fluid, chloride, glucose and amino acids, is reabsorbed in this portion of the tubule (PCT). Active reabsorption of sodium is performed by the basolateral Na^+/K^+-ATPase. Water is passively absorbed as it flows into the tubular cells along the osmotic gradient created by the reabsorption of sodium. Fifty percent of urea in tubular fluid is also absorbed. Thus, tubular fluid in the PCT becomes increasingly hypertonic as it reabsorbs salt and water. Sodium transport also operates as a symporter for glucose, galactose, amino acids and inorganic phosphate. Antiporters for potassium and hydrogen ions also exist.[6,29]

b. The descending limb of the loop of Henle: Tubular fluid entering the descending limb of the loop of Henle becomes progressively more concentrated as water is reabsorbed (20%).[6,29]

c. The ascending limb of the loop of Henle: A further 30% of sodium ions are absorbed in this part of the renal tubule. A symporter for sodium/potassium/chloride is present that extrudes the ions from the tubular lumen across the cells of the tubules into peritubular capillaries. This symporter also transports calcium and magnesium anions along with sodium ions. The Na^+/K^+-ATPase pump is also present here. Water is reabsorbed as it flows into tubular cells along osmotic gradients; tubular fluid thus becomes increasingly hypo-osmolar.[6,29]

d. The distal tubule: Here, 5-10% of sodium is actively reabsorbed along with chloride ions by the Na^+/Cl^+ symporter.

e. The collecting tubule: Its proximal two-thirds of the distal convoluted tubule are impermeable to water, while the later third is permeable under the influence of antidiuretic hormone (ADH). Antidiuretic hormone, also known as vasopressin, is secreted from the posterior pituitary gland.

2.2.2 The counter-current mechanism

This mechanism takes place in juxtaglomerular nephrons in the medulla. Blood in the vasa recta (straight peritubular capillaries) contains venous blood on its way back into the general circulation. Blood in the descending part of the peritubular capillary becomes increasingly hyperosmolar due to diffusion of electrolytes into it from the ascending limb of the loop of Henle. As noted above, this part of the tubule in its turn becomes progressively hypo-osmolar. In the same manner, as

blood in the ascending part of the peritubular capillary passes by the descending limb of the loop of Henle, water is reabsorbed by this capillary and so blood within it increasingly becomes hypo-osmolar.

2.2.3 Measurement of tubular clearance

Tubular clearance denotes the volume of plasma cleared of a certain substance over a given period of time. The formula is the same as for glomerular clearance. Tubular clearance is best measured by substances wholly excreted by renal tubular secretion, which are highly protein-bound, not reabsorbed, and also not toxic to the body. These substances should not influence the rate of tubular clearance. Para-aminohippuric acid (PAH) is the ideal agent. When this substance, which is solely cleared by tubular secretion, is assayed in venous blood, it yields the effective renal plasma flow (ERPF) in ml/min. The adjective "effective" makes allowance for the fact that venous, rather than arterial measurements were performed. ERPF as measured by PAH is 800 ml/min. Other agents which have been used are I-131 ortho-iodohippuric acid (OIH) which gives a smaller value of 600 ml/min, while Tc-99m MAG3 yields gives an even smaller value of 340 ml/min.

Chapter 3: Paediatric renal nuclear medicine

The practice of nuclear paediatric renography is an established one, including dynamic studies such as the diuretic renogram, indirect radionuclide cystography (IRC), transplant renography and the ACE-inhibitor renography, as well as static imaging of renal morphology (renal cortical scintigraphy), and scrotal scintigraphy to detect testicular torsion. Direct radionuclide cystography (DRC) is the other option to the indirect radionuclide cystogram, but it is not as popular on account of the need for bladder catheterization. GFR can also be determined.

In the paediatric age group, most procedures in the average Nuclear Medicine department are of the urinary tract (50-60%), while in the general pool such procedures constitute only about 5%. This relative preponderance of renal and urological Nuclear Medicine investigations in children has been credited to the high frequency of urinary tract infections (UTIs) in childhood, the subsequent complication of UTIs by VUR in about 30% of patients, and the need to monitor such children for the development of further sequelae. The higher pick-up rate of antenatal nephro-urological abnormalities has also been quoted as contributory, as Nuclear Medicine assists the clinician in evaluating urological function from early infancy, and in monitoring impaired function, and/or the results of medical and surgical intervention.[31]

Nuclear Medicine studies have the advantages of using radionuclides in sub-physiologic doses, giving relatively less radiation doses (< 1 mSv)[32] to the patient when compared to their radiologic counterparts, such as fluoroscopic voiding cystourethrogram (VCUG), with the average absorbed dose to skin and midplane in under-fives reported as 0.66 and 2.37 mGy, respectively, while the absorbed dose to the bladder from radionuclide cystography in the same children 0.3 mGy. [33]

Another study[34] compares absorbed doses to the ovaries and reports higher doses from VCUG: 2.52 – 10 mGy in neonates to 15-year-olds, respectively, and from radionuclide cystography (with Tc-99m pertechnetate) as 0.04 – 0.05 mGy.

These studies also provide reproducible and sensitive physiologic assessment, without side-effects, are usually free from allergic reactions, and being generally non-invasive.[35] Approximately 6 adverse reactions are experienced in every 100 000 radiopharmaceuticals administered.[36] The study will focus on the paediatric diuretic renogram, indirect cystography and cortical scintigraphy.

3.1 Renal radiopharmacy

The ideal agent for depicting renal function should be handled exclusively by the kidneys, have no effect on renal metabolism, be non-toxic and possess good imaging characteristics. Protein-binding is desirable in agents assessing tubular function whilst glomerularly-cleared agents should be neither secreted nor reabsorbed and thus should not be protein-bound. Currently, the radiotracer that best fits this description is Tc-99m MAG3.

3.1.1. Tc-99m MAG3

Mercaptoacetyltriglycine or mercaptoacetylylglycylgycylglycine (MAG3) labeled with Tc-99m is the agent of choice for performing paediatric renography.[37] While it is excreted mainly by tubular secretion (80%), about 2-5%[38,39] of the injected dose also undergoes glomerular filtration. A significant proportion (90%) of injected dose is protein-bound. Blood clearance is rapid and biphasic, with initial and later half-lives of 3 and 17 minutes, respectively. By 30 minutes post-injection, 73% of dose has been excreted, and 94% by 3 hours. Hepatobiliary excretion is an alternative route for Tc-99m MAG3; normally 2%, this value is elevated in the presence of renal dysfunction. Initially radiolabelled by boiling, newer kits are now simpler to prepare, requiring only

mixing and incubation with Tc-99m pertechnetate. A photosensitive radiopharmaceutical agent, it should be stored in the dark until its use is required. It has the advantage of better uptake in the immature paediatric renal system in children less than 2 years of age, because it is retained intravascularly due to its high-protein binding. It is administered in doses of 5-10 mCi (185-370 MBq) scaled to body surface area. It has got a long shelf-life of more than 6 months.[37,40]

Compared to radiolabelled I-131 OIH, Tc-99m MAG3 has a smaller distribution pool than OIH as the former is not distributed into red blood cells. Thus, it has a greater renal excretion (78% vs. 68% at 30 minutes). The critical organ for Tc-99m MAG3 is the urinary bladder; radiation dose is reduced by frequent voiding.

3.1.2. Tc-99m DTPA

Radiolabelled pentasodium or calcium trisodium diethylenetriaminepentaacetic acid (DTPA) is excreted solely via glomerular filtration. The addition of calcium to the preparation is to reduce the risk of DTPA chelation of calcium. However, the risk of this happening is unlikely, as sub-physiological doses of DTPA are used. The precaution assumes greater importance when DTPA is to be used for cerebrospinal fluid imaging. Protein-binding is minimal and variable depending on the kit used (up to 5-10%). Its binding to red blood cells is minimal. The radiotracer is rapidly cleared from plasma in the presence of good glomerular function; peak renal activity (5% of injected dose in each kidney) is reached 3 minutes after tracer injection.[41] The radiotracer then diffuses into extracellular fluid, after which renal uptake and excretion occur. The plasma half-life of Tc-99m DTPA is 70 min. Approximately 90% of the injected dose is excreted within 24 hours; an initial 69% is excreted with a biologic half-life is 1.73 hours, while the remainder is excreted with a biologic half-life of 9.23 hours. Its low extraction ratio (20%) results in a poor target-to-background

ratio especially in patients with poor renal function.[42,43] The critical organ that receives the largest radiation dose is also the urinary bladder; the effective dose ranges from 0.024-0.0027 mSv/MBq in neonates to 15-year-olds one hour post-void.[32] Another source[44] states that a five-year old child would receive an effective dose of 0.54 – 0.82 mSv (lower value representing the dose at one hour after bladder void).

