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Antibiotic therapy of chronic bacterial prostatitis is more effective considering antibiotic susceptibility of all pathogens isolated

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Purpose: Because of the insufficient efficacy of the current treatment of chronic bacterial prostatitis (CBP), it is justified to search for a more effective antibiotic therapy (ABT).

Materials and Methods: This single-centre prospective observational comparative study was conducted in 2012 to 2019 (patients: 60 men with CBP; age: 20–45 y). The clinical examination was performed on admission and at 1, 3, 6, or 12 months. All patients underwent the Meares–Stamey test to obtain expressed prostatic secretion (EPS) and/or post-massage urine (PMU) samples for extended bacteriological examination. The patients were randomly divided into 2 treatment groups (30/30 patients): group I, fluoroquinolones (FQs); group II, a combination of FQs with cephalosporins/macrolides with a treatment duration of 1 month.

Results: Patients of both groups had severe symptomatic CBP with an average duration of 4 years. Twenty-three microorganisms (15 aerobes, 9 anaerobes) were identified in PMU. At 3 months follow-up, a positive clinical effect was noted in both groups, which was significant ($p<0.05$) only in group II concerning NIH-CPSI questionnaire, leukocyturia, prostate volume, maximum urine flow, and decreased pathospermia. At 6 months follow-up, in group II the frequency of *Escherichia coli* and *Enterococcus* spp. decreased significantly. In group I aerobes changed only insignificantly from the initial level, but anaerobes increased significantly. In group II the titers of both, aerobes and anaerobes, were significantly lower ($p<0.05$) at 6 months follow-up as compared to initial values.

Conclusions: ABT targeting all taxa in EPS/PMU is a more effective alternative to standard therapeutic regimens for CBP.

Keywords: Anti-bacterial agents; Bacterial load; Bacteriological techniques; Drug resistance, bacterial; Prostatitis

INTRODUCTION

Chronic bacterial prostatitis (CBP category II, NIH-NID-DK classification, 1999) is an infection difficult to respond to oral antibiotic therapy (ABT) due to decreased intraprostatic penetration of antibacterial drugs (ABDs) [1-8]. At the same time, fluoroquinolones (FQs) are recognized as the classic first-line antibiotics of choice [9]. However, their clinical and microbiological efficacy is only 60% after 6 post-therapy months, and the recurrence rate during the one year follow-

up ranges from 25% to 50% [10].

The reasons for this are multiple: an increase in the prevalence of multidrug-resistant (MDR) microorganisms, including bacterial pathogens with broad-spectrum β-lactamase activity, and production of biofilms [6,7]. Along with this, the etiological underestimation of CBP is recognized as one of the reasons [9,11]. The established opinion about the exclusive role of Enterobacteriaceae and *Enterococcus faecalis* in the development of CBP has been shaken in recent years because the evidence was obtained confirming involvement of *Chlamydia trachomatis*, *Mycoplasma genitalium*, *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, *Staphylococcus* spp., *Corynebacterium* spp., *Candida* spp. to the chronic course of prostatic inflammation [8,11-15]. In addition, a wide spectrum of anaerobes in the expressed prostatic secretion (EPS) and post-massage urine (PMU) was also shown in healthy men and cases of CBP, but also the presence of both, aerobes and anaerobes [16-18].

Based on current research, it is impossible to determine the causal relationship between the different groups of bacteria present in the EPS/PMU and chronic prostatic inflammation. Even if we assume that the inflammation was initiated by one of the microorganisms, co-infection by other bacteria may increase the likelihood of a more severe course of CBP. Therefore, determining the ABD-susceptibility of commonly recognized CBP-pathogens (one or several) only may be questioned by the need to determine the ABD-susceptibility of all bacteria identified in the EPS/PMU to choose ABDs for therapy or a combination thereof with possible efficacy against all potential pathogens.

To carry out a comparative analysis of the clinical and bacteriological efficacy of two therapeutic approaches based on the established antibiotic susceptibility of microorganisms: the first approach–the choice of a FQ, to which the Enterobacteriaceae and *Enterococcus* spp. cultured in the biomaterial showed the highest susceptibility; the second approach – the choice of a FQ only to which all bacteria identified in EPS/PMU showed susceptibility, otherwise a combination therapy of a FQ with cephalosporin (CEP) and/or macrolide (MAC) was used to reach this aim.

MATERIALS AND METHODS

1. Research design

A single-centre prospective observational comparative study conducted in 2012 to 2019. The protocol for this research project has been approved by the Ethics Committee of the Rostov State Medical University (approval number: 17/12; signed 4 December, 2012) and it conforms to the provi-

sions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013). All patients signed informed consent to participate in the study.

