"OVIDIUS" UNIVERSITY CONSTANTA
FACULTY OF GENERAL MEDICINE

ABSTRACT OF

Ph. D. THESIS

CONSIDERATIONS OF NONSPECIFIC URINARY INFECTIONS IN CHILDREN WITH VESICOURETERAL REFLUX

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Content

Key words:

Urinary tract infection

Vesicoureteral reflux

Children

Antibiotics

Uroculture

Voiding cistourethrography

INTRODUCTION

Thesis importance

URINARY TRACT INFECTIONS (UTI) are inflammatory diseases of infectious etiology of urinary tract and / or kidney interstice. Infection may affect the kidneys (pyelonephritis or renal abscess), the collector (pyonephrosis), ureters (ureteritis), bladder (cystitis), urethra (urethritis). The presence of infection in children should alert the physician to investigate a reno-urinary anomaly. Urinary tract infections are one of the most common infections of childhood. It is a trouble for child, a concern of parents, and can cause permanent kidney damage. (1)

VESICOURETERAL REFLUX (VUR), the most common malformation uropathy of the child, being revealed in most cases by a urinary infection at systematical ultrasound examination and more frequently today by ((late) chronic renal insufficiency.

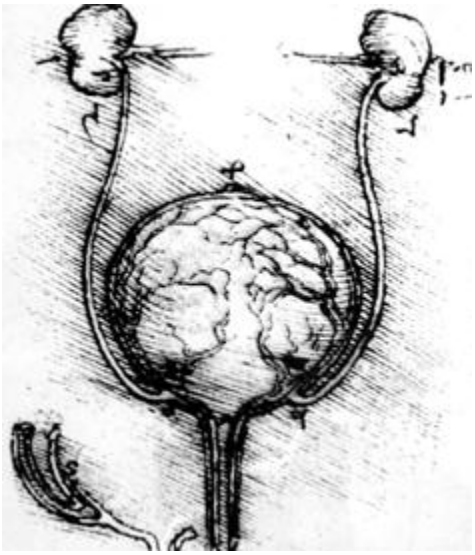


Fig.1. Leonardo da Vinci: engraving in the collection of the Royal Museum of London

VESICOURETERAL REFLUX is the retrograde passage of urine from the bladder to the ureter, which normally is provided with anatomical antireflux mechanism. (2) This reflux occurs sometimes in renal cavities, the risk being in these cases of primarily infectious pyelonephritis, leading on long term, unless a correct treatment, to renal parenchyme destruction, followed by renal insufficiency. Observations on the pathology dates from the Middle Ages, Leonardo da Vinci being the first scientist who intuits and presents the disease in an engraving kept today at the Royal Museum of London (Figure 1). (3) The association of vesicoureteral reflux with urinary tract infection is recognized and can lead to a secondary nephropathy characterized by renal scarring, and called reflux nephropathy.

There are still some contradictions known regarding VUR therapeutic attitude among pediatricians and pediatrics surgeons, coming not from data interpretation of literature but perhaps from the very heterogeneous casuistry found. (4)

We are trying to present in this paper, firstly, a general overview of the diagnostic conditions of urinary tract infections, as well as organic and physiological conditions of VUR diagnosis, and then, by analysis of study groups, to bring a uniform protocol for diagnosis and treatment of cases of UTI in children with VUR, taking into account both our current opportunities and experience of the Romanian school of pediatrics and pediatric surgery.

Thesis organization

This paper was approached trying to define as precisely we can the entity of VUR in terms of association with nonspecific urinary tract infections.

In this thesis we tried to establish clear criteria for the diagnosis of an VUR when we have a first episode of nonspecific UTI diagnosed. Then, after early and correct diagnosis, we chose to compare VUR cases treated medically and surgically to indicate differences of them and to show once again that the correct treatment of urinary infection, and the prophylaxis of urinary can reduce surgery inteventions.

For this purpose we analyzed a number of cases of nonspecific urinary tract infections in children with VUR of several medical centers in Romania: the Department of Pediatrics in Children's Hospital "St. Mary" in Iassy, the Pediatric Surgery Clinic of Children's Hospital "Grigore Alexandrescu" in Bucharest, and Constanta County Emergency Hospital. We studied the cases in terms of history and unitary diagnosis for all cases, and separately in terms of therapeutic indication, treatment and evolution for those cases under the medical treatment, or under surgical treatment associated with

medical treatment. This allowed us a more detailed and accurate analysis of these cases that proved to be very heterogeneous.

List of abbreviations used in the paper

ACE	angiotensin converting enzyme
AM	adrenomedullin
RS	renal scarring
E.coli	Escherichia coli
FDA	Food and Drug Administration
HBA	high blood pressure
ICAM-1	intercellular adhesion molecule-1
Iv	intravenous
CRI	chronic renal insufficiency
IRSCA	"International Reflux Study in Children"
IRR	intrarenal reflux
UTI	urinary tract infection
UVJ	uretero-vesical junction
kgc	kilogram of body weight
mg	milligrams
NAPRTCS	"North American Pediatric Renal Transplant Cooperative Study"
RN	reflux nephropathy
p.o.	per os (oral administration)
GFR	glomerular filtration rate
RS	renal scarring
VUR	vesicoureteral reflux
Mid JT	middle jet technique
BTCollect	collecting bag technique
CFU	colony forming units
UPK3	uroplakin III
EGF	endothelial growth factor

PERSONAL CONTRIBUTION

PAPER OBJECTIVES

We found in Romania a lack of unitary medical attitudes regarding diagnosis, treatment and tracking of cases of urinary tract infections, especially the lack of a diagnostic protocol in children with associated VUR. A heated topic of debate among pediatric surgeons and pediatricians is the selection of cases which could only benefit from medical treatment or of medical and surgical associated treatment. Although proven to be effective in preventing renal scarring relapse, we will try to define better in terms of time management and means of tracking the prophylaxis treatment of urinary tract infections with long term antibiotics.

We excluded from the study patients with specific urinary tract infections (syphilis, tuberculosis, HIV).

The diagnosis arsenal currently available was enriched with fetal sonography before birth, which is important for early diagnosis and treatment of VUR. These children detected before birth have remained asymptomatic longer than those detected after birth? We will try to study these cases and show how much contribution has this expanding investigation is in our country in recent years, consisting in monitoring children with VUR. Surgical therapeutic arsenal was enriched by sub-ureteral injection endoscopic technique that extends the surgical treatment, and we will also try to show that this treatment, which is still under implementation in some universities in our country, has important results in curative treatment of VUR associated with UTI.

Another issue studied in this paper was that a relatively important part of these cases, after diagnosis and after surgery attempting to resolve the vesicoureteral reflux, migrated. These cases were monitored in a much smaller number, the patients preferring often to go in other medical centers in the country, to confirm the diagnosis and then to monitor treatment, returning after that in a much smaller number. The paper wishes to be a multicenter and differentiated study, on the diagnosis, treatment and monitoring of urinary tract infections and vesicoureteral reflux in children from many places in the country.

The results of this study are based on: analysis of patient records of observation and each case study, long-term monitoring of the patients, multicenter studies.

At the end of this paper we have tried to create a diagnostic and therapeutic behavior protocol, based on the results of this study, protocol which could be used both in pediatric services and in pediatric surgery services in our country.

MATERIAL AND METHODS OF STUDY

Selection and presentation of study groups

In this paper we chose to study a total of 124 patients hospitalized in Romania for nonspecific urinary tract infections on a background of vesicoureteral reflux. We chose children hospitalized in three clinics in the country, Section 1 for Surgery of the Pediatric Surgery Clinic of Emergency Hospital for Children "Grigore Alexandrescu" Bucharest, Department of Pediatrics in Children's Hospital "St. Mary" in Iassy and Constanta County Emergency Hospital, where I am employed.

There were also included in the study 70 children hospitalized for an initial spurt of nonspecific UTI where imaging demonstrated that is not associated with VUR, in order to compare the clinical and laboratory characteristics of these children to the group of 124 children with associated VUR. We chose to draw a parallel between the cases of UTI with VUR which received only medical treatment with cases of UTI with VUR treated both surgically and medically.

Under these conditions, we divided the 124 children studied in two groups, a group of children medically treated for prophylaxis of urinary infections relapse in conditions of vesicoureteral reflux after a clear diagnosis of urinary tract infections, and a group of children after a tracking period under proper medical treatment, or in case of high grade vesicoureteral reflux were subjects of surgery.

We chose, besides Constanta County Emergency Hospital, where I was trained as a doctor and where I work, the two clinics in the country because they are medical centers with tradition, as well as modern, with performance and highly professionalized. Thus, Pediatric Surgery Clinic "Grigore

Alexandrescu" is the place that manages to provide a high addressability to people, and while serving as emergency clinic, the surgical cases submitted to it transforms the clinic into a tertiary medical center. The Pediatric Clinic of Iassy, having as clinical specific the pediatric nephrology, the cases diagnosed of VUR and taken into tracking and treatment here have an unified and coherent medical approach.

The study was conducted over a period of 8 years (2004-2011). Patients included in the study came from:

- 27 cases from Constanta County Emergency Hospital, 14 from Department of Pediatrics, and 13 from the Clinic of Pediatric Surgery, 4 of these children being diagnosed before birth,
- 38 cases from the Emergency Hospital for Children "Grigore Alexandrescu" Clinic of Pediatric Surgery, Section 1, of Bucharest, 8 of these children being diagnosed before birth,
- 59 cases from Emergency Hospital for Children "St. Mary" in Iassy, Department of Pediatrics, 7 of these children being diagnosed before birth,
- 70 cases from Constanta County Emergency Hospital, Department of Pediatrics.

The work was divided into 2 major critical retrospective studies. The first study compared 2 lots as follows: **group 1** of 70 children with nonspecific simple UTI, not associated with VUR, with **group 2** of 124 children with UTI and VUR. The second study conducted a parallel, analyzing the second lot of 124 cases with UTI and VUR, trying to establish some features of each medical university center separately.

At the beginning of second study were established general characteristics of clinical and laboratory diagnosis of VUR in children with UTI or first relapse of UTI, and then we analyzed the evolution and therapy behavior, dividing this group into ***two subgroups*** as follows:

The first subgroup of study **(subgroup M)** included all cases of urinary tract infections on a background of VUR being currently under care in clinical departments, whether it's primary or secondary VUR, which were treated only medically. There were treated correctly episodes of urinary tract infections and in most cases was instituted fair treatment for the prophylaxis of urinary infections relapse in order to prevent renal scarring and implicitly reflux nephropathy.

The second subgroup of study **(subgroup K)** formed by the analysis of all VUR cases which received surgical treatment, included VUR cases that were initially diagnosed as urinary tract infections, or who were diagnosed before birth with certain renal abnormalities and to which was started prophylaxis of urinary infections since birth, and to which in relatively short time after birth was diagnosed a urinary tract infection.

This study group was subdivided according to the type of surgery followed into a **group IE** (endoscopic injection) of 31 cases of patients who received cystoscopy and endoscopic injection, and a **group R** (antireflux reimplantation) of 19 cases that received a ureteral reimplantation after different surgical techniques (type Cohen, you Politano, type Lich-Gregoire). The effectiveness of sub-ureteral injection endoscopic therapy should be assessed as it is a new technique applied in Romania. In drawing conclusions on this study group we rely on the fact that it received endoscopic treatment with the latest substance of Vantris collagen type.

These cases of **group 2** cases were divided into primary and secondary VUR in accordance with the norms in literature across the world. Thus, all cases with pyeloureteral duplicity were considered as cases of primary VUR associated with urinary tract malformations, because it is the most common renal malformation and it determines, as shown, an abnormal ureter opening into the bladder, both in terms the place of opening and as submucosal tunnel length. The megaureter is described in various works either as a primary cause of secondary VUR, either as a secondary appearance of primary VUR, but we analyzed it as being associated with primary VUR. Posterior urethral bladder is a considerable cause of secondary VUR. Neurogenic bladder appears as a disorder caused by bladder compliance, which is a cause of secondary VUR. The two groups were compared according to their specific items.

In this thesis we followed the effectiveness of the model of diagnosis and treatment used in medical clinics, and in case of patients with complicated VUR (surgically treated cases) we tried to analyze the adverse developments. In conclusions, we analyzed the results of the comparison of the two study groups, specifically trying to formulate a correct protocol of tracking urinary tract infections in

children, especially of early diagnosis of urinary tract anomalies, and particularly of vesicoureteral reflux.

We examined the effectiveness of medical treatment, and especially the adherence to this treatment, the understanding of parents on long-term prognosis of renal function for the future adult, particularly in children with urinary tract infections due to vesicoureteral reflux.

Selection and presentation of study methods

We made the two critical retrospective studies analyzing data collected from observation and tracking records. Each patient was studied after a protocol which we have deemed fit for purpose of work, which included: age, gender, family history and personal medical history, physical exam, laboratory tests, imaging examinations, therapeutic conduct, and development. We chose to present in a different way to the common norms the distribution by specific age groups in order to beter underline the guidelines for inclusion in a treatment group or another. Thus we analyzed the number of patients in 5 age categories; 0-12 months, 1.3 years, 3-5 years, 5-12 years and over 12 years. We considered the age of inclusion in statistics from the first record into the clinic where the patient was monitored. The idea of classification into these age groups was taken from the pediatric literature according to the clinical and therapeutic features of these children. The **protocol** used by us to track cases was structured as follows:

1. Analysis in terms of **civic data:** age, gender, city of residence, new case or revaluation, transfer for clinical and therapeutic revaluation
2. **Historical data.** There was placed emphasis on questions to the patiens about the existence of unexplained fever other than those allegedly caused urination. The family was mandatory asked about making an ultrasound before birth of the renourinary apparatus of the fetus during pregnancy, and if changes were detected.
3. **Reasons for hospitalization and medical history.** A very important part of these studies were comparative analysis of clinical signs and symptoms that sent the patient to the hospital, and how they have evolved since their appearance and until hospitalisation. We followed the symptoms of fever, micturition disorders: pollakiuria, dysuria, lumbar pain, abdominal pain, urinary incontinence, day and / or night enuresis, cloudy urine, macroscopic hematuria, fetid smell of diapers for infants and little children, digestive disorders: nausea, vomiting, diarrhea, pale skin, hypotrophy in length and weight, headache, convulsions.
4. **Data from clinical examination:** somatometric evaluation: height, weight, blood pressure, palpable abdominal or lumbar formations.
5. **Paraclinical evaluation**

Complete blood count (hematocrit, hemoglobin, leukocytes, platelets), blood urea, serum creatinine, ESR, fibrinogen, C-reactive proteinr, urine analysis, urine culture + antibiogram

6. **Imaging evaluation**
   - Ultrasound of the renourinary apparatus
   - Simple renovesical radiography + UIV with mictional and postmictional cliché
   - Anterior and / or retrograde mictional cystography
   - Cystoscopy
   - Renal scintigraphy + / - Isotopic renogram
7. **Therapy conduct** - drug therapy, (which includes treatment of acute UTI attacks and prophylaxis treatment of UTI relapse prevention) and surgical treatment consisting of sub-ureteral endoscopic injection and / or surgical treatment of antireflux reimplantation, and surgical treatment of the basic disease in cases of secondary VUR
8. Evolution of cases

ANALYSIS OF THE LOTS OF STUDY

Comparison of control group 1 of children with UTI without diagnosed VUR substrate with group 2 of children with UTI and VUR background

To determine the clinical, paraclinical and treatment characteristics of children with urinary tract infections with a background of vesicoureteral reflux, we tracked in comparison a control group of children hospitalized in the Emergency County Hospital Constanta for simple urinary tract infections, consists of 70 children.

Thus we analyzed patients' gender in comparison for two groups of children, the group of children with UTI and VUR and the group of childern with simple nonspecific UTI. Although not statistically significant, we can say that according to the literature the girls were prevalent, but more boys have malformative substrate of renourinary apparatus (41.9%) compared with control group (31.4%).

Analyzing the environment of origin, we observed that for the lot of cases with UTI and VUR there was a rate of 69.4% of children from urban areas, while for the control group their percentage is reduced at 60.7%.

Patients included in the study were divided into the following age groups: 0-1 years, 1-3 years, 3-5 years, 5-12 years and above 12 years. Analyzing the two groups by age groups we found the results presented in the table below.

