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ФГАОУ ВО ПЕРВЫЙ МОСКОВСКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ ИМЕНИ И.М. СЕЧЕНОВА МИНИСТЕРСТВА ЗДРАВООХРАНЕНИЯ РОССИЙСКОЙ ФЕДЕРАЦИИ (СЕЧЕНОВСКИЙ УНИВЕРСИТЕТ)

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ООО "БИОНИКА МЕДИА"

CONTENTS

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ONTO-PHYLOGENETIC PREREQUISITES FOR DEVELOPMENT OF CHRONIC CYSTITIS IN WOMEN

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Introduction. Urinary tract infections (UTIs) are among the most common bacterial infections. At the request "cystitis", there are 12,067 publications in the RSCI system (e.library) as of 10/08/2023 and 16,332 articles were screened in the Pubmed. This is evidence that the problem of cystitis is far from being resolved.
Material and methods. A total of 425 patients with bacterial vaginosis and 77 women with chronic recurrent cystitis were included in the study. In all patients, the vaginal biocenosis was assessed through molecular genetic testing. The examination included filling out the Russian version of the Acute Cystitis Symptom Score (ACSS), urinalysis, and urine culture. In addition, local microcirculation was measured using laser Doppler flowmetry (LDF). After examination, patients were prescribed basic therapy and randomly assigned to one of three groups. In a control group (n=17), only basic therapy, consisting of fosfomycin 3.0 once at night + furagin 100 mg after meals 3 times a day for 5 days was prescribed. In the main group 1, 29 women received basic therapy plus Superlymph® suppositories 10 units 2 times a day vaginally for 10 days. In the main group 2, 31 patients received basic therapy plus suppositories Superlymph® 10 units (rectally in the morning) and Acylact Duo (vaginally in the evening) for 10 days.
Results. Among 425 patients with bacterial vaginosis, 78 (18.3%) complained of various urinary disorders, but only 21 women (4.9% of those with vaginal dysbiosis and 26.9% with dysuria) had a diagnosis of cystitis. In all cases, it was an exacerbation of a chronic disease. Among 77 patients with chronic cystitis, normal vaginal flora was initially present in 32 patients (41.6%), and bacterial vaginosis was found in 45 (58.4%) cases. After therapy, positive results were noted in patients of all groups. Complete eradication of the pathogen occurred in 15 women (88.2%) who received only basic therapy; in the main groups 1 and 2, uropathogens were not detected in 27 (93.1%) and 28 (90.3%) cases, respectively. In the control group, the proportion of patients with normal vaginal flora remained virtually unchanged (41.2% [n=7] vs. 47.1% [n=8]). In the main group 1, the proportion of patients with normal vaginal flora almost doubled: from 41.4% (n=12) to 79.3% (n=23). In main group 2, restoration of vaginal flora was noted in 87.1% of cases.
Conclusion. According to our data, only 4.9% of patients with bacterial vaginosis were diagnosed with chronic cystitis, however, 58.4% of patients with chronic cystitis had vaginal dysbiosis. The use of a complex of antimicrobial peptides and cytokines has significantly increased the bidirectional effect of therapy. Suppositories Superlymph in a combination with vaginal use of Acylact Duo allow to obtain the best results.

K e y w o r d s: *cystitis, chronic cystitis, urinary tract infection, treatment, fosfomycin, furazidin, superlymph, cytokines, antimicrobial peptides*

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Introduction. Urinary tract infections (UTIs) are among the most common bacterial infections. At least 150 million people suffer from UTIs each year [1–2]. Women are most susceptible to cystitis, and approximately 60% of them have experienced at least once episode in their lives [1]. In 1/4 patients the disease recurs several months after antimicrobial treatment [3–4]. It is unclear why recurrent UTIs are so resistant. The reasons for recurrent UTI have been cited as resistance of the uropathogen to antibacterial drugs [5], intracellular persistence of the pathogen [6–7], bacterial filamentation and the formation of L-forms [1]. It is believed that filamentation, at least partially, serves as an innate protective mechanism against the human immune system. As a result of the accumulation of additional mass, the filaments may have an increased ability to adhere to host cells and an improved ability to resist to shear forces of urine in the bladder.

Studies using sterile collection of urine (suprapubic aspiration or transurethral catheterization) have shown that 50% of women have bacteria in the bladder [8], while

many authors deny the sterility of urine [9]. It should be noted that in many cases bacteriuria is not accompanied by any symptoms. But even in the presence of dysuria, its cause is not always clear. The development of cystitis may depend not only on the bacteria present, but also on its amount, the expression of virulence factors, and the response of the host immune system [8]. Epidemiological studies show that high level of lactobacilli (with the exception of L. iners) protects women from bacterial vaginosis (BV) and from UTIs [4, 10]. Lactobacilli metabolize vaginal glycogen into lactic acid, which results in a low vaginal pH, which in turn inhibits many other uropathogens [10].

When searching for a term "cystitis" in the RSCI system (elibrary), as of 10/08/2023, a total of 12,067 publications were found and 16,332 articles were present in the Pubmed system. This is evidence that the problem of cystitis is far from being resolved.

Materials and methods. Study design. A two-stage retrospective and prospective, open, multicenter randomized comparative controlled study, involving a total of 425 patients with bacterial vaginosis and 77 women with chronic recurrent cystitis, was carried out. In all patients, the vaginal biocenosis was assessed through molecular genetic analysis of epithelium scrapings from the posterolateral vaginal wall. The material was placed in 1.5 ml plastic Eppendorf tubes containing 300 μg of sterile saline solution. DNA was isolated from the biomaterial using a set of Femoflor Screen reagents (NPO DNA-Technology LLC, Russia). Further, an amplification program was launched with detection of fluorescent signals in real time. After this, the total bacterial mass (TBM) of lactobacilli, as well as the opportunistic and pathogenic microorganisms was automatically calculated and the state of the vaginal biocenosis was determined based on their ratio. Femoflor allows to quantify normal flora (*Lactobacillus* spp.), facultative anaerobes, which include the *Enterobacteriaceae, Streptococcus* spp., *Staphylococcus* spp., *Gardnerella vaginalis* + *Prevotella bivia* + *Porphyromonas* spp., *Eubacterium* spp., *Sneathia* spp. + *Leptotrichia* spp. + *Fusobacterium* spp., *Megasphaera* spp. + *Veillonella* spp. + *Dialister* spp., Lachnobacterium spp. + Clostridium spp., Mobiluncus spp. + *Corynebacterium* spp., *Peptostreptococcus* spp. and *Atopobium vaginae*. In addition, yeast-like fungi, such as *Candida* spp., Mycoplasma hominis and Ureaplasma (urealyticum+parvum), as well as pathogenic Mycoplasma genitalium were assessed.

The vaginal biocenosis was defined as a normocenosis with the content of lactobacilli in an amount of at least 80% of TBM. Absolute normocenosis was identified in case of the dominance of lactobacilli (a share of more than 80% of TBM); associates of microbiota (*Ureaplasma* spp., *Mycoplasma hominis, Candida* spp.) were absent or determined in quantities less than 10^4 GE/ml, and conditional normocenosis is a variant of vaginal microbiota, where the proportion of lactobacilli is less than 80% of the TBM, but Ureaplasma spp. and/or M. hominis are also present in an amount of more than 10^4 GE/ml. In conditional normocenosis of mixed etiology, along with the predominance of lactobacilli (more than 80% of the TBM), *Candida* spp. and opportunistic mycoplasmas (*Ureaplasma* spp., *M. hominis*) in an amount of more than 10^4 GE/ml was present.

Anaerobic dysbiosis was defined as a variant of vaginal microbiota, characterized by the predominance of obligate anaerobes with a simultaneous decrease in the proportion of *Lactobacillus* spp. With moderate anaerobic dysbiosis, the proportion of *Lactobacillus* spp. and the proportion of anaerobic bacteria ranged from 20 to 80% of TBM. With pronounced anaerobic dysbiosis, the proportion of *Lactobacillus* spp. was below 20%, and the proportion of anaerobic bacteria exceeded 80% of TBM.

Aerobic dysbiosis was defined as a variant of vaginal microbiocenosis, characterized by a predominance of facultative anaerobic bacteria (aerobes) with a decrease in the proportion of *Lactobacillus* spp. Depending on the severity, moderate aerobic dysbiosis was diagnosed, when the proportion of *Lactobacillus* spp. and facultative anaerobic bacteria ranged from 20 to 80% of TBM, while pronounced aerobic dysbiosis was established when the proportion of *Lactobacillus* spp. was below 20%, and the proportion of facultative aerobic bacteria exceeded 80% of TBM [11].

The examination of patients with cystitis included self-completion of the Russian version of the Acute Cystitis Symptom Score (ACSS), urinalysis, and urine culture. For microbiological studies, time-of-flight mass spectrometry was used on a Microflex mass spectrometer (Bruker, Germany). For some cultures, species identification and determination of antibiotic resistance were carried out on BD PhoenixTM combined panels for gram-negative, gram-positive microorganisms and streptococci using an automatic system for identifying microorganisms and determining sensitivity to antibacterial drugs Phoenix 100, USA; Becton Dickinson. For the standardized disc diffusion method, antibiotic-impregnated discs, Mueller–Hinton agar, and Bio-Rad disc dispensers, USA, were used.

In patients with cystitis, local microcirculation was measured using laser Doppler flowmetry (LDF) in the area of the external urethral meatus and at the level of the middle of the urethra from the vagina using the LAKK-02 device (NPP "Lazma", Russia). We determined the dynamics of the microcirculation index (MI) and the change in the coefficient of variation (CV) during treatment.

After this, patients received basic therapy and were randomly assigned to one of the groups:

- in the control group (n=17), women received only basic therapy: fosfomycin 3.0 once at night + furagin 100 mg after meals 3 times a day for 5 days;
- in the main group 1 (n=29), basic therapy plus Superlymph® suppositories 10 units 2 times a day vaginally for 10 days were administered;
- in the main group 2 (n=31), basic therapy plus suppositories Superlymph® 10 units (rectally in the morning) and Acylact Duo (vaginally in the evening) for 10 days was given.

Superlymph® is a natural complex of antimicrobial peptides and cytokines, which act as universal stimulants of the immune system, secreted by leukocytes in the peripheral blood of pigs. Superlymph® has antiviral, antimicrobial and fungicidal effects, and is also an immunomodulator [12–14]. Acylact Duo is a combination product containing, along with cytokines, acidophilus bacteria (*Lactobacillus acidophilus* 107).

A follow-up examination was carried out upon completion of the course of treatment.

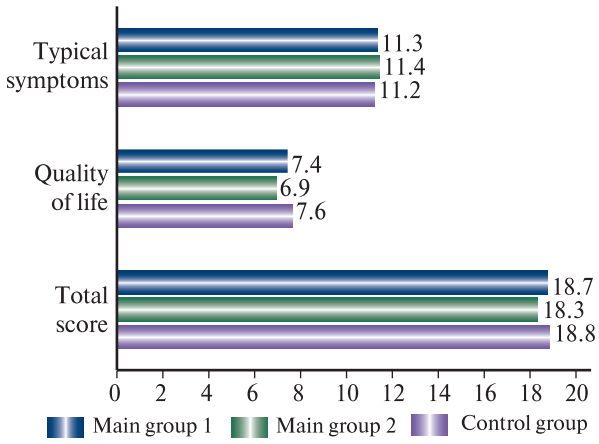
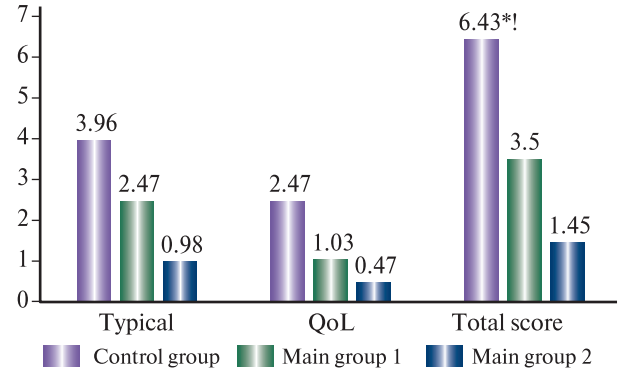


Fig. 1. Baseline ACSS scores in three groups of patients, n=77



Note: *- statistical difference was significant (p<0.001) compared to the control group; ! – statistical difference was significant (p<0.001) compared to the main group 2.

Fig. 2. Dynamics of ACSS scores in three groups of patients after treatment, n=77

Statistical analysis. The results were processed using Microsoft Excel spreadsheets from the Microsoft Office software package, 2007. All quantitative data were described as mean (M)±standard deviation (SD). When describing qualitative data, absolute values (n) and percentages (%) were used. The hypothesis about the absence of a statistically significant influence of the factor was rejected at $p>0.05$.

Results. Among 425 patients with bacterial vaginosis (BV), 78 (18.3%) complained of various urinary disorders, but only 21 patients (4.9% of those with BV and 26.9% of women with dysuria) were diagnosed with cystitis. In all cases it was an exacerbation of a chronic disease. The age of patients with BV ranged from 21 to 48 years, with an average of 36.4±5.9 years. The average age of patients with BV, who also had chronic cystitis, was 48.5±6.4 years (significant difference). Among patients with two disorders, moderate anaerobic dysbiosis was established in 8 (38.1%), pronounced anaerobic dysbiosis in 9 (42.9%), and moderate aerobic dysbiosis in 4 (19.0%) cases.

In all 77 patients with chronic cystitis, there was microbiological verification. The spectrum of uropathogens is presented in *Table 1.* As we can see, the leading uropathogen was E. coli, the frequency of which ranged from 65.5 to 70.6%. In the second place was *Enterobacter* spp. Not a single isolate had sensitivity to all antibacterial drugs; resistance to fluoroquinolones (46.7%) and amoxiclav (44.1%) predominated. The sensitivity of the microflora to basic therapy was preserved.

According to the ACSS scale, all patients had a total score exceeding the threshold level. There were no significant differences between the groups, as demonstrated by *Fig. 1.*

When studying the vaginal biocenosis, it was found that among 77 patients with chronic cystitis, normocenosis was initially present in 32 (41.6%), moderate anaerobic dysbiosis in 27 (35.1%), severe anaerobic dysbiosis in 14 (18.1%) cases and 4 (5.2%) women had moderate aerobic dysbiosis. Thus, 45 (58.4%) patients with chronic cystitis had impaired vaginal microbiocenosis.

Upon completion of therapy, positive results were noted in all groups of patients. Complete eradication of the pathogen was seen in 15 (88.2%) women who received only basic therapy; the remaining two still had *Enterobacter* spp., but in an extremely low concentration (102 CFU/ml). In main groups 1 and 2, no growth of microflora was detected in 27 (93.1%) and 28 (90.3%) patients, respectively; in the remaining five cases, clinically insignificant (102 CFU/ml) growth of uropathogens was detected (*Klebsiella* spp., *Proteus* spp., *Enterococcus* spp., *Enterobacter* spp. and *E. coli*).

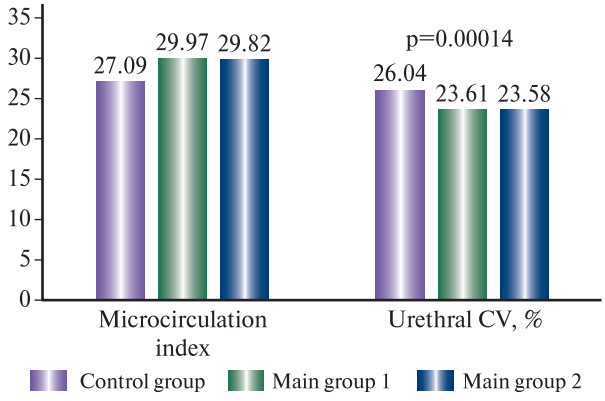
Thus, combined etiologic therapy had excellent immediate efficiency. However, when analyzing the dynamics of symptoms on the ACSS scale, statistically significant differences between the groups were found (*Fig. 2*).

A comparison of microcirculation in the urethral area after therapy also showed the advantage of main groups compared to the control group, although there was a

Table 1

Results of microbiological examination of urine in patients with chronic cystitis (*n*=77)

Uropathogen	Control group, *n*=17		Main group 1, *n*=29		Main group 2, *n*=31		Total, *n*=77	
	abs.	%	abs.	%	abs.	%	abs.	%
E. coli	12	70.6	19	65.5	21	67.8	52	67.5
Klebsiella spp.	0	0	1	3.4	2	6.5	3	3.9
Proteus spp.	1	5.9	2	6.9	1	3.2	4	5.2
Enterobacter spp.	3	17.6	5	17.2	4	12.9	12	15.6
Acinetobacter spp.	1	5.9	1	3.4	1	3.2	3	3.9
Enterococcus spp.	0	0	1	3.4	2	6.5	3	3.9



Note: CV – coefficient of variation.

Fig. 3. Indicators of microcirculation in the urethral area in three groups of patients after treatment, n=77

statistically significant difference between the main groups receiving rectal and vaginal suppositories Superlymph®. The results are shown in *Fig. 3*.

The dynamics of the vaginal biocenosis are shown in *Table. 2*. The best results (normocenosis in 87.1% of cases) were demonstrated in main group 2, in which patients, along with Superlymph® rectal suppositories, received Acylact Duo vaginally. In the control group, the proportion of patients with normocenosis remained unchanged (7/41.2% vs. 8/47.1% after treatment). In main group 1, receiving only Superlymph® vaginally, the proportion of patients with normocenosis almost doubled, from 41.4% (*n*=12) to 79.3% (*n*=23).

Discussion. The increase in resistance of uropathogens, the evolution of E. coli, which has led to a radical change in its properties (high ability to adhere to the urothelium, intracellular persistence, formation of dormant forms), makes it increasingly difficult to select antibacterial therapy in patients with UTIs. In order to solve this problem, it is suggested to prescribe combination of antibiotics [15, 16]. Previously, the combined drug biseptol was popular; now pharmaceutical companies are increasingly bringing to market not a single drug, but a combination of modern antibacterial agents, for example, cefoperazone and sulbactam.

Traditionally, the association between BV and chronic cystitis is considered undisputable. O.H. Harmanli et al. [17] examined 129 gynecological patients, and in 67 (51.9%) BV was diagnosed. Among them, 15 (22.4%) had recurrent cystitis, and among gynecological patients without BV, cystitis was detected in only 6 (9.7%). According to I.V. Kosova et al. [18], among 75 women with chronic cystitis aged 19 to 76 years, BV was detected in 47 (62.7%), with moderate BV in 25 (33.3%), and severe BV in 22 (29.3%) patients. The authors found a correlation between the presence of BV and the number of relapses of cystitis (r=0.310; p=0.007). It was also found that BV is significantly more common in older patients with chronic cystitis who are in menopause. The authors conclude that disruption of the vaginal microflora increases the risk of developing of cystitis and contributes to more severe manifestations. Yu.S. Kovaleva et al. [19] found that 79.5% of patients with chronic cystitis had a complicated gynecological history, including BV.

A.H. Sumati et al. [20] diagnosed BV in 119 (68.39%) of 174 women; 58 (48.7%) of them were also had chronic cystitis. The authors suggest that the association of BV with UTI, and vice versa, is likely due to an increase in vaginal pH and a decrease in the number of vaginal lactobacilli that produce lactate and hydrogen peroxide. Frequent sexual intercourse also increases the risk of developing both BV and cystitis. Taking into account the relationship of these diseases, it is recommended that all patients with BV be examined for UTI, and in those with UTIs, BV should be excluded.

V.L. Handa et al. [21] recently published a comprehensive chapter "Does Bacterial Vaginosis Contribute to Urinary Tract Infection?" in a thematic collection on female genital tract infections. The authors emphasize that the available data are not enough to draw any definitive conclusions. Limited evidence suggests that BV may increase susceptibility to UTIs and, conversely, that a lactobacilli-dominated vaginal microbiota may protect against these infections. However, there is currently a paucity measures that clinicians can use to alter the relationship between BV, the vaginal microbiome, and UTIs. There is no evidence to support treating BV with antibiotics to reduce the incidence of UTIs. Additional research into the role of BV and vaginal microbiota in the pathogenesis of UTIs is warranted and in future may

Table 2

Changes of biocenosis after etiologic therapy as monotherapy and in combination with antimicrobial peptides

Vaginal biocenosis	ГС, *n*=17		ОГ-1, *n*=29		ОГ-2, *n*=31		Всего, *n*=77	
	At baseline	After treatment	At baseline	After treatment	At baseline	After treatment	At baseline	After treatment
Normocenosis	7/1.2%	8/44.1%	12/41.4%	23/79.3%	13/41.9%	27/87.1%	32/41.6%	58/75.3%
Moderate anaerobic dysbiosis	6/35.3%	8/44.1%	10/34.5%	4/13.8%	11/35.5%	4/12.9%	27/35.1%	16/20.8%
Severe anaerobic dysbiosis	3/17.7%	1/5.9%	6/20.7%	2/6.9%	5/16.1%	0	14/18.2%	3/3.9%
Moderate aerobic dysbiosis	1/5.9%	0	1/3.4%	0	2/6.4%	0	4/5.2%	0
Total cases with vaginal dysbiosis	10/58.8%	9/52.9%	17/58.6%	6/20.7%	18/58.1%	4/12.9%	45/58.4%	19/24.7%
Total patients	17/100%	17/100%	29/100%	29/100%	31/100%	31/100%	77/100%	77/100%

lead to the development of new treatments for UTIs and improved genitourinary health in women.

Our findings are also contradictory. On the one hand, UTIs in patients with BV were detected in only 4.9% of cases; on the other hand, BV was diagnosed in 58.4% of patients with chronic cystitis. The main question is what comes first? Possibly, multiple repeated courses of antibiotic therapy for cystitis led to the development of BV, and it was not the disruption of the vaginal microbiota that contributed to the development of cystitis? This disproportion can also be explained by the fact that cystitis has more apparent manifestations than BV, which may have more obscure course, and a patient attends a doctor with cystitis, while BV is identified as a secondary disease or is not diagnosed at all.

N.M. Gilbert et al. [22] proposed the activation of latent intracellular reservoirs of E. coli in the bladder mucosa as one of the mechanisms of UTI. Exposure of the urinary tract to G. vaginalis during sexual activity leads to detachment of the bladder epithelium. After exfoliation, E. coli leaves the intracellular reservoirs into bladder lumen and causes inflammation. Thus, UTI may be caused by short-term but severe exposure of the urinary tract to vaginal bacteria that are not "pathogenic" in the classical sense.

This "latent pathogenesis" paradigm may apply to other latent infections (e.g., tuberculosis) or to diseases that are currently defined as noninfectious since routine cultural study fails to detect relevant pathogens [23].

In an open-label phase II clinical trial, 28 participants used vaginal suppositories containing Lactobacillus Crispatus for 1 year or every 2 days, or 3 times a week. The primary endpoint was response rate, assessed by the number of episodes of recurrent cystitis during a year. Secondary endpoints were response rate assessed by episodes of recurrent cystitis within 1 year after completion of therapy; total number of episodes of recurrent cystitis before, during and after therapy; adverse events; changes in the spectrum and severity of bacteriuria and the dynamics of the vaginal microbiome. A total of 18 (86%) patients achieved an effective clinical response. The suppressive effect of vaginal Lactobacillus suppositories on episodes of cystitis lasted up to 1 year after the last suppository was administered. Authors concluded that vaginal suppositories containing the Lactobacillus crispatus strain were effective in preventing episodes of recurrent cystitis both during treatment and for at least 1 year [24–25].

Another study also showed that eliminating risk factors, which include BV, significantly reduces the number of relapses and lengthens the relapse-free period in women with recurrent UTI [3].

I.A. Apolikhina and D.A. Malyshkina [26] published the results of an anonymous survey of 102 obstetricians and gynecologists regarding the treatment of women with cystitis. Interestingly, only in 42% of cases gynecologists send a patient with dysuria to a urologist, and in 51% they administer therapy on their own, which, of course, requires them to know the relevant guidelines. Gynecologists noted that in 31% of patients receiving monotherapy with antibiotics, the effect was short-term and the disease recurred. The authors also emphasize that antibacterial therapy leads to intestinal dysbiosis and BV, which is a risk factor for the development of relapse of chronic cystitis.

We believe that the difference in results in our study is due to the multicomponent pathogenesis of cystitis, the influence on the clinical manifestations of not only the pathogen, but also the degree of disruption of microcirculation and vaginal biocenosis. This hypothesis is confirmed by the significant differences between groups.

Conclusion. There are ontological and phylogenetic prerequisites for the chronic course of the inflammatory process in the bladder wall in women. The bladder trigone has a common origin with the vagina [4], which explains the mutual influence of BV and cystitis. According to our data, 4.9% of patients with BV were diagnosed with chronic cystitis, but 58.4% of patients with chronic cystitis had vaginal dysbiosis. Perhaps this discrepancy is explained by incomplete diagnosis and insufficient attention of doctors to concomitant pathology; carrying out an examination of all patients with cystitis for BV, and all patients with BV for cystitis, would allow us to obtain a true situation.

The use of a complex of antimicrobial peptides and cytokines allows to significantly increase the bidirectional effect of therapy, with the best results obtained with rectal use of Superlymph suppositories and vaginal use of Acylact Duo.

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SAFETY AND EFFICIENCY OF RETROGRADE INTRARENAL SURGERY WITHOUT X-RAY GUIDANCE

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Introduction. The main stages of flexible ureteroscopy in patients with renal stones are usually performed under X-ray guidance. Long-term exposure of ionizing radiation can have negative effects on the patients with nephrolithiasis and the operating team.

Aim. To study the results of retrograde intrarenal surgery (RIRS) without fluoroscopic guidance.

Materials and methods. The results of flexible ureteroscopy (fURS) without X-ray-guidance in 76 patients were analyzed. There were 46 (53.3%) men and 30 (46.7%) women. The average age was 50.4±14.6 years. All patients underwent laboratory tests and non-contrast-enhanced computed tomography to determine the size and density of the stone. In all cases, preoperative ureteral stenting was performed. The average stone size was 10.5±4.2 mm. First, ureteroscopy with a rigid endoscope was done to assess the ureter and determine the depth of the introducing ureteral access sheath. After removing the ureteroscope along the guidewire, a ureteral access sheath was put at this distance. An inspection of the collecting system and laser fragmentation of kidney stones were performed using a flexible ureteroscope. In 64 (84.2%) patients, a 4.7 Ch stent was put at the end of the procedure, while in the remaining 12 (15.8%) patients, a ureteral catheter was left for 1–2 days. The operation time, stone-free rate, and the number of intra- and postoperative complications were studied.

Results. All fURS were successful and performed without X-ray guidance. The average operation time was 42.5±8.0 minutes. After the first session, stone-free rate was 92.1% (70/76). In 6 (7.9%) cases, residual stones were found, which were completely removed after the second session. Intraoperative complications, namely perforation of the upper calyx by the distal end of the ureteral access sheath, were observed in 2 (2.6%) patients, which did not require any additional interventions. Postoperative complications occurred in 10 (13.2%) patients, including fever in 6 (7.9%) and hematuria in 4 (5.3%) cases. There were no serious complications, such as ureteral perforation or sepsis, and no blood transfusion was performed.

Conclusion. Flexible ureteroscopy with laser lithotripsy can be performed safely and effectively without X-ray guidance.