The study included 60 patients aged 20 to 45 years with CBP who were sequentially examined at the Urology Division, Rostov State Medical University Clinic. Each patient was examined before starting treatment and at 1-, 3-, 6-, and 12-months follow-up. Inclusion criteria were pain in the typical localization, presence of lower urinary tract symptoms for more than 3 months, leukocyturia, and positive culture of PMU with more than 10-fold excess as in the 1st (first voided urine) and 2nd (midstream urine) portion of the Meares–Stamey test. Exclusion criteria were acute lower urinary tract infections, sexually transmitted infections, prostate cancer, heart/kidney/liver failure, previous prostate and lower urinary tract surgery, radiation therapy, drug/alcohol dependence, and ABDs-allergy.

All patients underwent assessment of CBP signs and symptoms at the first visit using the National Institutes of Health Chronic Prostatitis Symptom Index Scale (NIH-CPSI), International Prostate Symptom Score-quality of life (IPSS-QoL), and International Index of Erectile Function-5 (IIEF-5) questionnaires. Determination of leukocyturia and bacterial microbiota of PMU and EPS was carried out using the Meares–Stamey test. The Meares–Stamey test was carried out both at the initial and the subsequent control examinations during the follow-up period. It should be mentioned that exceptionally PMU colonization was assessed in the subsequent data processing since the insufficient volume of EPS was obtained in 15% of cases. Bacteriological analysis of PMU was performed on an expanded (n=15) nutrient media set (HiMedia Laboratories Pvt., Maharashtra, India) using aerobic and anaerobic (AnaeroHiGas Pack; HiMedia Laboratories Pvt.) cultivation conditions to determine the maximum possible spectrum of aerobes and anaerobes. Leukocyturia and bacteriuria were also determined at 1, 3, 6, and 12 months after treatment. The lowest valid bacteriuria count was 10^3 CFU/mL. Uroflowmetry (Synectics-Dantec Menuet Compact Urodynamic System; Dantec Medical A/S, City, Denmark) and transrectal prostate sonography (Ultrasound Diagnostic System GE Logiq P6-Pro, convex sensor 4–9 MHz; GE Healthcare, Chicago, IL, USA) were performed before treatment, as well as at 3, 6, and 12 months of follow-up. Ejaculate analysis was performed according to World Health Organization (WHO) 5 criteria (2010) before and 12 months after treatment [19].

The susceptibility of microorganisms isolated from PMU was determined to 11 ABDs, including 4 FQs, 4 oral cephalosporins (CEPs), and 3 MACs.

All patients were prospectively randomized into 2 ABT groups. In group I, ABT was administered orally with one of the FQs to which one or more CBP-related pathogens had the highest susceptibility. In group II, the task was to choose an oral ABT covering all CBP-related pathogens. A FQ monotherapy was only prescribed if all identified bacteria were susceptible to it. Otherwise, if the susceptibility of the bacteria was unsatisfactory to FQ, then a combination of a FQ with CEP and/or MAC was used. The list of ABDs prescribed for treatment in groups I and II are presented in Table 1. Treatment with ABDs was carried out for 1 month and patients were followed up to 12 months without additional ABT, irrespectively whether the cultured pathogens were eliminated or not after the ABT.

2. Statistical analysis

Statistical data processing was performed using Statistica 10.2 software (StatSoft Inc., Tulsa, OK, USA). Descriptive statistics are presented as an estimate of the mean±standard deviation. The indicators distribution normality was determined using the Shapiro–Wilk W-test. Comparison of variables in groups was performed using statistical methods: Student t-test (unpaired and paired t-test for dependent and independent samples), Pearson's χ^2-test. The accepted level of significance was p<0.05.

RESULTS

The baseline general demographics of patients are presented in Table 2.

Thus, young men in the two groups had a severe symptomatic CBP for an average of 4 years, associated with erectile dysfunction (23.3%–30.0% of cases) and high-level amount of pyospermia (86.7%–100.0% of cases) (Table 3).

The detection rates and quantitative characteristics of bacteria initially isolated in the PMU of both groups are shown in Fig. 1.