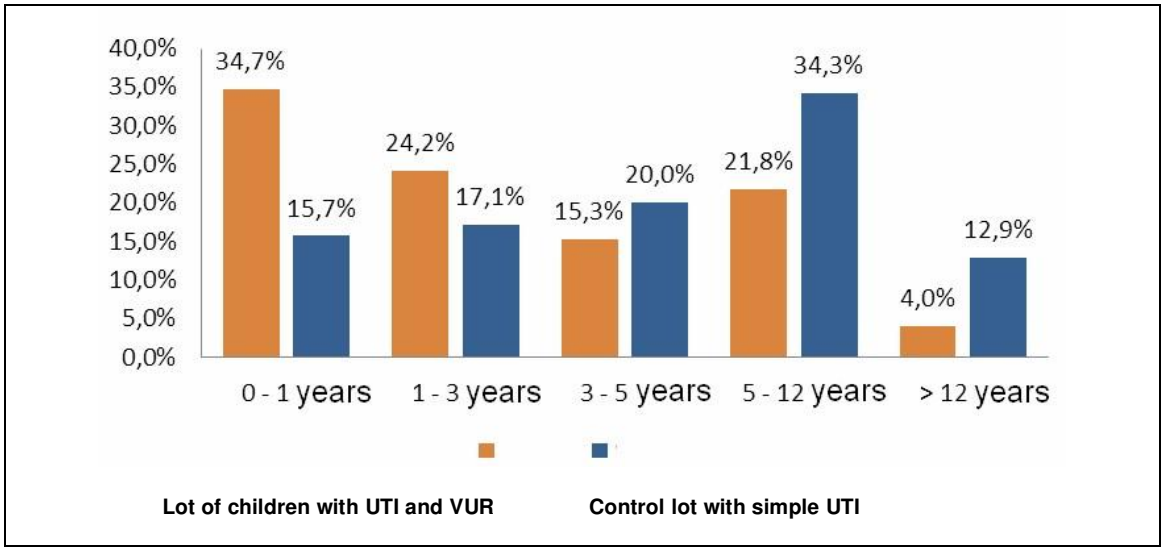


Figure 1. Age groups in the 2 lots

Symptoms and clinical signs

A very important part of this study was the comparative analysis of symptoms and signs that sent the patient to the hospital.

Fever. Analyzing fever we found that for the group of patients with UTI and VUR can be observed a rate of 76.6% of patients with fever, or 23.4% of the patients without fever. For the group with simple nonspecific UTI, there is a higher percentage of those without fever, representing 60%, and patients who experienced fever, as we will show in the next analysis, with higher UTIs, are 40%. It can be noted that there is a statistically significant association between the presence of VUR with UTI background and the presence of fever as a symptom. Thus, we can say with a high degree of

confidence ($p<0.001$) that in children with UTI with VUR background fever occurs primarily, so that the infection rate is much higher in children with VUR than in cases of simple UTI.

Disorders of micturition. Afterwards we studied in comparison the presence of micturition disorders, dysuria and pollakiuria, between the groups of children diagnosed with VUR and the control group with simple UTI. These clinical signs of micturition disorders are essential in the diagnosis of UTI, but hard to reveal in infants and young children.

Dysuria. Overseeing the presence of dysuria we found that for the group of cases with UTI and VUR can be observed a rate of 34.7% of patients with dysuria, and 65.3% of patients without dysuria. For the control group we observed a higher percentage of children with dysuria, representing 48.6% and of patients without dysuria, only of 51.4%

Pollakiuria. This specific micturition disorder for low UTIs, but also present in high UTIs in older children, shows by comparative analysis of study groups that the lot of cases of UTI with VUR, has pollakiuria in percentage of 40.3%, compared to 54.3% in the control group of simple UTI. The other children did not show the clinical signs.

Lumbar pain. This, as a specific sign for the diagnosis of urinary infections, especially on malformation background in children with relapse of urinary tract infections, should immediately expand the aim of clinical and laboratory investigations to vesicoureteral reflux. **Abdominal pain.** There are no statistically significant differences regarding distribution of abdominal pain between the two groups. ($p=0.936$).

Urinary incontinence. Analyzed in children older than 3 years who have urinary sphincter control, this urinary sign was present in the two groups in similar percentages. Urinary incontinence was present in children with UTI and VUR at the rate of 4.8%, against 2.9% in the control group. As we will show further urinary in the study, urinary incontinence was detected in 4 cases in the group with UTI and VUR, in children who had secondary VUR (operated myelomeningocele, flaccid paraparesis caused by spinal cord trauma). In the control group 2 cases had urinary incontinence associated to psychomotor retardation and spastic tetraparesis. Analyzing urinary incontinence associated in the lot of UTI with VUR we found a statistically significant association between the secondary VUR presence and the presence of urinary incontinence. It can be stated as follows ($p<0.001$) that for the group with UTI and secondary VUR the presence of urinary incontinence occurs in a proportion of 33.3%, compared to only 1.8% for primary VUR.

Enuresis. Night enuresis in children older than 5 years, according to new studies into force, was also studied in comparison for the two groups. We found this symptom, associated with urinary incontinence, especially in the secondary VUR, produced by anatomical and functional disorders of the bladder, in a percentage slightly higher in the first group studied. We found statistically significant differences in the analysis of night enuresis in the two groups, and in accordance with the literature, is more common in group 2 with UTI and VUR ($p=0.040$).

Macroscopic hematuria. Analyzing the presence of macroscopic hematuria we found that for group of cases with VUR ca be observed a percentage of 4% of patients with macroscopic haematuria, and in the control group a higher percentage of children with macroscopic hematuria, representing 11.4% ($p=0.048$).

Fetid smell of diaper. An important clinical sign for pediatricians in the diagnosis of UTI in infant and little child is the fetid smell of the diaper, possible only through careful questioning of holders. Analyzing descriptive we can say that out of 73 children aged under 3 years with UTI and VUR, only 36 had a fetid smell of the diaper, as a sign of orientation towards UTI, compared to 3 out of the 33 children aged under 3 years with simple UTI. It can be found a relatively high percentage of those with VUR diagnosed with this sign compared to those with simple UTI, proving once again the young age of diagnosis with VUR. It can be noted that there is a statistically significant association between the presence of VUR and fetid smell of diapers ($p<0.001$).

Pale skin. The study found that the group of cases with UTI and VUR showed a rate of 48.4% of patients with pale skin, and for the control group with simple UTI can be observed a lower percentage of patients with pale skin, representing only 21.4%. Thus, there is a statistically significant association between the presence of VUR and the presence of pale skin. It can be said then with a high degree of confidence ($p<0.001$) that in the group of UTI with VUR the presence of pale skin is

much higher than in the control group. This sign can be discussed clinically. Children who can hide VUR have pale skin, and with the following clinical signs of hypotrophy in length and weight - they may be distinct very important signs in the diagnosis of renal malformations, respectively vesicoureteral reflux, with its relapse infections.

Fig. 2. Child with recurrent UTI and VUR Ist degree with antibiotic prophylaxis with hypotrophy in length and weight - collection Pediatric Surgery Constanta (girl 6 year old, height = 106 cm, -1.8 DS, weight = 14kg, -1.6 DS)

Hypotrophy in length and weight. Like we said, hypotrophy in length and weight, an important sign in clinical directing of diagnosis of congenital renourinary abnormalities, was studied in comparisonin the two groups. For the group of cases with UTI and VUR the percentage was of 43.5% of children with hypotrophy in length and weight, while in the control group the percentage was only 20%. Then, it can be stated ($p<0.001$) that patients with recurrent urinary tract infections presenting VUR are generally below WHO standards on length and weight, while children with simple UTIs are normal developped in length and weight in a much higher percentage, the causes of hypotrophy being nutritional in cases first mentioned, namely dietary defficiences.

Paraclinical laboratory explorations. Turning to paraclinical **laboratory tests,** we analyzed complete blood counts compared in the two groups. We studied: hemoglobin, the red cell indices (signs of anemia deficiency and / or inflammatory), WBC count (leukocytosis), and platelet counts.

Hemoglobin. Hemoglobin can be observed at a statistically significant difference between the two groups, patients with VUR having values are significantly lower of hemoglobin (11.35 mg / dl) compared with control group (11.82 mg / dl).

WBC count. Very important in assessing infections in children, in this case to establish the type of urinary infection, high or low, was the presence of leukocytosis in the group with both UTI and VUR. Average of leukocyte count in the group with both UTI and VUR is 13249/mm against a normal average in the control group (9980/mm ³). There is a statistically significant difference between values of measured leukocytes in the two groups, in favor of group 2 compared to group 1 ($p<0.001$). Increased number of leukocytes, with the presence of fever, previously studies, and inflammatory syndrome studied below, come to confirm, as in the literature, that high urinary infections are more common when associated with vesicoureteral reflux.

C-reactive protein (CRP). Analyzing the presence of CRP we noticed that although relatively made in a small number, especially in the control group, for the group of cases with UTI and VUR the percentage is of 44.6% of children with positive CRP, whereas in the control group the percentage is 50%.

Important in assessing renal function of children in the study groups are also monitoring **blood urea and serum creatinine,** especially in creatinine clearance. In both groups studied, these laboratory tests performed in all cases studied were normal throughout the monitoring cases.

Another step in this comparative study is the analysis of **urine samples,** very important in supporting positive diagnosis of urinary tract infection. **Concise urine analysis.** We studied concise urine analysis and we analyzed the presence of proteins in urine, of leukocytes, erythrocytes, of nitrite and bacteria in fresh centrifuged urine. **Proteinuria.** Presence of physiological proteinuria (0-30 mg / ml urine), equivalent trace of albumin occurred in similar percentages in the two groups, 16.1% versus 17.1% in the control group.

Nitrite test. This test called the Greiss test, which detects nitrite formation by nitrate reducing with bacteria, is useful for directing a rapid diagnosis of emergency in severe infectious states with undiagnosed location and etiology in infant and child. For the lot of cases with the UTI and VUR we observed a rate of 79.5% of patients with positive nitrites, and for the control group we observed a lower percentage of 65.7%. We found statistically significant differences between the two groups studied, indicating that this sample should be taken into account and studied when we have not the emergency result of "gold standard" uroculture of urinary infections.

Leucocyturia. For the lot of cases with the UTI and VUR we observed a rate of 45.2% of patients with frequent leukocytes in urine, and of 51.6% of patients with rare leukocytes, and only of 3.2% with absent leukocytes in urine. For the control group with simple UTI, we observed a higher percentage of cases with frequent leukocytes in urine, counting for 58.6%, while the number of cases with rare leukocytes in urine is 28 (40%). We analyzed these leukocytes in the first examinations of urine during the first hospitalization. In the subsequent tracking of cases with UTI and VUR, these percentages changed, some cases having UTI relapses, and in other cases UTI and VUR being resolved and never repeated. (p=0.017), which therefore shows that there is a statistically significant difference between values of leucocyturia measured in these two groups.

Presence of **erythrocytes in urine.** For the control group with simple UTI we observed a percentage of 11.4% of patients with frequent erythrocytes in concise urine analysis, and of 27.1% of patients with rare erythrocytes, erythrocytes being absent in urine in 61.4% of cases. For group of cases with UTI and VUR there was a smaller percentage of cases with frequent erythrocytes in urine, representing only 1.6% of cases and number of cases with rare erythrocytes in urine of 26 (21%). It can be noted that there is a statistically significant association between the simple UTI and the presence of erythrocytes in urine (p= 0.005).

Bacteriuria. An important element in urine analysis, alongside leukocytes and nitrite test in guiding rapid diagnosis of urinary tract infection, is the frequent presence of bacteria in urine. For the group of children with UTI and VUR, frequent presence of bacteria is 50% and for the group of children with simple UTI is 30% (p=0.025).

Pyuria. We found the importance of this sample in the diagnosis of simple urinary tract infection. It can be stated then (p=0.004) that simple UTI is associated with pyuria in percentage of 100%.

Table. 1. Etiology of UTI in the 2 groups

Urine culture-Etiology	Lots		Total
	Cases with UTI and VUR	Control group	
E.coli	*62*	*32*	*94*
Many germs	*20*	*0*	*20*
Unidentified (superinfection)	*14*	*21*	*35*
Proteus	*10*	*4*	*14*
Klebsiella	*8*	*5*	*13*
Enterococcus	*0*	*1*	*1*
Campylobacter	*1*	*0*	*1*
Staphylococcus aureus	*1*	*0*	*1*
Sterile	*8*	*7*	*15*
Total	*124*	*70*	*194*

Uroculture. Analyzing urine culture, "gold standard" in the diagnosis of urinary tract infections in the two groups we found that etiology is dominated by E.coli. This germ is present in 50% of cases with UTI and VUR group and 45.7% in the control group. In our study, also, were found Proteus and Klebsiella in the etiology of urinary tract infections in percentages similar in the 2 groups. Proteus was diagnosed as being present in 10 cases in the group with UTI and VUR, and in 4 cases in the group with simple UTI. Klebsiella was diagnosed as being present in 8 cases in the group with UTI and VUR, and in 5 cases in the group with simple UTI. Analyzing the above table we see that for the group with

UTI and VUR we found a number of 20 children with multiple bacteria in urine cultures identified during monitoring these cases.

Table. 2. Association of germs in the etiology of recurrent UTI associated with VUR

E coli + Enterobacter	1
E coli + Proteus	6
E coli + Klebsiella	2
E coli + Candida	3
E coli + pseudomonas	3
Enterobacter + Klebsiella + group D streptococcus	1
E coli + pseudomonas + Klebsiella + Enterobacter	1
Enterobacter + Candida + mixed flora	1
Proteus + Klebsiella + enterococcus + mixed flora	2

Carefully analyzing cases of UTI and VUR in regard to urinary infections etiology, cases with complex malformations, and secondary VUR cases, as we follow in the second part of the paper, showed a variable combination of germs, but in this case E. coli was present in most cases. There is statistically significant association between the presence VUR and etiology of urinary tract infections (p= 0.002).

Paraclinical imaging

Abdominal ultrasound. Analysing the results, we found that the group of cases with UTI and VUR can be observed a rate of 88.62% of patients with abdominal ultrasound showing changes of renourinary apparatus, and for control group and control the ultrasound with changes being present only in 5 children (7.14%). Renourinary ultrasound showed different changes in the two groups. A significant number of children had pelvis ecstasia, unilateral or bilateral, showing slight dilatation of pelvis, explained when associated with VUR by the urine flow variations due to anatomical changes described in VUR. Described in cases cases with varying degrees of hydronephrosis, we can say that these cases, when diagnosed with VUR, had already been changes of urinary anatomy.

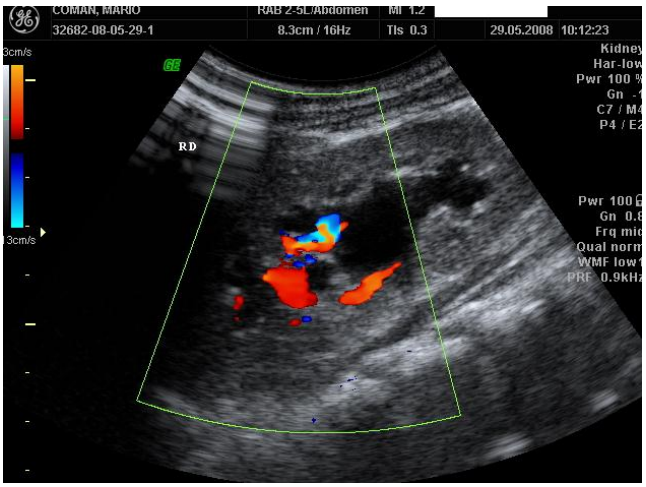


Figure 3. Right kidney hydronephrosis in a child with UTI and VUR - collection of Pediatric Surgery Clinic Constanta

Figure 4. Normal intravenous urography in a child of 3 years with simple UTI and congenital solitary kidney, collection of Pediatric Clinic Constanta

Retrograde cystography. Imaging to diagnose vesicoureteral reflux was carried out for technical reasons in the control group with simple UTI in a number of 37 cases, especially in cases

which were presented a second relapse of urinary infection, but was normal in all cases. Of the 70 patients, 52.86% of patients in the control group made micturition cystography. In group 2 with UTI and VUR retrograde cystography was performed in all cases both at diagnosis and for monitoring cases, as we will show in the second part of the study.

Intravenous urography. In our country, intravenous urography with contrast substance is still a method used to determine the renal function and morphologic changes of renourinay apparatus. UIV was performed in the group of cases with UTI and VUR for a number of 76 children and in the control group for a number of 28 children, to those who had the second episode of high urinary infection. We analyzed renourinary abnormalities associated and we found in 4 children in the control group associated renourinary abnormalities associated. On 3 children was diagnosed congenital hydronephrosis without associated VUR, and a child was diagnosed with congenital solitary kidney.