K e y w o r d s: *urolithiasis, nephrolithiasis, kidney stones, intracorporeal lithotripsy, flexible ureteroscopy, laser lithotripsy, RIRS, lithotripsy without X-ray control*

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Introduction. Currently, flexible ureteroscopy (URS) is actively used in the treatment of kidney stones [1–3]. The widespread development is undoubtedly associated with the active introduction of flexible endoscopes and laser lithotripters. This method has become more popular among urologists due to its less invasiveness compared to percutaneous nephrolithotomy. According to the guidelines of the European Association of Urology, flexible ureteroscopy is an alternative to extracorporeal shockwave lithotripsy and a first-line treatment for small renal stones (<10 and 10–20 mm) and a second-line treatment for renal stones >20 mm [4]. X-ray control is used at various stages of the procedure, including insertion of a guidewire and ureteral access sheath (UAS), inspection of the collecting system, clarification of the stone location or the presence of residual fragments, and putting a ureteral stent. The use of fluoroscopy in urological interventions is associated with risks such as inducing malignancies as a result of radiation exposure to the patient and surgical team [5–7]. According to the International Commission on Radiological Protection, radiation exposure received during the diagnosis stage, treatment and follow-up is cumulative, which is especially important, considering high risk of stone recurrence [5]. This concern has led specialists to search for ways not only to reduce, but also to eliminate radiation exposure during endourological procedures [8]. Therefore, publications began to appear in the literature on the results of X-ray-free endoscopic interventions for ureteral stones [9–15]. The first studies were dedicated to the results of X-ray-free URS for ureteral stones [9–12, 14, 15].

Subsequently, publications appeared on the possibility of performing retrograde intrarenal surgery (RIRS) without fluoroscopy, but the number of such works is

Fig. 1. Ureteroscopy with a rigid endoscope before using flexible ureteroscope for lithotripsy. The distance from the external opening of the urethra to the renal pelvis is determined

limited [13, 16–20]. The aim of our study was to evaluate the safety and efficiency of X-ray-free RIRS in the treatment of small kidney stones.

Materials and methods. This study included the results of X-ray-free URS in 76 patients who were treated at the Center of Urology with Robot-Assisted Surgery of the Mariinsky Hospital. There were 46 (53.3%) men and 30 (46.7%) women. The average age of the patients was 50.4±14.6 (from 28 to 70) years. Patients with renal anomalies, bilateral ureteral and kidney stones, and past urinary tract procedures were excluded from the study. All patients underwent laboratory tests and non-contrast computed tomography to determine the stone size and density, and preoperative ureteral stenting was performed in all cases. The average stone size was 10.5±4.2 mm. The characteristics of patients undergoing X-ray-free URS are shown in the *Table*.

All interventions were planned as flexible URS. The procedure was performed under general anesthesia in the lithotomy position by an experienced urologist, who previously performed more than 250 cases. Immediately prior to RIRS, preoperative antibiotic therapy with a third-generation cephalosporin was usually administered. The fluoroscopic C-arm was always in the operating room for use if necessary. Initially, diagnostic URS was performed using a 9.5 Ch rigid ureteroscope to exclude any pathological changes in the ureter (stone, stricture or deviation) that could cause difficulties during placement of UAS. It also allows optical dilatation of the ureter, which can help with insertion of the UAS. URS was performed using a 0.038-inch hydrophilic guidewire with a flexible tip. The endoscope was passed to the collecting system, and the flexible part of the guidewire was insert into the pelvis under visual control. After localizing the distal end of the endoscope in the pelvis for correct and safe insertion of the UAS, the distance was determined by marking on the outer part of the ureteroscope (*Fig. 1*). After insertion of the guidewire, the ureteroscope was removed, again for aligning it with UAS in order to the establish the depth of insertion (*Fig. 2*). Next, a rigid ureteroscope was passed parallel to the guidewire into the bladder to visually control the adequate passage of the UAS along the guidewire for a set distance

Table

Data of patients with kidney stones, who underwent RIRS without fluoroscopy

Studied indicators Abs..		Number of patients	
		%	
Number of patients		76	100.0
Gender	Male	46	53.3
	Women	30	46.7
Age of patients, years		50.4±14.6 (28–70)	
Body mass index, kg/m^2		25.4±7.2 (24.2–36.5)	
Stone size, mm		10.5±4.2	
The side of the stone	Left	42	55.3
	Right	34	44.7
Baseline symptoms	Ipsilateral pain	36	47.4
	Hematuria	14	18.4
Number of stones	Single	68	89.5
	Multiple	8	10.5
Localization of stones	Pelvis	36	47.4
	Middle calyx	10	13.2
	Lower calyx	22	29.0
	Pelvis + lower calyx	8	10.4
Recurrent stones	No	60	79.0
	Yes	16	21.0
Past procedures	PCNL	10	13.2
	ESWL	6	7.9
Pre-stenting		76	100.0

Note. PCNL – percutaneous nephrolithotomy, ESWL – extracorporeal shock-wave lithotripsy.

Fig. 2. The rigid ureteroscope and the ureteral access sheath are compared to determine the depth of its advancement

until resistance develop or any deviation was observed. Typically, the UAS was placed at a predetermined distance to avoid perforation of the collecting system (*Fig. 3*). During deep placement, isolated cases of perforation of the upper calyx were observed, but they did not require additional measures (*Fig. 4*). For flexible URS, a disposable endoscope Lithovue (Boston Scientific) was used, which was passed through the ureteral access sheath to the collecting system. Initially, an inspection was performed in order to evaluate the anatomical features and to localize the stone. When a stone was found in the lower calyx, a Dormia basket was used to relocate it to the upper calyx or pelvis for more convenient fragmentation. In all patients, an Auriga 200 holmium laser with 230 μm laser fiber were used for lithotripsy. When crushing the stone, a high-frequency and low-power mode (10–15 Hz) was chosen (0.8–1.0 J). At the end of the procedure, a final inspection of the collecting system was performed to identify residual stones. Next, UAS was removed, and URS was done using a rigid endoscope to exclude any damage to the ureter. In 64 (84.2%) of 76 patients, the procedure was completed with the insertion of a stent 4.7 Fr with a length of 24 or 26 cm. The localization of the upper end of the stent was determined visually and using renal ultrasound, while the position of distal end was assessed using ureteroscope. The stent was usually removed after 2–3 weeks. In 12 (15.8%) patients, a ureteral catheter was put for 1–2 days.

Duration of the procedure and its efficiency, the number of intra- and postoperative complications were studied. Surgical time was measured from the time of cystoscopy with stent removal to drainage of the upper urinary tract. Postoperative complications were classified according to Clavien–Dindo. The efficiency of RIRS was assessed using plain urography for radiopaque and non-contrast computed tomography for radiolucent stones before discharge from the hospital. The procedure was considered effective in the absence of residual stones or their presence ⩽3 mm in size.

Results. All procedures were successful and performed without X-ray control. In all cases, it was possible to place UAS and perform lithotripsy. The operation time ranged from 35 to 80 minutes (average of 42.5±8.0). First-session RIRS was effective in 70 (92.1%) of 76 patients. In remaining 6 (7.9%) patients, residual stones were identified, which were completely removed during the second session. Intraoperative complications, including perforation of the upper calyx by the distal end of the UAS were observed in 2 (2.6%) patients. However, they did not require any additional interventions. Postoperative complications occurred in 10 (13.2%) cases, among them

Fig. 3. The ureteral access sheath is introduced to a predetermined distance

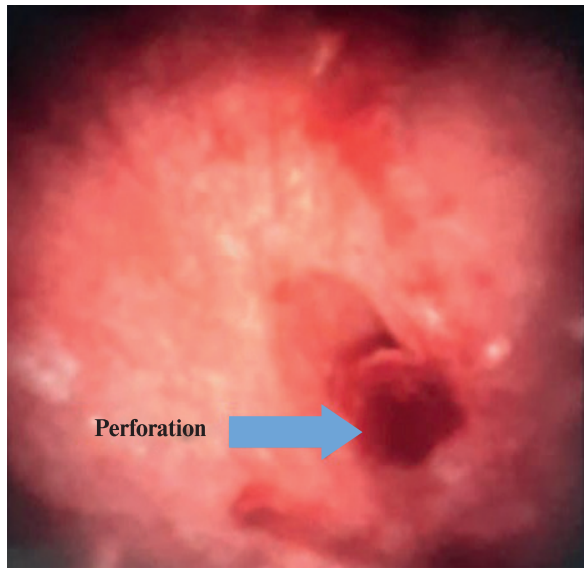

Fig. 4. Perforation of the upper calyx during deep advancement of the ureteral access sheath

fever in 6 (7.9%) and hematuria in 4 (5.3%) patients. There were no serious complications, such as ureteral perforation or sepsis, and no blood transfusion was performed.

Discussion. RIRS is an effective and reliable method for patients with kidney stones with a high success rate. Use of fluoroscopy is one of its disadvantages, as well as for other endourological procedures performed for urolithiasis. Medical radiation poses a potential risk of carcinogenesis in both patients and surgical team. Particularly, malignant neoplasms of the thyroid gland, skin, and hematological diseases can develop [21, 22]. The main criterion of radiation exposure is fluoroscopy time. According to a study of R.S. Hsi et al. [10], for standard URS it was 144 s, while G.O. Hellawell et al. [23] reported a mean time of about 78 (6-414) s. Further, M.E. Lipkin et al. [24] found that in 30 nonobese men

who underwent URS, the mean fluoroscopy time was 47 s and the radiation dose was 0.31-7.17 mSv.

According to their data, one pulse per second roughly corresponds to a radiation dose of 0.01–0.02 mSv, which is equal to that obtained with chest X-ray (0.02 mSv) [25]. As a result, the dose of ionizing radiation is the same as for one chest film multiplied by the number of fluoroscopy pulses during URS. Therefore, the patient and medical personnel are exposed to a higher dose of ionized radiation, the reduction of which is important for the safety of the procedure.

The first study of X-ray-free URS was performed in patients with distal ureteral stones [9]. The authors reported the need for fluoroscopy in 4% of cases, with no complications. In another publication in which half of the patients had proximal and mid-ureteral stones, fluoroscopy was required in 7.52% and minor complications were observed in 11% of cases [26].

In a retrospective comparative study that included 100 patients with ureteral and renal stones, G. Olgin et al. [11] described the technique of X-ray-free URS in 50 cases. In this study, URS was performed using a stepwise technique, and the results were similar in two groups. The authors reported that X-ray-free URS is feasible and effective for the treatment of kidney and ureteral stones.

In recent years, there have been published the results of X-ray-free RIRS [13, 16-20]. H.I. Cimen et al. [17] performed X-ray-free procedures in 93 patients. In all cases, URS with a rigid endoscope was initially performed, with subsequent insertion of UAS along the guidewire under visual control. Next, flexible URS with laser lithotripsy was done. Prestented patients were excluded from the study. The mean stone size was 14.7±5 (7–32) mm and 42 (45.1%) patients had inferior calyx stones. In another work, S. Senel et al. [18] studied 350 patients who underwent RIRS for renal and upper ureteral stones. This retrospective study compared RIRS with and without fluoroscopy. There were 255 patients in the X-ray-free group. The authors found that there was no difference in stone-free status and complications between two groups (86.3 vs. 87.0%, 17.9 vs. 15.7%, respectively). The authors concluded that X-ray-free RIRS is a feasible and safe method. M. Kiras et al. [19] performed flexible URS in 576 patients without the use of fluoroscopy, which was successful in 96.7% (557/576), and the remaining 19 cases required fluoroscopy for various reasons. The average stone size was 11.6±5.2 mm, and the procedure time was 39.4±8.2 min. The efficiency of first-session RIRS was 83.3%. The second and third sessions were performed in 32 (5.7%) and 7 (1.2%) cases, respectively. Overall, the complication rate was 11.8% and all of them were minor (Clavien–Dindo grade I or II). We performed X-ray-free RIRS in 76 patients with renal stones to avoid X-ray radiation dose. The efficiency of the first procedure was 91.6%, and the number of postoperative complications was minimal.

The data from various authors and our results show that X-ray-free RIRS is technically possible and most justified in simple cases. However, the possible serious complications should be kept in mind, especially for inexperienced endourologists. Insertion of UAS is accompanied by risks of damage to upper urinary tract at any level, which undoubtedly limits the enthusiasm for completely eliminating X-ray guidance during RIRS. This conclusion is one of the main recommendations of the International Stone Disease Alliance from 2023 and should be followed until evidence of the efficiency of alternative techniques with a high degree of reliability becomes available [27]. In our work, we analyzed the results of X-ray-free URS in the treatment of patients without renal anomalies and with a small solitary kidney stone, as well as without previous procedures on the upper urinary tract, which indicates the limited possibility of using the results obtained in the entire population of patients with urolithiasis.

It should also be mentioned that radiation exposure depends not only on intraoperative fluoroscopy, but also on imaging methods performed preoperatively. A low-dose CT scan provides a "safe exposure window" for intraoperative fluoroscopy, ensuring that the total radiation dose remains within acceptable limits. In all cases included in our work, non-contrast CT was performed in a standard mode, with an average radiation dose of 10 mSv. In order to further limit radiation exposure, in such cases we suggested X-ray-free URS.

However, we do not encourage young and inexperienced urologists to perform RIRS without fluoroscopy, which can cause serious complications. With the gaining of sufficient experience in a selected group of patients with solitary kidney stones, it is possible to safely done URS without fluoroscopy. For these purposes, we also recommend actively using 3D models of the collecting system, which allow to plan the procedure and practice its stages. In addition, these interventions are performed in the endourological operating room, where there is a constant presence of a C-arm, which can always be used if necessary.

In addition to the advantages of X-ray-free URS, the limitations of the study should be pointed out. First of all, our work is a retrospective analysis of patient data, which does not exclude the influence of other parameters. Secondly, the study does not have a control group, therefore the precise comparison with the standard technique is not possible. As a consequence, further prospective randomized studies are needed to compare the results of RIRS with and without fluoroscopy.

Conclusion. Analysis of literature and our data show that URS without fluoroscopy is effective and safe method for kidney stones in patients without renal anomalies and previous procedures. In addition, X-ray-free URS may be useful in certain clinical situations, such as urolithiasis in pregnant women, and is more convenient for surgeons since heavy lead aprons are not required. However, one should be aware of the associated risks and perform X-ray-free URS only if the surgeon has sufficient experience.

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TAXONOMIC CHARACTERISTICS AND ANTIBIOTIC SUSCEPTIBILITY OF MICROORGANISMS VERIFIED IN THE EXPRESSED PROSTATE SECRETION IN POST-COVID-19 PATIENTS WITH RECURRENT CHRONIC BACTERIAL PROSTATITIS

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Introduction. Recurrent chronic bacterial prostatitis (rCBP) is a hard-to diagnosis-and-treat disease which there is no consensus. A particularly difficult cohort is represented by patients who had COVID-19. The study aimed to evaluate the taxonomic structure and sensitivity to antibacterial drugs of microorganisms verified in expressed prostate secretion (EPS) in rCBP-patients who had COVID-19.

Materials and methods. A multicenter, prospective, randomized study was conducted with the inclusion of 52 rCBP patients who had COVID 19, in which the taxonomic structure and susceptibility were studied to antibacterial drugs of microorganisms that were verified and dominated in the EPS. Bacteriological study was carried out using an extended set of selective nutrient media and special cultivation conditions. Antibiotic susceptibility was determined in the taxa of microbiota dominating in the EPS.

Results. The mean age of the patients was 34.8±5.2 years, the duration of rCBP was 5.7±2.3 years. In all patients, various variants of aerobic-anaerobic compositions of microorganisms were recorded in the life cycle. A total of 27 microbiota taxa were isolated. The aerobic cluster was represented by 16 genera and/or species, the anaerobic cluster by 11. When studying antibiotic susceptibility to antibacterial drugs, an increase in antibiotic resistance of the most microorganisms isolated was revealed.

Conclusions. The taxonomic structure of microorganisms in rCBP-patients who had COVID-19 in all cases was characterized by complex and new variants of aerobic-anaerobic associations of microorganisms. When studying the antibiotic susceptibility, multi-resistant and pan-resistant bacteria were identified that is a real threat to this category of patients.

Key words: prostatitis, prostate secretion, antibiotic sensitivity, COVID-19

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Introduction. Currently, there is no consensus in diagnosis and treatment of chronic recurrent bacterial prostatitis [1–3]. This is due to the multifaceted pathogenesis of the disease with the development of hemodynamic, neuroendocrine, immunological and other changes in the prostate [4, 5]. Patients with chronic recurrent bacterial prostatitis often have polymorphic clinical manifestations, which may be accompanied by pain of various localizations (in the perineum, suprapubic, inguinal areas, etc.), often during or after ejaculation. A number of patients (30.0–45.0%) report lower urinary tract symptoms, various sexual disorders, as well as depressive symptoms [6, 7].

Etiologic therapy for chronic recurrent bacterial prostatitis is primarily aimed at the bacterial component. Therefore, according to the guidelines of the Russian Society of Urology (RSU) and the European Association of Urology (EAU), certain antibacterial drugs are the first line of therapy [8].

The efficiency of antibacterial therapy depends on several components, including an activity of the drug against typical/atypical pathogens, good safety and bioavailability, its pharmacokinetic characteristics, as well as the ability to achieve optimal concentrations in the tissue and prostatic secretions [9, 10]. For the latter point, an important characteristic of antibiotic is its lipophilicity and high acid dissociation constant. As a consequence, a number of antibiotics for the treatment of chronic recurrent bacterial prostatitis is quite low and includes fluoroquinolones, in some cases trimethoprim and macrolides [11–14]. However, given the polymorphism of the clinical manifestations, antibacterial therapy alone is less effective than the use of a multimodal treatment, including also α-blockers, antioxidants, anti-inflammatory drugs, immunoactive and phytotherapeutic drugs, etc. [3].

However, certain difficulties in the antibacterial therapy in chronic recurrent bacterial prostatitis are in the context of the global problem of multidrug resistance, which has worsened during COVID-19 pandemic [15]. Therefore, despite the use of modern diagnostic methods, strict adherence to the RSU and EAU guidelines on examination and treatment, the percentage of its relapses remains high [16, 17]. The increase in antibiotic resistance of uropathogens is also due to the irrationally widespread and active use of antibacterial drugs for infections that do not require their use not only in urological practice, but also in other medical specialties. Antibacterial therapy

for chronic recurrent bacterial prostatitis, especially in patients who have had COVID-19, is often ineffective, which dictates the need for the development and use of other alternative treatment methods [18].

Aim. To study the taxonomic structure and sensitivity to antibacterial drugs of microorganisms verified in the expressed prostatic secretions (EPS) of patients with chronic recurrent bacterial prostatitis who have had COVID-19.

Materials and methods. A multicenter prospective randomized study out including 52 patients with chronic recurrent bacterial prostatitis who previously had COVID-19, was carried. All patients signed informed consent to participate in the study and publish personal data.

Inclusion criteria: age over 18 years, previous history of COVID-19, clinically and laboratory confirmed diagnosis of chronic recurrent bacterial prostatitis.

Non-inclusion criteria: presence of sexually transmitted infections, other prostate diseases (benign hyperplasia, cancer), infectious and inflammatory diseases of the urinary tract and reproductive organs (vesiculitis, urethritis, pyelonephritis); primary or secondary immunodeficiency, bladder outlet obstruction (urethral stricture, bladder neck sclerosis, urolithiasis, neurogenic lower urinary tract dysfunction, etc.), abnormalities of the urinary tract and reproductive organs, past or present oncological diseases of the urinary and reproductive organs; concomitant cardiovascular, neurological, endocrine, systemic and other disorders that could affect the results of the study; an episode of taking antibacterial or other drugs with antibacterial, prostate-protective, anti-inflammatory, immunostimulating properties within 30 days before inclusion in the study.

The average age of patients was 34.8 (29.4–40.5) years, the average duration of the disease was 5.7 (3.2–8.1) years.

In all patients, EPS was taken for bacteriological examination, followed by inoculation on special media for aerobic and anaerobic microorganisms (HiMedia), respectively, in aerobic (at 37°C, 24 hours) and anaerobic (AnaeroHiGas Pak, at 37°C, 48–72 h) conditions.

Table

Detection rate of bacteria and levels of contamination of expressed prostate secretions

Microorganisms	Detection rate, %	Contamination, CFU/ml			
		Average	Standard deviation	Minimum	Maximum
CNS	100.0	2.00	0.91	2.00	4.60
S. lentus	40.0	2.00	0.72	2.00	5.00
S. haemolyticus	28.8	2.00	1.36	2.00	6.00
S. warneri	26.9	2.00	0.83	2.00	5.00
S. saprophyticus	13.5	2.00	0.49	2.00	3.00
S. epidermidis	5.8	2.00	1.15	2.00	4.00
Enterobacteriaceae:	13.4	4.00	1.97	2.00	6.00
E. coli	11.5	3.00	1.97	2.00	6.00
K. oxytoca	1.9	6.00	–	6.00	6.00
Enterococcus spp.*:*	44.3	3.00	1.07	2.00	4.50
E. faecalis	30.8	2.00	1.14	2.00	5.00
E. faecium	7.7	4.00	1.00	2.00	4.00
Enterococcus spp. *(unspecified)*	5.8	2.00	2.31	2.00	6.00
***Corynebacterium* spp.**	71.2	3.00	1.04	2.00	5.00
S. aureus	26.9	2.00	0.63	2.00	4.00
***Micrococcus* spp.**	7.7	2.00	0.50	2.00	3.00
***Streptococcus* spp.**	3.8	3.50	2.12	2.00	5.00
Anaerobes:	100.0	2.37	0.89	2.00	3.5
Eubacterium spp.	34.6	4.00	1.31	2.00	6.00
Propionibacterium spp.	25.0	2.00	0.97	2.00	5.00
Peptococcus spp.	23.1	2.00	0.39	2.00	3.00
Veillonella spp.	21.2	2.00	0.90	2.00	5.00
Peptostreptococcus spp.	9.6	4.00	1.52	2.00	5.00
Megasphaera spp.	7.7	2.00	0.50	2.00	3.00
Bifidobacterium spp.	5.8	2.00	0.58	2.00	3.00
Prevotella spp.	1.9	2.00	–	2.00	2.00
Bacteroides spp.	1.9	2.00	–	2.00	2.00
Fusobacterium spp.	1.9	2.00	–	2.00	2.00
Mobiluncus spp.	1.9	2.00	–	2.00	2.00
***Candida* spp.:**	5.8	2.00	–	2.00	2.00
C. albicans	3.8	2.00	–	2.00	2.00
C. glabrata	1.9	2.00	–	2.00	2.00

Note. CNS – coagulase-negative staphylococci; CFU/ml – colony-forming units per milliliter.

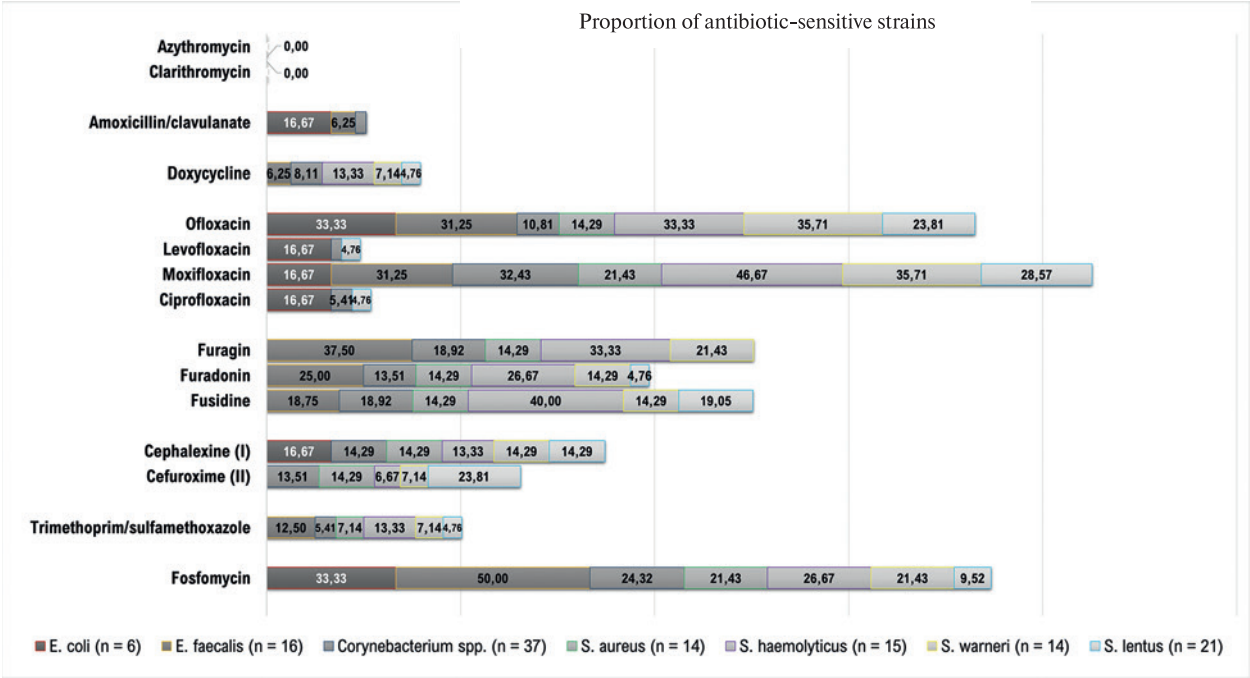

Fig. 1. Antibiotic sensitivity to oral forms of various drugs of aerobic pathogens, which were predominant in expressed prostate secretions

Identification of pathogens isolated from EPS was carried out according to standard methods. When determining antibiotic sensitivity, the relevant recommendations were followed [19].

The study was carried out as part of the scientific work "Assessment of the influence of SARS-COV-2 on the reproductive potential of men with idiopathic infertility" (approved by the Scientific Local Ethical Committee of the Rostov State Medical University, Ministry of Health of the Russian Federation on October 22, 2021). The work was done in accordance with the provisions of the Declaration of Helsinki (revised in Fortaleza, Brazil, October 2013).

Statistical analysis was carried out using the application package IBM® SPSS Statistics 26.0 ("SPSS: An IBM Company", IBM SPSS Corp., Armonk, NY, USA). Descriptive statistics included calculation of detection rates (%), mean (M) and standard deviation (±SD).

Results. The average age of the patients was 34.8±5.2 years, the duration of chronic recurrent bacterial prostatitis was 5.7±2.3 years. In all cases, various aerobic-anaerobic combinations microorganisms in EPS were recorded. A total of 27 species were identified. The aerobic pathogens were represented by 16 types and/or species, while anaerobic agents by 11. Among aerobic bacteria (see *table*), coagulase-negative staphylococcus species (CNS) were documented in all cases, represented by five species with a predominance of Staphylococcus lentus (40.0%), as well as Corynebacterium spp. (71.2%).

The spectrum of isolated causative pathogens included Enterococcus spp. (44.3%), Staphylococcus aureus (26.9%) and Enterobacteriaceae (13.4%). In the anaerobic microbiota Eubacterium spp. were predominated (34.6%).

The concentration of bacteria in EPS ranged from 102 to 106 CFU/ml. A level of 103 CFU/ml was recorded for 7 (25.9%) pathogens. However, for 21 (77.8%) species, in some cases, the concentration in EPS ranged from >103 to 106 CFU/ml.

The sensitivity to antibiotics of predominant aerobic strains isolated from EPS was studied. In descending order, the strains were represented by the following genera and/or species: *Corynebacterium* spp. (*n*=37), *S. lentus* (*n*=21), *Enterococcus faecalis* (*n*=16), *S. aureus* (*n*=15), *Staphylococcus warneri* (*n*=15), *Escherichia coli* (*n*=6). *E. coli* was isolated from EPS only in 11.5% of cases, but since their role is generally proven in the etiology of the disease, its sensitivity to antibiotics was also studied.

