GUIDELINES FOR INDIRECT RADIONUCLIDE CYSTOGRAPHY

Isky Gordon[1], Paula Colarinha[2], Jure Fettich[3], Sibylle Fischer[4], Jörgen Frökier[5], Klaus Hahn[4], Levent Kabasakal[6], Mercedes Mitjavila[7], Pierre Olivier[8], Amy Piepsz[9], Ute Porn[4], Rune Sixt[10], Jeannette van Velzen[11].

Great Ormond Street Hospital for Children, London, UK[1]; Instituto Português de Oncologia, Lisboa, Portugal[2]; Department for Nuclear Medicine, University Medical Centre Ljubljana, Slovenia[3]; Dept of Nuclear Medicine, University of Munich, Germany[4]; Aarhus University Hospital - Skejby, Denmark[5]; Cerraphasa Tip Fakultesi, Nukleer Tip Ana Bilim Dali, Aksaray, Turkey[6]; Hospital Universitário de Getafe, Madrid, Spain[7]; CHU Nancy, France[8]; CHU St Pierre, Brussels, Belgium[9]; The Queen Silvia Children's Hospital, Göteborg, Sweden[10]; liaison person ARPES[11]

Under the Auspices of the Paediatric Committee of the European Association of Nuclear Medicine

I Purpose

The purpose of this guideline is to offer to the nuclear medicine team a framework, which could prove helpful in daily practice. This guideline contains information related to the indications, acquisition, processing and interpretation of Indirect radioisotope cystography (IRC).

The present document is inspired by the desire of the EANM and the American Society of Nuclear Medicine to have guidelines for most nuclear medicine procedures. [1] However this guideline contains information more specifically adapted to the European practice. This guideline summarises the views of the Paediatric Committee of the European Association of Nuclear Medicine.

II Background and Definition

Cystography is undertaken most commonly to detect vesico-ureteric reflux (VUR). [2,3,4,5,6,7] The generally accepted reference method is the radiological micturating cystogram (MCU) although the direct catheter isotope cystogram (DIC) is as sensitive as and has a lower radiation burden than the MCU [2]. The indirect radionuclide cystogram (IRC) offers the possibility of detecting VUR without a bladder catheter, and allows micturition to be studied under physiological conditions [8,9,10] . With MCU and DIC both the filling and micturition phases can be studied, however only the micturition phase may be studied with the IRC [11,12,13,14] . IRC may be undertaken in any child, however it is easier when the child is toilet trained i.e. over 3 years of age. The IRC is done following a dynamic renogram whenever the child wishes to void.

Detection of Reflux (VUR): Although some reports show close correlation between detection of VUR using the IRC and DIC [14] , other studies however demonstrated reflux only in the filling phase of the DIC and suggested that imaging of the micturition phase only will miss reflux in a significant number of children [15,16,17] . VUR is an intermittent phenomenon, such that, even using the same examination on different occasions, its incidence varies [18,19,20] . Evaluating any technique for the detection of VUR will remain difficult since there is no absolute reference method. Considering the reservations on the sensitivity of the IRC, there is agreement that the IRC is contributory only when positive, whereas a negative examination cannot exclude VUR.

Bladder Function: The renogram plus IRC is useful to evaluate the overall function of the kidneys, drainage from the upper tracts but also voiding under normal physiological conditions. The two clinical settings where this overall evaluation is useful are firstly in the older girl with recurrent UTIs who has a normal ultrasound and normal DMSA scan. In this setting a physiological investigation of the entire nephro-urological system may suggest voiding abnormalities such as an unstable bladder or incomplete voiding. The second clinical setting is the child with known bladder outflow pathology e.g. posterior urethral valves, where assessment of entire nephro-urological system is relevant. In children with significant retention of tracer either in the bladder or ureter post micturition it may be useful

to suggest double or even triple micturition to ensure complete drainage of the entire system.[21]

The low radiation burden and avoidance of bladder catheterisation, makes IRC a valuable technique for the detection of renal reflux and observation of physiological micturition.

III Common indications

Indications

1. Detection and follow up of VUR in children who are toilet trained [22,23,24,25]
2. Assessment of the effect of the full and empty bladder on the drainage of the dilated upper tracts. [10, 21, 26]

Contra Indications

There are no contraindications. However, children who are not toilet trained may not be able to undergo this examination.

IV Procedure

A. Information about previous examinations relevant to this procedure

The clinical history, ultrasound data and previous radionuclide imaging should be reviewed.

B. Patient Preparation

B.1 Information with appointment letter:

Full explanation of the IRC which includes the renogram and the micturition which follows should be given. This includes the need for adequate hydration plus the wait for the child to micturate after the renogram (see guidelines for Renogram).

B.2 Prior to injection:

Same as for the renogram.

B.3 Prior to Voiding:

The child should be offered drinks freely at the end of the renogram.

