PEDIATRIC URINARY TRACT INFECTION: IMAGING TECHNIQUES WITH SPECIAL REFERENCE TO VOIDING CYSTOURETHROGRAPHY

URINEWEG INFECTIES BIJ KINDEREN: BEELDVORMENDE TECHNIEKEN, MET SPECIALE AANDACHT VOOR MICTIECYSTO-URETHROGRAFIE

(met een samenvatting in het Nederlands)

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ABBREVIATIONS

UTI	=	urinary tract infection
UPJ	=	ureteropelvic junction
UVJ	=	ureterovesical junction
US	=	ultrasound
EU	=	excretory urogram
VCUG	=	voiding cystourethrography
VUR	=	vesicoureteral reflux
RN	=	refluxnephropathy
UD	=	urodynamics
RNC	=	radionuclide cystogram
PUV	=	posterior urethral valves

I GENERAL INTRODUCTION

General Introduction

Urinary tract infection (UTI) is the second most common infection in childhood. Large hospital-based pediatric series report an incidence of 3-5%. Dickinson prospectively determined that 1.7/1000 boys and 3.1/1000 girls annually present with a UTI. This corresponds to about 780 girls and 430 boys per million population aged 0-14 years.[1,2,3] Under age 6 years, a UTI furthermore is an indicator of an anatomic and/or functional urinary tract disorder in 35-50% of these patients. Vesicoureteral reflux (VUR) is present in 30-35% of these, but is present in 85% of children with evidence of renal scarring.[4,5] This scarring, in turn, is responsible for 20-40% of end-stage renal failure in patients under 40 years of age[6]. From these figures it can be estimated that the risk for hypertension or renal failure after a first, laboratory and clinically proven (index) UTI is about 1% for boys and 0.5% for girls.[7]

The imaging evaluation of these children has a dual purpose. On the one hand, it is intended to establish that the kidneys, bladder and urethra are normal, so that subsequent UTIs can be treated by a 10 day course of antibiotics without risking renal damage. This affords the opportunity to make sure that normal kidneys remain normal. On the other hand, appropriate imaging is intended to a) identify and grade the severity of VUR, b) to define the extent of renal scarring and to c) determine the site of obstruction, if any. This allows for minimizing renal damage.[8] Early identification of these abnormalities, the anatomic basis of which will be discussed later, thus offers the prospect of preventive medicine and sound advice to the clinician regarding antibiotic (for lower grades of VUR) or surgical (for higher grades of VUR and obstructive etiologies) therapeutic measures.[9,10]

The available imaging modalities (VCUG, EU, US, Urodynamics and Radionuclides) all have different capabilities and limitations and should not be used indiscriminately as some employ ionizing radiation, others are invasive, uncomfortable and expensive.[7,9] (table I.I).

Table 1.1. Comparison of imaging methods and imaging objectives in UTI

1 = excellent, 2 = average, 3 = poor

	Hydronephrosis	Reflux Nephropathy	Reflux
Ultrasound (US)	1	2	3
Excretory urography (EU)	1	1	3
Cystourethrography (VCUG)	3	3	1
^{99m}Tc-DTPA	2	2	2
^{99m}TC-DMSA	3	1	3

The order in which to use two or more of these modalities effectively without the need for repeating either the study or already garnered information is a subject of much debate in the literature and formed the basis for this treatise.

a. The VCUG is the most frequently used method to show VUR and evaluate bladder anatomy and function. However, a catheter needs to be inserted into the bladder, which can be uncomfortable, may cause infection and can be frightening for children. Gonadal and bone marrow irradiation is unavoidable. This is cause for its avoidance in, for instance, Britain, while many in the USA minimize these concerns if the study is standardized and closely monitored.[9,11]

b. The EU is capable of providing useful information about the entire urinary tract except the urethra. It is universally available and relatively easy to perform. Tomography to better visualize the renal contours used to be employed. There is more exposure to ionizing radiation than a VCUG, especially if tomography is used and it carries the risk of allergic reaction to the intravenously administered contrast material. Finally it is dependent on intact renal function. It does identify

scarring with a high degree of accuracy laterally, less so on the anterior or posterior renal surface. As to its place in the imaging sequence, it is considered to be the gold standard by many[12]. However, Leonidas et al[13] feel that a 1 film examination is as diagnostic as a multi film study and can be sufficient. In Britain the EU is used interchangeably with a radionuclide study and is tomography routinely employed[14], while in the U.S.A. this is not the standard.

c. US is well suited for anatomic evaluation of the upper tract; to a lesser degree the bladder. It is extremely operator dependent and cannot reliably demonstrate the presence or absence of VUR[15,16,17]. There is no evidence for adverse effects. Some[17,18,19] advocate using US as the initial screening modality and perform a VCUG or EU only if abnormal. They accept the risk of missing low grades of VUR. Others are less definite[16,17].

d. Urodynamic investigation has recently shed some light on pressure/flow relationships in patients with UTI[21-23]. This suggests that a grading system for VUR and/or obstruction based on static images only may not be sufficient and in fact urodynamics may be more predictive in identifying those at risk for recurrent UTI's[21-23]. It is invasive, but does not employ radiation and is available only in specialized children's hospitals.

e. Radionuclide studies of bladder and kidneys are much less specific but, especially regarding VUR, much more sensitive than conventional imaging methods. Their radiation dose is 5-10% of VCUG and EU respectively, while no allergic reactions are known[14]. Their primary use is as follow-up in UTI patients after antibiotic or surgical treatment for VUR.[24,25] They will therefore not play on important role in this treatise.

The task for the imager is thus to decide what combination of modalities is most diagnostic and efficient in the use of radiation, time and money. This has been the source of some controversy.[7,9,16,26]
As there is a direct causal relationship between VUR and scarring, it would seem that the VCUG is definitely necessary in the work-up, contrary to especially British thinking[17].
To evaluate this, we studied 389 consecutive patients who presented with an index UTI with VCUG, an EU and US.[27] After 122 of these, the literature published two studies showing that for anatomic information the EU and the US were equally diagnostic, which was then confirmed

in our group. Subsequently, we modified our approach: after an initial VCUG patients with VUR had an EU; those without an US. This study addressed how many US examinations could be avoided by doing the VCUG first, what mistakes could be avoided and what the radiation and cost implications were.

In a group of 81 patients I then prospectively assessed the additional information acquired by renal tomography as to whether therapy was affected.[28]

If the VCUG is such an important and pivotal examination, what are the risks and complications of the VCUG? This was studied in 958 consecutive patients and contrasted with the current literature.

Finally, I reviewed the contribution of urodynamic evaluation in 51 patients with recurrent UTI's unresponsive to conventional therapies.

This may lead to a logical sequence of imaging studies. Will this sequence be sufficient to diagnose even complicated patients presenting with UTI correctly? The imaging sequence was therefore analyzed in two groups of patients where VUR coexisted with either upper (21) or lower (9) urinary tract obstruction.[29,30] Would not using this sequence lead to errors in diagnosis or increased morbidity?
In summary, the aim of this treatise is to prove that when a child under age 6 years presents with an index UTI:

=upper urinary tract imaging alone is not sufficiently diagnostic;

=an initial VCUG can safely determine appropriate upper tract imaging;

=tomography need not be employed routinely;

=the VCUG is a safe imaging modality;

=and that urodynamics, like radionuclide studies, should be reserved for follow-up purposes.

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II EMBRYOLOGY

2.1 Upper urinary tract

2.2 Lower urinary tract

2.3 Ureterovesical junction

2.1 Upper urinary tract[1,2]

The development of the kidneys differs from that of the viscera. Organs such as the liver or pancreas evolve by a direct, continuous process beginning with and incorporating the primordium. In the case of the kidneys, three sets of structures appear successively, and only the last one differentiates into the full-grown organ.

The set of structures that appears in the first 2 embryonic weeks is called the pronephros. In humans it is only rudimentary and disappears by the fifth embryonic week. It consists of several tubules formed from mesodermal cells of the intermediate cell mass in the cervical region. It is nonfunctional and glomeruli do not develop; tubules do not open into excretory ducts. The first formed tubules regress before the more caudally placed last ones are formed, leaving the pronephric duct as their only remnant. The mesonephros is then formed overlapping the caudal part of the pronephros. It originates from the mesodermal cells of the intermediate cell mass in the thoracic and lumbar regions, and it consists of between 30 and 40 nephrons that have primitive glomeruli, no loop of Henle, and drain into the mesonephric (or Wolffian) duct, which in turn opens into the cloaca. Its blood supply comes through small arteries from the ventrolateral aorta. The mesonephros disappears completely during the third month, except for a few caudal mesonephric tubules that become associated with the genital system in the male.

The metanephros develops (around the fifth embryonic week) from two sources: the ureteric bud from the mesonephric duct and the metanephrogenic cap from the intermediate cell mass of the lower lumbar and sacral regions (the nephrogenic blastema). The ureteric bud elongates and penetrates the metanephric blastema at the end of the nephrogenic ridge. The ureteric bud forms the primitive ureter of the metanephric kidney and dilates at its upper end to become the renal pelvis enveloped by the metanephrogenic cap. Once this occurs, calyceal branches form that subdivide and form minor calyces and

collecting tubules. This process is completed toward the end of the fifth month of intrauterine life. The metanephrogenic cap forms Bowman's capsule, the proximal and distal convoluted tubules, and the loop of Henle. This development is intimately associated with the development of the ureteric bud so that each new tubule has its own cap of mesoderm. This explains why the fetal kidney is at first lobulated, the developing "units" being "visible" until these lobulations disappear after birth.

As this process progresses, the nephrogenic mass starts its 90-degree medial rotation and ascent toward the renal fossa. This so-called ascent up the posterior abdominal wall is largely apparent as a result of the growth of the lumbar and sacral regions of the body and straightening of its curvature. The ureter elongates until the kidneys eventually reach their normal position opposite the second lumbar vertebra.

The blood supply is furnished by successively higher levels of splanchnic arteries off the aorta. The venous drainage is for a large part derived from the supracardinal anastomoses.

There are three critical events in the development of the normal kidney: 1) the appearance of the ureteric bud at the end of the fifth week, 2) the ureteric bud invagination of the nephrogenic blastema during the sixth week and, 3) the ascent of the kidney during the sixth and seventh weeks.

Failure to develop properly at either of the first two stages results in absence, aplasia, or hypoplasia of the kidney. Splitting of the ureteric bud will result in various duplications of kidney and ureter. Failure or arrest of ascent results in ectopia of the kidney.

2.2 Lower urinary tract[2,3]

The structures of the lower urinary tract are formed from endoderm in contradistinction to the upper tract structures, which are formed from mesoderm. Necessarily, the development of these structures is intimately tied to that of the anus, rectum, and lower reproductive tract.

The future bladder can first be identified as the allantois, a ventral outgrowth of the hindgut at about the thirteenth day of development. This structure reaches the chorion through the extraembryonic mesoderm of the body stalk. At the end of the fourth week, the cloacal membrane forms the medioventral wall of the cloaca. The mesonephric (Wolffian) ducts enter the bladder laterally, just caudal to the allantoic stalk. The urorectal septum then starts to divide the cloaca in a transverse coronal direction. The cloacal membrane ruptures, and the anal and urogenital orifices are formed. The ventral aspect of the cloaca then elongates and forms the following structures in the male: 1) the prostatic and membranous part of the urethra (formed from the pelvic portion of the urogenital sinus), 2) the distal or phallic part of the urethra and, 3) the urachus, which is identifiable in the adult as the medial umbilical ligament (the connection of the allantoic stalk to the cloaca).

In the female, the pelvic portion of the urogenital sinus develops into the urethra.

The ureteric bud of each side arises near the termination of the corresponding mesonephric duct. With the development and growth of the bladder, the ureters migrate laterally and cranially to open at the lateral angles of the trigone, while the mesonephric (Wolffian) ducts remain midline and migrate distally.

In the male, the remaining mesonephric duct forms the epididymis, vas deferens, and the common ejaculatory duct. In the female, the duct totally regresses.[4]

The gonads initially appear as a genital tubercle, a slight midline

protuberance just cephalad to the distal end of the cloaca. Cloacal folds are located on both sides; these become labioscrotal swelling with a central phallus. In the absence of stimulation by androgens, it forms the female external genitalia. This complex, under the influence of androgens, becomes the male external genitalia. The labioscrotal folds swell and fuse to form the scrotum. The ridges of urethral folds fuse to form the cavernous urethra by 12 to 14 weeks.

2.3 Ureterovesical junction

The course of the ureter to the bladder muscle is oblique, continuing into a submucosal part of varying length until it opens into the bladder at the corner of the trigone. The musculature here is arranged in longitudinal fibers, while the distal part of the ureter is surrounded by the Waldeyer sheath, which consists of an outer sheath that is part of the detrusor muscle and an internal sheath derived from the ureter.[5-8]

This anatomical arrangement implies that the UV junction exerts a passive valve function opposing VUR.

A congenital abnormally short submucosal part of the ureter (normally about 1.5 cm. in length) is a frequent cause of abnormal valve function. This can be traced to a congenital abnormality in the fourth fetal week when the formation of the ureteric bud begins.[8] The more lateral the origin of the bud, the more lateral the ostium of the ureter, the more it resembles a "golf hole" and the shorter the submucosal part of the ureter, facilitating VUR and/or the ascent of bacteria up the ureter.

Surgical destruction of the submucosal part of the ureter resulted in VUR in 50% of pigs studied by Jörgensen, where all animals developed VUR when the bladder outlet was obstructed.[13] This substantiates that bladder/urethral dysfunction with development of high intravesical pressure are important in the development of VUR even with a normally placed ureteric opening.[5-8]

A normally functioning ureter is one of the factors determining the presence or absence of VUR. Efflux prevents reflux in the presence of an anatomically normal ureteric bladder position.[9,10]

Other factors influencing the presence of VUR include (1) inflammatory changes[11,12] (2) bladder-urethra dysfunction[13] and (3) age. The age dependency of VUR can be explained by the fact that the maximum contractibility force of the ureter increases with age. There is also a progressive increase in the population of smooth muscle cells and a small increase in the average size of the individual muscle cell.[14]

The preceding focuses attention on the fact that diagnostics of the uretero-vesical junction must pay attention to bladder-urethral structure and function. Imagers of children with UTI must therefore pay increasing attention to both the imaging evaluation as well as the urodynamic investigation.

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III. IMAGING METHODS IN URINARY TRACT INFECTION; IS AN ORDERED APPROACH USEFUL?

3.1 Lower urinary tract imaging: detection and grading of vesicoureteral reflux

3.1.1 Ultrasound

3.1.2 Radionuclide evaluation

3.1.3 Voiding cystourethrography

3.1.4 Voiding cystourethrography as the initial study in the child with urinary tract infection (Adapted from: Radiology 1985; 156:659)

3.1.5 Urodynamics: how and why

3.2 Upper urinary tract imaging: detection of dilatation, scarring and growth disturbances

3.2.1 Ultrasound

3.2.2 Functional imaging with isotopes

3.2.3 Excretory urography

3.2.4 Excretory urography in children; is (routine) tomography useful? (J Can Assoc Rad 1984; 35:363)

3.3 Summary

3.3.1 Flow chart

3.1 Lower urinary tract imaging: detection and grading of vesicoureteral reflux

3.1.1 Ultrasound

Ultrasonic evaluation of the retrovesical region is unsatisfactory for the detection of reflux[1]. Although peristalsis can be noted in the dilated ureter and techniques have been developed to attempt the demonstration of vesicoureteral reflux, the VCUG is much more sensitive[1]. Real-time US of the retrovesical region has, however, shown promising developments in patients with incontinence; it can be combined easily with function parameters (urodynamics), as will be discussed in 3.1.5. Real-time US can be useful in the prenatal diagnosis of VUR, as discussed in 3.2.1.

3.1.2 Radionuclide evaluation

Because of improvements in equipment the use of scintigraphy in both the neonatal and infant age group has increased. Radionuclide cystography permits the continuous monitoring of bladder filling and emptying and registers the refluxing urine volume. VUR can thus be detected and quantitated, making this a more sensitive study with lower grades of reflux[2,3]. Simultaneous recording of intravesical pressures permits assessment of the relationship between bladder volume, bladder pressure, and VUR[2].

The radiation dose to the bladder and gonads is about 5 percent of the dose of the conventional VCUG.[2] In the child, particularly when frequent follow-up examinations are required, this reduction is paramount.

It is important to realize that grading of VUR is based on morphology of the upper tracts: thus in this respect a radionuclide

cystogram is not as useful as a VCUG. It is however, good for followup and allows an overview of the entire GU tract.

3.1.2.1. Indications: Follow-up of patients with VUR on prophylactic antibiotics. Cessation of the VUR eliminates further therapy; conversely, worsening necessitates a change in therapy. After anti-reflux surgery, the preferred method for following these patients is an initial post-operative VCUG with subsequent radionuclide cystography at 1 year. Radionuclide cystography is also used to screen siblings of patients with familial VUR.

3.1.2.2. Preparation: is the same as for the VCUG.

3.1.2.3. Execution: is identical to the VCUG but the fluoroscopy is replaced by the gamma camera. Technetium-99m as pertechnetate is used in a 1mCi/500ml saline solution.

3.1.3 Voiding cystourethrography

The VCUG is used to evaluate functional anatomy of the bladder and urethra, as well as to determine the presence and grade of vesicoureteral reflux (VUR).

3.1.3.1. Indications for this study include a documented urinary tract infection, as well as (suspected) voiding problems and (suspected) dilatation of upper urinary tracts. In addition, anorectal malformations, prune-belly syndrome, and myelodysplasia require a VCUG to evaluate the bladder/pelvic floor coordination during micturition.

3.1.3.2. Preparation: The patient needs no physical preparation for

this examination. Both the patient and parent(s) should be prepared psychologically for the VCUG by having the procedure explained to them before they enter the uroradiologic suite.

3.1.3.3. Technique: The patient, if old enough, is asked to void and then is positioned on the fluoroscopic table.
In the male the glans penis is washed with povidone-iodine solution (Betadine) and rinsed with warm saline. If the patient is over 2 years of age, a lidocaine 0.5% solution (Xylocaine) for topical anesthesia is introduced into the urethra using a cone adapter. Next, a small (usually F08), pediatric feeding tube is inserted with the aid of lidocaine 2% jelly (Xylocaine) for lubrication.

In the female, after the perineum has been washed with povidone-iodine solution and saline, the same size feeding tube is inserted into the bladder. In infants a F04 feeding tube may be used. Residual urine is drained and sent for culture and sensitivity. The contrast agent, a 17% iodine solution (Cystografin), is dripped in by gravity via the pediatric feeding tube, with the bottle suspended approximately 2-3 feet above the table top.[14] The height of the reservoir really has little effect on the amount or speed of entry of contrast compared with the effect of the diameter of the connecting tube and the intervesical pressure. With the standard tubing used, measuring approximately 4 1/2 feet, the effective filling pressure does not exceed 30 cms. of water. This can be considered near physiologic.

3.1.3.4. Complications or why a VCUG should <u>not</u> be performed, whether as the primary study or at all, should be mentioned. At The Children's Hospital, Harvard Medical School, Boston USA, approximately 1400 VCUG's are performed yearly as the initial evaluation

after a first documented (index) urinary tract infection. About 2/3 of these 958 patients are referred by a group of urologists at The Children's Hospital. The other 1/3 are referred by pediatricians in the surrounding referral area. Data gathered from the former group (n=958) form the basis for this review.