Table. 3. Analysis of associated renourinary abnormalities

Type of renourniary abnormality	Lot		Total
	Cases with UTI and VUR	Control group	
TOTAL	***124***	***70***	***194***
Without abnormalities	***63***	***66***	***129***
Renal associated abnormalities	***10***	***0***	***10***
Unilateral hydronephrosis	***13***	***3***	***16***
Bilateral hydronephrosis	***4***	***0***	***4***
Unilateral ureterohydronephrosis	***2***	***0***	***2***
Bilateral ureterohydronephrosis	***4***	***0***	***4***
Congenital unilateral megaureter	***4***	***0***	***4***
Congenital bilateral megaureter	***6***	***0***	***6***
Unilateral pyeloureteral duplicity	***10***	***0***	***10***
Bilateral pyeloureteral duplicity	***1***	***0***	***1***
Unilateral pyelocaliceal duplicity	***2***	***0***	***2***
Congenital kidney	***4***	***1***	***5***
Unilateral cystic renal dysplasia	***1***	***0***	***1***

Therapeutic conduct. Therapeutic conduct and subsequent monitoring of cases was different for the 2 groups. For the second group of cases with UTI with VUR background, we will study the detailed treatment in the second part of the paper.

The treatment applied in hospitalization for cases in group 1 of nonspecific UTI without VUR substrate consisted in antibiotics or chemotherapy, initially empiric, and where antibiogram showed a germ that required antibiotic change that was made. There were administered IV or PO antibiotics or chemotherapy for an average of 10 days, with a range between 7 and 14 days. After sterilization of uroculture to 7 days, treatment was continued at home PO, up to 14 days with control of the patient in hospital patient at 14 days. Altought originally started empirically with ampicillin and / or gentamicin, after obtaining the uroculture result, the treatment was continued with ampicillin only in 11 cases, associated in 5 cases with also gentamicin, according to antibiogram. After discharge from the hospital until complete healing of the UTI, the treatment was continued with PO antibiotics.

Table. 4. Treatment administered in hospital for the group with simple UTI

Administered drug	Dose	Way of administration	Number of cases
Ampicillin	50-100 mg / kgc / day	IV	11
Gentamicin	5-7 mg / kgc / day	IV	18
Nalidixic acid	5 mg / kgc / day	PO	2
Ceftriaxone	50-100 mg / kgc / day	IV	14
Ceftazidime	50-100 mg / kgc / day	IV	5
Ceftibuten	9 mg / kgc / day	PO	7
Cefuroxime	20 mg / kgc / day	PO	3
Trimethoprim-sulfamethoxazole	3-5 mg / kgc / day	PO	10

Table. 5. Treatment given after discharge up to the healing of simple UTI

Administered drug	Dose	Way of administration	Number of cases
Nalidixic acid	5 mg / kgc / day	PO	8
Cefaclor	30-50 mg / kgc / day	PO	14
Ceftibuten	9 mg / kgc / day	PO	16
Cefuroxime	20 mg / kgc / day	PO	13
Trimethoprim-sulfamethoxazole	3-5 mg / kgc / day	PO	19

Table. 6. Analysis of the number of UTI episodes in the history of group 1

Number of episodes of UTI for which he was hospitalized	**Frequency**	**Percentage**	**Percentage from cases evaluated**	**Cumulative percent**
1	*44*	*62.9*	*68.8*	*68.8*
2	*5*	*7.1*	*7.8*	*76.6*
3	*5*	*7.1*	*7.8*	*84.4*
4	*8*	*11.4*	*12.5*	*96.9*
5	*1*	*1.4*	*1.6*	*98.4*
6	*1*	*1.4*	*1.6*	*100.0*
Total	*64*	*91.4*	*100.0*	
Absence of data	*6*	*8.6*		
Total	*70*	*100.0*		

Studying the number of urinary infections, for which went to the hospital children in the control group, we found that 20 children had at least two episodes of urinary tract infections. To all children

was performed retrograde cystography, which was normal, and as we shall see later in the study, they were included in a monitoring program by taking antibiotics for prophylaxis of relapse. We noticed that while 20 cases have been entered in the prophylaxis of relapse, only 15 cases from group of simple UTI were presented to monitoring by the lack of compliance of their tutors.

Table. 7. Treatment administered for prophylaxis of relapse to the group of simple UTI

Administered drug	Dose	Way of administration	Number of cases
Nalidixic acid	5 mg / kgc / day	PO	1
Cefaclor	10-15 mg / kgc / day	PO	5
Ceftibuten	9 mg / kgc / day	PO	1
Cefuroxime	5 mg / kgc / day	PO	2
Trimethoprim-sulfamethoxazole (sumetrolim)	1-2 mg / kgc / day	PO	6

Analyzing the table above, we notice that under antibiogram obtained after urocultures, the treatment of prophylaxis of relapse was performed at a rate similar with cefaclor (33.33%) and sumetrolim (40%). In these cases, subsequent monitoring by conducting monthly urocultures, showed recurrence of UTI in 2 cases, by omitting correct prophylaxis antibiotic treatment.

Subsequent monitoring of cases in group 1 with simple UTI was completed only in 28 cases (15 cases received treatment for prophylaxis of relapse) by conducting monthly urocultures for only 3 months in 10 cases, and for conducting monthly urocultures 3 months and then every 3 months up to 6 months in 18 cases.

Analysis of group 2 of cases with UTI and VUR

As mentioned in “Paper objectives” in the second part of the thesis we tried to make a parallel between VUR cases treated exclusively with medical means (subgroup M) and cases treated with medical means associated with surgery (subgroup K)

Gender distribution. In terms of gender distribution there was a slight overall dominance of girls, representing 58.1% of cases, over boys, representing 41.9% of cases.

Environment of origin of children in group 2. Dominated by urban areas.

Age of registration of patients. We notice that, as in the literature, the age group of first diagnose of UTI in these children, subsequently diagnosed with VUR is dominated by the age of 0-1 years in Bucharest group (36.8%), and Iassy group (54.2%). In case of Constanta group UTI was diagnosed at the first hospitalization in greater proportion in the age group 5-12 years (33.3%), the difference from the 0-1 age group consisting in only one patient (29,6%).

Clinical signs and symptoms at the time when UTI was diagnosed and was raised suspicion of VUR in the three clinics were treated separately for each clinic.

Table 8. Presence of symptoms and signs in the 3 medical centers

		Medical Center			Total
		Bucharest	Constanta	Iassy	
Fever	Number	*29*	*22*	*44*	*95*
	%	*76.3%*	*81.5%*	*74.6%*	*76.6%*
Dysuria	Number	*12*	*13*	*18*	*43*
	%	*31.6%*	*48.1%*	*30.5%*	*34.7%*
Pollakiuria	Number	*16*	*14*	*20*	*50*
	%	*42.1%*	*51.9%*	*33.9%*	*40.3%*
Lumbar pain	Number	*6*	*7*	*10*	*23*
	%	*15.8%*	*25.9%*	*16.9%*	*18.5%*
Abdominal pains	Number	*14*	*16*	*15*	*45*
	%	*36.8%*	*59.3%*	*25.4%*	*36.3%*
Cloudy urine	Number	*29*	*19*	*36*	*84*
	%	*76.3%*	*70.4%*	*61.0%*	*67.7%*
Haematuria	Number	*2*	*2*	*1*	*5*
	%	*5.3%*	*7.4%*	*1.7%*	*4.0%*
Enuresis	Number	*0*	*6*	*8*	*14*
	%	*0.0%*	*22 .2%*	*13.6%*	*11.3%*
Incontinence	Number	*0*	*2*	*4*	*6*
	%	*0.0%*	*7.4%*	*6.8%*	*4.8%*
Fetid smell of diaper	Number	*10*	*5*	*21*	*36*
	%	*26.3%*	*18.5%*	*35.6%*	*29.0%*
Pale skin	Number	*15*	*12*	*33*	*60*
	%	*39.5%*	*44.4%*	*55.9%*	*48.4%*
Hypotrophy in length and weight	Number	*16*	*12*	*26*	*54*
	%	*4 2.1%*	*44.4%*	*44.1%*	*43.5%*
Headache	Number	*2*	*0*	*1*	*3*
	%	*5.3%*	*0.0%*	*1.7%*	*2.4%*
Seizures	Number	*0*	*0*	*2*	*2*
	%	*0.0%*	*0.0%*	*3.4%*	*1.6%*
Digestive disorders	Number	*16*	*5*	*17*	*38*
(vomiting and diarrhea)	%	*42.1%*	*18.5%*	*28.8%*	*30.6%*

Paraclinical laboratory blood tests. We can notice overall a number of 77 cases (62.1%), of anemia (deficient and intra-infectious anemia) with average Hb values of 11.235 g / dl, with a minimum value of 7.9 g / dl which is to be correlated with the percentage of hypotrophy in length and weight caused by development of renal suffering (43.5%). Leukocytosis is found in 85 of the cases studied, the average being of 13249/mm³ WBC, with a maximum of 34500/mm³. We analyzed values of blood urea and serum creatinine. We found an average of blood urea of 0.29 g / l and an average of serum creatinine of 0.74 mg / dl. For patients in Bucharest hospital "Grigore Alexandrescu" were observed transient alterations in these parameters at 5 cases, 4 cases in Iasi, and 5 cases in Constanta, patients presenting diagnosis elements of acute pyelonephritis. In one case, a boy was late diagnosed in Constanta with bilateral megaureter, with VUR bilateral grade of IV, who received also a bilateral ureteral reimplantation, being monitored after being no more subject to pediatrics, after 16 years, we found that was subsequently diagnosed with chronic renal insufficiency and therefore was established dialysis.

There were also studied inflammatory samples. **ESR** with increased values were recorded in 20 (60.60%) cases in lots from "Grigore Alexandrescu" hospital, namely values >12 mm/1h, with a maximum value of 102 mm/1h. In the group from Iassy increased values were recorded in 28 children (51.85%), with a maximum of 60 mm/1h, and the group from Constanta maximum was 54 mm/1h, 15

children having ESR increased (55.55%). ***Fibrinogen*** was dosed and selected in the "Grigore Alexandrescu" hospital, being reserved for cases presenting a clinical septic frame, and there were increases in 16 cases, with values between 256 and 783 mg%. In hospital "St. Maria" in Iassy were increases of 18 children, with maximum values of 683 mg% and with an average of 421 mg%. In the group from Constanta there were recorded in 9 children, with a maximum of 769 mg%, and an average of 414 mg%. **C-reactive protein (CRP)** was determined in cases of suspected urosepsis, when positive values marked the infection existence with the possibility of septicemic development – situation noticed in Constanta group for 7 children, in Bucharest group for 16 children, and in Iassy group for Iasi 28 children, where, however, the therapy sample consisting in PO antibiotic depending on antibiogram on uroculture allowed retrospective assessment of the CRP significance.

To all children in this group a careful anamnestic, clinical and paraclinical evaluation showed the presence of UTI. At first diagnosis, readmissions or controls all the patients had at some point urinalysis with UTI significant changes. We could have the following findings regarding the urine: Proteinuria is present in 18.4% cases in Bucharest group, 14.8% in Constanta group and 17% in Iassy group. Leucocyturia is present in 38 cases (89.5%) in "Grigore Alexandrescu" group and constantly present in Constanta and Iassy groups, and the pyuria, the true pus in the urine is described in similar percentage in the 3 centers from 57.9% to 71.1% of cases. The presence of **positive nitrites** on urine analysis was observed in 86.5% of patients in Iassy group, 75% of cases in Constanta group and 72.2% in Bucharest group, data consistent with those in the literature.

Table. 9. Frequency of germs detected in uroculture at first admission

Type of germ		Medical Center			Total
		Bucharest	Constanta	Iassy	
E.coli	number	*21*	*15*	*34*	*70*
	% In medical center	*55.3%*	*55.6%*	*57.6%*	*56.5%*
Mixed flora	number	*3*	*6*	*6*	*15*
	% In medical center	*7.9%*	*22.2%*	*10.2%*	*12.0%*
Proteus	number	*7*	*0*	*3*	*10*
	% In medical center	*18.4%*	*0.0%*	*5.1%*	*8.0%*
Klebsiella	number	*1*	*2*	*5*	*8*
	% In medical center	*2.6%*	*7.4%*	*8.5%*	*6.5%*
Staphylococcus aureus	number	*1*	*0*	*0*	*1*
	% In medical center	*2.6%*	*0.0%*	*0.0%*	*0.8%*
Campylobacter	number	*0*	*0*	*1*	*1*
	% In medical center	*0.0%*	*0.0%*	*1.7%*	*0.8%*
Enterobacter	number	*0*	*1*	*2*	*3*
	% In medical center	*0.0%*	*3.7%*	*3.4%*	*2.5%*
Sterile	number	*5*	*3*	*8*	*16*
	% In medical center	*13.2%*	*11.1%*	*13.5%*	*12.9%*
Total	number	*38*	*27*	*59*	*124*
	% In medical center	*100.0%*	*100.0%*	*100.0%*	*100.0%*

Uroculture. Statistical evaluation of germ involved in the etiology of UTI is important in searching prediction criteria for VUR development, but difficult to assess because for VUR patients the reinfections are common and may involve different germs. We believe that may have a higher importance the germ infecting urinary at admission in clinic because the stem would be the result of bacterial selection in order to establish a correct treatment. Therefore were introduced in the statistical analysis of data on microbial etiology of UTI at first admission to clinics. In "Grigore Alexandrescu"

hospital of 38 patients included in the study only 33 were detected as infected at first admission. At "S. Mary" from Iassy in 8 patients uroculture was sterile at first admission and 24 patients in Constanta were detected as infected at first admission. But in all cases with sterile urocultures at first admission, urinary infections were found in medical history of children concerned.

For Surgery Clinic "Grigore Alexandrescu" there is a frequency of 55.3%, lower than the literature data, of E. coli (70-90%) and a higher percentage of infection with Proteus 18.4%. We found the presence of mixed flora on 2 consecutive urocultures in 3 cases, and the presence of Klebsiella in only one case. The relationship between the presence of urinary infection and a history of positive uroculture at the first admission indicates that 86.8% of cases with a history of UTI urocultures were still positive by recurrence, relapse or reinfection. A total of 8 cases, in the monitoring period, were found reinfected even under a properly administered preventive treatment of recurrences, with other germs, and reinfections with Proteus were found in 4 cases. In the group of Pediatric Clinic in Iassy, E. coli infection was detected in a proportion of 57.6% (34 cases) and Klebsiela, Proteus, Enterobacter and Campylobacter infection were present in 11 cases. At Constanta was maintained a similar percentage of presence of E. coli in the etiology of urinary infection at first admission of 55.6% and of Klebsiella and Proteus at a rate of 13.6%. During monitoring we found three cases with reinfection with other germs, in a case with Proteus and Candida in 2 cases.

Table. 10. Associations of germs in cases of Bucharest group

Germs present during monitoring	Number of cases
E coli + Klebsiella	1
E coli + Candida	2
E coli + pseudomonas	1
E coli + Proteus	4

Table.1 1. Associations of germs in cases of Iassy group

Germs during monitoring	Number of cases
Proteus + Klebsiella + Enterococcus + mixed flora	2
Mixed flora + candida + Enterobacter	1
Mixed flora + candida	1
E.coli + Enterococci + + group D streptococcus	1
E.coli + Enterobacter + Pseudomonas	1
E. coli + Enterococci + Pseudomonas + Klebsiella	1
Enterobacter + E.coli	1
Proteus + E.coli	1

Imaging

Abdominal ultrasound (renovesical side) has become the first line investigation in the diagnosis of urinary tract morphology and monitoring progess of renal patient. In terms of suggesting diagnosis before birth of VUR the experience of ultrasound specialists brings closer medical practice to new contributions literature. As we noted 18 children were diagnosed before birth with congenital hydronephrosis, unilateral or bilateral associated or not with hypotonic ureter or megaureter.

Retrograde cystography is a diagnostic exam in VUR. This is a method of classification by degree of VUR in accordance to the classification in five degrees of "International Reflux Study Committee" (IRSCA). We found a similar percentage of cases in groups of cases studied with moderate VUR, grade II and grade III. This statistical finding is of less practical implication for prognosis in general, also highlighted by low grade of taking in calculation in the literature, because the mere presence of VUR involves the risk of UTI. An analysis of the prognostic value of each degree will be detailed in the analysis of therapeutic indications for each lot.

