Most Commonly Isolated Bacteria in Urine and their *In Vitro* Sensitivity to Antibiotics in Men with Benign Prostatic Hyperplasia

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Abstract: Benign prostatic hyperplasia (BPH) and associated lower urinary tract symptoms commonly affect older men. Men with BPH in Podgorica in almost half (47.5%) cases have positive urine culture, out of which 14.2% have polyinfection. Urinary tract infections are most common in the age group 71 to 80 years. Although both groups of men (with and without BPH) are more prone to gram-negative bacterial infections of the urinary tract, *K. pneumoniae* is significantly more common in men with BPH compared with men without BPH. The results indicate that treatment of men with BPH is much more complex than in men without BPH due to the fact that in the treatment, a number of strains are resistant to levofloxacin (resistance of gram-negative bacteria to levofloxacin at the level of 80.4%, with 89.7% of resistant strains of *K. pneumoniae* and 73.3% of *E. coli* strains, as well as resistance of gram-positive bacteria at level of 24.8%, with resistant strains of enterococci in 64.7% of the strains) and β-lactam antibiotics (53.4% of isolated gram-negative bacteria synthesize ESBL enzymes out of which *K. pneumoniae* in up to 89.7% of the strains). Also, men with BPH have multi drug resistant strains in 53.1% of gram-positive bacteria and 79.7% of gram-negative bacteria. Carbapenems still represent a reserve group of drugs that have a good therapeutic effect in 93.2% of urinary tract infections in men with BPH.

Keywords: Benign prostatic hyperplasia, bacterial infection, antimicrobial susceptibility.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is the most common prostatic disorder affecting elderly men. It is defined as a noncancerous enlargement of the prostate due to occurrence and growth of new prostate cells. Previously, it was thought that BPH is a physiological process that occurs with aging, regardless of race, ethnicity or region [1, 2]. Recent epidemiological studies suggest that BPH is more prevalent in the Asian population [3, 4]. It is believed that multiple factors are responsible for the pathophysiology of BPH disease (hormonal imbalance, disruption of cell proliferation, hereditary, chronic inflammation) [5, 6]. Histopathologic evidence of BPH is present in approximately 8% of men in their fourth decade and in 90% of men by their ninth decade [7]. Therefore, it is often said, "Men will develop benign prostatic hyperplasia if they live long enough."

One of the most important reasons why BPH attracts attention of the doctors is that untreated BPH may lead to complications including urinary tract infection (UTI), acute urinary retention, and obstructive nephropathy [8]. Consequently, men with significant clinical BPH are probably at risk of UTI, and men with UTI should be assessed for signs of BPH. That was the reason for the American Urological Association to recommend routine urinalysis which can reveal pyuria and bacteriuria suggesting infection [9]. In this case, use of antibiotics and urinary tract antiseptics is justified due to the existing urinary tract infection, according to the findings of urine culture and antimicrobial susceptibility [10, 11]. As a rule, antibiotics that achieve the highest concentration in the prostate are used: co-trimoxazole, doxycycline, ciprofloxacin, ofloxacin, levofloxacin, erythromycin, carbenicillin [11].

According to the specified, BPH represent significant challenges for health-care systems in most parts of the world for what every physician need be familiar. The primary motivation for developing this paper rose from this statement: to make contribution to the complex interpretation and treatment of men with BPH through microbiological approach.

The purpose of the present study was: to investigate the presence of bacteria in the urine of men with BPH and bacterial sensitivity to levofloxacin, often used in the treatment and prophylaxis of prostate infection. In addition, the aim was to investigate the presence of extended-spectrum beta-lactamases (ESBL)-producing strains with determination of the sensitivity of enterobacteria to β-lactam antibiotics. It also examined in what extent these men can have a failure in antibiotic treatment due to the presence of multi drug resistant and carbapenem resistant strains.

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MATERIALS AND METHODS

Materials

672 investigated and nonduplicate urines from urogenital tracts of men adults were collected during 2013 at the Institute of Public Health – Podgorica, Montenegro. Of these, 356 urine samples belonged to men diagnosed with BPH and 316 urine samples were collected from men diagnosed with uncomplicated urinary tract infections and without BPH. The men were aged 30 to 90 years.