First, infections can be introduced into the bladder or urethra by catheterization, or the catheter can cause exacerbation of a previous infection. Glynn and Gordon[4] reported a 6 percent incidence of new infections, or exacerbation of a previous infection, closely related to cystography. Although organisms introduced into the urethra have been shown to pass up into the kidney in refluxing animals[5] and reflux of infected urine has been shown to result in pyelonephritis and subsequent renal damage[6], there have been only three possible cases in our material in which a UTI was diagnosed within two weeks after a VCUG had been performed[7]. In not one of these three cases was the culture obtained at the time of performance of the VCUG positive. In view of the excellent follow-up experience that is enjoyed by the group of urologists at The Children's Hospital, it is felt therefore that the risk of infection after performing a VCUG is extremely low ($\leq$ 0.3%). This confirms previous observations[8].

Second, the catheter can cause erosion of the urethra and bladder with subsequent hematuria, bladder rupture[9], or after removal of the catheter, urinary retention. Catheterization is successful in almost all boys except those with urethral abnormalities, while girls who present with synechiae or interlabial masses, need surgical correction before catheterization is attempted[10]. Catheterization is deemed successful when urine flows freely from the catheter. Fluoroscopic confirmation is done only after this occurs. An F08 feeding tube is most commonly used (a balloon catheter is never used; it

carries the risk of overdistention of the bladder). The catheter is secured by taping it to the thigh. Fluoroscopic control of the filling phase and monitoring of the volume of contrast dripping in have contributed greatly to the overall safety of the procedure, because overdistention is avoided and reflux can be seen the moment it occurs. Bladder volume in fluid ounces can be estimated by the equation: (age in years plus 2). Multiplying this number by 30 determines the bladder volume in milliliters[11]. This is a rough guideline, applicable only in normal children under age 6 years. Any bladder dysfunction from detrusor muscle instability to neurogenic bladder would render this guideline impractical. Over the last five years, there have been no complications employing this method at The Children's Hospital. "False passage" occurred once in the 958 cases studied, in a patient with previous surgery for implantation of an artificial urinary sphincter.

Third, contrast medium can cause an irritative response in the bladder wall as has been well documented[12]. The higher the concentration (osmolarity) of the medium, the greater the irritative response. In approximately 14% of the patients studied, there was evidence of dysuria, or very mild hematuria, or both, up to 24 hours after the VCUG. Hospitalization was not necessary at any time; the only outpatient treatment necessary was reassurance.

Fourth, in girls vaginal filling with contrast medium during voiding is common. Mechanisms proposed are a) prominent labia majora in this age group, b) negative intravaginal pressure during voiding and c) so-called female hypospadias. It could therefore be argued that contrast medium can enter the peritoneal cavity through the vagina, uterus, and fallopian tubes[13]. This has not happened in our experience and is anyhow extremely unlikely.[14]

If performed correctly, therefore, the VCUG is a safe and

reliable imaging procedure and it should not be avoided for any of the above-mentioned possible complications.

3.1.3.5. Execution: The contrast-filling stage described above is completed under intermittent fluoroscopic control. The cessation or reversal of flow in the line is the end point of filling. This usually occurs some time after the child has become uncomfortable. Oblique views of the bladder where the ureters insert are taken (the locus minoris resistentiae of the bladder), and if VUR is noted at this stage, the ipsilateral renal bed is imaged. The patient then commences voiding and the catheter is withdrawn. In about 10-15% of patients, this is much easier said than done.

During voiding the urethra is imaged. In the male at least three views, including both proximal and distal (i.e. fossa navicularis) areas are taken. In the female, one (AP) exposure is sufficient unless pathology is noted (extremely rare).

VUR during voiding necessitates imaging of the kidneys: this is the phase where "high-pressure" VUR occurs. On completion of voiding, a post-void bladder film is obtained to evaluate for residual urine. Both renal beds are then imaged to evaluate for post-voiding residual contrast medium in the upper urinary tracts. This results in an examination of about 9 exposures in a boy, 7 in a girl.

3.1.3.6. Results of a VCUG can be influenced by some variables. These warrant discussion.

A. Infusion techniques: Obviously, the method of choice is that which will least irritate the urethra and trigone. It is difficult to assess whether an easily passed, small, malleable catheter or a suprapubic puncture is the least traumatic, but age is an important factor. At The

Children's Hospital, we use the former method, since it can be done in all age groups. Only in infancy is the bladder intra-abdominal, thus allowing for easy suprapubic puncture[16]. Finally, if the contrast is too cold or infused too fast, this may provoke detrusor instability.

B. Timing of study: It is customary to wait at least two weeks after treatment of a documented UTI before performing a VCUG. During an acute UTI, edema of the bladder wall is present. Since bladder pressures may be elevated during the UTI, especially during voiding, the possibility that during the period of an acute UTI the grade of reflux may be higher than when infection is not present is suggested[17,18]. Conversely, in a recent abstract, it was shown that in three cases the examination was negative during the infection, but did show reflux after the infection had cleared[19]. In these latter cases, edema of the bladder wall may have closed off the ureteral orifices to reflux. Until further documentation of this phenomenon has been procured, the VCUG should not be performed before the index UTI has been fully treated. A urine culture obtained at the time of catheterization will provide assurance that no infection is present at the time of the VCUG.

C. Recording techniques: Fluoroscopy alone or in conjunction with videotape, spot filming (100mm, 105mm or digitally), or cine films have all been used. The objective is to make VUR visible; therefore, fluoroscopy with positioning of the patient and spot films is the suggested technique. This results in reported doses to the gonads of less than 700mR in boys and an average 300mR in girls[15]. (Table 3.1.3.1). The average fluoroscopy time in the 958 consecutive VCUG's studied was 14 (±8) seconds in girls and, 24 (±14) seconds in boys. Recently, we have been able to achieve much lower gonadal exposure doses through the aid of digital technique.[19a] This technique resulted in an average does reduction to the gonads of 40-50% as compared to 100 mm/105 mm spot filming.

Table 3.1.3.1. VCUG gonadal exposure (10^{-5} Gy)

	Male	Female
Meradji (Personal Comm.)	389 (±400)	280 (±71)
ref.19A (Cleveland/Blickman)	521 (±200)	239 (±75)
ref. 15 (Leibovic/Lebowitz)	≈ 700	≈ 300

D. Standardization of technique: The position of the patient has been thought to influence the results of the VCUG. Experimental work has suggested that laying a puppy on its side allows reflux to occur[20,21]. Human studies have not as yet been performed. Using our technique, the ureterovesical junction is seen in the supine and both oblique positions.

Anesthesia or sedation has two counterproductive effects. Most commonly used anesthetic agents inhibit the normal ureteric peristalsis to a certain degree[22]. Because efflux prevents reflux[23], VUR may thus occur when the flow down the ureter slows too much in the patient under anesthesia. Second, dehydration may occur during anesthesia, again reducing efflux.

The following section will consider the arguments in favor of VCUG as the initial study in children with a documented index UTI.

3.1.4 Voiding cystourethrography as the initial study in the child with urinary tract infection (Adapted from Radiology 1985; 156:659)

Introduction

When a young child has a well-documented urinary tract

infection, uroradiologic evaluation is usually performed to determine if there is some structural problem that predisposes to infection or if there is vesicoureteral reflux. It is important to detect reflux because pyelonephritis in the otherwise normal child is usually an ascending infection, i.e., the bacteria reach the kidney because there is reflux of infected urine. The order in which the imaging tests are performed or even if all are necessary, is not standardized. For example, it has been recommended that excretory urography (or renal ultrasonography) be the first study performed, and if normal, the only one[24-26]. The purposes of this study were both to test this hypothesis and to determine a logical sequence of uroradiologic examinations in the child with UTI.

Materials and methods

The urographic studies of 389 consecutive children referred for the first time during a nine-month period (June 1983 to February 1984) for evaluation of one or more UTI's were reviewed. In all cases, the VCUG was the initial radiologic examination. If the voiding study was normal, the upper urinary tract was examined by ultrasonography. If reflux or any other abnormality was discovered by VCUG, or if US was unsatisfactory or abnormal, EU was performed. Results were tabulated according to the highest grade of reflux on each study and the age of the child. Reflux was graded using the classification of the International Reflux Study in Children[27]. Any abnormality detected on US, e.g. scarring, hydronephrosis, duplex system (Figures 3.1.4.2 and 3.1.4.3), necessitated a subsequent EU
to confirm the finding.

Results

389 consecutive children (115 girls) were studied. Thirty-one

were excluded because abnormalities other than reflux were discovered on the VCUG. These included ureteroceles, diverticula, posterior urethral valves and a trabeculated bladder. In these conditions the need for a subsequent EU is self evident. Of the 358 children remaining, 37% (133/358, 63% girls) were found to have reflux (64% unilateral), and in this latter group 22.5% (30/133) had an abnormal EU (either focal scarring, or a small kidney when compared to the contralateral kidney, or to standards for age). Table 3.1.4.1 shows the correlation between the grade of VUR and findings on EU. Table 3.1.4.2 analyzes whether, with a given grade of VUR, the findings on EU were related to the child's age. Reflux of grade 2 or greater was found in 82% (109/133) of the children, and of these 73% (80/109) had a normal EU. Fifty % (15/30) of children with grade 3 reflux had a normal EU, as did more than 30% (4/11) of children with grade 4/5. No correlation was found between either the age of the child and the degree of reflux or, within each grade of reflux, between the age of the child and the percentage of children with abnormal EU.
($p>.5$, Student's t-test)

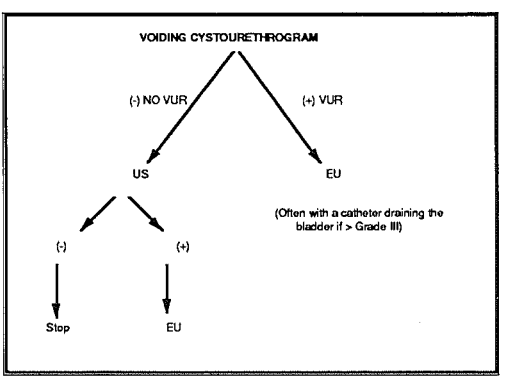


Figure 3.1.4.1. Proposed imaging scheme for an uncomplicated well documented index UTI. **EU** = excretory urography. **US** = ultrasound. **VUR** = vesicoureteral reflux.

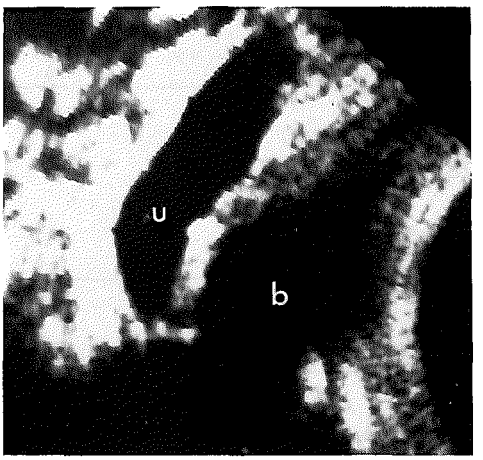


Figure 3.1.4.2. US of a 6-day-old boy with a UTI and a normal VCUG, showing a dilated calyceal system and ureter.
b = bladder **u** = ureter

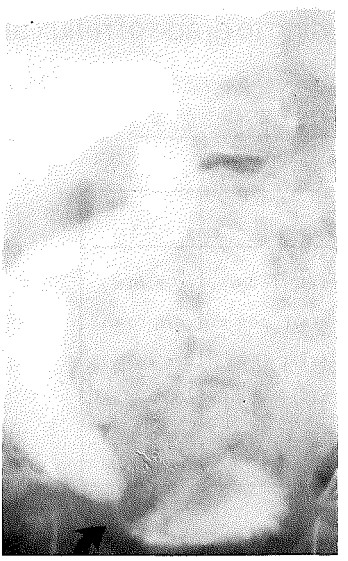


Figure 3.1.4.3. Excretory urography confirmed a primary (obstructed) megaureter in the patient from figure 3.1.4.2

Table 3.1.4.1. Correlation between the grade of reflux and findings on excretory urography (n=133)

Grade of VUR (%)	No. of Patients	abnormal EU	
1	24	1	(96%)
2	70	8	(87%)
3	28	14	(50%)
4/5	11	4	(36%)
Totals	133	27	(79%)

Table 3.1.4.2. Urography findings according to grade of reflux and age of child (n=133)

NORMAL EU/TOTAL (%)

Age in Years	Gr 2	Gr3	Gr 4	Gr 5
0 - 2	2/2 (100%)	8/8 (100%)	2/2 (100%)	0/3 (0%)
1/2 -2	6/6 (100%)	12/12 (100%)	4/8 (50%)	0/0 (0%)
3 - 6	9/10 (90%)	29/36 (81%)	6/13(56%)	2/6 (33%)
7 - 10	5/5 (100%)	12/13 (92%)	2/5 (40%)	0/0
- >10	0/0	2/2 (100%)	1/2 (50%)	0/0

- 109/133 (81.9%) had ≥ grade 2/5 VUR
- 80/109 (73.3%) had ≥ grade 2/5 VUR and normal EU

Discussion

Our data show that an EU is a relatively insensitive method for detecting the presence of reflux[1,28-30] (Figure 3.1.4.4). The reasons for this include:

1. EU provides a relatively brief glimpse of the kidney over a short period of time. Reflux, however, is a dynamic phenomenon, occurring in waves many times during the day, or, in 20 percent of children, occurring only during voiding[31].

2. It is well known that the reflux of infected urine can cause renal scarring.[32,32A+B] However, scars can take up to four to six months to develop after an episode of pyelonephritis, so that images of a recently infected kidney may still be normal[32].

There is an unrelated but important practical reason for performing VCUG before the EU. If the EU is done and significant reflux is present but has not yet been detected, the reflux can cause misleading appearances that can lead either to underestimation (Figure 3.1.4.5) or overestimation (Figure 3.1.4.6) of kidney function. Then, once VUR is discovered, the EU needs to be repeated with a catheter draining the bladder to prevent the reflux and its secondary effects[33].

Conversely, a normal VCUG may hide significant upper tract abnormalities such as a ureteropelvic or ureterovesical obstruction. Even a ureterocele can be hidden by contrast material. The first reason for following the VCUG with an upper tract study[34,35] is then to detect dilatation of the upper urinary tract. If these upper tract abnormalities are detected with equal sensitivity by both modalities, it makes sense to use the quicker and noninvasive modality (US) first. If this is normal, the cost, discomfort, potential risk of anaphylactic reaction associated with the administration of intravenous contrast, and the use of ionizing

radiation is avoided by foregoing the EU. A second reason for following the VCUG with upper tract imaging is to evaluate renal outline and size for signs of reflux nephropathy. The question whether US and EU are equally sensitive and specific in this respect will be addressed in depth in section 3.2.1.

The VCUG, in conclusion, is the most specific imaging method, since it mimics the filling and emptying of the bladder by urine. It therefore not only shows VUR directly, but also depicts the anatomy optimally.

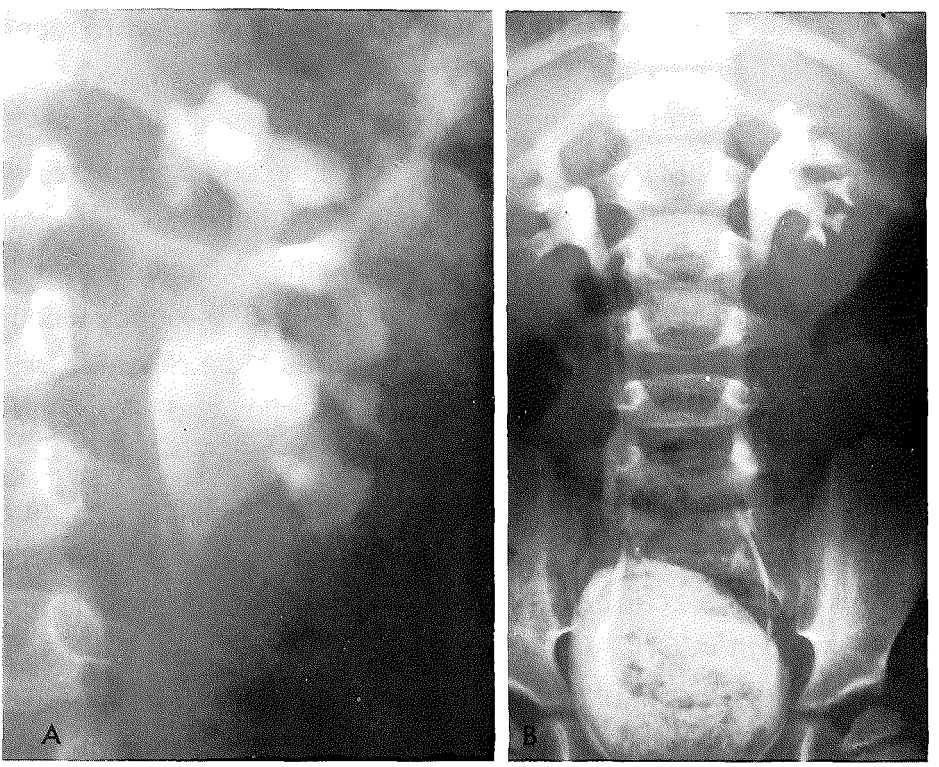


Figure 3.1.4.4.
A:VCUG in a 2-year-old boy shows grade 4/5 reflux on the left.
B: EU done 30 minutes after the VCUG is entirely normal, as was the US.

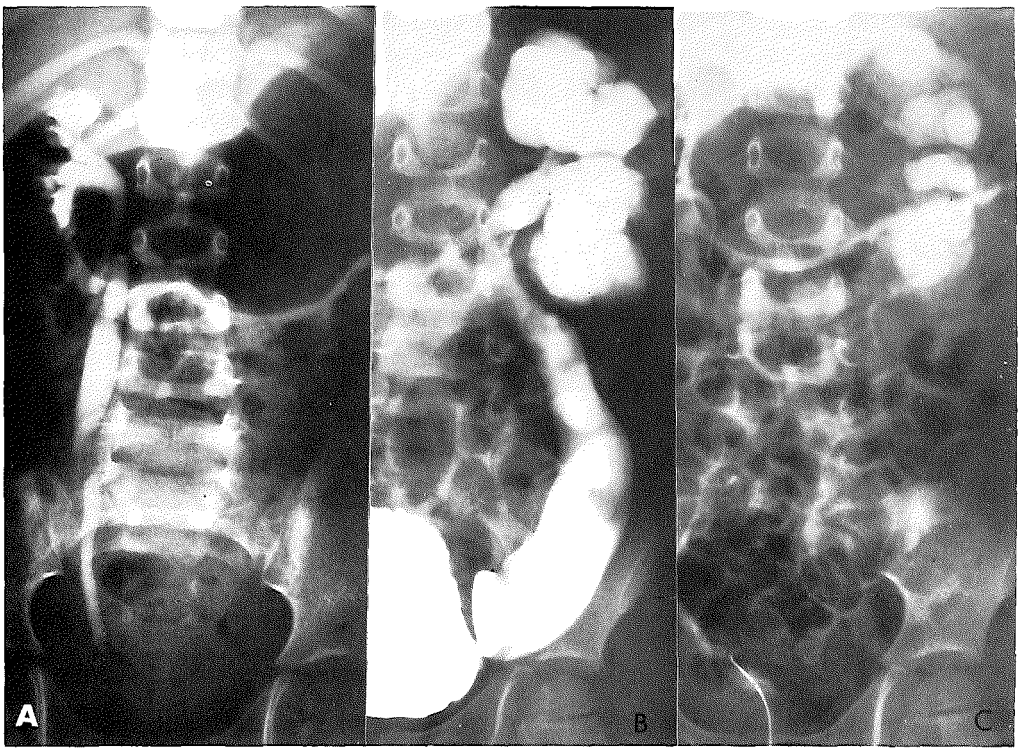


Figure 3.1.4.5.