For chronic recurrent bacterial prostatitis, the recommended drugs are levofloxacin or ciprofloxacin. We assessed the sensitivity of isolated microorganisms not only to the recommended fluoroquinolones, but also to other tablet drugs of various groups (macrolides, penicillins with β-lactamase inhibitors, tetracyclines, cephalosporins, etc.) in order to objectify the problem of multidrug resistance in a cohort of patients who had COVID-19 and repeatedly received different drugs, but not for relapse of chronic recurrent bacterial prostatitis (*Fig. 1*).

In this cohort of patients, catastrophically low sensitivity of a wide range of antibiotics, including recommended ones, was found. In total, the highest sensitivity of the identified aerobic pathogens was seen to only two drugs from the group of fluoroquinolones, namely moxifloxacin and ofloxacin, as well as fosfomycin.

Despite the good sensitivity to moxifloxacin, we are convinced that it should not be used in routine outpatient practice, but should be a "reserve" antibiotic.

Of the six *E. coli* strains isolated from EPS, only one (16.67%) was sensitive to levofloxacin and ciprofloxacin. Of the 15 tableted drugs, only three (ofloxacin, moxifloxacin, fosfomycin) had minimal activity against the dominant aerobic pathogen in EPS. he maximum

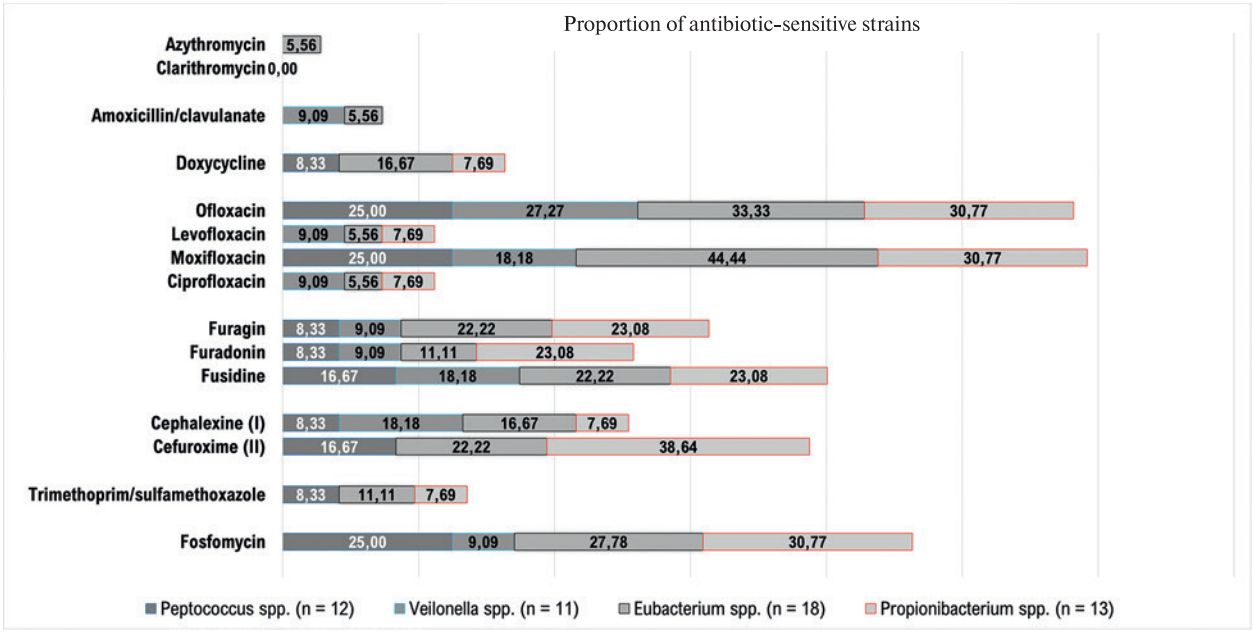

Fig. 2. Antibiotic sensitivity to oral forms of various drugs of anaerobic pathogens, which were predominant in expressed prostate secretions

sensitivity (50.0%) was observed for *E. faecalis to fosfomycin*.

Paradoxically, macrolides, which are traditionally used in the treatment of infections of the reproductive organs, were completely ineffective, since none of pathogens demonstrated sensitivity.

Of the anaerobic pathogens, the following species were predominated in EPS: *Eubacterium* spp. (*n*=18), *Propionibacterium* spp. (*n*=13), *Peptococcus* spp. (*n*=12), and *Veillonella* spp. (*n*=11). There is practically no data on the activity of the studied oral forms of drugs against a broad spectrum of non-clostridial anaerobic bacteria, with the exception of some fluoroquinolones.

In particular, 30.8% of *Propionibacterium* spp. strains isolated from EPS were sensitive to ofloxacin and moxifloxacin, 25.0% of Peptococcus spp. to moxifloxacin. Susceptibility to levofloxacin was drastically minimal and distributed as follows: *Peptococcus* spp. (9.1%), *Propionibacterium* spp. (7.7%), *Eubacterium* spp. (5.6%) (*Fig. 2*).

When analyzing the sensitivity to antibiotic therapy of the aerobic species dominant in EPS, there was a trend of multidrug resistance to parenteral drugs of six different groups, similar to oral forms. From the group of aminoglycosides, 66.7% of *E. coli* strains were sensitive to gentamicin and tobramycin. The highest sensitivity rate (56.25%) to amikacin/sulbactam was observed for E. faecalis (*Fig. 3*).

Cephalosporins of the third- and four-generations were characterized by minimal efficacy. About 40.0% of *Corynebacterium* spp., *S. haemolyticus*, and *S. warneri* strains isolated from EPS were sensitive to linezolid.

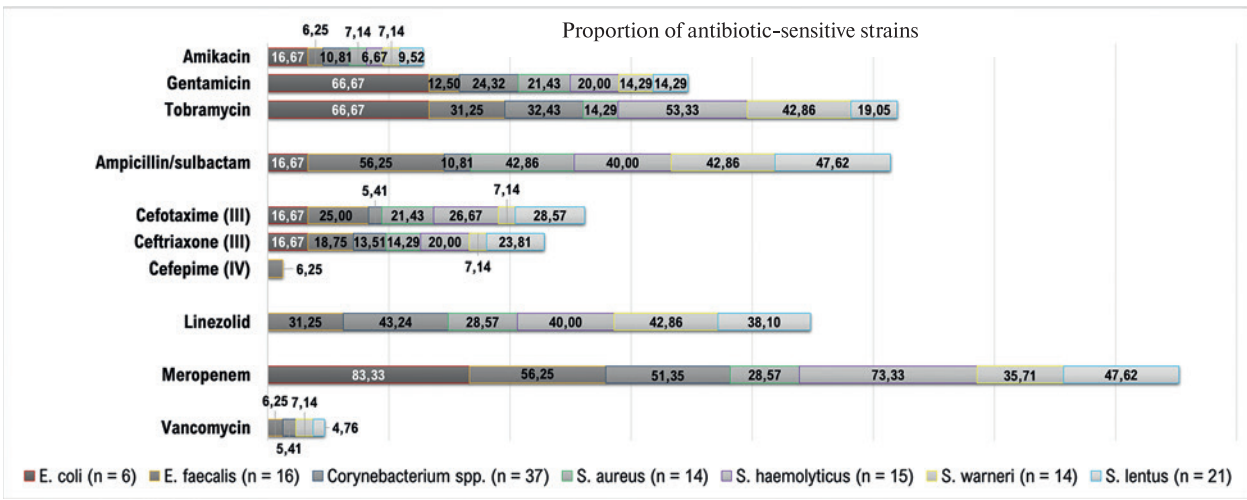

Fig. 3. Antibiotic sensitivity to parenteral drugs of aerobic pathogens, which were predominant in expressed prostate secretions

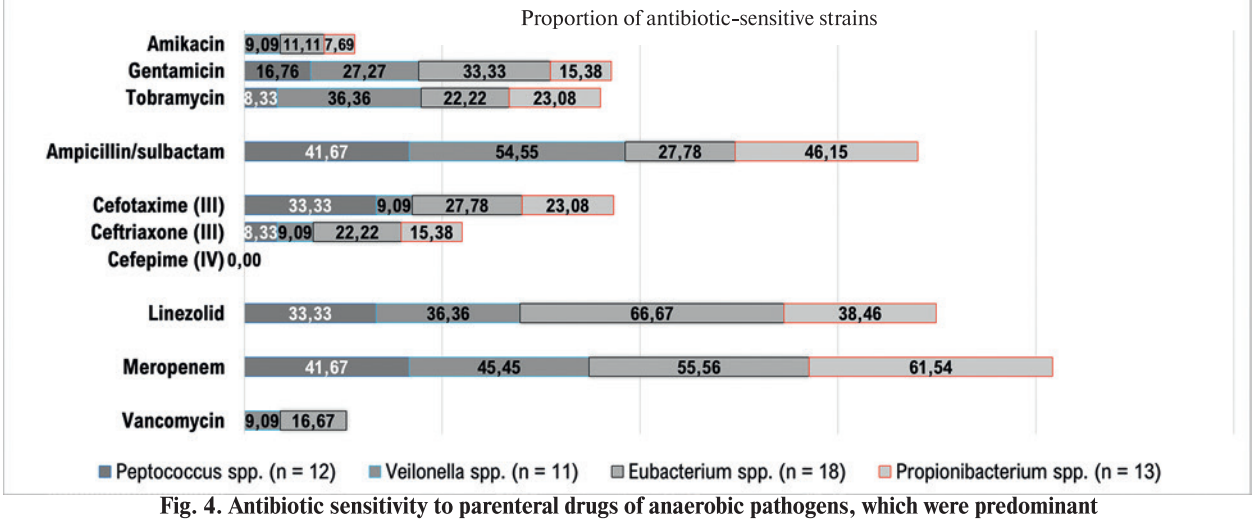

Fig. 4. Antibiotic sensitivity to parenteral drugs of anaerobic pathogens, which were predominant in expressed prostate secretions

For the dominant anaerobic pathogen in EPS, the most effective drug was meropenem with the maximum (61.54%) sensitivity for *Propionibacterium* spp. (*Fig. 4*).

Discussion. Patients with chronic recurrent bacterial prostatitis represent a special cohort for treatment, and those who have had COVID-19 and received antibiotics of various groups are an extremely difficult subgroup.

In the context of antibiotic resistance, therapy for patients not only with this pathology, but also with a number of other disorders, the etiology of which is based on the bacterial component, apparently can be divided into pre- and post-Covid stages. It is confirmed by our data on multidrug resistance of the dominant pathogen in EPS. We do not extrapolate these results to other centers, but only discuss the specific cohort of patients. Following the national guidelines, the drugs of choice for chronic bacterial prostatitis are levofloxacin and ciprofloxacin. In our previous publication [17], we already pointed out the low sensitivity rates to these drugs not only of Enterobacteria spp., but also of enterococci and CNS. In this work, we noted a catastrophic decrease in sensitivity compared to the previously described level. The data obtained are not align to results of a number of authors on antibiotic resistance, in particular in terms of fluoroquinolones [6, 18]. In our cohort of patients, there is not even a dilemma about the use of oral cephalosporins, which in case of the presence of strains with pan-resistance to traditional antibiotics, can be prescribed if there is confirmed sensitivity as step-down therapy [20]. More than 10 years ago, V. Lipsky et al. [21] showed that cefixime accumulates in the prostate similar to ciprofloxacin.

A previous study found that combination antibacterial therapy is preferable for multidrug-resistant mixed infections. At the same time, fluoroquinolones in combination with cephalosporins are the most effective against the majority of associates isolated in EPS of patients with chronic recurrent bacterial prostatitis, represented by both aerobes and anaerobes [10].

It can take quite a long time to discuss all data on sensitivity of various pathogens to antibiotics in order to recommend therapy for chronic recurrent bacterial prostatitis, but it must be remembered that they were carried out in the pre-pandemic period [22].

An absolutely logical question arises, why are we observing such a fatal situation? The answer lies on the surface. All 52 patients included in this study had confirmed COVID-19, including two times in 27 (51.9%) and three times in 16 (30.8%). Absolutely all patients received not only fluoroquinolones, but also other antibiotics. Therefore, for those with chronic recurrent bacterial prostatitis who have had COVID-19, it is quite difficult to choose monotherapy or combination of drugs in the context of not only typical, but also disputable pathogens. Moreover, chronic recurrent bacterial prostatitis is a disease, which is caused, as a rule, not only by one microorganism, but their associations.

Empiric therapy, aimed, for example, at one microorganism (enterobacteria, enterococci, etc.), will not change the situation as a whole for some patients, since the inflammatory process in the prostate can be supported initially by minor pathogen. In addition, a rate of their detection can increase with the elimination of one or more species from the bacterial association. The underestimation of the importance of bacterial associations is also indicated M.A. Mulvey et al. in his monograph "Urinary tract infection" (2017) [23].

Conclusions. The taxonomic structure of microorganisms in EPS of patients with chronic recurrent prostatitis who had COVID-19 was characterized by complex and new variants of aerobic-anaerobic associations. When studying the antibiotic sensitivity, multi-resistant and pan-resistant bacteria were identified, which pose a significant threat due to the impossibility of appropriate therapy.

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OUTPATIENT TREATMENT AND QUALITY OF LIFE OF PATIENTS WITH INTERSTITIAL CYSTITIS AND HUNNER'S LESION: COHORT CROSS-SECTIONAL STUDY

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Aim. To assess the quality of life of patients with interstitial cystitis (IC) and to study effective options used to control symptoms on outpatient basis.
Materials and methods. The results of a descriptive prospective cross-sectional cohort study are presented. The medical charts of patients who were treated in the City Clinical Hospital named after Spasokukotsky from 2021 to 2023 were analyzed. Eighty inpatient medical charts of various patients with a final diagnosis of IC with Hunner's lesion were identified. Only 53 patients were interviewed due to the inclusion/exclusion criteria. Respondents were asked to complete a survey consisting of 15 questions. The survey was carried out online for patients who did not require surgical treatment at the time of the study, and offline for patients admitted for repeated surgical treatment.
Results. The average age of respondents was 59.0±11.1 years. 58% (31) of patients noted the presence of constant pain in the pelvic area during the day, while 85% (45) of patients reported pain outside the bladder area, in the urethra and perineum. The intensity of pain in the pelvic area was 4.9 (2.3-5.6) points. Higher pain scores 6.24 (5.8-9.0) were observed in 47% (25) of patients admitted for repeat surgical treatment. 62% (33) of patients had a titer of bacteria in a urine test above 104, while 51% (27) of patients experienced relief of symptoms after taking antibacterial drugs. For the treatment and symptomatic relief, the following are most often used: pentosan sodium polysulfate (26%, n=14), antibacterial drugs of the nitrofuran group (25%, n=13), amitriptyline (15%, n=8), non-steroidal anti-inflammatory drugs (11%, n=6) patients. 23% (12) of respondents received intravesical therapy. The time from the onset of symptoms to the final diagnosis was 48 (24-96) months.
Conclusions. Although infection is a criterion for excluding the diagnosis of IC, more than 62% of patients have positive urine culture. The results obtained indicate the need to improve existing approaches to the diagnosis of IC, as well as to develop treatment algorithms for painful bladder syndrome to control symptoms.

K e y w o r d s: *bladder pain syndrome, interstitial cystitis, pentosan, Hunner's lesion*

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Introduction. Painful bladder syndrome/interstitial cystitis (BPS/IC) is a severe debilitating disease that occurs predominantly in women [1, 2]. In the 2023 Guidelines of the European Association of Urology (EAU), BPS/IC is discussed as a component of chronic pelvic pain syndrome and represents chronic or recurrent episodic pain localized in the bladder area with additional manifestations, which include increased pain when filling the bladder, frequent urination, often in small portions, during the day and/or night [3].

IC has been known since the 19th century, but its definition, diagnosis, and approaches to treatment in the acute and latent periods are still under discussion. According to the 2022 guidelines of the American Urological Association (AUA), a stepwise approach to the treatment of patients with BPS is recommended. The described tools allow to start treatment, but only during short period and in terms of improving the quality of life. Moreover, current recommendations have a number of unresolved issues. According to AUA guidelines, the definition of IC involves the absence of bacterial growth in urine culture, and cystoscopy is an acceptable option if the diagnosis of BPS is unclear or the presence of Hunner's lesions is suspected [3]. However, clear clinical signs of Hunner's lesions have not been described, and lower urinary tract infections have been seen in IC [4]. Moreover, the optimal regimens and options for intravesical pharmacotherapy have not yet been clarified, which complicates outpatient treatment of patients. These contradictions, coupled with the lack of consensuses regarding the diagnosis and treatment of IC, certainly has an effect on the quality of life of patients.

Aim. To assess the quality of life of patients with IC and to study effective outpatient measures to resolve the symptoms.

Materials and methods. At the Department of Urology of Moscow State Medical University named after A.I. Evdokimov a descriptive prospective cross-sectional cohort study was carried out. The medical charts of patients who applied to S.I. Spasokukotsky City Clinical Hospital No. 50 from 2021 to 2023 were analyzed. A total of 80 medical inpatient records of patients with the

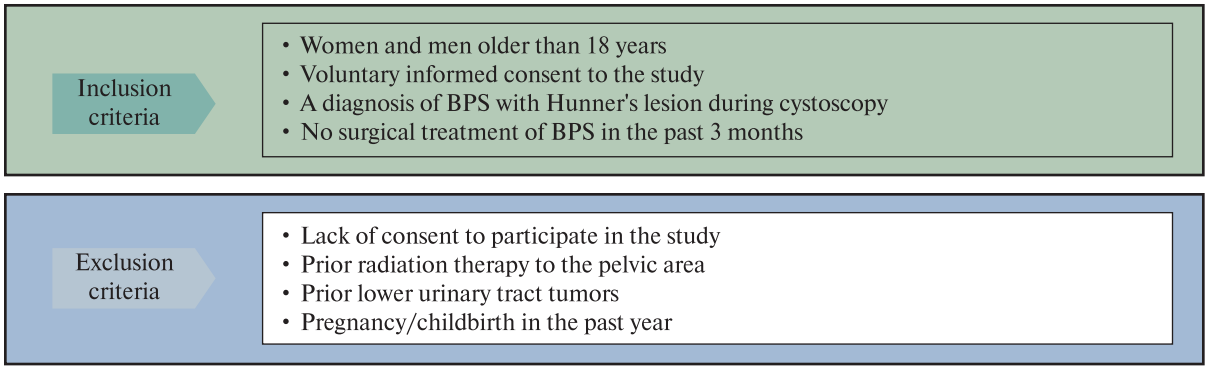

Fig. 1. Inclusion/exclusion criteria

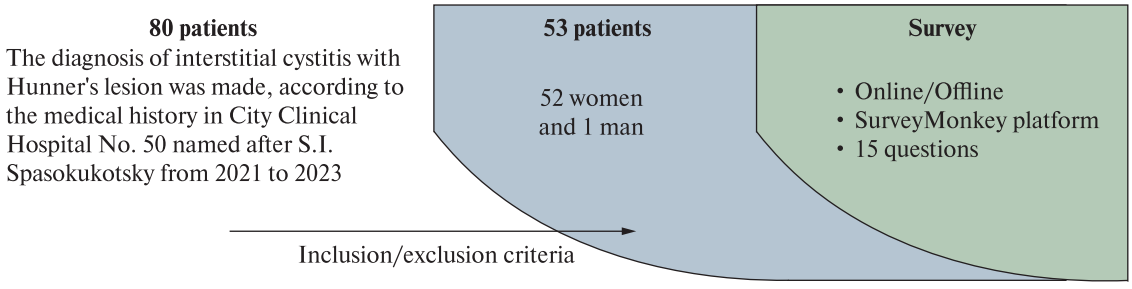

Fig. 2. Study design

final diagnosis of "IC with Hunner's lesion" were found. During hospital stay, all patients underwent cystoscopy under anesthesia, fulguration of Hunner's lesions, and hydrodistension of the bladder. Only 53 patients met the inclusion and exclusion criteria (*Fig. 1*).

Patients were asked to complete a 15-item survey. Those respondents who did not require surgical treatment at the time of the study, had an opportunity to complete the survey online (using the SurveyMonkey platform). For respondents admitted for repeat surgical treatment, the survey was carried out as part of a personal consultation (*Fig. 2*).

Statistical analysis. For the purpose of statistical processing of data, descriptive methods were used. For the characteristics that had a normal distribution, the mean and standard deviation were calculated. For the characteristics with a non-normal distribution, the median and indicators of the 1st and 3rd quartiles (25–75%) were used. The Shapiro–Wilk test was done to assess the normality of distribution.

Results. A total of 53 patients took part in the survey, including 1 man and 52 women. The average age was 59.0±11.1 years. The median number of daytime urinations was 17 (13.0–20.0), the median number of nighttime micturition was 6 (4–8). The functional bladder volume was 140 ml (100–200 ml). According to the survey, 92% (n=49) of respondents noted increased pain in the bladder area when filling, 81% (n=43) of patients noted a decrease in pain intensity after voiding.

The median pain severity score on the visual analogue scale (VAS) was 4.9 (2.3–5.6) points. Higher median VAS scores were observed in 47% (n=25) of patients admitted for surgical treatment (6.24 [5.8–9.0] points) (*Fig. 3*).

Since diagnosis, 62% (33) of patients at least once noted the presence of bacteria in a culturological examination of urine in a titer of more than 104, while the use of antibacterial drugs in 51% (27) of cases resulted in resolution of clinical manifestations (*Fig. 4*).

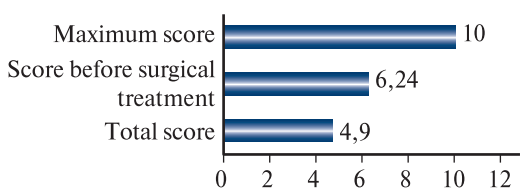

Fig. 3. Pain intensity according to VAS

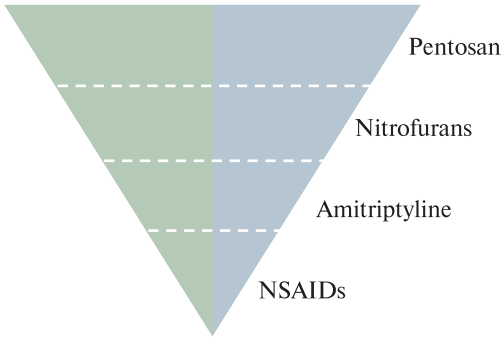

Fig. 4. Most used drugs for treatment/relief of symptoms based on frequency of use

For the relief of symptoms, oral pentosan polysulfate (PPS) was used in 26% (n=14) of patients, antibacterial drugs of the nitrofuran group in 25% (n=13), amitriptyline in 15% (n=8), non-steroidal anti-inflammatory drugs (NSAIDs) in 11% (n=6). In addition, 23% (n=12) of respondents received intravesical pharmacotherapy (Fig. 4). Optionally, herbal preparations and PRP (platelet rich plasma) therapy were administered.

When describing pain, 58% (31) of respondents mentioned the presence of constant pain in the pelvic area throughout the day. Moreover, 85% (45) of patients also described pain in areas of the pelvis other than the bladder. The most commonly there was pain in the urethra, perineum and groin area.

During the study, we found that 60% (n=32) of respondents were not sexually active at the time of the survey, and only 40% (n=21) of patients remained sexually active. In the general structure, 19% (n=10) of patients experienced pain/discomfort in the pelvic area during sexual intercourse, compared to 48% sexually active respondents (n=10) (*Fig. 5*).

In addition, 55% (29) of respondents had a history of gynecological interventions, most commonly removal of uterine fibroids, reconstruction of the vaginal walls (including the use of synthetic prostheses), and hysterectomy.

The median time from the onset of symptoms to the final diagnosis for respondents was 48 (24–96) months or 4 years.

These facts are reflected in the time interval for establishing the diagnosis, which was 4 years (48 months). The low prevalence and awareness of specialists, and the lack of clear indications for cystoscopy may be causative factors for late detection. However, atypical presentation is the most important component of this problem. According to S.L. Parsons, about 81% of patients with IC had dysuria by the age of 30. The most common misdiagnosis was urinary tract infection in 74% of cases, and candida vaginitis in 42%. Almost immediate appearance of complaints after sexual activity in 82% patients contributed to a presumption of infectious etiology of IC. The specific manifestation, namely frequent urinations in the early stages, with subsequent development of pain, can be also misleading when making a diagnosis [5].

A constant pain symptom in almost 2 (58%) out of 3 patients with an average pain intensity score, according to VAS (4.9 points), convincingly shows that there is no complete control over clinical manifestation of BPS. The above-described features of the pain symptom and the presence of extravesical pain in 81% of cases results in not only physical, but also psychological discomfort. In addition, insufficient attention is paid to extravesical symptoms (anxiety, depression, fatigue). Their importance is highlighted in the AUA guidelines, which suggest the use of behavioral therapy and stress management at the initial stages of treatment. An integrated approach to the treatment of IC with the participation of a psychologist is suggested to be more effective than standard treatment alone. Cognitive behavioral therapy and stress management do not change objective disturbances, but provide subjective improvement in the severity of anxiety, refractory to traditional therapy [6].

According to the AUA, the absence of a urinary tract infection is important for the diagnosis of BPS. This causes a certain contradiction to the results obtained. The presence of bacteria in culturological examination of urine in patients with IC in 62% may be due to inadequate samples. However, the active use of antibacterial drugs by every second (51%) patient in order to relieve the symptoms of BPS convincingly shows that urinary tract infection should not be a criterion for excluding the diagnosis of IC.

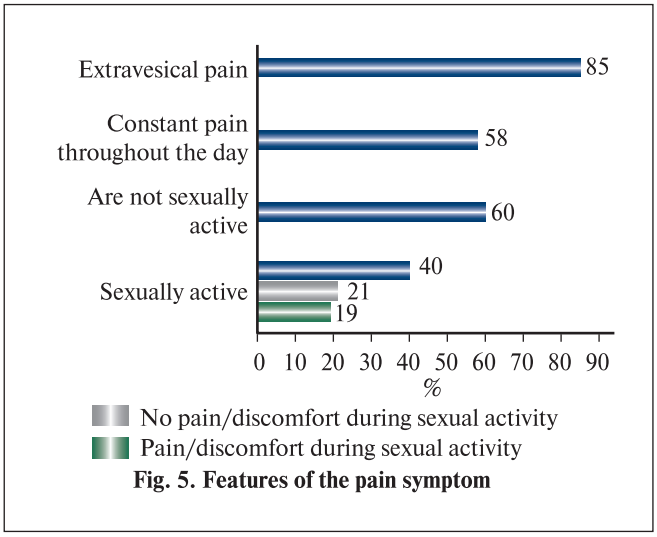

Fig. 5. Features of the pain symptom

Discussion. IC continues to be a challenging problem for the global community. Among the most common complaints are pain in the bladder area when filling, decreased pain after voiding, frequent urination in small portions, and pelvic pain of other localization. Despite the specific clinical manifestations of BPS, the diagnosis and approach to the management of patients with IC still remain inconsistent.

It should be noted that non-steroidal anti-inflammatory drugs are actively used. Although this class of medicines are not highly recommended for the treatment of chronic pelvic pain syndrome, they are still relevant along with already proven options, including pentosan polysulfate and amitriptyline. This once again proves the lack of effective tools to control the symptoms of the disease.

A limitation of our study was the inability to reliably confirm the presence of Hunner's lesions in all respondents at the time of the survey. This may lead to an underestimation of the correlation between clinical manifestations and endoscopic findings.

