Lithuanian University of Health Sciences
Faculty of Medicine
Department of Pediatrics

Title of Thesis :

COMPARISON OF DIFFERENT DIAGNOSTIC METHODS FOR THE DIAGNOSIS OF VESICOURETERAL REFLUX IN CHILDREN

A Dissertation submitted in Partial Fulfillment of the Requirements
for the Degree Master of Medicine

Author : Shiama Zuhairy

Supervisor: Dr Šarūnas Rudaitis

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1. SUMMARY

Author name: Shiama Zuhairy

Research Title: Comparison of different diagnostic methods for the diagnosis of vesicoureteral reflux in children.

Aim: To analyse and compare different diagnostic methods for the diagnosis of vesicoureteral reflux in children.

Objectives:
1. The role of Voiding Cystourethrogram as a diagnostic method of Vesicoureteral reflux (VUR).
2. Comparison of Voiding Cystourethrogram and Nuclear Cystography (NC) in diagnosing VUR.
3. To evaluate the accuracy of Voiding Cystourethrogram with Contrast enhanced voiding urosonography (ceVUS) in diagnosing VUR.

Methodology: Relevant studies were obtained from the following source; Pubmed. References cited where less than 10 years old. The search term used were “Vesicoureteral reflux”, “diagnosis”, “methods”, “children”, “Voiding Cystourethrogram”, “Voiding Urosonography”, and “Nuclear Cystography”. The database search identified 1500 titles in PubMed, narrowed down to 60 articles. 21 articles that met the criteria were analysed, while the remaining 39 articles were excluded from the study as it didn’t meet the criteria. 14 studies were eligible in the study who met inclusion criteria.

Results: VCUG is the test of choice to diagnose the presence and degree of VUR. In three studies included a total of 203 patients at the age ranging from 1 months to 13 years. A total of 406 PUUs were compared. Results were found in 88% with VUR being detected only on VUS in 11% and only on RNC in 20% of the refluxing PUUs.

Conclusions:
2. In comparison with VCUG, Indirect radionuclide cystography can be used for follow up for patients with VUR. It can be used in the diagnosis of VUR as an alternative to VCUG in selected cases. Indirect radionuclide cystography can’t show precise anatomical changes, but it has less radiation rate. Therefore VCUG is the best method to use.
3. The accuracy of ceVUS compared to VCUG, with sensitivities ranging from 26% to 53% and specificities up to 80%. It is a safe, but not sufficient precise method.
2. ACKNOWLEDGEMENTS

Many thanks to my supervisor Dr Šarūnas Rudaitis for his guidance and encouragement throughout my research. Also I would like to thank my family for all their help and support.
3. CONFLICT OF INTEREST

The is no conflict of interests declared regarding the publication of this paper.

4. ETHICS COMMITTEE CLEARANCE

There was no clearance issued required for this publication.
5. ABBREVIATIONS

VUR - vesicoureteral reflux
IRC - indirect radionuclide cystoureterography
UTI - urinary tract infection
VCUG -voiding cystoureterography
DRNC- direct radionuclide cystography
RNC - radionuclide cystography
ceVUS - contrast enhanced voiding urosonography
EAU - European Association of Urology
VUS -voiding urosonography
CSG –cystosonography
NC- nuclear cystography
KUU -kidney ureter units
UCA -ultra contrast agents
RPD – renal pelvis dilation
DMSA- dimercaptosuccinic acid
PUU - pelvic ureter unit
US - ultrasonography
Tc99mMAG3 - mercaptoacetyltrimglycine
PUV- posterior urethral valve
2DUS- two dimensional contrast enhanced voiding urosonography
6. INTRODUCTION

Urinary tract infection is common in children and vesicoureteral reflux is one of its predisposing factors. The infection can affect different parts of the urinary tract, including the bladder, kidneys, and urethra. VUR is found in 30–45% of infants at presenting with a febrile UTI. VUR is associated with an increased risk of recurrent UTI and renal scarring. [1] Prevalence of VUR is 25% in children younger than 4 years with febrile UTI, 12% in children between 4-12 years and 5% in adults. [1]

