

VACCINE PROPHYLAXIS OF RECURRENT URINARY TRACT INFECTIONS IN CHILDREN

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Abstract

Currently, one of the most common problems in childhood are urinary tract infections (UTI). The recurrent UTI is the risk of irreversible damage to the renal parenchyma, replacing it with connective tissue and a further outcome in chronic kidney disease (CKD). The aim of the study: to study the effectiveness of immunovaccination in the complex anti-relapse therapy in children with urinary tract infection.

Materials and methods. The study involved 70 patients who were hospitalized at the City Children's Hospital Academician B. Ya. Reznik. In the dynamics of the observations conducted a general analysis of blood and urine, bacteriological examination of urine, if necessary, Rg-urological examination. In the period of acute UTI, all patients received treatment according to the International European Recommendations. For the prevention of UTI, uroseptic (nitrofurantoin) was used in prophylactic regimens in combination with a lyophilized preparation.

Results. In the course of anti-relapse treatment, there was a decrease in the number of recurrences of the disease in children after completing the course in 39 of 70 patients, which amounted to 55.71% and clinical and laboratory remission of UTI was achieved. The number of relapses with a microbial number $\geq 10^5$ was significantly reduced (from 5.21 to 2.36, $p < 0.05$). The number of relapses with a bacteriuria level of $> 10^4$ CFU also decreased. At the time of the survey in the first control point (after 3 months), a decrease in the microbial number was noted in 37.14%, and in the control after 6 months – in 52.86%. The recurrence rate of UTI for the 6-month period decreased from 3.38 ± 0.48 to 1.67 ± 0.24 times a year. The obtained effect allowed reducing the use of antimicrobial agents in 34.3% of patients. At the same time, the effectiveness of antimicrobial therapy has increased.

Conclusion. Thus, the results of our studies showed a high efficacy of vaccine prophylaxis using lyophilized preparations for UTI in children, which can be used to prevent the occurrence of relapses. A reduction in the frequency of relapses and the need to use antibacterial drugs, sanitation of urine and the absence of side effects during vaccination have been established.

All human studies were conducted in compliance with the rules of the Helsinki Declaration of the World Medical Association "Ethical principles of medical research with human participation as an object of study". Informed consent was obtained from all participants.

Key words: *children, urinary tract infections, vaccine prophylaxis, lyophilized preparations, antimicrobial therapy*

Introduction

Currently, one of the most common problems in childhood are urinary tract infections (UTI) [1-2]. It is also known that among the bacterial infections in children, UTI is in the first place. An important aspect of the problem is its socio-economic significance. Thus, according to the annual statistics of the United States, the frequency of seeking medical help for UTI is 11 million cases, estimated at \$ 3.5 billion. In developing countries, the frequency of occurrence of UTI reaches 37% [2-3].

It has been established that in one fifth of children under 2 years of age with the presence of kidney damage, after suffering a UTI, there is a risk of kidney deterioration and these children are recommended to be followed up by a nephrologist [4]. Every third child less than 1 year old is diagnosed with UTI, and repeated episodes are recorded for three years, and 18% of children have a relapse within a few months. Relapse of UTI in younger children is observed in 35% of boys and 32% of girls, while 50% of girls have a repeated infection within a year after remission, and in 75% of cases within two years [5-6].

As a rule, recurrences of UTI are detected in children with abnormalities of the urinary system, vesicoureteral reflux (MRR) or neurogenic bladder dysfunction [7-8].

The recurrent UTI is the risk of irreversible damage to the renal parenchyma, replacing it with connective tissue and a further outcome in chronic kidney disease (CKD) [5, 8-10]. Cicatricial changes of the parenchyma based on the results of static nephroscintigraphy are determined in 17 of 38 patients with UTI associated with MTCT [11].

The nature and course of the inflammatory process of the urinary tract also depends on infectious agents, among which potentially pathogenic enterobacteria are priorities. Gram-negative coliforms, mainly *Escherichia coli*, are the most common bacterial isolates that were isolated from urine cultures in IMAI [6]. According to research data, along with *E. coli*, UTIs are also called *Proteus* spp., *Klebsiella* spp. and *Enterobacter* spp., *Staphylococcus saprophyticus*, *Enterococcus faecalis* [5]. It is important to note that in the occurrence of complicated forms of the disease

microbial associations are of great importance [8-10].