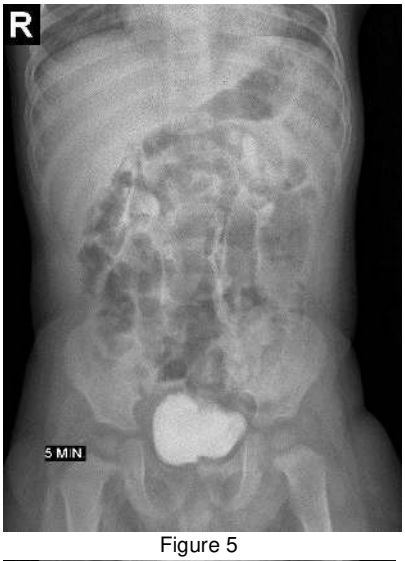


Figure 5

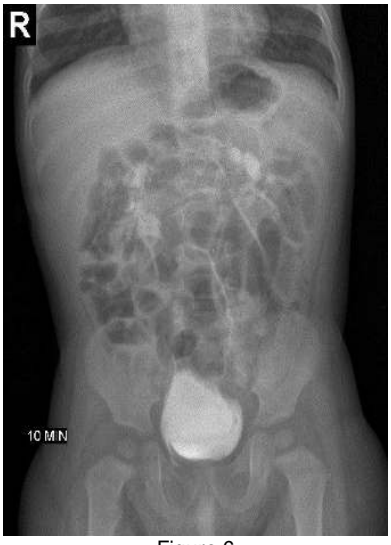


Figure 6

Figure 7

Figure 8

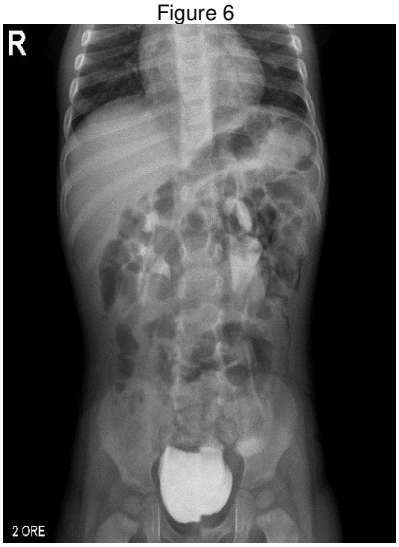


Figure 9

Figure 10

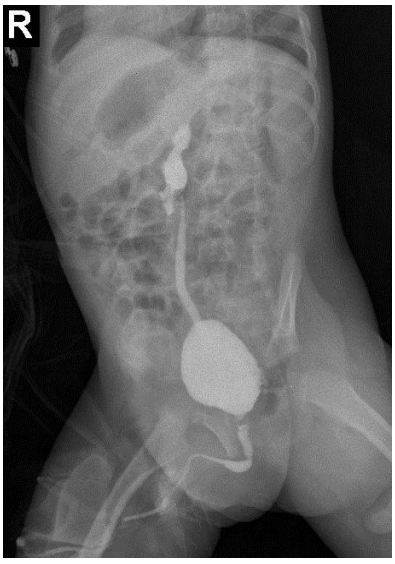


Figure 11

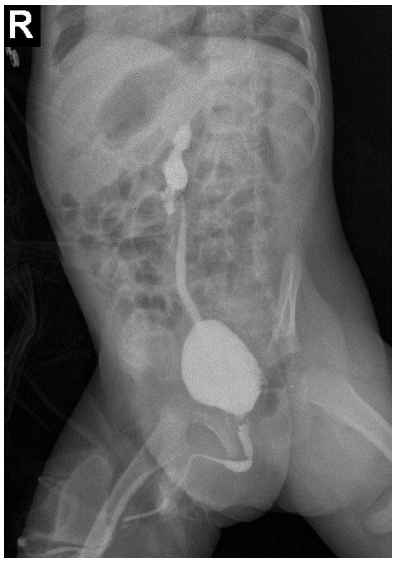


Figure 12

Figure 5 to 11: intravenous urography, collection lassy, bilateral hydronephrosis, bilateral megaureter

Fig 12. Mictional cliché - VUR unilateral primary right

Intravenous urography, considered in our country still queen of the urinary tract imaging investigations currently tends to be dethroned by abdominal ultrasonography and renal scintigraphy. This investigation remains beloved for the wealth of data provided which allows complete evaluation of each case. The utmost importance of urography is represented in our country by the possibility of deciding about VUR type, primary or secondary, in megaureter cases, or in cases of duplication or discovery of a congenital or functional solitary kidney. We followed in this work, as in literature, also cases where intravenous urography made was normal but retrograde mictional cystography showed primary unilateral VUR grade IV.

Static ***renal scintigraphy*** with 99mTc DMSA (technetium marked with dimercapto-succinic acid) shows the emergence and evolution of VUR current complications, renal scarring, allowing assessment of progress towards reflux nephropathy. *Dynamic renal scintigraphy* with 99mTc DTPA shows the evolution of glomerular filtrate, assesing correctly renal function of kidneys. In Clinic of Surgery "Grigore Alexandrescu" and Hospital "St. Mary" Iassy scintigraphic investigation was studied only episodic and unsystematic, by poor access to technology, being carried out for a low percentage of cases. In Constanta Clinic scintigraphic investigation by both techniques was available at a number of 5 children due to technical limitations. We will discuss later in a subchapter the importance of scintigraphic monitoring of kidney glomerular filtration rate of children with VUR under treatment.

Development and treatment in group 2 of study with UTI and VUR

Evolution of therapeutic conduct of cases were analyzed separately for each of the two subgroups of study (I and K) to allow more precise criteria for inclusion in a treatment group or another. We repeated to the same end for each group the analysis of distribution mechanism depending on vesicoureteral reflux occurrence. We found a small number of children with secondary VUR, given that in the group with primary VUR were included children with primary VUR associated with urinary apparatus malformations such as pyeloureteral or pyelocaliceal duplications, congenital megaureter, ureterocel, ectopic ureter.

Patients in the study received **antibiotics.** As can be seen from table 118 patients received antibiotics at first hospitalization, administered orally, intravenously or intravenously at the beginning and after 72 hours administered orally. Duration of antibiotic treatment of acute UTI episode was 10-14 days.

Once set the diagnosis of acute UTI, antibiotic therapy was initiated orally or intravenously, first empirically and then as antibiogram, often 3 days intravenously, then orally until complete healing of urinary infection and sterilization of control uroculture.

Table. 12. VUR Classification by type of kidney damage

VUR classification according to type of kidney damage		Medical Center			Total
		Bucharest	Constanta	Iassy	
Bilateral	number	*12*	*9*	*28*	*49*
	%	*31.6%*	*33.3%*	*47.5%*	*39.5%*
Unilateral	number	*26*	*18*	*31*	*75*
	%	*68.4%*	*66.7%*	*52.5%*	*60.5%*
Total	number	*38*	*27*	*59*	*124*
	%	*100.0%*	*100.0%*	*100.0%*	*100.0%*

After acute episode being resolved all patients were included in the program of antibiotic prophylaxis of urinary tract infections relapses with antibiotics according to antibiogram in daily doses, administered once, 1/3 of the dose, usually in the evening. For treatment of vesicoureteral reflux we analyzed the groups in terms of the type of treatment used to solve VUR, dividing them into two sub groups, one group who received only medical treatment and a group who received also associated surgery treatment.

Table.13. Way of antibiotic administration in patients with UTI

Way of administration of antibiotic		No. cases	%	% for those who received treatment
	intravenous	*49*	*39.5*	*41.5*
	intravenously and orally	*11*	*8.9*	*9.3*
	per os	*58*	*46.8*	*49.2*
Total treatment		*118*	*95.2*	*100.0*
Without treatment		*6*	*4.8*	
Total cases		*124*	*100.0*	

Table. 14. Type of treatment administered

The type of treatment administered	Number of cases	Percentage
Associated surgery treatment	*50*	*40.3*
Subsequently scheduled for surgery treatment	*7*	*5.6*
Medical treatment only	*67*	*54.1*
Total	*124*	*100.0*

Evolution of M subgroup of children with UTI and VUR exclusively medically treated, who did not received surgical treatment for VUR correction during the study

Includes 74 patients who are under monitoring and medical treatment for VUR. Out of these 7 patients were then scheduled for surgery after being properly treated medically administered for prophylaxis of UTI recurrences and no improvement in VUR, therefore cases being scheduled for surgical treatment. Subgroup M contains pediatric patients structured in terms of gender distribution as follows: 28 boys and 46 girls. From the sudy of the group results a relatively large number of cases diagnosed to VUR older than five years, 23 cases, a percentage of 31% of cases, 10 cases were diagnosed with grade IV and V.

Table. 15. Distribution by degree of VUR and age of cases under medical treatment only

Age / grade VUR	Grade I	Grade II	Grade III	Grade IV	Grade V
0-1 years	3	11	10	8	1
1-3 years	1	5	2	3	1
3-5 years	0	3	2	0	1
5-12 years	1	9	1	9	0
> 12 years	0	1	1	1	0

Monitoring patients in group was made clinically, aiming somatic development on the basis of anthropometric WHO criteria and looking in particular size and weight of childern, and their psycho neurological development. 12 of the children, 8 girls and 4 boys, showed defficiency of growth with stationary weight curve in correct nutritional conditions, thus falling into malnutrition protein-calorie grade 1 (dystrophy grade 1), all these children having also hypochromic iron deficiency anemia with Hb below 12 g / dl. Biological monitoring was done according to the protocol by performing urinalysis and monthly uroculture. 2 children had also common deficiency rachitis. 32 childern associated intra-

infectious anemia, and as we mentioned 12 of them had mixed intra-infectious anemia and deficiency anemia.

UTI etiology. Repeated positive urine cultures were found especially in cases with secondary VUR and primary VUR associated with malformations of urinary system. As can be seen from the table below the etiology in this lot was also dominated by E. Coli at the rate of 63.5%. Of these children, 17 boys and 33 girls had high fever at admission associated with micturition disorders in children older than 3 years. Infants and young children who had no other known history of urinary malformations diagnosed before birth presented besides fever also restlessness unexplained by other causes and a fetid smell of the diaper. It was also a case with febrile seizures at admission, who had not other clinical signs.

Table. 16. Etiology of UTI in children by gender

Etiology / sex	Female	Male
E.coli	30	17
Klebsiella	5	2
Campylobacter	1	0
Proteus	1	2
Many germs evolving	5	4

Imaging

Renovesical ultrasound. From the 74 scans performed at presentation in this group were found in 44 cases pelvic ectasia, unilateral or bilateral, in 11 cases pyelon with hydronephrose grade 2-4 with disappearance of triangular morphology and ureter post pyelitic with increased diameter, visibly hypoton along the entire length. In 9 cases the only ultrasound sign was the hydronephrotic kidneys, in 10 of the cases we have not ultrasound morphological information, the ultrasound being normal. As we can see there have been cases of primary VUR associated with malformations of the renal and urinary apparatus, ureterocel, unilateral or bilateral duplications. We will present the case of a child from Constanta diagnosed with left obstructive megaureter and left ureterocel, who was diagnosed with RUV grade IV left, being at the moment of study in conservative treatment for the prophylaxis of recurrences of urinary infections with trimethoprim-sulfamethoxazole syrup 5ml / daily taken at bedtime for two years, and who was scheduled for surgery (ureterocel resection and antireflux reimplantation type Cohen).

Fig. 12. Ureterocel left at a case with left VUR grade IV - Collection of Pediatric Surgery Clinic Constanta

Retrograde cystography carried out after acute attack of UTI. When installing the cystographic probe, was collected urine for uroculture. There were performed 74 retrograde cystographies with contrast substance that allowed the diagnosis and classification of the grade of reflux. In 5 cases of VUR first grade, in 29 cases VUR second grade without pyelon view, in 16 cases VUR III grade, in 21 cases VUR IV grade and in 3 cases VUR V degree.

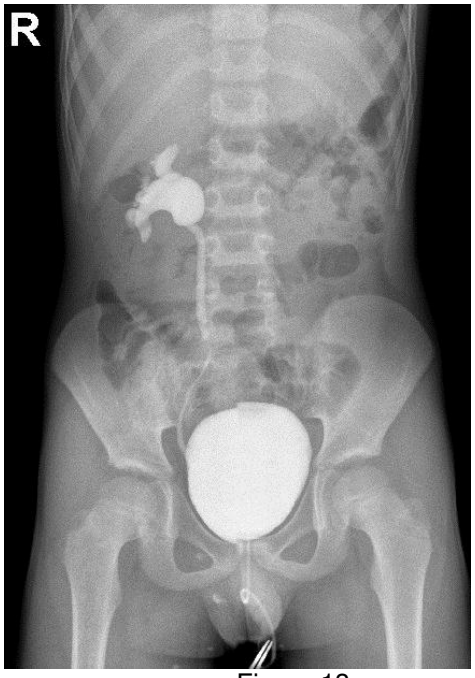


Figure 13

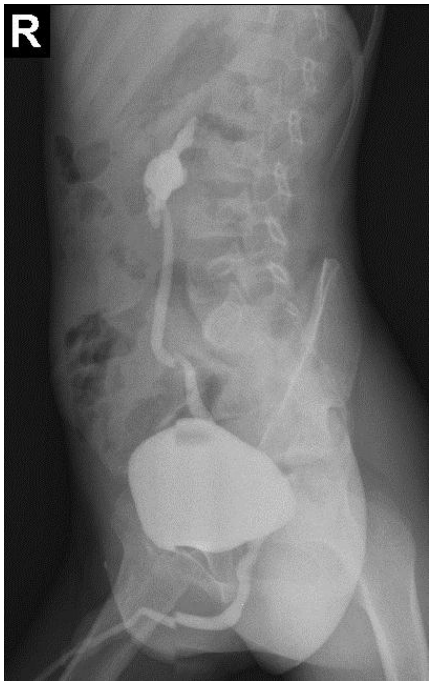


Figure 14

Figure 13-14 Retrograde cystography clichés in dynamics with unilateral right VUR grade IV – collection Iassy

Intravenous urography with contrast substance. It was performed in 41 cases to elucidate the morphofunctionality with Urografin or Omnipache and revealed changes only in 17 cases, in 24 cases the intravenous urography being normal although the children had VUR, thus confirming the medical literature that say that in some cases, although the intravenous urography is normal, the pacient may have VUR, so it is necessary, as we mentioned, to perform the cystography.

Scintigraphy. In the study group scintigraphic exploring could be carried out only in 13 cases. Main information being the glomerular filtrate, all cases showed a normal glomerular filtration of over 100 ml/min/1.73m²sc. In 3 cases were performed both static and dynamic scintigraphy and in 2 of the 3 cases static scintigraphy showed bilateral renal scarring, morphologically presenting reflux nephropathy, but GFR was normal. The third case in which both types of scans were performed was a case diagnosed late at the age of 3 years with secondary VUR of grade V unilateral, determined by posterior urethral valve, that, although at static scintigraphy has already shown left renal scarring, glomerular filtration rate was normal (109 ml/min/1, 73 m² sc).

Therapeutic conduct. The anti-infective treatment aimed both UTI healing and prophylaxis of UTI relapse, maintenance factor of VUR and possibly progression of VUR to RN (reflux nephropathy). We tried a therapeutic protocol in three steps:

1. At the moment of diagnosis VUR the children in this group were divided into three classes

- Urinary tract infection clinically and biologically manifested 50 of 74 cases,
- Urinary tract infection manifested by uroculture only 17 of 74 cases,
- Urinary tract infection clinically manifested but with sterile urcultures, 7 of 74 cases and with history of recurrent UTI.

2. Treatment of acute episode. Patients with urinary tract infection clinically and / or biologically manifested underwent a course of antibiotics for 14 days parenterally initiated in 39 cases and continued orally after discharge, and orally for 35 children with good oral tolerance oral and general good condition at admission. It was administered in first intention intravenously Ampicillin in dose of 100 mg / kg / day in 78% of cases treated IV, but the subsequent development of children and antibiogram obtained after uroculture allowed further treatment with ampicillin only in 6 cases, showing increased resistance of germs in recent years. In 39 (52.7%) of cases of third-generation cephalosporins has allowed, depending on the antibiogram on the isolated from uroculture, to heal UTI. Therapy aimed allowing the right of urinary sterilization. There were administered in 33 cases

intravenous doses of 50-100 mg / kgc / day and in 3 cases PO at a dose of 9 mg / kgc / day. In the patients who, as we said, their general condition allowed, we administered in first intention cephalosporins in 12 cases, augmentin in 9 cases, nitrofurantoin in 3 cases, biseptol in 2 cases, loracarbef in 3 cases.

Table. 17. Antibiotics used to cure acute UTI at first admission

Type of antibiotic	Way of administration	No cases	Dose in mg / kgc / day
Ampicillin	IV	6	100
Ceftriaxone	IV	31	50-100
Cefotaxime	IV	2	50-100
Ceftibuten	PO	6	9
Cephalexin	PO	2	30-50
Cefaclor	PO	10	30-50
Loracarbef	PO	3	15
Amoxicillin + clavulanate potassium	PO	9	50-70
Trimethoprim + sulfamethoxazole	PO	2	5-8
Nitrofurantoin	PO	3	5

Monitoring cases showed clinical and biological re-acute moments which were also treated with antibiotics. Ampicillin was the first choice – an empirical choosing, being then corrected on antibiogram on germ obtained by uroculture, as well as at the first hospitalization, in most cases, with third generation of cephalosporins administered IV or PO, which allowed sterilization of acute episode relapsed of UTI. It is worth to mention that in 11 cases we found that bacteria developed resistance to antibiotics during monitoring of cases, especially those with secondary VUR and primary VUR associated with other reno-urinary malformations, requiring the use of different antibiotics during hospitalization for new episodes of UTI and even of imipenem, a backup antibiotic in 2 cases.

