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## INFLUENCE OF VACCINE THERAPY ON CLINICAL AND LABORATORY PARAMETERS IN PATIENTS WITH RECURRENT URINARY TRACT INFECTION

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**Ключевые слова:** *инфекция мочевой системы, девочки, антибактериальная резистентность, вакциноterapia*

**Abstract. Influence of vaccine therapy on clinical and laboratory parameters in patients with recurrent urinary tract infection. Budnik T.V., Kvashnina L.V.** Recurrent urinary tract infection (UTI) remains a pressing issue in the era of large-scale antibiotic resistance (ABR). Modern discoveries testify to the paradigm's error regarding sterility of urine, pointing to the decisive role of the microbial symbiote in the persistence of infection. The purpose of the study was to study the clinical and laboratory efficacy of vaccine therapy in children with recurrent UTI. During the period 2018-2019, 21 children (girls) aged 7-18 years with recurrent UTI in the exacerbation phase were observed. By the nature of therapy, children were divided into groups: Ia - received vaccine therapy (VT) in the complex of therapy, Ib - a combination of VT and ABT, II – ABT. In addition to the generally accepted methods of assessing the clinical and laboratory status of a nephrological patient, modern non-routine diagnostic methods such as the identification of a microbial pathogen by MALDI TOF mass spectrometry and the determination of the susceptibility of microorganisms by the MIC 90 method were used. As vaccine therapy, the original multicomponent drug was used: *Escherichia coli* (CCM 7593), *Enterococcus faecalis* (CCM7591), *Klebsiella pneumonia* (CCM 7589), *Proteus mirabilis* (CCM 7592), *Pseudomonas aeruginosa* (CCM 7590), *Propionibacterium acnes* (CCM 7083). The drug was prescribed according to the instructions, the duration of use was determined individually by clinical indicators, from 3 to 12 months. According to the study, it was determined that VT leads to the restoration of the sensitivity of resistant strains of pathogens. The probability of recovery of sensitivity after the 3rd cycle of treatment was  $OR=1,87\pm 1,13$  [0,2; 17,3] at CI 95% ( $p<0,05$ ), after the 6th cycle of therapy –  $OR=4,5\pm 1,32$  [0,33; 60,1], which is 2.4 times higher than the previous one. The effect of restoring the sensitivity of the strains was significantly confirmed in patients after the 9th cycle of therapy ( $p=0,008$ ). A high association strength according to the Spearman criterion indicated the dependence of bacterial efficacy of VT on its term of application –  $p=-0,97$ , ( $p<0,05$ ). It is shown that the probability of reinfection after 3 cycles of vaccine therapy is 20.5 times lower than after the course of ABT.

**Реферат. Влияние вакцинотерапии на клинико-лабораторные показатели у пациентов с рекуррентной инфекцией мочевой системы. Будник Т.В., Квашнина Л.В.** Рекуррентная инфекция мочевой системы (ИМС) остается актуальным вопросом в эру масштабной антибиотикорезистентности (АБР). Современные открытия свидетельствуют о ложности парадигм относительно стерильности мочи, указывают на определяющую роль микробной симбиоты в персистенции инфекции. Целью исследования стало изучение клинико-лабораторной эффективности вакцинотерапии у детей с рекуррентной ИМС. В течение 2018-2019 гг. велось наблюдение за 21 ребенком (девочки) в возрасте 7-18 лет. с рекуррентной ИМС в фазу обострения. По характеру терапии дети были разделены на группы: Ia - получали вакцинацию (ВТ) в комплексе терапии, Ib - комбинацию ВТ и АБТ, II – АБТ. Кроме общепринятых методов оценки клинико-лабораторного состояния пациента нефрологического профиля, были использованы современные не рутинные методы диагностики, такие как идентификация микробного возбудителя путем масс-спектрометрии MALDI TOF и определение чувствительности микроорганизмов методом МИК 90. В качестве вакцинотерапии применялось оригинальное поликомпонентное средство европейского производства. В составе препарата – лиофилизированные штаммы уропатогенов: *Escherichia coli* (CCM 7593), *Enterococcus faecalis* (CCM7591), *Klebsiella pneumonia* (CCM 7589), *Proteus mirabilis* (CCM 7592), *Pseudomonas aeruginosa* (CCM 7590), *Propionibacterium acnes* (CCM 7083). Препарат назначался по инструкции, длительность применения определялась индивидуально по клиническим показаниям от 3-х до 12-ти мес. По результатам исследования было определено, что ВТ приводит к восстановлению чувствительности резистентных штаммов патогенов. Вероятность восстановления чувствительности после 3-го цикла лечения составляла  $OR=1,87\pm 1,13$  [0,2; 17,3] при ДИ 95% ( $p<0,05$ ), после 6-го цикла терапии –  $OR=4,5\pm 1,32$  [0,33; 60,1], что в 2,4 раза выше предыдущей. Максимально достоверно эффект восстановления чувствительности штаммов был подтвержден у пациентов после 9-го цикла терапии ( $p = 0,008$ ). Высокая сила ассоциации по критерию Спирмена указывала на зависимость бактериальной эффективности ВТ от длительности ее применения –  $p=-0,97$  ( $p<0,05$ ). Показано, что риск реинфекции после 3-х циклов вакцинотерапии в 20,5 раз меньше, чем после проведенного курса АБТ.