Recently, more and more data on increasing the resistance of uropathogens to antimicrobial drugs. Thus, the resistance of *E. coli* and other enterobacteria is constantly changing, while sensitivity is reduced not only to first-line drugs, such as ampicillin, nitrofurantoin and trimethoprim, but recently to fluoroquinolones. This significantly reduces the possibility of treatment and prevention of UTI [9-11].

An alternative approach to the treatment of UTI is to stimulate the patient's own protective mechanisms against the pathogenic flora, using immunotherapeutic effects [5, 10-12]. It has been shown that immune-active prophylaxis stimulates mucosal lymphoid tissue and leads to a generalized immune response, and the use of oral forms of bacterial extracts provides activation of both specific and nonspecific immunity [11].

In preclinical and clinical studies, lyophilized preparations contributed to the stimulation of the protective activity of macrophages; increased concentration of secretory IgA on the surface of the mucous membranes of the urinary tract; an increase in the population of T-lymphocytes (CD4); stimulated the formation of protective adhesive molecules [13].

Bacterial lysates are also recommended to be used as an additional source of inactivated microorganisms that induce a topical inflammatory response in the urinary system and contribute to an increase in resistance of urothelial [10, 13].

Thus, the high frequency of UTI, the recurrent nature of its course, the absence of unified anti-relapse therapy schemes initiated this study.

The aim of the study: to study the effectiveness of immunovaccination in the complex anti-relapse therapy in children with urinary tract infection.

Methods

The study involved 70 patients who were hospitalized at the City Children's Hospital. Academician B.Ya. Reznik. Selection of patients in the study was conducted in accordance with the inclusion criteria (age of the child from 7 to 18 years; recurrent UTI with a frequency of episodes 2 times in 6 months or 3 times in 12 months; informed consent) and exceptions (informed consent not

obtained; indwelling catheter or current urinary collection device; current anti-infective therapy for the child; for immunocompromised children, children under 7 years of age;

In the dynamics of the observations conducted a general analysis of blood and urine, bacteriological examination of urine, if necessary, Rg-uropathological examination.

In the period of acute UTI, all patients received treatment according to the International European Recommendations. For the prevention of UTI, uroseptic (nitrofurantoin) was used in prophylactic regimens in combination with a lyophilized preparation (brand name Urivac®). The preparation contains a combination of purified lysates (highly purified inactivated microorganisms) from 6 original bacterial strains of typical uropathogens patented by the manufacturer. One capsule of the drug (250 mg) contains the active ingredients, including: *Propionibacterium acnes* lysatum cryodessicatum (CCM 7083) - 1.66 mg, *Klebsiella pneumoniae* lysatum cryodessicatum (CCM 7589) - 0.67 mg, *Pseudomonas aeruginosa* lysatum cryodessicatum - 0.67 mg, *Enterococcus faecalis* lysatum cryodessicatum (CCM7591) - 0.67 mg, *Escherichia coli* lysatum cryodessicatum (CCM 7593) - 0.67 mg, *Proteus mirabilis* lysatum cryodessicatum (CCM 7592) - 0.67 mg.

Vaccinal prophylaxis was carried out according to the scheme: 10 days in the morning on an empty stomach, 1 capsule, the course of treatment was continued after a 20 day break. The basic course of treatment was 6 months. Test points of the study: 3 months and 6 months. Control tests conducted a general analysis of urine, analyzed the frequency of relapses, urine sterility, evaluated the need for further therapy.

The control group consisted of the same patients in the last 12 months before joining the study, when they received uroseptics for the prophylactic treatment of UTI. The history of the course of previous episodes of UTI in the control group was analyzed retrospectively.

Statistical analysis was performed using the Statistica program (StatSoft, Inc. (2001). STATISTICA (data analysis software system), version 6. www.statsoft.com).

Results

The general characteristics of the studied group of patients were as follows: the average age of the examined children was 8.86 ± 2.31 years. At the age of 7 to 9 years old there were 49 people (70.0%) of the total number of patients; from 10 to 12 years - 9 (12.86%) patients; from 13 to 15 years - 12 patients, which amounted to 17.14%. Among the examined children there were boys - 11 (15.71%) and girls - 59 (84.29%).