3.1.3. Tc-99m DMSA

Dimercaptosuccinic acid (DMSA) was initially developed for the treatment of heavy metal poisoning. As a radiotracer, it localizes by cortical fixation in the proximal renal tubules following direct uptake from peritubular vessels and is an indicator of functional cortical renal mass.[45,46,47] Up to 90% of the injected dose is protein-bound by 24 hours, initially and at 6 hours after injection, this figure is lower (60%). Rapid plasma clearance occurs within 10 minutes of injection. In all, blood clearance is tri-exponential: 44% has a biologic half-life of 20 minutes, another 44%, 50 minutes and the remaining 12%, 18 hours.[46] Twelve percent of the injected dose is retained by the kidneys at 1 hour post-injection. In all, up to 44% of the radiotracer localizes in the kidneys. The half-time for renal uptake is one hour. Even higher figures of cortical binding have been reported.[46,47] The precise mechanism of tubular uptake is as yet unclear.

Yee et al[48] assessed factors influencing renal uptake of Tc-9m DMSA in rats. In particular, they were interested in the effect of acidosis, alkalosis, dehydration, osmotic diuresis, and infarction as these scenarios were often present in the patients referred for renal procedures. Uptake was markedly reduced in rats with acidosis (61.8% less than in control kidneys), and less so in alkalotic rats (20.6% less than in control kidneys). There was a tendency toward decreased uptake in dehydrated rats and in those which had received osmotic diuretics; however, this was not

statistically significant. Reduced renal uptake was associated with increased background and hepatic activity. They also observed adequate uptake of radiotracer despite the presence of reduced GFR, renal uptake in functioning tissue remaining adequate. Being highly protein-bound, it would be expected that Tc-99m DMSA would not be cleared by glomerular filtration. Rather, it should be retained in tubular fluid. Its uptake in the kidneys is not affected by inhibitors of tubular secretion, such as probenecid, which inhibits Tc-99m MAG3 uptake.[25]

Tc-99m DMSA is prepared by addition of Tc-99m pertechnetate to the stannous-DMSA kit and incubating. Radiolabelling of DMSA occurs in two steps. In the first step, Tc-99m pertechnetate and a stannous ion-DMSA complex combine to form an initial complex I. The second step is less rapid; it is also the rate-determining step. Here, complex I is converted to complex II. Complex II has the higher protein-binding and renal uptake of the two. Highest yields of complex II occur in the absence of oxygen at an acidic pH of 2.5. Complex II may revert to complex I by oxidation. The radiotracer should thus be used within 30 minutes of preparation as it is very sensitive to air oxidation. Complex I is the undesirable form because it is readily excreted by the kidneys, and thus yields poor renal uptake. It should also be shielded from light as it is photo-sensitive. The prepared solution should not be refrigerated as this may cause it to precipitate. It is worth noting that the oxidation state of Tc-99m DMSA to be used for cortical renal imaging is 3+, the pentavalent form of DMSA is used as a tumour imaging agent. The critical organ for Tc-99m DMSA is the kidney itself, specifically the cortex. The radiation dose per kidney from an average dose of 5 mCi (185 MBq) is 3-3.5 rad. Renal radiation dose decreases with worsening renal function, as renal uptake would likewise diminish.[49]

3.2. Diuretic renography in children

The renogram is indicated :

a. To derive differential renal function

b. To differentiate dilated non-obstructed kidneys from dilated obstructed ones

c. To evaluate efficacy of corrective surgery e.g. placement of stent in obstructed renal systems

d. Prior to indirect radionuclide cystography

e. Evaluation of renovascular hypertension

f. Baseline and follow-up assessment of function of renal transplants

Patient preparation requires adequate hydration. In infants this infers breastfeeding, in older children an initial 200ml of 0.9% normal saline followed by an infusion of 15ml/kg body weight for the duration of the study is one suggestion. Otherwise, the child may have the equivalent of this fluid orally.[50]

Renography is a dynamic scintigraphic study monitoring radiopharmaceutical arrival, uptake and transit through the kidneys. The renogram is a graphical description of this process on a time-activity curve. There are three phases to the renogram: perfusion, uptake and excretory phases. There is an initial set of dynamic frames of perfusion acquired over 1 minute. This is the upslope, the steep part of the renogram curve. The remaining 30-40 minutes of the study show uptake and excretion of the radiotracer. Uptake of radiotracer is assessed at the point of equilibrium, where maximal tracer uptake has occurred prior to its excretion. On the renogram, this is the peak of the

curve. For Tc-99m DTPA, this occurs at 3-5 minutes, and at 2-3 minutes for Tc-99m MAG3. After this period, uptake cannot be accurately assessed as tracer excretion would have set in. Normally, less than 10% of the injected dose should be left at the end of the study. Excretion on the renogram is seen as a swiftly falling curve over time.

The addition of a diuretic to renography improves specificity in distinguishing functional obstruction from anatomical obstruction. Dynamic imaging should continue for at least 20 minutes post-diuretic injection for the effect of the latter to be adequately assessed. The rapid diuresis thus elicited increases urinary flow past the site of suspected obstruction.[50] This is especially important in the dilated upper urinary tract, to differentiate between functional and anatomical obstruction. The former would display improved drainage following the furosemide challenge, while the latter exhibits progressive accumulation of radiotracer. Moreover, it can be used to assess the effects of corrective surgical intervention.[51]

In children, furosemide has a variable effect, and it may take up to 15 minutes before its effect is evident. Also furosemide would produce suboptimal/no diuresis in malfunctioning kidneys; in such instances obstruction cannot then be excluded if drainage of radiotracer is poor. Intravenous injection of furosemide (1mg/kg body weight) may be made before, simultaneously or after radiotracer injection. These are the F-15 (15 minutes before), F0 (simultaneous) and F+20 (20 minutes after) protocols. The first two protocols are indicated in patients in whom the reservoir effect is anticipated; that is, massively dilated collecting systems which would require a longer period of observation for the effect of injected diuretic and radiotracer washout to be seen. It should be noted that comparison of two diuretic renograms which were performed using different protocols of diuretic injection is not feasible.[52]

With normal renal perfusion the kidneys should be visualized within 4-6 seconds of appearance of the abdominal aorta. Renal uptake is seen as uniform concentration of radiotracer in symmetrical, normal-sized kidneys, with no areas of parenchymal loss or cortical amputation. Tc-99m MAG3 has been described as yielding almost as much information about functioning cortical mass as Tc-99m DMSA. As such, it may also detect cortical scars or parenchymal defects, on the uptake image. Gordon et al[53] investigated the role of Tc-99m MAG3 in detecting parenchymal defects; a sensitivity and specificity of 88 % was demonstrated. They also found a close correlation between differential renal function derived using both agents. Thus they concluded that as well as providing differential renal function, Tc-99m MAG3 imaging also has a high probability of detecting focal parenchymal defects. However, Piepsz et al[54] refuted this claim in a different study which showed that Tc-99m MAG3 scintigraphy missed half of the less pronounced lesions seen on Tc-99m DMSA scans, while corresponding with the Tc-99m DMSA results in normal or markedly abnormal kidneys.

Renal transit time is the period between radiotracer injection and peak renal activity; its normal value is 3-5 minutes. Prolonged values are seen in acute vasomotor nephropathy, renovascular hypertension and obstruction.

3.2.1 Renogram analysis

Dynamic images are assessed frame by frame as well as on the ciné display; the latter is a looped display of the dynamic images. Visual assessment of renal perfusion, radiotracer uptake and its excretion is performed. Thereafter, the study is processed using either the integral method or the Rutland-Patlak plot. The integral method utilizes cumulative uptake in the area under the time-activity curve, whilst the Rutland-Patlak plot measures the mean slope of the uptake phase of the

renogram curve. The calculation in the latter involves the division of background-corrected renal counts by cardiac counts. The results are then plotted as a function of the integral of cardiac counts divided by cardiac counts.