Despite the limited understanding of etiological factors, urologists continue to search for effective approaches to the treatment of patients with BPS in the postoperative period and between recurrences. Currently, the main therapy is aimed at the pathogenetic component of IC. Significant information about the disease was obtained through morphological studies of bladder biopsies. In patients with IC with Hunner's lesion, desquamation of the epithelium, pronounced lymphohistiocytic infiltration, edema of the lamina propria, mastocytosis, and perineuritis are observed [7].

Regeneration of the bladder mucosa is one of the most important areas of treatment for patients with BPS. Among the narrow range of drugs, pentosan sodium polysulfate is commonly used, which is an oral heparinoid. A lot of scientific work has already been published regarding its efficiency, and it continues to strengthen its place within

the guidelines on IC therapy [8, 9]. However, a possible systemic side effect, maculopathy, is a reason to find new ways to deliver the drug to the bladder. One such example is intravesical instillation of pentosan sodium polysulfate solution, which also demonstrates its efficiency and safety [10, 11].

Submucosal injection of platelet-rich plasma (PRP) is one of the emerging and promising methods for patients with IC. Growth factors found in platelets may contribute to the regeneration of the bladder mucosa, increase the duration of the recurrence-free period and reduce the intensity of manifestations. The efficiency of this technique is confirmed by a lot of studies [12–14]. Nevertheless, due to the lack of unified standard protocols for colecting PRP and optimal modes for it using, PRP is still experimental technique.

Conclusion. BPS continues to be a challenging problem for the global community. Constant moderate pain, frequent urination, the need to use absorbent underwear, and refusal to have sexual activity allow to classify IC as disabling. Although urinary tract infection is an exclusion criterion for IC, more than half of patients have bacterial growth on urine culture. Imperfect approaches to definition, diagnosis, and treatment do not allow for complete resolution of the symptoms and require further improvement.

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IMMUNOLOGICAL PARAMETERS OF URINE IN DIFFERENTIAL DIAGNOSIS OF CHRONIC RECURRENT CYSTITIS IN WOMEN

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Introduction. Chronic recurrent cystitis (CRC) is a complex multifaceted problem of modern uroinfectology.

Objective. To study the immunological parameters of urine in patients with chronic recurrent cystitis depending on the etiological factor.

Materials and methods. The prospective study included 71 patients aged 20–45 years who had previously been diagnosed with recurrent lower urinary tract infection: chronic recurrent cystitis (CRC) during an exacerbation period. Based on the results of bacteriological and PCR studies of urine, scraping of the urethra and vagina, depending on the dominant etiological factor, the patients were divided into three groups: group 1 (n=30) – with papillomavirus CRC (PVI-CRC), group 2 (n=30) – with bacterial CRC (B – CRC), group 3 (n=11) – with candida CRC (C – CRC). Analysis of the assessment of immunological parameters of urine was carried out using an enzyme-linked immunosorbent assay (ELISA-BEST).

Results. Based on the results of an immunological study of urine in the study groups, characteristic specific changes in the level of interleukins and interferons were identified, which made it possible to determine a protocol for the differential diagnosis of CRC.

Conclusions. Our study shows the advisability of testing interleukins in urine (IL-1 beta, IL-6, IL-8); these indicators can serve as scoring criteria in the differential diagnosis of CRC of various origins.

Conclusions, it is reasonable to study the level of IFNα-2b and IFNγ; when identifying the functional inferiority of the IFN system in women with CRC, correction of the IFN system is necessary.

K e y w o r d s: Chronic cystitis, interleukins, interferons, bacteria, candida, human papillomaviruses

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Introduction. Chronic recurrent cystitis is a complex multifactorial problem of modern urologic infectiology [1–3]. Owing to the development of new diagnostic methods and recent advancements in the studying of pathogenetic basis of infectious and inflammatory lower urinary tract diseases, associated with the new paradigm that urine is not sterile, as well as the whole urinary tract, the traditional opinion about the etiological structure, pathogenesis, and diagnostic methods and treatment has been changing [4–7]. It is known that under certain predisposing factors, cystitis can be caused not only by aerobic pathogens, but also by anaerobic bacteria, viruses, and fungi [8–10]. In this regard, diagnostic methods also change, and is not always consistent with clinical guidelines [11–13]. In addition, given that treatment of chronic recurrent cystitis, in accordance with generally accepted recommendations, is accompanied by a high rate of relapse, the feasibility of a differential approach to the diagnosis and treatment is emphasized [14, 15].

In this regard, with current knowledge of the etiology, pathogenesis and diagnosis of chronic recurrent cystitis of any origin, the pathophysiology is recognized as multifactorial, despite the fact that some dominant mechanisms are postulated, such as infectious, autoimmune, neurological, endocrine and psychological [16, 17].

It has also been proven that chronic nature of the infectious and inflammatory process in the bladder is associated with dysfunction of local immunity. It is known that the mucosa-associated lymphoid tissue of the urinary tract includes various cells of innate and adaptive immunity: epithelial cells, lymphocytes, macrophages, dendritic and mast cells, natural killer cells. Their dysfunction is one of the leading pathogenetic mechanisms for the development of cystitis [18].

Moreover, the bladder has passive protection, such as mucus, antimicrobial peptides, secretory immunoglobulins, etc., which protect it from microbial colonization. Under certain predisposing factors, including dysfunction of local immunity, these mechanisms may be impaired. In this case, the urothelium and resident immune cells produce additional protective molecules, cytokines and chemokines, which attract inflammatory cells to the infected tissue.

Resident and recruited immune cells act together to eliminate bacteria in the bladder and to develop robust immunological memory against infection [19, 20]. Some active peptides and cytokines can be used in screening and differential diagnosis of chronic recurrent cystitis.

Aim. To study the immunological parameters of urine in patients with chronic recurrent cystitis depending on the etiological factor.

Materials and methods. Ethical statement. The study was planned, carried out in accordance with the provisions of the Declaration of Helsinki (revised in Fortaleza, Brazil, in October 2013) and approved by the Local Independent Ethical Committee of the FGBU VO Rostov State Medical University of the Ministry of Health of the Russian Federation based on review of the design and work implementation plan (protocol No. 16/17 from 05.10.2017).

The study was carried out as part of the scientific work "Optimization of differential diagnosis and selection of first-line therapy for chronic recurrent cystitis in women" and had no sponsorship.

Patients. The prospective study included 71 patients aged 20–45 years who had a diagnosis of chronic recurrent cystitis in acute phase. The inclusion and non-inclusion criteria to participate in the study are shown in *Table 1*.

The initial examination included assessment of complaints, taking medical history, culturological and polymerase chain reaction (PCR) analysis of the morning midstream specimen of urine, urethral and vaginal swab test, and cytological examination of urine. The survey methodology was described in detail in previous works [14, 17]. Based on the results of bacteriological and PCR studies of urine, urethral and vaginal swab test, patients were divided into three groups, depending on the dominant etiological factor: group 1 (n=30) with papillomavirus etiology, group 2 (n=30) with bacterial causative factor (B-CRC), group 3 (n=11) with candida cystitis.

Analysis of immunological parameters of urine was carried out using an enzyme-linked immunosorbent assay (ELISA-BEST). The following pro-inflammatory cytokines were determined: interleukin 1-beta (IL-1 beta) (normal range: 0–11 pg/ml), interleukin-8 (IL-8) (0–12.0 pg/ml), interleukin-6 (IL-6) (0.0–7.0 pg/ml). In addition, anti-inflammatory cytokines were also studied: interleukin-4 (IL-4) (0–4 pg/ml), as well as tumor necrosis factor (TNF) (<6 pg/ml), interferon-alpha 2b (IFNα-2b) (0–20 pg/ml), and interferon-gamma (IFNγ) (0–20 pg/ml).

The determination method was based on a three-stage "sandwich" version of solid-phase ELISA using mono- and polyclonal antibodies to IL-1 beta and antibodies to IL-6, monoclonal antibodies to IL-8 and IL-4, TNF, IFNα -2b and IFNγ. An important stage was to study the levels of IFNα-2b and IFNγ in urine, since it can serve as a guide not only for diagnosis, but also for treatment of patients with chronic recurrent cystitis of various origins. In addition, calibration samples were used containing a known amount of IL-1 beta, IL-6, IL-4, IL-8, TNF streptavidin-horseradish peroxidase conjugate, which is ready-to-use solution for the recovery of calibration and control samples of IL (RBO), solution for sample dilution, phosphate-buffered saline solution with Tween (PBS-T×25) and tetramethylbenzidine solution (TMB plus). After measuring the optical density of the solution in the wells, the concentration in the analyzed samples was calculated based on the calibration graph.

Methodology for studying immunity indicators. An enzyme immunoassay using antibodies to IFNα-2b and IFNγ in the wells, when a test sample of serum was added during the first incubation, IFNα-2b or IFNγ binds to monoclonal antibodies immobilized on the inner surface of the wells of the plate. During the second incubation, the peroxidase conjugate of polyclonal antibodies to IFNα-2b or IFNγ binded to interferon alpha immobilized during the first incubation. During incubation with a tetramethylbenzidine solution, the solution in the wells became colored. The degree of coloring was directly proportional to the levels of IFNα-2b or IFNγ in the analyzed samples.

Statistical analysis was performed using Excel spreadsheets (Office, 2019) and Statistica 10.0 software (StatSoft Inc., USA). Numerical data are presented as a median value (Me) and quartiles (Q1; Q3). The statistical significance of intergroup differences was assessed using nonparametric tests: the Mann–Whitney test when comparing two groups and the Kruskal–Wallis

Table 1

Selecting parameters for the study

Inclusion criteria	Non-inclusion criteria
• Age over 18 years. • Clinical and laboratory confirmation of a diagnosis of chronic recurrent cystitis (according to the RSU and EAU Guidelines). • Signing informed consent to participate in the study	• Age over 45 years. • Cystitis due to other established non-infectious causes (IC/BPS, radiation, chemical, foreign bodies, drug-induced). • Proven NLUTD and associated diseases/idiopathic DO. • Active STDs. • Infectious and inflammatory diseases of the upper respiratory tract. • Infectious and inflammatory diseases of female reproductive system. • Bladder stones. • Bladder outlet obstruction. • Concomitant cardiovascular, neurological, endocrine, systemic and other diseases. • Hormonal disorders associated with female reproductive system. • Past or present oncological diseases. • The urinary tract and female reproductive system anomalies. • Immunodeficiency states of various origins. • Pregnancy/lactation. • Menopause. • Contraindications to anesthesia

Note: DO – detrusor overactivity; STDs – sexually transmitted diseases; IC/BPS – interstitial cystitis/bladder painful syndrome bubble; NLUTD – neurogenic dysfunction of the lower urinary tract; RSU – Russian Society of Urologists; EAU – European Association of Urology.

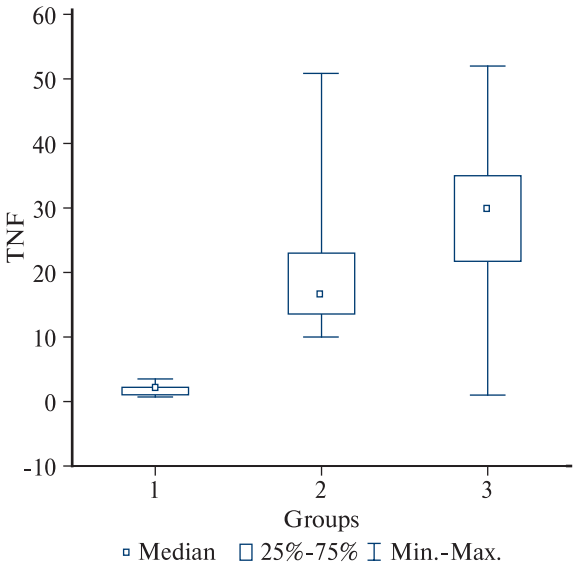

Fig. 1. Level of TNF in three groups (range diagram by group)

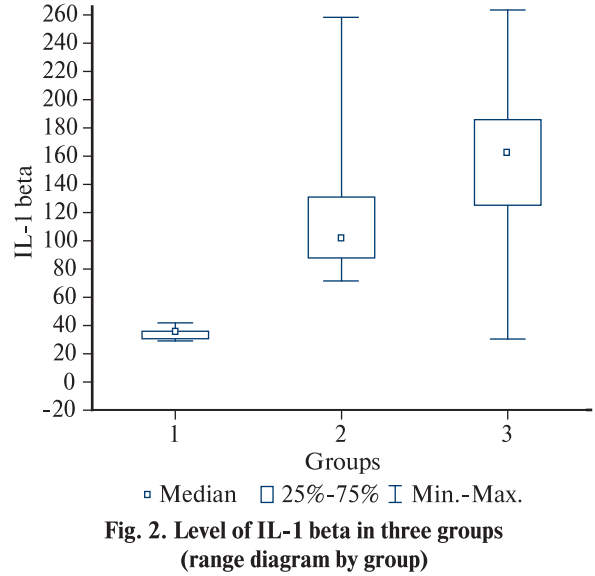

Fig. 2. Level of IL-1 beta in three groups (range diagram by group)

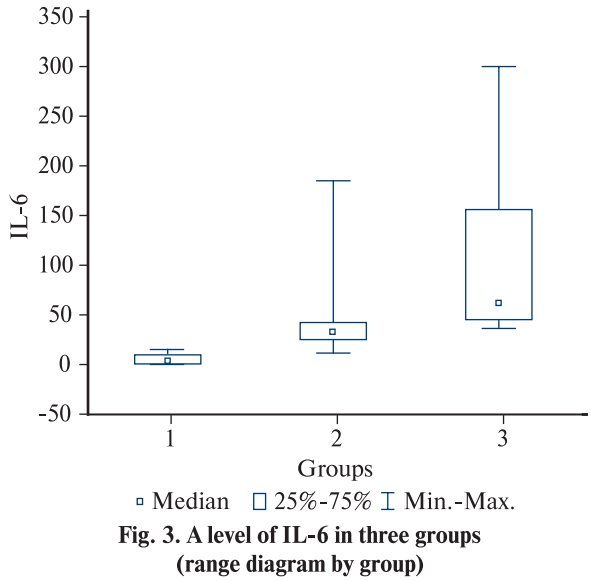

Fig. 3. A level of IL-6 in three groups (range diagram by group)

test if three or more independent groups were compared. A Chi-square test (with Yates correction) and Fisher's exact test were used for comparison of the proportions of qualitative data. The generally accepted criterion for significance was used ($p \leqslant 0.05$). The Bonferroni test for multiple comparisons was taken into account. Conventional significance levels were used ($p<0.05$).

Results. All groups were comparable in age of patients. In terms of the duration of the disease, significant differences were found between groups I and III. Moreover, there were significant differences in the number of recurrences during the year between groups I and II, on the one hand, and group III, on the other ($p<0.05$) (*Table 2*).

When assessing TNF levels, significant differences were found between the study groups. Me (Q1; Q3), and the maximum and minimum values corresponded to the normative values only in patients of group I. Me, Q3 and minimum values in groups II and III were significantly different, while maximum values were almost equivalent (*Fig. 1*).

Me of IL-1 beta and IL-6 corresponded with TNF levels, and were significantly higher in patients of group III; in group I, Me and (Q1; Q3) remained within the reference values (*Fig. 2, 3*).

Regarding the IL-8 levels, it was almost identical in groups II and III, with equivalent Me, although there were differences in (Q1; Q3), maximum and minimum values.

Table 2

Characteristic of groups

Group	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=11)	p	p_{1-2}	p_{1-3}	p_{2-3}
Values	Me (Q1; Q3)	Me (Q1; Q3)	Me (Q1; Q3)				
Age, years	36.0 (31.0; 42.0)	37.0 (30.0; 42.0)	40.0 (39.0; 44.0)	0.11	1	0.11	0.20
Duration (years)	6.0 (4.0; 7.0)	5.0 (4.0; 6.0)	4.0 (3.0; 5.0)	0.0028	0.18	0.0050	0.090
Number of recurrences per year	5.0 (4.0; 7.0)	5.0 (4.0; 6.0)	10.0 (10.0; 12.0)	0.0000	0.071	0.0002	0.0001

Note. Comparison of mean ranks.
p_{1-2} significance of differences between groups 1 and 2, two-sided test for multiple comparisons, p_{1-3} significance of differences between groups 1 and 3, two-sided test for multiple comparisons, p_{2-3} significance of differences between groups 2 and 3, two-tailed test for multiple comparisons.

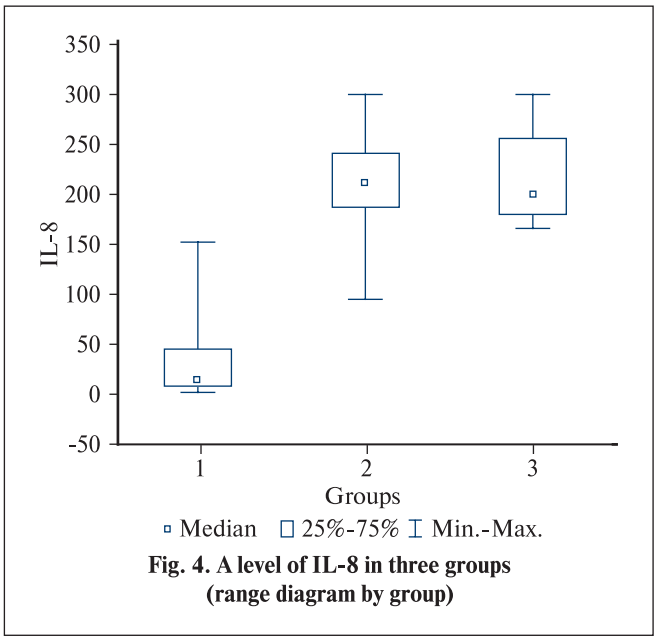

Fig. 4. A level of IL-8 in three groups (range diagram by group)

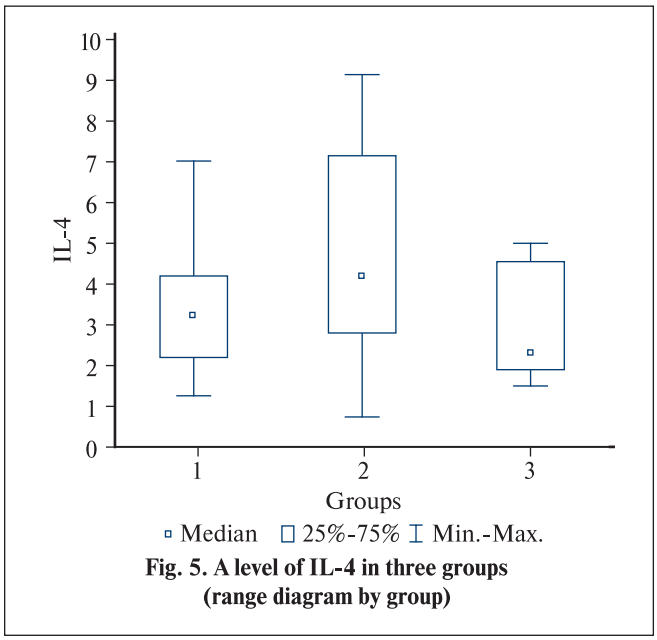

Fig. 5. A level of IL-4 in three groups (range diagram by group)

In addition, values in groups II and III were significantly different compared with group I. Despite some differences in IL-8 levels, in all groups it corresponded to an infectious and inflammatory process, which was more severe in groups II and III (*Fig. 4*).

The level of IL-4 in all groups was within normative values, which indicates the absence of an allergic component in the pathogenesis (*Fig. 5*).

Meanwhile, IFNα-2b level was identical in patients of groups I and III, both in terms of Me and (Q1; Q3) and maximum and minimum values. However, in group II, Me, Q3 and the minimum value corresponded to the reference levels, while Q1 and the maximum value were above the norm (*Fig. 6*).

The level of IFNγ in all groups was within the acceptable values (*Fig. 7*). Thus, the studied groups were virtually comparable in terms of the level of TNF, IFNα-2b and IFNγ (*Table 3*).

Discussion. In our study the immunological parameters of urine of patients with chronic recurrent cystitis of various origins were analyzed. At the same time, significant differences were found between patients in the levels of TNF and IL-1 beta, IL-6, and IL-8. In those with bacterial and fungal cystitis, there was a significant and significant increase in the levels of IL-1 beta and IL-8, which indicates the active participation of the macrophage component. It is known that an increase in the level of macrophages indicates an active bacterial inflammatory process, in which degranulation of macrophages and neutrophils leads to an increase in the level of interleukins [19]. Definitely, the analysis of interferon levels must be considered align with other laboratory and clinical data. However, a decrease in the production of alpha and gamma interferon during an acute inflammatory process may be a consequence of a chronic viral infection (group I) or the result of a long-

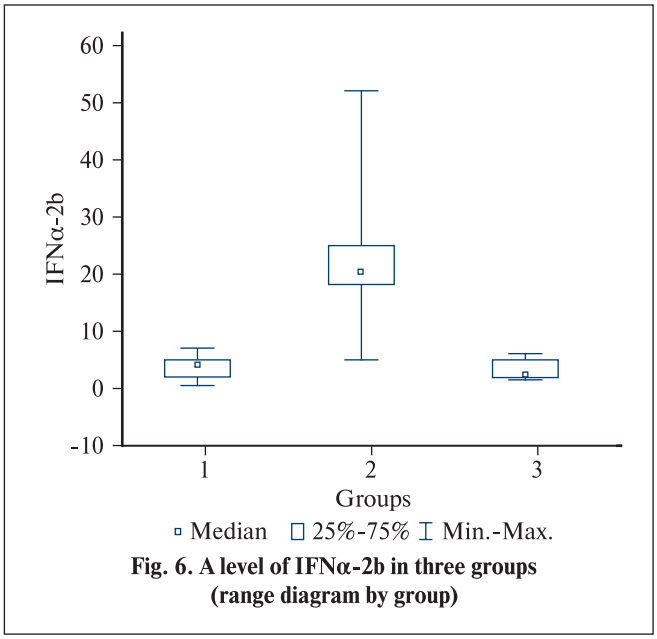

Fig. 6. A level of IFNα-2b in three groups (range diagram by group)

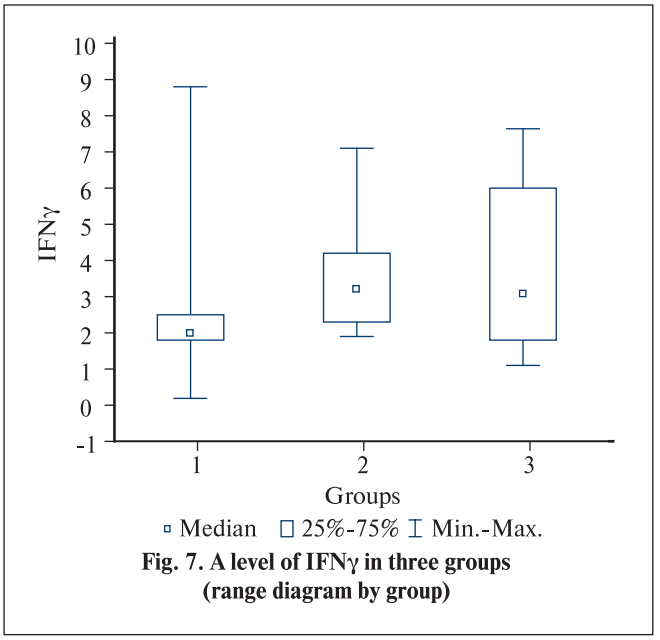

Fig. 7. A level of IFNγ in three groups (range diagram by group)

Table 3

Immunological parameters of urine in groups

Group	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=11)	p	p_{1-2}	p_{1-3}	p_{2-3}
Values	Me (Q1; Q3)	Me (Q1; Q3)	Me (Q1; Q3)				
TNF, pg/ml	1.91 (1.04; 2.2)	16.4 (13.5; 23.0)	29.9 (21.7; 35.0)	0.0000	0.0000	0.000	0.73
IL-1 beta, pg/ml	2.43 (1.0; 4.29)	16.28 (12.7; 35.0)	200.0 (169.0; 211.0)	0.0000	0.0000	0.0000	0.015
IL-6, pg/ml	2.68 (0.6; 9.8)	33.6 (22.6; 60.0)	60.9 (45.2; 156.0)	0.0000	0.0000	0.0000	0.26
IL-8, pg/ml	13.8 (8.16;45.2)	213.0 (189.0;251.0)	200.0 (180.0;256.0)	0.0000	0.0000	0.0000	1.0
IL-4, pg/ml	3.21 (2.2; 4.2)	4.15 (2.8;6.2)	2.3 (1.9-4.5)	0.060	0.17	1.0	0.13
IFNα-2b, pg/ml	4.05 (2.0;5.0)	20.5 (17.3;22.3)	2.30 (1.9;5.0)	0.0000	0.0000	1.0	0.0000
IFNγ, pg/ml	2.0 (1.8;2.5)	3.2 (2.3;4.2)	3.1 (1.8;6.0)	0.0019	0.0015	0.22	1.0

Note. Comparison of mean ranks.
p_{1-2} significance of differences between groups 1 and 2, two-sided test for multiple comparisons, p_{1-3} significance of differences between groups 1 and 3, two-sided test for multiple comparisons, p_{2-3} significance of differences between groups 2 and 3, two-tailed test for multiple comparisons.

term persistent inflammatory process (groups II and III), but in both cases congenital deficiency or acquired depletion of the interferon system is evident, which can be considered an indication for interferon-stimulating therapy.

According to the literature, the stable expression of cytokines and the active and pronounced inflammatory infiltration of various cells in the bladder during the activation of a urinary infection depends on the type of bacteria and gender [20]; women are more likely to develop chronic recurrent cystitis. Moreover, there are some species differences in causative microorganisms [4].

In addition, recent studies have shown differences in immune status by gender, which affect the outcome of inflammatory processes in the urinary tract [21]. Multicenter randomized trials are required.

Our results indicate that the levels of TNF and IL-1 beta, IL-6, and IL-8 can be used as screening criteria in the differential diagnosis of chronic recurrent cystitis of various origins, in order to start correct etiologic therapy, which can be adjusted after obtaining urine culture. Taking into account the levels of IFNα-2b and IFNγ, it is possible to determine the degree of impairment of the immune response and the need for immunostimulating therapy.

Conclusions. Chronic recurrent cystitis is a polyetiological disease, and identification of the etiological factor is a complex task that determines the successful treatment. Our study showed the feasibility of analyzing interleukins in urine (IL-1 beta, -6, -8), since they can serve as a criterion in the differential diagnosis of chronic recurrent cystitis of various origins. In addition, it is reasonable to study the level of IFNα-2b and IFNγ, since when identifying the functional impairment of the IFN system in women with chronic recurrent cystitis, its correction is necessary.

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PROGNOSIS OF URETERAL DILATATION DURING PROCEDURES USING A URETERAL ACCESS SHEATH IN PATIENTS WITH UROLITHIASIS

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Aim. To improve the results of treatment of patients with urolithiasis who underwent endoscopic interventions using a ureteral access sheath (UAS) by developing a predictive model of ureteral dilatation without pre-stenting.

Materials and methods. A total of 180 patients with kidney stones up to 20 mm were included in the study. They were divided into two groups: in the group 1 (n=79) UAS of 12/14 Ch was used, while in group II (n=101) UAS of 10/12 Ch was inserted. In group I, 48 (60.8%) patients underwent micropercutaneous nephrolithotomy and in 31 (39.2%) retrograde intrarenal surgery was done, compared to 42 (41.6%) and 59 (58, 4%) of patients in group 2. A non-inclusion criterion was a history of ureteral stenting. At the stage of preoperative diagnosis, 60 minutes before the X-ray examination, the patient took a single dose of 80 mg of furosemide per os to improve visualization of the upper urinary tract. After digital processing of computed tomography data and 3D-reconstruction of the upper urinary tract using the DICOM image processing program "RadiAnt DICOM Viewer," a visual assessment of the ureter was carried out to exclude significant deviations and strictures. The ureteral width was measured at three points: pyeloureteral junction, at the iliac vessel crossover and intramural part.