A: EU of a 4-year-old boy (7 min. film). The left kidney is not seen. He was referred to The Children's Hospital for left nephrectomy.
B: VCUG at The Children's Hospital shows severe left reflux.
C: Repeat EU with catheter draining the bladder to temporarily prevent reflux. Good function on the left is demonstrated (20 min. film). Therefore, reimplantation of the left ureter was performed.

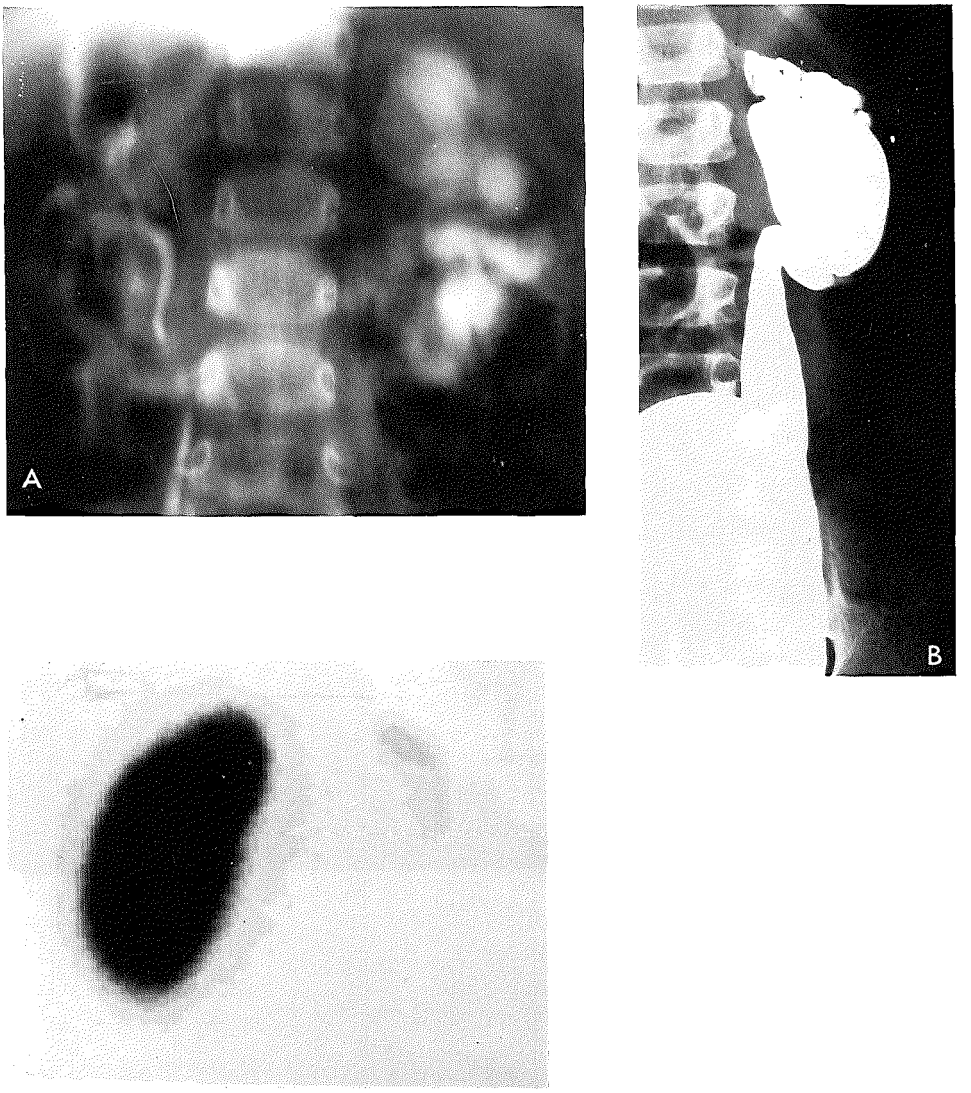


Figure 3.1.4.6

A: EU of a 7- year-old boy (tomogram) shows a distorted and dilated but well opacified left collecting system and ureter, suggesting that the left kidney functioned well or that there is VUR.
B: VCUG reveals severe left reflux. The patient was referred to The Children's Hospital for reimplantation of the left ureter.
C: ^{99m}Tc-DMSA scan with a catheter in the bladder to prevent reflux, shows only 3% of the injected activity on the left. Therefore, left ureteronephrectomy was performed.

Some have argued that if the kidneys are normal on EU (or US), the detection of VUR is not important since the kidneys have remained normal in spite of the reflux[24,26]. This may be true in the older child or adolescent, but it can be argued just reverse: in the young child with UTI whose kidneys are normal, the discovery of VUR provides the opportunity, through proper surveillance and treatment, to insure that they remain normal. This philosophy is the rationale behind the proposed imaging scheme (Fig 3.1.4.1).

If it is important to detect VUR, and in the young child with UTI it is, an initial VCUG (or nuclear cystography), should be used. The EU or US are relatively insensitive methods for detecting VUR and its immediate sequelae, and in many children, even those with significant VUR, these latter studies may be normal when the children first undergo uroradiologic evaluation. If both upper and lower urinary tract are thus evaluated and normal, significant VUR, and thus risk for renal damage, is unlikely. On the other hand, when a child is treated medically for a year for low-grade reflux, it is recommended that a functional study of the upper tracts (EU or radionuclide imaging) be done before terminating the antibiotic regimen.

3.1.5 Urodynamics: how and why

In the etiology of RN there is now considerable evidence that urodynamic factors play a key role in creating damage to the renal parenchyma of the growing kidney subjected to VUR[36-38]. Urodynamic investigations have revealed that increased urethral resistance (functional obstruction due to urethral hyperactivity in patients with neurogenic bladder called "detrusor-sphincter dyssynergia") during voiding and instability of the detrusor muscle in the filling phase create high pressures in the bladder, that are transmitted -in the presence of VUR

- to the renal pelvis. This is difficult to appreciate, even on a well-performed VCUG. A combination of VCUG and urodynamic investigation should lead to a more complete assessment by obtaining bladder pressures at the same time as images of the bladder and upper urinary tract. At any given moment the bladder pressure can then be correlated with the degree of VUR appearing in the VCUG.

To prove that a combination of urodynamics and radiographic evaluation is necessary, the effect of each modality on treatment of recurrent UTI's was assessed.

Material and methods

The records of 51 patients who had recurrent UTI and who had both a conventional imaging workup as well as a urodynamic evaluation were reviewed. Eighteen children were less than six years of age while 33 were between the ages of six and 14 years of age. In the group under six years old, all patients had a VCUG to evaluate the lower tract and either EU or US to evaluate the upper urinary tract upon presentation with the UTI. Within four to six weeks after VCUG, the urodynamic study was performed. In the over six-year-old group, all had had conventional VCUG and EU evaluation more than 3 years prior to presenting with the current illness, and this was repeated upon current presentation. Again, urodynamic studies were undertaken within four to six weeks after VCUG.

All urodynamic studies involved the combined registration of bladder pressure, electromyographic (EMG) activity of the pelvic floor muscles, and urine flow rate. Flow rate recordings were also obtained during spontaneous micturition, previous to the introduction of urethral catheters for recording bladder pressure during a complete cycle of bladder filling and emptying. Therapeutic interventions, including

behavioral modification, long-term chemoprophylactics, antispasmodics, or anticholinergic therapy, were recorded also, and the clinical course was noted over a mean of three years.

Methods, definitions and units conform to the standards proposed by the International Continence Society, except when specifically noted.

Results

The urodynamic studies revealed urethral hyperactivity in 7 of the 51 patients, and detrusor instability in 34; a variety of other conditions made up the remaining 10 patients. This last group was treated on a primary basis. There was no statistically significant correlation ($p>0.05$, Fisher's exact test) between the prevalence of VUR and any of the urodynamic patterns of vesicourethral dysfunction, as shown in Table 3.1.5.1. Of the 41 patients not treated primarily, only the combination of long-term chemoprophylaxis with another therapeutic intervention (behavioral modification, antispasmodics or anticholinergics) was successful in keeping 23 infection-free in the subsequent 3 years follow-up.

Table 3.1.5.1. 51 patients with recurrent UTI, evaluated with imaging techniques as well as with urodynamics.

	Urethral hyperactivity	**Detrusor instability**	**Other**
VUR	2	7	5
No VUR	5	27	5

Discussion

In the previous sections it has been proven that an organized and properly executed upper and lower tract imaging approach to children presenting with a UTI leads to excellent anatomical delineation. However, it has also been suggested that this method of examination is limited, if not inappropriate, for evaluating vesicourethral function[41,42]. This belief arises from recent reports that in addition to the previously described avenues that lead to UTI, vesicourethral dysfunction may not only predispose to recurrent UTI's and/or high-grade VUR, but may even be a primary factor[36-40]. Repeatedly increased intravesical pressures may lead to anatomic changes such as trabeculation of the bladder, diverticula and alterations of ureteric orifices and ureterovesical junction complexes. In the presence of VUR, transmission of these high pressure will lead to reflux nephropathy. Because urodynamic studies are seldom performed in patients at this hospital who were treated for an uncomplicated UTI, the causal relationship between anatomical abnormalities and an unstable bladder is just recently being recognized.

The result of this study points out that urodynamic studies have a distinct function in children who fail treatment based on conventional anatomic evaluation. This is borne out by approximately 56% (23/41) of children with normal anatomy being relieved of their dysfunctional voiding and incontinence after treatment was based on urodynamic results. However, out of the 958 anatomic studies reviewed earlier (see 3.1.3), it is obvious that the majority of children, whose treatment was based upon radiographic evaluation of their urinary tract only, will not need urodynamic evaluation. This would seem to suggest that only children who fail to respond to antibiotic treatment and long-term chemoprophylaxis should have urodynamic evaluation, i.e., those with

recurrent UTI.

Thus: urodynamics should be done in:

1) high grade VUR in the young children (high-risk for RN)[38]
2) persistent symptoms of dysfunctional voiding or vesicourethral dysfunction,
3) children with recurrent UTI, regardless of anatomical findings or imaging results.

As urodynamic studies are as easily tolerated by children as are the conventional imaging studies, the combination of urodynamic with imaging studies could result in findings that permit total treatment of the underlying abnormalities resulting in a UTI. Neither time, money or availability of these methods in all hospitals would permit this.

Recently, however, a slight modification of the VCUG technique has been described that enables the diagnosis of vesicourethral dysfunction while performing a VCUG[41]. A manometer was installed to measure the pressure/flow of the contrast used in performing the VCUG. Although the age group studied was not the same age group in which UTI's present most commonly, the results of that study seem to indicate that the use of standardized height of the infusion bottle permits reliable functional evaluation of cystometric characteristics albeit not as extensive. If these results can be extrapolated to all children presenting with recurrent UTI, this may be a possible intermediate route.

3.2 Upper urinary tract imaging: detection of dilatation, scarring and growth disturbances

3.2.1 Ultrasound

Fetal US is becoming commonplace, and the fetal kidney can be seen from 20 weeks on, the bladder at 18 weeks. Depending on the US-operator's skill and patience, fetal voiding can be observed in detail: fetal VUR can be diagnosed, as well as intravesical obstruction, by imaging the fetal bladder and urethra during voiding. Measurement of intrauterine growth of the kidneys is also becoming useful. A 5 or 7.5 MHz scanhead can perfectly delineate the anatomy of all known abnormalities both in utero as well as postnatally. The 3.5 mHz scanhead is most useful in the prenatal period.

Real-time US has thus become the screening method of choice in the work-up of the pediatric abdomen; certainly in the neonate with urosepsis and in all children with urinary symptoms.[43-46] Abnormalities, such as clinically suspected urinary tract obstruction, can be demonstrated and the point of obstruction localized. Renal morphology as well as scars can be imaged, and in addition, intervention can be guided and passage of needles and catheters facilitated. Real-time US can identify blood vessels, and estimate renal blood flow, with Doppler-techniques. Abdominal masses can be divided into cystic or solid entities by US[47,48], while extension into the renal vein of tumor masses can be determined[47]. Screening for renal abnormalities is done in patients with hemihypertrophy, aniridia, myelodysplastic disorders or familial polycystic kidney disease[48-50].

A standardized set of images is obtained: each kidney is scanned in the coronal plane (upper, middle and lower pole) and axial plane (3 views). Subsequently, the bladder is imaged in both axial and

coronal planes.

In children with UTI, US imaging of the urinary tract can answer two main questions: 1) is there dilatation of the lower or upper urinary tract. Minimal dilatation of the central renal echo complex need not be pathologic; increased urine flow can be detected with today's technology[1] 2) has adequate renal growth taken place. A third question, whether scarring has occurred, is much more difficult to answer with US, as global reduction in kidney size is difficult to appreciate on one single examination by an inexperienced investigator. An experienced investigator however can detect renal scars easily. The normal anatomic variant, such as the column of Bertin or the inter renal renunculus need to be appreciated if present as well.[28,29]

In order to evaluate whether EU or US are indeed equally sensitive in detecting upper tract sequelae of VUR (i.e., signs of RN), 122 consecutive studies were reviewed. Scarring is seen either as a focal area of increased echogenicity juxtaposed to a calyx or as global reduction of renal parenchyma. In 20/122 dilatation or scarring or both was noted on US, confirmed on EU, while in 14 patients EU showed scars while the US was normal. Suspicion for VUR revealed a similar pattern. This corresponds with the available literature[1,28,29] (table 3.2.1.1). VUR imaging by ultrasound is thus limited by extreme operator dependency.

Table 3.2.1.1. Sensitivity and specificity of ultrasound (US) versus excretory urography (EU) in the detection of reflux nephropathy (RN)

		US		
		RN	**No RN**	**Total**
EU	RN	20	14	34
	No RN	3	85	88
	Total	23	99	N=122

Sensitivity = 87%
Specificity = 85.9%

3.2.2 Functional imaging with isotopes

As the neonatal GFR does not reach adult levels until 1 year of age, and the dose of EU contrast is relatively high, radionuclide scintigraphy is particularly useful at this time[51,52]. ^{99m}Tc-dimercapto-succinic acid (^{99m}Tc-DMSA) is primarily used for static imaging of the renal cortex (scarring) and ^{99m}Tc-diethylene-triaminepentacetic acid (^{99m}Tc-DTPA) is used for dynamic evaluation of relative renal function (obstruction). The ability to provide data of excretion versus time is especially useful. Anatomic specificity is low, however, but further

improvements continue to make it a complement to EU[52,53], if not in some instances the equal. This thesis stresses anatomic evaluation of the urinary tract, so the role of radionuclides is de-emphasized.

3.2.3 Excretory Urography

A urogram denotes the visualization of the urinary tract by means of opaque contrast agent, regardless of its mode of administration. It previously was the "gold standard" in imaging of the urinary tract.

3.2.3.1. Indications: Any abnormality noted on VCUG; hematuria; suspicion of calculous disease. Neurogenic dysfunction of the bladder, in the follow up of anti-reflux surgery, as well as for screening in aniridia, hemihypertrophy, and to exclude anomalies of the urinary tract in complex syndromes as for instance anorectal malformations and intersex problems[8].

Dehydration and shock are absolute contraindications to performing an EU. Knowledge of previous allergic reactions to contrast agent or shellfish may constitute a contraindication.

To minimize possible contrast reactions, low osmolar contrast agents are used particularly in young infants, but increasingly among all pediatric age groups.

3.2.3.2. Preparation: Solids, milk or apple juice should be avoided due to their prolonged gastric transit time. Clear fluids should be given to prevent dehydration especially in infants. Previous examinations should be reviewed prior to the study and the patient and parents spoken to.

3.2.3.3. Technique: Slightly warmed intravenous contrast agent is injected intravenously. Dosage is 2cc/pound up to 20 lbs. A "tailored" urogram is then performed: a 3-minute film of the upper abdomen is followed by a 15-minute post-void abdominal film. Only if the upper tracts are poorly seen are tomograms obtained (see 3.2.4). Delayed films may be useful in the younger patient. The renal length is measured, as well as the total length of the first three lumbar vertebral bodies, and compared to nomograms. The renal contour is searched for scarring. Kidney pelvis and calyceal systems are screened for blunting: the first sign of incipient scarring. Visualization of an entire ureter is highly unusual, abnormal and should suggest (1) distal obstruction or, (2) the presence of grade 2 or greater VUR. (Scholtmeijer, personal communication) The yield of specific bladder films is low, and these films should also be tailored.

3.2.3.4 Complications: Although the advantages of non-ionic contrast agents are not totally proven yet, infiltration at the injection site, incidence of allergic reactions and patient tolerance (renal failure) all are significantly reduced. (5-8% vs. 2%)[54]. Biochemical hematologic changes due to osmolarity of the contrast agents seem to be more pronounced with the osmolar agents. (M. Meradji, personal communication)

3.2.4 Excretory urography in children; is (routine) tomography useful? (Adapted from: J Can Assoc Rad 1984; 35:363)

The sequence for performing an EU differs from institution to institution. It is dictated by experience and understanding of the physiology of excretion of contrast medium. At the University Hospital, Leiden, The Netherlands, EU's are performed according to a scheme

that is identical for adult and pediatric patients: a preliminary film of the abdomen is followed 3 minutes after injection of contrast agent by an AP film of the kidneys. Two to three "thick slices" (zonography) of the kidneys follow, after which children ingest a carbonated drink. A full-length film of the abdomen and a post-void film of the bladder complete the examination. Oblique views and compression films are occasionally obtained. The comparison of this protocol with that at several children's hospitals in the United States prompted this study.