In evaluating the topic of microbial inflammation, in 56 (80.0%) patients, lesions of the upper urinary tract (pyelonephritis) were found, in 14 people (20.0%) - in the lower urinary tract (cystitis). Background conditions for the development of the microbial-inflammatory process were: congenital anomalies of the urinary system (CAUS) - doubling of the kidneys in 10 (14.29%) people, VUR in 17 patients (24.29%), crystalline nephropathy in 10 children (14.29%), polycystic kidney disease - 2 children (2.86%), neurogenic bladder - 1 (1.43%) and hydronephrosis - 1 (1.43%) people.

Exacerbation of upper urinary tract infection was accompanied by hyperthermia over 37.5°C (38.57%), changes in the general condition (88.57%), pain in the lumbar region (14.28%) and urinary syndrome (100%). Recurrence of lower urinary tract infection was characterized by the presence of dysuria events (25.71%) and changes in urinary sediment (100%).

During the period of exacerbation, significant leukocyturia (78.57%), microproteinuria (40.0%), microhematuria (24.29%) was determined in the examined children. At the same time, in 22.86% of patients, regardless of the period of the disease, the number of leukocytes during urine microscopy did not exceed $10 / \text{mm}^3$, which indirectly indicated that the local immune response was insufficiently reactive.

According to a retrospective analysis, it was established that all children in history had received anti-relapse therapy: antibiotic therapy (85.71%), uroseptics (92.86%), phytotherapy (68.57%). The average recurrence rate of UTI was (3.38 ± 0.48) episodes per year.

An analysis of the etiology of UTI showed the predominance of microorganisms of the family of enterobacteria. Microbiological examination of urine in the structure of uropathogens was most often determined by *E. coli* - in 65.7% of cases (Fig. 1). Representatives of the *Proteus* genera (5.71%) and

Enterobacter (5.71%) were significantly less common. *Pseudomonas aeruginosa* (4.29%) was also isolated in the spectrum of gram-negative bacteria. Among gram-positive microorganisms, *Enterococcus* (11.43%), *Staphylococcus* (4.29%) was detected most frequently.

In most cases, microorganisms were isolated as monocultures, but in 21.73% of patients microbial associations were determined: *E. coli* in combination with *Staphylococcus aureus* - 1.43%, with *Enterococcus faecalis* - 4.29%, with *Enterobacter aerogenes* - 1, 43%. *Enterococcus* spp. in combination with *Enterobacter aerogenes* (1.43%).

When determining the microbial number in urine samples, the degree of bacteriuria $\geq 10^5$ CFU is established - in 65.71%, $10^3 - 10^4$ - in 30.0%, $<10^3$ - in 4.29%) children.

The results of the evaluation of antibiotic resistance of the isolated microorganisms are shown in Fig.2.

Microbiological examination of urine revealed *E. coli* resistance to the following drugs: aminoglycosides - 4 people (5.71%), carbapenems - 5 (7.14%), cephalosporins - 5 (7.14%), fluoroquinolones - 10 (14.29%), protected penicillins - 11 (15.71%), macrolides - 16 (22.86%) and penicillins - 19 (27.15%). It should be noted that in most cases bacterial pathogens were multiresistant to antibacterial drugs.

In some cases, with simultaneous isolation of several pathogens and identified cross-resistance, it was necessary to take two antibacterial drugs, which, on the one hand, reduced the compliance, and, on the other, could have a negative effect on the intestinal microbiocenosis, and also lead to a decrease in the body's immunological reactivity.

Obtained in a retrospective analysis of the data on the high recurrence rate of UTI, the characteristics of the microflora and antibiotic resistance indicated the need to optimize anti-relapse therapy. In this regard, all patients were vaccinated with a drug containing bacterial lysates of the most significant uropathogens.

The effectiveness of vaccination was assessed by the number of recurrences of UTI, the need for the appointment of concomitant antimicrobial agents, the characteristics of urinary syndrome, and also

taking into account the subjective assessment of patients.