C. Precautions

If a dilated ureter is seen behind the bladder on Ultrasound and one wishes to detect reflux into the "megaureter" then the IRC may be inappropriate.

The presence of a low or ectopic kidney makes the detection of reflux difficult or impossible because of the relationship of the ectopic kidney to the bladder.

Over hydration or the use of a diuretic during the renogram may reduce the detection of VUR. [20,27]

Delayed drainage from the pelvis and/or ureter will make detection of reflux difficult.

D. Radiopharmaceutical

D.1 Radionuclide

^{99m}Tc

^{123}I

D.2 Pharmaceutical

MAG3 (Mercaptoacetyltriglycine)

EC (Ethylenedicysteine)

Hippuran

The tubular agents have a high clearance rate thus providing a low kidney to background ratio as well as a high bladder activity at the time of micturition. DTPA is used in some institutions.

D.3 Dose schedule

As for renogram.

D.4 Technique

At the end of the renogram, the child & parent return to the waiting area, the child is offered drinks freely and is instructed to call the technologist as soon as s/he wishes to go to the toilet. The child is then taken back to the gamma room where the camera is vertical and the child can be placed sitting on a commode (the girls) or standing (the boys) with his/her back close to the camera face. To prevent or limit movement during micturition, sitting on a commode even for boys may be helpful. If voiding is incomplete or there is activity in the upper tracts then the entire procedure should be repeated when the child wishes to void for a second time.

D.5 Radiation burden

The IRC does not give any additional radiation burden compared to the dynamic renogram, however since the child is encouraged to void, the actual radiation is less than the theoretical calculated burden [28,29].

E. Image Acquisition

E.1 Camera	Vertical at a slight angle
E.2 Collimator	Same as for renogram (General Purpose)
E.3 Patient position	Sitting or standing with back to camera
E.4 Views	Posterior

E.5 Computer acquisition set up -

Matrix:	64 x 64
Dynamic/Static:	Dynamic
Frame rate:	Maximum of 5 sec./frame. If compressed images will be generated then 1sec/frame.

Length of Acquisition: This will vary with the time it takes for the child to void. The dynamic acquisition should begin before the child starts to micturate and be continued until micturition is complete. Thirty seconds of data acquisition both before and after micturition is ideal, this allows the extent of the background noise to be evaluated as well as bladder emptying.

Measure the voided volume with each micturition.

If micturition is incomplete or if there is isotope left in the collecting system, then allow the child to return to the waiting area, offer additional drinks and repeat the entire procedure when the child wishes to void again.

F. Interventions

Nil

G. Processing

Process the renogram as per renogram protocol.

Check the remaining activity in the upper tracts at end of the renogram.

IRC - View all images in cine mode and compare these images to the activity in the kidneys at the beginning of the IRC before micturition begins. This must be done carefully with the appropriate (low) window setting.

Draw ROI over bladder and kidney regions, generate curves of all 3 ROI. Background subtraction may be useful, beware that the liver normally takes up ^{99m}Tc MAG3. A ROI over the ureteric region is not usually helpful, the images usually give sufficient information about the status of the ureter.

The voided volume of urine can be measured (volume or weight), the count difference between the pre-void and post-void bladder curve may be converted to ml thus allowing estimation of residual bladder activity as well as estimate the volume of renal reflux in ml [10].

A compressed image may be created if the data has been acquired in 1 sec./frame. This requires the entire acquisition to be divided vertically into two halves, each containing half the bladder and the right and left kidney respectively. The compressed image technique allows the entire study to be displayed as two ”histograms” with time on the X-axis, anatomy on the Y-axis and the degree of blackness representing the activity in the region.

H. Hard copy output

Images should be displayed in 5 sec/frame including micturition episode

Curves of bladder and kidneys. The renal curves must either be displayed separately from the bladder or else the bladder curve must be rescaled so as not to overshadow the kidney curves.

If the voided volume has been measured this should appear as well as the calculated volume of reflux, if this has been observed. Similarly the residual bladder volume should be calculated and reported.

If obtained, the compressed images of the bladder and each kidney may be displayed. See issues requiring further clarification.

I. Interpretation/Reporting/Pitfalls

The diagnosis of VUR is based on an increase of activity in the renal pelvis. Since there is no ”gold standard” for the diagnosis of reflux, the diagnosis of renal reflux should take all the different processing into consideration. When the images, curves and compressed image all show an increase in renal activity the confidence of a positive diagnosis of reflux is more secure. Simply to use any one parameter may lead one to over diagnose reflux especially when the images are viewed on a window with a very low threshold level. The classical appearances are on the 5 sec. images which show an increase in renal pelvic activity as the bladder starts to empty. The renal curve will also show an increase activity as bladder activity falls. However, the kidneys may be virtually empty at he beginning of the IRC and the bladder full of isotope, under these circumstances, the bladder curve may so dominate the renal curves, that the renal curves should either be displayed on their own or the bladder curve rescaled. For the same reason, viewing the images will require a different setting for the bladder than for the kidneys.