The most important information obtained from the renogram is the differential renal function, to approximate contribution of each kidney to global renal function, the normal value of which is 45-55% per kidney. Split renal function is calculated utilizing the relative uptake of radiotracer by each kidney after having performed background subtraction. The 1-2 minute image of the renogram is used, at this period, excretion is yet to begin. When used in conjunction with absolute GFR values, split or differential GFR can then be derived. Accordingly, regions of interest (ROIs) are drawn manually or automatically around the kidneys. Background regions of interest are also created to correct for activity in the structures overlying the kidneys. These may be elliptical and perirenal or crescenteric ones drawn above and below each kidney. Care must be taken in drawing these regions of interest as inaccurate values of falsely high or falsely low renal function may be obtained from incorrectly drawn ROIs. When processing for differential renal function, ROIs should be drawn around parenchyma to exclude activity in the collecting systems. But when one is assessing excretion of tracer, the ROIs should also include the collecting systems. In children, care must be taken for these ROIs not to extend beyond the body, else under-subtraction of background activity is the result. Blood pool ROIs are used in the integral method of renogram analysis described above.

Post-micturition images are important parts of the study. Voiding removes the “reservoir effect” exerted by a full bladder which impedes renal drainage. Residual renal activity on the post-void images is expected to be negligible. Urinary retention in the bladder could be causative of

patient's presentation e.g. recurrent UTIs and VUR. Residual renal activity post-void expressed as a percentage of the 2-minute activity is termed the normalized residual activity or the NORA.[52]

3.2.2. Parametric indices of renal function

Quantitative parameters are also useful when assessing the renogram.

a. T_{max} is the time taken for peak renal uptake of radiotracer to occur. Normal values are 3-5 minutes. A prolonged T_{max} denotes impaired drainage from radiotracer retention in pelvi-calyceal collecting system.

b. The T-1/2 is the time taken for 50% of peak renal activity to clear from the kidneys. Normal values are less than 12 minutes. While some authorities deem T-1/2 that exceeds 20 minutes as denoting obstruction, dissenting voices regard the value as inconclusive, preferring rather to monitor differential renal function and defining obstruction as previously described above.

c. T20/3[55] represents the ratio of activity in the kidney at the end of the study (20 minutes) compared to that in the kidney initially at 3 minutes.

d. Output efficiency[56] may be defined as the radioactivity which was cleared by the kidney by a certain time period compared to the total amount of radioactivity that had entered the kidney. It is calculated by initially adjusting the early part of the renogram to the integral of the cardiac curve, and then by subtracting the renal curve from the integral of the cardiac curve.

e. "NORA" [52] normalized residual activity, is another parameter coined to evaluate residual renal activity at the end of the renogram as compared to renal uptake of activity 2minutes after injection of radiotracer.

3.3 Indirect radionuclide cystography

Indirect radionuclide cystography (IRC) is a procedure performed to detect vesicoureteric reflux. The patient micturates at the end of usual renogram procedure once the bladder is filled. The child is instructed not to void until positioned sitting (girls) or standing (boys) in front of the collimator and empties his or her bladder; meanwhile images of the kidneys, ureters and bladder are acquired until the child has completed void. IRC can also be started before the end of the renogram in those instances where the child exhibits a strong desire to void and can no longer control the urge to do so. It is obvious then, that this study is only suitable for toilet-trained children (about ages 2 years old and upwards). Images are reviewed visually and semi-quantitatively in order to detect episodes of reflux.[21] Reflux is reported if renal images and time-activity curves concur in demonstrating an increase in activity; this is followed by a subsequent secondary increase in bladder activity. Milder levels of reflux reaching the ureters but not the kidneys may also be detected. More episodes of reflux can be detected if the study is repeated with residual bladder activity.[57] The assessment of residual bladder urine volumes post-void is also important, as inability to fully empty the bladder results in residual urine, which may result in colonization of urine and ascending infection.[22,58,59] Studies to evaluate IRC have been validated.

As reflux is an intermittent phenomenon, it is understood that a negative study does not exclude it. In the presence of a high clinical index of suspicion, the study can be repeated. IRC can detect refluxate as little as 1 ml.[21] The main advantage of IRC is its non-invasive nature; it is a

physiological alternative to the voiding cystourethrogram which involves catheterization. In addition, performing the IRC also means that the child automatically gets a standard renogram as well. In children with repeated urinary tract infections, IRC helps confirm vesicoureteric reflux (VUR), which may be the cause of patient's symptoms and has also been cited as a causative factor in renal scarring. However, this connotation has been disputed in that not all children with demonstrable reflux have infections. Nor do all patients with demonstrable VUR have renal scarring on Tc-99m DMSA scans, and vice versa. This will be discussed in greater detail in the section on renal cortical scintigraphy.

3.4 Direct radionuclide cystography

The micturating cystourethrogram (MCUG) involves bladder catheterization, contrast instillation and voiding while fluoroscopic images are acquired. Direct radionuclide cystography, (DRC), which was first described by Winter[60] in 1956, also involves bladder catheterization and bladder filling with radiotracer. The procedure has since evolved after having been modified by Willi and Treves[61] to that in which children are catheterized using sterile feeding tubes. Tc-99m sulphur colloid, which is not absorbed by the urinary tract, is then instilled via the tubing into the bladder. An initial acquisition of 15-second frames was performed during bladder filling, followed by a subsequent 5-second set of images during voiding of radiolabelled urine. Frame rate of acquisition was altered for the second set of images in order to increase sensitivity for reflux. Visual assessment of images was carried out; vesicoureteric reflux was judged to have occurred if radiotracer was seen refluxing into the (upper) ureter. Reflux may be demonstrated during bladder filling, bladder emptying or both. Both these latter two studies have a risk of introducing infection as well as the traumatic experience of catheterization as mentioned above. A study of DRC in children also by Willi and Treves[62] revealed an incidence of filling phase-only reflux in 3% of

direct cystograms. Thus, differences among micturating cystourethrogram (MCUG), DRC and IRC are as follow. MCUG and DRC evaluate both bladder filling and emptying, while IRC assesses bladder emptying only.[26] IRC also detects mainly renal reflux while the other two modalities detect renal and ureteric reflux. Grading of vesicoureteric reflux on the indirect cystography is more limited as less anatomic detail is available than from the MCUG. However, it would be difficult to miss the grosser volumes of reflux with this modality.[21]Direct radionuclide cystography, which is the radionuclide alternative to MCUG, gives a much lower radiation dose than MCUG; so also IRC has an associated radiation dose which is even smaller than that from DRC.[26,63] The radiation dose to the child from IRC has been quoted as being less than that from MCUG by a factor of 20. Both direct and indirect methods of radionuclide cystography lack the adequate spatial resolution to allow the assessment of anatomy of the bladder or urethra. Anatomic evaluation is best left to the MCUG, which also grades reflux severity with the greatest accuracy.[64]

Several studies have compared direct and indirect scintigraphic methods of cystography. The reference point for most of these studies was MCUG. Handmaker et al[65] found that in 8 kidneys, MCUG had a sensitivity of 100% while IRC missed reflux in one kidney. A few years later, Bower et al[66] studied 54 kidneys and detected 6 cases of reflux missed by IRC but positive on DRC, as well as 5 cases of reflux detected by IRC but not by DRC. Likewise, Chapman et al[67] studied 85 kidneys for VUR. Nineteen percent of cases of reflux detected by MRC were not seen on IRC, and 20% of those seen on IRC were not visualized on DRC. Furthermore, IRC detected more cases of severe reflux than MCUG.

Khriesat et al[68] studied 45 children aged 5 months to 10 years, who underwent MCUG, Tc-99m sulphur colloid DRC and Tc-99m DTPA IRC. The time interval between the scintigraphic examinations was an average of 30.4 hours, and between radiographic and nuclear medicine scans

was 2-12 months. Not unexpectedly, 4 patients aged less than 2 years were unable to void on command. Comparing the IRC to the DRC while retaining the latter as the standard for comparison, IRC had a sensitivity of 62% and a specificity of 82% for reflux. They concluded that DRC was the preferred replacement for MCUG in their practice, in order to accommodate non-toilet-trained children.