Urinary tract infection (UTI) remains an unresolved clinical issue for most doctors and patients today [5, 10]. In modern conditions of widespread antibiotic resistance, monitoring of selection of resistant strains among patients with various aspects of UTI (gender, age, region, nature of the course, comorbid states on the part of the urinary system and/or others) becomes relevant [4, 6]. Such observational studies are quite rare, especially in the pediatric population [9, 11].

Currently, an international global study of the prevalence of infections in urology (GPIU), was initiated by the European Division of Infections in Urology (ESIU). According to its results, in the period from 2003 to 2010, 19756 hospitalized patients were analyzed [8]. According to this study, in Ukraine, polyresistance among adults with UTI is 50% of cases, that is, every second patient does not respond to therapy with a combination of 2 or even 3 antibacterial drugs.

In such realities, other treatment strategies, alternative antibiotic therapies, should continue to be explored to reduce the use of AB [1]. Therefore, the aim of our study was to study the clinical and laboratory efficacy of the effect of vaccine therapy on the course of recurrent urinary tract infection in children.

#### MATERIALS AND METHODS OF RESEARCH

The study involved 21 children (girls) aged 7 to 18 years with recurrent UTI in the active phase of the disease. The study was a prospective clinical randomized, lasted 1 year (2018-2019) in the settings of the pediatric nephrology unit of the CCH No. 1, Kyiv, and was conducted with the informed consent of parents in accordance with the Helsinki Declaration of Human Rights.

The verification of diagnoses and the choice of therapeutic tactics was carried out in accordance with the unified clinical protocol of the Ministry of Health of Ukraine No. 627 of November 3, 2008 "On approval of the protocol of treatment of children with urinary tract infections and tubulointerstitial nephritis".

The contingent of the subjects was divided into 3 groups of observations: Ia (n=7) included patients who received VT without antibacterial support, in the group Ib (n=7) patients received a combination of VT+ABT, in group II (n=7) – only standard therapy with ABT which lasted 10-14 days. There were no children with a systemic inflammatory response (SIR) in the observation groups – there was no combination of clinical features such as hyperthermia  $\geq 38.0^{\circ}\text{C}$  and leukocytosis  $\geq 12 \times 10^9/\text{L}$ .

In addition to the standard diagnostic methods used to assess the status of patients with a nephrological profile, we have used modern highly-accurate methods for the identification of microorganisms, such as MALDI-TOF mass-spectrometry and determination of the minimum inhibitory concentration 90 (MIC 90), regulated by the EU standard, ECCA standard, 2018 [3].

For the purposes of VT, a multicomponent original vaccine comprising *Escherichia coli* (CCM 7593), *Enterococcus faecalis* (CCM7591), *Klebsiella pneumoniae* (CCM 7589), *Proteus mirabilis* (CCM 7592), *Pseudomonas aeruginosa* (CCM 7590), *Propionibacterium acnes* (CCM 7083) was used. The drug was prescribed according to the instructions internally, 1 capsule in the morning on an empty stomach, cycles of vaccination from 3 to 12, which was determined by clinical need. The peculiarity of the application was the alternation mode – 10 days of drug taking and 20 days' break. Efficacy was

evaluated in 1, 3, 6, 9 and 12 months. The expected result in the case of VT is a positive clinical and microbiological effect aimed at reducing the number and severity of UTI exacerbations.