The taxa of Enterobacteriaceae and *Enterococcaceae*

were isolated from half of the PMU samples from group I and group II, and in addition to them, a wide range of aerobes and anaerobes were also identified in all PMU specimens. Significant differences in the spectrum of bacteria (detection rates) between the groups were noted for *Coryne-*

Table 2. Demographics, disorders, and comorbidities of patients in the two comparison groups

Variable	Group I (n=30)	Group II (n=30)
Demographics		
Age (y), mean±SD	34±2.6	33±2.9
BMI (kg/m^2), mean±SD	27.6±2.1	27.0±2.4
History of CBP (y), mean±SD	4.2±0.7	4.1±1.1
Number of treatment cycles, mean	6.2	5.9
Disorder associated with CBP		
Pain, %	100.0	100.0
Symptoms, NIH-CPSI scale (pts), mean±SD	27.7±2.8	26.2±2.1
LUTS, rate, %	63.3*	53.3*
LUTS, NIH-CPSI scale (pts), mean±SD	6.7±0.8	6.1±0.7
Leukocyturia in PMU, %	100.0	100.0
Prostate volume (cm^3), mean±SD	24.0±1.7*	27.2±1.5*
Uroflowmetry (mL/s), mean±SD	21.3±1.6*	19.8±0.9*
Normozoospermia, %	13.3*	-
Comorbidity		
Arterial hypertension, n (%)	4 (13.3)	3 (10.0)
Ischemic heart disease, n (%)	2 (6.7)*	4 (13.3)*
Diabetes, n (%)	1 (3.3)	-
Irritable bowel syndrome, n (%)	6 (20.0)	7 (23.3)
Sexual activity (last month), n (%)	26 (86.7)	28 (93.3)
Contraception use, n (%)	20 (66.7)	17 (56.7)
Erectile dysfunction, n (%)	7 (23.3)	10 (33.3)
Erectile dysfunction, IIEF-5 scale (pts), mean±SD	17.5±0.4	18.2±0.6

SD, standard deviation; BMI, body mass index; CBP, chronic bacterial prostatitis; NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index Scale; pts, points; LUTS, lower urinary tract symptoms; PMU, post-massage urine; IIEF-5, International Index of Erectile Function-5; -, not available.
*Significant differences between indicators (p<0.05).

Table 1. Antibacterial drugs are used for therapy

Antibacterial drugs	Group I (n=30)		Group II (n=30)	
	n	%	n	%
Levofloxacin	15	50.0	3	10.0
Ofloxacin	8	26.7	9	30.0
Ciprofloxacin	7	23.3	-	-
Cefixime+Ofloxacin	-	-	6	20.0
Cefixime+Levofloxacin	-	-	4	13.3
Cefixime+Josamycin	-	-	8	26.7

-, not available.

bacterium spp., *Staphylococcus warneri*, *Staphylococcus lentus*, *Streptococcus* spp., *Propionibacterium* spp., *Eubacterium* spp., and *Prevotella* spp. At the same time, in group II, the level of PMU colonization was higher in 86.4% of cases but significantly higher only in 31.6% of cases.

The general clinical results of the treatment during the follow-up year are presented in Table 3.

A positive clinical response to treatment was obtained by 3 months follow-up in both groups. In group II, it was significantly higher in all parameters of the NIH-CPSI, leukocyturia level in the PMU, prostate volume, and maximum urinary flow rate (Qmax). However, the reduction of CBP symptoms in the two groups of patients was different thereafter. In group II, a gradual decrease in subjective and objective CBP indicators continued from 3- to 12-months follow-up, but in group I, regression or stabilization of all parameters were observed from 3- to 12-months follow-up. The positive response of ejaculate to therapy was significantly higher in group II as compared with group I.

Bacteriological dynamics in PMU after treatment of patients in both groups are presented in Figs. 2, 3 and Table 4. The spectrum of PMU microbiota in the two comparison groups changed slightly within 6 months after treatment. At the same time, changes in the spectrum of microbiota were especially subtle in group I after 1 and 3 months. Thus, ABT for CBP did not lead to the eradication of bacteria from PMU. Nevertheless, in group II, the bacteriuria associated with *Escherichia coli* and *Enterococcus* spp. significantly decreased by about 5 times and more than 2 times, respectively.

The microbial load of PMU 1 month after treatment decreased in both groups. However, in group I significant decrease was related to only 3 aerobes, and in group II, it was related to 12 aerobes and 8 anaerobes. Also, in group I, there was an increase in the colonization of PMU by 8 anaerobes, with only 3 of them significantly. In group I, bacteriuria of aerobes remained relatively stable by 3 to 6 months compared to 1 month, but the colonization with anaerobes increased for this follow-up period. In group II, the average bacteriuria amounts of aerobes and anaerobes were balanced by 6 months at a level of 10^1–10^3 CFU/mL, or complete elimination of some taxa was observed.