Thus, in the bid to detect VUR at the lowest radiation dose to the vulnerable paediatric population, IRC is an excellent option in children more than 5 years old.

3.5 Renal cortical scintigraphy

This is static imaging performed to assess cortical functioning renal tissue. It is carried out using Tc-99m dimercaptosuccinic acid (DMSA), which has been validated as the gold standard agent for the detection of renal scarring.[69] It is usually administered in doses of 2-5 mCi (74-185 MBq) scaled to the body surface area. Delayed imaging at 2-3 hours post-injection is performed to allow for background clearance.[46] Maximal uptake has been quoted as occurring 6-9 hours following tracer injection. The child is placed as close to the detector as possible. He/she may be placed on the collimator. Posterior and posterior oblique views are acquired as well as anterior projections in order to help compute the geometric mean per kidney (which corrects for differences in kidney depth) and thus derive differential renal function.

A normal scan shows uptake in the relatively thinner cortex and diminished uptake in the renal medulla. Internal renal architecture may be visualized, depicting columns of Bertin. The intensity of activity in the columns may create an impression of photopaenic defects in adjacent tissue. This is an artifact that interpreting physicians must be aware of. The upper pole of the left kidney may also display a tapered appearance which is an artifact created by splenic impression. Triangular

kidneys are also a normal variant, as are lobulated kidneys. Non-functioning tissue appears photopaenic on the scan.

The scan is indicated for the evaluation of renal morphology for cortical scars, confirmation of non-functioning multicystic kidneys, detection of acute pyelonephritis, ectopic kidneys and renal abnormalities such as duplex kidneys. The DMSA scan is more sensitive than ultrasonography for detecting renal scars, the latter having a sensitivity of 24-40% for pyelonephritis and about 65% for scars, while DMSA has an overall sensitivity and specificity for detecting acute and chronic pathology of 88% and 85%, respectively. Its sensitivity for detecting pyelonephritis has been difficult to determine as it is itself the gold standard.[25] However, defects on the scan are non-specific for pathology, correlation with renal ultrasonography helps improve specificity. Scanning for the detection of renal scars is best done at least 6 months after the last UTI experienced by the child. This is done in order to improve the specificity of defects seen on the scan. The DMSA scan may also predict lesions which are likely to improve or resolve. "Large polar hypoactive lesions with indistinct margins without deformity of cortical outlines" are likely to heal, while those which cause volume loss/markedly deformed cortical outlines are not.[70]

It is important to identify those children at risk of developing renal damage and the sequelae of renal scarring, such as hypertension. Sixt and Stokland[24] assert that "the ultimate goal in handling children with UTI must be to prevent renal scarring and preserve renal function." It is especially important in infants, who are said to have the highest incidence of UTIs and are at the greatest risk of renal damage.[71]

Due to the fact that it has the highest renal uptake of all renal radiotracers, it has been advocated the best agent with which to assess relative functional mass. It can provide relative renal function

in the absence of ureteric obstruction.[72] Tc-99m DMSA uptake shows good correlation with GFR and creatinine clearance values.[73,74] Use of the geometric mean has been advocated, as analysis of renal function based on the posterior static view alone would yield erroneous values due to depth difference in the kidneys.[75] A retrospective study of 261 DMSA scans assessed DRF using posterior views only and using both anterior and posterior views. Results were significantly erroneous in 22% of scans (8% of children aged less than 13 years, 28% of patients 13-20 years, and 32% of patients over 20 years old). The geometric mean was seen to have adequately corrected for photon attenuation especially in malpositioned and malrotated kidneys. However, the EANM guideline for Tc-99m DMSA imaging recommends that geometric mean not be routinely utilized unless for ectopic/anteriorly displaced kidneys.[70]This may be due to the fact that children reportedly have smaller renal depths and differences in DRF using posterior views and geometric means may be less significant.[75] The scan is not advisable in the hydronephrotic kidney as its renal function would be overestimated owing to tracer accumulation in the renal pelvis. DMSA that accumulates thus would then be excreted by glomerular filtration.[31,72,76] However, with renal dysfunction the liver assumes a more significant role in the excretion of Tc-99m DMSA. An increased hepatic-to-renal uptake ratio may result in overestimation of right renal function owing to abnormally increased hepatic uptake.[48] In the study performed by Wujanto et al,[75] it was found that liver activity would have to reach 20% of renal activity for a significant (≥ 5%) difference to exist between right renal function derived from posterior views only and that derived from geometric means.

The use of SPECT imaging has come under scrutiny in view of its improved spatial resolution (<1cm as against 1.5-2 cm for planar imaging). It is said to have a greater sensitivity for the detection of renal lesions with either single-or multiple-headed SPECT.[77,78,79,80] Volume rendering also helps

detect more lesions than inspection of selected slices on SPECT. Although renal SPECT displayed an excellent sensitivity and specificity of 97% and 93% respectively in piglets, in humans these values are reduced. The introduction of SPECT increased the sensitivity but reduced specificity of cortical scintigraphy. The interpreter must beware these pitfalls.

De Sadeleer et al[81] compared findings on planar images and triple-headed SPECT images in the kidneys of 10 healthy adult volunteers. While planar images depicted normal kidneys, SPECT images showed more abnormalities. The authors also observed that SPECT slices required reorientation for correct interpretation of the scan. SPECT also depicted hypoactive upper poles in 7/20 kidneys despite reorientation, with the ratio of maximal cortical activity between upper and lower poles as high as 35%. In the remaining kidneys, this ratio was 0.83 to 1.02. Mouratidis et al[82] also performed a comparative study in 41 children with 90 kidneys altogether. Using a single-head SPECT, they refuted the claim of greater sensitivity with SPECT Tc-99m DMSA when compared to planar imaging. This was also the experience of Joseph et al.[78] A slightly greater number of lesions (24 vs. 20) were detected on SPECT than on planar imaging, although the difference was not statistically significant. Furthermore, these defects were discovered in children who had recently been treated for UTIs, therefore their significance as regarding scarring was not certain then. Another disadvantage of SPECT is the longer imaging time required, which then increases the probability that the child will be sedated in order to avoid artifacts from patient motion. Movement of the kidneys as the patient breathes may also degrade image resolution.

Chapter 4: Guidelines for paediatric renal imaging

International protocols have been formulated to *guide* good clinical practice of Nuclear medicine involving various systems of the body including the kidneys. They are meant to *support* the nuclear technologist and physician in image acquisition, analysis and interpretation of results. Individual departments may adapt these guidelines to suit the peculiarities of their environment and practice.

Such guidelines have been published by the European Association of Nuclear Medicine (EANM) and the American Society of Nuclear Medicine (SNM). O'Reilly et al [50] stated in a consensus report on renal scintigraphy that the report would:

a. Ensure standardization of protocols and help to improve reproducibility between different centres

b. Highlight and assess variations from such protocols in the interests of discouraging unacceptable standards

Chapter 5: Audits in clinical Nuclear Medicine

A medical/clinical audit may be defined as "a systematic, critical analysis of the quality of medical care, including procedures used for diagnosis and treatment…"[83] Audits of Nuclear Medicine have therefore been recommended to compare departmental practice to the guidelines provided. They serve as quality control/ assurance measures for these units.[84] Failure to comply with these protocols would be construed as malpractice or negligence, which could be particularly dangerous in the setting of Radiation Medicine, where radiation safety rules that radiation should be utilized "as low as reasonably achievable" or the so called "ALARA" principle.