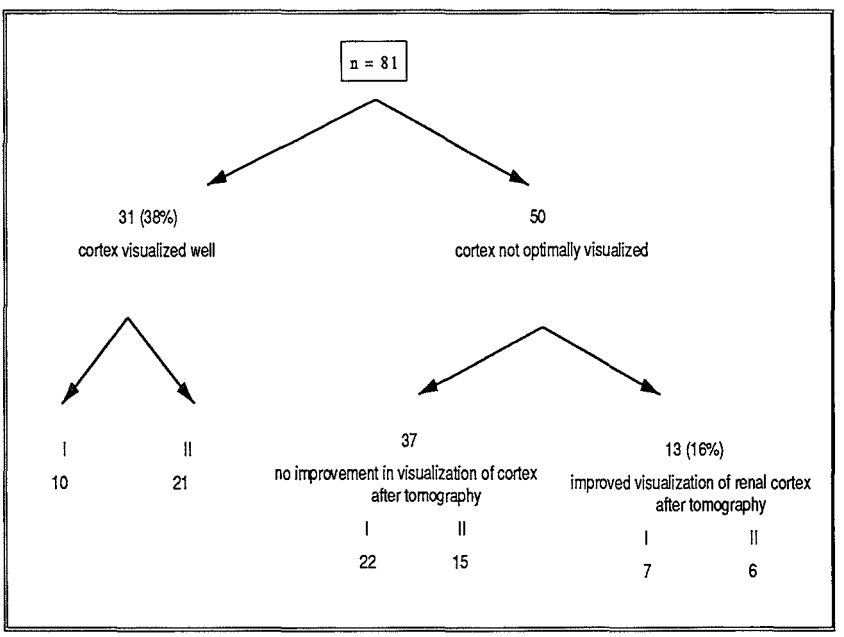
Materials and methods

All EU's from July 1981 to December 1982, a total of 81 examinations were reviewed. The age spread was 12 days to 12 years. The patients were divided into group I, 43 children under 5 years old, and therefore considered unable to cooperate; and group II, 39 children aged 5 through 12 years of age, who are usually able to cooperate. The reason for the EU in 80 percent was either urinary tract infection or enuresis. Infants under 1 year of age had no special preparation and fluids were not restricted. Older patients were prepared only with oral laxatives. Neonates up to 10 kg/body weight received a bolus injection of 2 ml/kg of the methyl glutamine salt of metrizoate (isopaque 280). Children above 10 kg received 1 ml/kg of iodithalamate (telebrix 380). All EU's were first reviewed independently by the authors without tomography. Subsequently, the tomographic cuts (average 2.4 per examination) were evaluated for additional information in a blinded fashion by two radiologists. The imaging of the contour of the kidney and of the calyceal system, including pelvis and ureters, was assessed. The cost of the additional films and the additional radiation to the gonadal region were calculated.

Results

From Table 3.2.4.1 it is seen that in 13 of 81 (16%) patients better delineation of the cortical margin was obtained from the tomographic cuts during the examination. Overall, the cortical margin was well seen in 41 of 81 (55%) of all patients examined. The calyces were well seen without tomography in 74 of 81 (91%). Tomography did not improve the visualization of the calyces.

Table 3.2.4.1. Effect of tomography on the visualization of renal cortical margins and calyces.
(**I** = poor cooperation, **II** = cooperative)



Discussion

The renal parenchyma can be assessed by US or EU, or in combination.

Precision in the selection of the sequence in which radiographs are taken is an important factor in achieving optimal images and in minimizing the child's exposure to radiation. Artifacts of motion are often encountered but can be minimized by using short exposure times. Tomography often necessitates longer exposure times depending on the length of the arc used, which was justified by the expectation that the renal contour and calyceal system would be better visualized[56].

Nephrotomography has been recommended in the adult patient to improve detection of renal masses, resulting often in an examination consisting of at least 7 or 8 exposures[56-58]. In children a more limited examination has been advocated, although to what extent has not been well documented[8,59-61]. It was found that the amount of diagnostic information is not compromised when routine tomography is omitted.

Good delineation of kidney contours without tomography was twice as often achieved in the group of patients that could cooperate. Conversely, tomography more frequently did not help in the group of children that could not cooperate. The conclusion from this was that the longer the exposure time, the less optimal the image quality. This contrasts markedly with the figures obtained in a study evaluating the better renal cortical delineation through nephrotomography in adults[61].

Imaging of calyceal systems is just as important as evaluating the renal contour[62]. It was found that in 95 percent of the patients, the calyces were visible at 3 minutes post injection without improvement of this number after tomography.

Additional aids, advocated to improve visualization of the kidneys, include the pneumatic compression paddle[63], prone positioning of the patient[64], and gas insufflation of the patient's stomach by tube or with a carbonated beverage. All had disadvantages. A late (30 minutes or more after injection) film can be useful in poor renal function. High dose urography is currently considered only indicated in special cases.

Tomography increases the cost of an EU by $50 per examination. It also significantly increases the radiation dosage to the patient (Table 3.2.4.2).

Table 3.2.4.2. Average gonadal radiation dose during excretory urography with and without tomography.

	Gonadal dose EU (3 exposures) in 10^{-5} Gy	
	Male	**Female**
no tomography	21 (± 29)	133 (±59)
with tomography	40 (±30)	247 (±62)

In conclusion, if an EU is indicated, a 3-film sequence is sufficient in more than 80% of patients. This is especially true when concomitant US and VCUG are used. Routine tomography is expensive in terms of effort, money, and radiation. Excellent technique, including short exposure times, is preferable to tomograms as a routine in infants and small children.

3.3 Summary

For children who present with a documented index UTI, various imaging techniques (VCUG, US, EU, radionuclide studies) are used: a) to detect structural or functional urinary tract obstruction, b) to detect and grade vesicoureteral reflux, c) to detect or monitor reflux nephropathy. In addition, urodynamic studies will be needed in selected cases to investigate vesicourethral function.

Since it is accepted that one needs to wait 7-10 days, during UTI treatment, before performing a VCUG, an initial renal US can be useful in excluding hydronephrosis.[67,68] If this study is normal, coupled with a subsequently normal VCUG, the child need not be at risk for renal damage in the face of subsequent UTI's.

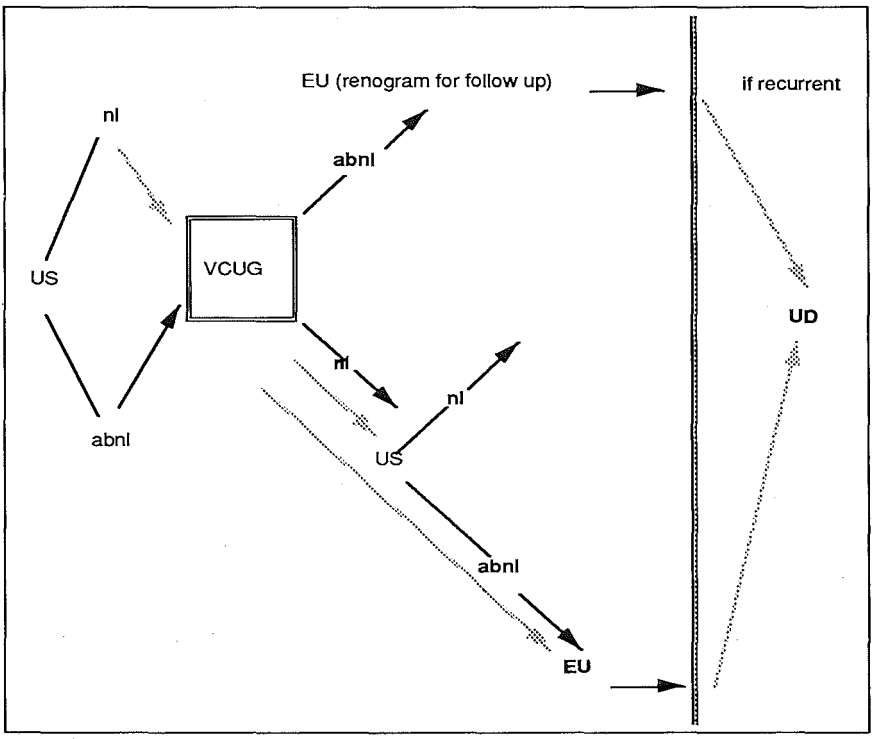


Fig. 3.3.1:
Flow chart illustrating the central role of the VCUG in the imaging sequence in children presenting with UTI.
(dotted arrow = next imaging step when clinically convenient)
(solid arrow = immediate next step)

A positive US examination will then serve to accelerate the diagnostic process resulting in faster treatment institution.

The crucial imaging study should thus be the VCUG (or, as some prefer, the radionuclide cystogram). This allows for accurate detection and grading of VUR, and has an additional benefit in that residual urine can be quantitated, bladder capacity determined and bladder outflow obstruction noted[41] (3.1.3).

If the cystographic findings are normal, coupled with a normal US, imaging is finished (3.2.1).

If the US is abnormal (e.g. upper tract dilatation), or if the VCUG (RNC) shows VUR, EU or radionuclide studies are necessary, with a tailored EU being the more specific study (3.2.4). A ^{99m}Tc-DMSA kidney scan may be more sensitive in showing the first signs of RN[65].

Important to keep in mind is the fact that VUR is a dynamic phenomenon and that static images can underestimate presence and grade of VUR. A normal imaging study of the entire urinary tract is the best guarantee for prevention of RN, as upper tract studies (US, EU) alone are inadequate (3.1.4). Should a UTI recur, then the question becomes whether vesicourethral dysfunction influences recurrence rate or grade of VUR.

Urodynamic evaluation in a group of children with recurrent UTI's confirmed that detrusor and external sphincter overactivity is associated with symptoms of frequency and urgency, and with recurrences of UTI. Treatment of vesicourethral dysfunction needs to include pharmacologic or behavioral manipulation of the dysfunctional voiding pattern[66] (3.1.5).

The next chapter will address whether symptomatology or specific urinary tract abnormalities affect this flow chart in its effectiveness.

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IV.COMMON URINARY TRACT ABNORMALITIES PRESENTING WITH A UTI: DO ANATOMIC CONSIDERATIONS INFLUENCE IMAGING SEQUENCE?

4.1 Vesicoureteral reflux

4.2 Anatomic obstruction of the upper urinary tract

4.2.1 Ureteropelvic junction obstruction

4.2.2 Ureterovesical junction obstruction

4.3 Anatomic obstruction of the lower urinary tract

4.3.1 Posterior urethral valves

4.3.2 Ectopic ureterocele

4.4 The coexistence of urinary tract obstruction and vesico-ureteral reflux

4.4.1 The coexistence of ureteropelvic junction obstruction and reflux (AJR 1983; 140:231)

4.4.2 The coexistence of primary megaureter and reflux (AJR 1983; 143:1053)

4.4.3 The coexistence of posterior urethral valves and reflux

4.4.4. The coexistence of neurogenic bladder and reflux

4.5 Summary

The five most common causes of upper urinary tract dilatation in children include vesicoureteral reflux (VUR), ureteropelvic junction (UPJ) obstruction, ureterovesical junction (UVJ) obstruction or primary obstructive megaureter, and bladder outlet obstruction by posterior urethral valves (PUV) and ureteroceles. These will most often present with urinary tract infection (UTI), although hematuria, voiding problems, or in the neonate, an abdominal mass and urosepsis with pseudo-hypoaldosteronism also occur. These five will be discussed next, with VUR, the most common, first and the other four in descending order of frequency.

4.1 Vesicoureteral reflux

VUR is classified as either primary or secondary. The former is the result of a congenital abnormality at the ureteral orifice characterized by an abnormal valve mechanism of the UVJ. This normal mechanism depends on the ureter's oblique entry into the bladder[1,2], and an adequate length of the intramural ureter, especially its submucosal segment[3,4]. The valve's effectiveness depends on the ratio of the submucosal tunnel length to the ureteral diameter, a passive mechanism aided by ureteral and trigonal longitudinal muscles that can close the ureteral meatus and submucosal tunnel during detrusor contraction[5,6]. Active ureteral peristalsis and antegrade urine flow are also felt to prevent reflux[7,8]. Secondary VUR occurs as a result of congenital lesions such as a Hutch diverticulum, and in post-surgical or post-traumatic states. In addition, peristaltic motion of the ureter may be impaired and thereby allow VUR to occur, as in atony of the ureter[9].

Conversely, recently a relationship between voiding dysfunction, recurrent UTI and VUR has been recognized. Urodynamic

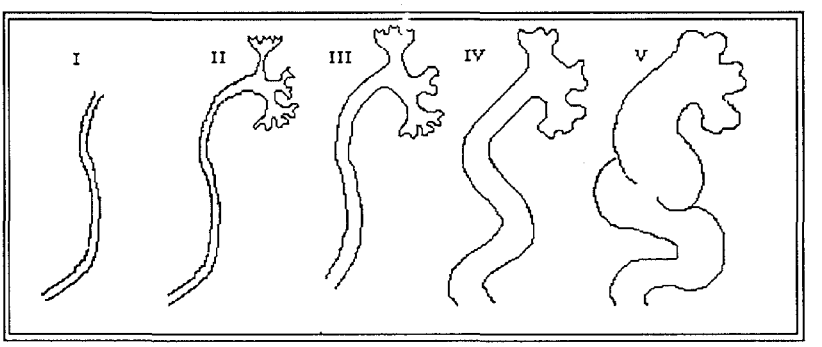
evaluation demonstrates detrusor and external spinchter hyperactivity, while when the detrusor contracts and the bladder attempts to empty, the urethral sphincter does not relax. This bladder-sphincter instability needs to be treated in addition to the conventional treatment and prevention of a UTI. It is thought that two different VUR/dysfunction complexes, one in which the VUR is associated with unstable bladder contractions while in the other the bladder contractions are stable but weak with intrinsically weak UV valve action.[9a]

The prevalence of VUR is reported to be about 40% in children with a UTI[10]. There have been few studies of noninfected populations, for obvious reasons[11]. Prevalence in a general population may be in the order of 0.5 percent[12]. Hereditary factors are also present. VUR has been found in 25 to 40 percent of nonsymptomatic siblings of children with VUR[13,14]. In addition, the incidence of VUR in black children is much lower than in white children[15]. Both indirect[16,17] and direct[18] evidence points to the fact that urinary tract infection is independent of VUR and therefore has no causal role in development of VUR.

There is a strong inverse correlation between the severity of VUR at the time of initial diagnosis and the likelihood of spontaneous resolution. Therefore, several grading schemes have been proposed, based on the appearance of VUR on VCUG, to delineate the risks for future kidney scarring in the individual patient, and to provide a rational approach to the choice between surgical and conservative treatment[20] (figure 4.1.1). The Parkkulainen grading system is currently used in the International Reflux Study in Children[10]. These individual grading systems are not comparable. The International Reflux Study committee has adopted the Parkkulainen system and that literature mostly refers to grading of VUR in this system. It is again to be noted that grading

systems only have validity if standardized conditions are being met while obtaining the study. This has been proven in the previous chapter. In addition, the dynamic factors involved in VUR are not reflected in this grading system or any grading system for that matter.

Figure 4.1.1. Grading systems for vesicoureteral reflux (system c is illustrated).



a. Rolleston et al	b. Dwoskin and Perlmutter	c. Heikel and Parkkulainen
mild	I	I
moderate } (no dilatation)	IIa	II
severe		
some dilatation	IIb	III
moderate dilatation	III	IV
gross dilatation	IV	V

a.Rolleston GL, Shannon FT, Uttley WLF: Relationship of infantile vesicoureteric reflux to renal drainage. Br Med J 1970; 1:430.
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c. Heikel PE, Parkkulainen KV: Vesicoureteral reflux in children: a classification and results of conservative treatment. Ann Radiol 1966; 9:37.

Finally, VUR into an already dilated system can not be graded and since reflux VUR is a dynamic phenomenon, it is wise to be aware that a VCUG is a document of only a moment in time, i.e., at other moments the grade of VUR may differ.

Currently treatment of VUR less than grade 3 consists of 1 year of low dose antibiotic prophylaxis. Grades 4 and 5 are usually treated with surgical reimplantation of the affected ureter if detrusor instability can be excluded. Otherwise this dynamic factor needs to be treated medically. Either method needs cystographic studies to follow the progress of healing, preferably radionuclide cystography as this is less burdensome[20] (3.1.2).

4.2 Anatomic obstruction of the upper urinary tract

4.2.1 Ureteropelvic junction obstruction

Ureteropelvic junction (UPJ) obstruction constitutes the most common form of upper urinary tract obstruction in children. The etiology of this condition has been debated through the years and can probably be divided into intrinsic and extrinsic causes[21].

Suggested extrinsic causes include:

Accessory vessels: compressing of the UPJ by accessory vessels to the lower pole of the kidney. The pounding of the vessel on the junction or the compression of the ureter by the vessel may be primarily responsible[22].

Kinking of the ureter: secondary to either accessory vessels or adherence of the ureter to the renal pelvis caused by a periureteritis secondary to a previous inflammatory process[23]. Kinking of a dilated ureter can also be secondary to vesicoureteral reflux[24].

Nephroptosis: excessive mobility was thought to be an important cause of obstruction, but the numerous failures of nephropexy did not substantiate this[25,26].

Fibrous bands: crossing the ureteropelvic junction alone or in conjunction with any of the above etiologies.

Suggested intrinsic causes of UPJ obstruction include:

Stenosis: of either a congenital or acquired origin caused by thickening of the musculature, development of excessive fibrous tissue, a fibrous contraction, or an ischemic type of hypoplasia[27,28]. A local area of developmental arrest, perhaps produced by fetal vessels compressing the ureter during early development, is another suggested cause[29,30]. Probably the best explanation is failure of the ureter to recanalize after a solid phase during its development[31]. Electron-

microscopic studies have shown increased deposition of collagen and disordered muscle in these cases[32,33].

Mucosal valves or high insertion of the ureter into the renal pelvis: high insertion was considered a possibility in 1878[34]; now it is considered secondary to ureteropelvic junction obstruction in that it is due to a rotation of the dilated medial pelvic wall upward, and a medial rotation of the proximal ureter (see 2.1).

Neuromuscular dysfunction of the ureteropelvic junction has been extensively studied: lack of inhibition, i.e., an absence of nerve cells, in an abnormal ureteropelvic junction[35], faulty innervation, or spasm were considered. Myogenic causes (a disturbance of tone or a congenital weakness of the pelvic musculature[36]) were also considered. A conducting defect, meaning a functional but not a structural obstruction, is the most reasonable explanation in this group[37]. Whether the conducting defect is caused by the abnormal ureteral segment or by an abnormal proximal renal pelvis is still not well understood[38].

Rare causes include entities such as **intussusception, inflammatory polyps** or **granulomata**[39].

UPJ obstruction is most often unilateral, although it is bilateral in about 30% of patients.

The clinical presentation can, in order of frequency, consist of pain associated with nausea and vomiting (40-50%), UTI (25-30%), hematuria (11-15%), or an abnormal mass (3-5%)[40]. As a rule the more severe obstructions will manifest themselves at a very early age, while moderate obstructions may remain clinically silent for years. However, in neonates and infants, the clinical expression often consists of urosepsis with pseudohypoaldosteronism, carrying a high morbidity and a high mortality. The combination of infection and obstruction

reduces the already compromised capacity for growth of the obstructed kidney(s), a reduction which may influence life expectancy. [40A]

In-utero ultrasound (US) has changed the management of neonatal UPJ obstruction drastically: the urosepsis syndrome can be prevented and the diagnostic work-up with US and "functional" imaging can be planned far in advance.

US has also changed the management of severe neonatal upper urinary tract dilatation by permitting percutaneous drainage and decompression of the system(s) if caused by obstruction.

Both radioisotope imaging and excretory urography (EU) depend on kidney function, US does not; combinations are thus mandatory in mapping out the complex patterns of obstruction or duplex kidneys with a non-functioning upper pole. The EU classically shows calyceal crescents[41], surrounding, on delayed films, a dilated pelviureteral system. Administration of a diuretic such as furosemide may stress the UPJ with increased urine flow, thus accentuating the obstruction[42]. Prone positioning may give the same result.