The number of cases of successful insertion of UAS and the rate of damage to the ureteral wall according to the classification proposed by O. Traxer and A. Thomas (2012) were analyzed. The prediction of successful insertion of a UAS was carried out using ROC analysis.

Results. In group 1, successful insertion of UAS was observed in 37 (46.8%) patients compared to 84 (83.2%) patients in group 2. In the remaining 42 (53.2%) and 17 (16.8%) cases, respectively, placement of UAS was not possible due to significant tissue resistance and high risk of traumatic injury. The average ureteral diameter at the points of physiological narrowing in patients with successful insertion of 12/14 Ch UAS were 2.0±0.1 mm, compared to 1.2±0.4 mm in those with failed insertion ($p<0.05$). In the group 2, similar indicators were 1.6±0.1 mm and 1.2±0.5 mm, respectively ($p<0.05$). According to ROC analysis, the diagnostic efficiency of the predictive model when using 12/14 Ch and 10/12 Ch UAS was confirmed by high AUC values (0.925 [95% CI 0.871-0.98] and 0.944 [95% CI 0.89=0.97], respectively). The total number of patients with ureteral injuries was 35 (44.3%) and 40 (39.6%) in groups with 12/14 Ch and 10/12 Ch UAS, respectively. At the same time, complications of the I degree were observed in 24 (30.4%) patients of the group 1 and in 31 (30.7%) patients of the group 2, while injuries of II degree were detected in 10 (12.7%) and 9 (8.9%) cases, respectively ($p>0.05$). Only in 1 (1.3%) patient, when 12/14 Ch UAS was inserted, grade III damage to the ureteral wall was determined.

Conclusion. The proposed technique for measuring the cross-section of the ureter allows to predict the successful insertion of UAS at the preoperative stage. The probability of successful passage of UAS of 10/12 and 12/14 Ch in patients with ureteral diameter in physiological narrowings of more than 1.6 mm and 2 mm, respectively, is 95%. An insertion of UAS is a safe procedure, and most complications are classified as grades I or II.

K e y w o r d s: *urolithiasis, ureteral access sheath, micropercutaneous nephrolithotomy, retrograde intrarenal surgery, ureteral dilatation, measurement of ureteral diameter*

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Introduction. Urinary stone disease is one of the most common urological diseases, and the proportion of patients with urolithiasis in specialized departments reaches 30–40% [1]. In recent decades there has been a rapid scientific and technological progress, which has led to the development and improvement of devices for intracorporeal lithotripsy, as well as endoscopic equipment for the removal of urinary stones [2, 3]. The current global trend in the surgical treatment is to reduce the proportion of extracorporeal shock-wave lithotripsy by increasing the number of endoscopic interventions, which have high efficiency, low rate of complications and provide a reduction in hospital stay due to the rapid recovery [4].

At the present stage, technological progress is aimed to improving flexible endoscopes and reducing the caliber

of instruments for percutaneous procedures, which led to the creation of disposable ureteroscopes and micro-nephroscope. The use of these modern instruments in the treatment of kidney stones involves the insertion of ureteral access sheath (UAS), which is necessary to maintain low intrapelvic pressure and optimal temperature of the irrigating fluid, as well as improve the elimination of fragments and ensure good visualization by increasing the transparency of the irrigation fluid. In addition to the positive effects, the placement of UAS also has negative consequences, which include the risk of damage to the ureteral wall and stricture formation [5–7].

The failure of insertion of UAS in an intact upper urinary tract varies in the range of 5.9–36.7% [8–11, 18, 26]. To increase the rate of successful placement, as well as to reduce the risk of complications, different techniques have been developed, mainly aimed at dilating the upper urinary tract before surgery. These include prestenting, oral administration of alpha-blockers, balloon and pharmacological dilatation of the ureter [12–15].

Currently, there are methods for measuring the ureteral diameter in the lower third in order to predict the outcome of treatment of vesicoureteral reflux [16, 17]. There are no technologies for reliably predicting the success of inserting UAS into an intact ureter.

Aim. To improve the results of treatment of patients with urolithiasis who underwent endoscopic interventions using UAS by developing a predictive model of dilation of the non-prestented ureter.

Materials and methods. The study design involved 180 patients with kidney stones up to 20 mm, who were treated at the Urology Clinic of the Military Medical Academy named after S.M. Kirov and included two stages, preoperative and intraoperative examination. The patients were divided into two groups. In the group 1 (n=79), 12/14 Ch UAS was used, while in group II (n=101) 10/12 Ch UAS was inserted.

In the first group, 48 (60.8%) patients underwent micropercutaneous nephrolithotomy (micro-PNL) and 31 (39.2%) retrograde intrarenal surgery (RIRS), compared to 42 (41.6%) and 59 (58.4%) patients, respectively, in group II. Patients of both subgroups had no differences in terms of gender, age, body mass index, number and stone size.

Inclusion criteria were age over 18 years, the presence of a kidney stone up to 20 mm, no history of ureteral stenting, previous surgery or taking alpha-blockers, and the presence of a glomerular filtration rate of more than 90 ml/min. The criteria for non-inclusion were pregnancy, acute infectious of the upper and lower urinary tract, lack of ipsilateral kidney function, coagulopathy, as well as an absence of the patient agreement to participate in the study.

At the preoperative stage, 60 minutes before the X-ray examination, the patient took 80 mg of furosemide orally once. Next, contrast-enhanced computed tomography of the abdominal and pelvic organs was performed using a standard technique on a Toshiba Aquilion 128 apparatus (Japan). The assessment of renal excretory function was carried out at the 7th minute. One of the necessary conditions was bladder filling before the patient had a physiological urge to void during a study. After digital conversion of obtained data and 3D-reconstruction of the upper urinary tract using the program "RadiAnt DICOM Viewer", a visual assessment of the ureter was performed

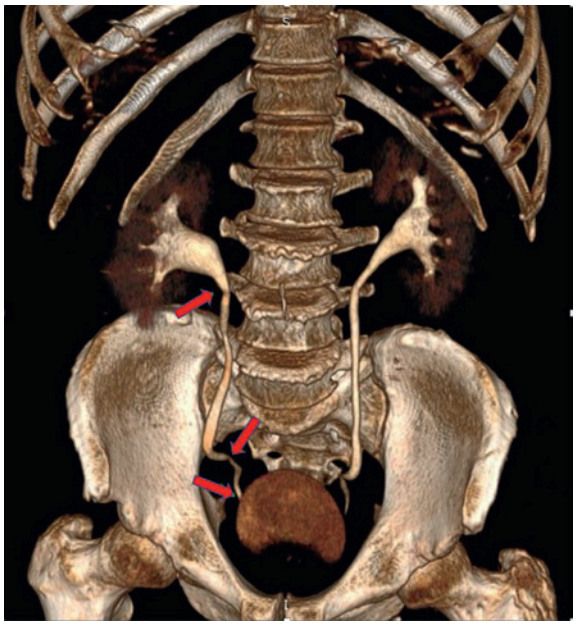

Fig. 1. Three-dimensional model created by computed tomography scan of the upper urinary tract (red arrows indicate the levels of measurement of the diameter in areas of physiological narrowings of the ureter)

to exclude significant deviations and strictures. Next, the ureteral diameter (dm) was measured at three points: in the pyeloureteral junction, at the iliac vessel crossover and in the vesicoureteric junction (*Fig. 1*). Forced diuresis while taking furosemide led to increased urine outflow from kidneys, which exceeded the ureteral capacity. As a result of tight filling, the contrast provided a clear image of the upper urinary tract, which allowed to take measurements in the narrowest points.

In order to standardize the technique, all patients underwent diagnostic ureteroscopy immediately before main procedure using a rigid ureteroscope 9.5 Ch. If it was not possible to examine the entire ureter with an endoscope due to its significant traction and high risk of trauma, an external 6 Ch ureteral catheter was put and micro-PNL was performed. In situations where ureteroscopy was performed without technical difficulties and the entire length of the ureter was accessible for inspection, UAS was inserted and RIRS or micro-PNL was done.

The number of cases of successful insertion of UAS was assessed, which meant its placement directly below the pyeloureteral junction for RIRS and in the pelvis for micro-PNL. The inability to introduce UAS to this level due to the significant tension and resistance was considered an unsuccessful attempt.

After surgery, all patients underwent ureteroscopy to diagnose ureteral lesions. The assessment of the ureteral trauma was determined according to the endoscopic classification (*Table I*), proposed by O. Traxer and A. Thomas in 2012 [19].

The prediction of successful insertion of UAS depending on the ureteral diameter in physiological narrowings was carried out using ROC analysis, which demonstrated the dependence of the number of correctly classified positive attempts on the number of incorrectly classified negative values. Reliability assessment was expressed

Table 1

Grade of ureteral injury

Grade	Injury
0	no lesion or only mucosal petechiae
I	mucosal erosion or a mucosal flap without smooth muscle injury
II	Injury to both the mucosa and smooth muscle while sparing the adventitia (no periureteral fat visualized)
III	ureteral perforation encompassing the full thickness of the ureteral wall, including the adventitia (periureteral fat is visualized)
IV	complete ureteral avulsion

in terms of sensitivity and specificity. Predictive ability was determined by area under the curves (AUC). It was believed that the closer the AUC value is to 1.0, the better the predictive ability of the model. In accordance with the expert scale, AUC results were considered excellent for AUC values between 0.9 and 1, very good for AUC values between 0.8 and 0.9, good for AUC values between 0.7 and 0.8, average for AUC values between 0.6 and 0.7, unsatisfactory for AUC values between 0.5 and 0.6. Quantitative data were described using arithmetic means and 95% confidence interval limits.

Results. At the stage of preoperative planning, a three-dimensional reconstruction of the urinary system allowed to measure the ureteral diameter at given points in all patients. It was established that of all physiological narrowings, the ureter has the greatest width in the pyeloureteral junction and in group I it was 3.04 ± 0.2 mm, compared to 2.9 ± 0.03 mm in group II. The smallest diameter was recorded in the juxtavesical region (1.9±0.06 vs. 1.84±0.7 mm, respectively) (*Table 2*). At the same time, there were no significant differences in the average values of dm between groups.

In group I (n=79), UAS was successfully inserted in 37 (46.8%), while in group II (n=101) in 84 (83.2%) patients (p<0.05). In the remaining 42 (53.2%) and 17 (16.8%) cases, respectively, placement of the 12/14 Ch and 10/12 Ch UAS was impossible due to significant tissue resistance and a high risk of trauma (*Table 3*).

At the same time, insertion of 12/14 Ch and 10/12 Ch UAS was the most commonly unsuccessful at the level of the juxtavesical region (23 [54.8%] vs. 9 [52.9%, respectively).

The efficiency of treatment did not depend on the diameter of UAS. Stone-free rate after micro-PNL using 12/14 Ch UAS was 87.3% (n=69), compared to 80.2% (n=81) in the group of 10/12 Ch (p>0. 05). The stone-free rate for RIRS in groups of 12/14 and 10/12 UAS also did not significantly differ (87.1 vs. 88.1%, respectively).

According to visual examination of the upper urinary tract after removal of UAS, the total number of ureteral injuries was 35 (44.3%) and 40 (39.6%), respectively, when using 12/14 Ch and 10/12 Ch UAS. At the same time, grade I complications were observed in 24 (30.4%) patients of the group 1 and in 31 (30.7%) patients of the group 2, while grade II trauma was detected in 10 (12.7%) and 9 (8.9 %) of patients, respectively (p>0.05). Only in 1 (1.3%) patient, when inserting 12/14 Ch UAS, damage to the mucous membrane with a smooth muscle layer and partial rupture of the adventitia, was found (grade III of complications).

ROC analysis is an objective graphical and mathematical method, which allows to clearly demonstrate the discriminative ability of the model. To determine the prognostic ability of quantitative indicator of dm for the possibility of placement of 12/14 Ch and 10/12 Ch UAS, ROC curves were used (*Fig. 2*).

In the first group, the AUC was 0.925 (95% CI: 0.871–0.98), and the significance level for the differences between the curve and the bisector did not exceed 5% (p<0.001), which indicated excellent predictive ability. The sensitivity and specificity of the predictive model for placement of 12/14 Ch UAS showed high sensitivity of 0.838 (95% CI: 0.689–0.923) and specificity of 0.89 (95% CI: 0.77–0.93), respectively. In the second group, the area under the ROC curve was 0.811 (95% CI: 0.661–0.96), and the significance level did not exceed 5% (p<0.001). Sensitivity was 0.833 (95% CI: 0.739–0.898) and specificity was 0.706 (95% CI: 0.496–0.867). The diagonal line corresponded to a "useless" classifier (AUC=0.5), i.e. complete indistinguishability of the two classes regarding the possibility and impossibility of UAS insertion. Thus, the diagnostic efficiency of the predictive model when using 12/14 Ch and 10/12 Ch UAS is confirmed by high AUC values of 0.925 (95% CI: 0.871–0.98) and 0.944 (95% CI: 0.89–0.97) respectively.

The separating value of the quantitative characteristic at the "cut-off point" was calculated based on the highest value of the Youden index. The determination of the optimal threshold was set according to the criterion of ensuring the minimum sensitivity of the test sensitivity

Table 2

Average values of ureteral diameter in physiological narrowings in both groups

Level of measurement of ureteral diameter	Average value of ureteral diameter in the study groups, mm		p
	I	II	
Pyeloureteral junction	3.04±0.2	2.9±0.03	0.648
The iliac vessel crossover	2.17±0.09	2.2±0.06	0.54
Vesicoureteric junction	1.9±0.06	1.84±0.7	0.48

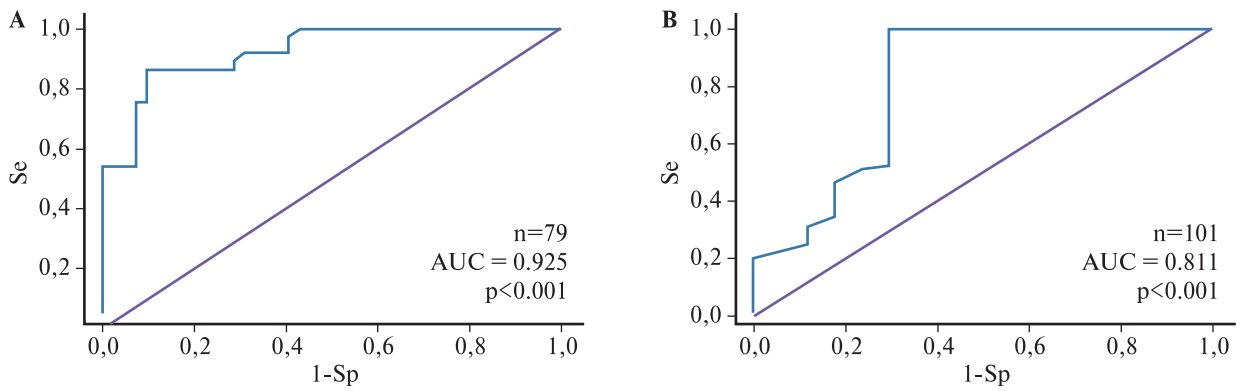

Fig. 2. ROC curves of dm for predicting the possibility of introducing a ureteral access sheath (a. for group I; b. for group II)

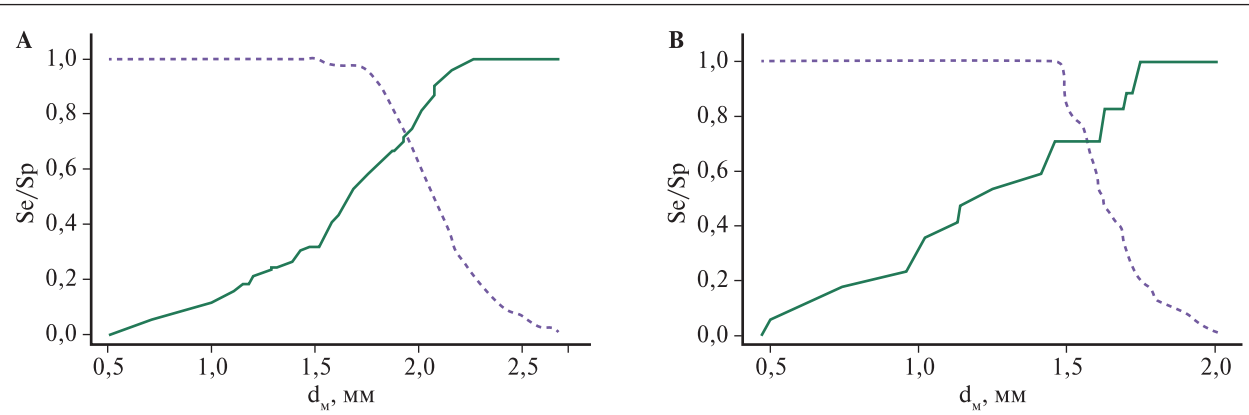

Fig. 3. Threshold "cut-off" for different diameters of the ureter in physiological narrowings (A – for group I; B – for group II)

⩾0.8. In the first group, the threshold value of dm at the "cut-off point" was 2 mm. As a result, the possibility of successful insertion of 12/14 Ch UAS was predicted with a ureteral diameter of ⩾2 mm at any level. In the second group, the threshold value of the dm indicator at the "cut-off point" was 1.6 mm, and a high probability of advancement of 10/12 Ch UAS was predicted when the ureter width was ⩾1.6 mm at each level (*Fig. 3*).

In the first group, the average ureteral diameter in areas of physiological narrowings with successful insertion of UAS was 2.0±0.1 mm, compared to 1.2±0.4 mm in those patients, in whom a placement of UAS was not possible ($p<0.05$). In the second group, similar indicators were observed with a dm value of 1.6±0.1 and 1.2±0.5 mm, respectively (*Fig. 4*).

Discussion. Different publications confirm that the use of UAS reduces intrapelvic pressure, the risk of infectious complications, as well as the temperature of the irrigation fluid by increasing outflow. Data on the impact of the outflow on the intensity of postoperative pain syndrome and the likelihood of developing ureteral strictures are contradictory [19, 21, 22].

Published data indicate the impossibility of placement UAS into a prestented ureter in 1.5–6.2% of cases [11, 26, 26]. In our study, UAS was inserted into the intact ureter after preliminary determination of its patency using a ureteroscope, without any dilating techniques.

Prestenting for at least 1 week improves the probability of UAS placement. Despite numerous reports of the beneficial effects of preoperative administration of alpha-blockers, the data remain conflicting. All these

Table 3

Number of unsuccessful placements of ureteral access sheath

Level in the ureter	Number of cases in two groups of patients, *n* (%)		*p*
	Group I (12/14 Ch)	Group II (10/12 Ch)	
Pyeloureteral junction	4 (9.5)	1 (5.9)	0.095
The iliac vessel crossover	15 (35.7)	7 (41.2)	0.251
Vesicoureteric junction	23 (54.8)	9 (52.9)	0.64
Total	42 (100)	17 (100)	

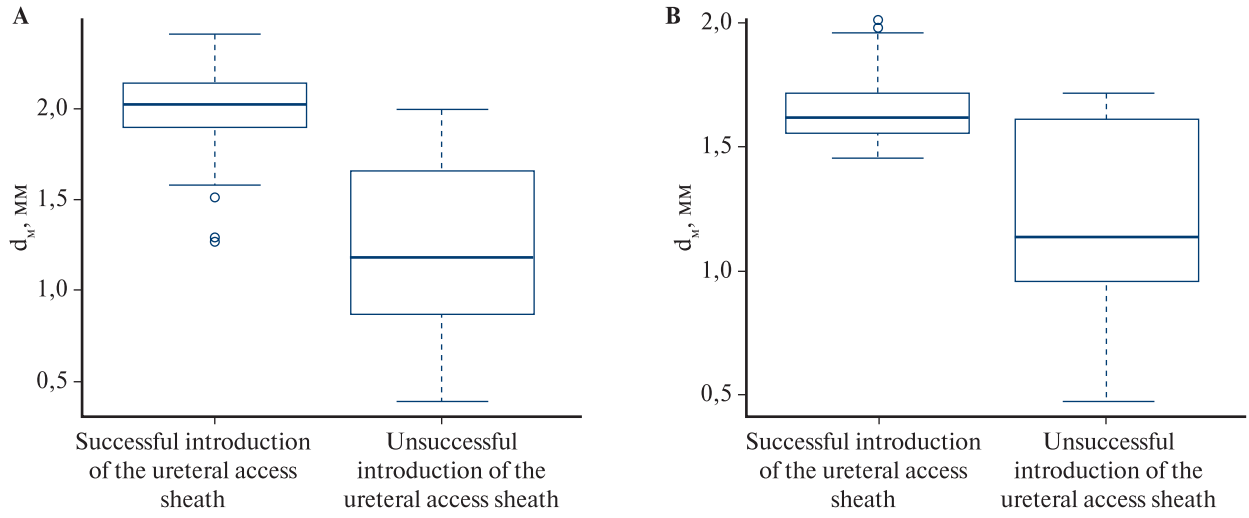

Fig. 4. Dependence of the introduction of the ureteral access sheath on the ureteral diameter (A – for group I; B – for group II)

discrepancies can largely be explained by the high risk of bias [12, 13, 23, 24].

The issue of the efficiency of using UAS of different diameters remains debatable. In accordance with a few publications, it has been established that smaller UAS (<12/14 Ch) reduce the risk of damage to the ureteral wall, and larger ones (⩾12/14 Ch) improve the surgical outcomes [6, 25].

Currently, there are no simple and accessible methods for non-invasively measuring the degree of ureteral dilation before inserting UAS.

In published literature there are references to various methods for studying ureteral diameter and different coefficients. M. Hellström et al. (1986) first proposed using the ureteral size based on determining its diameter in lower third in order to predict the results of treatment of vesiureteral reflux in children [16]. In 2016, B. M. Lolaeva et al. improved the method by developing its expansion coefficient to evaluate the results of surgical and endoscopic treatment of obstructive megaureter [17]. A distinctive feature of these methods was the measurement of the ureteral diameter at only one level and the subsequent calculation of the author's coefficients with reference to anatomical landmarks. The most modern method of measuring the ureteral diameter in order to reduce the risk of injury was proposed by J. Fulla et al. (2021). It is based on the study of non-contrast computed tomography. The lack of the excretory phase was a negative aspect of this technique, since it did not allow assessing important factors influencing the insertion of UAS, including deviations, pathological narrowing, as well as the ability of the ureter to expand [18]. In contrast, our method for predicting the degree of ureteral dilation is devoid of these disadvantages and has a high diagnostic potential when planning surgical intervention on the upper urinary tract.

Conclusion. Measuring the ureteral cross-section at the level of physiological narrowings using the proposed method allows to predict the possibility of free placement of UAS at the preoperative stage. The probability of successful placement of 10/12 Ch and 12/14 Ch UAS with ureteral diameter in physiological narrowings of more than 1.6 and 2 mm, respectively, is 95%. A placement of UAS is a safe procedure, and most complications include ureteral damage of I or II degrees.

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ONCOLOGICAL RESULTS OF REPEAT PARTIAL NEPHRECTOMY IN PATIENTS WITH RECURRENCE AFTER NEPHRON-SPARING PROCEDURES

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Aim. To carried out a comparative analysis of the risk of complications and oncological results of repeat partial nephrectomy and radical nephrectomy in patients with local recurrence after previous organ-sparing procedures.

Materials and methods. Retrospective and prospective data of 64 patients with local recurrence of kidney cancer after nephron-sparing procedures. who underwent surgical treatment in the department of oncourology of the National Medical Research Center of Oncology named after N.N. Blokhin in the period from 2000 to 2022. A total of 37 (57.8%) patients of the main group underwent repeat partial nephrectomy, while in 27 (42.2%) patients in the control group a radical nephrectomy was done. Median follow-up was 35 (3–131; Q1–Q3: 13–57) months. Both groups were comparable in terms of demographic and clinical characteristics (p>0.05). The median time to detect relapse after previous partial nephrectomy was 24 (2–172) months.

Results. Complications were noted in 8 (21.6%) patients after repeat partial nephrectomy, compared to 29.6% in the control group (n=8) (p=0.563). A comparative analysis revealed a significant advantage in overall survival in patients of the main group (p=0.042). There were no significant differences between groups in cancer-specific and disease-free survival (p=0.369 and p=0.537, respectively).

Conclusion. Repeat partial nephrectomy for local recurrence of kidney cancer leads to an increase in overall survival compared to radical nephrectomy, in the absence of significant differences in cancer-specific and relapse-free survival.

K e y w o r d s: *kidney cancer, repeat partial nephrectomy, relapse, partial nephrectomy, nephron-sparing procedure*

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Introduction. Currently, partial nephrectomy (PN) is the preferred treatment method for clinically localized renal cell carcinoma [1]. In modern oncourology, organ-preserving procedures are applicable even for more complex and larger and, therefore, potentially more aggressive tumors [2]. A consequence of the widespread use of nephron-sparing surgery (NSS) is an increase in the number of local recurrences in the kidney, which are excluded during radical nephrectomy (RN) [3–5].

Management of local recurrence after PN can be a clinically challenging situation. Only a few studies have specifically dedicated to oncologic and functional outcomes, and published data are limited [6]. Treatment options for relapses after PN include various ablative interventions (eg, cryotherapy or radiofrequency ablation) or RN. However, in other cases, repeat PN may be the most appropriate procedure [6, 7].

Aim. To carry out a comparative analysis of the risk of complications and oncological outcomes of repeat PN and RN in patients with local recurrence after previous NSS.

Materials and methods. In the department of oncourology of the National Medical Research Center of Oncology named after. N. N. Blokhin, 64 patients with local recurrence of renal cell cancer after NSS underwent surgical treatment from 2000 to 2022.

Thirty-seven (57.8%) patients in the main group underwent repeat PN, while in the control group, 27 (42.2%) RNs were done. Median follow-up was 35 months (3–131; Q1–Q3: 13–57). In the study group, the median age was 59 years (27–73; 95% CI/Q1–Q3: 52–65). There were 26 men and 11 women (ratio 2.4:1). Primary nephron-sparing surgery was performed at the National Medical Research Center of Oncology named after N.N. Blokhin in 12 (32.4%) cases, and in other

clinics in 25 (67.6%) patients. Histological type of tumors during primary PN was clear cell renal cell carcinoma in 30 (81.1%), papillary renal cell carcinoma in 4 (10.8%), and chromophobe renal cell carcinoma in 1 (2.7%) case. In 2 (5.4%) patients, there were no results of histological examination. Tumor grade (G) according to Fuhrman [8] was as following: G1 in 4 (10.8%), G2 in 26 (70.3%), G3 in 1 (2.7%) patient, and no data in 6 (16.2%) cases.

The median period for detecting relapse after primary PN was 24 (2–172) months. The median RENAL score [9] was 8. Recurrence in the right kidney was diagnosed in 45.9%, while the left kidney in 55.6%. In 18 (48.6%) cases the tumor was located in the middle pole, while in 9 (24.3%) and 10 (2.7%) patients the upper- and lower-pole lesions were present, respectively. The median largest tumor size at re-PN was 2.5 cm (1-6; 95% CI/Q1-Q3: 2-3). Primary multiple malignant tumors were identified in 12 (32.4%) cases, including 10 (27%) bilateral tumors, while 7 (18.9%) patients had a single kidney after previous RN. One patient had agenesis of the contralateral kidney. Average body mass index was 31±6 (21–47). The functional state of patients according to the ECOG score was 0 (n=24; 64.9%) and 1 point (n=13; 35.1%).