This assumes, of course, that the guidelines to be used as standards are themselves constantly kept updated so as to be abreast of modern Nuclear Medicine practice.[85] Moreover, in the setting of paediatric renal scintigraphy, where many patients undergo monitoring of renal function, it is self-apparent that consistency of method and adherence to the *correct* standards is of the utmost importance. As recently as 6 years ago, it was acknowledged that discrepancies of practice still existed among doctors.[86] An even more recent publication reiterated the persistence of disparity of practice between the nuclear physician and the urologist.[87] Another such disparity is discussed in the setting of DMSA scans for the detection of renal scarring; clinicians are usually not comfortable with the wait required before the scan may be performed. This has led to additional radiation exposure in children prematurely scanned.[88] Audits of nuclear medicine software have also been performed in order to certify that the procedures used are in accordance with standard protocols.[89]

Audits can be carried out between institutions or within an establishment in comparison to set standards of practice. Clinical audits such as the one performed include peer review audits in

which previously reported scans are selected and discussed by a group of reviewers. The patient satisfaction survey is another medium of evaluating departmental performance. Care should be taken such that the personnel whose practice(s) are being examined do not feel that they are being put on the spot, but rather feel that they are on a quest for better performance. Confidentiality is also a major feature of a responsible audit.[84]

Audits are beneficial in that while they may point out discrepancies, the underlying reason for them may be unearthed (such as the type of software used). The lapses can then be rectified afterwards, thereby improving the quality of services rendered.[89]

In reviewing peer audits, factors to consider would be:

a. Patient factors such as movement, which is very important in children, as well as hydration (dehydration could mimic renal obstruction)

b. Technical factors arising from the equipment and analytic procedures used

c. Human factors involving the technologist and the reporting physician.

The nuclear physician is the last port of call before the report leaves the department, therefore the onus lies on him/her to interprete the completed study rightly, recognizing artifacts and dealing with pitfalls. It is also important for the referring physician that the report does not lose its credibility.

Chapter 6: Methods

Aim of study

The department of Nuclear Medicine at the CMJAH has promoted the use of the EANM guidelines for the practice of renal scintigraphy for many years but we wished to assess if they were always adhered to. The primary objective was to perform a renal workup (diuretic renograms, indirect radionuclide cystograms and renal cortical scans) on patients aged 0-19 years between January 2006 and December 2009. In addition a prospective audit of all diuretic renograms, indirect radionuclide cystograms and renal cortical scans was performed on all children between May and November 2010.

Objectives of the study are:

i. To assess all these studies on the basis of criteria compared to set standard guidelines

ii. To assess the impact of the human factor on image quality

iii. To disseminate information generated from the study to referring physicians as well as nuclear technologists and physicians to help improve quality of studies performed in the unit.

6.1 Study design

This is a descriptive study based on the combination of an analysis of retrospective data, as well as the prospective evaluation of studies.

6.2 Study population and sampling

a. The retrospective aspect of the study entailed data collection from archives of renal imaging at the Charlotte Maxeke Johannesburg Academic Hospital over 4 years (January 2006 – December 2009). The EANM guidelines in the form of the checklists of criteria was applied to the studies.

b. Prospectively, the imaging component of the checklist was applied to studies performed in the department over 6 months (from June – November 2010); these were checked by the radiographers performing the scans.

Renal imaging was performed according to department protocol on General Electric and Philips gamma cameras.

6.2.1 Inclusion and exclusion criteria: All renal studies done for children were included, except scans of renal transplants and ACE-inhibitor scintigraphy. Patients whose ages were not available were also not recruited.

6.3 Ethical considerations

Regarding the retrospective study involving data collation from archived records, there was no need to obtain informed consent. The prospective aspect of the study did not influence the process of accepting or declining children for studies, nor did it affect the manner in which the studies were done, because the clinical investigations were performed routinely.

6.4 Confidentiality

Patient confidentiality was protected as no names were divulged in the study; patients were identified by their initials and hospital numbers in order to avoid confusion and duplications during data analysis.

6.5 Data management and analysis

Data generated was analyzed for qualitative assessment to detect :

a. conformity to the respective EANM guidelines

b. deviations from the respective EANM guidelines.

Descriptive analysis of data was done to show the frequency distribution of variables with their percentages and proportions. The SAS software version 9.1 was used for analysis of all variables.

Chapter 7: Results

7.1 Retrospective studies

Table 7.1.1: Descriptive analysis of numeric variables of Tc-99m MAG3 diuretic renograms

Variable	Mean ± standard	Median	Range
Age (mth)	44.1 ± 44.4	30.5	0.2 - 154
Dose *Tc-99m MAG3(mCi)	1.88 ± 0.87	2	0.37 - 5
Dose *furosemide (mg)	18.29 ± 8.12	11.5	0.3 - 40
Time of furosemide (min)		20	-15 - 39

***Both Tc-99m MAG3 and furosemide were administered intravenously**

Table 7.1.2: Descriptive analysis of compliance of retrospective renograms using Tc-99m MAG3 with EANM guidelines (N = 170 studies)

EANM recommendation for diuretic renograms	Guideline compliant; N (%)	Non- guideline compliant; N (%)
Written informed consent	89 (52.35)	74 (43.53)
Tc-99m MAG3	160 (94.12)	
Straight positioning	55 (32.35)	5 (2.94)
Heart, kidneys, bladder in field of view	106 (62.35)	
Posterior acquisition	109 (64.12)	
Matrix 128 x 128	62 (36.47)	
Zoomed images (1-2 times)	58 (34.12)	
Post-micturition images	75 (44.12)	
Perirenal, elliptical or rectangular renal ROIs	113 (66.47)	
Generous renal ROIs not cutting off renal outline	90 (52.94)	10 (5.88)
Background ROIs	111 (65.29)	
ROIs on summed images		114 (67.06)
TACs generated per scan	114 (67.06)	

EANM recommendation for diuretic renograms continued	Guideline compliant; N (%)	Non- guideline compliant; N (%)
Integral analysis	115 (67.65)	
Awareness normal DRF shown	66 (38.82)	23 (13.53)
DRF compared to first-minute image	3 (1.76)	112 (65.88)
Tmax generated	111 (65.29)	
Response to furosemide evaluated	150 (88.23)	
1-minute/frame displays	65 (38.23)	4 (2.35)
% peak renal activity excretion	155 (91.18)	
Residual renal activity evaluated	3 (1.76)	110 (64.70)
Labeled timed hard copies printed	113 (66.47)	
Time furosemide injection shown on hard copies	93 (54.70)	12 (7.06)

Table 7.1.3: Descriptive analysis of numeric variables of retrospective audit of Tc-99m DMSA scans

Variable	Mean ± standard deviation	Range	Median
Age (mth)	56.03 ± 54.3	0.2 - 156	56.03
Dose Tc-99m DMSA in mCi (MBq)	2 ± 1.21 (74±44.77)	1-5 (37-185)	2 (74)

Table 7.1.4: Descriptive analysis of compliance of retrospective scintigrams using Tc-99m DMSA with EANM guidelines (N= 17 patients)

EANM recommendation for cortical scintigraphy	**Guideline compliant; N (%)**	**Non- guideline compliant; N (%)**
Written informed consent obtained	9 (52.94)	8 (47.06)
Appropriate indication	15 (88.23)	1 (5.88)
Adequate history provided	16 (94.12)	
Dose of Tc-99m DMSA 0.4 – 2.7 mCi/ 14.8-99.9 MBq	12 (70.59)	3 (17.65)
Scan performed 2-3 hours after radiotracer injection	10 (58.82)	3 (17.65)
Minimum of posterior and posterior oblique views acquired	11 (64.70)	
Straight patient positioning	10 (58.82)	2 (11.76)
Static acquisition	15 (88.23)	

EANM recommendation for cortical scintigraphy continued	Guideline compliant; N (%)	Non- guideline compliant; N (%)
Zoomed images (1-2 times)	12 (70.59)	
DRF estimated	15 (88.23)	
Generous renal ROIs	13 (76.47)	
Background correction applied	14 (82.35)	
Awareness of normal DRF exhibited	4 (23.53)	5 (29.41)
Awareness of normal variants exhibited	13 (76.47)	1 (5.88)
Awareness of abnormal patterns exhibited	13 (76.47)	
Internal architecture visualized	2 (11.76)	7 (41.18)

Indirect radionuclide cystograms: Seven children were eligible for analysis. As one would expect, children in this group were older than those who had presented for renograms and cortical scintigrams. This was because the children need to be toilet-trained in order to control the micturition urge and to be able to void on command for the study. The mean age was 77.4 ± 14.7 months compared to 44.1 ± 44.4 months and 56 ± 54.3 months for renograms and cortical scintigrams, respectively.