3. Maintenance treatment, prevention of recurrence. Aiming to maintain sterility. Consists of administration of antibiotics, chemotherapy in 1/3 of the dose only once per day, most frequently at bedtime. Considering the specific age, the study considered administration of cefaclor in most cases (43 cases). They also received nitrofurantoin in 4 cases, trimethoprim in 9 cases, cephalexin in 2 cases, and negram in one case. 8 children did not receive antibiotic treatment, although it was indicated the hospital. Of these, 3 cases were presented at subsequent assessments after diagnosis of VUR and the other five children by parents' lack of compliance did not receive a prophylaxis antibiotic treatment.

Subgroup M monitoring

During study we found 23 cases with VUR resolved, and 51 cases in which VUR remained persistent. Among children with persistent VUR, we noticed that in 22 children (29.72%) the reflux grade decreased during the study, they being mostly still in clinics' observation. The decrease in reflux grade was established by performing in dynamics retrograde cystographies during monitoring. For patients were made urocultures performed monthly and if they were positive the patiens were treated accordindg to the antibiogram. They were evaluated clinically and in laboratory at 3 months, when patients in the study were hospitalized and was performed the balance presented at the beginning of our study (blood count, inflammatory tests, blood urea, serum creatinine, urine analysis, urine culture, abdominal ultrasound). As we said at the beginning of this study group presentation, 7 children, to whom, according to the study, VUR was persistent, the retrograde cystography performed in dynamics showed the same degree of VUR, and therefore they were subsequently scheduled for endoscopic surgery to solve VUR, but they did not return for evaluation, and 3 children were present at the hospital, diagnosed with recurrent UTI associated with VUR, was initiated antibiotic prophylaxis and then they did not return to clinical and paraclinical evaluation of VUR.

We can say that for children who had solved VUR, compliance of parents was present, the antibiotic prophylaxis recommended was correctly given to children, and these children had no new episodes of UTI clinically and / or in laboratory diagnosed. Analyzing children to whom VUR was solved we noticed that for 69.56% of cases, age at diagnosis VUR to which subsequently VUR was resolved was under 1 year, and 82.6% were aged under 3 years, age when literature data confirms vesicoureteral junction maturation.

In terms of the type of primary or secondary VUR the subgroup is distributed as

Table. 18. Distribution VUR on renal units, subgroup M

	Primary VUR	Secondary VUR
unilateral right	6 1	3
unilateral left	1 2	2
bilateral	6 2	6

In subgroup M studied the group of children with secondary VUR has the following primary causes:

- 1 child with occult spina bifida L5-S1 with severe sensibility disorder of the perineum associated with neurogenic bladder mixed type.
- 1 child with Melnick-Fraser syndrome, psychomotor retardation with congenital left kidney
- 3 children with bladder instability syndrome with neurogenic bladder dysfunction
- 1 child with bladder instability syndrome associated with right pyeloureteral duplicity
- 1 child with posterior urethral valve which was then scheduled for resection of urethral valve

Patients with secondary VUR and pathological associations did not receive surgical indication considering the benefit thus obtained does not justify a complex surgical act, so it was decided to include them only in a therapy with permanent antibiotic prophylaxis treatment anti UTI, as mentioned earlier. All these children show a grade of disorder of neurologic bladder function, organic or secondary to the lack of neurological of control of micturition. However, 2 children late diagnosed with secondary VUR (1 child of 7 years and 1 child of 11 years) with neuromuscular dysfunction of the bladder, with normal neuropsychological status, by combined treatment of antibiotic prophylaxis with driptane, we found after 2 years of proper monitoring, along with complementary measures indicated below, led to remission of VUR.

It is important to note that of the 11 children with secondary VUR, treated medically only for VUR, 3 children received also surgery and underlying disease of the child as follows:

- 1 child underwent surgery immediately after birth for lumbosacral myelomeningocele, yet subsequently developed bladder dysfunction and VUR occurred,
- 1 child suffered spinal cord trauma, subsequently complicated by a intrathecal bscess and surgical intervention to resolve abscess, and flaccid paraplegia and neurologic bladder dysfunction secondary installed led to the production of VUR,
- 1 child diagnosed with posterior urethral valve underwent valve resection of the urethra and subsequently was diagnosed with VUR.

Along with properly administered antibiotics treatment combines compulsory general hygiene measures. Thus caregivers were taught

- to alert at early signs and symptoms of UTI and perform urocultures,
- not to use bubble bath and feminine sprays,
- to make children showers personal hygiene instead bath,
- avoid constipation of children.

• girls were taught to make toilet of perineal area using wiping from front to behind,
• children were encouraged to empty bladder at regular intervals

In cases with multiple resistance, disinfection therapy with urinex and immunostimulatory therapy with urovaxon were usefully proven in 3 cases.

Table.1 9. Period of monitoring children treated exclusively medical

	Number of cases	Minimum (months)	Maxim (months)	Average (months)	Standard deviation
Monitoring period (months)	***74***	***1***	***72***	***20.92***	***14,408***

Looking at the table above we can say that the children in the group treated medically only, by treatment of acute recurrent episodes of UTI, with ongoing prophylaxis antibiotic treatment, with complementary methods presented above, were studied for an average of 20.92 months, with a minimum of 1 month and a maximum of 72 months.

Evolution of subgroup K (surgical) of children with UTI and VUR who have benefited from the surgery along with medical treatment

In the following we present the evolution of the patients in the study who received open surgery treatment and endoscopic injection

Table. 20. Number of patients who received surgical treatment

Surgery			**Medical Center**			**Total**
			Bucharest	**Constanta**	**Iassy**	
	YES	**Number**	***36***	***5***	***9***	***50***
		%	***94.7%***	***18.5%***	***15.3%***	***40.3%***
	NO	**Number**	***2***	***22***	***50***	***74***
		%	***5.3%***	***81.5%***	***84.7%***	***59.7%***
Total		**Number**	***38***	***27***	***59***	***124***
		%	***100.0%***	***100.0%***	***100.0%***	***100.0%***

We have seen that most of the patients who received surgical treatment were grade III and IV VUR, and as we shall see later in Bucharest group, 50% of patients with grade III VUR received surgical treatment, while in Jassy group proportion was equal for VUR grade III and IV (37.5%). All patients in this subgroup received prophylaxis antibiotic treatment of relapse.

Group IE of patients who received endoscopic treatment

In group Iassy we found a case who underwent endoscopic injection with DEFLUX, a girl diagnosed at birth with cloak, operated immediately after birth, with congenital solitary kidney right, firstly UTI diagnosed at age of 2 months, secondary VUR grade IV right, diagnosed as the age of 6 months, right ureterohydronephrosis.

Table. 21. Endoscopic treatment of VUR

Endoscopic treatment		Medical Center			Total
		Bucharest	Constanta	Iassy	
Number of cases that received endoscopic treatment		*29*	*1*	*1*	*31*
	%	*76.3%*	*3.7%*	*1.7%*	*25.4%*
Total number of cases		*38*	*27*	*59*	*124*
	%	*100.0%*	*100.0%*	*100.0%*	*100.0%*

After endoscopic injection at the age of 7 years, with single-dose prophylaxis antibiotic treatment correctly administered at bedtime, Ceclor 200 mg in the evening, we found at 1 year the decrease of VUR from IV to III, and at 2 years from injecting a reduction of the grade of VUR at II, without occuring new episodes of UTI in the correct prophylaxis antibiotic treatment.

At the Constanta lot we found one case who underwent endoscopic injection with DEFLUX, a boy diagnosed prior to birth with hydronephrosis and confirmed immediately after birth with congenital bilateral hydronephrosis, registered at the age of 2 months when he was first diagnosed with urinary infection with E. coli, with primary bilateral VUR grade IV diagnosed at age 3 months.

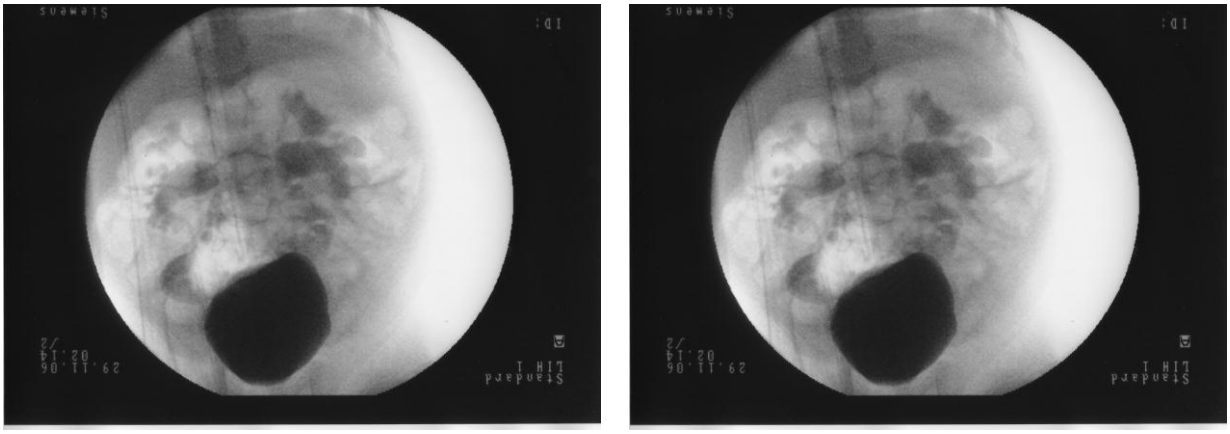
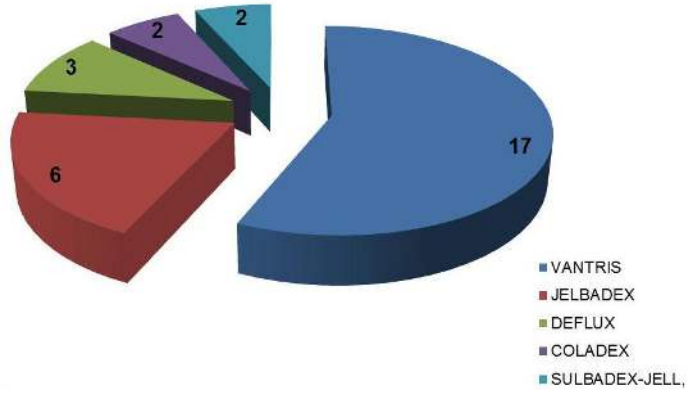


Figure 15-16 Retrograde cystography - VUR grade IV bilateral - Collection of Pediatric Surgery Clinic Constanta

In Bucharest group we studied most cases with VUR treated by endoscopic injection.



Graph 8. Type of substance endoscopic injected in group Bucharest

For cases in study of primary VUR we found a predominant percentage for indication of subureteral injection to lower grades of reflux, reaching levels 2 and 3 with a combined percentage of 75.82%. In 4 cases it was necessary to use subsequent reimplantation type Cohen for primary VUR healing, development being steady after injection. Case in Iassy of secondary VUR grade IV having received endoscopic injection as shown above, and the case of Constanta being of primary bilateral VUR grade IV.

Analyzing patients who have secondary VUR we noticed significant difference arising from the use of endoscopic subureteral injection method in these cases. This attitude is explained by the desire to use all available therapeutic arsenal, medical and surgical, to the most difficult cases in trying to achieve a reduction of reflux. These cases and other associate malformations can be seen in the table below.

All cases of secondary VUR presented received complementary surgical interventionand. This is due to recognition by pediatricians of necessity of treatment for these cases of the underlying disease, which is always surgical. The number of patients affected by primary VUR in the group of patients who underwent subureteral injection was 27 and in cases of secondary VUR 4 patients.

Table. 22. VUR secondary cases who received endoscopic treatment

Gender	Grade VUR	Associated malformations
Female	Grade IV right	Cloak, solitary congenital kidney right
Male	Grade IV left	Posterior urethral valve, congenital left kidney
Male	Grade IV bilateral	Posterior urethral valve, bilateral megaureter
Male	Grade V left	Lumbosacral myelomeningocele after surgery, neurogenic bladder mixed type

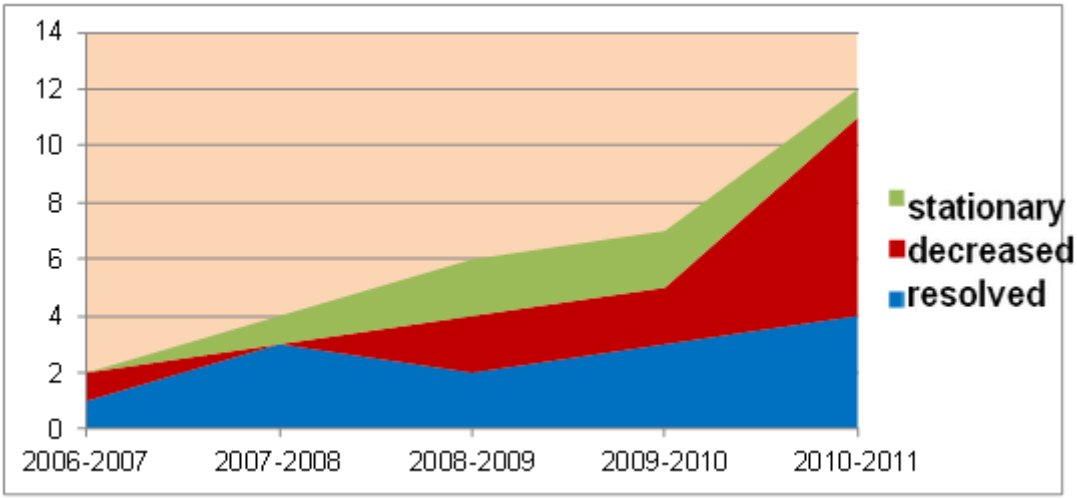
Cystoscopy subureteral injection method was used for secondary VUR for 4 patients, 2 unilateral and 2 bilateral, the two cases with unilateral injection associating also congenital kidney.

Evolution of the cases in IE group treated endoscopically

After injection, ultrasound bladder will prove injection nodule, which is a valuable sample on subureteral location correctness and of maintaining substance at place of injection.

Figure 17. Ultrasound at 3 months after injection with VANTRIS, collection of Pediatric Surgery Clinic in Grigore Alexandrescu Hospital Bucharest

Thus, after the first injection is found for primary VUR a recovery rate of 44.44%% of cases and for secondary VUR only a decrease in the grade of reflux.



Graph. 9. Evolution of endoscopic injection cases

For cases of VUR the attUTIde after control of first injection at 3-6 months was not uniform. Thus, 2 cases received a new injection, while in 4 cases was appealed directly to reimplantation surgery. Seven cases, after injection failure, were lost from records and one was removed from the records being passed to adults records. On 2 cases were performed initial percutaneous eco-guided pyelonephrostomia for preservation of renal function pending subureteral injection surgery.

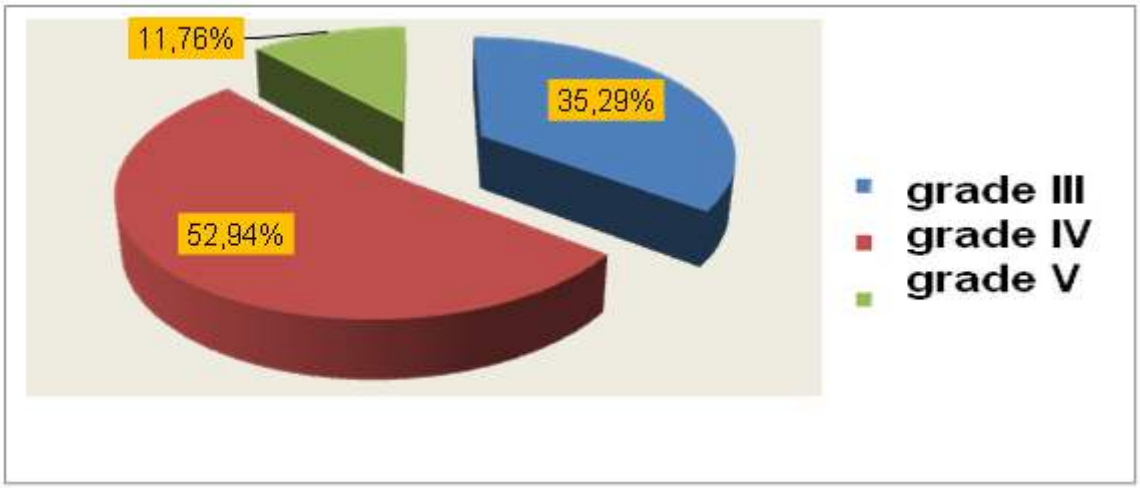
Thus there is a global healing rate after reinjection of primary VUR of 48.14%. Of the two reinjections, just in one case VUR was resolved, and in the other case the grade of VUR decreased. It appears necessary to analyze data by year and grades of reflux to better determine the factors that affect the success of the method. It can be noticed an increase of the number of subureteral injections for VUR associated with recurrent UTI. In the group of children injected in 2010-2011 (12 children) at the end of the year VUR was already resolved for 4 children, and for 7 the grade of VUR was decreasing, so we can say that the success of the method is up to 91%, comparable with literature data . Substance used for injection, in 2010-2011, was VANTRIS, a gel very well tolerated by children with far fewer side effects. In terms of the grade of reflux we found successful healing in 50% of cases of primary VUR grade II, 50% for grade III and for grade IV only 28%. In patients with grade V of VUR, it was only managed to reduce the grade of reflux in a case, which confirms data from the literature saying high grade reflux benefits from the reimplantation surgery.