Functional imaging with ^{123}I Hippuran or ^{99m}Tc-DTPA, using a standardized method for forced diuresis (e.g. furosemide), offers quantitative analysis of uptake of the tracer by the kidney and of excretion to the bladder. A significantly reduced rate of uptake and/or an obstructive pattern are indications for surgical intervention[28]. In doubtful cases, and when the degree of dilatation makes assessment of the excretory curve impossible due to pooling of the radionuclide tracer, a percutaneous nephrostomy catheter will be necessary to perform antegrade pressure/flow studies.[43]

A recent development is the so-called MAG3 scan which is performed with ^{99m}Tc MAG 3 (not currently available in the US) when a UPJ stenosis is suspected. This tracer avoids the shortcomings of

the DTPA scan by being more reliable, associated with less radiation dose, is less expensive and gives superior images. It is also useful as a predictor of functional outcome of reconstructive surgery of UPJ obstruction.[28A]

4.2.2 Ureterovesical junction obstruction

There are few terms that have created more confusion and differences of opinion than the term megaloureter or megaureter. Since 1980 the term has come to mean literally "large ureter", and it no longer denotes a specific disease process. There are three major types[44]: (1) the refluxing megaureter, (2) the obstructed megaureter, and (3) a wide ureter not associated with either. This results in the current concept that a megaureter can either primarily obstructive, obstructive and refluxing, refluxing only, and neither obstructive nor refluxing. The latter can be seen in atony of infection.

In this section only the primary (obstructed) megaureter will be discussed.

The primary (obstructed) megaureter is a ureter that is dilated because it has a short, extravesical, distal segment that is normal in caliber but functionally obstructed. The submucosal tunnel and orifice are normal. Cystoscopic examination reveals a normal trigone and ureteral orifices[44]. It is one of the major causes of obstructive uropathy in children, and more common in boys; it is found with all degrees of severity at all ages, and it tends to be stable when not complicated by infection.

Many etiologies have been proposed to explain primary (obstructed) megaureter, from a persistent ureterovesicular valve[45] to a circular muscle band proximal to a hypoplastic segment[46,47] to a decrease in the amount of muscle in the narrowed areas[48,49] to a

persistence of Chwalle's membrane[50]. Collagen infiltration[51] secondary to crossing vessels in intrauterine life, with or without concomitant arrest of development of the distal ureter[52,53], has also been implicated. An analogy with the colon in Hirschsprung's disease has been drawn, but the parallel is not exact because primary (obstructed) megaureter is not due to an absence of intramural ganglion cells[54,55].

The imaging appearance, most often demonstrated on US but possible on EU (figure 3.1.4.3), consists of a distal progressively dilating ureter with a normal-caliber, aperistaltic, juxtavesical segment. The functional obstruction will cause delayed emptying of the affected ureter on post-void examination. The degree of obstruction dictates the appearance of the ipsilateral renal pelvic and parenchyma.

There are three grades of dilatation: [44]

Grade 1: dilatation is limited to the ureter
Grade 2: dilated ureter with some pyelocaliectasis
Grade 3: dilated and tortuous ureter with marked hydronephrosis

This grading has an influence on therapy. Grade 1 and uncomplicated grade 2 can be treated expectantly, while complicated grade 2 and grade 3 need surgical intervention.[55A]

Treatment, if the obstruction in significant, consists of excision of the distal, aperistaltic segment of the megaureter and subsequent reimplantation of the ureter[55A]. The diagnosis can be confirmed at the time of operation.

4.3 Anatomic obstruction of the lower urinary tract

4.3.1 Posterior urethral valves

Congenital urethral valves occur most frequently as mucosal folds in the posterior urethra of males. Anterior urethral valves have been noted rarely in both males and females[56].

There has been considerable debate as to the etiology of the posterior urethral valves (PUV), especially after case reports by Budd and Tolmatschew in the mid-nineteenth century[57,58]. These valves have been classified into three types by Young: type I consists of two folds extending from the verumontanum to just proximal to the external sphincter; type II consists of folds extending cephalad from the verumontanum to the bladder neck; and type III consists of a diaphragm unrelated to the verumontanum[59]. This classification has been modified. Now only type I is considered when mention is made of posterior urethral valves[60], the type II and III entities are not really valves, just mucosal folds.

The source of these valves has at different times been described as a remnant of the urogenital membrane[61], or a defective development[62] or integration[63] of the Wolffian ducts into the walls of the urethra. An abnormal regression of the ventrolateral folds of the urogenital sinus[60] or simply enlargements of folds or ridges normally present in this area[58] may well be the same thing, but the exact mechanism of their formation remains elusive.

Associated congenital anomalies have been reported[64,65], but these are rare. The combination of PUV with vesicoureteral reflux (VUR) can present with a broad spectrum of findings, ranging from normal upper tracts to classic, severe obstructive uropathy and reflux nephropathy.

The clinical features depend on the degree of obstruction and whether or not there is vesicoureteral reflux. Obstruction can be mild, as seen in older patients, and can be manifested as voiding disturbances only, or it can be severe, primarily in infants, and can be manifested as repeated infections of the urinary tract or an abdominal mass due to the distended viscus. Urinary ascites and urosepsis with pseudo-hypoaldosteronism are seen commonly in the neonatal period. These valves are best demonstrated on VCUG. VUR can occur in one or both of the ureters, although it is most often unilateral. If no VUR is present, a secondary obstructive megaureter is present. Sonographic findings lead, for the most part, to an inferred diagnosis upon demonstration of dilatation of the upper tract, thickening of the bladder wall and dilatation of the posterior urethra[66].

Thus, early diagnosis of urethral valves is very important because only mild cases will escape severe renal damage if untreated, and although rare, a few associated congenital abnormalities have been noted. Retrograde evaluation will miss these valves, so early antegrade evaluation of the urethra is mandatory.

Therapy consists of endoscopic fulguration of the offending "valves".

4.3.2 Ectopic ureterocele

A ureterocele is a congenital balloon-like dilatation of the terminal end of the ureter, which lies between the mucosa and the muscle of the bladder[67]. It is best classified depending on the relationship of the ureteral orifice to the trigone and the urethra. The degree of renal dysplasia is related to the position of the ureteric orifice. The intravesical ectopic ureterocele almost always occurs in association with a duplex ipsilateral system, but in 50% of cases may be associ-

ated with a duplicated system on the contralateral side also[68]. Incidence on the right and the left side are equal, while the male:female ratio is 5:1[68,69]. Intravesical ureteroceles with an orthotopic position of the orifice are sometimes associated with a single kidney. Most often ureterocele presents in children who are less than 1 year old with a UTI. The ectopic ureter will drain the cephalad part of the duplex kidney in a more caudal location than the normal ureter, the Weigert-Meyer "rule". In males, caudal sites of drainage include the bladder neck, posterior urethra, vas deferens, epididymis, and seminal vesicle; in females, additional sites are the urethra and vagina. Ureteroceles often cause VUR by altering the normal valve mechanism of the orthotopic vesicoureteral junction. They may, however, reflux by themselves. In the ectopic type the ureterocele may occlude the bladder neck or the ipsilateral as well as the contralateral ureter. Bilateral ectopic ureteroceles occur in 10 percent of the patients.

Ectopic ureteroceles have been classified into stenotic and sphincteric types. Each type is found in approximately 40% of cases, the remaining 20% are sphinctero-stenotic, blind ectopic, and non-obstructed ectopic ureteroceles[69]. When obstructed, irreversible damage to the affected portion of the kidney frequently results.[69]

Several theories about the etiology of ectopic ureteroceles have been proposed. They are: persistence of Chwalle's membrane[70], persistence of the membrane between the looped Wolffian duct and the vesicoureteral canal[71], and failure of expansion of the ureteral orifice[72]. The first two theories may explain stenotic, ectopic ureteroceles, the third may explain an ectopic ureterocele with a normal or larger than normal orifice.

Radiographic diagnosis is made frequently on VCUG, on which the appearance of the ureterocele changes at different stages of bladder filling and during voiding. In early filling and after voiding, the

ureterocele may be distended and therefore radiographically visible; however, in a full bladder, the ureterocele may be compressed or overshadowed and thus not visible unless repeated filling and emptying is employed. VUR can be demonstrated not only in the unaffected ureters, but also in the ectopic ureter itself with the double voiding technique[73]

A ureterocele can be easily diagnosed by an EU. An oval or occasionally round, smooth, filling defect may be noted in the bladder. Bladder outlet obstruction occurs when these defects occur bilaterally or when a single ureterocele prolapses over the trigone.[74] Because of the upper pole's dysplastic nature, opacification is poor, and only the lower pole will fill, revealing the "wilting lily" sign, i.e., lateral displacement of the visualized pelvis and upper ureter with a diminished number of opacified calyces. Lateral displacement of the ureter by the non-opacified, dilated ectopic ureter may also occur.

Treatment depends on the degree of the obstructive component. Simple or orthotopic ureteroceles often require surgery when they are large enough to cause obstruction. Electro incision of the ureterocele combined with ureteral reimplantation usually in a second sitting is recommended. In association with a duplicated system, the degree of damage to the upper pole as well as concomitant reflux into the lower moiety dictates the surgical approach[75]. There is general agreement that heminephrectomy of the poorly functioning upper pole segment is essential in the treatment. Heminephrectomy and total or partial ureterectomy are curative, with the former needing reimplantation and the latter leaving the insertion undisturbed. In some cases where there is a reasonable functioning upper pole, and anastomosis of the upper pole ureter with the lower pole collecting system may be successful.[75,76]

4.4 The coexistence of urinary tract obstruction and vesico-ureteral reflux

4.4.1 The coexistence of ureteropelvic junction obstruction and reflux (Am J Radiol 1983; 140:231-238)

Since ureteropelvic junction obstruction is the most common upper urinary tract problem in children, and vesicoureteral reflux the most common lower tract problem, it is not surprising that these entities sometimes coexist in the same child. Over a 10 year period this uncommon phenomenon has been noted 21 times (in about 2,800 children with reflux and 200 children with ureteropelvic junction obstruction). Significant ureteropelvic junction obstruction in association with mild reflux can mimic severe reflux, but the operation needed is not reimplantation but pyeloplasty. Conversely, when significant ureteropelvic junction obstruction coexists with significant reflux, both operations may be necessary, but the order in which they are done (pyeloplasty first) seems to be crucial. Voiding cystography with appropriate postvoid drainage films, excretory urography, often with a catheter draining the bladder to prevent reflux, and provocative diuretic excretory urography and/or renography can determine that ureteropelvic junction obstruction does coexist and quantitate the severity of each problem.

Obstruction at the ureteropelvic junction is the most common problem of the upper urinary tract in children. It occurs with all degrees of severity and is bilateral about a third of the time[1]. Vesicoureteral reflux is the most common abnormal condition of the child's lower urinary tract. It too occurs with all degrees of severity, and the milder degrees of reflux tend to resolve spontaneously[2]. Therefore, it should not be surprising that these conditions sometimes coexist in the same patient. Our aim was to document how often this happens, how to recognize it, and the implications thereof.

Materials and Methods.

Using a computer, we reviewed the records of the Department of Radiology and the Division of Urology at Children's Hospital Medical Center for the 10 year period 1971-1981. About 200 children had undergone pyeloplasty for obstruction at the ureteropelvic junction, and about 2,800 children had been found to have vesicoureteral reflux. Significant ureteropelvic junction and/or significant reflux were seen to coexist in the same child 21 times **(fig. 1)**. Their medical records, radiographs, radionuclide examinations, operative notes, and follow-up studies were reviewed.

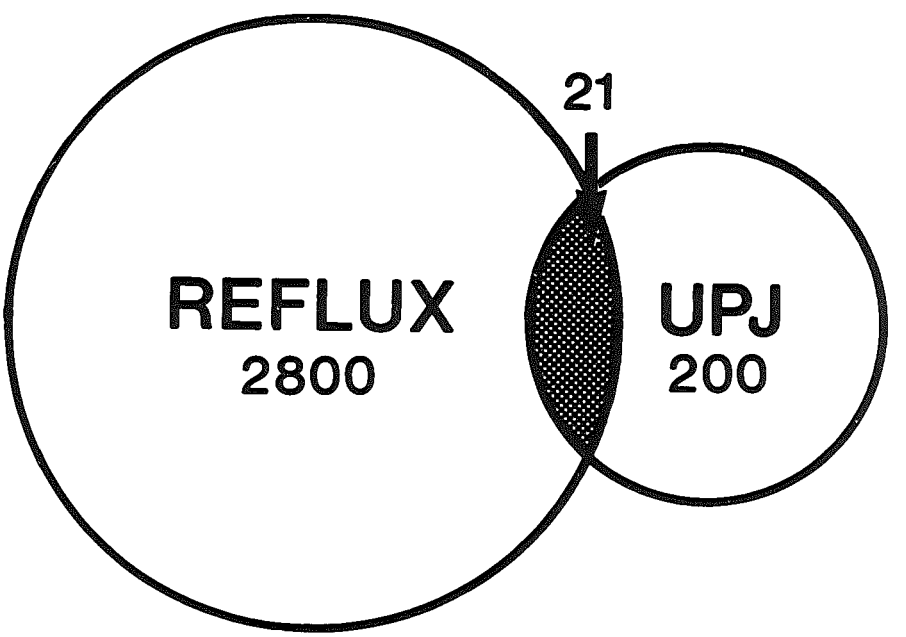


Fig 1 - Approximate frequency of coexistence of ureteropelvic junction obstruction (UPJ) and reflux at Children's Hospital Medical Center over the 10 years 1971-1981 (not to scale).

Results

The 21 children with coexisting ureteropelvic junction obstruction and reflux ranged in age at the time of diagnosis from 3 months to 20 years. Eleven were boys. The reasons for the initial uroradiologic examination included urinary tract infection (nine) pain (five), (both in three), failure to thrive (two), and anomalies elsewhere (one). In one infant, the abnormality was discovered incidentally during cardiac catheterization.

One child had a solitary kidney, and in one the reflux and obstruction coexisted in a pelvic kidney. One child had a complicating renal abscess, and another had a stone impacted at the ureteropelvic junction. This latter child had congenital heart disease and was being treated with furosemide.

Seven children had severe reflux, and in one this reflux was into the lower pole of a duplex collecting system. four had secondary reflux; this was a complication of ureteral reimplantation in two, was due to a paraureteral diverticulum, in one, and was into an "unused" ureter after cutaneous pyelostomy in one. In three patients, there was acute exacerbation of ureteropelvic junction obstruction after reimplantation that, in retrospect, should have been performed after pyeloplasty. Three patients had unnecessary reimplantation because the degree of reflux was overestimated.

Five children had ureteropelvic junction obstruction that was probably secondary to severe reflux. In one of these (a 3-month-old boy) the causative ureteropelvic adhesions were lysed through the suprapubic incision at the time of reimplantation, and a pyeloplasty was not necessary. Five had bilateral obstruction, but only one needed bilateral pyeloplasty. In once child, the obstruction affected the lower pole of a duplex collecting system.

Representative Case Reports

Case 1: Significant Ureteropelvic Obstruction and Mild Reflux (only pyeloplasty necessary)

A 35-month-old girl was sent for uroradiologic evaluation after successful treatment of urinary tract infection. Voiding cystography showed bilateral reflux. On the left, the reflux was into a normal ureter and pelvicaliceal system and was mild in degree. There was no discrepancy in size or density between the pelvicaliceal system and ureter. On the right, however, the reflux was into a mildly dilated ureter and a very dilated pelvicaliceal system. It was initially thought to be quite severe **(figs. 2A and 2B).** However, there was a discrepancy in both size and density between the ureter and the pelvicaliceal system, suggesting that the latter was dilated for some reason other than reflux and that it contained a significant volume of nonopaque urine. A "drainage" film a few minutes after voiding showed that the entire left side and the right ureter had emptied promptly, but there was delayed drainage of the right pelvicaliceal system suggesting obstruction at the ureteropelvic junction **(fig. 2C).** A subsequent excretory urogram with a catheter draining the bladder to prevent reflux confirmed the presence and site of the suspected obstruction **(fig. 2D).** The child underwent right pyeloplasty, and the mild bilateral reflux was then treated as an independent problem. Two years later, the mild reflux was still present on each side, but because the family was moving to an underdeveloped area and careful follow-up could not be assured, she underwent bilateral ureteral implantation. At the time of operation, the ureteral orifices were seen to be identical in appearance and only mildly abnormal.

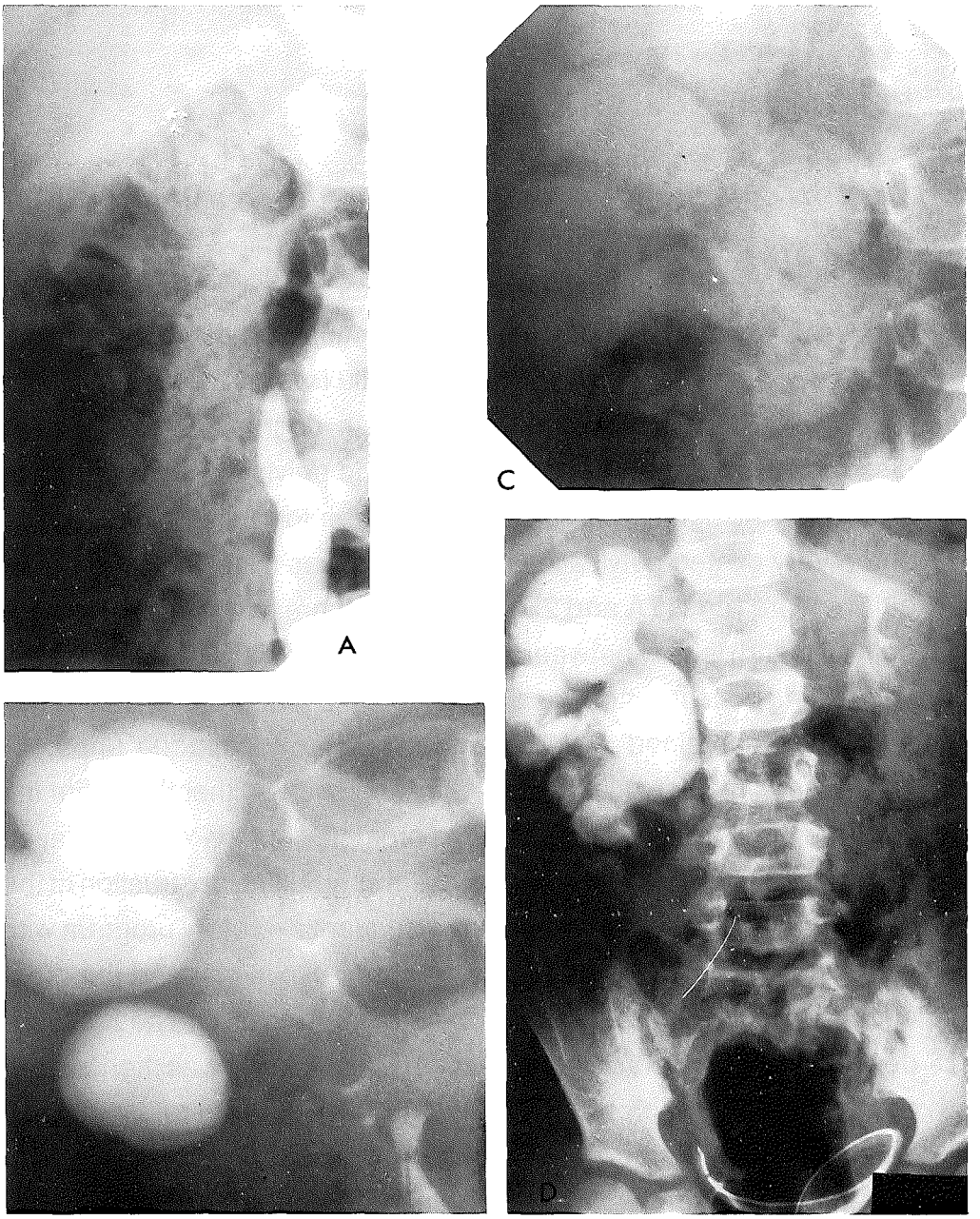


Fig. 2 - Case 1. Significant ureteropelvic obstruction and mild reflux. A and B, Voiding cystogram shows right reflux, first into ureter **(A)** and then after slight delay, into pelvicaliceal system **(B)**. Discrepancy in both size and density of contrast agent between pelvicaliceal system and ureter. (mild left reflux not shown). Right ureter was slightly more dilated than left, probably because of obstruction at ureteropelvic junction (see fig. 7A). **(C),** Postvoid "drainage" film. Left pelvicaliceal system and ureter and right ureter have emptied completely, but diluted contrast material remains in dilated right pelvicaliceal system. **(D)**, Excretory urogram performed with catheter draining bladder to prevent reflux. Right ureteropelvic junction obstruction.