In 73% of cases, patients did not have any complaints. One (2.7%) patient had an episode of hematuria, 5.4% complained of moderate weakness and shortness of breath. Taking into account the presence of a kidney tumor, a diagnosis chronic kidney disease was established in all patients according to the Kidney Disease Improving Global Outcomes (KDIGO) guideline [10], with a significant decrease in GFR (<60 ml/min/ 1.73 m^2, which corresponds to CKD>stage II), in 12 (32.4%) cases. In addition, CKD of stage IV was detected in 1 (2.7%) patient. The average glomerular filtration rate in the main group was 69±25 ml/min/1.73 m^2.

In the control group, twenty-seven patients with local recurrence after previous PN underwent RN. Both groups were comparable in the gender, age, time interval from primary PN to diagnosis of recurrence, side of the affected kidney, histological type and grade of the tumor during the first procedure, the presence of concomitant diseases, ECOG status, renal function, and body mass index (Table 1). A significant difference (p=0.012) was found in the median largest tumor diameter, which was 2.5 cm in the re-PN group and 3.0 cm in the control group (95% CI/Q1–Q3: 2.0–3.0 and 2.4–4.0 cm, respectively). This difference, in our opinion, was not clinically significant.

Table 1

Comparative characteristics of patients undergoing to repeated PN and RN

	Characteristic	Re-PN	RN	p
Gender	Men	26 (70.3)	17 (63.0)	0.539
	Women	11 (29.7)	10 (37.0)	
Age, Median	years	59	62	0.282
Age⩾60	years	17 (45.9)	15 (55.6)	0.448
Time interval from primary PN to progression	months	24	35	0.719
Double primary tumors	Presence	12 (32.4)	7 (25.9)	0.574
Affected side	Right	17 (45.9)	14 (51.9)	0.641
	Left	20 (54.1)	13 (48.1)	
RENAL	Points	8	8	0.348
Tumor diameter, median	cm	2.5	3.0	0.012
Localization of the tumor in the kidney	Upper	9 (24.3)	8 (29.6)	0.295
	Middle	18 (48.6)	16 (59.3)	
	Lower	10 (27.0)	3 (11.1)	
Access	Laparotomy (subcostal)	30 (81.1)	24 (88.9)	0.498
	Laparoscopic	7 (18.9)	3 (11.1)	
Histological type of the tumor during primary PN	Clear cell renal cell carcinoma	30 (85.7)	25 (92.6)	0.351
	Papillary renal cell carcinoma	4 (11.4)	1 (3.7)	
	Chromophobe renal cell carcinoma	1 (2.9)	0 (0.0)	
	Malignant epithelioid angiomyolipoma	0 (0.0)	1 (3.7)	
Grade (G) of primary tumor	no data	6 (16.2)	1 (3.7)	0.304
	1	4 (10.8)	5 (18.5)	
	2	26 (70.3)	19 (70.4)	
	3	1 (2.7)	2 (7.4)	
ECOG	0	23 (62.2)	12 (44.4)	0.359
	1	12 (32.4)	11 (40.7)	
	2	2 (5.4)	3 (11.1)	
	3	0 (0.0)	1 (3.7)	
Stage of CKD before treatment according to KDOQI classifications	1	7 (18.9)	4 (14.8)	0.765
	2	18 (48.6)	11 (40.7)	
	3a	7 (18.9)	8 (29.6)	
	3b	5 (13.5)	4 (14.8)	
Single kidney		7 (18.9%)	2 (7.4)	0.282
GFR by CKD-EPI before treatment	ml/min/1.73 m^2	69±25	69±23	0.934

Results. The median duration of repeat PN was 150 minutes, compared to 130 for RN (p=0.243). The median volume of blood loss in the main group was 500 ml, in RN group 400 ml (p=0.477).

Complications after repeat PN were noted in 8 (21.6%) patients, with the same number in the control group (29.6%) (p=0.563). Complications of grades I and II according to the Clavien–Dindo classification [10] amounted to 18.9% after repeat PN and 25.9% after RN, and complications of grade III were observed in 2.7 and 3.7%, respectively (p=0.630). There were no grade IV or V complications.

A comparative analysis of the histological type of tumors after re-PN and RN showed clear cell renal cell carcinoma in 34 (91.9%) and 24 (88.9%), papillary renal cell carcinoma in 2 (5.4 %) and 1 (3.7%), translocation renal cell carcinoma in 0 and 1 (3.7%), and chromophobe renal cell carcinoma in 1 (2.7%) and 1 (3.7%), respectively. This difference was not significant (p=0.675). The tumor grade according to Fuhrman was as follows: G1 in 19.4%, G2 in 70.3%, G3 in 10.8% in PN group, compared to G1 in 11.1%, G2 in 55.6%, and G3 in 10.8% of cases in RN group (p=0.081).

In 8 (21.6%) cases after PN, the second recurrence was detected, of which 3 (8.1%) patients had second local relapse, while in 5 (13.5%) both local relapse and distant metastases developed. The average time for second relapses in this group was 21.5 (6–57) months. For isolated local relapses, 3 (8.1%) patients underwent surgical treatment including RN. When distant metastases were diagnosed in combination with local recurrence in the kidney, systemic therapy was prescribed; in 1 (2.7%) observation, palliative nephrectomy was performed due to ongoing gross hematuria with further recommendation for drug therapy.

In the control group, local recurrence was defined as a tumor not originating from other organs in the kidney fossa. In 1 (3.7%) case, an isolated tumor was detected and removed 20 months after RN. In 3.7% of cases, a local recurrence was diagnosed with invasion into the ipsilateral adrenal gland, as well as with metastasis to the retroperitoneal lymph nodes. Surgical treatment consisted of removal of the tumor, adrenalectomy and retroperitoneal lymphadenectomy. In 7.4%, relapse manifested with distant metastases without the development of a tumor in the kidney fossa. In 1 (3.7%) patient, metastases in the T1-2 causing neurological symptoms were identified, which were resolved after decompressive laminectomy. Pathomorphological study confirmed a metastasis of clear cell kidney cancer. In 3.7%, metastasis to the ovary was detected 11 months after RN, for which adnexectomy was performed. In this patient, lung metastases were diagnosed after 14 months, requiring targeted antiangiogenic therapy. A stabilization of disease was achieved.

The median follow-up of patients undergoing repeat PN was 35 (3–131) months. From them, 34 (91.9%) are still alive, including 29 (78.4%) without manifestations of the disease and 5 (13.5%) with signs of metastasis. In addition, 3 (8.1%) patients died, including 2 (5.4%) from progression of kidney cancer, 1 (2.7%) from other causes. In the RN group, the median follow-up was 37 months. 19 (70.4%) patients are alive, including 18 (66.7%) without signs of relapse, 1 (3.7%) with metastases. Three patients (11.1%) died from progression of kidney cancer, 5 (18.5%) from other causes.

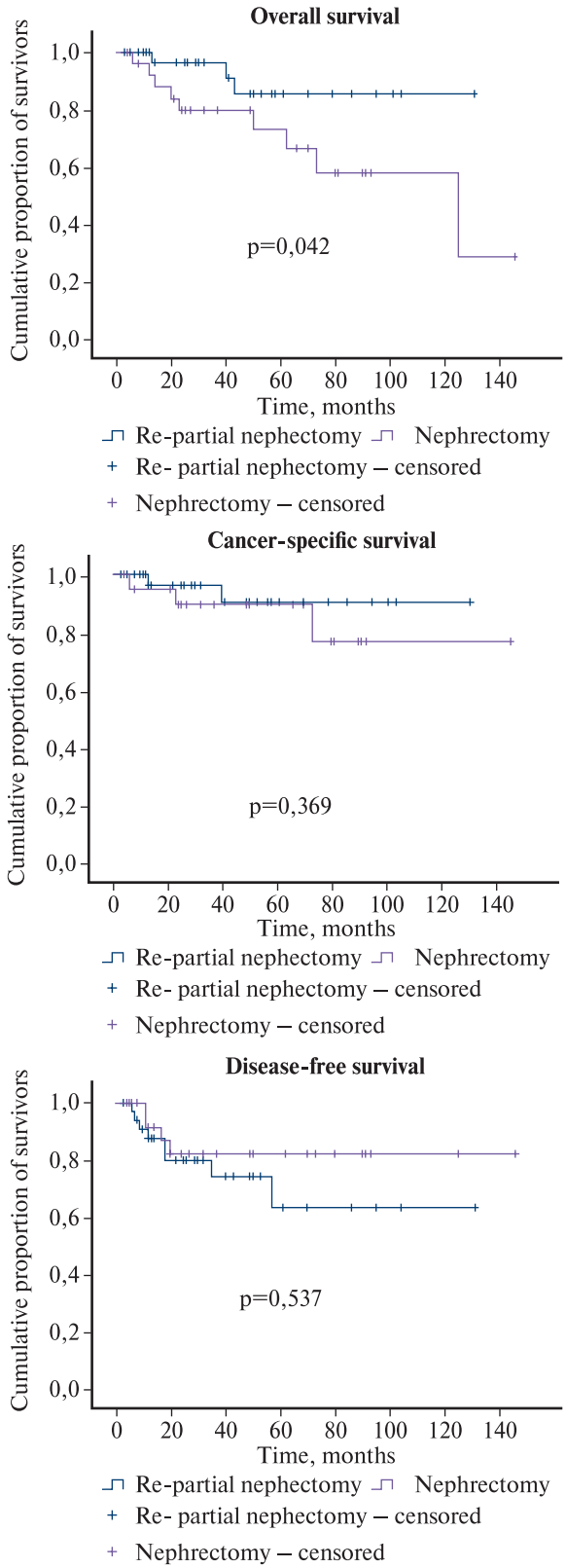

Fig. Survival rate of patients with recurrent kidney cancer after previously undergoing organ-preserving surgery, undergoing repeated resection and radical nephrectomy (Kaplan-Meyer)

A comparative analysis revealed a significantly better overall survival in the main group in (p=0.042). There were no significant differences between groups in cancer-

Table 2

Survival of patients with recurrent kidney cancer after previous organ-preserving surgical treatment undergoing undergoing to repeated PN and RN

Three-year survival rate	Re-PN, %	RN, %	*p*
Overall	91.9	70.4	0.042*
Cancer-specific	94.4	87.0	0.369
Disease-free	78.4	85.2	0.537

specific and relapse-free survival (p=0.369 and p=0.537, respectively) (see *figure, 2*).

Discussion. Management of local recurrence of renal cell cancer after NSS is a clinically challenging situation. The literature does not report a standard strategy for patients with local recurrence after PN [11]. Although RN is traditionally considered standard option, in the case of recurrence, repeat PN may still be a preferable alternative as it maximizes the preservation of renal function, which in turn may affect overall survival [12]. This also fits favorably with the concept that the majority of so-called renal recurrences are associated with the multifocality and bilateral nature of the kidney cancer, further supporting the role of NSS [13].

There are few data in the literature on the safety and oncological outcomes of repeat RP in patients with sporadic renal cell carcinoma. We present our experience in a comparative study of repeat PN and RN as a treatment option for patients with recurrent tumors after primary PN.

To prove the safety and feasibility of PN, we analyzed data on complications and oncological outcomes of repeat PN and RN. In the re-PN group, complications were observed in 21.6%, while in the RN group in 29.6% (p=0.563) of cases. Although this difference was non-significant, the incidence of complications in the re-PN group was lower, demonstrating safety of the technique.

There are only a few studies examining the use of NSS in patients with a recurrence after PN.

Magera et al. [14] performed 22 repeat PN in 18 patients. Primary and repeat interventions were done via an open access. In this study, the results of repeat PN (group 2) were compared with results after primary NSS (group 1) in the same patients. 8 (44%) of 18 patients had cancer of the solitary kidney at the time of primary procedure and 12 (67%) at the time of repeat PN. Von Hippel–Lindau disease was reported in 7 (39%) of 18 patients and 10 (45%) of 22 kidneys. The average time between the first and second interventions was 3.9 years (range 0.4 to 13.7 years). The mean time between the second PN and the last follow-up was 8.1 years (range 1.8 to 16.2). Preoperative clinical and postoperative pathological characteristics were similar between groups. Complications occurred in 7 (39%) of 18 patients in the main group, and in 5 (28%) patients in the control group. This fact is associated with more complex dissection during re-PN due to changes in anatomy and perinephric scarring. 5-year overall and cancer-specific survival rates after repeat PN were 71 and 83%, respectively.

K. Yoshida [15] et al. compared the results of repeat PN (n=11) and primary PN (n=68) in 79 patients with a solitary kidney. In the re-PN group, there was smaller tumor size (p=0.0432), longer operative time (p=0.0432) and higher blood loss (p=0.0002). However, there were no significant differences in hemodialysis-free (p=0.7392) and disease-free survival (p=0.4924). According to the authors' conclusions, the oncological and functional outcomes of primary and repeat PN did not differ significantly [15].

A recent prospective multicenter study by Okhawere [16] included 58 patients with recurrent kidney cancer after PN. Of these, 22 (38%) underwent robot-assisted radical nephrectomy (RARN), while in 36 (62%) cases robot-assisted partial nephrectomy (RAPN) was done. One intraoperative complication was seen with RARN, compared to three complications in RAPN group (p=1,000). In 5% of cases after RARN, a recurrence was diagnosed, while after RARP recurrence rate was 3%. RARN and RAPN have similar operative and perioperative outcomes. The authors noted that RAPN for local recurrence is a safe and feasible procedure if surgeon has an appropriate experience [16].

A. Johnson et al. [12], presented results of a study of 51 cases of repeat PN in 47 patients with recurrent kidney cancer. In 48 (94%) cases, von Hippel–Lindau syndrome was diagnosed. Complications or reoperations occurred in 10 of 51 (19.6%) cases, which is higher than in patients undergoing PN for the first time. The authors noted that PN was technically feasible and was especially relevant for patients at risk of developing multiple bilateral, synchronous and metachronous tumors, as well as in those with a single functioning kidney. It should be noted that in this study the overall survival rate was 100% with a median follow-up of 56 months [12].

Our study showed the safety and feasibility of PN in patients with local recurrence of kidney cancer after previous NSS. Complications, cancer-specific, disease-free survival in the re-PN group were comparable to those in the RN group, as well as with published data. Meanwhile, overall survival was significantly higher after repeated PN compared to RN, which may be a consequence of improved cardiac-specific survival in patients with better renal function, as mentioned in a number of publications [11–16].

Conclusion. Repeat PN for local recurrence of kidney cancer may improve overall survival compared with RN with equivalent disease-free survival. Analysis of a larger cohort of patients will clarify this question in the future.

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CLINICAL CASE

УДК 616.66-001

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CLINICAL CASE OF PENILE FRACTURE

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A clinical case of a penile fracture as a result of an unsuccessful sexual intercourse, which later required surgical treatment in the form of corporoplasty with opening and draining of the hematoma, is discussed in the article. Penile fracture is a rare urological emergency that requires immediate medical attention to avoid long-term complications, including penile curvature and erectile dysfunction.

K e y w o r d s: *penile fracture, sexual trauma, hematoma, surgical intervention, erectile dysfunction, penile curvature*

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Penile fracture is a urological emergency characterized by unilateral or bilateral rupture of the tunica albuginea and cavernous bodies of the penis. This is a rare condition that predominantly occurs as a result of traumatic flexion of the erect penis, mainly during sexual (intercourse and masturbation) and non-sexual activity (penile manipulation, rolling over in bed injury, the practice "tagaandan", blunt trauma), and less commonly due to injury, for example, from a direct blow with a hard object.

Penile fractures are usually accompanied by severe pain and a cracking sound, immediate loss of erection, curvature, swelling, and hematoma. During erection, the cavernous bodies are tightly filled with blood, and the thickness of the tunica albuginea of the cavernous bodies decreases from 2 to 0.25 mm, which leads to easy rupture with minor physical impact.

In most cases, the diagnosis is made clinically, but in equivocal cases, imaging tests (e.g., ultrasound [US], magnetic resonance imaging [MRI]) may be required. Retrograde urethrography is recommended in all patients with confirmed penile fracture to exclude concomitant urethral injury.

Complications can be very diverse, including secondary infection, abscess formation, urethral rupture, penile deformation, which prevents sexual activity, and/or erectile dysfunction of varying severity, from mild to complete absence.

The problem of penile fracture and its consequences is a rather rare, which explains the small number of studies in the Russian literature. Certain questions were reflected in the foreign publications. There is a fairly extensive description of identical clinical cases, some points of which should be discussed in more detail.

According to modern data, the vast majority of penile fractures occur during sexual intercourse. In a study by R. Barros et al. 288 observations of penile fracture were reviewed, of which in 88.5% the main etiological factor was sexual trauma [1]. According to another study, this figure was slightly lower and amounted to 76.5% (69/90) [2] (Table 1).

After analyzing the information from these studies, we can conclude that the most highly traumatic position is the "doggy style", and the least traumatic is the "woman on top". Penile injury occurs in adult men, with an average age of 38–39 years. Accordingly, in order to avoid penile fracture, it is recommended to use positions with the lowest risk of injury.

J. Ory and G. Bailly independently studied the mechanism of injury. The erect penis comes out of the vagina and does not go back in properly, buckling as the pelvis moves forward, resulting in injury [3].

Non-sexual causes of penile trauma include masturbation, rolling over in bed injury with spontaneous nocturnal erections, and the Middle Eastern practice "tagaandan", which is forceful bending of the erect penis to achieve detumescence. The most common symptoms, the so-called triad, are presented in Table 2.

Urethral rupture is a rare condition, mostly associated with high-energy trauma. There are 14 cases described in the literature, where 11 were with partial and 3 with complete rupture of the urethra [10]. In the study of R. Barros et al. urethral rupture was observed in 18.7% of cases, of which 13.5% of patients had a partial rupture, and 5.2% had a complete rupture. Authors observed the following relationship: high-energy trauma leads to bilateral damage to the cavernous bodies, which in turn is complicated by complete rupture of the urethra.

Our clinical case, which will be presented below, is characterized by a unilateral fracture of the corpus cavernosum, which corresponds to the vast majority of similar observations, occurring in 69% of patients, while a bilateral fracture is seen in 31%.

Table 1

The most common causes of penile fracture according to the literature [1, 2]

Study	R. Barros et al., 2020 [1]	R. Barros et al., 2017 [2]
Total number of cases	288	90
Average age, years	38.2 (18–66)	39 (18–66)
	Etiology (%)	
Sexual intercourse, positions:	255 (88.5)	69(76.8)
- "doggy style"	110 (43.1)	37 (53.6)
- "man on top"	103 (40.3)	23 (33.3)
- "woman on top"	31(12.1)	9 (13.1)
- other	11 (4.3)	–
Masturbation	9 (3.1)	–
Penile manipulation	18 (6.3)	16 (17.7)
Rolling over in bed injury	1 (0.3)	3 (3.3)
No data on the mechanism of injury	5 (1.7)	–
Blunt trauma	–	2 (2.2)

R. Barros et al. believe that the typical manifestations do not require additional examinations. The diagnosis is established clinically. However, in doubtful cases, additional examination methods such as US and MRI must be used to confirm the diagnosis [6].

J. Ory and G. Bailly indicate that 36 hours after penile injury, MRI is the preferred image method. One cannot but agree with this approach, since MRI shows a higher quality of visualization [3]. Retrograde urethrography is performed when urethral injury is suspected [1], although some studies indicate that it may produce false-negative results in 28.5% of cases [7]. Most authors agree that in case of a penile fracture, it is necessary to perform emergent surgical treatment [1–5], which is demonstrated in our observation.

J. Ory and G. Bailly emphasize, that if the clinical manifestations indicate penile fracture, then surgical intervention should be immediate. A delay may be only in case of a questionable diagnosis, but provided that additional examination can be carried out quickly. Early surgery (within 24 hours) resulted in a complication rate of only 7.6% compared with 68.7% for later surgery (within 24 hours to 4 days) [3]. Therefore, the British Association of Urological Surgeons recommends to perform repair within the first 24 hours.

Recurrent fracture is extremely rare. In the foreign literature, only 7 cases are described in which patients received re-injury with an interval of 90 days to 9 years, and only in 2 cases, the cause of repeat fracture was sexual activity [8].

In a study by R. Barros et al., postoperative complications, sexual and urinary function were assessed. Among the complications, 9 (14.7%) patients had erectile dysfunction, and in 8 (13.1%) penile curvature was developed [1]. Zargooshi, assessing long-term complications in 352 patients, found only 8 people with complaints of premature ejaculation, erectile dysfunction, decreased libido, and family conflicts [9]. El Atat et al. described 300 cases and recorded complications in 40 (13.3%) patients, of whom 14 (23.3%) developed penile curvature and 2 (0.6%) had erectile dysfunction.

A description of a clinical case

A 50-year-old patient had a trauma during sexual intercourse. The first aid was provided by himself, including application of ice and a tight bandage, after that he arrived at the emergency room at "City Hospital No. 1". After examination he was hospitalized in the uroandrology department.

History of trauma: the injury was received during sexual intercourse with his wife in the "woman on top" position. They did not notice any blood in the urine. Upon admission of the patient to a hospital, there were complaints of acute pain in the groin area. A "cracking sound" was noticed. The penis had a dark purple color.

Medical history: hypothyroidism, chronic cholecystitis and pancreatitis. Patient had an allergic reaction to wormwood, manifesting by hives. Bad habits included smoking, frequent drinking of alcohol (at least 1-2 times a week, about 300-500 ml of a 40-degree drink over the past 15 years). He had hemorrhoidectomy 11 years ago. No pathological changes were observed in other organs and systems.

Examination and palpation: the external genitalia were developed according to age. Status localis: the penis was

Table 2

The most common symptoms of penile fracture [1, 2]

Symptoms	Number of examined patients	Proportion of symptoms in the total number of cases, %
Hematoma	288	100.0
Penile detumescence	238	82.6
"Cracking sound"	220	76.3
"Eggplant deformity"	200	69.4
Acute pain	191	66.3
Urethral bleeding	37	12.8
Acute urinary retention	1	0.3

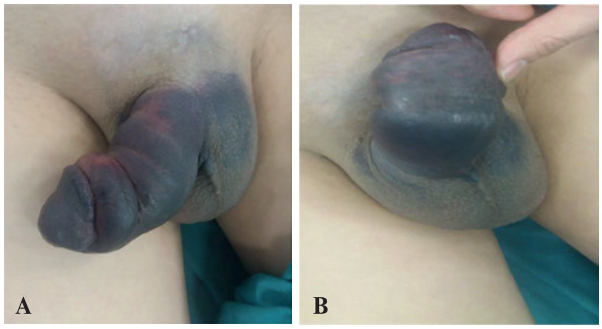

Fig. 1. Features of fracture before surgery
A – lateral view; B – frontal view.

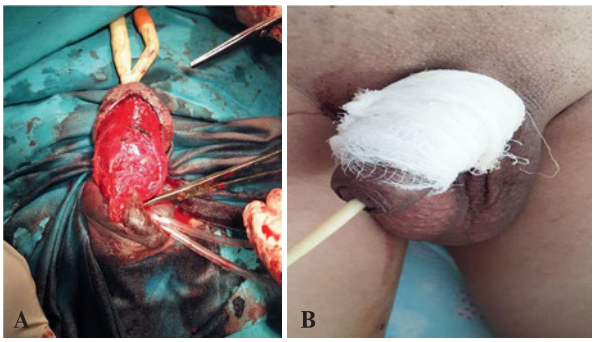

Fig. 2. Surgical reconstruction
A – intraoperative view; B – dressing after reconstruction

swollen, had a dark purple color, the deviation to the left from the central axis by 45 degrees was visually determined. On the right, at the level of the lower third of the penile shaft, a hematoma was observed in a form of swollen area 6x5 cm of dark bluish color. The scrotum was swollen, painful on palpation, the testicles were unremarkable and difficult to palpate (Fig. 1: A, B).

Laboratory tests, including complete blood count blood, urinalysis, biochemical profile and coagulation test were within normative values. On US, rupture of the tunica albuginea with unilateral damage of the right corpus cavernosum was found, however, urethral trauma was excluded.

A clinical diagnosis of penile fracture without urethral rupture was made.

Management: emergency hospitalization (according to the guidelines of the British Association of Urological Surgeons, which recommend repair within the first 24 hours).

Surgical treatment was performed under spinal anesthesia. A corporoplasty with opening and draining of the penile hematoma was done. After positioning the patient, the surgical field was painted three times with alcohol. Under spinal anesthesia, a circular (subcoronal) incision was made in the skin of the penis 1 cm downward from the coronary sulcus, after which it was retracted to the base of the penis. There was a 6x5 cm hematoma in the lower third of the right cavernous body. The Buck's fascia of the penis was dissected in this area, exposing the tunica albuginea. A total of 40 ml of blood with clots were evacuated. Further, a cavity was rinsed with a 3% solution of hydrogen peroxide. Upon further inspection, an area of 0.5–0.6 cm rupture of the tunica albuginea and the corpus cavernosum on the right was found. The edges of the wound were sutured with vicryl. Hemostasis was checked (Fig. 2A). Buck's fascia and the superficial fascia of the penis were sutured with vicryl. The penile skin was returned towards the glans. The skin was sutured with interrupted sutures. A compressive bandage was applied (Fig. 2B).

The Foley catheter was removed after 3 days. Further, urination was painful, but without difficulties. In the postoperative period, Bruzepami 10 mg IM was prescribed to prevent erection. Next dress changing was done after 7 days. Ketorol was prescribed for 3 days. Antibacterial therapy included ceftriaxone 1 g BID for 7 days. Strict restriction of sexual activity was recommended for 1 month. After 3 months the International Index of Erectile Function-5 score was 26 points (no erectile dysfunction). No postoperative complications were observed (Fig. 3).

Fig. 3. Penis after surgical treatment
A – after 2 months, B – after 3 months.

Currently, surgical management of patients with penile fracture is the most relevant, which is confirmed by the described clinical case. The AUA (American Urology Association) also recommends surgical treatment to preserve penile function. Diagnosis should be based on MRI or US.

The EAU (European Association of Urology) guidelines are somewhat different from the AUA. The EAU suggests urinalysis in all patients with genital trauma, and any amount of micro- or gross hematuria should be an indication for retrograde urethrography. Among the diagnostic methods, most urologists often perform cystoscopy and additionally US. MRI or cavernosography can be done only if the diagnosis cannot be established clinically.

The EAU guidelines also emphasize that simple penile hematomas that are not associated with severe detumescence are usually easily diagnosed and can be treated with nonsteroidal anti-inflammatory drugs and ice.

According to the EAU guidelines, early intervention (<24 hours from injury) resulted in a complication rate of 7.6% compared with 68.7% with later procedure, and the rate of erectile dysfunction was only 1.3%. Conversely, conservative management is associated with erectile dysfunction in 62% cases [13].

Penile fracture is an acute urological emergency and requires immediate surgical treatment to avoid long-term complications, including penile curvature and erectile dysfunction. In our opinion, to prevent long-term complications, it is necessary to perform emergency intervention.

According to most studies, the diagnosis of penile fracture can only be made based on the typical clinical manifestations. However, we believe that US or MRI allows to confirm the diagnosis, localize the site of rupture of the tunica albuginea and exclude the damage to the urethra.