In the course of anti-relapse treatment, there was a decrease in the number of recurrences of the disease in children after completing the course in 39 of 70 patients, which amounted to 55.71% and clinical and laboratory remission of UTI was achieved. The number of relapses with a microbial number $\geq 10^5$ was significantly reduced (from 5.21 to 2.36, $p < 0.05$). The number of relapses with a bacteriuria level of $> 10^4$ CFU also decreased. At the time of the survey in the first control point (after 3 months), a decrease in the microbial number was noted in 37.14%, and in the control after 6 months - in 52.86%. The recurrence rate of UTI for the 6-month period decreased from 3.38 ± 0.48 to 1.67 ± 0.24 times a year. The obtained effect allowed reducing the use of antimicrobial agents in 34.3% of patients. At the same time, the effectiveness of antimicrobial therapy has increased.

During the period of anti-relapse therapy, no side effects were identified. According to the subjective assessment, an improvement in the condition was noted by 28.57%.

Discussion

Analyzing the group of examined children with UTI, the traditional prevalence of girls was noted - 84.29% of cases, which corresponds to the data of many studies conducted in children [2, 4, 8, 10, 12]. The clinical course of UTI is accompanied by the presence of dysuric (25.71%), pain (14.28%), intoxication (88.57%) and urinary syndromes (100%). The recurrences of UTI in children were most common in patients with VUR (45.71%), CAUS (37.14%), neurogenic bladder (24.29%).

E. coli is one of the most frequent strains in the study of urine flora in children and is noted in 65.7% of cases, while in 21.73% of patients it is determined in combination with other strains. The analysis made it possible to identify the association between the frequency of recurrence of UTI and the presence of polyvalent microflora ($\chi^2 = 6.529$, $p < 0.05$) in the group of children examined.

Antibiotic resistance is currently one of the most difficult problems when deciding on antibiotic therapy, especially in children. Existing recommendations regarding the use of long-term low-dose antibiotic prophylaxis for UTI in children

today are undergoing review. Prolonged use of antibiotics contributes to the selection of resistant microorganisms, violates the body's microbiome, has a suppressive effect on the factors of the immune system, and has a nephrotoxic effect.

In our study, the high frequency of detection of antibiotic resistance indicates the need for mandatory microbiological monitoring of urine culture results, predicts the lack of effectiveness of antibiotic therapy, and emphasizes the need to choose alternative approaches, including vaccination.

When using the oral vaccine, containing in its composition a complex of lyophilized forms of the most frequently encountered uropathogens, prolongation of remission is observed with recurrent UTI in children, as evidenced by our study results.

Below is the data of a patient treated with Urivak® bacterial lysate for the purpose of UTI vaccine prophylaxis.

A patient:

Girl 7 years old. For the first time, a diagnosis of UTI was established in the second year of life, based on complaints of frequent, painful urination, an increase in body temperature to 37.5, and the presence of urinary syndrome in the form of leukocyturia and bacteriuria. Subsequently, exacerbations were noted 5-6 times a year.

At the age of 3 years, a vaginal cystography was performed and vesicoureteral reflux (VUR) was determined (Fig. 3). The child underwent surgical endoscopic correction of the left VUR. On the control ascending cystogram VUR was not detected. Despite the surgical treatment and prophylactic treatment of uroseptics, UTIs were recorded with a frequency of 4-6 times a year.

In February 2018, another exacerbation of UTI was recorded, which was accompanied by dysuric syndrome, hyperthermia, and leukocyturia ($8 \cdot 10^4$ /ml) urinary sediment and bacteriuria. Bacteriological examination of urine showed the presence of *Escherichia coli* 10^4 CFU/ml. When evaluating antibiotic resistance, drug resistance was determined: ampicillin, azlocicillin, doxycillin, tetracycline, clindamycin, lincomycin, chloramphenicol, rifampicin, chlorophyllipt, linezolid, vancomycin, furagin, fluoroquinolones. At the end of the 14-day course of therapy (with the

use of antibacterial drugs with sensitivity preserved to them), a clinical improvement, a decrease in the level of leukocyturia was observed.

In order to prevent relapse, in March 2018, immunomodulating therapy was started with the drug Urivak® according to the following scheme: 10 days in the morning on an empty stomach, 1 capsule each, the course of treatment was continued after a 20 day break. The basic course of treatment was 6 months.

According to the survey after 3 months from the start of vaccination, there was no recurrence of UTI, no changes in the microscopy of the urinary sediment, which allowed canceling the reception of uroseptic. Subjective assessment is positive. At the time of the survey after 6 months from the start of vaccination, recurrences of UTI were not registered. Side effects from taking the drug were not detected. According to the subjective assessment of the patient and parents, the child's condition was improved. The girl began attending primary school.