Case 2: Coexisting Significant Ureteropelvic Junction Obstruction and Mild Reflux after Pyeloplasty.

A 4 1/2-year-old child had mild bilateral reflux and right ureteropelvic junction obstruction. After right pyeloplasty with nephrostomy drainage, she did not void **(fig. 3).** It seemed as if an appropriate total volume of urine was draining via the nephrostomy tube. After the nephrostogram showed that the pyeloplasty anastomosis was widely patent, the nephrostomy tube was removed but copious amounts of urine continued to drain via the tube tract. After a catheter was placed in the bladder, the urinary drainage stopped almost immediately and the tract closed spontaneously.

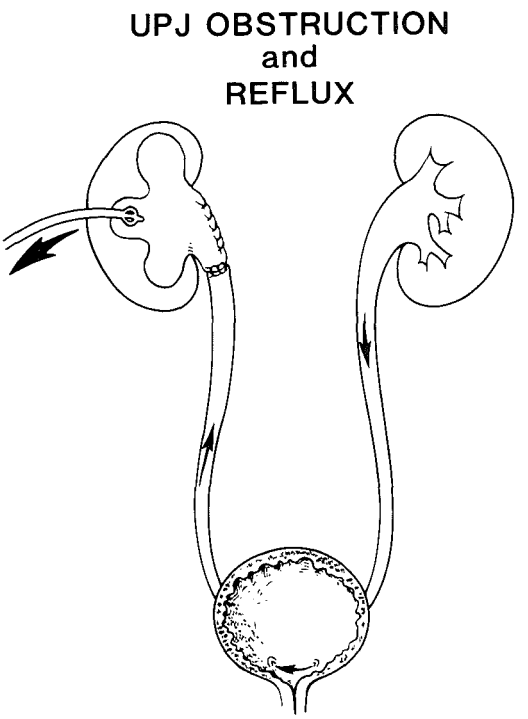


Fig. 3 - Case 2. Urinary drainage through nephrostomy tube after pyeloplasty with coexisting ipsilateral reflux.

Case 3: Significant Ureteropelvic Junction and Significant Reflux (both pyeloplasty and reimplantation necessary).

A 4 5/6-year-old boy was sent for urography after successful treatment of urinary tract infection. Voiding cystography showed severe reflux into the ureter and pelvicaliceal system on the right. On the left, the reflux was into a dilated, tortuous ureter, but almost no contrast material flowed into the pelvicaliceal system **(fig. 4A)** so coexisting secondary ureteropelvic junction was suspected. Excretory urography done with a catheter draining the bladder to prevent reflux confirmed the obstruction on the left **(fig. 4B)**. Cystoscopy showed patulous ureteral orifices. The boy first underwent left pyeloplasty and then, after the anastomosis had been shown to be patent, bilateral ureteral reimplantation.

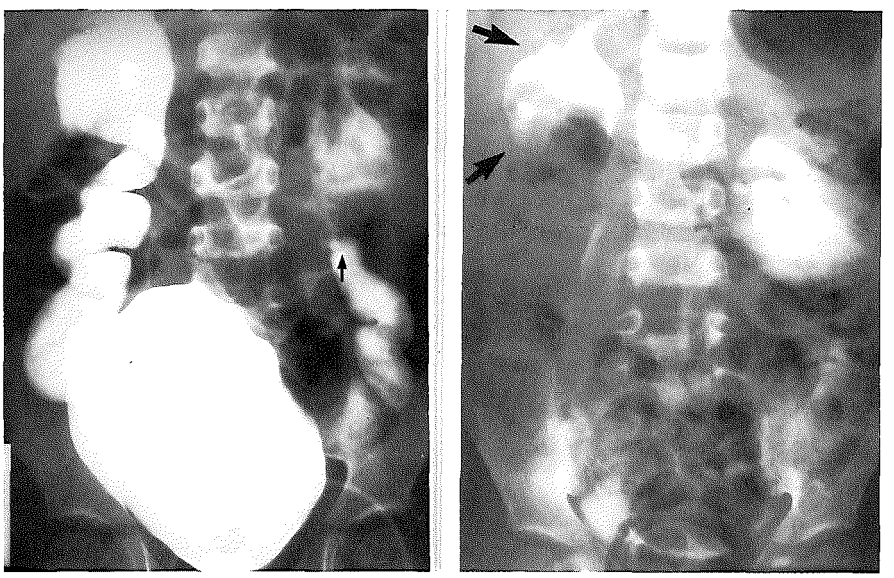


Fig. 4 - Significant ureteropelvic junction obstruction *and* significant reflux. **(A)**, Voiding cystogram, severe right reflux with dilatation and tortuosity of right ureter and dilatation of right pelvicaliceal system. No difference in density of contrast material in pelvis compared to ureter. On left, there is reflux into markedly dilated and tortuous ureter, but virtually no flow through obstructed ureteropelvic junction *(arrow)* **(B)**, Excretory urogram with catheter draining bladder to prevent reflux. No hold-up at right ureteropelvic junction and, in addition to contrast material, bubbles of gas have refluxed freely into pelvicaliceal system *(arrows)* On left, there is obstruction at ureteropelvic junction.

Case 4: Acute Postreimplant Ureteropelvic Junction Obstruction

An 8-year-old boy had bilateral severe reflux and coexisting bilateral secondary ureteropelvic junction obstruction, left worse than right. Therefore, she underwent pyeloplasty *and* reimplantation of the ureter **(fig. 7E)**.

Discussion

The coexistence of significant ureteropelvic obstruction and vesicoureteral reflux is rare. Any degree of one can coexist with any degree of the other, and this often complicates interpretation of the urograms. For example, the grade of reflux on a properly performed voiding cystogram has proven to be a very accurate predictive indicator of the degree of immaturity or maldevelopment of the ureterovesical junction and the fate of the reflux[2,5,6]. However, this correlation is valid only if the reflux is the cause of thedilatation[7]. Mild reflux into a collecting system already dilated because of coexisting obstruction at the ureteropelvic junction, for example, may lead to overestimation of the reflux. It is also confusing if the ureter distal to the obstruction is more dilated than usual for the degree of reflux. This occurs when the wave of reflux meets the obstructed ureteropelvic junction, the urine has "no place else to go," and the ureter distends **(figs. 2A and7A).**

Overestimation of the degree of reflux and subsequent unnecessary antireflux surgery that might follow can be avoided and the significant coexisting obstruction at the ureteropelvic junction suspected if the refluxed contrast agent 1. does not flow freely into the pelvicaliceal system **(figs. 2A, 4A, 8A, and 9A)**; 2. is diluted in pelvicaliceal system **(figs. 2B, 7A, 8A, and 9B)**; and 3. does not drain freely from the pelvicaliceal system **(figs. 2C, 7B, 8B and 9C)**. Confirmation is by excretory urography, often with a catheter draining the bladder to

prevent reflux **(figs. 2D, 4B, and 7C)**. (This latter study also predicts the appearance on excretory urography after either spontaneous resolution of reflux or successful antireflux surgery.) If the presence of significant coexisting obstruction is not clear using the above criteria, a provocative diuretic excretory urogram [1, 8, 9] **(fig. 7D)**, a radionuclide renogram [9-11], or a Whitaker test [12, 13] (all usually should be done with a catheter draining the bladder) will answer the question.

With significant coexisting ureteropelvic junction obstruction is

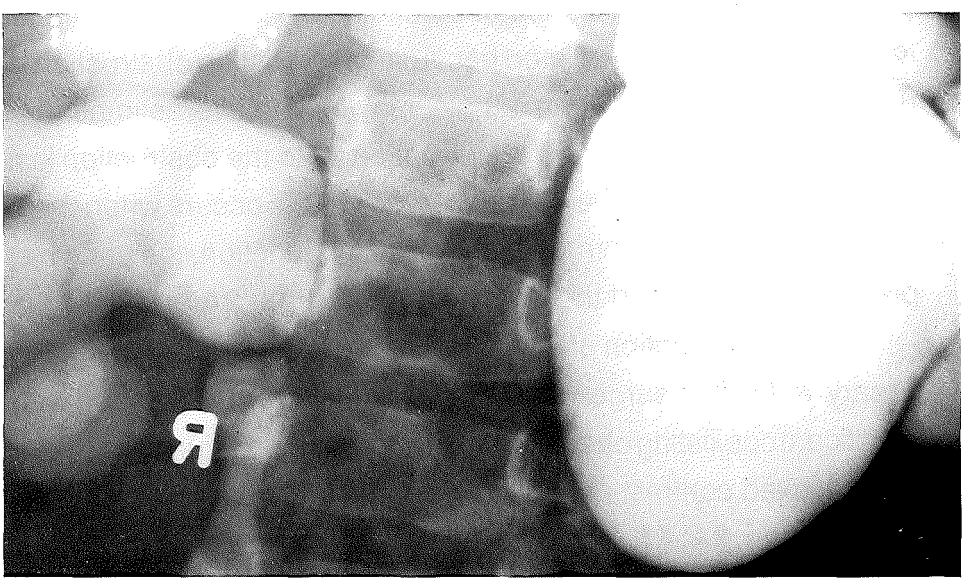


Fig. 5 - Case 4. Postvoid "drainage" film from preoperative voiding cystogram Significant obstruction at left ureteropelvic junction and suggestion of similar problem on right.

diagnosed and surgically corrected, the reflux can then be treated on its own merits. In fact, as the rate of flow of urine down the ureter increases after relief of obstruction, the reflux may disappear spontaneously even more rapidly than expected [14, 15].

If a nephrostomy tube was placed for temporary drainage at the time of pyeloplasty, all of the urine from both kidneys may temporarily

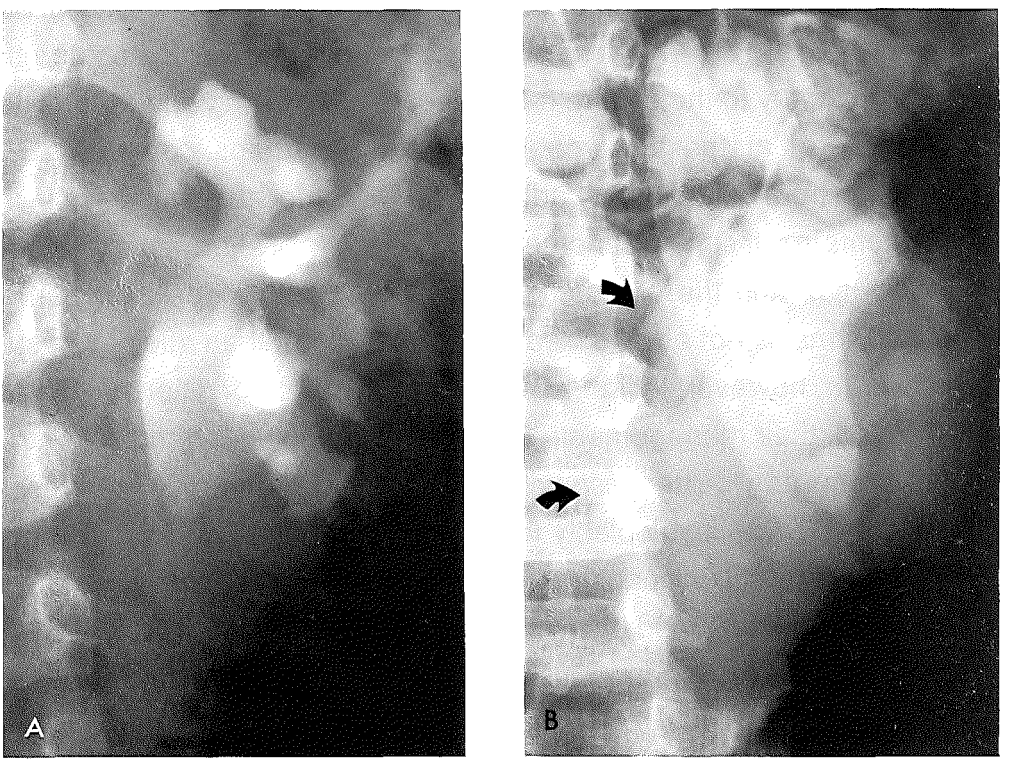


Fig. 6 - Case 5. Acute postreimplant ureteropelvic junction obstruction. **(A)**, Postvoid "drainage" film from voiding cystogram. Hold-up at ureteropelvic junction suggesting coexisting obstruction there. **(B)**, Immediate postoperative excretory urogram. Severe ureteropelvic junction obstruction characterized by "obstructed" nephrogram, dilated calices, and very dilated pelvis *(arrows)*..

exit via the tube, that is, the patient may pass no urine per urethra (as in case 2). This happens when the urine from the contralateral kidney does not collect in the bladder but refluxes up the opposite ureter, the path of least resistance, and then exits via the tube **(fig. 3)**. The refluxed urine may also keep the sinus tract open after the nephrostomy tube is removed (also as in case 2). A catheter in the bladder for a few days will temporarily prevent the reflux and will allow the pyelocutaneous fistula to close.

Significant reflux should be suspected to coexist with significant ureteropelvic junction obstruction when the ureter is severely dilated and tortuous **(fig. 4A)**. It has been postulated [16-18] that the obstruction is secondary to the severe reflux because of kinking and tortuosity of the ureter at the ureteropelvic junction, perhaps complicated by fixation from inflammatory adhesions as seemed to be the case in five patients in our series. Whether this is the case, or alternatively whether the reflux and the obstruction are independent, coexisting primary conditions, is not always clear. More important than etiology in such children, however, is first, recognition that both conditions exist, and second, their management. Repair of both the upper and lower tract problems may be necessary, but the order in which the operations are performed (i.e., pyeloplasty first) is crucial for these reasons:

1. Significant ureteropelvic junction obstruction can be confidently confirmed by using a catheter to drain the bladder during the excretory urogram the excretory urogram. This temporarily prevents the coexisting reflux. The converse, temporary relief of obstruction to see what happens to the reflux, cannot be easily done.

2. The obstruction is the more "fixed" of the two conditions. The natural history of reflux is to improve (or not change) [2], while that of ureteropelvic junction obstruction is to stay the same (or worsen) [1].

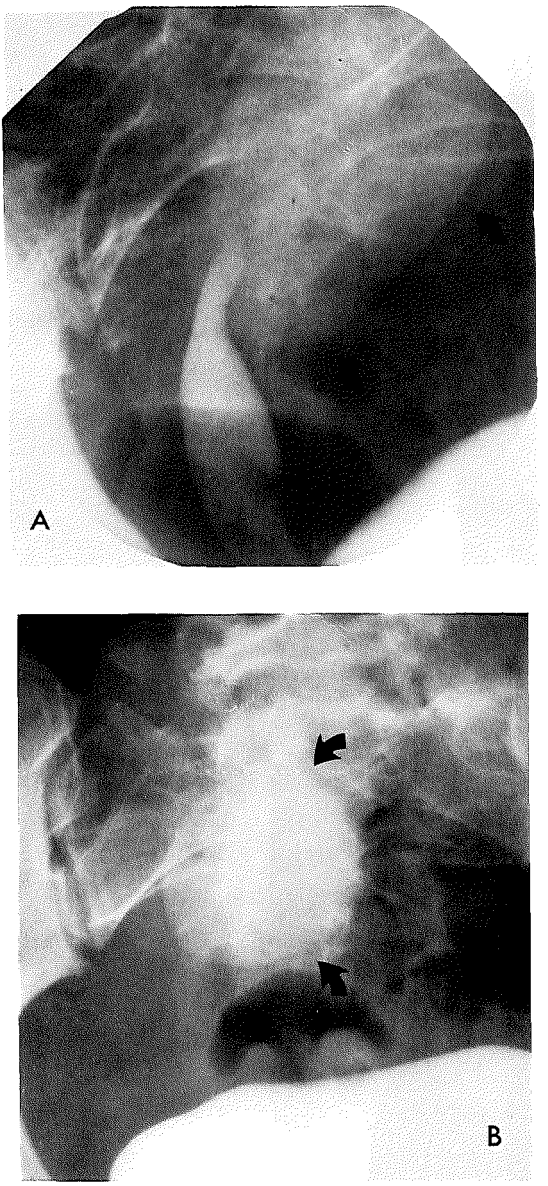
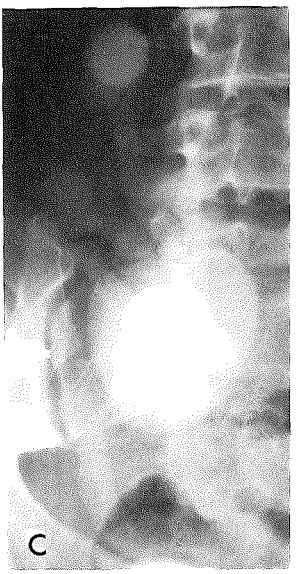
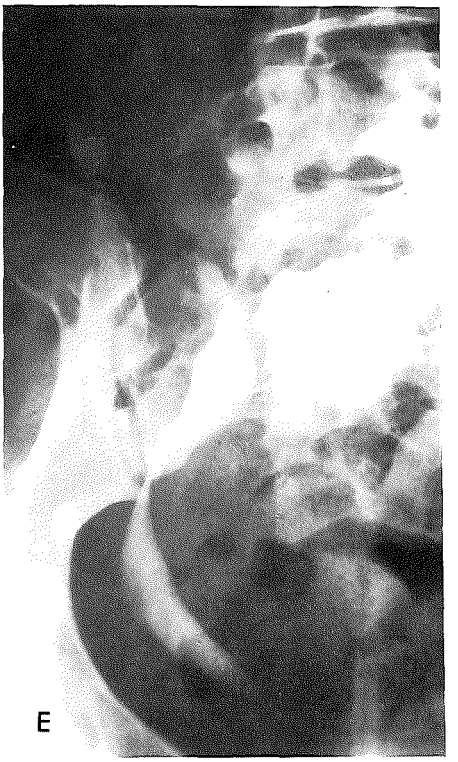
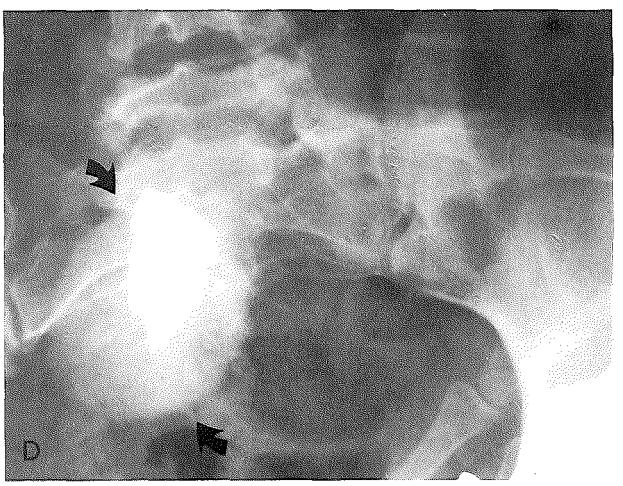


Fig. 7 - Case 6. Significant coexisting ureteropelvic junction obstruction confirmed by "diuretic" excretory urography.
(A), Voiding cystogram. Reflux into right pelvic kidney, and difference in density between renal pelvis *(arrows)* and ureter. Ureter is slightly dilated, but is not tortuous. This ureteral dilatation has probably occurred because refluxed urine cannot flow freely through obstructed ureteropelvic junction, so it distends the ureter (see fig. 2A).
(B), Postvoid "drainage" film. Right ureter has emptied, but there is retention of contrast material in a dilated renal pelvis *(arrows)*. (Patient did not empty her bladder completely).