The etiology of penile fracture is mainly due to sexual activity and, to a lesser extent, other causes. Repeated fracture rarely occurs. The most "dangerous" positions are "doggy style", "woman on top", "man on top". The more high-energy the injury, the more severe bilateral cavernous damage develops. Timely hospitalization and surgical intervention within the first 24 hours is associated with a low level of postoperative complications, allowing men to return to a full sexual activity.

Regardless of the type of penile injury, surgical treatment has the same goals:

- restoration of the anatomical structure,
- prevention of erectile dysfunction and penile curvature;
- maintaining the penile length and normal urination.

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LITERATURE REVIEWS

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ROBOT-ASSISTED PROSTATECTOMY FOR PT3. ONCOLOGICAL AND FUNCTIONAL OUTCOMES

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In 2020, prostate cancer (PCa) ranked third in the structure of the most significant oncological diseases. In the Russian Federation, in terms of the frequency of detection among men, prostate cancer is second only to tumors of the upper respiratory tract and lungs, accounting for 14.9%. Radical prostatectomy (RP) in various modifications is still the most common treatment for localized prostate cancer, despite the existence of alternatives such as active surveillance, hormonal and radiation therapy, cryoablation, and others. And the technological pinnacle of the surgical treatment of prostate cancer at the moment is robot-assisted prostatectomy, the widespread use of which was marked by the publication of J. Binder back in 2002. This technology combined the advantages of minimally invasive laparoscopic RP with improved surgeon ergonomics and technical ease of vesicourethral anastomosis reconstruction and has now become the preferred minimally invasive approach. This article will consider the use of a robot-assisted technique in the stage of T3 prostate cancer.

K e y w o r d s: prostate cancer, robot-assisted prostatectomy, stage pT3

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In 2020, prostate cancer (PCa) took third place in the structure of the most prevalent oncological diseases [1]. In the Russian Federation, PCa is the second only to upper respiratory tract and lung tumors, amounting to 14.9% of all malignant lesions [2]. Radical prostatectomy in various modifications still remains the most common and only definitive treatment for localized PCa, despite the availability of active surveillance, hormonal and radiation therapy, cryoablation and others [3]. The technological pinnacle of surgical treatment of PCa at the moment is robot-assisted prostatectomy (RARP), the popularization of which was marked by the publication of J. Binder back in 2002 [4]. This technology combined the advantages of minimally invasive laparoscopic radical prostatectomy (LRP) with improved ergonomics and technical ease of vesicourethral anastomosis creation and has now become the preferred approach. The first comparative studies were presented already in 2003, when A. Tewari et al. demonstrated the advantages of robotic technology over open radical prostatectomy (ORP), mainly in the aspect of urinary continence [5]. A randomized phase III trial demonstrated in 2016 that RARP reduced hospitalization time and intraoperative blood loss in comparison with OPR, providing similar oncological outcomes [6]. It should be noted in that study a robotic surgeon had experience in 200 procedures, while a surgeon who performed ORP had experience in about 1500 cases [7]. Currently, more and more scientific works are being published, according to which ORP, LRP and RARP are equally effective, and the results depend mainly on the qualifications and experience of the surgeon [8, 9]. Most of publications include patients with clinical stages T1–T2. In this regard, the issue of expanding the indications for RARP and studying the oncological results in men with a stage T3 becomes extremely relevant.

One of the first publications which it would be logical to begin this review with is a work of Vipul R. Patel from November 2006, presenting the results of 500 patients with PCa who underwent RARP. Among them, 15% (75) had pathological stage T3a and 5% (25) had stage T3b. The results showed that stage T3 is not associated with the increased incidence of intraoperative complications. After one year, 95% of patients didn't have biochemical relapse (prostate-specific antigen level [PSA] was <0.1 ng/ml) [10].

Six years later, in 2012, a large meta-analysis under the leadership of Novara with the participation of Alexandre Mottrie and Vipul R. Patel was published in European Urology that examined the oncological results of RARP. Data from 12,900 patients were evaluated. One of the

studies was carried out by Nazareno Suardi in 2012, where the 5-year oncological outcomes of patients with high-risk PCa who underwent RARP were assessed [11]. It involved 184 patients treated in ORSI Hospital (Aalst, Belgium). The average age of patients was 62 years, PSA 8.7 ng/ml. A total of 56 (30.4%) men had clinical stage T3a, 15 (8.2%) had stage T3b, Gleason score was 6 or lower in 111 (60.5%), 7 in 53 (29 %) and 8–10 in 20 (10.5%) cases. The median follow-up was 67.5 months. Disease-free survival for patients with stage T3a during 3.5 and 7 years of follow-up was 94%, 84 and 84% compared to 69%, 43 and 43% for stage T3b, respectively.

In 2014, Mehrdad Alemozaffar published a paper in European Urology, dedicated to the postoperative results of RARP and ORP. The authors included 903 patients who underwent ORP (n=621) or RARP (n=282) between 2000 and 2010. Of the 282 patients in RARP group, 22.2% had a stage T3. The 5-year disease-free survival rate in RARP group was 88.0%.

In the same year and in the same journal, Jim C. Hu et al. presented a large retrospective analysis of 13,402 men with PCa, comparing the efficiency of ORP (n=7878) and RARP (n=5524) between 2004 and 2009 in terms of tumor progression [12]. The study revealed an interesting finding regarding the incidence of positive margins in stage T3a. In RARP group, it was 28.8% (286) compared with 37.2% (334) in ORP group. This work also demonstrated the advantage of RARP in terms of relapse-free survival, since lower proportion of patients received additional therapy (radiation or hormonal) within 12 (95% CI: 0.79) and 24 (95% CI: 0.72) months.

In February 2017, Lei Wang et al. published a large meta-analysis in Springer Science that assessed 5- and 10-years oncological outcomes in patients who underwent RARP. A total of 19,954 patients from 20 studies were analyzed. From them, 34.5% (n=6884) had pathological stage T3. The 5-year disease-free survival rate in the high-risk group was 71% (95% CI: 0.66–0.77). The cumulative 5-year cancer-specific survival rate was 97% (95% CI: 0.96–0.98). No significant heterogeneity or publication bias was noted. When studies were stratified by preoperative PSA level, 5-year cancer-specific survival was 97% (95% CI: 0.96–0.99) for low- and intermediate-risk and 98% (95% CI: 0.96–0 ,99) for high-risk PCa. When studies were stratified by time to adjuvant therapy, 5-year cancer-specific survival was 98% (95% CI: 0.95–0.99) for patients who did not receive adjuvant therapy and 97% (95% CI: 0 .96–0.98) for those receiving adjuvant therapy after the development of biochemical relapse. During the 10-year follow-up, 79% (95% CI: 0.72–0.86) out of 11,408 patients didn't have any signs of the disease [17].

One of the key studies comparing RARP with other surgical treatments for PCa, in particular LRP, was presented in November 2016 in European Urology by Francesco Porpiglia et al. [18]. The authors carried out a prospective randomized controlled trial comparing 5-year oncologic outcomes between LRP and RARP. The study included 120 patients with localized PCa who were treated from 2010 to 2011. PSA levels were assessed after 1, 3, 6 and 12 months with subsequent measurements every 6 months within 5 years. Patients with stage T3 accounted for 36.7% (22 people) in both groups. RARP has demonstrated an undeniable functional advantage. Relapse-free survival of patients in both groups was comparable and amounted to 81.6% during the 5-year follow-up.

In July of 2016, Huang Xing et al. published a large meta-analysis in Springer that compared intraoperative, functional, and oncologic outcomes between LRP and RARP. A total of 9178 patients were included in the meta-analysis (n=5064 and 4114, respectively). A stage pT3 was diagnosed in 383 patients in LRP group and in 359 in RARP group. It is worth emphasizing that the rate of positive surgical margins was approximately the same and amounted to 35.8 and 34.3%, respectively.

John W Yaxley et al. in 2016 demonstrated the results of a landmark phase III randomized trial that compared oncological outcomes after ORP and RARP [19]. A total of 326 patients undergoing surgery at the Royal Brisbane & Women's Hospital (RBWH) from 23/08/2010 to 25/11/2014 were randomized. Both groups included 163 patients. Stage pT3 was diagnosed in 30 (10%) patients, including 12 (8%) after ORP and 18 (11%) in RARP group. RARP was shown to be advantageous in terms of such parameters as operation time, volume of blood loss and length of hospitalization.

Another interesting work was presented in the European Urology in April 2017 by Annika Herlemann et al. The publication also assessed surgical outcomes after open and robotic prostatectomy [20]. In addition to oncological outcomes, urinary continence and erectile function were also evaluated. The study included 1892 patients with localized PCa who had undergone radical prostatectomy and did not have neoadjuvant and/or adjuvant therapy. ORP group included 1137 patients vs. 755 in RARP group. Stage pT3 was confirmed in 112 (10%) and 116 (17%), respectively. Authors concluded that the rate of positive margins was approximately equal between the groups (9% vs. 10%, respectively). Disease-free survival rates were also similar (87% vs. 85%).

Concerning the quality of life after surgery, it is necessary to mention the prospective study of Anna Wallerstedt, published in the European Urology Focus in December 2017 [21], which compared ORP and RARP. Data from 4,003 men from 14 different clinics were analyzed. There were 942 men in ORP group, and 2764 in RARP group. According to the results of the morphological study, stage pT3 was diagnosed in 252 (28%) patients in ORP group and 753 (28%) in RARP group. It should be noted that, even significant percentage of patients had pT3 stage, there were no differences in quality of life within 24 months between two approaches.

In 2018, Lan Cao et al. presented a meta-analysis in the Open Medicine, which compared RARP, LRP and ORP. In addition to oncological results, operation time, intraoperative blood loss, frequency of blood transfusion, hospitalization time, catheterization and other complications were also assessed. The meta-analysis included 8522 patients from 11 studies (5051 in RARP/LRP group, 3471 in ORP group). It is noteworthy that in the subgroup of patients with PCa of stage ⩾pT3, the rate of positive margin was lower in RARP/LRP than in ORP group (41.4% [434/1049] vs. 50.1% [419/830], respectively). Taking this into account, there was no clinically significant difference in the rate of biochemical relapse after 3 (OR=0.74, 95% CI: 0.32–1.73, p=.49), 12 (OR=1.60, 95% CI: 0.41–6.15, p=0.50), and 24 months (OR=0.63, 95% CI: 0.38–1.06, p=0.08). Regarding

urinary continence, no significant advantages were found for any of methods [22].

The results of one of the key studies (LAPRO) comparing functional and oncological outcomes between ORP and RARP were published on April 16, 2018 in the European Urology [23]. Of the 2,625 participants, 1,847 were undergone to RARP and 778 to ORP. A pathological stage T3 was detected in 511 (28%) and 190 (24%) cases, respectively. As in many similar studies, the incidence of urinary continence disorders between groups was virtually the same and amounted to 19 and 16% in the RARP and ORP groups, respectively. There was no clinically significant difference in oncologic outcomes at 24 months. Biochemical relapse was found in 12.5% of patients after RARP and 13.1% after ORP.

Authors from the UAE presented a similar study in October 2020 with a follow-up of 19 months, which compared ORP and RARP [24]. They randomized men who underwent open or robotic procedure between 06/01/2013 and 10/01/2016. There were 211 men in RARP group, including 27 (21.6%) patients with stage pT3a, while ORP group involved 67 men, from whom 14 (23.7%) had stage pT3a. The results showed that RARP was superior in terms of mean hospital stay (4 days vs. 5 days), postoperative blood transfusion rate (2.4% vs. 10.2%), and severity of pain syndrome. In ORP group, the average amount of nonsteroidal anti-inflammatory drugs per patient was 52 mg, compared to 34 mg in RARP group. Oncologic outcomes were not significantly different. The rates of positive surgical margins were 28.8 and 24.8%, respectively. The biochemical recurrence rate was also similar (16.9% in ORP group vs. 13.6% in RARP group), as well as recurrence-free survival over 3 years (72.9% vs. 75.7%, respectively). When analyzing the results, should be mentioned that for all oncological outcome p was >0.05.

Wang Deng et al. carried out a study comparing RAR and LRP, which was published in Frontiers in Oncology in September 2021 [25]. The authors retrospectively analyzed the data of 231 patients who were treated in Nianchang University Hospital in China, including 126 men in RARP group and 105 in LRP group. Postoperative morphological study showed that stage pT3 was detected in 33 (26.2%) and 20 (19.0%) patients, respectively. Notably, the rate of positive surgical margins was slightly lower in RARP group (24.2% vs. 30.0%).

In February 2021, Zilberman et al. published the results of a small but essential study in the Israel Medical Association Journal, which assessed the oncological outcomes of patients with clinical stage T3 after RARP [26]. The study included 79 men who underwent RARP at Sheba Medical Center in Tel Aviv from 2010 to 2018. The PSA level, the biochemical relapse rate and the need for salvage treatment within 3-6 months were assessed. The average age of the patients was 64 years. The perioperative PSA level was 7.14 ng/ml, the average prostate volume was 53 cc. Downstaging to T2 stage was seen in 23 patients, while the rate of positive surgical margins was 42%. Median follow-up was 74 months. The overall 5-year disease-free survival rate was 61%, while cancer-specific survival rate was 92%.

The important work of Taiwanese colleagues led by Ching Wei Yang was published in Scientific Reports on July 12, 2021. The authors' goal was to retrospectively evaluate the rate of positive margins and biochemical recurrence after RARP in 419 patients who were treated from December 2010 to January 2018 at Taipei Veterans General Hospital [27]. According to the morphological study, 44.8% of patients had a stage pT3a and 11.8% stage pT3b. The rate of positive surgical margins in stage T3 was 43.6%, which is comparable to or better than the results with ORP demonstrated in most studies. In addition, this trial showed that the key factor in the development of biochemical relapse is the initial PSA level, rather than the presence of a positive surgical margin.

The Da Vinci® Surgical System has rapidly gained popularity around the world due to its 3D, 10x magnification view of the surgical field, as well as the increased flexibility, maneuverability and precision of movement achieved through the integration of EndoWrist® technology. Despite its technical and financial issues, robotic surgery is confidently replacing traditional open procedures for many diseases. In the early days of robotic surgery, critics warned the scientific community that the lack of tactile feedback, as well as the educational opportunities available at the time, would negatively impact oncology results. This has led to more careful selection of patients with PCa in routine practice as well as in clinical trials, which is why the majority of them are clinical stage T1-2. In this review, we presented comparative studies and meta-analyses, which focused on patients who were diagnosed with a stage pT3. Based on the results, it should be noted that there were no advantages of OPR or LRP in this subgroup. RARP seems to be better, or at least no worse, than other procedures in both oncologic and functional outcomes. However, two comparative studies and one review report a clinically significant benefit of RARP in the postoperative quality of life.

Thus, we can conclude that RARP is a safe and effective procedure for PCa of stage pT3 and, probably, the indications should be reviewed, expanding them to T3 tumors.

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LECTURE

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THE USE OF A URETHRAL CATHETER WITH AN ULTRASOUND-INDUCED BIOPOLYMER DRUG COATING FOR THE PREVENTION OF RECURRENT BLADDER NECK SCLEROSIS IN PATIENTS AFTER ENDOSCOPIC TREATMENT OF BENIGN PROSTATE HYPERPLASIA

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Recurrent bladder neck sclerosis is one of the common complications of endoscopic treatment of benign prostate hyperplasia, which often leads to multiple re-operations, including complex open and laparoscopic reconstructive procedures. One of the most promising minimally invasive methods for preventing recurrence of bladder neck sclerosis is balloon dilatation under transrectal ultrasound guidance. To improve the results of using this technique, a urethral catheter with a biopolymer coating, capable of depositing a drug and eluting it under the influence of diagnostic ultrasound, was proposed.

Key words: BPH, TURP, bladder neck sclerosis

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Bladder neck sclerosis (BNS) is characterized by the development of scar tissue due to inflammation in the area of the bladder neck with partial involvement of the urethra and the bladder wall [1]. BNS was first described by the American urologist F. M. Denslow in 1918 as a complication of open surgical treatment of benign prostatic hyperplasia [2]. Currently, BNS is the most common complication of endoscopic procedures on the prostate [3–5]. Among complications after transurethral resection of the prostate (TURP), the incidence of BNS is in the range from 4.9 [5] to 12.3% [6], while after simple prostatectomy, according to the European Association of Urology, is 6% [7]. According to an analysis of more than 2000 patients with BNS, there was no significant difference between TURP and enucleation [8].

For the treatment BNS, cold knife incision, bipolar and monopolar electroresection, laser incision, and prostatic stent placement are suggested [5]. As a rule, the first-line option is endoscopic treatment, and its efficiency does not exceed 72% [9]. If a recurrence occurs, patients are considered resistant to endoscopic treatment, then more radical treatment can be performed, including open or laparoscopic reconstruction, in some cases up to prostatectomy [10, 11].

Taking into account the high incidence of development of BNS, as well as the low efficiency of primary treatment, many alternative techniques have been proposed, among which are a combination of endoscopic treatment with subsequent administration of antiproliferative agents (mitomycin C, triamcinolone), regenerative agents (hyaluronidase, collagen preparations), and also the use of endourethral brachytherapy. The efficiency of combination treatment does not exceed 72–93% [9, 12–14].

One of the most promising minimally invasive methods for preventing recurrence of BNS is balloon dilatation of under transrectal ultrasound guidance. The method was developed and proposed by the team of the Department of Urology and Andrology, Faculty of Fundamental Medicine, Moscow State University named after M.V. Lomonosov in 2019 [15].

Balloon dilatation of BNS under transrectal ultrasound guidance

Balloon dilatation of BNS is a minimally invasive procedure that can be performed on an outpatient basis as a method of preventing recurrence after the endoscopic treatment.

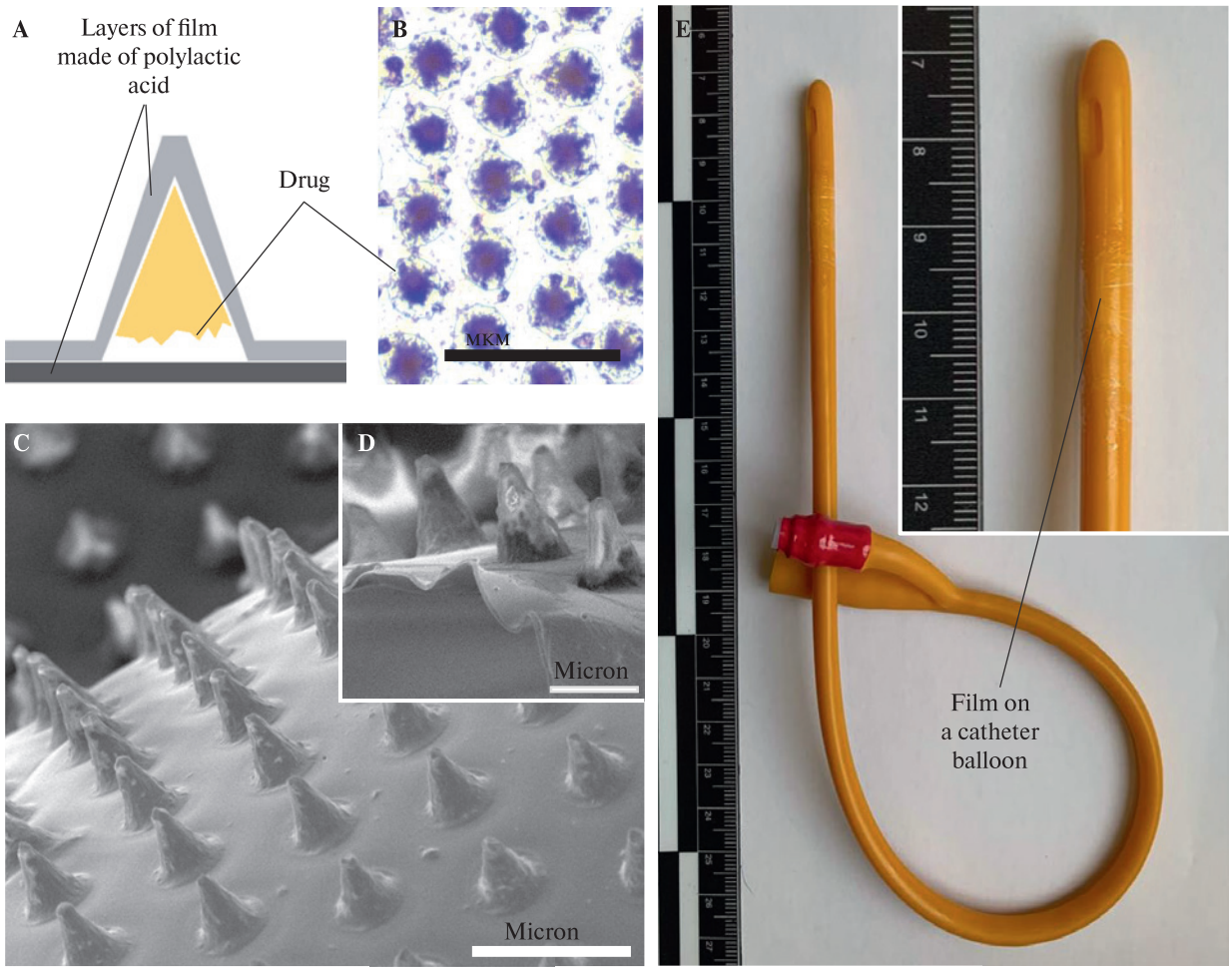

Fig. 1. Modification of urethral catheters using a biopolymer film made of polylactic acid
A – diagram of the structure of a microcontainer with a medicinal substance; B – microcontainers after saturation with the drug; C, D – electron micrographs of the film surface; E – coated urethral catheter [18].

This technique involves putting a urethral Foley catheter under transrectal ultrasound, positioning the balloon across the scar ring and inflating it until it forms a "waist". This allows for gradual elastic stretching of the bladder neck, protecting it from excessive trauma and aggressive scarring, after which a similar inflation is performed directly in the bed of the prostate bed with exposure duration in both cases for 5 minutes. The therapeutic effect in this case is achieved by stabilizing the scar ring at a urodynamically acceptable level with systematic and non-aggressive stretching with a balloon. The procedure is carried out in several sessions until the desired effect is achieved and stretching the bladder neck is preserved. The optimal time to start treatment is 3 weeks from the endoscopic treatment. Repeated sessions are carried out according to the scheme once every 3–6 weeks with a gradual increase in the interval between sessions, with at least 4 procedures [16].

According to an open, randomized, prospective, parallel-groups, single-center study [17], the efficiency of endoscopic treatment of BNS in combination with standard drug therapy in a group of 75 patients was 72.0% compared to 86.7% in the group of endoscopic treatment in combination with standard drug therapy and programmed balloon dilatation of the bladder neck under ultrasound control (n=45).

Our data showed high effectiveness of this technique compared to existing alternative methods, however, the percentage of recurrence in the main group remained quite high, up to 13.3%.

Modification of the surface of urethral catheters using ultrasound-induced drug coating

In order to improve the results of treatment, a urethral catheter with a biopolymer coating, capable of depositing a drug and releasing it under the influence of diagnostic ultrasound, was proposed. This coating is a thin biopolymer film (from one to several microns) made of polylactic acid (PLA) with many ordered, hermetically sealed microcontainers containing the drug substance [18] (*Fig. 1*).

Using in vitro and in vivo models, it has been proven that such a method of encapsulation allows to preserve the biologically active properties of the drug, as well as release it under the influence of ultrasound [19–24]. According to one of the experimental studies, when a biopolymer film with encapsulated adrenaline hydrochloride was implanted under the skin of the thigh of a laboratory animal, extracorporeal exposure of low-intensity therapeutic ultrasound on the implant area led

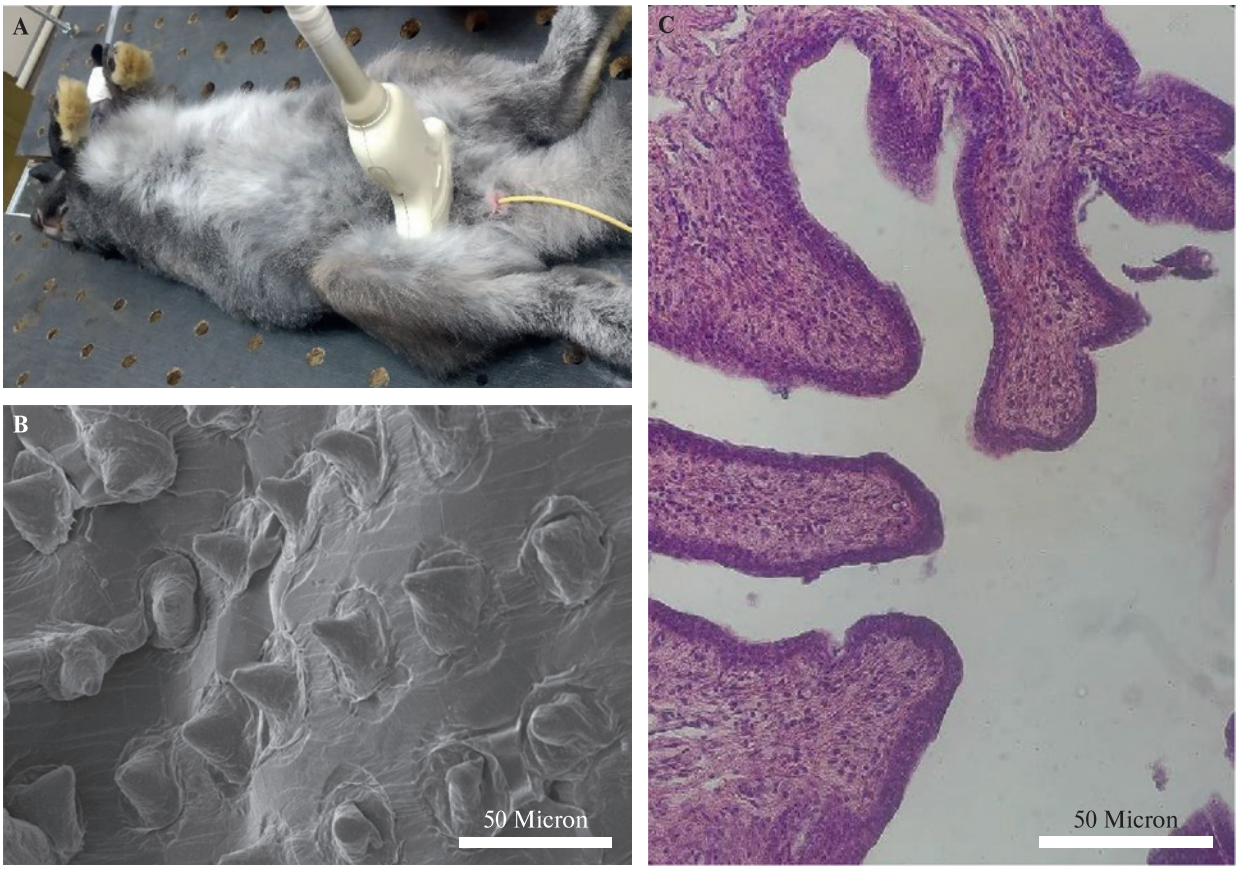

Fig. 2. Experimental safety assessment of a urethral catheter coated with a biopolymer film with ultrasound-induced release of methylprednisolone in an animal model [18]

A – position of the laboratory animal when targeting diagnostic ultrasound at the balloon of the urethral catheter; B – electron micrograph of the PLA coating after the experiment; B – histological picture of the urethra of a laboratory animal 24 hours after putting of a drug-coated urethral catheter.

to the release of the drug from microcontainers, which was confirmed by pronounced vasoconstriction recorded on the implantation side [25].