An exacerbation of UTI was documented in February 2019 (12 months of remission), was provoked by hypothermia and caused by psycho-emotional stress. Characteristic features of this exacerbation were a decrease in the degree of activity of the inflammatory process compared with previous episodes, which allowed for an outpatient procedure, without the need for hospitalization. Within 5 days of taking an antibacterial drug, urine tests were sanitized. During antibioticograms, there was a decrease in the microbial number from 10^4 CFU/ml to 10^2 CFU/ml, as well as expansion of the spectrum of sensitivity to antibacterial drugs (including fluoroquinolones, macrolides, furagin).

Thus, when taking a bacterial lysate Urivak®, the child maintained a long-term remission with a relapse 1 time per year, as well as a decrease in the degree of activity of the process, sanitation of the urine after 5 days of antibiotic intake and increased sensitivity to antibacterial drugs suggest an increase in the effectiveness of vaccine prevention.

Conclusions

Thus, the results of our studies showed a high efficacy of vaccine prophylaxis using lyophilized preparations for UTI in children, which can be used to prevent the occurrence of relapses. A reduction in the frequency of relapses and the need to use

antibacterial drugs, sanitation of urine and the absence of side effects during vaccination have been established.

Acknowledgments

The authors declare that there are no conflicts of interest.

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Figure 1. Species composition of uropathogenic flora in children with UTI