Methods of Isolation and Identification

A urine culture was used for diagnosis. Isolation was performed on CPS (chromogenic) agar (bioMerieux, France) and blood agar (bioMerieux, France). Urine samples which had ≥ 10^5 CFU (colony forming unites)/ml of urine after seeding on the agar was defined as positive urine culture. For identification, our Microbiology Department used the VITEK® 2 system and biochemical range. Isolates were tested with the same batch of identification cards and under the same conditions to maintain comparability.

Methods for the Determination of Antibiotic Sensitivity

Antimicrobial susceptibility was determined by GN and GP cards VITEK® 2 system and disk diffusion method. Antimicrobial susceptibility of gram-negative and gram-positive bacteria was determined by using GN077 and GP580 Vitek cards. Multi drug resistance (MDR) was determined based on the presence of resistance to three or more groups of antibiotics [12].

ESBL-producing enterobacteria and gram-negative bacteria resistant to carbapenems were detected by disk diffusion method according to CLSI instructions and Vitek therapeutic Interpretation Guideline of phenotypic parameter from the AES Detail Report [13].

At the end, the results were summarized in the following form: sensitivity to levofloxacin (in gram-positive and gram-negative bacteria), and carbapenems (in gram-negative bacteria), the presence of ESBL-producing strains (in enterobacteria) and multi drug resistant strains (in gram-positive and gram-negative bacteria)

RESULTS

For the purpose of this paper, 672 urine samples of men with and without BPH were bacteriologically tested. Out of 356 urine samples belonging to men diagnosed with BPH, 169 (47.5%) had positive urine culture and UTI. Out of 316 urine samples belonging to men without BPH, 81 (25.6%) had positive urine culture and UTI. Statistical analysis showed that men with BPH were significantly more likely to have UTI compared to men without BPH (χ^2 = 34.17, $p < 0.01$). Further analysis followed up the men with positive microbiological findings of urine.

Age Distribution

Test results showed that men with BPH with aging had the continued growth of positive urine culture and UTI, with the highest incidence in the age group 71 to 80 years (Table **1**). Men without BPH constantly had positive urine culture and UTI in the range from 12.3% to 25.9%. Men without BPH and UTI were not present

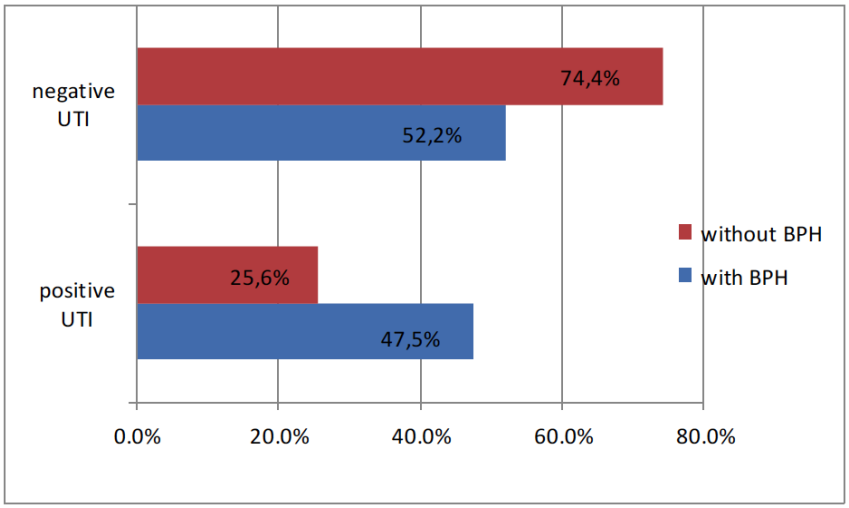

Figure 1: Men with and without BPH and their findings of UTI obtained by diagnosis of urine culture.