Methylprednisolone in the form of a lyophilizate was used as a deposited substance for coating urethral catheters, which is a highly water-soluble low-molecular drug with high bioavailability, as well as a pronounced antiproliferative and anti-inflammatory effect.

The safety of using the urethral catheter coated with a biopolymer film with ultrasound-induced release of methylprednisolone to perform balloon dilatation of the bladder neck was experimentally assessed in vivo in rabbits [18]. For this experiment, 12 healthy adult male rabbits were divided into two groups: experimental and control, 6 individuals in each. Under general anesthesia, studied animals underwent inserting of urethral catheter 6 Ch with an inflation inside the bladder neck. In the experimental group, urethral catheters with a coating were used, while in the control group standard uncoated catheter were put. The exposure duration in both groups was 10 minutes, while in the experimental group, during the entire exposure time, a local impact by ultrasound on the urethral catheter balloon was done (*Fig. 2*).

A histological study of the urethra and bladder neck of laboratory animals 24 hours after putting urethral catheters did not show significant differences between groups and demonstrated the absence of negative consequences of using a urethral catheter coated with a biopolymer film with ultrasound-induced release of methylprednisolone compared to an uncoated catheter.

Introduction into clinical practice

The novel technique, in comparison with standard balloon dilatation of the bladder neck under transrectal ultrasound control, differs only in the sequence of inflation of the catheter balloon, since to create a high concentration of the drug directly in the scarring area, it is most advisable to perform the first inflation of the balloon directly in the area of the prostate bed. Next, the balloon is deflated and moved to the area of the scar ring, after which it is inflated again in the narrowest place. The exposure duration in both positions is 10 minutes in total (5 minutes each). The improved effect compared to standard balloon dilatation of the bladder neck is ensured by the delivery of the drug to the area of the scar ring under the influence of ultrasonic waves and the antiproliferative effect on fibrous tissue (*Fig. 3*).

The proposed methodology received approval from the local ethical committee of the Moscow State University named after M.V. Lomonosov, after that an open, prospective, single-center study was launched in 2021.

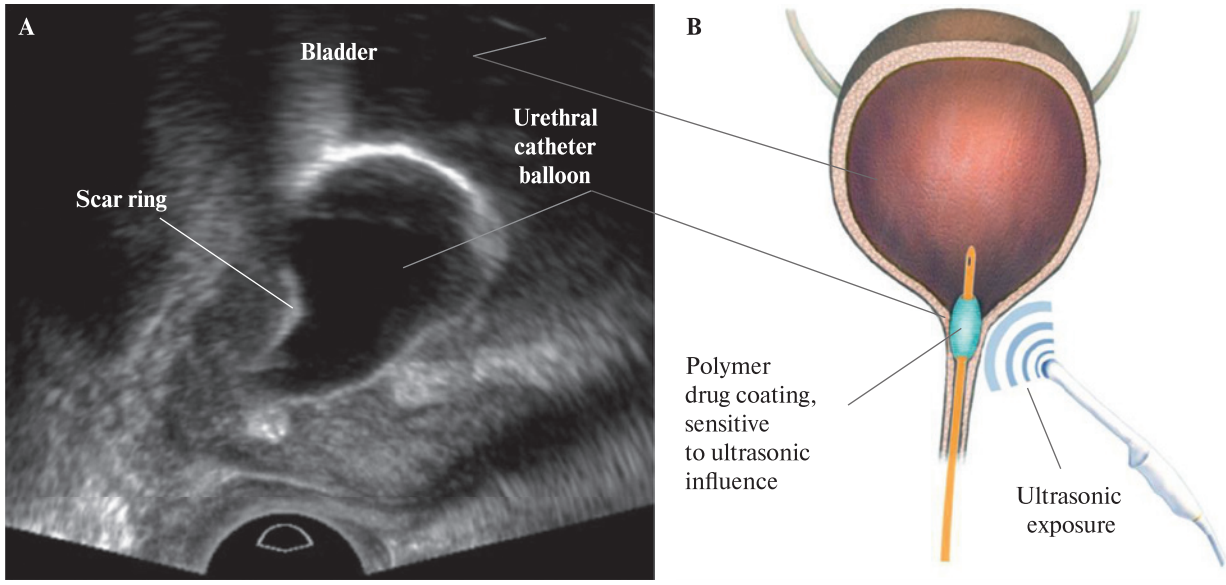

Fig. 3. A balloon dilation of bladder neck sclerosis under transrectal ultrasound control using a urethral catheter with an ultrasound-induced biopolymer drug coating

A – Transrectal ultrasound of the bladder neck and urethral catheter balloon during the procedure;
B – Schematic representation of the process of balloon dilatation of the bladder neck using a urethral catheter with an ultrasound-induced biopolymer drug coating.

To date, the study has included 13 patients with two or more recurrences of BNS after endoscopic removal of benign prostatic hyperplasia. The planned number of participants is 40 patients, and currently recruitment is ongoing.

The existing experience has demonstrated the high potential of the balloon dilatation of the bladder neck using a standard urethral Foley catheter. Literature data on the combination of endoscopic treatment with local and systemic use of antiproliferative agents, including corticosteroids, allow to expect improved results of treatment of recurrent BNS while maintaining minimally-invasiveness and the possibility of performing the procedure on an outpatient basis.

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CONSIDERATIONS

Z.K. Gadzhieva

URINARY TRACT INFECTION AND OVERACTIVE BLADDER. IS THERE AN ASSOCIATION?

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A discussion of key research findings dedicated to the relationship between urinary tract infection (UTI) and overactive bladder (OAB) is presented in the article. The results of the publications support the concept that UTI may be an underappreciated contributor to the development of OAB in some patients and vice versa. This information raises a number of questions regarding the treatment and diagnosis of OAB and UTI. The main question is the potential use of antibiotics, anti-inflammatory drugs, and other drugs in the treatment of patients with OAB, as well as the rationale for the use of therapy that normalize lower urinary tract (LUT) function in the presence of chronic recurrent UTI.

K e y w o r d s: *chronic recurrent cystitis, recurrent infection, bacterial infection, lower urinary tract dysfunction, overactive bladder*

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Urinary tract infection (UTI) is among the most common bacterial infections, affecting more than 150 million people worldwide every year [1, 2]. Recurrent UTIs are traditionally defined as 2 or more acute UTIs within 6 months or 3 in a year [3]. It was estimated that 27% of young women who had a first episode of UTI experienced at least one recurrence within the next 6 months, compared to 53% of women over 55 years of age [5]. Recurrent UTIs are usually not life-threatening, but its high incidence can significantly increase healthcare costs and negatively impact patients' quality of life [6, 7]. New evidence suggests a different pathogenesis between primary and recurrent UTI.

Overactive bladder (OAB) is a clinical syndrome characterized by urinary urgency, increased urinary frequency, and/or nocturia, with or without urgency urinary incontinence [8]. Urgency is the main symptom of OAB syndrome [9]. OAB is clinically characterized by the absence of other organic causes, including UTIs.

According to the literature, the prevalence of OAB symptoms in European countries in patients over 40 years of age is 17% [10]. These symptoms negatively impact on the quality of life, contributing to significant psychosocial comorbidities, including increased incidence and severity of depression, anxiety, and social isolation, resulting in poor mental and physical health [11, 12].

Currently, the main drugs used in the treatment of OAB are M-anticholinergic blockers or β3-adrenergic agonists. According to literature, anticholinergics may not always be effective and has limitations on the duration of therapy [13–15]. After 8 years, only 20% of patients receiving antimuscarinics showed sustained improvement. Unfortunately, some studies showed that about 30-40% of patients do not respond to drug treatment.

In this case, "refractory OAB" is suggested. Treatment of OAB with botulinum toxin type A is invasive, may be associated with side effects, and requires repeated injections at approximately 6-month intervals, which may indicate that the treatment masks rather than treats the underlying cause of OAB [16–18].

Recent evidence has shown that chronic bacterial colonization of the bladder may aggravate OAB symptoms and cause recurrent UTIs [21]. Functional impairment further compromises the integrity of the urothelial barrier and makes it vulnerable to invasion by uropathogens. Impaired barrier function, insufficient basal proliferation and cell maturation may be a consequence of chronic suburothelial inflammation, leading to activation of sensory innervation (causing OAB) and the inability to eliminate intracellular bacterial communities (resulting in recurrent UTIs). Accurate diagnosis and a multidisciplinary approach to understanding the pathophysiology of OAB and recurrent UTI are necessary.

Chronic bladder inflammation also inhibits basal cell proliferation, causing defective apical cell maturation and impaired barrier function [22]. Chronic "neural plasticity" due to chronic inflammation and activation of sensory receptors can alter afferent activity, impairing antinociceptive activity, and lead to bladder hypersensitivity or detrusor overactivity (DO).

According to a study of urothelial dysfunction, in women with recurrent UTI an increased cell apoptosis,

defective E-cadherin, and chronic inflammation were found compared with controls, suggesting that defective urothelial barrier function may be a cause [23]. There is also an increase in urinary biomarkers of inflammation, including monocyte chemoattractant protein-1, macrophage inflammatory proteins, and epidermal growth factor, suggesting that inflammation is involved in the pathogenesis of OAB [24]. One study found that serum C-reactive protein levels were significantly higher in those with OAB (p=0.012) or interstitial cystitis (IC) (p=0.049) than in controls. However, there was no significant difference in C-reactive protein levels between patients with OAB and IC (p=0.43). These data support the association between chronic bladder inflammation in patients with OAB and IC [25].

Manifestations of cystitis in women may mimic OAB, which makes exclusion of UTI a key component of the diagnosis of OAB. Clinically, OAB is differentiated from acute UTI by the absence of bacteriuria and/or leukocyturia on urine dipstick. Since symptoms of OAB and chronic recurrent cystitis in women are similar, in most patients OAB is often misdiagnosed as UTI and treated empirically without urine culture as a routine approach. In fact, when urine culture results are obtained, less than half of women are positive, suggesting that empirical treatment without urine culture is usually associated with misdiagnosis of URI [26].

In a prospective, blinded, case–control study, 23% of patients with OAB were found to have positive urine culture compared with 10% of controls [27]. The proportion of patients with OAB and positive urine culture increased from 15% at 105 CFU/ml to 21% at 102 CFU/ml [28].

An increasing number of publications has shown that uropathogenic *Escherichia coli (E. coli)* invades urothelial cells and forms intracellular bacterial colonies. In addition, various studies have identified large numbers of bacteria not detected by conventional tests in specimens obtained from bladder biopsies or isolated urothelial cells from patients with OAB examined by immunohistochemistry or confocal microscopy of centrifuged/cytospin samples [29–36].

According to Cheng et al. (2016), a detailed analysis of urothelial cell samples obtained from urine showed that filamentous bacteria are significantly more common in patients with OAB compared to a control group [32]. Filamentous bacteria are associated with intracellular bacterial growth and the release of bacteria from urothelial cells to recolonize the bladder [34].

In this context, *E. coli* as a major uropathogen was more closely associated with urothelial cells from urine sediment (by confocal microscopy) only in OAB patients [31]. Similarly, further study of urothelial cells showed that high level of intracellular bacteria correlated with the severity of symptoms (urinary frequency and urge incontinence) [35].

According to some publications, patients with OAB are significantly more likely to have leukocyturia (39 versus 9%) than the control group [36], and 30–40% of them have pyuria on urinalysis [31, 37]. In a study by K. Gill et al. (2018) patients with OAB were also more likely to have leukocyturia compared to the control group [33]. Interestingly, the authors showed that pyuria detected by urinalysis is the most important correlate of symptom severity, with urgency being highly correlated with both pyuria and epithelial cell yield [33].

The normal urothelium is essentially quiescent with a low turnover rate and regenerates after bladder damage due to bacterial infection, toxins, or trauma [38–41].

Changes in urothelial differentiation may lead to increased permeability and decreased protective function of the urothelium [42]. Acute bacterial inflammation (cystitis) damages the urothelium, causing tissue swelling and accumulation of large numbers of inflammatory cells in the urothelium and suburothelium. These inflammatory cells can trigger a cascade of inflammatory changes in tissues involving several sensor proteins and cytokines, accompanied by pain and symptoms of OAB [23].

Proliferation and differentiation of basal layer stem and progenitor cells regulate the integrity of the bladder epithelium. Chronic inflammation in the bladder can affect the proliferative capacity of these basal cells and alter the rate of proliferation, leading to defects in apical urothelial cells and barrier function [43].

According to N.T. Liu et al. (2015), urothelial dysfunction is common in patients with recurrent UTI and other bladder disorders, such as OAB and bladder outlet obstruction (BOO). In addition, severe urothelial inflammation and urothelial cell apoptosis appear to share a common pathophysiology of various lower urinary tract symptoms (LUTS) [44]. As a result, urothelial dysfunction and underlying chronic inflammation may be part of the pathogenesis of bladder hypersensitivity, bladder pain, and recurrent UTIs in the presence of certain LUTS.

Cytokines are important regulators of both the innate immune response to infection and the inflammatory response to injury. Urinary cytokine level correlates with UTI symptoms [45]. Bacterial inflammation of the bladder stimulates the release of large amounts of pro- and anti-inflammatory cytokines and chemokines. Various studies have reported increases in the levels IL-1β [47, 48], IL-6 [47–49], TNFα [47–49], IL-8 [48–51], and c-10 [48, 51].

Several trials have examined urinary cytokines as biomarkers of UTI in patients with OAB. In support of the concept that in some patients with OAB, symptoms are due to inflammation, a number of publications showed altered cytokine and chemokine profiles in urine [49, 52–56]. This may manifest as changes in either pro- or anti-inflammatory cytokines, or both. In addition, some studies have demonstrated that changes in urinary cytokine level correlate with the severity of OAB symptoms [1, 36, 56], as well as bacterial growth and the severity of leukocyturia [36]. There is no doubt that large-scale studies are needed to expand our understanding of the problem of changes in cytokines in urine of patients with OAB and their role in the development of this syndrome.

It is also possible that bacteria are able to directly or indirectly sensitize sensory neurons that modulate the pain sensation [57]. In addition, studies have shown that toxins and metabolites released during bacterial growth and invasion can sensitize neurons and indirectly activate neurons and cause pain [57–60]. A number of experimental studies in mice proved that various inflammatory mediators increase the excitability of sensory neurons innervating the bladder [61, 62].

According to experiments, in addition to direct activation of the bladder afferent nerves, the infectious and inflammatory process also contributes to the

urothelium exfoliation, i.e. a protective mechanism that quickly removes infected urothelial cells from the bladder wall [29, 63–65]. Although this mechanism is effective in preventing bacterial adhesion, it temporarily increases bladder permeability until the infection is cured and injury-induced proliferation of urothelial cells restores the integrity of the urothelial barrier [40, 41]. Increased urothelial permeability allows toxic urine contents to impact underlying sensory nerves. By developing a model of experimentally induced bladder permeability in mice, the authors of a study showed that increased urothelial permeability causes excitability of mechanosensitive bladder afferent neurons [66], suggesting that it may cause dysfunction manifested by sensory impairments.

To test the hypothesis of a relationship between UTI and increased bladder sensory activity, the authors examined how inflammatory mediators released during acute UTI in mice altered sensory nerve activity ex-vivo [66–69]. Inflammatory supernatants containing a set of cytokines were isolated from mice 8 hours after infection with uropathogenic *E. coli*. Then, this combination was injected into the bladder lumen of healthy mice. After that, both intravesical pressure and sensory nerve activity during gradual distension of the bladder were recorded. Through these experiments, the authors showed that in UTI, inflammation can sensitize bladder sensory neurons to distension, enhancing the response to bladder filling [68]. Thus, neurons that normally respond only to bladder overdistension produce robust reaction to physiological distension in the presence of UTI supernatant. There is considerable experimental evidence that increased excitability of sensory neurons innervating the bladder is triggered by inflammation and may play a critical role in the pathogenesis of OAB [69, 70].

Another study showed that microorganisms in urine may have an important place in the etiology of refractory OAB or aggravate symptoms [71]. Additionally, the urinary microbiome in the human is thought to have a potential association with LUTS [72]. A decrease in urinary microbiome diversity has been found to correlate with the severity of urge urinary incontinence [71]. Certain Lactobacillus species may contribute to maintenance of a bladder environment, and higher bacterial diversity in the absence of Lactobacillus dominance has been associated with urge urinary incontinence and resistance to antimuscarinic therapy [73].

K.J. Thomas-White et al. (2016) found that women with urge urinary incontinence had more bacteria and a more diverse urine microbiome. Patients who did not respond to the M-anticholinergic drug solifenacin had a more diverse bacterial community, including bacteria not typically found in responders [74]. *E. coli* and *G. vaginalis* induce calcium influx and detrusor contraction, whereas *Lactobacillus crispatus* and *Lactobacillus gasseri* do not [75]. From 39 women who had refractory urge urinary incontinence and concomitant recurrent UTIs, 9 (23.1%) patients with significant clinical manifestations had a diverse urinary microbiota, determined by bacterial 16S RNA profiling, suggesting that persistent urinary colonization may exist and aggravate the manifestations of OAB [76]. Based on these data, patients with OAB refractory to anticholinergic therapy may have a subclinical form of UTI in which the pathogen cannot be cultured by conventional methods. Imbalance of urinary microbiota may play an important role in refractory OAB.

E. coli can replicate in the bladder urothelium, forming loose colonies, and then penetrate into the bladder lumen [77, 78]. *E. coli* typically forms intracellular complexes in the superficial umbrella cells of the bladder in mice [79] with formation permanent intracellular reservoir within 2 weeks [80]. Immunofluorescence data showed that 18% of women with recurrent uncomplicated cystitis had intracellular bacterial colonies in the bladder [29]. In patients with OAB, intracellular bacterial colonies can be identified in urothelial cells when concomitant pyuria has been observed [37].

Chronic inflammation in the bladder wall may contribute to urothelial dysfunction and impairment of barrier function, followed by recurrent UTIs. This urothelial dysfunction can occur in several different lower urinary tract diseases, such as IC/chronic pain syndrome, BOO, spinal cord injury, and recurrent UTI [81]. Elimination of chronic inflammation may improve urothelial regeneration and differentiation and restore protective mechanisms in the bladder.

Studying urine microbiome in case of the absence of bacteriuria during standard bacteriological examination is important in patients with OAB who are resistant to traditional treatment [76]. In an analysis of 100 women with recurrent UTI, P.J. Lee and H.C. Kuo (2020) found that 90% of those with recurrent UTI had lower urinary tract dysfunction (LUTD) detected by videourodynamic testing, despite receiving individualized treatment. LUTD included bladder neck dysfunction (19%), detrusor overactivity with abnormal contractility (6%), DO (5%), detrusor underactivity (10%), dysfunctional voiding (25%), bladder hypersensitivity (6%) and poor relaxation of the pelvic floor muscles (20%). Only 10% of patients had normal urodynamic parameters. Interestingly, although a UTI was identified and treated accordingly, only 11.3% of women with recurrent UTIs remained relapse-free after individual treatment of LUTD [81]. Among patients with recurrent UTIs, DO was observed in a quite large percentage of patients (DO with impaired contractility in 100%, dysfunctional urination in 72%, bladder neck dysfunction in 36.8% and poor relaxation of the pelvic floor muscles in 15.8% of cases) [81]. According to S. Hijazi et al. (2016), a videourodynamic study in women with recurrent UTI revealed detrusor hypoactivity in 22%, detrusor-sphincter dyssynergia in 17%, their combination in 11%, and OAB in 28% of patients [82].

Most of these patients with recurrent UTI experienced frequent urination and urgency. These data imply that OAB (as well as LUTD in general) and recurrent UTI are closely interrelated. When treating recurrent UTIs, these functional impairments should be considered in the early stages.

In 2009 and 2013 we published our results of studying of functional state of the urinary tract in 116 patients with chronic recurrent cystitis (average age of 44.56 ± 16.51 years, average duration of the disease from the first episode of acute cystitis of 4.3 ± 1 ,4 years) and 51 patients with chronic non-obstructive pyelonephritis (average age of 37.1±16.28 years) to determine the pathogenetic therapy [83, 84]. According to urodynamic study, 76.7% of women with recurrent cystitis had functional disorders of the urinary tract. In patients with chronic non-obstructive pyelonephritis, urgency and obstructive symptoms were most commonly documented. In all cases, where there was vesicoureteral reflux (VUR) on

cystography, urinary tract dysfunction was also diagnosed. The results of our study allowed to change our view on urinary disorders in this category of patients. Inflammatory diseases of the urinary tract occurred and could be a consequence of urinary tract dysfunction as urgency caused by DO and/or urethral instability (in a form of severe detrusor hypotension), or due to detrusor-sphincter dyssynergia, causing functional obstruction.

In 53 (45.68%) patients with chronic cystitis, urethral instability was detected. The maximum urethral pressure in this group was 82.46±29.26 cm H2O (range of 34.86±19.6). Intravesical pressure at maximum flow rate was 68.48±26.39 cm H2O, and detrusor pressure was 34.6±12.1 cm H2O. DO was detected in 10 (8.62%) patients with chronic cystitis. Fluctuations in detrusor pressure were 22.16±15.8 cm H2O, intravesical pressure at maximum urine flow rate was 79.57±35.22 cm H2O, detrusor pressure was 50.57±28.98 cm H2O. In 26 (22.4%) patients with chronic cystitis, a combination of urethral instability and DO was diagnosed. The maximum urethral pressure was 75.5±21.44 cm H2O, fluctuations in urethral pressure were 37.45±17.44 cm H2O, fluctuations in detrusor pressure were 23.57±14.48 cm H2O.

Detrusor hypotension was detected in 35 (30.17%) patients. Moreover, it was accompanied with urethral instability in 36 cases. A decrease in detrusor contractility was recorded in 25 (21.55%) patients. Symptoms of detrusor-sphincter dyssynergia were seen in 29 (25%) patients. Postvoid residual of more than 50 ml was found in 12 (12.63%) cases.

In the group of those with chronic non-obstructive pyelonephritis, intravesical pressure at maximum urine flow rate reached 67.8±34.16, maximum urethral pressure 83.05±29.9 cm H2O.

Normally, the vesicoureteric junction is able to resist to intravesical pressure up to 60–80 cm H2O [85], while maximum detrusor pressure 70 cm H2O and higher reliably causes upper urinary tract dysfunction [86]. When examining patients with detrusor areflexia, R. Gerridzen et al. [87] found that the upper urinary tract impairment occurred with an average detrusor pressure of 58 cm H2O, while renal dysfunction in those with an average detrusor pressure of 24 cm H2O was absent. In our study, 16 (31.37%) patients had VUR confirmed by cystography. In all patients with chronic non-obstructive pyelonephritis, in whom cystography revealed VUR, urinary tract dysfunction was registered, including urethral instability in 56.25%, severe detrusor hypotonia in 25% and DO in 31.25% cases.

In the group of patients with OAB, fluctuations in detrusor pressure were 30.61±24.8 cm H2O. In the group of those with urethral instability, the fluctuations in maximum urethral pressure were 38.19±26.40 cm H2O. The bladder volume in patients with detrusor hypotension was 573.83±167.9 ml.

After carrying out these studies, we suggested that in the presence of a chronic recurrent inflammation in the urinary tract, a "vicious circle" of dysfunction-inflammation occurred. This is how we imagined the connection between impairment of urinary tract innervation and chronic UTI in women. Based on our results, we hypothesized that a chronic inflammatory process in the bladder and kidneys may be a consequence of urinary tract functional disorders associated with impairment of nervous regulation.

Consequently, inflammation in the bladder wall in combination with functional changes in the bladder and/or urethra may impact the normal functioning of the urinary tract. As a result, pathogenetic treatment of recurrent infection and the urinary tract dysfunction should be aimed at breaking this "vicious circle".

This formed the basis for the pathogenetic treatment strategy for this category of patients, which includes drugs that correct functional urinary tract disorders identified during a urodynamic study in addition to antibacterial and anti-inflammatory therapy [83, 84].

Confirming our assumption about the connection between recurrent infection and the urinary tract dysfunction, as well as proposals to revise treatment approaches, some studies showed very similar data. In 76% of patients, along with main diagnosis of "chronic recurrent cystitis", there were severe functional urinary disorders found during a urodynamic study [88].

Thus, numerous studies indicate the involvement of true UTI in the pathogenesis of OAB in a subgroup of patients who are not susceptible to standard therapy. Detection of bacterial invasion of urothelial cells and subsequent inflammation have been shown to be key elements in sensitizing the sensory nerves to bladder distension, which then causes uncreased frequency during the day and at night (nocturia), as well as urgency. Small studies have shown that antibiotics can help treat patients with OAB, but the growing risk of antibiotic resistance makes prescribing them undesirable. Thus, there is a need for alternative treatments for infection and pro-inflammatory conditions in this subgroup, which may include anti-inflammatory agents or target the microbiome and urothelium. Such opportunities can be provided by the use of immunoactive prevention and treatment of UTIs, which has the highest levels of evidence and recommendations, according to European and Russian guidelines.

Uro-Vaxom contains a lyophilized bacterial lysate of 18 strains of *E. coli*, which is the most common causative agent of UTIs. This drug is an oral immunostimulating agent that activates the immune defense mechanism through the lymphoid tissue of the main mucous membrane (MALT, mucosa associated lymphoid tissue, GALT, gut-associated lymphoid tissue and UALT, urinary-mucosa associated lymphoid tissue) and maintains the activity of these mechanisms at a high level [89]. The drug also stimulates humoral and cellular immune responses, which strengthens natural defense against infections caused by various microorganisms. Moreover, Uro-Vaxom may provide protection against a wider range of pathogens that cause UTIs, and not just against *E. coli* [90]. The drug provides immunoactive prevention by enhancing the response of the immune system. Concentrations of immunoglobulins of classes A and G in patients receiving Uro-Vaxom are several times higher than those not taking this drug [91]. A positive feature of the drug is the possibility of using it both for the treatment and for the prevention of UTIs. The frequency of bacteriuria by the end of the 3rd month of taking Uro-Vaxom in combination with an antibiotic is 3 times lower than in patients receiving only an antibiotic [92].

In a study by N.K. Akhmatova et al. (2016) the clinical and bacteriological efficiency of Uro-Vaxom® in women with recurrent cystitis was evaluated. It was shown that a negative urine culture after 3 months of therapy

was preserved after 6 months [93]. Thus, Uro-Vaxom® reduces the frequency of recurrences of UTI, the number and severity of symptoms, the need for antibiotics. The duration of the relapse-free period reaches up to 6 months after stopping taking the drug.

We agree that effective etiologic treatment of cystitis does not always lead to the elimination of urination disorders. Therefore, to clarify the nature of these changes and determine further treatment tactics, it seems appropriate to study the functional state of the urinary tract. Detected disorders may concern all phases of bladder cycle. Functional disorders of the urinary tract can be caused by various processes accompanied by changes in the nervous regulation.

Conclusion. The lack of a systematic approach to the assessment of urinary disorders in patients suffering from chronic recurrent UTI can lead to incorrect interpretation of the clinical manifestations and the development of ineffective treatment tactics. When prescribing treatment for patients with chronic recurrent cystitis, the role of the autonomic nervous system in regulating the bladder contractions is often not considered. It is necessary to emphasize that the treatment of UTIs must be comprehensive with taking account the pathogenetic mechanisms. In addition, we can say that every year there is more and more evidence that clinical manifestations of OAB should be reconsidered, given the their connection with UTI [94]. Thus, it is necessary to continue a more in-depth study of these interrelated chronic conditions and improve methods of examination and treatment of patients with UTI and OAB.

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