To evaluate the nature of the distribution of quantitative characteristics and to test the null hypothesis  $N_0$ , the Shapiro – Wilk W test was used, for the qualitative characteristics – the criterion  $\chi^2$ . Values were presented as median (Me) and interquartile range ( $Q_1 - 25\%$ ;  $Q_3 - 75\%$ ). To compare three independent groups by one attribute, the Kruskal - Wallis test was used. The calculation of absolute and relative probability frequencies was performed by the odds ratio (OR) method with the standard error assuming a 95% of confidence interval (CI). Spearman correlation analysis was used to analyze the dependence of the two attributes. When testing statistical hypotheses, the threshold for the significance level is set at  $\leq 0.05$  [7].

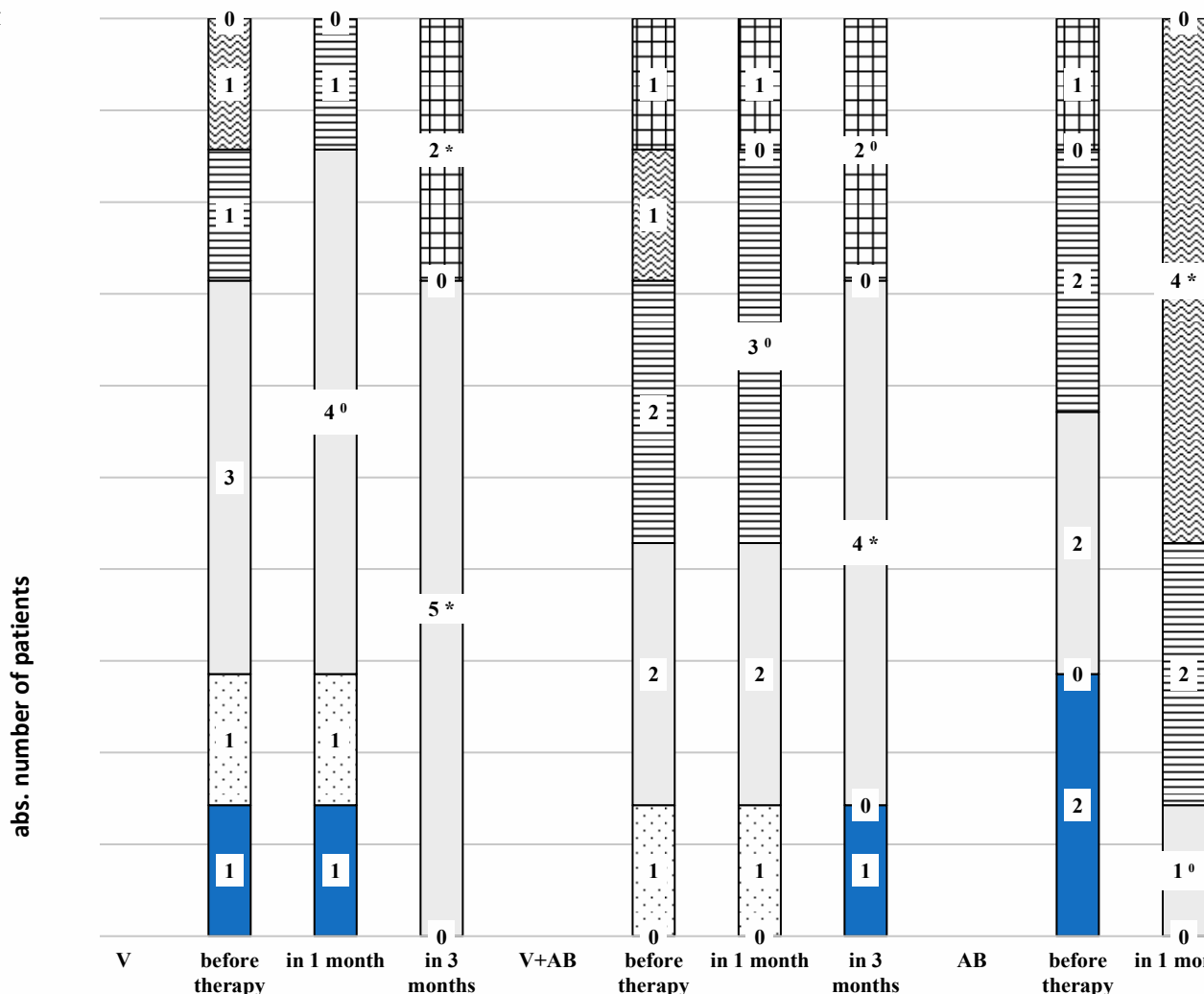
The data were mathematically processed using the following software: Microsoft Excel Products (Microsoft Office 2013 Professional Plus, License Agreement (EULAID: O15\_RTM\_VL.1\_RTM\_RU) and STATISTICA 13.0 (StatSoftInc., Serial No. ZZS9990000099100363DEMO-L).