Children commonly present to the medical imaging department needing for a voiding cystourethrogram (VCUG) due to frequent urinary tract infections. One major indication that testing may be needed is due to recurrent urinary tract infection and anatomical abnormalities. Voiding cystourethrogram for a long time has been the gold standard of imaging for diagnosing VUR, despite the child's exposure to radiation. This test can aid in diagnosis of abnormal structures or function of the urinary system. Radionuclide cystography which has limited value because of its inability to show precise anatomic detail.[2]

There are many discussions about the best imaging technique in children. That’s why we decided to analyse the problem. VCUG, RNC and VUS has its advantages and drawbacks of this modality in being performed which are discussed in this review. It is important that the chosen diagnostic method should be accurate and be safe as possible. Treatment recommendations depends on grade of VUR. [3] It is important for clinicians to use the grading system of VUR developed by International Reflux Study Committee [4]

| Grade I | Reflux does not reach the renal pelvis; varying degrees of ureteral dilatation. |
| Grade II | Reflux reaches the renal pelvis; no dilatation of the collecting system; normal fornices |
| Grade III | Mild or moderate dilatation of the ureter, with or without kinking; moderate dilatation of the collecting system; normal or minimally deformed fornices |
| Grade IV | Moderate dilatation of the ureter with or without kinking; moderate dilatation of the collecting system; blunt fornices, but impressions of the papillae still visible |
| Grade V | Gross dilatation and kinking of the ureter, marked dilatation of the collecting system; papillary impressions no longer visible; intraparenchymal reflux |
7. AIMS AND OBJECTIVES

Aim: To analyse and compare different diagnostic methods for the diagnosis of vesicoureteral reflux in children.

Objectives:

1. The role of Voiding Cystourethrogram as a diagnostic method of Vescicoureteral reflux.
2. Comparison of Voiding Cystourethrogram and Nuclear Cystography in diagnosing VUR.
3. To evaluate the accuracy of Voiding Cystourethogram with Contrast enhanced voiding urosonography in diagnosing VUR.
8. LITERATURE REVIEW

Diagnostic methods of VUR

8.1 Voiding Cystourethrogram

Voiding Cystourethrogram has been the gold standard of imaging for diagnosing and grading of VUR. It is a fluoroscopic examination, utilizing radiographic contrast medium and X-ray screening. The procedure involves bladder catheterization and intravesical administration of radiographic contrast via a urinary catheter, followed by examination of the lower abdomen and pelvis. This method involves exposure to ionizing radiation. The mean effective dose of VCUG is 0.4 to 0.9mSV. Effects of radiation on developing tissue in children is more sensitive. VUR can sometimes be missed by intermittent fluoroscopic screening techniques. The dilution of little amount of radiographic contrast in the already dilated collecting system, and obscuration by overlying bowel shadow, contribute to the lower sensitivity of VCUG.[5]

8.2 Radionuclide cystography

There are two methods for radionuclide cystography (RNC): direct RNC and indirect RNC. The procedure for direct RNC is similar to that for VCUG but the urinary bladder is instilled with radionuclide and imaging is performed with agamma (scintillation) camera connected to a computer. Indirect RNC does not need bladder catheterization, but the examination can only be performed on toilet trained children following a dynamic renogram preceded by intravenous administration of the radionuclide.[5]

DRNC involves bladder catheterization and intravesical administration of radioactive medicine. The advantages are that there is continuous examination of the kidneys and bladder during the filling phase, and the lower gonadal radiation dose. In comparison with VCUG, it has lower spatial resolution and inability to show precise anatomic detail. It is recommended for follow up of VUR.[5]
8.3 Contrast-enhanced voiding urosonography

ceVUS is a new technique for diagnosis of VUR. The second generation of ultrasound contrast agents and higher quality ultrasound machines, with contrast-specific software technology, have allowed the diagnostic imaging process of ceVUS without ionizing radiation. Contrast enhanced US for detection of VUR has been performed by creating air bubbles from normal saline solution by flushing the material in and out of a syringe or shaking it within the container before administration into the bladder to enhance visualization.