(C), Excretory urogram with catheter draining bladder. Pelvicaliceal system is dilated, suggesting ureteropelvic junction obstruction. However, pelvic kidneys often have "extrarenal" collecting systems which can mimic obstruction (3, 4). Therefore, furosemide was administered.
(D), 20 min after administration of furosemide intravenously. Incomplete "washout" of contrast material from right renal pelvis *(arrows)* . (Contrast material from left pelvicaliceal system had "washed out" completely). Patient's left hand is over her pelvis. Administration of diuretic reproduced her pain!
(E), Follow-up excretory urogram 6 months after pyeloplasty and reimplant. Complete decompression.

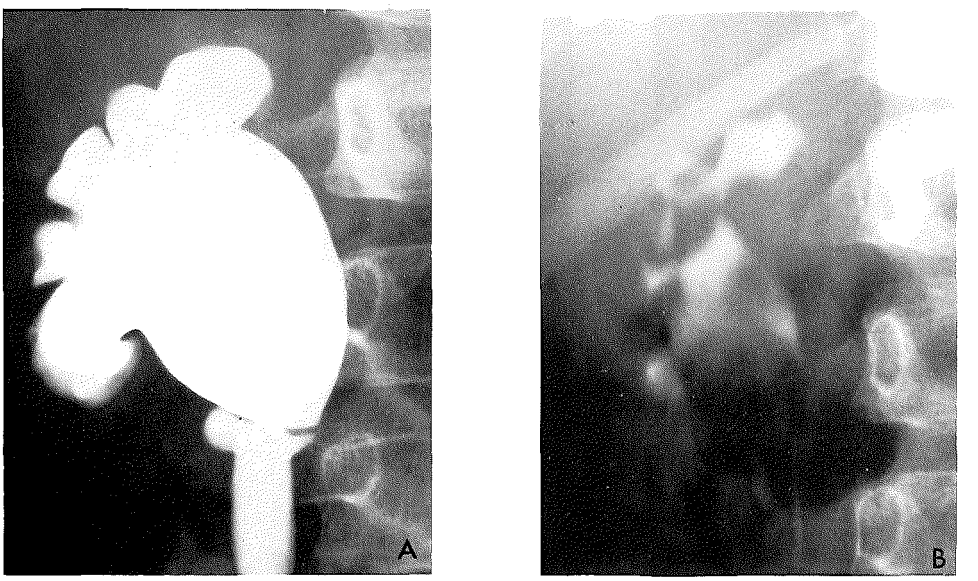
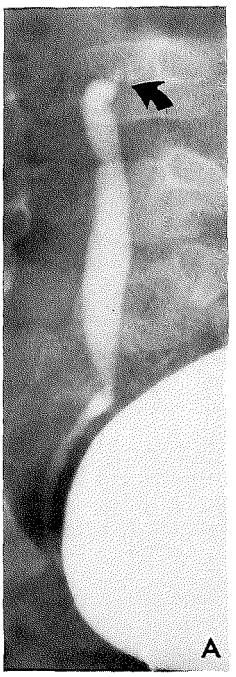
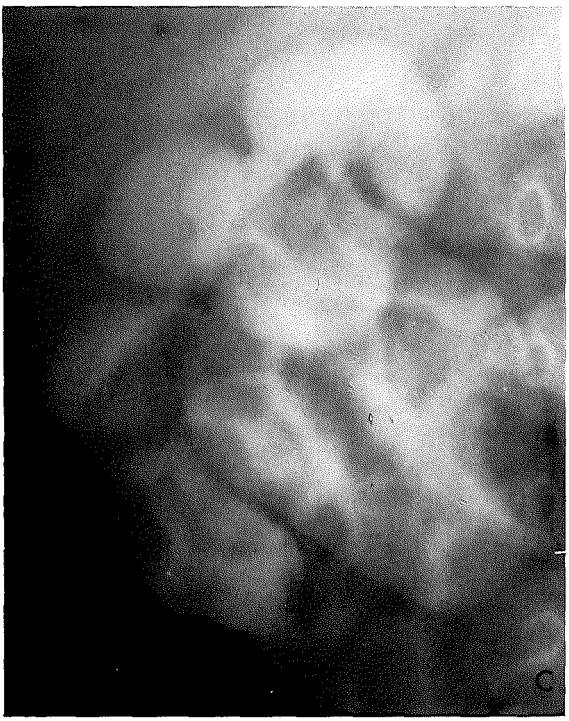


Fig. 8 - Drainage film excludes coexistence of significant ureteropelvic junction obstruction.
(A), Voiding cystogram. Significant right reflux with kinking at ureteropelvic junction. However, no discrepancy in density or degree of dilatation between pelvicaliceal system and ureter.
(B), Postvoid "drainage" film confirms there is no obstruction, also confirmed by excretory urogram with catheter draining bladder to prevent reflux (not shown). As would be expected, after ureteral reimplantation, there were no problems.

3. Temporary postoperative obstruction at the lower end of the ureter (e.g., from edema) may make the obstruction at the ureteropelvic junction acutely worse and may necessitate emergency intervention [17, 18]. The converse, significant acute severe worsening of reflux after pyeloplasty, does not occur.

The reason that previously subcritical obstruction at the ureteropelvic junction sometimes worsens after antireflux surgery is not clear. This phenomenon has been reported several times [19-21], but no convincing hypothesis has emerged.





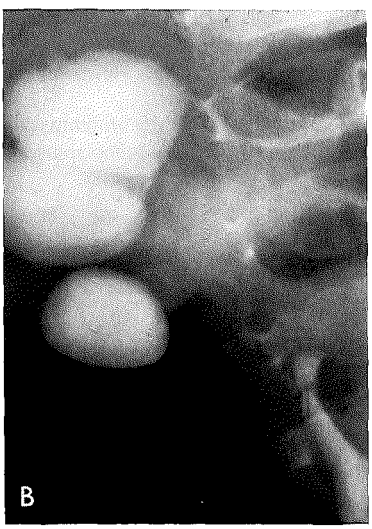


Fig. 9 - Voiding cystogram criteria for coexisting ureteropelvic junction obstruction and reflux.
(A), Wave of reflux is impeded at ureteropelvic junction *(arrow)*
(B), Pelvicaliceal system is dilated out of proportion to ureter and contrast agent in pelvis is less dense than that in ureter. (Heavier contrast agent has settled to more dependent calices [7]).
(C), Obstruction to drainage of diluted, refluxed contrast agent from pelvicaliceal system.

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4.4.2 The coexistence of primary megaureter and reflux (Am J Radiol 1984; 143:1053-1097)

A primary megaureter is dilated because it has a short extravesical distal segment that is normal in caliber but is aperistaltic and thus is functionally obstructed **(fig. 1).** It is one of the major causes of obstructive uropathy in children, is often detected sonographically, and is confirmed by excretory urography. It varies in its severity but usually neither progresses nor improves [1].

Primary vesicoureteral reflux is due to immaturity or maldevelopment of the ureterovesical junction **(fig. 2)** and occurs with all degrees of severity. It is a common abnormality of the child's lower urinary tract and is diagnosed most directly by conventional or radionuclide voiding cystography. The degree of reflux is directly proportional to the degree of abnormality at the ureterovesical junction and when mild, tends to resolve spontaneously [2,3].

These conditions occasionally coexist in the same child [4,6]. This report documents how often this happens, how to recognize it and what the implications are.

Materials and Methods

A review of records of the Department of Radiology and the Division of Urology at the Children's Hospital for 10 years (1973 to 1983) revealed about 2800 children who had primary vesicoureteral reflux. Over the same time, about 75 children had surgical correction of primary megaureter. In nine, the two conditions were found to coexist. The medical records, radiographs, operative notes, and follow-up of these nine cases were reviewed. Reflux was graded by the International Reflux Study classification [3].

Results

The five boys and four girls in whom reflux and primary megaureter coexisted ranged in age from 3 months to 20 years at the time of diagnosis. The reasons for their initial radiologic evaluation included urinary tract infection (nine children), high fever (six), and bacteremia (three). Primary megaureter was unilateral in all nine children, but in two, the reflux was bilateral. Histopathologic examina-

tion of the resected distal ureteric segment revealed fibrous tissue, chronic inflammation with edema, and/or minimal hypertrophy of the muscularis with fibrosis of the submucosal layer. The histopathology is discussed with the representative case reports when it was available.

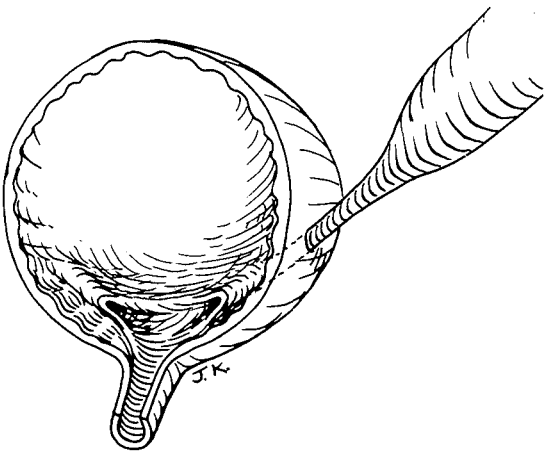

Fig. 1 - Primary megaureter. Representation of juxtavesical aperistaltic segment that is normal in caliber but that is functionally obstructed. When reflux does *not* coexist, ureteral orifice and submucosal tunnel are normal.

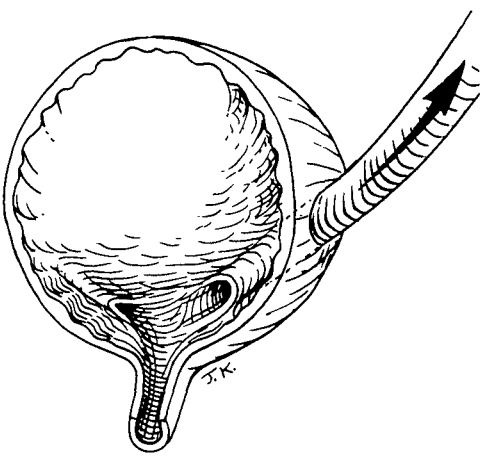

Fig. 2 - Incompetent ureterovesical junction (primary reflux). Representation of abnormality at ureterovesical junction that permits reflux. Orifice may be larger than normal and/or submucosal tunnel shorter than normal.

Representative Case Reports

Case 1

A 5-year-old girl with Larsen syndrome (multiple joint dislocations and flat facie) had a voiding cystourethrogram (VCUG) that showed bilateral reflux, grade 4/5 on the right and grade 2/5 on the left. There was a difference in the density of the contrast material in the bladder compared with that in the right ureter, that is, the refluxed contrast agent had been diluted by urine trapped in the ureter. The juxtavesical segment of ureter was not well seen. A repeat VCUG 1 year later **(fig. 3)** showed an obstructing distal ureteral segment of normal caliber. After resection of the distal segment on the right and reimplantation of both ureters, follow-up studies revealed the collecting system and ureters to be of normal caliber and showed no reflux. Histopathologically there was chronic inflammation and edema of the resected ureter.

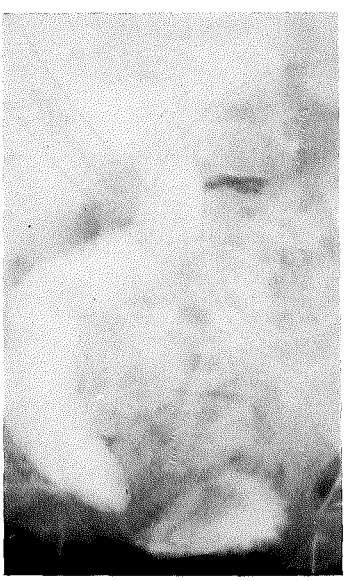

Fig. 3 - *Case 1.* Voiding cystourethrogram, postvoid film. Reflux on right into megaureter: dilated pelvicaliceal system. Distal juxtavesical segment normal in caliber but functionally obstructed *(arrow)* Refluxed contrast material is trapped above it.

Case 2

A 20-month-old girl had a history of recurrent fevers of unknown origin, ultimately proven to be due to infection of the urinary tract. Sonography showed left hydroureteronephrosis. After an ill-advised left ureteral meatotomy, an excretory urogram revealed persistence of the hydroureteronephrosis. She was then referred to the Children's Hospital, where a VCUG showed grade 4/5 reflux on the left and a difference in density of the contrast agent between the bladder and the dilated left ureter **(fig. 4A)**. A drainage film showed trapping of the refluxed contrast agent in the ureter **(fig. 4B)**. An excretory urogram with a catheter in the bladder to temporarily prevent the reflux revealed left hydroureteronephrosis with a normal caliber juxtavesical segment of ureter. A renal radionuclide scan using technetium-99m diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) with provocation by furosemide confirmed obstruction at the distal end of the ureter. The distal aperistaltic segment was resected and the ureter reimplanted. Follow-up studies revealed a nonrefluxing left ureter and a collecting system of normal caliber. Histopathologic evaluation of the distal ureter revealed mild mononuclear inflammatory infiltrate with muscular hypertrophy and an increase in collagen.

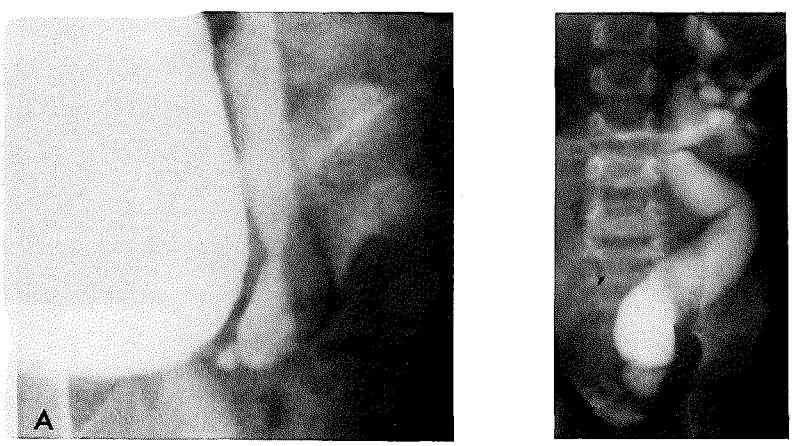

Fig. 4 - *Case 2.* Voiding cystourethrogram. **(A)**, Density of contrast agent in megaureter and dilated pelvicaliceal system is noticeably less than that in bladder, suggesting dilution by trapped nonopaque urine.**(B)**, Postvoid film. Trapping of refluxed contrast material above aperistaltic distal ureteral segment.

Case 3:

A 2-month-old girl had urinary tract infection and fever. An excretory urogram showed fullness of the left collecting system and slight dilatation of the ureter: the right side was normal. VCUG showed bilateral vesicoureteral reflux **(fig. 5A)**. Left distal obstruction was suggested because a juxtavesical segment of normal caliber was seen on that side with trapping of the refluxed urine above it **(fig. 5B)**. The child underwent resection of the distal left ureteral segment and bilateral ureteral reimplantation. No histopathologic report is available.

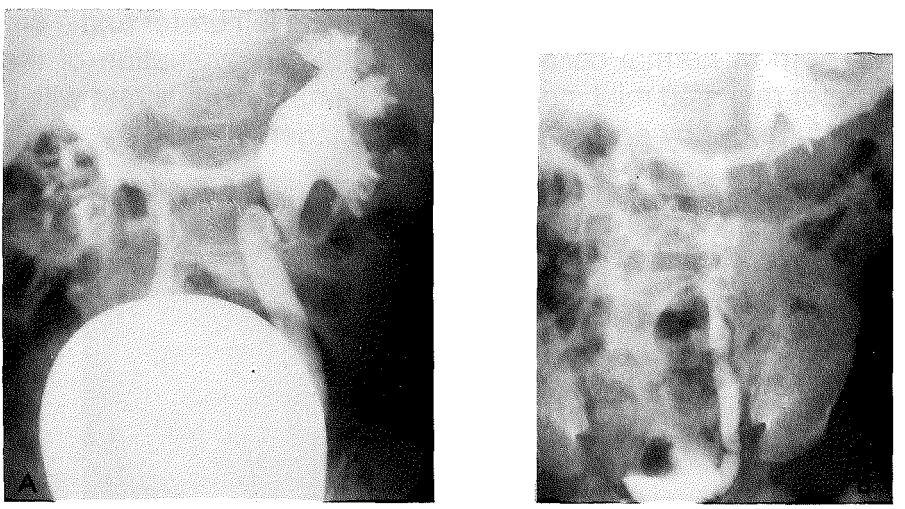

Fig. 5 - *Case 3.* Voiding cystourethrogram.
(A) Bilateral reflux grade 3-4/5 on left and grade 2/5 on right.
(B) Postvoid film. Right side drained promptly, but there is trapping of refluxed contrast material above juxtavesical segment on left.

Discussion

Primary megaureter is a condition that is more common in boys than in girls (2. 4:1) [1]. It varies in severity, is found at all ages, and tends to be stable when uncomplicated. It is due to an as yet undefined abnormality in the wall of a short segment of the juxtavesical ureter. The ureteral orifice and the submucosal tunnel are normal [1] (**fig. 1**). There have been many speculations on its pathogenesis. It was first thought to be a ":persistent uretᵉ rovesical valve" [7]; subsequently its cause has been thought to be crossing intrauterine vessels, [8] infiltration of collagen [9], a circular muscle band proximal to a hypoplastic distal ureteral segment [10,11], or atrophic musculature in the lower ureter [12,13]. An aganglionic segment analogous to that in the colon in Hirschsprung disease has also been postulated[14] but has never been proven. (Normally there *are* ganglion cells in the distal part of the ureter[15]. The treatment of primary megaureter is either expectant or surgical; the latter consists of excision of the distal aperistaltic segment and reimplantation of the ureter, either with or without tapering of the distal segment [16,17]. The upper ureter and pelvicaliceal system often return to normal caliber after successful surgery.

Primary vesicoureteral reflux is the most common abnormality of the child's lower urinary tract[2]. The actual incidence of reflux is either the same in girls and boys or slightly more common in girls[2]. However, more girls than boys are seen with reflux because urinary tract infection, the main indication for performing the voiding cystogram, is more common in girls. Its treatment depends on its severity. Mild reflux tends to resolve spontaneously; the more severe degrees require surgical treatment (reimplantation)[3]. Reflux in children is occasionally secondary, as in case 2.