Thus, in groups I and II, the dynamics of bacteriuria were significantly different in a wide range of aerobes and anaerobes.

DISCUSSION

FQs are still considered as the "cornerstone" of first-line treatment for CBP [9]. At the same time, the widespread increase in resistance of uropathogens to FQs may explain the insufficient efficacy of therapy. In two clinical studies [6,7] in men with CBP FQ-resistance was found in 33 of 44 (75%) and 10 of 15 strains (67%), respectively, whereas only one of the strains finally developed resistance to fosfomycin during therapy [6,7]. Most strains were MDR (59%) and 23% had an extended-spectrum beta-lactamase phenotype [6].

Another explanation for insufficient efficacy of ABT may be, that in clinical practice, urologists usually ignore the presence of so-called debatable bacteria in the biomaterial, orienting their prescriptions only for the elimination of so-called causative uropathogens. To consider all bacteria in the biomaterial as possibly causative may increase the need for combination therapy. In a retrospective observational study to investigate the efficacy of levofloxacin monotherapy versus combination therapy against CBP in a real-life setting the clinical records of >2,500 CBP patients was reviewed [20]. Pathogen eradication was achieved in 79% of the cases treated with levofloxacin as a single agent and 87.8% of patients who received a combination of levofloxacin and azithromycin. The 11% increase in the eradication rate in the latter group was statistically significant. In addition, the levofloxacin-azithromycin combination caused a significant decrease in prostate volume and significantly increased the bladder-voided volume. IPSS and NIH-CPSI values and the urinary peak flow rate decreased to a similar extent in both treatment groups.

Previously it was demonstrated that acute bacterial prostatitis could also be reproduced in an animal model both with transurethral inoculation of *Staphylococcus haemolyticus* and of the anaerobe *Peptococcus niger*, both considered so far only as debatable pathogens of CBP [20]. Therefore, we have to consider, that not only Enterobacteriaceae and *Enterococcus* taxa belong to the causative uropathogens of bacterial prostatitis [10,21,22]. And secondly, it turned out that a microbial load of 10^3 CFU/mL causes a comparable inflammatory process in the prostate, as in the case of 10^5–10^7 CFU/mL. The microbial load did not have a direct relationship with the severity of prostatic inflammation [23].

To summarize, we assume that not only so-called causative, but also so-called debatable taxa (present in the prostate or penetrating it somehow) can initiate inflammation under certain conditions. Several microorganisms may be already present within the prostate, even in a healthy man, then other microorganisms may join and cause prostatic inflammation. Therefore, we propose the hypothesis that the entire spectrum of bacteria in the PMU with its antibiotic susceptibility needs to be considered when prescribing ABDs.

Table 3. Results of treatment in patients from groups I and II

Demographic	Group I (n=30)				Group II (n=30)			
	Initial	3 mo	6 mo	12 mo	Initial	3 mo	6 mo	12 mo
Symptoms (NIH-CPSI scale, pts)	27.7±2.8	14.1±2.5*	16.2±2.2*	16.9±2.4*	26.2±2.1	9.2±0.8*	5.2±0.2*	6.0±0.1*
Pain (NIH-CPSI scale, pts)	12.3±1.3	4.9±0.6*	6.0±0.5*	6.8±0.9*	11.2±1.3	3.9±0.6*	3.2±0.1*	3.2±0.1*
LUTS (NIH-CPSI scale, pts)	6.7±0.8	4.1±0.9*	4.9±0.8*	4.7±0.6*	6.1±0.8	1.2±0.2*	0.0	0.0
QoL (NIH-CPSI scale, pts)	8.7±0.7	5.1±1.0*	5.4±0.8*	5.2±0.7*	8.9±0.7	4.1±0.2*	2.0±0.1*	2.9±0.3*
Qmax (mL/s)	21.3±1.1	22.7±1.2	25.9±1.1*	22.3±1.0	19.9±0.9	25.5±1.2*	26.0±0.9*	27.5±1.2*
Prostate volume (cm^3)	24.0±1.7	20.2±1.2*	20.9±1.2	21.3±1.0	27.2±1.5	21.5±1.1*	19.0±0.8*	19.1±1.1*
The number of leukocytes in the FoV (frequency)								
<10	-	16.7*	10.0*	-	-	43.0*	50.3*	57.0*
11–50	7.6	40.0*	23.3*	36.7*	23.4	44.0*	39.7*	43.0*
51–100	42.9	33.3*	50.0	33.3*	26.6	3.0*	10.0*	-
>100	49.5	10.0*	16.7*	30.0*	50.0	10.0*	-	-
Changes in the ejaculate (frequency)								
Normozoospermia	13.3	-	-	40.0*	0.0	-	-	73.3*
Pyospermia	86.7	-	-	60.0*	100.0	-	-	23.3*
Oligoasthenozoospermia	16.7	-	-	23.3	26.7	-	-	3.3*
Teratozoospermia	13.3	-	-	10.0	6.6	-	-	0.0*

Values are presented as mean±standard deviation or percentage only.

NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index Scale; pts, points; LUTS, lower urinary tract symptoms; QoL, the quality of life index; Qmax, maximum urinary flow rate; FoV, field of view; -, not available.

*Show intragroup significant differences between indicators at different follow-up periods concerning the initial data ($p<0.05$).
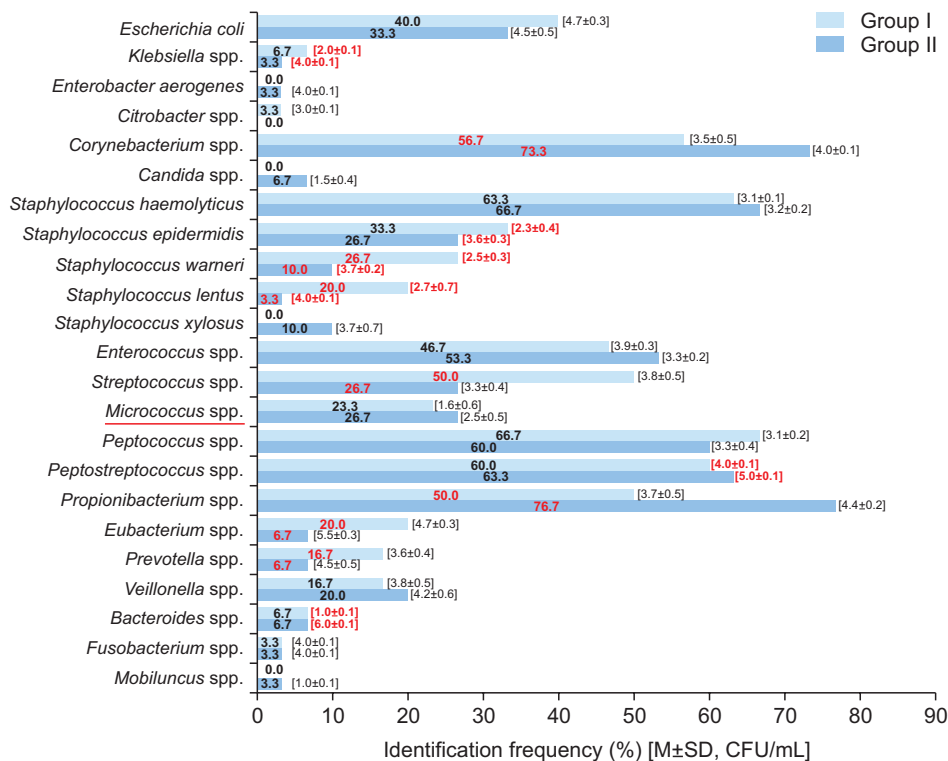
Fig. 1. Identification frequency (%) and quantitative characteristics of micro-organisms (in brackets, 10^n CFU/mL) isolated from post-massage urine of patients of the two comparison groups at admission (significant differences [p<0.05] in indicators between the two groups are highlighted in bold red; aerobic and anaerobic microorganisms are separated by a red line).
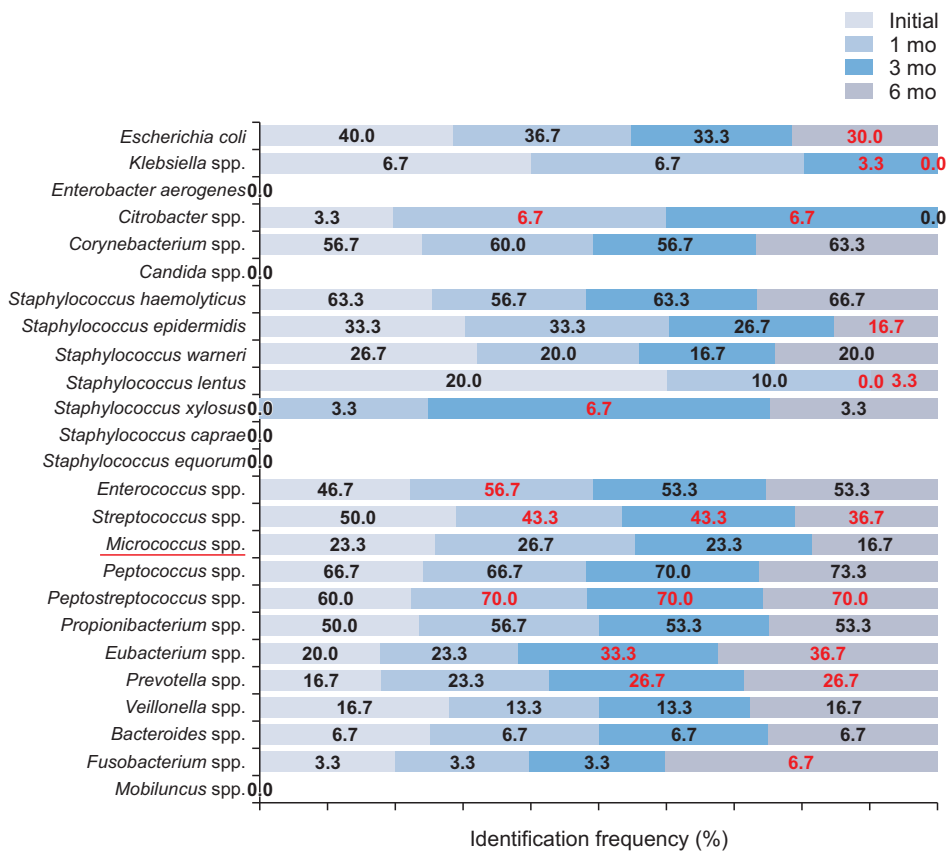