#### RESULTS AND DISCUSSION

The entire cohort of subjects with recurrent UTI course was presented by the girls aged 7 to 18 years. The mean age of the patients was  $10 \pm 3.84$  years with interquartile range [8.5;15]. All patients had clinical and laboratory signs of exacerbation of UTI at the time of examination and from 3 to 8 episodes of UTI in history.

The leading nosology among patients in our study was chronic pyelonephritis 13/21 (61.9%), chronic cystitis was presented in the number of 7/21 (33.3%) cases, one patient was found to suffer from chronic pyelonephritis and chronic cystitis 1/21 (4.8%) simultaneously. Among the concomitant conditions that should be considered favorable for the development of complicated recurrent course of UTI there were the following: unilateral vesico-ureteral reflux (VUR) of II – 3/21 and IV degree – 2/21, hyperactive urinary bladder (HAUB) – 4/21, HAUB with enuresis – 2/21, hypoactive UB – 2/21, dysmetabolic nephropathy – 9/21. One patient – 1/21 had reflux – nephropathy and 2/21 patients had grade II chronic renal failure.

As a result of the therapy, quantitative and qualitative restructuring of the composition of uropathogens according to the results of bacterial analysis of urine by the MALDI TOF method was observed (Fig. 1).



Notes: AB –antibacterial therapy, V+AB –vaccine+antibacterial therapy, V –vaccine; divergence of indices by  $\chi^2$  criterion with Yates' correction denoted as \* – at  $p < 0.05$  and <sup>0</sup> – at  $p > 0.05$ .

Fig. 1. Dynamics of microorganisms spectrum during therapy in comparison groups by results of MALDI TOF

In group Ia (VT) and Ib (VT+ABT) 1 month after therapy changes in composition almost did not happen, but in 3 months of VT *Escherichia coli* was typed in most patients of the Ia group ( $p=0.09$ ) and in the Ib group ( $p=0.1$ ) as monoagent. In most patients of group II (ABT) at the end of the 1st month of the observation no microbial agent ( $p=0.002$ ) was revealed and at the end of the 3rd month there was no statistically significant difference in urinary contamination compared to before treatment. One patient 1/7 had flora replacement by a pathogenic representative of *Klebsiella pneumoniae*.