Other manifestations of VUR are when the final image of the renogram shows almost complete drainage of the tracer, yet at the beginning of the IRC the kidney contains significant amounts of tracer. If the child voids on more than one occasion, again there may be more tracer in the kidney at the start of the second void than there was at the end of the first void. Some children, especially girls have the desire to micturate, but on coming in-front of the gamma camera are unable to void. If this acquisition, without micturition shows VUR, this may be due to an unstable bladder.

In the presence of dilated upper tracts, as may be seen in boys with posterior urethral valves, the response of the upper tract to bladder emptying provides the urologist with information as to the need for double or even triple micturition to empty the entire urinary tract.

The value of the 30-second acquisition immediately prior to micturition will allow the observer to note the kidney activity before micturition and so ensure that fluctuation due to noise (especially on the curves) is not misinterpreted as VUR.

To diagnose VUR on the renal curves, the images must also show this activity. Beware of movement which force the bladder into kidney ROI and so suggest a false positive VUR which will not be seen on the images.

Other causes of an apparent increase in renal activity include movement in the anterior - posterior projection so that the kidney moves away from the gamma camera face and then may come back in contact with the camera; also because of the liver activity, in the presence of very low renal activity, noise may be the reason for the change in 'apparent' renal activity.

The pattern of bladder emptying should also be observed. The normal curve shows a rapid fall virtually to the base line, this curve is usually very steep. Abnormal patterns include step wise micturition where the child has a start-stop micturition, slow emptying with a curve falling gradually, this may be either with complete or incomplete emptying. One may also observe incomplete voiding, the significance of this increases if this has occurred on more than one micturition episode of the same IRC. Whilst none of these patterns are specific to make a particular diagnosis, they should alert the clinician to the possibility of abnormal bladder function.

J. Quality control

Movement of the child during acquisition- may not allow meaningful curves to be generated but still allows visual assessment of the renal areas for VUR.

V Issues requiring further clarification

1. Movement correction
2. Sensitivity of compressed image. Some departments consider this as a very sensitive index of VUR, however further work is required for clarification.
3. There are conflicting reports as to the sensitivity in the detection of VUR when compared to the DIC or MCU. Since the IRC only shows the micturition phase while the DIC shows both filling and micturition, one is not surprised at this discrepancy [16,17,18,19,20,30,31]. However there is agreement that if VUR is seen on the IRC, then it is present. What may be more relevant is to compare the results of DIC/MCU with IRC in the context of renal damage.
4. If there is only slight increase in renal activity and there is doubt as to whether this represents VUR, there may be no technique which can confirm or deny the VUR since VUR is in itself an intermittent condition immaterial the method used to detect it.
5. VUR on IRC can not be graded according to the 5 classical radiological grades. Some clinicians use the radiological grading of VUR to effect management, this inability of the IRC to use the radiological grading may be a drawback.

VI Concise Bibliography:

1. Mandell GA, Eggli DF, Gilday DL, Heyman S, Leonard JC, Miller JH, Nadel HR, Treves ST. Procedure guideline for radionuclide cystography in children. Society of Nuclear Medicine. J Nucl Med. 1997 Oct; 38(10): 1650-4
2. Rothwell DL, Constable AR, Albrecht M. Radionuclide cystography in the investigation of vesico-ureteric reflux in children. Lancet 1977; 1: 1072-1075.
3. Maizels M, Weiss S, Conway JJ, Firlit CF. The cystometric nuclear cystogram. J Urol. 1979 Feb; 121(2): 203-5
4. Nasrallah PF, Conway JJ, King LR, Belman AB, Weiss S. The quantitative nuclear cystogram: an aid in determining the spontaneous resolution of vesicoureteral reflux. Trans Am Assoc Genitourin Surg. 1978; 70: 52-5
5. Canivet E, Wampach H, Brandt B, Toupance O, Lavaud S, Lardennois B, Liehn JC, Chanard J Assessment of radioisotopic micturating cystography for the diagnosis of vesicoureteric reflux in renal transplant recipients with acute pyelonephritis. Nephrol Dial Transplant. 1997 Jan; 12(1): 67-70
6. Kuzmanovska D, Tasic V, Sahpazova E. Detection of vesicoureteral reflux with radionuclide cystography. Srp Arh Celok Lek. 1996; 124 Suppl 1: 78-81
7. Saraga M, Stanicic A, Markovic V.The role of direct radionuclide cystography in evaluation of vesicoureteral reflux. Scand J Urol Nephrol. 1996 Oct; 30(5): 367-71
8. Treves ST, Zurakowski D, Bauer SB, Mitchell KD, Nichols DP . Functional bladder capacity measured during radionuclide cystography in children. Radiology. 1996 Jan; 198(1): 269-72