The UCA is administered intravesically via a urinary catheter, followed by alternate examination of the kidneys, urinary bladder and retrovesical region during filling and voiding phases, also the urethra, by transperineal or interscotal approach during the voiding phase. Kis et al. reported ceVUS to be more sensitive than VCUG since it is a real time imaging method, allowing prolonged, continuous scanning, and therefore has the potential to detect VUR.[6]

The diagnosis of VUR is determined by the presence of moving echogenic microbubbles from the ultrasound contrast in the upper urinary tract. The five-tier grading system developed by Darge and Troeger[7] which is similar to the international reflux system: Grade I Microbubbles only in the ureter; Grade II Microbubbles in the renal pelvis; no significant renal pelvic dilatation; Grade III Microbubbles in the renal pelvis + significant renal pelvic dilatation + moderate calyceal dilatation; Grade IV Microbubbles in the renal pelvis + significant renal pelvic dilatation + significant calyceal dilatation; Grade V Microbubbles in the renal pelvis + significant renal pelvic dilatation and calyceal dilatation + loss of renal pelvis contour + dilated tortuous ureters. [7]

Many efforts have been made to use ultrasonography for non-invasiveness and lack of radiation for diagnosis of VUR. It doesn’t require urethral catheterization, avoiding anxiety for parents to refuse treatment. [8]
8.4 Diagnosis of VUR

Primary Reflux is diagnosed after presence of UTI or during follow up for congenital anomalies of the kidney and urinary tract. Secondary reflux occurs as a result of a bladder obstruction. Children with VUR are also at increased risk of renal scarring, developing proteinuria, hypertension and renal disease. [21]

Main risk factors that should be assessed on management of VUR including family history, gender, age, symptoms, VUR grade, and other voiding dysfunctions. For basis of diagnosis and further management standard imaging tests are used such as VCUG, RNC and ceVUS. Careful monitoring should be carried out in all examinations and imaging. The choice of imaging depends on presentation of patient. VUR and urinary tract infections may affect renal function in affected children. When urine waste is not expelled properly from the body, bacteria can grow, leading to infection. [21]

The initial presentation of the child with VUR should undergo a careful general medical examination including measurement of height, weight, blood pressure and serum creatinine. Urinalysis for proteinuria and bacteriuria is essential. If the urinalysis indicates infection, a urine culture and sensitivity is recommended. [4] Performing renal ultrasound to assess the upper urinary tract is recommended. DMSA (technetium-99m-labeled dimercaptosuccinic acid) renal imaging can be obtained to assess the status of the kidneys for scarring and function. [18]

We investigate for the presence of VUR by the finding of hydronephrosis on prenatal ultrasonography, bladder and bowel (voiding) dysfunction and febrile UTI infection. If the VCUG is normal and the RPD >15 mm, a functional renal scan with Tc99mMAG3 is performed to detect possible ureteral obstruction. [19]
9. RESEARCH METHODOLOGY AND METHODS

The study which we dealt with VUR in children. We searched PubMed and screened articles and abstracts. Limiting the search to English Language.

Relevant studies were obtained from the following source; Pubmed The search term used were “vesicoureteral reflux”, “diagnosis”, “methods”, “children”, “voiding cystourethrogram”, “voiding urosonography”, and “nuclear cystography”. References cited where less than 10 years old.

Relevant papers were selected by screening the titles (first step), abstracts (second step) and entire articles (third step), retrieved during the database searches. During each step, the title, abstract, or entire article was screened to ensure that it met the criteria listed above. The database search identified 1500 titles in PubMed, narrowed down to 60 articles. 21 articles that met the criteria were analyzed, while the remaining 39 articles were excluded from the study as articles were more than 10 years. 14 studies were eligible in the study who met inclusion criteria.

Search Methods: We searched Pubmed, and the Cochrane Studies. The related articles were searched to identify additional studies not found through the electronic search.

Selection Criteria: We searched the literature, determined study eligibility, assessed quality extracted and entered data. Also reviewed published cross-sectional or cohort studies that compared the results of the tests VCUG and VUS with the results VCUG and NC in children less than 18 years of age.
Fig 1 Steps taken to find relevant articles associated with objectives

Records identified through database searching (n=1500) using the terms "VUR" and "VCUG"

Additional records identified through other sources (n=2)

Records after duplicates removed (n=200)

Studies screened and assessed for eligibility (n=21)

Records identified (n=60) using terms "VUR in children" age group birth to 18 years

Records excluded as articles were more than 10 years (n=39)

Studies included in quantitative synthesis (meta-analysis) (n=14)

Articles assessed for eligibility and relevance in accordance with objective 1 (n=3)