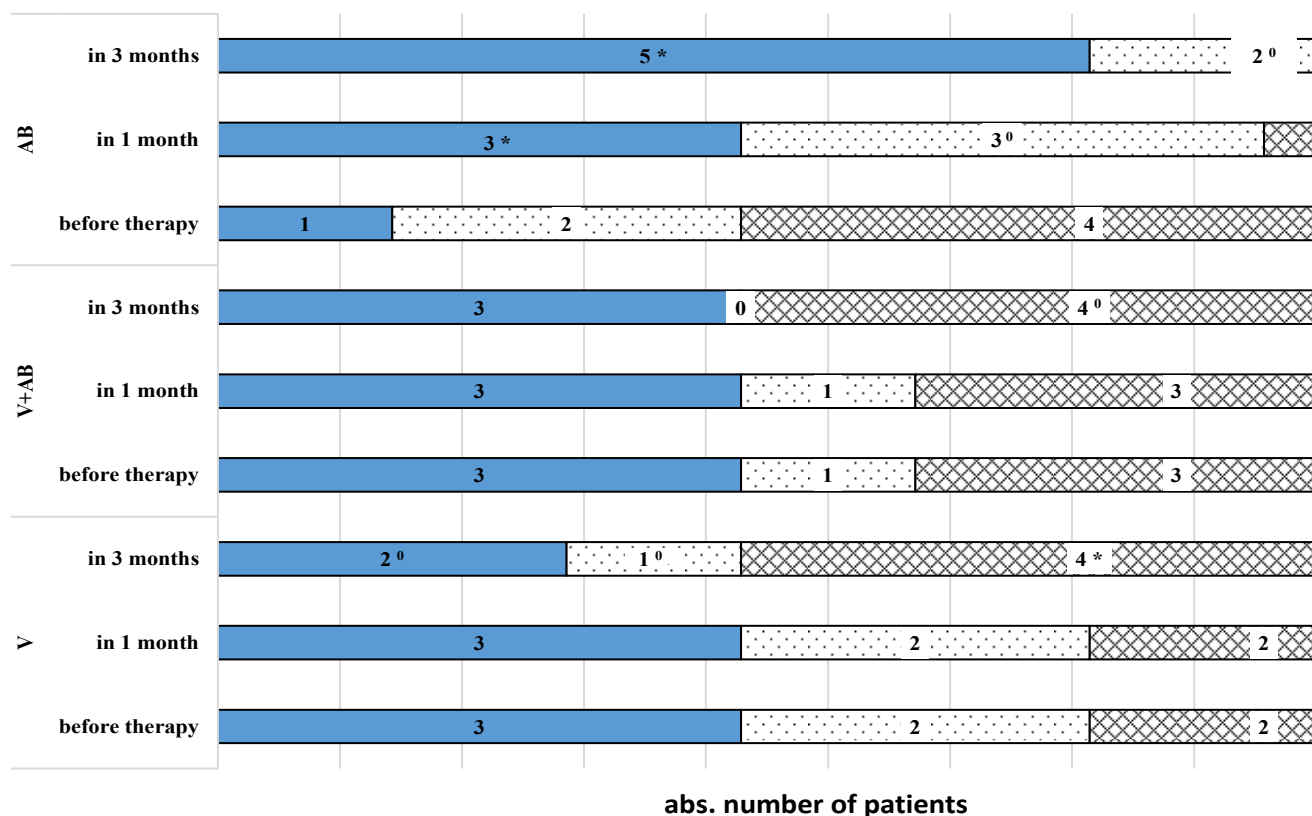
The dynamics of the sensitivity of urological pathogens in the comparison groups is shown in Figure 2.

The total number of resistant uropathogenic strains among the subjects was 33.3% (7/21) at the onset of therapy. An analysis of the dynamics of changes in the sensitivity of the strains during therapy showed that in the groups of patients (Ia and Ib) who received VT, after the 3rd cycle the number of patients with susceptible strains increased and the number of patients with the resistant ones decreased ( $p=0.1$ ). In patients of group II due to ABT at the end of the 1st month of observation a significant increase in resistant strains ( $p=0.001$ ) and complete absence of sensitive strains after 3 months of the therapy was revealed.

Resistance monitoring during 12 months in study groups (Table) made it possible to reveal the following tendencies.

After the 3rd cycle of VT, a statistically significant difference in the number of resistant strains was found between the patients of group Ia (VT) and group II (ABT), ( $p=0.01$ ). Follow-up of patients of groups Ia (VT) and Ib (VT+ABT) during the year allowed to make conclusions about the

therapeutic effect of VT in the direction of leveling ABR. The sensitivity of the strains to antibiotics was recovered in patients, as evidenced after the 6th cycle during the personal evaluation of MIC90 of patients and this effect was statistically significantly confirmed in patients after the 9th cycle of VT ( $p=0.008$ ).