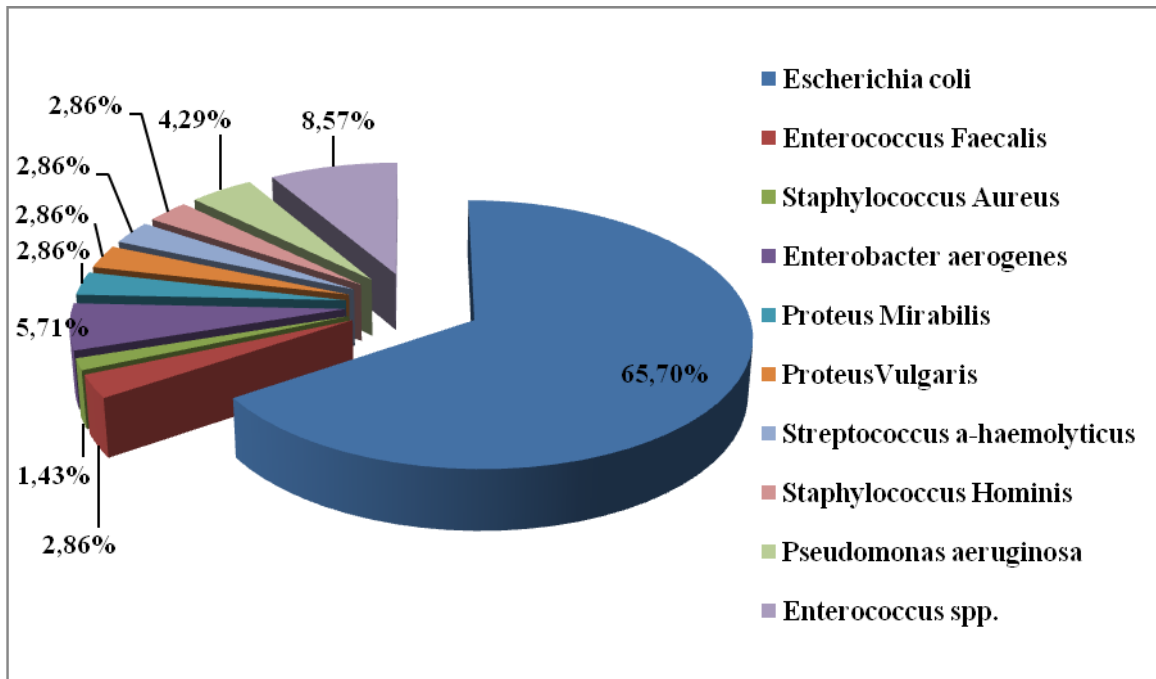


Figure 2. Resistance of uropathogens to antibacterial drugs in children with UTI

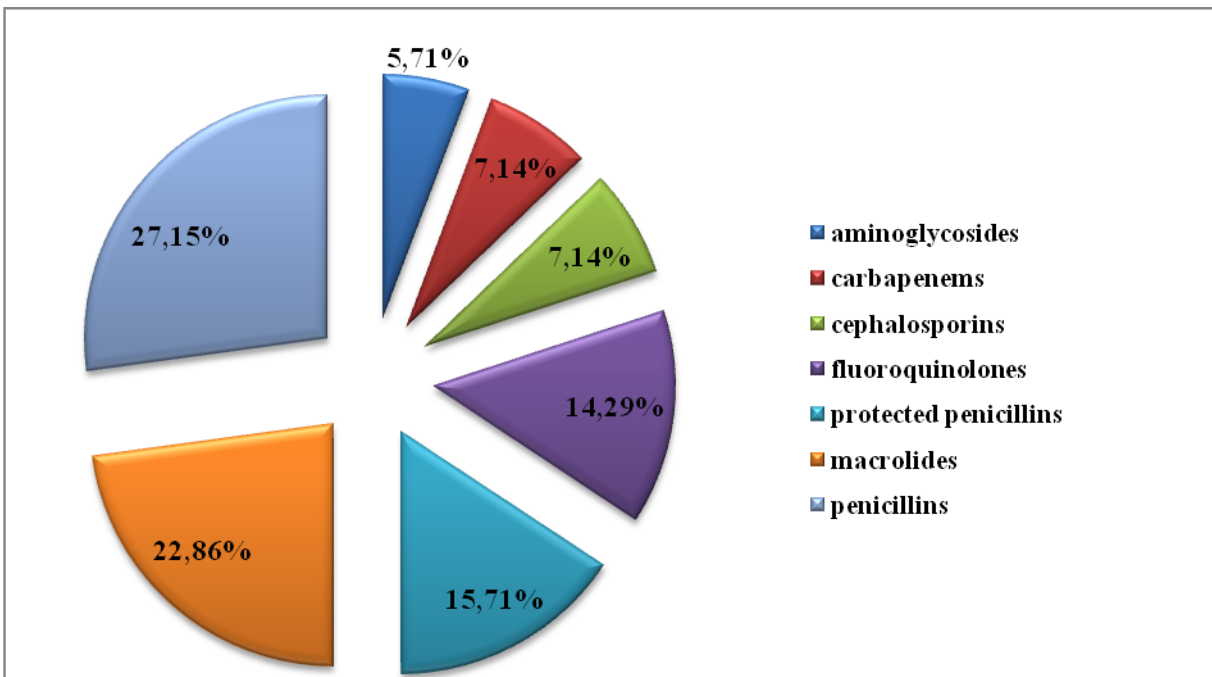
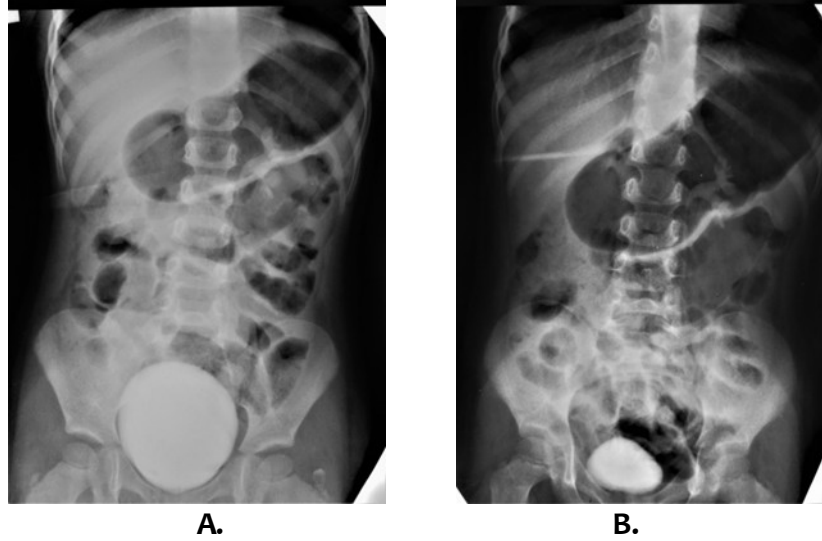


Figure 3. X-ray examination - vascular cystography of a 3-year-old child with VUR III on the left



A - against the background of filling the bladder with a contrast, B - during urination