Table 1: Men with and without BPH and Positive Urine Culture in Different Age Groups

Age group	Men with positive urine culture					
	with BPH n=169		without BPH n=81		total n=250	
	No.	%	No.	%	No.	%
31-40	2	1.2	21	25.9	23	9.2
41-50	11	6.5	16	19.7	27	10.8
51-60	21	12.4	14	17.4	35	14.0
61-70	39	23.1	20	24.7	59	23.6
71-80	83	49.1	10	12.3	93	37.2
81-90	13	7.7	0	0.0	13	5.2

in the age group 81–90 years. Statistical analysis shown that men with BPH were significantly more likely to have UTI and positive urine culture in the age group 71 to 80 years, compared to men without BPH (χ^2 = 72.44, p < 0.01).

Microbiological Findings of Urine Culture

Out of 169 positive urine culture obtained from men with BPH and UTI, 197 bacteria were identified, and the most dominant were gram-negative bacteria (75.2%) (Figure **2**). Very similar findings was found in the group of men without BPH where 82 bacteria were identified, among which gram-negative were prevailing (73.2%) (Figure **2**).

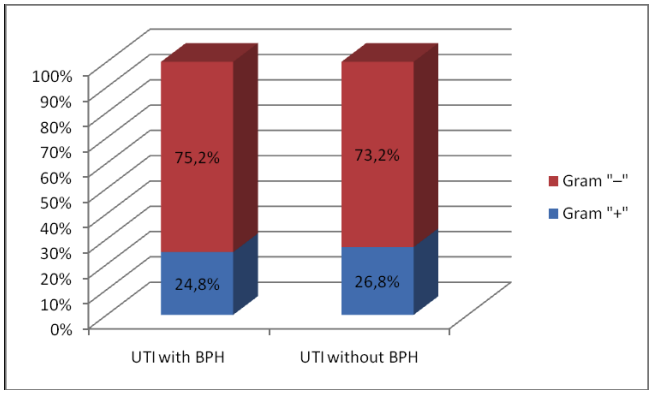

Figure 2: The total number of bacteria isolated from urine of men with and without BPH.

Examined groups differed in relation to the number of bacteria present per man: ≥ 2 bacteria (polyinfection) in men with BPH it was present in 24 (14.2%) cases, while in men without BPH, infection caused by one cause was dominant (monoinfection) and it was found in 80 (98.8%) cases (Figure **3**). Statistical analysis showed that men with BPH were significantly more likely to have polyinfection compared to men without BPH (χ^2 = 11.38, p <0.01).

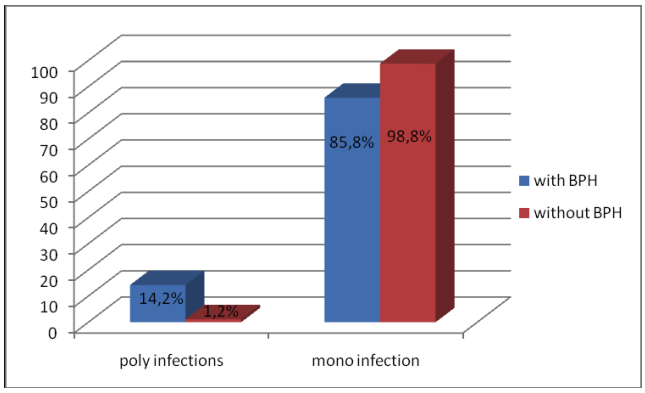

Figure 3: UTI monoinfection and poly infections in men with and without BPH.

Gram-positive and gram-negative bacteria were diagnosed in the urine samples. A total of 71 gram-positive bacteria were diagnosed, 49 in men with BPH (with 6 different strains) and 22 in men without BPH (with 3 different strains) (Figure **4**). *Enterococcus faecalis (E. faecalis)* was the most frequently isolated gram-positive bacteria in both groups (69.4% in men with BPH, 68.2% in men without BPH). On the other hand, a total of 208 gram-negative bacteria were diagnosed, out of which 148 were found in men with BPH (with 14 different strains) and 60 were found in men without BPH (with 7 different strains). *Escherichia coli* was the most frequently isolated gram-negative bacteria in men without BPH, and it dominated with 63.3% (Figure **5**). *Klebsiella pneumoniae ssp. pneumoniae (K. pneumoniae)* (26.4%) and *Escherichia coli (E. coli)* (20.3%) were the most frequently isolated gram-negative bacteria in men with BPH (Figure **5**). Considering that two more strains belonging to the species *Klebsiella* (*K. pneumoniae ssp ozaenae* and *K. oxytoca*) were isolated, then it can be concluded that *Klebsiella* was the most frequently isolated gram-negative bacteria in patients with BPH, with the presence of more than 1/4 (28.4%). Other isolated bacteria are shown in Figures **4** and **5**.