Notes: AB –antibacterial therapy, V+AB –vaccine+antibacterial therapy, V –vaccine; R – resistant strains, MR – moderately resistant, S – sensitive; divergence of indices in comparison groups assessed by  $\chi^2$  criterion with Yates' correction and denoted as \* – at  $p<0.05$  and <sup>0</sup> – at  $p>0.05$ .

Fig. 2. Dynamics of strains sensitivity due to 3 cycles of VT in comparison groups by results of MIC 90

Analysis of correlation association by Spearman between resistance values and the number of VT cycles allowed us to determine a high degree feedback in both study groups receiving VT. Spearman correlation coefficient in group Ia (VT) was equal to  $p=-0,97$  ( $p<0.05$ ), in group Ib (VT+ABT) –  $p=-0,94$  ( $p<0.05$ ), i.e. deprivation of resistance directly depended on the duration of the VT.

The analysis of odds ratios (OR) confirmed the high probability of resistance development ( $OR=4.5\pm 1.32$  [0.33; 63.5] at CI 95%) due to ABT during the first month of follow-up and 3.3 times higher probability of ABT at the end of the 3rd month of follow-up after ABT ( $OR=15\pm 1.4$  [1.03; 218.3]). There was a probable likelihood of recovery of sensitivity of microorganisms as a result of VT after the 3rd cycle ( $OR=1.87\pm 1.13$  [0.2; 17.3] at CI 95%),  $p<0.05$ ) and

2.4 times higher after the 6th cycle of therapy ( $OR=4.5\pm 1.32$  [0.33; 60.1] at CI 95%).

In Ib group (VT + ABT), repeated episodes of UTI were not observed until 12 months of clinical follow-up. In group II (ABT), 3/7 patients had reinfection of the urinary system within 3 months of follow-up.

The analysis of OR findings indicated a high probability ( $p<0.05$ ) of a high likelihood of reinfection ( $OR=4.5\pm 1.32$  [0.34; 60.2] with CI 95%) when using ABT compared with 3 cycles of VT ( $OR=0.22\pm 1.32$  [0.02; 2.9] with CI 95%). Thus, the risk of a recurrent UTI episode was 20.5 times higher after the course of ABT than with the use of 3 cycles of VT.

The results obtained are consistent with the literature data [2] regarding the prospect of a comprehensive study of the alternative antibiotic option – vaccine therapy for the prevention and treatment of recurrent UTI in children.

## Dynamics of resistance of urologic strains in comparison groups

Duration of therapy	Ia group	Ib group	II group	p
0 month.	3/7	3/7	1/7	'p=1.0 ''p=0.03
1 month.	3/7	3/7	3/7	'''p=1.0
3 months.	2/7	3/7	5/7	'p=0.44 ''p=0.09 °p=0.01
6 months.	1/7	2/7	-	'p=0.4
9 months.	0	1/7	-	'p=0.008
12 months.	0	0	-	-

Notes: Ia – group received vaccine, Ib – vaccine + antibiotic, II – antibiotic. ' - compared groups Ia and Ib; ° - compared groups Ia and II; '' - compared groups Ib and II by  $\chi^2$  criterion with Yates' correction

## CONCLUSIONS

1. Vaccine therapy has shown a great efficacy in patients (girls aged 7-18 years) with recurrent UTI and has led to the recovery of antibacterial sensitivity to urological agents.

2. The probability of recovering sensitivity of the strains after the 3rd cycle of treatment with the vaccine was  $OR=1.87\pm 1.13$  [0.2; 17.3] at CI 95% ( $p<0.05$ ), after the 6th cycle –  $OR=4.5\pm 1.32$  [0.33; 60.1]. Most significantly the effect of recovery of sensitivity of the strains was confirmed in patients after the 9th cycle of vaccine therapy ( $p=0.008$ ).

3. A high strength of the association according to Spearman's criterion testified to the dependence of bacterial efficacy on the duration of vaccine therapy,  $p=-0.97$  ( $p<0.05$ ).

4. The risk of reinfection of the urinary system after 3 cycles of vaccine therapy was 20.5 times lower than after the course of antibacterial therapy.

Conflict of interests. The author declares that there is no conflict of interest.

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