Fig. 2. Microbial spectrum (identification frequency, %) of post-massage urine from patients of group I during the follow-up periods (significant differences [p<0.05] are highlighted in bold red for each microorganism compared to the initial identification frequency; aerobes and anaerobes are separated by a red line).

It was found that this approach to ABT was more effective from both clinical and microbiological aspects. Remission of CBP symptoms was achieved within a year in 86.7% of patients in group II, while in the comparison group I only 46.7% of cases showed these results. A decrease in the microbial load of PMU ≤10^3 CFU/mL by aerobes and anaerobes

Legend: Initial | 1 mo | 3 mo | 6 mo

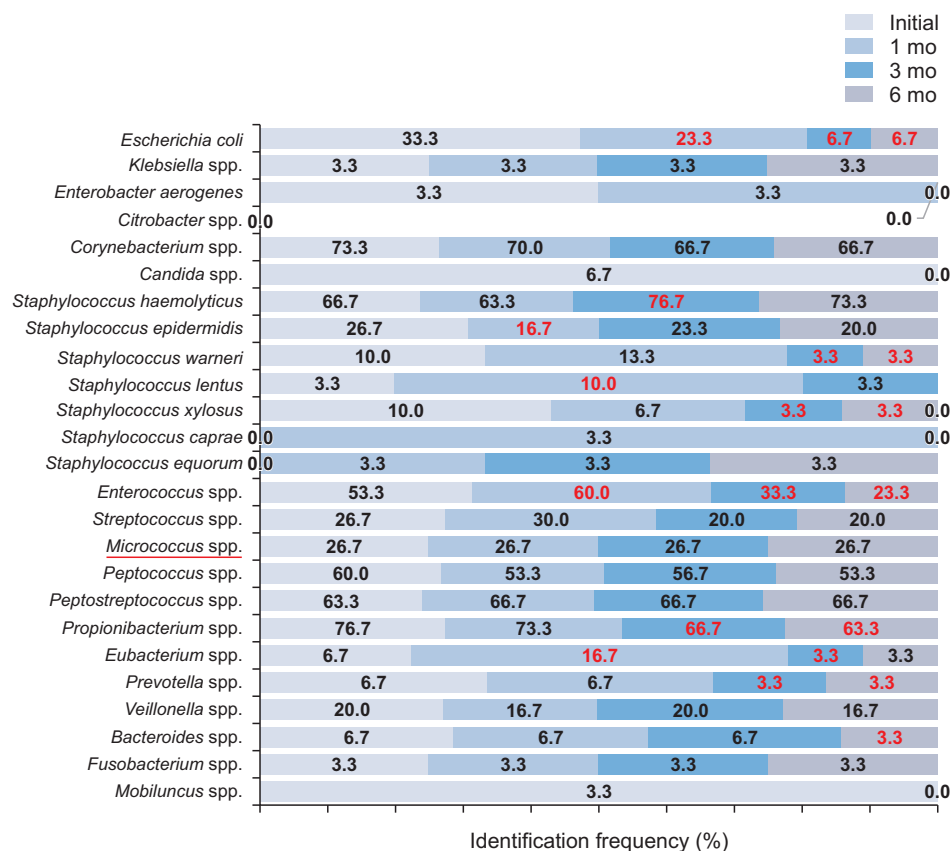| Microorganism	Initial	1 mo	3 mo	6 mo
Escherichia coli	33.3	23.3	6.7	6.7
Klebsiella spp.	3.3	3.3	3.3	3.3
Enterobacter aerogenes	3.3		3.3	0.0
Citrobacter spp.	0.0			0.0
Corynebacterium spp.	73.3	70.0	66.7	66.7
Candida spp.		6.7		0.0
Staphylococcus haemolyticus	66.7	63.3	76.7	73.3
Staphylococcus epidermidis	26.7	16.7	23.3	20.0
Staphylococcus warneri	10.0	13.3	3.3	3.3
Staphylococcus lentus	3.3	10.0		3.3
Staphylococcus xylosus	10.0	6.7	3.3	3.3 / 0.0
Staphylococcus caprae	0.0	3.3		0.0
Staphylococcus equorum	0.0	3.3	3.3	3.3
Enterococcus spp.	53.3	60.0	33.3	23.3
Streptococcus spp.	26.7	30.0	20.0	20.0
Micrococcus spp.	26.7	26.7	26.7	26.7
Peptococcus spp.	60.0	53.3	56.7	53.3
Peptostreptococcus spp.	63.3	66.7	66.7	66.7
Propionibacterium spp.	76.7	73.3	66.7	63.3
Eubacterium spp.	6.7	16.7	3.3	3.3
Prevotella spp.	6.7	6.7	3.3	3.3
Veillonella spp.	20.0	16.7	20.0	16.7
Bacteroides spp.	6.7	6.7	6.7	3.3
Fusobacterium spp.	3.3	3.3	3.3	3.3
Mobiluncus spp.		3.3		0.0

Identification frequency (%)

Fig. 3. Microbial spectrum (identification frequency, %) of post-massage urine from patients of group II during the follow-up periods (significant differences [p<0.05] highlighted in bold red for each microorganism compared to the initial identification frequency; aerobes and anaerobes are separated by a red line).

was detected in 100% cases in group II and 100% of cases in group I regarding only Enterobacteriaceae and *Enterococcus*. This was, however, not the case for so-called debatable uropathogens and anaerobes.