Articles assessed for eligibility and relevance in accordance with objective 2 (n=4)

Articles assessed for eligibility and relevance in accordance with objective 3 (n=7)
## RESULTS

<table>
<thead>
<tr>
<th>Author</th>
<th>Main Results</th>
</tr>
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<tbody>
<tr>
<td>Fernández-Ibieta M</td>
<td>The indication for the test was suspicion of VUR (36 patients) and PUV follow-up (4 patients). For 3 of these patients with bilateral VUR demonstrated in the serial VUS, the VCU...</td>
</tr>
<tr>
<td>Darge K</td>
<td>In the first group VCU was followed by VUS and in the second group VUS was followed by VCUG. VUR was detected in 34% and 38% of PUUs.</td>
</tr>
<tr>
<td>Stokland E, Hellstrom M</td>
<td>The three studies included a total of 203 patients with age group from 1 month to 13 years old. Total of 406 PUUs compared. Results showed in 88% with VUR being detected only in VUS in 11% and DRNC 20% of refluxing PUUs.</td>
</tr>
<tr>
<td>Berrocal et al</td>
<td>Comparison between CSG with VCUG showed that both methods with respect to presence or absence of VUR and grade of VUR in 83.7% of renal units.</td>
</tr>
<tr>
<td>Uhl M, Kromeier J</td>
<td>VCUG and VUS were carried out in the same patient. Total of 24 children mean age 3.5, referred for reflux examination. Results showed VUS had 84% sensitivity, 100% specificity, and 90% positive and negative predictive values. In 16 units the reflux was detected by both VCUG and VUS. In 3 KUU reflux was detected only by VCUG. All 3 cases were grade 1.</td>
</tr>
<tr>
<td>Berrocal et al</td>
<td>216 pediatric patients by cystosonography enhanced with levovist versus VCUG. VUR was detected in 123 kidney units at cystosonography and in 104 in VCUG.</td>
</tr>
<tr>
<td>Galia M, Midiri M, Pennisi F</td>
<td>Total of 8 of 26 (69%) refluxing ureters were detected by DRC in comparison to VCUG detected reflux in 22 out of 26 (85%).</td>
</tr>
<tr>
<td>Darge K. 2002</td>
<td>Results were found in 88% with VUR being detected and VUS 11% and only in RNC 20% of the refluxing PUU.</td>
</tr>
<tr>
<td>Pinthus JH et al</td>
<td>From 109 ureters, 29 with urinary reflux were detected by IRC method, whereas only 15 were diagnosed using VCUG.</td>
</tr>
</tbody>
</table>
11.DISCUSSION OF RESULTS

11.1 ceVUS versus VCUG

The accuracy of ceVUS compared to VCUG, with sensitivities ranging from 26% to 53% and specificities up to 80%.

Four studies comparing these methods were included in the review. Second-generation contrast SonoVue and of software for harmonic makes it possible to color code the conventional signal, allowing for dual image on the same screen. The examination by VUS carries out 2 examinations simultaneously echo and VUS.

One of the papers conducted in general practice in Spain included 40 patients (80 renal units) between the ages of 2 months and 13 years. The indication for the test was suspicion if VUR (36 patients, group A) and PUV follow-up (4 patients, group B). The test was correlated with VCUG in 16 patients (12 cases with high suspicion of VUR in group A and with 4 cases of PUV in group B). The visualization of the urethra was appropriate in cases of dilation or urethral stricture. For 3 of these patients with bilateral VUR demonstrated in the serial VUS, the VCUG showed only unilateral VUR in 2 of the patients and no VUR in 1 of the patients.[9]

In additional to Fernández study, Wozniak reported studies 2DUS and 3DUS/4DUS urosonography diagnosed 10 more refluxes than VCUG and in 3 refluxes, detected a higher grade. In 9 refluxes 3DUS/4DUS urosonography and cystourethography diagnosed a higher grade than 2DUS. There was a significant disimilarity between cystourethography and 3DUS/4DUS urosonography where number of refluxes and grading were compared.[10]
Table 2 Number and grading of refluxes detected by 3DUS/4DUS ceVUS taken from Magdalena et al.