7.2 Prospective data analysis

Table 7.2.1: Descriptive analysis prospective audit of pediatric renograms using Tc-99m MAG3

Parameter	**Mean and standard**	**Median**	**Range**
Age (mth)	41.79 ± 29.64	48	2-112
Dose Tc-99m MAG3 (mCi)	1.25 ± 0.68	2	1-3.2
Dose furosemide (mg)	14.33 ± 5.26	15	3-20
Time furosemide (min)	13.87 ± 7.80	14	3-28

Table 7.2.2: Descriptive analysis of compliance of prospective scintigrams using Tc-99m MAG3 with EANM guidelines (N = 19 patients)

EANM recommendation for diuretic renograms	Guideline compliant; N (%)	Non- guideline compliant; N (%)
Written informed consent	13 (72.22)	5 (27.78)
Appropriate indication	18 (100)	
Hydration	13 (81.25)	1(6.25)
Tc-99m MAG3	100 (100)	
Dose Tc-99m MAG3 (0.4-2.7 mCi/14.8-99.9 MBq)	10 (83.33)	2 (16.67)
Bolus IVI administration	16 (84.21)	3 (15.79)
Extravasation checked	12 (63.16)	
Heart, kidneys, bladder in field of view	19 (100)	
Posterior view acquired	18 (94.74)	
Supine position	18 (94.74)	
Straight positioning	17 (89.47)	
Matrix 128 x 128	17 (89.47)	
Zoomed acquisition	8 (42.11)	

EANM recommendations for diuretic renograms continued	Guideline compliant; N(%)	Non-guideline compliant; N (%)
Study duration at least 20 min	19 (100)	
Post-micturition images	18 (94.74)	1 (5.26)
Perirenal/elliptical/rectangular renal ROIs	17 (89.47)	
Generous renal ROIs not cutting kidneys	15 (78.95)	1 (5.26)
Background ROIs drawn	16 (84.21)	
ROIs on summed images		16 (84.21)
Output efficiency generated		
% peak renal activity calculated	16 (84.21)	
Dose furosemide (mg/kg to maximum 20 kg)		
Timing of furosemide (min): F+20, F-15, F0.	16 (84.21)	
Response to furosemide evaluated	16 (84.21)	
1-minutes image display	17 (89.47)	
Percent excretion of peak renal value	15 (78.95)	
Assessed residual renal activity post-micturition	8 (42.11)	7 (36.84)
Labeled timed hard copies	15 (78.95)	1 (5.26)

Chapter 8: Discussion and conclusion

8.1 Discussion

The definition of clinical audit has been previously provided.[89] The goal of our audit was to perform an internal assessment of the performance of renal scintigraphy in children at the CMJAH Nuclear Medicine Department. It had been reported by Jamtvedt et al[90] that the main predictive factor in audit studies is a deviation from set standards. The results obtained from this study depict satisfactory compliance with particular elements of EANM guidelines in performing and reporting these studies. (See **Tables 7.1.2, 7.1.4, 7.2.2**)

The audit has confirmed the quality of work produced by the department. Radiographers participating in patient preparation, positioning, injection and acquisition appear adept at their tasks. However, there is the need to improve on providing patients with information about the procedure, hydration, and checking for extravasation of injection. The dose of radiopharmaceuticals for paediatric procedures has recently been reviewed.[91] Most of the doses (97.5%) administered for diuretic MAG3 renograms examined retrospectively, and all retrospective/prospective procedures were still within the recommended limits of the new guidelines.

A similar experience was found with the doctors who report the scans and reprocess images. A degree of interobserver variability is to be expected but good reproducibility has been demonstrated for the scans provided the same software and protocols were followed. While reporting, we have developed a format such that normal differential renal function might not be implicitly stated but the body of the report conveys the message as to whether the renal system(s)

are functioning well or not. Some recommendations of the EANM are also not followed in the Department, such as the processing of the renogram using summed images. Nevertheless, reports are still of good quality; they provide answers to the referring physician's clinical question, which is what all reports are intended to do.

When no written criteria are available for use in a clinical audit, it is recommended that the audit utilize expert opinion or "consensus of a relevant expert group."[83] This was the case in the Department, where paediatric renal scan protocols are based on the EANM guidelines. There are a few differences, which are permitted, as local institutions can develop standards of good practice better suited to their peculiar environments. For now, there appears to be no pressing need for South African guidelines, the EANM ones being quite adequate. As this audit has shown, satisfactory results have been achieved from their use in the Department. However, some deficiencies need to be addressed, such as need for informed written consent from all patients, hydration, and provision of hard copies which enhance the written reports. The standardization of time of diuretic administration is an extremely important one as otherwise, comparison between studies would not be possible. While allowing for those kidneys requiring the F-0 protocol, a decision needs to be made regarding all other diuretic scans as to whether the F+15 or F+20 protocols should be adhered to. The F+15 protocol is presently considered as standard of reference for all transplant renograms; perhaps that should be adopted for non-transplant renograms as well. This is because it allows enough time to observe for the unaided drainage pattern of the kidney, during which the decision to facilitate diuresis may be made. Thereafter, in a 40- or 45-minute scan, there would be adequate time to comment on the effect (if any) of the administered diuretic.

On a larger scale, different departments have their peculiar methods of performing and analyzing renograms. Referring clinicians/urologists become familiar in time with the manner in which members of their local Nuclear Medicine Departments perform and report these studies. However, a wide inter-departmental variation may indicate a need to revise the protocol for that region, which would have local nuclear physicians agreeing on salient points.

8.2 Conclusion

Clinical audits in Nuclear Medicine are a good quality control measure to help improve the timbre of services rendered by the unit. Results of such audits provide objective data with which to perform self-improvement programmes as necessary, and revision of current operating standards of practice. Especially in the field of Nuclear Medicine, which is a rapidly changing one, it is important that personnel of Nuclear Medicine departments are up-to-date with what has been termed "good Nuclear Medicine practice". Referring physicians at CMJAH, for example, appear current with the latest recommendations for the processing of these renal studies, while the proficiencies of the radiographers have been mentioned above. Regular Continuing Medical Education (CME) programmes should be organized at the convenience of each Unit; audits of the efficacy of these programmes may also be performed afterwards.

Limitations and recommendations

Missing data constituted the main drawback to the study. Also, retrospective assessment of the manner in which scans were performed e.g. patient positioning, hydration, administration of bolus injections, was not possible, or was limited to the information provided in the referral forms and patient reports.

In the prospective study, once the first few questionnaires had been administered, it was noted that most responses followed the same trend. The trend was toward the giving of ideal answers rather than actual ones. A shortage of radioactivity during the study period also limited the number of eligible scans to 19. Normally, this number would have been at least 12 times the quoted one.

In this instance, a larger prospective study of the institution and other sister departments would yield more robust data on which stronger deductions might be made. Another recommendation would be the computerization of departmental archives which would save space and facilitate future research. The latter recommendation is already in place for our PET studies and hopefully would extend to the planar and SPECT studies soon.

References

[1] Sandler TW. Urogenital system. In: *Langman's medical embryology*. 10th ed. Philadelphia; Lippincott Williams & Wilkins; 2006.

[2] Moore KL, Persaud TVN. The urogenital system. In: *The developing human*. 6th ed. Philadelphia: WB Saunders; 2008.

[3] de Bruyn R, Marks SD. Postnatal investigation of renal disease. Seminars in fetal & neonatal medicine. 2008; 13:133-141.

[4] Moore KL, Dalley AF, Agur AMR. Clinically oriented anatomy. 6th ed. Philadeplhia; Lippincott Williams & Wilkins: 2009.

[5]Young B, Lowe JS, Stevens A, Heath JW, Deakin PJ. Urinary system. In: *Wheater's functional histology: a text and colour atlas*. 4th ed. Edinburgh; Churchill-Livingstone: 2002.

[6] Ganong WF. Renal function and micturition. In: *Review of medical physiology*. 22nd ed. Boston: McGraw-Hill; 2005.

[7] Noia G, Masini L, De Santis M, Caruso A. The impact of invasive procedures on prognostic, diagnostic and therapeutic aspects of urinary tract anomalies. In: Cataldi L, Fanos V, Simeoni U, editors. Neonatal nephrology in progress. Lecce: Agora; 1996, pp 67-84.

[8] Thomas DFM. Prenatally detected uropathy: epidemiological considerations. Br J Urology 1998; 81, Suppl 2:8-12.