There is no reason to consider the spectrum of CBP-related causative uropathogens to be paradigmatic. Therefore, all microorganisms cultured in the EPS/PMU of male patients with CBP should be investigated for their potential prostate-directed pathogenicity. For successful selection of an ABD or a combination of ABDs antibiotic susceptibility testing of the microorganisms or in case of mixed infections their combinations is also mandatory. The real portrayal of the spectrum of prostatic uropathogens will make it possible to carry out personalized ABT, following modern trends.

In addition, our results showed that ATB should primarily not be directed towards the complete eradication of all microorganisms, but rather aim to minimize the microbial load. At the same time, microbiological monitoring is advisable to control the microbial composition and possible changes in the antibiotic susceptibility. This strategy will allow to carry out timely replacement of the ABDs in case of ineffectiveness and particularly to guide ABT in patients with a recurrent, symptomatic CBP event during the follow-up period.

The restrictions of our study include the single-centre recruitment of patients by one of the authors and the small sample size of patients. There are, however, no studies on CBP reported in the literature, based on an extended bacteriological study of EPS/PMU similar to our method. Therefore, further clinical studies should be encouraged.

CONCLUSIONS

ABT for CBP based on the antibiotic susceptibility of the entire bacterial spectrum identified in the biomaterial should include an individual combination of ABDs as an alternative treatment considering the underestimated aetiology of CBP and MDR of the pathogens. Combined ABT insignificantly alters the microbiota of EPS and does not lead to the complete eradication of causative and so-called debatable pathogens. But at the same time, it causes a significant microbial load reduction of the biomaterial (from 10^1 to 10^3 CFU/mL).

CONFLICTS OF INTEREST

The authors have nothing to disclose.