At first it may seem paradoxical that distal obstruction and reflux

can coexist in the same ureter. However, the relatively low intraluminal pressure in an obstructed ureter[1] can be overcome by the intermittently higher normal intravesical pressure[18]. Thus, urine (or contrast agent) can intermittently reflux through an incompetent orifice and be forced through the aperistaltic segment into the megaureter and the dilated pelvicaliceal system. This leads to a continuing increase in both the degree of dilatation and the volume of trapped urine. It seems to be this aliquot of stagnant urine, when it is infected that results in more severe symptoms and more renal damage than are seen in children who have reflux without coexisting obstruction [19].

The coexistence of reflux and primary megaureter is rare and had been misunderstood [4-6]. Since they are independent condition, any degree of one can coexist with any degree of the other. Their coexistence can complicate both the interpretation of the urogram (reflux into an already dilated ureter may lead to overestimation of the degree of reflux[20]) and the surgical treatment. This rare coexistence can be diagnosed by VCUG when 1. the distal 1-1.5 cm of extravesical ureter is normal in caliber and the adjacent ureter is dilated, without evidence of a localized obstruction **(figs. 1, 3, and 6)**; 2. the density of the contrast agent in the megaureter and pelvicaliceal system is less than t=in the bladder **(fig. 4A)** (or less than on the other side if simple reflux is present there as well); this reflects dilution of the refluxed contrast agent by the stagnant urine trapped above the aperistaltic segment; and 3. there is obstruction to drainage of contrast-laden urine back into the bladder (trapped urine) **(figs. 3, 4B, and 5B).**

Confirmation of the findings noted on the VCUG is by excretory urography (or radionuclide renal scan using ^{99m}Tc-DTPA) with a catheter draining the bladder to temporarily prevent reflux. Either of these latter studies will show the picture of primary megaureter alone

(i.e., dilated calices, pelvis, and ureter down to the obstructing segment). Provocation by furosemide during either the excretory urogram [21] or the radionuclide scan [22] also can help to confirm and quantitate the degree of distal ureteric obstruction.

The technique of antireflux surgery changes when distal ureteral obstruction coexists with ipsilateral reflux. Under usual circumstances (uncomplicated reflux), the distal part of the ureter is not resected [23]. When an obstructing distal segment is present as well, it must be resected [16,17]. Then the normally-functioning dilated ureter can be reimplanted and tapered, should this be necessary. If the distal aperistaltic segment is not resected, even if the reimplantation is technically successful, the child will be left with a nonrefluxing but still obstructed distal ureter.

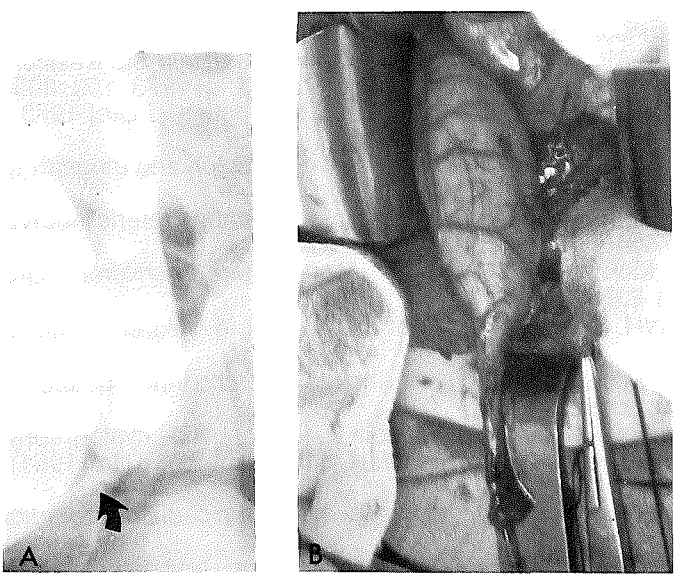

Fig. 6 - (A) Voiding cystourethrogram. Megaureter with distal segment of normal caliber *(arrow)* **(B)** Operative photograph shows distal aperistaltic segment and gradual fusiform widening into megaureter above it, without localized constriction.

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4.4.3 The coexistence of neurogenic bladder and reflux.

In the vast majority of children the neurogenic bladder is secondary to congenital anomalies of the spinal cord or nerve roots, most often a myelomeningocele, less commonly occult spinal dysraphism or cecal agenesis. Injury to the spinal cord, nerve roots or neoplasms as well as osteomyelitis may also be the cause for neurogenic bladder dysfunction.

The principal manifestation of neurogenic bladder is dysfunction of the detrusor muscle and the external urethral sphincter. The urethral resistance is usually increased and the most frequent presenting symptom is UTI. Urinary calculi are not uncommon.

The VCUG is the imaging modality of choice and in more advanced cases shows a hypertonic and trabeculated bladder. Upon voiding, the bladder neck and proximal portion of the urethra are frequently dilated. There is frequent VUR and often this is associated with ureterectasis. The VUR is often bilateral but may be limited to one side for longer periods of time. Large residual volumes are common.

4.4.4. The coexistence of posterior urethral valves and reflux.

The pathogenesis of posterior urethral valves is covered in 4.3.1.

The VCUG manifestations include bladder wall hypertrophy, elongation and dilatation of the posterior urethra. About half of the patients have massive bilateral VUR; in others the VUR is unilateral. They may be dysplastic or poorly functioning kidneys and in severe grades of obstruction urinary extravasation resulting in urine ascites may be present[66]. It is important to follow the VCUG with an EU or radioisotope study of the upper tract. US has been somewhat useful in suggesting the diagnosis, but definite anatomic depiction is by VCUG[66].

4.5 Summary

As neonatal kidney function is immature, radioisotope studies and EU are less useful initial imaging methods, while US is an excellent screening modality to answer questions as to presence, size and shape of the kidneys, and the presence or absence of a dilated ureter[77] (4.1).

If the US study is normal, only the presence of a UTI or symptoms of bladder-sphincter dysfunction demand immediate further investigation with a lower tract study (VCUG).

If these studies are abnormal, the need to again fully evaluate the entire urinary tract is shown by the fact that coexisting abnormalities do occur and may lead to long-term damage of kidney function (UPJ obstruction, e.g. 4.4)[78], primary (obstructive) megaureter, PUV or neurogenic bladder coexisting with VUR[78].

The flow chart presented in 3.3 is thus proven useful incorporating symptomatology and structural factors. It allows for minimizing potential or existing renal damage.

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V CONCLUSION

5.1 Conclusions and Summary

5.2 Samenvatting

5.1 Conclusions and Summary

Acute urinary tract infection (UTI) is an important cause of morbidity in children and may be complicated by congenital urinary tract abnormalities of a functional or anatomic nature which predispose to recurrent UTI's that in turn may lead to renal failure and hypertension. Early radiologic and ultrasonographic investigation may reveal these anatomic anomalies in particular because the urinary tract specifically in children is not readily accessible to adequate clinical examination.

Excretory urography (EU) has been considered as the "gold standard" of upper urinary tract visualization, while the voiding cystourethrogram (VCUG) was thought to be the preferential method of imaging of the lower urinary tract. Recently, major technical advances have altered this commonly accepted diagnostic workup. Although ultrasonography, radionuclide scanning and urodynamics have become important contributors to the understanding of the pathophysiology of UTI's their value and place in assessment of the sequence of imaging has not been comprehensively studied.

The VCUG is thought to be superior to other techniques in evaluating functional anatomy of the bladder and urethra as well as determining the presence and grade of VUR, but, by many who favor other modalities, thought to have major risks as well.[1] The accuracy of this method set against unfavorable side effects was studied in 958 consecutive children who had an index UTI. (3.1.3). The major complication of infection from the procedure was less (<0.3%) than the 6-10% quoted in the literature. These marked differences can simply be ascribed to small series in the literature but refined techniques and well trained personnel may also be instrumental. Erosion of the

urethra or damage to the bladder alluded to in many anecdotal cases in the literature, did not occur in our large series. Irritative effects of the contrast agent occurred in 14%, similar to what was quoted in the literature, while peritoneal irritation was never noted, lending credence to the highly speculative nature of the few reported cases of peritonitis after VCUG. Variables that may influence the results of a VCUG were found to be much smaller and of considerably less importance than currently thought.

Vesicoureteral reflux (VUR) is a dynamic phenomenon, and consequently static overhead imaging is not sufficient. Fluoroscopy allows for physiologic observation and recording, but exposes the child to low doses of radiation. Average fluoroscopy time and radiation exposure in our standardized protocol was 14 seconds in girls and 24 seconds in boys, considerably less than the several minute exposures referenced in the literature[2]. Especially digital fluoroscopy allows for radiation exposures not yet quite as low as the RNC but only a few percentage points different. However, these modifications of previously held beliefs allow for adapting the VCUG to a streamlined lower tract procedure, shorter and more specific than the RNC, much more definitive and with fewer contraindications than the US; thus exquisitely suited for the definitive lower tract study. These results were obtained while confirming the literature in that in all our 958 patients with an index UTI, 31% had VUR, 85% of those with reflux nephropathy (RN)[1].

Subsequently, the question as to whether a US or EU should be used in the face of a normal initial VCUG was addressed prospectively. US revealed a sensitivity of 87% and a specificity of 82% with regard to the detection of RN if we use EU as the gold standard. They can therefore be regarded as equal with respect to structural imaging of the

upper tracts, confirming other literature.[3,4]

The VCUG was found to be the crucial and often initial imaging study of the lower urinary tract in a prospective study of 398 patients presenting with an index UTI. (3.1.4). Our hypothesis was that if upper tract studies could predict abnormalities in the lower urinary tract studies, we would no longer need lower tract studies. However, VUR greater than grade 2/5 (1=little, 5 = severe) was found in 73% of children by VCUG with an otherwise normal EU irrespective of age, VUR grade or abnormalities on EU.

Thus, EU and, by extension, renal US[5] are insensitive methods for detecting the presence of VUR, the most frequent anatomic abnormality in children with UTI.[5] Moreover, relying on normal upper tract studies without appreciation of VUR will mislead the radiologist. Renal damage can thus be over- or under estimated and seriously affect the choice and efficacy of therapy. This means that VUR should be sought aggressively and the VCUG should be the crucial imaging procedure as a positive results may alter the manner of upper tract imaging. Some have argued that, if the kidneys are normal on upper tract imaging studies, the detection of VUR is not important since the kidneys have remained normal in spite of the VUR.[3,4] As scars herald RN, and may take up to six months to develop after the infection, this may be true in the older child but not in the under age 6 years group, where UTI is more common: thus, in the young child with a index UTI, whose kidneys are normal, the discovery of VUR provides the opportunity to insure that they remain normal by proper surveillance and therapy. The initial results of the International Reflux Study undeniably demonstrated that VUR tends to diminish with age, while obstructions usually get worse.[6]

However, recent studies found that the bacterial organisms

which cause the UTI can result in abnormalities of contractility patterns of the collecting systems due to their adherence properties to the mucosa.[7,8] These bacteria can thus persist and find their way to the kidneys, potentially causing RN. In a recent study, the positive predictive value in a series of 84 children was 30%, the negative predicative value 96%. Furthermore, even with demonstrated normal urinary tract, UTI's recur in 10% to 15% of all patients under age six years.[9] Unfortunately, even on a well performed VCUG, this recently demonstrated detrusor-sphincter instability during voiding and over-activity of the detrusor muscle in the filling phase are difficult to appreciate. Since these are transmitted in the presence of VUR to the renal pelvis, patients with this complex of underlying physiologic abnormality, might comprise a significant portion of this percentage of recurrent UTI patients. In a small group of patients it was shown that urodynamic studies have a distinct function in children who failed treatment based on conventional anatomic evaluation. (3.1.5) Approximately half (56.1%) of patients in this small series treated based on urodynamic evaluation were cured, while 70% of the remainder showed a decrease in reinfection rate (<5%).

If the VCUG is abnormal an upper tract study should be performed to evaluate renal function. To eliminate the effects of VUR, if VUR is greater than grade 2, a catheter is then placed in the bladder while performing the EU. It was previously though that, because in adult patients nephrotomography had been recommended to improve the understanding of renal abnormalities of structure and function, this should apply in the pediatric population as well. It was conclusively shown that tomography leads to better delineation of the renal contours in only 16% of patients and more importantly did not alter choices of therapy. (3.2.4). The implications are evident in patients with need for

EU: a tailored study of two or three exposures is sufficient in obtaining the information of the upper tract and the results will not be influenced by VUR. This minimizes radiation exposure by factor 10 in patients under age 3 and factor 100 in children over age 3 due to higher exposures in patients with larger body surfaces while the sex differences are explained by location of the gonads. Tomography increases the cost of an EU by about $50 per examination, which in these days of cost containment must be a consideration when a test is used with such a low yield.

The flow chart presented at the end of Chapter 3 needed to be tested in clinical practice, as well as for all children under age 6. This was done by addressing whether symptomatology or specific urinary tract abnormalities affect this flow chart in its effectiveness. It was therefore tested in two groups of patients where VUR co-existed with upper or lower tract obstructive lesions to see if therapy would have been different if the flow chart was not followed. (4.4.1 and 4.4.2) The proper identification of these coexisting abnormalities and their subsequent treatment are totally dependent on the interpretation of the imaging studies. The interpretation is significantly facilitated and more efficient by following the flow chart to keep time, radiation and morbidity to a minimum. The order in which surgery is done (whether to relieve an obstruction or correct VUR) turns out to be crucial to avoid a significant increase in morbidity and potential mortality. Without consultation of this flow chart one could inadvertently remove a functioning kidney or exacerbate existing obstruction (see 3.1.4). Therefore an ordered approach, centered around the VCUG, is not only efficient but crucial for proper therapeutic planning. Even though these co-existing lesions are rare, these results underscore that by following this flow chart mistakes in diagnosis and thus in therapy are

minimized, thereby keeping long-term complications of RN to a minimum.

Finally, ultrasound can be the initial study, especially in neonates as obstructive hydronephrosis is a crucial diagnosis in urosepsis, as well as when complicated UTI's are suspected.

This thesis thus underscores the belief that it is not possible to identify subgroups of children under 6 years of age in whom the risk of progressive renal damage after an index UTI is so low that imaging of the entire urinary tract is not needed. This is substantiated by the fact that:

-upper or lower urinary tract imaging alone is not sufficient;

-a VCUG is the necessary and pivotal imaging study, most often in combination with US;

-when a VCUG is done first, depending on its results, a responsible imaging choice regarding the upper tracts can be made whether to utilize EU for upper tract evaluation;

-an EU without tomography can be sufficient;

-RNC and UD should be reserved for second line imaging studies in recurring UTI's.

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5.2 Samenvatting

Urineweginfectie (urinary tract infection = UTI) is één van de meest voorkomende bacteriële infecties bij de zuigeling en het jonge kind. Urineweginfectie kan een belangrijke aanwijzing zijn voor het bestaan van structurele afwijkingen aan de urinewegen.

Zowel met als zonder structurele urinewegafwijkingen kan recidiverende UTI leiden tot latere nierbeschadiging met functieverlies, hypertensie, en uiteindelijk zelfs nierinsufficiëntie.

Voor het opsporen en behandelen van UTI en eventueel daaraan ten grondslag liggende structurele afwijkingen zijn, naast de nierfunctietests, de beeldvormende techieken zeer belangrijk.

Dit proefschrift gaat over het optimaliseren van de keuze en de volgorde van de verschillende beeldvormende techieken bij de evaluatie van kinderen jonger dan 6 jaar met UTI.

Tot voor kort was het intraveneuze pyelogram (EU) het belangrijkste onderzoek voor de evaluatie van de hoge urinewegen, en het mictiecysto-urethrogram (VCUG) van de lage urinewegen. Nieuwe technische ontwikkelingen maken een herwaardering van deze beeldvormende technieken noodzakelijk.

Wij beschikken immers nu over een aantal nieuwe onderzoek-methoden zoals echografie, urodynamisch onderzoek, radio-isotopen, computertomografie en kernspinresonantie-afbeelding (MRI).
Hierover kan het volgende worden opgemerkt:

- echografie geeft gedetailleerd anatomisch inzicht, is niet invasief, werkt zonder ioniserende straling en is daardoor geschikt als "screenings-onderzoek".
- de waarde van urodynamisch onderzoek is steeds duidelijker.

- radio-isotopen geven de mogelijkheid de pathofysiologie van de urinewegen (reflux) te bestuderen bij veel lagere stralingsdoses dan bij het conventionele röntgenonderzoek. De specifiteit is echter lager.
- computertomografie (CT) blijkt slechts van nut te zijn bij kinderen met gecompliceerde afwijkingen in een later stadium. Het zelfde geldt voor MRI.

Deze nieuwe methoden moeten worden geïntegreerd met het EU en VCUG.

In dit proefschrift wordt onderzocht

-of volstaan kan worden met beeldvorming van slechts de hogere of de lagere urinewegen;

-of het VCUG onontbeerlijk dan wel schadelijk zou zijn voor patiëntjes met UTI;

-of de volgorde van de verschillende onderzoeksmodaliteiten belangrijk is;

-en welke plaats urodynamisch onderzoek moet innemen.

In hoofdstuk 2 wordt een overzicht gegeven van embryologie en fysiologie van hoge en lage urinewegen met speciale aandacht voor de inmonding van de ureter in de blaas.

In hoofdstuk 3 wordt een overzicht gegeven van de gebruikte afbeeldingstechnieken. Deze gegevens worden vergeleken met de resultaten van auteurs zoals deze in de literatuur worden vermeld.

De voor- en nadelen van het VCUG worden beoordeeld op grond van 958 onderzoeken bij eigen patienten. In het bijzonder wordt bij een groep van 389 patienten met index UTI prospectief nagegaan hoe de VCUG past in de volgorde van de onderzoeken. Een prospectief onderzoek naar de afbeeldings-mogelijkheden van de hoge urinewegen, waarbij inbegrepen de waarde van de aanvullende

tomografie, wordt bij twee afzonderlijke groepen patienten verricht. (n=122 en n=84)

Het grote belang van het urodynamisch onderzoek wordt hierbij belicht in een geselecteerde groep patientjes(n=52). Deze evaluaties worden verwerkt in een beslissingsboom waarbij het VCUG centraal staat.

In hoofdstuk 4 wordt aangetoond dat de centrale plaats van het VCUG van grote klinische betekenis is. De beslissingsboom wordt gevolgd en de waarde ervan getoetst aan twee groepen patienten met een combinatie van afwijkingen. Het volgen van de beslissingsboom blijkt van onschatbare waarde voor de juiste volgorde en correcte therapie.

Bij de neonaten en kinderen met een gecompliceerde UTI komt het VCUG niet noodzakelijk als primair onderzoek in aanmerking, omdat obstructieve hydronephrose met US is vast te stellen.
Hoofdstuk 5 vat de bewijsvoering van hoofdstukken 3 en 4 samen.

Het gevolg van deze bewijsvoering is dan:

-dat beeldvorming van óf de hogere óf de lagere urinewegen niet voldoende is;

-dat het VCUG in combinatie met US een veilig, onontbeerlijk en centraal onderzoek is, geschikt om het juiste eropvolgende onderzoek aan te geven om daardoor de therapie te optimaliseren;

-dat een EU onderzoek zonder de stralenbelasting van tomographie diagnostisch voldoende is;

-en dat een urodynamisch onderzoek, net als isotopen onderzoek, pas in een later stadium overwogen dient te worden.

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