In conclusion primary VUR benefits of subureteral injecting cystoscopy for healing only for low and medium cases. High grade primary VUR cases are unlikely to be cured by this method. Four of the cases who had primary VUR injection failure were all surgically type Cohen reimplanted. The analysis of this study group confirms efficacy in healing VUR by subureteral injection, but also highlight the need for careful selection of cases included in treatment by this technique.

Group R of patients who received surgery for reimplantation

Table. 23. Antireflux surgery

Type of antireflux surgery		Medical Center			Total
		Bucharest	Constanta	Iassy	
COHEN	Number of cases	*10*	*4*	*2*	*16*
	%	*90.9%*	*100.0%*	*50%*	*82.4%*
POLITANO	Number of cases	*0*	*0*	*2*	*2*
	%	*0.0%*	*0.0%*	*50%*	*11.8%*
Lich-GREGOIRE	Number of cases	*1*	*0*	*0*	*1*
	%	*9.1%*	*0.0%*	*0.0%*	*5.9%*
Total	Number of cases	*11*	*4*	*4*	*19*
	%	*100.0%*	*100.0%*	*100.0%*	*100.0%*



Graph.10. Primary VUR reimplanted cases reported to grades of reflux

When analyzing the cases that were treated by reimplantation in relation to gender of patients it is to be noted the dominance of boys to girls for primary VUR. Distribution analysis by age showed a

tendency to surgery mainly in case of high-grade primary VUR. Grade IV and V totaled 64.7% of cases. VUR average grades were included in the primary surgical treatment after discussion between pediatricians and surgeons because we, pediatricians, monitorl their development after diagnosis, establishing proper medical treatment after antibiogram of acute UTI episodes and prophylaxis of UTI recurrence.

Thus, surgical indication criteria were as follows: lack of compliance to drug prophylaxis of relapse on long term, relapse of UTI under properly administered treatment, preference of parents and extended tracking of cases.

For cases of primary VUR of this group studied was associated a malformation of renourinary apparatus in the percentage of 82%. Thus there were 4 cases of pyeloureteral duplicity, 2 cases of ureterocel, one case of hypospadias, a case when VUR manifested on congenital kidney, but most cases were associated with unilateral or bilateral megaureter, which explains in the same way as in literature the severity of these cases and the need for introduction in protocol for immediate surgery prior to occurrence of reflux nephropathy.

In this group, surgery performed consisted in an antireflux reimplantation (ureteroneocystostomia) in 19 cases of primary VUR. Technique of reimplantation Cohen was preferred in 84% of cases, Politano technique in 2 cases and Lich-Gregoire technique in one case. Presence of subureteral cystoscopy injection in medical history of 4 cases has increased the difficulty of the operation.

In 2 cases was associated either a dorsal Duhamel debridement, for a boy, or a lysis of vulvar adhesions, for a girl. So were eliminated predisposing factors of UTIs. In 4 cases were performed initial percutaneous eco-guided pyelonephrostomia for preservation of renal function pending reimplantation surgery.

Evolution of R group of cases treated by reimplantation

Ureteral reimplantation surgery has a primary success in 6 cases, decreasing level of VUR in 8 cases and being stationary in 5 cases. Out of these cases, 6 cases are still under investigation, and 5 patients were removed from records after 3 months. Therefore success rate of reimplantation reaches 82.31% for primary VUR. Most cases of received a type Cohen reimplantation, but we have to mention that onecase of the two in which surgical intervention was made after Politano technique is resolved, it having the peculiarity of being a child diagnosed at 3 years with UTI and VUR, with congenital kidney left and obstructive megaureter left. Postoperatively, after antireflux reimplantation for primary VUR, the following complications were recorded: loss of prevesical urine in 4 cases, which resolved spontaneously, bleeding bladder in 2 cases, postoperative fever in 11 cases, postoperative UTI in 2 cases and parietal suppuration in 1 case.

Monitoring cases of subgroup K which received surgical treatment

Table 24. Monitoring period of subgroup K

	No. cases	Minimum	Maximum	Average	Standard deviation
Monitoring period (months)	***50***	***2***	***120***	***28.82***	***25,292***

Looking at the table above we can say that the children of the group treated both medical and surgical by the surgical associated therapy with the treatment of recurrent episodes of acute UTI with prophylaxis antibiotic treatment preoperatively and postoperatively continuously until remission of VUR, with complementary methods presented above, were studied during an average of 28.82 months, with a minimum of 2 months and a maximum of 120 months.

Scintigraphic study of cases in group 2

As previously presented an important stage in monitoring cases of VUR is renal scintigraphy. In our country, for technical reasons, this monitoring of renal function in international standards cannot be performed, and therefore, just to show the importance of this intervention, we made this study. Static scintigraphy is very important in demonstrating the presence or not of renal scarring, usually occuring after recurrent UTI, which when associated with alteration of renal function indicate the occurrence of reflux nephropathy.

Although made on technical grounds on a few cases, we showed renal scarring only in one child in group Constanta (of the 5 studies), while those in group Iassy of 9 children, 6 children had renal scarring but with normal renal function.

Renal dynamic scintigraphy with 99mTc DTPA [technetium-marked pentetic dietilentriaminopentaacetic acid (pentetic acid)] is the method of choice for morphology and renal function allowing through the information on renal filtrate to accurately assess renal function. It is known that the rate of occurrence of severe complications of VUR which can progress as reflux nephropathy increases exponentially under values of 70 ml/min/1.73 m² s.c. Being a radiotracer method, with radiation, it is deemed necessary to be made a first scintigraphy at diagnostic and then at the moments of therapeutic decision. However we can say that radiation is much smaller compared with intravenous urography.

In Surgery Clinic "Grigore Alexandrescu" and Hospital "St. Mary" Iassy scintigraphic investigation of was studied episodic and unsystematic by poor access to technology, being performed at a low percentage of cases as was seen in the tables above. In Constanta Clinic scintigraphic investigation by both techniques was available at a number of 5 children due to technical limitations. Analyzing these 19 cases, we found in all cases from the first scintigraphy normal renal function with normal glomerular filtration rate, with several features that we present below. A case from Constanta diagnosed prior to birth with bilateral hydronephrosis confirmed by ultrasound performed immediately after birth, included at birth in prophylaxis of urinary tract infections with Sumetrolim, was diagnosed with bilateral megaureter at the age of 2 months, cystography done showing VUR grade V right.

Table. 25. Scintigraphic findings with 99mTcDMSA in 3 centers

Static scans 99mTcDMSA		Medical Center			Total
		Bucharest	Constanta	Iassy	
DMSA without renal scarring	Number	*5*	*4*	*3*	*12*
	%	*13.1%*	*14.8%*	*5.1%*	*9.7%*
DMSA bilateral renal scarring	Number	*0*	*1*	*3*	*4*
	%	*0.0%*	*3.7%*	*5.1%*	*3.2%*
DMSA right renal scar	Number	*0*	*0*	*2*	*2*
	%	*0.0%*	*0.0%*	*3.4%*	*1.6%*
DMSA left renal scarring	Number	*0*	*0*	*1*	*1*
	%	*0.0%*	*0.0%*	*1.7%*	*0.8%*
Total cases studied	Number	*38*	*27*	*59*	*124*
	%	*100.0%*	*100.0%*	*100.0%*	*100.0%*

Renal scintigraphy performed showed a GFR of 78.8 ml / min, a value which, being the lower limit of normal raises problems of renal function of the child on long term. Being still monitored by monthly urine culture, the child was diagnosed UTI with E. coli, which has been treated correctly after antibiogram, and continued prophylaxis with Sumetrolim for relapse. Subsequent urine cultures performed for 1 year have not revealed further attacks of acute UTI. Dynamic scintigraphy was repeated 1 year after the child received the subureteral injection cystoscopy right.

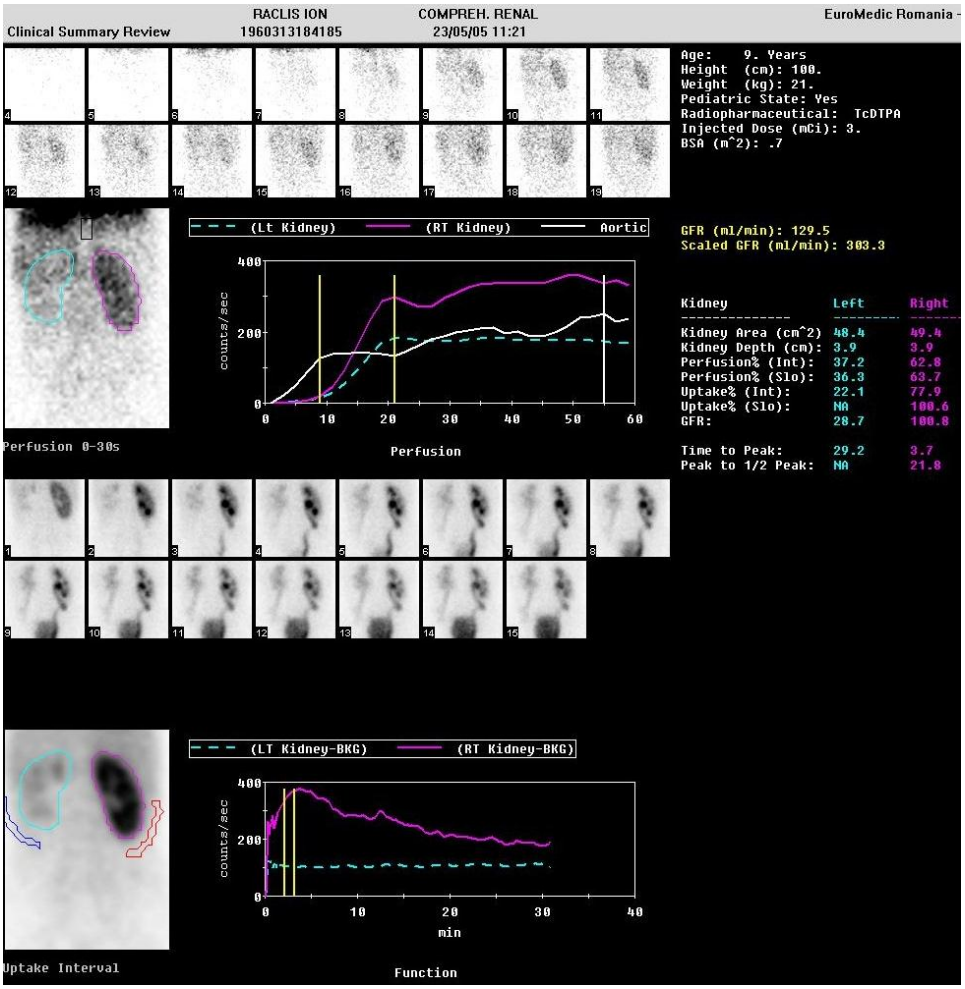


Figure 18. Dynamic renal scintigraphy with TcDTPA, VUR grade IV bilateral with bilateral megaureter. Glomerular filtration rate = 129.5 ml / min, curve type II O'Reilly - Collection of Pediatric Surgery Clinic Constanta

Carefully studying this scintigraphy we can see that although renal function is paraclinically normal (blood urea, serum creatinine is normal), GFR is the lower limit of normal, which indicates the need for antireflux surgery. Postoperative evolution of case was very good with VUR remission. Analyzing this case, scintigraphy shows that although renal function is normal, left kidney only functions at 25% capacity, which indicates the need for surgery, the need for surgical antireflux reimplantation operation. We prove the importance of scintigraphy through this case.

While presented these cases, we tried to demonstrate how important it is to perform scintigraphy in monitoring cases with VUR.

Through these demonstrations we suggest performing VUR scintigraphy in all children with diagnosed UTI after the first attack and even after recurrent UTI, especially its dynamic performance during monitoring cases.

Discussions

The aim of the paper is an attempt to clarify the diagnosis, prognosis and therapeutic indication of VUR when associated with UTI.

Studying the issue of nonspecific urinary tract infections in children with vesicoureteral reflux, we hope I managed to show how important is screening urinary tract infections, sometimes from the first attack. Unfortunately in our country we are faced with serious public health problems, sub-diagnosis of UTI, recognizing relapses and failure to investigate urologic cases presenting recurrent UTIs. We tried by the 2 studies just to answer to the first question that arises from diagnosis and especially to the question "When should we seek the presence of vesicoureteral reflux when we face with an urinary tract infection?".

In the first part of the paper, where we studied in comparison two groups of patients with urinary tract infections, with or without VUR, we were able to show significant differences.

When we analyzed the patients' ages hospitalized for urinary tract infection, as we expected, we observed that patients who had vesicoureteral reflux have also presented the first episode of UTI diagnosed at much younger ages than patients in the control group. This shows the need for screening for renal abnormalities at first hospitalization for UTI, regardless of the sex of the child, during the newborn, infant and little children periods.

We found, following the analysis the symptoms of addressability at the hospital, that very important fever symptoms in children, however nonspecific, were present in significantly more important percentage of children who had also vesicoureteral reflux ($p<0.001$). Then, associating the presence of inflammatory syndrome (ESR> 10 mm / h, fibrinogen> 400 mg / dl, CRP positive), and leukocytosis (average = 13249.52 / mm ^{3}), we showed that high urinary infections associate statistically in higher significant percentage the vesicoureteral reflux. We think this makes necessary performing abdominal ultrasound as screening at any hospitalization, especially for fever, and if abdominal ultrasound is normal and if it is established that fever is associated with a UTI, we consider necessary to conduct an intravenous urography with mictional cliché at the end of exploration wherever possible, especially during a retrograde cystography immediately following after sterilization of urine. Analysis of specific clinical signs of UTI (dysuria and pollakiuria) revealed no significant differences in the two groups compared in study, as well as analysis of symptoms suggestive of UTI, abdominal and especially lumbar pains. Still worth mentioning the results of comparing the two groups on the fetid smell of diaper association with UTI, an important clinical sign for the diagnosis of UTI on infant and little children, possible only by careful questioning of tuturos. There is a statistically significant association ($p<0.001$) of the UTI with VUR with these clinical signs, which proves once again that the UTI at young ages associates in high percentage a malformation of renourinay tract, and therefore in our study VUR. From this first study, we found statistically significant differences on the association of enuresis and urinary incontinence, raising suspicion of VUR and causing to extend investigations. Likewise, a special issue raises the presence of anemia and hypotrophy in length and weight to little children with repeated fever without a special cause. There was found statistically significant higher percentage for children with VUR and we consider necessary to extend the diagnostic protocol of such children who had urinary tract infections, in regard to the presence of a substrate urinary malformation.

Comparing the UTI etiology, by the study of antibiograms obtained after urine cultures, we found that regardless of UTI type, simple or associated with VUR, the etiology was dominated by E.coli, coming to confirm the literature. However we found that in the group with UTI and VUR were 18.1% complex cases, which along with the UTI and VUR had other renourinary malformations or other conditions associated and which had other conditions favoring urinary infections, thus associating many more types of evolving UTI with different etiology of E. coli, coming to confirm the gravity of these cases.

Abdominal ultrasound, performed in all cases followed, showed changes only in small numbers in the control group with simple UTI (5 children), yet cystographies made in these cases denied VUR. Cystography, although made to a number of 37 cases in group 1 of control with simple UTI, was normal in all cases, and we must stress that was performed in all cases that were presented at the second attack of UTI in the hospital.

We consider necessary making mictional cystography to all cases of UTI, especially to those high since the first attack. All children in the first study were treated appropriately for episodes of UTI, and a total of only 15 children were included in UTI prevention program against relapses.