9. Godley ML, Ransley PG, Parkhouse HF, Gordon I, Evans K, Peters AM. Quantitation of vesico-ureteral reflux by radionuclide cystography and urodynamics. Pediatr Nephrol. 1990 Sep; 4(5): 485-90
10. van der Vis Melsen MJE, Baert RJM, Rajnherc JR. 1989 Scintigraphic assessment of lower urinary tract function in children with and without outflow obstruction. Br J Urol 64: 263-269.
11. Dugal B, Nerdrum HJ. Vesicoureteric reflux at the end of renography. Clin Nucl Med. 1991 May; 16(5): 364
12. Gordon I, Peters AM, Morony S. Indirect radionuclide cystography: a sensitive technique for the detection of vesico-ureteral reflux. Pediatr Nephrol. 1990 Nov; 4(6): 604-6
13. Peters AM, Morony S, Gordon I. Indirect radionuclide cystography demonstrates reflux under physiological conditions. Clin Radiol. 1990 Jan; 41(1): 44-7
14. Gordon I. Indirect radionuclide cystography - the coming of age. Nucl Med Commun. 1989 Jul; 10(7): 457-8
15. Willi U, Treves S. Radionuclide voiding cystography. Urol Radiol. 1983; 5(3): 161-73, 175
16. De Sadeleer C, De Boe V, Keuppens F, Desprechins B, Verboven M, Piepsz A. How good is technetium-99m mercaptoacetyltriglycine indirect cystography? Eur J Nucl Med. 1994 Mar; 21(3): 223-7
17. Majd M, Kass EJ, Belman AB Radionuclide cystography in children: comparison of direct (retrograde) and indirect (intravenous) techniques. Ann Radiol Paris. 1985; 28(3-4): 322-8
18. Fettich JJ, Kenda RB. Cyclic direct radionuclide voiding cystography: increasing reliability in detecting vesicoureteral reflux in children. Pediatr Radiol. 1992; 22(5): 337-8
19. Tromholt N, Hesse B, Munck S, Veje B. Fallacy in direct cystourethrography. Clin Nucl Med. 1991 Oct; 16(10): 741-2
20. Cremin B J. Observations on vesico-ureteric reflux and intrarenal reflux. A review and survey of material. Clin Radiol 1979, 30; 607-621.
21. Dinneen MD. Duffy PG. Lythgoe MF. Ransley PG. Gordon I. Mercapto-acetyltriglycine (MAG 3) renography and indirect radionuclide cystography in posterior urethral valves. British Journal of Urology. 74(6):785-9, 1994 Dec.
22. Chapman SJ, Chantler G, Haycock GB, Maisey MN, Saxton HM Radionuclide cystography in vesicoureteric reflux. Arch Dis Child. 1988 Jun; 63(6): 650-1
23. Carlsen O, Lukman B, Nathan E. Indirect radionuclide renocystography for determination of vesico-ureteral reflux in children. Eur J Nucl Med. 1986; 12(4): 205-10
24. Rizzoni G, Perale R, Bui F, Pitter M, Pavanello L, Boscolo R, Passerini Glazel G, Macri C. Radionuclide voiding cystography in intrarenal reflux detection. Ann Radiol Paris. 1986; 29(3-4): 415-20
25. Nielsen JB, Jensen FT, Jorgensen TM, Charles P, Djurhuus JC. The diagnosis of vesico-ureteral reflux. Radiologic and nuclear medicine methods. Scand J Urol Nephrol. 1985; 19(2): 109-12
26. Padhy AK, Gopinath PG, Mitra DK, Bhatnagar V Direct radionuclide cystogram (DRCG) and urine flowmetry (UFMT) in the evaluation of patients with vesicoureteral reflux (VUR) and/or associated obstructive or neurogenic pathology of the lower urinary tract. Indian J Pediatr. 1989 Jul-Aug; 56(4): 483-92
27. Corso A, Ostinelli A, Trombetta MA. "Indirect" radioisotope cystography after the furosemide test: its diagnostic efficacy compared to "direct" study. Radiol Med Torino. 1989 Dec; 78(6): 645-8
28. Stabin MG, Gelfand MJ. Dosimetry of pediatric nuclear medicine procedures. Q J Nucl. Med. 1998; 42: 93-112
29. Smith T Gordon I. An update of radiopharmaceutical schedules in children. Nucl Med. Comm 1998; 19: 1023-1036
30. Majd M, Belman AB. Nuclear cystography in infants and children. Urol Clin North Am. 1979 Jun; 6(2): 395-407
31. Merrick MV, Uttley WS, Wild R. A comparison of two techniques of detecting vesico-ureteric reflux. Br J Radiol. 1979 Oct; 52(622): 792-5