[9] Avner ED, Chavers B, Sullivan EK, Tejani A. Renal transplantation and chronic dialysis in children and adolescents: the 1993 annual report of the North American Paediatric Renal Transplant Co-operative Study. Pediatr Nephrol. 1995; 9:61-73.

[10] Ehrich JHH, Rizzoni G, Brunner FP, et al. Renal replacement therapy for end-stage renal failure before 2 years of age. Nephrol Dial Transplant 1993; 7:1171-1177.

[11] Parkhouse HF, Barratt TM, Dillon MJ, et al. Long-term outcome of boys with posterior urethral valves. Br J Urol. 1988; 62:59-62.

[12] Cortran RS, Kumar V, Robbins SL, editors. The kidney. In: *Robbins' pathologic basis of disease*. 8th ed. Philadelphia: Saunders Elsevier; 2010.

[13] Moffatt DB. Developmental abnormalities of the urogenital system. In: Chrisholm GD, Williams D, editors. *Scientific foundations of urology*. 2nd ed. London: Heinemann Medical; 1982.

[14] Thomas DFM. Prenatally diagnosed urinary tract abnormalities: long-term outcome. Seminars in fetal and neonatal medicine. 2008; 13:189-195.

[15] Chitty LS, Pembrey ME, Chudleigh PM, Campbell S. Multicentre study of antenatal calyceal dilation detected by ultrasound. Lancet 1990; 336:875.

[16] Shukla AR, Cooper J, Patel RP, et al. Prenatally detected primary megaureter: a role for extended follow-up. J Urol. 2005; 173:1353-1356.

[17] Hansson S, Dhamey M, Sigström O, Sixt R, Stokland E, Wennerström, Jodal U. Dimercapto-succinic acid scintigraphy instead of voiding cystourethrography for infants with urinary tract infection. J Urol. 2004; 172:1071-1074.

[18] Vlajković M, Ilić S, Bogićević M, Raijć M, Ristić M, Petronijević, et al. Radionuclide voiding patterns in children with vesicoureteric reflux. Eur J Nucl Med Mol Imaging 2003; 30:532-537.

[19] Griffiths DJ, Scholtmeijer RJ. Vesicoureteral reflux and lower urinary tract dysfunction: evidence for 2 different reflux/dysfunction complexes. J Urol. 1987; 137:240-244.

[20] Chandra M, Maddix H, McVicar M. Transient urodynamic dysfunction of infancy: relationship to urinary tract infections and ureterovesical reflux. J Urol. 1996; 155:673-677.

[21] Ziessman HA, O'Malley JP, Thrall JH, editors. *The requisites in radiology: nuclear medicine*. 3rd ed. Philadelphia: Elsevier; 2006.

[22] Hellstrøm A, Hanson E, Hansson S, Hjälmås K, Jodal U. Association between urinary symptoms at 7 years old and previous UTI. Arch Dis Child. 1991; 64: 232-234.

[23] Elder J. Prenatally diagnosed reflux: current guidelines. Dialog Paediatr Urol. 1998; 21:5.

[24] Sixt R, Stokland E. Assessment of infective urinary tract disorders. Q J Nucl Med 1998; 42:119-125.

[25] Fettich J. Direct and indirect voiding cystography. In: Piepsz A. Symposium on radionuclides in paediatric nephro-urology. Nucl Med Comm. 2003; 24:11-22.

[26] Gordon I, Peters MA, Morony S. Indirect radionuclide cystography: a sensitive technique for the detection of vesico-ureteric reflux. Pediatr Nephrol 1990; 4:604-606.

[27] Gordon I, Barkovics M, Pindoria S, et al. Primary vesicoureteric reflux as a predictor of renal damage in children hospitalized with urinary tract infection: a systemic review and meta-analysis. J Am Soc Nephrol. 2003; 14:739-744.

[28] Wheeler D, Vimalahandra D, Hodson EM, Roy LP, Smith G, Craig JC. Antibiotics and surgery for vesicoureteric reflux: a meta-analysis of randomized controlled trials. Arch Dis Child. 2003; 88:688-694.

[29] Guyton AC, Hall JE. *Textbook of medical physiology*. 9th ed. Philadelphia; WB Saunders: 1996.

[30] Campbell MG, Powers TA. Renal radionuclides and *in vitro* quantitation. In: Sandler MP, Coleman RE, Patton JA, Wackers FJ, Gottschalk A, editors. In: *Diagnostic nuclear medicine*. 4th ed. Philadelphia: Lippincott Williams-Wilkins; 2003.

[31] Piepsz A. Introduction. In: Piepsz A. Symposium on radionuclides in paediatric nephro-urology. Nucl Med Comm. 2003; 24:11-22.

[32] Smith T, Gordon I. An update of radiopharmaceuticals in children. Nucl Med Commun. 1998; 19:1023-1036.

[33] Cleveland RH, Constantinou C, Blickman JG, Jaramillo D, Webster E. Voiding cystourethrography in children: value of digital fluoroscopy in reducing radiation dose. AJR 1992; 152:137-142.

[34] Ward VL, Strauss KJ, Barnewolt CE, Zurakowski D, Venkatakrishnan V, Fahey FH, et al. Pediatric radiation exposure and effective dose reduction during voiding cystourethrography. Radiology 2008; 249:1002-1009.

[35] Beschi RJ, Dubovsky EV, Kontzen FN, et al. Genitourinary system. In: Bernier DR, Christian PE, Langhan JK, editors. *Nuclear medicine technology and techniques*. 3rd ed. St Louis; Mosby Year Book: 1994.

[36] Silberstein EB, Ryan J. The pharmacopoeia committee of the Society of Nuclear Medicine. Prevalence of adverse reactions in nuclear medicine. J Nucl Med 1996; 37:185-192.

[37] Itoh K. Tc-99m MAG3: review of pharmacokinetics, clinical application to renal diseases and quantification of renal function. Annals Nuclear Medicine 2001; 15:179-190.

[38] Sfakianakis GN, Sfakianakis E. Renal scintigraphy in infants and children. Urology 2001; 57:1167-1177.

[39] Bubeck B, Brandau W, Weber E, Kälble T, Parekh N, Georgi P. Pharmacokinetics of technetium-99m-MAG3 in humans. J Nucl Med. 1990; 31:1285-1293.

[40] Saha GB. Fundamentals of radiopharmacy. 3rd ed. Cleveland; Springer Science and Business Media: 2004.

[41] Kidney and genitourinary systems. In: Kowalsky RJ, Perry R, editors. *Radiopharmaceuticals in Nuclear Medicine practice (current practice in nuclear medicine*). Boston: Appleton & Lange; 1987.

[42] Piepsz A. Antenatal detection of pelviureteric junction stenosis: main controversies. Semin Nucl Med. 2011; 41:11-19.

[43] Al-Nahhas AA, Jafri RA, Britton KE, Solanki K, Bomanji J, Mather S, et al. Clinical experience with 99mTc-MAG3, mercaptoacetyltriglycine, and a comparison with 99mTc-DTPA. Eur J Nucl Med. 1988; 14:453-462.

[44] Gordon I, Colarinha P, Fettich J, Fischer S, Frökier J, Hahn K, et al. EANM guidelines on standard and diuretic renogram in children. Available from: http://www.eanm.org/publications/guidelines/index.php?navId=37

[45] Rossleigh MA. Renal infection. In: Ell PJ, Gambhir SS, editors. Nuclear medicine in clinical diagnosis and treatment. 3rd ed. Edinburgh: Churchill Livingstone; 2004.

[46] Arnold RW, Subramanian G, McAfee JG, et al. Comparison of Tc-99m complexes for renal imaging. J Nucl Med. 1975; 16:37.

[47] Muller-Suur R, Pingent A. Radiopharmaceuticals; their intrarenal handling and localization. In: Ell PJ, Gambhir SS, editors. Nuclear medicine in clinical diagnosis and treatment. 3rd ed. Edinburgh: Churchill Livingstone; 2004.

[48] Yee CA, Lee HB, Blaufox MD. Tc-99m DMSA renal uptake: influence of biochemical and physical factors. J Nucl Med. 1981; 22:1054-1058.

[49] Kidney and genitourinary systems. In: Kowalsky RJ, Perry R, editors. *Radiopharmaceuticals in Nuclear Medicine practice (current practice in nuclear medicine*). Boston: Appleton & Lange; 1987.