Concordance between VCUG and 3DUS/4DUS contrast enhanced voiding urosonography (ceVUS) in detection and grading of reflux. Green—number of refluxes detected by both methods. Yellow—number of refluxes detected by VCUG and missed by 3DUS/4DUS ceVUS. Red—number of refluxes detected by 3DUS/4DUS ceVUS and missed by VCUG. Blue—number of refluxes detected by both VCUG and 3D/4D ceVUS but graded differently by each method.

In another study included 308 children, Sono Vue-enhanced VUS and VCUG were carried out simultaneously. In the first group VCUG was followed by VUS and in the second group VUS was followed by VCUG. VUR was detected in 34% and 38% of PUUs, but the difference in reflux between the two groups was not significant.[13]

There are three comparative studies of Levovist-enhanced VUS in children with RNC. Only two of these included comparison of reflux grades. Kenda et al. conducted VUS and RNC filling the bladder with both UCA and radionuclide and scanning at the same time. No adverse effects reported. The three studies included a total of 203 patients with age group from 1 month to 13 years old. Total of 406 PUUs compared. Results showed in 88% with VUR being detected only in VUS in 11% and DRNC 20% of refluxing PUUs. From the results shown DRNC is more sensitive than VUS in detecting VUR.[12]

The major factors restricting its widespread use is the higher cost of ultra contrast agents compared to radiographics contrast agents. Advances in both US and UCA have positive
effect in reducing examination time. The major advantages the the possibility of avoiding the exposure of children to radiation.

Using urosonography particularly grade 1 showed difficulties of low grade refluxes, which was a limitation of this diagnostic method. However low grade reflux seemed less harmful than missed diagnosis of high grade reflux as low grade reflux resolves eventually. In the study of Berrocal et al comparison between CSG with VCUG showed that both methods with respect to presence or absence of VUR and grade of VUR in 83.7% of renal units.[7] There was correlation in detection of VUR but not in grade of VUR in 3.8% of renal units. CSG detected a higher grade of VUR than VCUG. Difference in detection rates between the two methods favoured cystosonography. [10]

According to recommendations of the American Society of Urologists treatment depends on grade of VUR. Therefore the diagnostic method for diagnosis of VUR should be safe, easy to perform, involve no radiation, and be noninvasive and inexpensive. CSG fulfils all, apart from being invasive and expensive. Also its more difficult to evaluate the urethra with cystosonography then with VCUG.

**11.2 VCUG vs VUS**

Many studies have been carried out demonstrating high diagnostic accuracy of VUS compared to VCUG. Both VUS and VCUG were carried out simultaneously. A study done in hospital in Germany, total of 24 children, mean age 3.5 years, 16 girls and 8 boys referred for reflux examination. VCUG and VUS were carried out in the same patient. Results showed VUS had 84% sensitivity, 100% specificity, and 90% positive and negative predictive values. In 16 units the reflux was detected by both VCUG and VUS. In 3 KUU reflux was detected only by VCUG. All 3 cases were grade 1. This reconfirms VUS to be a reliable in verification of reflux. [11] VCUG has high radiation which high gonadal dose is unavoidable, because of the location of the gonads. In comparison with RNC has less radiation, and another method for detection of VUR, although it lacks spatial resolution. Kenda et al detected difficulties arising in interpreting low grade VUR by direct RNC. [12]
Advantages and Disadvantages of VUS

One of the major factors restricting its widespread use is the higher cost of UCAs in comparison to radiographic contrast agents. Also VUS takes a longer time for examination. Urosonography is only carried out in few centres, its not widely accepted. Also inadequate evaluation of bladder morphology and lack of view of urinary tract. The major advantage is no exposure to radiation. Not only can it be performed by paediatricians but also other paediatric subspecialists, including sonographers. It is more sensitive and detects higher grades of reflux. No bladder catheterisation is involved. Comparative studies have shown that direct radionuclide voiding cystography is more sensitive for diagnosis of VUR than Xray voiding cystourethrography. Both methods involve exposure to radiation. Although echo enhanced agents were well tolerated by patients, their availability is limited.