The second study, on the development and treatment of cases diagnosed with UTI and VUR raised us as many problems. We tried to show in this paper that VUR is a complex disease closely intertwined with UTI in association with severely anatomic affecting the child's kidney function.That is why we chose to analyze throughout this second study of the paper the M subgroup exclusively medically treated and the subgroup K surgically treated. We believe that differences of opinion between the pediatrician and pediatric surgeon occur in not setting a common protocol for treatment and proper monitoring of these cases. We think that all cases until the correct necessity of surgery or not need to be placed in a program for the prevention of UTI recurrence with cefaclor or sumetrolim (as tolerated by the patient).

The first step in proper treatment is the correct diagnosis of primary or secondary type of VUR. The two types of VUR have different needs of therapy and monitoring. Equally important is the establishment of reflux grade. At the start of the second study as we expected we found the presence of higher secondary VUR in the subgroup M, the group of patients treated medically only due to the complexity of these cases, the obstructive nature of the malformations involved in its appearance, the associated neurological conditions, thus being exceeded the time of surgery. The surprise was the large group of patients diagnosed at higher ages diagnosed with VUR Thus the age of three years has a rate of 40.3%, and there are even 4 cases diagnosed with VUR at the age of 12 years. This, we think, is still due to the fact that patients were not properly investigated during medical care leading to delays in diagnosis. Thus, for achievingg an improvement in prognosis of VUR is required as we said a unitary approach on this disease (pediatric and surgeon) both in terms of diagnosis and determining therapeutic indication.

To be able to answer to the question above "When should we seek the presence of vesicoureteral reflux when we face with an urinary tract infection?", we tried to propose the following algorithm for proper diagnosis of VUR adapted to new diagnostic possibilities, a different one for each age.

1. *Newborn and infant (0-1 year)*

- If we set a diagnosis before birth of renal dilation or a first diagnosis of UTI the next mandatory step is to develop a renovesical ultrasound, and a cystography. If they were normal the patient will be placed in a program of antibiotic prophylaxis for the recurrence of UTI, and will be monitored monthly clinically and by uroculture in the first 3 months, then every 3 months up to 6 months, and 6 months to 1 year.
- If by ultrasound found renal dilation and / or ureteral and exploring by retrograde cystography shows the presence of VUR will be completed urologic imaging by intravenous urography and paraclinical laboratory explorations of blood urea, serum creatinine, blood ionogram. At least 1 month after infectious episode will be performed a scan to indicate renal function present at diagnosis.
- VUR cases will be monitored clinically and by uroculture monthly up to 1 year. Cystography will be made at 6 months after diagnosis of VUR, then annually or where available may be substituted by ecocystography up to 3 months. Scintigraphic revaluation is required at 6 months of clinical observation especially if new infectious episodes have occurred and annually thereafter to determine surgical indication.
- All cases of VUR will be introduced in UTI relapse prevention program with antibiotics administered at bedtime, 1/3 of the dose daily for a period defined by the VUR development.

2. *Little and preschool children (1-5 years)*

- At this age will be followed the same guidelines for the diagnosis and monitoring of cases of UTI associated with VUR.
- Diagnosis of UTI or incidental discovery of renal or ureteral dilatation by ultrasound requires a new anamnesis in searching possibly unrecognized suggestive UTI episodes.

- After 3 years of age, a finding of urinary incontinence based on physiological micturitions ("permanent wet panties"), especially in girls, and establishing a diurnal and / or night enuresis should require entering a diagnostic protocol requiring a new anamnesis in searching possibly unrecognized suggestive UTI episodes, conducting an ultrasound of renourinary apparatus, a simple renal radiography, intravenous urography with mictional cystography, and even retrograde cystography.
- Paraclinical monitoring of VUR after diagnosis is made by performing uroculture with antibiogram monthly or at any febrile episode, and at 3 months by performing blood count, blood urea, serum creatinine, inflammatory tests, urine analysis, and uroculture with antibiogram.
- By imaging means, ultrasound monitoring will be performed at 3 months and at 6 months by cystography or ecocystography, and then annually. Scintigraphic monitoring will be at one year, or when there is reflux increased at cystography. Cystoscopy examination should be included as a standard method of diagnostic and therapeutic evaluating when diagnosed with VUR.
- All cases of VUR will be introduced in UTI relapse prevention program with antibiotics evening, 1/3 of the dose daily for a period defined by the VUR development.

3. School (over 5 years)

- At first diagnosed UTI attach, will be carried out an ultrasound of urinary apparatus. If it was normal the patient will be placed in a program of antibiotic prophylaxis of UTI recurrence of UTI, and will be monitored monthly clinically and by uroculture within 3 months. If normal, the antibiotic prophylaxis will be stopped, and will be continued performing urine cultures from 3 months up to 6 months, and 6 months to 1 year.
- At the second episode of UTI or renal or ureteral dilatation discovery is required entering into the diagnostic protocol which will meet the same criteria as for the previous age group, as well as tracking of patient criteria. At this age should be given importance in scintigraphy in formulating therapeutic indication in particular for decisions regarding recommendation for surgical option of VUR.

As we presented, therapeutic options in VUR associated with UTI recognize the medical treatment that combines therapy of acute episode and antibiotic prophylaxis, endoscopic injection and surgical reimplantation. Antibiotic prophylaxis on long term proven to be effective in preventing progression of VUR to reflux nephropathy and we think that has a therapeutic character for VUR particularly in small and medium grade in preventing the occurrence of renal scars. In the study subgroup M treated only medically we found a success rate of healing VUR of 31.08% at the end of the study, noting that 82.6% of cases of VUR were below 3 years old, age which in some specialized studies is considered as of maturing vesicoureteral junction.

Surgeries were performed differently, depending on the grade of reflux and studying separately the 2 groups we established some differences. Thus, subureteral cystoscopy injection was performed, especially in small and medium VUR grades (II and III at a rate of 75.82% of cases), with a success global rate of 48.44% at the end of study, but we have to note that during the study we found an increased proportion of solving VUR, in 2010-2011 the success rate reaching to 91% (some cases are still under study, but the grade of VUR has already decreased).

We can say that the subureteral cystoscopy injection method is a big leap in the last 10-15 years VUR therapy, and after method spreading, specifying the indications, and the discovery of substances that meet safety and tolerability, has increased the success rate of this therapeutic method. Regarding the mechanism of correction, the subureteral cystoscopy injection tries to strictly follow the correct anatomical and physiological principles. By injection the ureter is entered into the bladder thus elongating submucous path as intravesically terminal ureter is anchored close by the distribution of its longitudinal fibers in the trigone structure and ureteral hiatus moves freely in the bladder. Nodule injection improves submucosal support of the ureter. Tensioning longitudinal fibers determines by tensioning their decussations a repositioning of ureteral ostium thus producing a correction of abnormal opening. After antireflux reimplantation surgery at the end of the study, the success rate was 31.6%. We have to mention that reimplantation was indicated especially in cases with high VUR (IV and V at the rate of 64.7% of cases).

By analysis of study groups in conjunction with data from the literature we suggest the following diagnostic and therapeutic scheme for UTI associated with VUR - Table 11-1.

To ensure the success of medical treatment for the prevention of UTI recurrences by antibiotic therapy is necessary the mandatory association and correct use of hygieno-dietary measures presented in this study. Following the studies made in this paper we can say:

- that is very important as early as possible diagnosis of VUR when the child is diagnosed by UTI, most often at the first attack
- that VUR treatment when associated with UTI is a circle of three treatment options that may overlap and succeed.

Representative clinical cases

We will present three clinical cases, chosen as examples that are defining this paper study regarding diagnosis, monitoring and therapeutic indication of urinary tract infections due to vesicoureteral reflux.

Case 1 ***B.A. - female with UTI with E. coli and right unilateral VUR grade III***

In the Clinic of Pediatric Surgery of Constanta County Emergency Hospital has abeen dmitted a patient female aged 11 years and 9 months, with fever and abdominal pain. Not present on admission micturition disorders, such as pollakiuria and dysuria.

Medical history indicates that abdominal pain started about 3 months, localized with character of cramp in right iliac fossa, lasting 2-3 days, ameliorated by the administration of the antispasmodic. In the last 2 days abdominal pain has increased and became permanent in last 6 hours when started also fever. The symptoms cause hospitalization in pediatric surgery department to specify the diagnostic. From past medical history were not present urinary infections, but we found the presence of febrile episodes without definite etiology. On examination we found a child with hypotrophy in length and weight (size 135 cm, weight 30 kg), but not with pale skin. At digestive examination, we found a spontaneous and diffuse abdominal pain on palpation, but no signs of muscle conctracture. By examining urogenital apparatus ascertain the presence of physiological mictions, spontaneous but with hyperchrome urine, without any pathological changes.

Paraclinic laboratory investigations revealed: hemoglobin = 13 g / dl, WBC = 20000/mm³, with predominance of granulocytes, ESR = 26 mm / h, normal blood urea and serum creatinine, CRP positive, urine analysis with frequent leukocyte, positive nitrites, pH 7, uroculture showed the presence of E. coli, with> 100 000 CFU / ml, antibiogram showed increased susceptibility to ceftriaxone, ceftazidime, cefuroxime, ofloxacin, norfloxacin. Imaging investigations have shown:

1. Abdominal ultrasound showed right pyelocaliceal duplicity with small right caliceal dilatations

2. Intravenous urography shows a right kidney 11.5 / 5.5 cm, a left kidney 11/5.1 cm. Form and renal topography are normal. Elimination of the contrast substance is bilaterally present, but the right kidney has pyeloureteral duplicity right

3. Retrograde cystography showed vesicoureterorenal reflux right grade III without urinary tract dilation, (figure 95-97)

4. Static renal scintigraphy with TcDTPA shows bilateral renal scarring already present, with renal function still normal, GFR = 114 ml / min,

Based on clinical and laboratory data the patient was diagnosed with E. coli urinary tract infection, primary right vesicoureteral reflux gradeIII associated with pyeloureteral duplicity right. Proper treatment was established for urinary tract infection with ceftriaxone 3 days intravenous, then

cefuroxime then, tablets of 250 mg every 12 hours 11 days, with repeated uroculture after 3 days, which became a sterile urine culture. Patient was placed in a program for prophylaxis of recurrences of urinary infections with the scheme: nalidixic acid, cefuroxime, trimethoprim-sulfamethoxazole for 10 days a month, alternating, 1/3 of the dose. Urine cultures were performed monthly for two months for control, being called for admission in hospital for clinical and paraclinical laboratory evaluation at 3 monts. We decided to delay surgery for technical reasons. But although diagnosis was late established, the patient did not follow the monitoring.

Discussions. We presented a special case of pediatric pathology (nephrology, urology), why? For not yet being implemented a protocol to establish pediatric urinary malformations, and hence vesicoureteral reflux. Positive diagnosis of malformation of renorinary ways was established very late, the child having 11 years, despite a hypotrophy in length and weight, for which was not known the cause. Positive diagnosis was facilitated by performing mictional cystography and static scintigraphy with TcDTPA. Although diagnosis was established very late, short-term prognosis was good, with better renal function, but with renal scarring, an indirect sign of reflux nephropathy. Long-term prognosis can not make an estimate taking into account the literature that say that the occurrence of reflux nephropathy leads to complications such as hypertension and chronic renal insufficiency. The patient never came for monitoring assessment. Relapse prophylaxis of urinary infections is important to prevent the emergence of new renal scarring, and thus is required introducing the child in antibiotic regimen on long term, 1/3 of the dose, daily at bedtime, 6 months, and then further evaluation. Further lack of compliance of patient and tutors aggravated long term prognosis.

Case 2 ***C.C. - male with renal malformation and UTI and VUR left***

Vesico-ureteral reflux (VUR) associated with kidney malformations and made evident by urinary infection is a common entity in pediatric pathology.

We will present a case of VUR grade IV associated with grade III hydronephrosis on left solitary congenital kidney. In Pediatric Clinic of the Children Hospital "St. Mary" in Iassy was hospitalized a male patient aged 3 years and 9 months for fever. Not present on admission micturition disorders, such as pollakiuria and dysuria. History of disease shows that fever began about 2 days before admission, initially treated with paracetamol, but in the last hours retreating only by administration of metamizol sodium, which resulted in deterioration of general condition and somnolence. These symptoms cause pediatric hospitalization for specifying of diagnosis. In past medical history were not present urinary infections, but we found the presence of 3 febrile episodes without definite etiology. On examination we found a child with normal development in length and weight (waist = 96 cm, weight = 16 kg) with normal colored skin. At urogenital apparatus examination, we found the presence of spontaneous micturition, without any pathological changes.

Paraclinic laboratory investigations revealed: hemoglobin = 12.3 g / dl, WBC = 19100/mm³, with predominance of granulocytes, ESR = 19 mm / h, blood urea = 0.24 g% and serum creatinine = 0 , 61 mg / dl, both normal, C-reactive protein positive, urine analysis with very frequent leukocyte, positive nitrites, pH 7.1, uroculture showed the presence of E. coli, with> 100 000 CFU / ml, antibiogram revealed increased susceptibility to ceftriaxone, ceftazidime, ofloxacin, norfloxacin, nitrofurantoin, nalidixic acid, cefaclor.

Initial imaging explorations revealed:

1. Renovesical ultrasound revealed hydronephrosis grade III with megaureter on the left solitary congenital kidney.
2. Retrograde cystography showed vesicoureteral reflux grade II on solitary congenital kidney, megaureter left.

We established the correct treatment of urinary tract infections with ceftazidime intravenously 5 days, then cefaclor suspension of 250 mg/5m, 4 ml to 8 hours 9 days, repeating uroculture after 3 days, which became sterile.

The patient was introduced in UTI relapse prophylaxis program by taking at bedtime nitrofurantoin 15mg daily, with monthly monitoring of urine cultures, and three months clinical and paraclinical laboratory monitoring. During this period the patient was presented only for two admissions in hospital, the balance made did not show any UTI, and ultrasonographic changes were

stationary. Subsequently he was lost from recordings, returning after 3 years at diagnosis of acute pasty tonsillitis. Repeating the paraclinic laboratory investigations and imaging showed: hemoglobin = 12.6 g / dl, leukocyte = 17000/mm³, pharyngeal exudate = flora without pathogenic significance, blood urea = 0.20 g%o, serum creatinine = 0.78 mg%, uroculture = sterile (<1000 CFU / ml), urine analysis = normal.

Retrograde cystography showed vesico-ureteral reflux grade IV, megaureter grade III and hydronephrosis on left kidney, right renal agenesis.

Renovesical ultrasound revealed hydronephrosis grade III solitary kidney with megaureter on the left.

Dynamic renal scintigram with 99mTc DTPA shows glomerular filtration fraction at the lower limit of normal, being made solely to the left kidney. (Figure 100-102)

Left kidney - accumulative curve of nephrographic type. Curve type II O'Reilly - with left kidney obstruction. Radiotracer accumulation is observed at the pyeloureteral junction left. In late scintigraphic image can be seen 1 / 3 lower of left ureter which appears to be dilated - 1.8 cm. Elimination of bladder is present. Kidney right - mute functionally - congenitally absent.

The patient was reintroduced in prophylaxis to prevent urinary reinfection with nitrofurantoin 50 mg / day, single dose administered at bedtime, although was not established the presence of a new UTI.

It was decided ureterovesical antireflux surgery with reimplantation after L.C. Politano technique, maintaining the splint on ureter 14 days, continuing with postoperative prophylaxis urinary for infection relapse prevention.

Being monitored in the study **3 years**, we established about the patient:

- By renovesical ultrasound, gradually reducing the degree of left hydronephrosis initially at grade II, then grade I,
- By retrograde cystography vesicoureteral reflux gradually decreases at 3 months postoperatively, and at 6 months postoperatively completely resolved VUR.

During this monitoring period

- was continued prophylaxis of recurrence of urinary infections with nitrofurantoin as a single dose at bedtime, well tolerated,
- were performed urine cultures monthly for control 6 months, then at 3 months 6 months, then at 6 months 3 years, taking account of the specificity of the case
- urocultures were performed in case of fever,
- blood pressure was monitored weekly,
- congenital single kidney function was monitored at 6 months (blood urea, serum creatinine) and they were normal.

After three years without being recorded in this period a relapse of urinary infection, it was decided interruption of prophylaxis of relapses with subsequent control of urocultures and of functioning of existing solitary kidney.

Conclusion. The case highlights the peculiarities of diagnosis and treatment in a patient with advanced renal malformation - **congenital solitary kidney associated with UTI and VUR.**

Case 3 ***C.M. – male, with UTI and bilateral VUR of IVth grade***

We will discuss a case of bilateral VUR of IVth grade associated with congenital hydronephrosis of IIIrd grade, diagnosed before birth with bilateral hydronephrosis, and taken into evidence at 2 months when he was first diagnosed with UTI. In the Pediatric Surgery Clinic of the Emergency County Hospital Constanta was hospitalized a male patient aged 1 year and 8 months, with no sympthoms on admission of fever or micturition disorders, such as polakkiuria or dysuria.