[50] O'Reilly PH, Aurell M, Britton K, Kletter K, Rosenthal L, Testa T. Consensus on diuretic renography for the investigating the dilated upper urinary tract. J Nucl Med. 1996; 37:1872-1876.

[51] O'Reilly PH, Brooman PJC, Mak S, Jones M, Pickup C, Atkinson C, Pollard AJ. The long-term results of Anderson-Haynes pyeloplasty. BJU Int. 2001; 87:1-4.

[52] Piepsz A, Tondeur M, Ham H. NORA: a simple and reliable parameter for estimating renal output with or without frusemide challenge. Nucl Med Comm. 2000; 21:317-323.

[53] Gordon I, Andersson PJ, Lythgoe MF, Orton M. Can technetium-99m-mercaptoacetyltriglycine replace technetium-99m-mercatosuccinic acid in the exclusion of a focal renal defect? J Nucl Med. 1992; 33:2090-2093.

[54] Piepsz A, Pintelon H, Verboven M, Keuppens F, Jacobs A. Replacing Tc-99m DMSA for renal imaging? Nucl Med Comm. 1992; 13:494-496.

[55] Russell CD, Japanwalla M, Khan S, Scott JW, Dubovsky EV. Techniques for measuring transit times. Eur J Nucl Med 1995; 22:1372-1378.

[56] Kuyvenhoven JD, Hamphrey RH, Piepsz A. Influence of renal function on renal output efficiency. J Nucl Med. 2002; 43:851-855.

[57] Biassoni I, Chippington S. Imaging in urinary tract infections. Semin Nucl Med. 2008; 38:56-66.

[58] Lindberg U, Bjure J, Haugstvedt S, Jodal U. Asymptomatic bacteriuria in girls. III. Relation between residual volume and recurrence. Acta Padiatr Scand. 1975;760:437-440. [Abstract]

[59] Shand DG. Nimmon CC, O'Grady F, Cattell WR. Relationship between residual urine volume and response to treatment of urinary tract infection. Lancet 1970; 760:1305-1306.

[60] Winter CC. A new test for vesicoureteral reflux: an external technique using radioisotope. J Urol. 1956; 81:105-116.

[61] Willi U, Treves S. Radionuclide voiding cystography. Urol Radiol. 1983; 5:161-175.

[62] Willi UV, Treves ST. Radionuclide voiding cystography. In: Treves ST, editor. *Paediatric nuclear medicine*. New York; Springer ; 1985.

[63] Rothwell DL, Constable AR, Albrecht M. Radionuclide cystography in the investigation of vesico-ureteric reflux in children. Lancet I 1977; 1:1072-1075.

[64] Lebowitz RL. The detection of vesico-ureteric reflux in the child. Invest Radiol. 1986; 21:519-531.

[65] Handmaker H, McRae J, Buck EG. Intravenous radionuclide voiding cystography (IRVC). Radiology 1973; 108:703-705.

[66] Bower G, Lovegrove FT, Geijsel H, van der Scaff A, Guelfi G. Comparison of direct and indirect radionuclide cystography. J Nucl Med. 1985; 26:465-468.

[67] Chapman SJ, Chantler C, Haycock GB, Maisey MN, Saxton HM. Radionuclide cystography in vesico-uretric reflux. Arch Dis Child. 1988; 63:650-651.

[68] Khriesat I, Khriesat S, Hazza S. Comparison of "direct" and "indirect" nuclear cystography in the diagnosis of vesicoureteric reflux. Saudi J Kidney Dis Transplant 2001; 12:28-31.

[69] Rossleigh MA. Renal infection. In: Ell PJ, Gambhir SS, editors. *Nuclear medicine in clinical diagnosis and treatment*. 3rd ed. Edinburgh: Churchill Livingstone; 2004.

[70] Piepsz A, Colarinha P, Gordon I, Hahn K, Olivier P, Roca I,et al. EANM guidelines on Tc-99m DMSA scintigraphy in children. Available from:

http://www.eanm.org/publications/guidelines/index.php?navId=37

[71] Piepsz A, Blaufoux MD, Gordon I, et al. Consensus report on cortical renal scintigraphy. Semin Nucl Med. 1999; 29:160-174.

[72] Bingham JB, Maisey MN. An evaluation of the use of Tc-99m dimercaptosuccinic acid (DMSA) as a static renal imaging agent. Br J Radiology 1978; 51:599-607.

[73] Daly MJ, Jones W, Rudd TG, Tremann J. Differential renal function using technetium 99m dimercaptosuccic acid (DMSA): in vitro correlation. J Nucl Med. 1979; 20:63-66.

[74] Bingham JB, Maisey MN, Joyce MR, Saxton HN. Use of 99Tcm-DMSA as a static renal imaging agent. Contrib Nephrol. 1978; 11:95-99.

[75] Wujanto R, Lawson RS, Prescott MC, Testa HJ. The importance of using anterior and posterior views in the calculation of differential renal function using Tc-99m DMSA. Br J Radiol. 1987; 60:869-872.

[76] Piepsz A. Cortical scintigraphy and urinary tract infection in children. Nephrol Dial Transplant 2002;17:560-562.

[77] Tarkington MA, Fildes RD, Levin K, et al. High-resolution single-photon emission computerized tomography (SPECT) technetium-99m-dimercaptosuccinic acid renal imaging: a state of the art technique. J Urol. 1990; 144:598-600.

[78] Joseph DB, Daniel DW, Young W, Jordon SP. Renal cortical scintigraphy and single-photon emission computerized tomography (SPECT) in the assessment of renal defects in children. J Urol. 1990; 144:595-597.

[79] Itoh K, Asano Y, Tsukamoto E. Single-photon emission computed tomography with Tc-99m dimercaptosuccinic acid in patients with upper urinary tract infection and/or vesicoureteral reflux. Ann Nucl Med. 1991; 5:29-34.

[80] Yen T, Chen W, Chang S, Liu R, Yeh S, Lin C. Technetium-99m-DMSA renal SPECT in diagnosing and monitoring acute pyelonephritis. J Nucl Med. 1996; 37:1349-1353.

[81] De Sadeleer C, Bossuyt A, Goes E, Piepsz A. Renal Tc-99m DMSA SPECT in normal volunteers. J Nucl Med. 1997; 37:1346-1349.

[82] Mouratidis B, Ash JM, Gilday DL. Comparison of planar and SPECT ^{99m}Tc DMSA scintigraphy for the detection of renal cortical defects in children. Nucl Med Comm. 1993; 14: 82-86.

[83] European Commission guideline on clinical audit. Available from:

ec.europa.eu/energy/nuclear/radiation_protection/doc/.../159.pdf

[84] Forbes E, Clarke SEM, Buxton-Thomas M, Burwood R, Nunan T, Craig J. The development of nuclear medicine audit in South Thames. Nucl Med Comm 1997; 18:693-697.

[85] Cosgriff PS. Quality assurance in renography: a review. Nucl Med Comm. 1998; 19:711-716.

[86] O'Reilly P. Quality assurance in renography: a review. Nucl Med Comm 1998; 19:711-716.

[87] Piepsz A, Gordon I, Brock A, Koff S. Roundtable on the management of renal pelvic dilatation in children. J Pediatr Urology 2009; 5:437-444.

[88] Jefferson NR, Owens EJ, Dunlop D. Audit of paediatric DMSA scanning: are we still scanning too many, too prematurely? A local experience. Nucl Med Comm. 2006; 27:305. (34th BNMS meeting: abstracts)

[89] Houston AS, Whalley DR, Skrypnuik JV, et al. UK audit and analysis of qualitative parameters obtained from gamma camera renography. Nucl Med Comm. 2001; 22:559-566.

[90] Jamtvedt G, Young JM, Kristoffersen DT, Thomson O'Brien MA, Oxman AD. Audit and feedback: effects on professional practice and health care outcomes [Update of Cochrane Database Syst Rev 2000(2):CD000259; PMID:10796520]. Cochrane Database Syst Rev 3

[91] Gelfand MJ, Parisi MT,Treves ST. Paediatric Radiopharmaceutical Administered Doses: 2010 North American Consensus Guidelines. J Nucl Med 2011; 52:318-322.