Table 4. The microbial load of post-massage urine in patients from groups I and II during the follow-up period (lgCFU/mL)

Microorganism	Group I (n=30)				Group II (n=30)			
	Initial	3 mo	6 mo	12 mo	Initial	3 mo	6 mo	12 mo
Aerobes								
Escherichia coli	4.7±0.3	2.6±0.4*	2.5±0.4*	2.0±0.1*	4.5±0.5	3.0±0.1*	2.0±0.1*	2.0±0.1*
Klebsiella spp.	2.0±0.1	1.0±0.1*	1.0±0.1*	0	4.0±0.1	2.0±0.1*	2.0±0.1*	2.0±0.1*
Citrobacter spp.	3.0±0.1	2.0±0.1*	1.5±0.3*	0	4.0±0.1	2.0±0.1*	0	0
Enterobacter aerogenes	0	0	0	0	4.0±0.1	1.8±0.4*	1.8±0.3*	1.7±0.4*
Corynebacterium spp.	3.5±0.5	2.4±0.2*	3.1±0.4	3.5±0.3	1.5±0.4	0	0	0
Staphylococcus haemolyticus	3.1±0.1	2.3±0.3*	2.1±0.3*	3.7±0.2	3.2±0.2	2.6±0.2	2.3±0.4	2.0±0.1*
Staphylococcus epidermidis	2.3±0.4	1.4±0.2*	1.6±0.5	2.4±0.5	3.6±0.3	1.6±0.3*	1.4±0.4*	1.3±0.3*
Staphylococcus warneri	2.5±0.3	2.2±0.3	1.6±0.4	2.5±0.8	3.7±0.2	2.0±0.1*	2.0±0.1*	2.0±0.1*
Staphylococcus lentus	2.7±0.7	2.0±0.1	0	1.0±0.1*	4.0±0.1	1.0±0.1*	2.0±0.1*	0
Staphylococcus xylosus	0	1.0±0.1	1.0±0.1	1.0±0.1	3.7±0.7	2.0±0.1*	1.0±0.1*	2.0±0.1*
Staphylococcus caprae	0	0	0	0	0	1.0±0.1	0	0
Staphylococcus equorum	0	0	0	0	0	2.0±0.1	1.0±0.1*	2.0±0.1
Enterococcus spp.	3.9±0.3	2.7±0.5*	2.3±0.3*	1.8±0.3*	3.3±0.2	1.5±0.3*	1.8±0.4*	1.6±0.6*
Streptococcus spp.	3.8±0.5	2.8±0.4*	2.5±0.5*	2.4±0.7*	3.3±0.4	2.0±0.1*	1.5±0.5*	1.5±0.5*
Micrococcus spp.	1.6±0.6	1.4±0.2	1.4±0.4	1.2±0.2	2.5±0.5	1.4±0.4*	1.5±0.3*	1.5±0.5*
Anaerobes								
Peptococcus spp.	3.1±0.2	3.5±0.3	3.6±0.6	3.8±0.3	3.3±0.4	2.5±0.5	1.8±0.3*	1.9±0.5*
Peptostreptococcus spp.	4.0±0.1	4.8±0.5	4.2±0.2	5.0±0.1*	5.0±0.1	2.4±0.3*	1.9±0.5*	1.7±0.4*
Propionibacterium spp.	3.7±0.5	4.6±0.4*	4.9±0.7*	5.2±0.2*	4.4±0.2	2.0±0.1*	1.7 ±0.7*	1.7±0.4*
Eubacterium spp.	4.7±0.3	4.8±0.4	4.9±0.6	4.4±0.4*	5.5±0.3	2.2±0.2*	1.0±0.1*	1.0±0.1*
Prevotella spp.	3.6±0.4	3.8±0.3	4.0±0.1	4.1±0.3	4.5±0.5	1.5±0.5*	2.0±0.1*	2.0±0.1*
Veillonella spp.	3.8±0.5	4.5±0.5	4.7±0.3*	4.6±0.5*	4.2±0.6	2.2±0.2*	2.0±0.1*	2.0±0.1*
Bacteroides spp.	1.0±0.1	3.0±0.1*	2.5±0.5*	2.5±0.5*	6.0±0.1	3.0±0.1*	2.0±0.1*	3.0±0.1*
Fusobacterium spp.	4.0±0.1	5.0±0.1*	5.0±0.1*	6.0±0.1*	4.0±0.1	2.0±0.1*	2.0±0.1*	2.0±0.1*
Mobiluncus spp.	0	0	0	0	1.0±0.1	0	0	0

Values are presented as mean±standard deviation.
*Shows intragroup significant differences between indicators at different follow-up periods concerning the initial data (p<0.05).

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