From physiological personal history, our case is a baby born at 39 weeks by caesarean section on maternal request, with a weight at birth of 3600 g, APGAR score = 9, without suffering at birth. From past medical pathological circumstances we discuss about a patient diagnosed before birth by ultrasound performed at 7 months of gestation to the mother with bilateral hydronephrosis. In evolution, at the age of 2 months after birth, when he was taken in evidence in the Department of Pediatrics, he was diagnosed with UTI with E.coli, despite the correct antibiotic prophylactic treatment made after antibiogramme with Sumetrolim, the patient has experienced other episodes of Proteus UTI 3 times, and Klebsiella and E.coli 2 times. At the age of 2 months was performed renal

scintigraphy and retrograde cystography highlighting a bilateral VUR of IVth grade. Disease history indicates that the patient was diagnosed before birth with bilateral hydronephrosis, at the age of 2 months was first diagnosed with urinary tract infection with E.coli and was introduced in the prophylactic treatment of urinary infections for prevention of relapses, after the correct treatment of acute flare. Given the high degree of reflux, IVth grade bilateral, with UTI recurrences in prophylactic antibiotic treatment administered correctly, the patient was hospitalized for surgical treatment by endoscopic injection with DEFLUX. On examination we found a child with normal length and ponderal development (waist = 81 cm, weight = 11 kg) with normal colored skin. At the urogenital apparatus examination, we found the presence of spontaneous micturitions, without any pathological changes.

Paraclinic laboratory investigations revealed the dynamics at admissions in hospital: hemoglobin = 12.3 g / dL - 12.5 g / dL - 12.4 g / dL, WBC = 14730/mm³ - 12800/mm³ - 33700/mm³ - 9800/mm³ with granulocyte predominance, ESR = 19 mm / h - 13 mm / h - 34 mm / h - 7 mm / h, CRP dynamic positive, negative at last hospitalization, blood urea = 0.24 g % o and serum creatinine = 0, 61 mg / dL, normal in dynamics, urine analysis with very common leukocyte, positive nitrites, pH 5, but normal at current hospitalization. Urine culture was sterile in the hospital. Initial imaging investigations highlighted

1. Plain abdominal ultrasound showed bilateral uretero-hydronephrosis of IIIrd grade,

2. Retrograde cystography showed bilateral vesicoureteral reflux of IVth grade at 2 months, and cystographies made in dynamics showed the same degree of VUR.
3. Renal scintigraphy with Tc DTPA performed at 2 months showed right kidney infused (40.3%), with a maximum of capture (52.1%) at 16 minutes after injection, removing a small amount of radiotracer, the glomerular filtration curve being on the set. Middle lame has stasis. Small pyelocalyceal reflux episodes throughout the study. Right ureter dilated, with stasis from minute 12 to the end of the investigation. Infused left kidney (59.7%), reaches a maximum of capture (47.9%) at 27 minutes after injection. Slowly accumulation of tracer, glomerular filtration curve being upward. Small pyelocalyceal reflux episodes throughout the study. Left ureter has stasis in its lower third. Glomerular filtration = 67 ml / min (right kidney = 34.9 ml / minute, left kidney = 32.1 ml / minute).

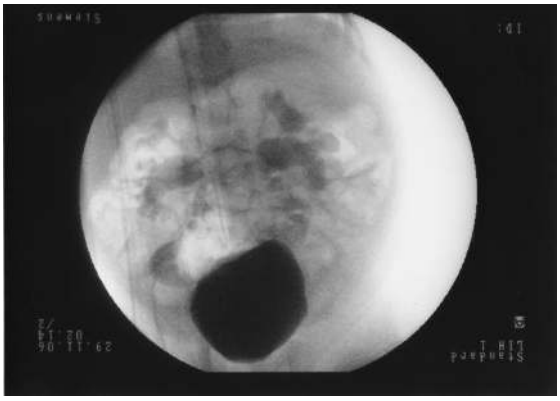


Figure 19

Figure 20

Figures 19-20 Retrograde cystography performed at 2 months showed VUR of IVth grade.

It has been decided the association of cystoscopy surgery, of submucosal injection with DEFLUX. It was performed cystoscopy, which showed ureteric ectopic layers in form of "soccer stadium ", during which endoscopic treatment was performed of VUR by submucosal injection of DEFLUX - 2 ampoules, and urethrorectal-bladder catheter for 24 hours. The post-surgery evolution was favorable under afebrile conditions, suppression of Foley probe being performed at 48 hours postoperatively. It was recommended further prophylactic treatment post-surgery with Sumetrolim, one single dose in the evening.

At 3 days after surgery was performed ultrasound for control of substance injected and were observed post-surgery injection nodules.

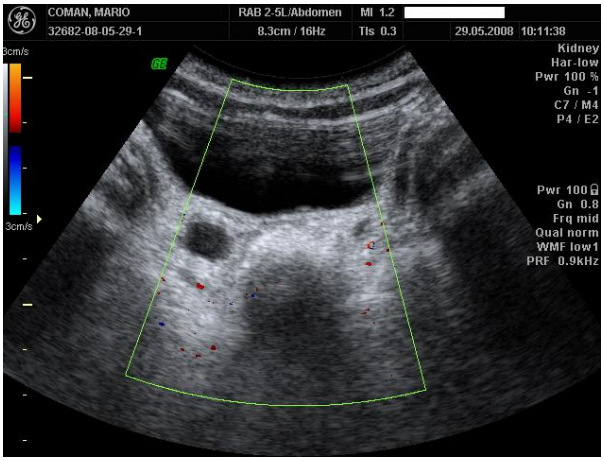


Figure 21. post-surgery injection nodules

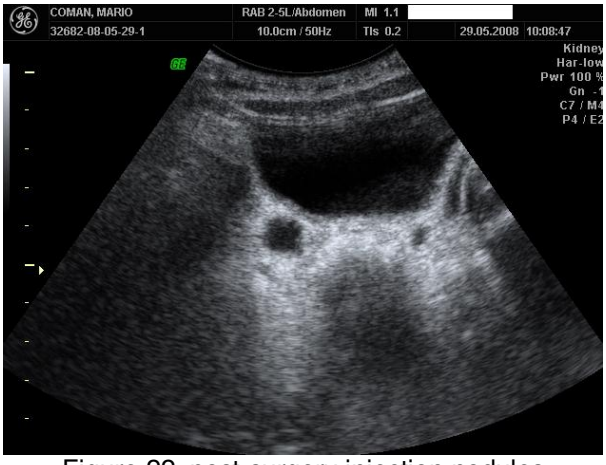


Figure 22. post-surgery injection nodules

At 3 months after surgery was performed retrograde cystography of control which showed the disappearance of right VUR and left VUR reduction in IIIrd grade, and scintigraphy which showed the improvement of renal glomerular filtration. The renal scintigraphy of control performed 3 months after surgery with TcDTPA showed the right kidney infused (49.3%), with a maximum of capture (67.8%) at 21 minutes after injection, glomerular filtration curve being upward. Multiple episodes of pyelocalyceal reflux. Stasis in pelvis until the end of investigation. Dilated right ureter, presenting stasis beginning at 10 minutes and until the end of investigation. Left kidney infused (50.7%), with a maximum of capture (32.2%) at 23 minutes after injection. Slow accumulating of tracer, glomerular filtration curve being upward. At the end of the investigation retain in parenchyma one small amount of tracer. Left ureter not being seen. Glomerular filtration A = 85.1 ml / minute (right kidney = 57.7 ml / minute, left kidney = 27.4 ml / min).

The patient was introduced in UTI relapse prevention program, immediately, by taking Zinat, 125mg/5ml suspension, 2.5 ml / day in the evening, 10 days / month, Negram ¼ tablet / day in the evening 10 days / month, Sumetrolim 25mg Trimetoprim / 5 ml, 3.5 ml / day in the evening 10 days / month, monthly monitoring of urine cultures, and clinical and paraclinical laboratory monitoring every 3 months. During this period the patient presented only two in hospital, the balance made showing 2 episodes of UTI. one with Proteus and one with E.coli, properly treated, 14 days, with Cefort 3 days 1g / day, in Department of Pediatrics, and Cedax suspension 3 ml / day 11 days at home, and ultrasound changes were stationary

Figure 23. Left kidney

Figure 24. Right kidney

Figure 23-240 Abdominal ultrasound which shows bilateral hydronephrosis of Ist grade, 4 years after surgery with antibiotic prophylactic treatment administered correctly 2 years after surgery.

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Subsequently was carried associated phimosis treatment with continuing the prophylactic antibiotic treatment with Sumetrolim 5ml / day in the evening for 1 more year with monthly monitoring of urine cultures, and three months clinical and paraclinical monitoring in the laboratory. No new UTI episodes have been recorded. For technical reasons could not been made other cystography of control until now.

Abdominal ultrasound performed showed reduction in dynamic of uretero-hydronephrosis, last ultrasound performed in May 2012 showing a right kidney = 9,3 / 3,6 cm, with hydronephrosis of Ist grade (anteroposterior diameter of the pelvis - 10.8 mm), and a left kidney = 8,2 / 3 cm, hydronephrosis of Ist (anteroposterior diameter of the pelvis – 13 mm).

Still being monitored, the patient aged 6 years, normally developed in length and weight, who has not experienced any episode of UTI during the last 2 years, makes at 3 months a clinical balance, with paraclinical tests (urine analysis, urine culture), and abdominal ultrasound every 6 months, being scheduled to repeat the cystography.

Conclusion. The case highlights the peculiarities of diagnosis and treatment for a patient with renal malformation - **congenital bilateral hydronephrosis diagnosed before birth associated with VUR, diagnosed with UTI at the he age of 2 months.**

Conclusions

1. Vesicoureteral reflux is part of the reno-urinary obstructive abnormalities, which are particularly serious, because unrecognized in time or recognized but treated improperly, lead to morphological and functional damage of the kidney. Nonspecific UTIs, although simple infections at first glance, are real problems of clinical and laboratory diagnosis, especially for infants and little children.

2. Nonspecific UTIs often hide VUR, their association worsening the renal function prognosis of the future adult. The vesicoureteral reflux is found in a proportion of 30-59% in children with urinary tract infections, who untreated can evolve from spontaneous remission to severe and irreversible damages to the upper urinary tract.

3. Spontaneous resolution occurs in 87.5% of cases in VUR grade I, 63% in grade II, 53% in grade III, 33% in grade IV.

4. In this study we chose to analyze a total of 194 patients hospitalized in our country for nonspecific urinary tract infections or for a vesicoureteral reflux fund. The first group of 124 children was hospitalized in three hospitals in the country, in the Department of Pediatric Surgery Clinic of Emergency Children Hospital "Grigore Alexandrescu" Bucharest - 38 cases, in the Pediatric Department of the Children Hospital "St. Mary Maria" in Iassy - 59 cases, and in Constanta County Emergency Hospital - 27 cases, where we work. There were also included in the study 70 children hospitalized in Constanta County Clinic Hospital for a first attack of nonspecific UTI, imaging proving to be non associated with VUR, to compare the clinical and laboratory characteristics of these children to the group of 124 children who associated VUR. The study was conducted over a period of 8 years (2004-2011).

5. The work was divided into 2 major critical retrospective studies. *The first study* compared 2 groups as follows: the first group of 70 children with nonspecific simple UTI, who did not associate VUR, with the group 2 of the 124 children with UTI and VUR. *The second study* conducted a parallel by analyzing the second group of 124 cases with UTI and VUR, trying to establish some characteristics for each universitary center. We studied a subgroup of children medicaly treated for prophylaxis of relapses of urinary infections in conditions of existence of vesicoureteral reflux after a definite diagnosis of urinary tract infections, and a subgroup of children who after a period of monitoring under medical treatment properly conducted, has also benefited of surgically treatement.

6. The most common symptoms were the symptoms of acute febrile urinary tract infection associated with nausea and vomiting, mucocutaneous pallor, hypotrophy in length and weight, for older children adding lumbar pain and dysuria.

7. The assessment was required in urinary tract infections with significant bacteriuria or with positive urocultures (more than 100 000 CFU / ml) together with clinical and blood pressure measurement and paraclinical laboratory assessment (blood urea, serum creatinine, ESR, fibrinogen, CRP), imaging assessment (by ultrasound of urinary apparatus, retrograde cystography and / or mictional, intravenous urography, renal scintigraphy).

8. Any UTI should be correctly diagnosed and in the presence of suggestive clinical and laboratory signs is required to the inclusion in a diagnostic protocol of VUR. Febrile syndromes in infants and small children who were suspected of urinary tract infection revealed at uroculture an etiology dominated by E.coli (50% in the group with UTI and VUR, and 45.6% in the group with simple UTI). In the group with UTI associated with VUR we found 20% of cases

with microbial associations (enterobacter, proteus, klebsiela, streptococcus group D, pseudomonas and E. coli).

9. Urinary infection can be prevented in VUR by antibiotics (acute episode therapy and antibiotic prophylaxis) which makes that VUR could be spontaneous remitted by age of 3 years through submucosal elongation of the ureter with child growth.
10. Ultrasound before and after birth should become obligatory in medical practice in Romania because is the easiest possibility for early diagnosis of the congenital malformations of urinary apparatus of the child.
11. VUR diagnosed in the after birth period on the base of fetal hydronephrosis diagnosed by ultrasound is most likely to disappear spontaneously regardless of reflux, by the correct treatment of urinary tract infections and antibiotic prophylaxis of recurrences.
12. First and second grade VUR do not require surgical treatment, they are remitted under proper treatment with antibiotics. In the acute phase of UTI, antibiotic treatments were made according the uroculture with antibiogram - most urinary tract infections being with gram-negative germs and the main antibiotics administered were cephalosporins, gentamicin, trimethoprim-sulfamethoxazole.
13. In this study we obtained good results with the long-term antibiotic therapy for preventing recurrence of urinary infections, 1/3 of the dose administered as a single dose at bedtime. We used - trimethoprim-sulfamethoxazole (2mg / kg / zi), cefaclor (10-15 mg / kg / day), nitrofurantoin (2mg / kg / day), nalidixic acid (5mg / kg / day), administrated until the VUR remission after chirurgical surgery, and for secondary VUR permanently. Besides antibiotic prophylaxis were associated additional measures (good hydration, urinary frequent micturitions at regular intervals, proper perineal toilet, avoiding constipation and for neurogenic bladder was associated administration of Driptane.
14. The monitoring of children with VUR associated with UTI was done by urocultures performed for 3 months (or any fever attack), then every 3 months when was also performed a paraclinical balance (hemoleukogram, blood urea, serum creatinine, inflammatory evidences, urinalysis, uroculture, ultrasound of urinary apparatus). VUR assessment by retrograde cystography was performed every 6 months-1 year), and the assessment of renal function by radioisotope scintigraphy, where possible, in 1-2 years. The maximum age of waiting was 10-11 years for VUR.
15. VUR exclusive medical treatment showed a healing rate of VUR of 31.08%, indicating that 82.6% of VUR cases were below 3 years age when is maturing the vesicoureteral junction.
16. Subureteral endoscopic injection of implant material was performed in 31 children (1 case in Iassy, 1 case from Constanța and 29 cases in Bucharest), with cure rates of 44.44% after the first injection and 48.14% after the second injection. Applied in Romania, in upward trend in recent years, in 2010-2011, by using VANTRIS type substance injection (12 children), the success rate reaches 91%.
17. Surgical treatment of antireflux reimplantation was performed in 19 cases with primary VUR, by Cohen technique in 16 cases (10 in Bucharest, 4 in Constanta and 2 in Iassy), the Politano technique in 2 cases in Iassy and Lich-Gregoire technique in one case in Bucharest. The success rate was 73.69%, with VUR reduction in 42.09% and VUR remission in 31.6% of cases. In any clinic of the studied ones were not used yet mixed techniques of endoscopic correction - transurethral and vesical transcutaneous.
18. VUR requires an early diagnosis, correct, precise for each case, the patient being under an individualized treatment for each case, depending on the grade of reflux and by its secondary complications.

19. At the diagnosis, treatment and monitoring of VUR must attend a complex medical team consisting in a family doctor, a neonatologist, a pediatrician, a pediatric surgeon, an urologist, a gynecologist, a laboratory doctor, a radiologist and a medical imaging doctor.
20. Urinary tract infections added to VUR lead to renal scleroatrophy, renal hypertension and renal insufficiency with fatal evolution despite current possibilities of dialysis or kidney transplantation.
21. It is important to consider the formation of multidisciplinary medical teams in major university clinics (regional) to properly resolve urogenital malformations of the child, which underestimated may compromise the health of the infantile population.
22. Romanian doctors competence coupled with the necessary equipment will be able to solve many problems of congenital urogenital malformations, and hence in our case VUR, in pediatric practice in our country

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