The use of echo enhanced renal sonography for detection of VUR in children has been investigated. Kenda et al carried out an investigation involving 99 children with 198 refluxing units by direct radionuclide voiding cystography and echo enhanced gray scale sonography. Results obtained were similar overall in sensitivity (79%), but higher specificity (92%). [14]

The use of US contrast agents in infants and children require specific considerations in comparison to its use in adults. However for children, taking into account CeVUs high diagnostic accuracy combined with extremely low rate of adverse events, likely done to the catherization and not the US contrast agent, along with the elimination of exposure to radiation and iodinated contrast agents.[14]

With the findings from Fallah et al, ultrasound should be considered for the diagnosis, grading, and follow-up of pediatric patients with vesicoureteric reflux. It is even more critical that the initial imaging should be done without ionizing radiation. [14]
VCUG versus RNC

VCUG is the test of choice to diagnose the presence and degree of VUR. RNC is an alternative modality. However, due to the increased radiation exposure associated with VCUG, VCUG provides greater anatomic detail. Specifically, RNC does not show bladder wall appearance or Grade I reflux. For this reason, RNC is not used as the initial study, but may be used to monitor for persistent reflux in follow up studies. Radionuclide cystography has the highest sensitivity in the diagnosis of VUR and because of its less radiation rate. [20]

In three studies included a total of 203 patients at the age ranging from 1 months to 13 years. A total of 406 PUUs were compared. Results were found in 88% with VUR being detected only on VUS in 11% and only on RNC in 20% of the refluxing PUUs. From the above discussion, comparative studies with RNC are few, as most studies compare the sensitive US methods. [13]

Berrocal et al evaluated 216 pediatric patients by cystosonography enhanced with levovist versus VCUG. VUR was detected in 123 kidney units at cystosonography and in 104 in VCUG.

A study carried out in a hospital in Turkey showed good relation between DRC and VCUG in evaluation of VUR. Total of 8 of 26 (69%) refluxing ureters were detected by DRC in comparison to VCUG detected reflux in 22 out of 26 (85%). This shows that VCUG is gold standard method for evaluating lower urinary tract, urethra, bladder and for detection of VUR. [15]
Table 3. Voiding cystourethrography and direct radionuclide cystography results in refluxing kidney(ureter units)[15]

<table>
<thead>
<tr>
<th>Method used</th>
<th>n</th>
<th>%</th>
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<tr>
<td>VUR (+) by VCUG</td>
<td>22</td>
<td>85</td>
</tr>
<tr>
<td>VUR (+) by DRC</td>
<td>18</td>
<td>69</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>100</td>
</tr>
</tbody>
</table>

DRC, direct radionuclide cystography; VCUG, voiding cystourethrography; VUR, vesicoureteral reflux.

"Fig 4"(Voiding cystourethrography and direct radionuclide cystography grading of vesicoureteral reflux. [16]
In another study carried out in an hospital in Iran of total of 38 children ranging from 6 months to 13 years. 70% of children older than 3 years had urinary control.

From 109 ureters, 29 with urinary reflux were detected by IRC method, whereas only 15 were diagnosed using VCUG.

The IRC method was better and power in diagnosing VUR in comparison with VCUG. The IRC method had some advantages such as no catheter is used, patient is exposed to less radiation and you can obtain information about kidney function. [17]

In a study by Pinthus JH et al, none of the patients who had normal IRC at the time of acute illness had VUR in the longterm. They discovered that early usage of IRC had high sensitivity and accurate negative predictive values for detecting VUR. Indirect IRC had some special features such as possibility for detecting VUR without bladder catherization and ability to assess upper tract. The result of this study showed that IRC was more powerful in detection and diagnosis of VUR in comparison with VCUG. [17]
12. CONCLUSION


2. In comparison with VCUG, Indirect radionuclide cystography can be used for follow up for patients with VUR. It can be used in the diagnosis of VUR as an alternative to VCUG in selected cases. Indirect radionuclide cystography can’t show precise anatomical changes, but it has less radiation rate. Therefore VCUG is the best method to use.

3. The accuracy of Contrast enhanced voiding urosonography compared to VCUG with sensitivities ranging from 26% to 53% and specificities up to 80%. It is a safe, but not sufficient precise method.
13. PRACTICAL RECOMMENDATIONS

According to the results of this literature review, it is recommended to carry out further studies in the VUR literature to permit ongoing review and assessment of progress.
14. REFERENCES


20. Clinical presentation, diagnosis, and course of primary vesicoureteral reflux Authors: Tej K Mattoo, MD, DCH, FRCP Saul P Greenfield, MD 2008.