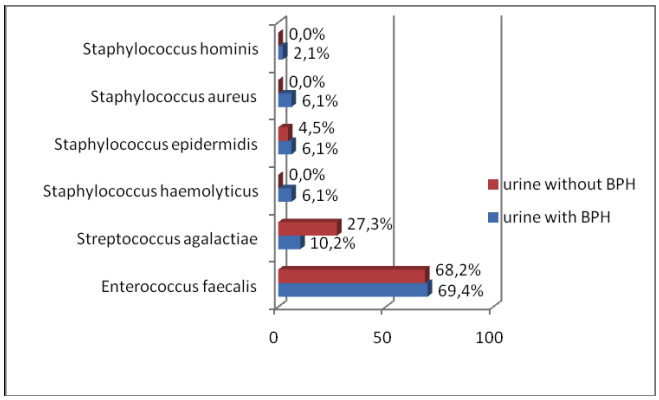

Figure 4: Gram-positive bacteria isolated from urine and identified by strains in men with and without BPH.

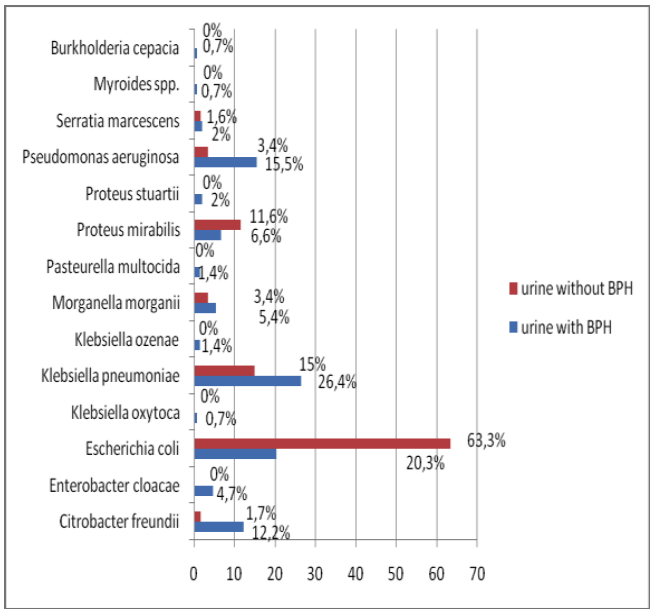

Figure 5: Gram-negative bacteria isolated from urine and identified by strains in men with and without BPH.

Statistical analysis proven that *K. pneumoniae* was significantly more common in men with BPH compared to men without BPH ($\chi^2 = 19.61$, $p < 0.01$). Although *E. coli* was a bacterium more frequently isolated from the urine of men without BPH (63.3%) compared to men with BPH (20.3%) there was no statistical significance ($\chi^2 = 1.51$, $p > 0.05$).

Sensitivity of Isolated Bacteria to Antimicrobials

a. Sensitivity to Levofloxacin

Depending on the health status of men and bacterial strain, bacteria showed different sensitivity to levofloxacin.

In men with BPH the leading were gram-positive bacteria, resistant to levofloxacin (57.1%), and the most commonly isolated gram-positive *E. faecalis* (64.7%) (Figure **6**). In men without BPH all gram-positive bacteria and their strains showed a high level of *in vitro* sensitivity to levofloxacin (95.5%), even in the case with the most commonly isolated *E. faecalis* (93.3%) (Figure **7**).

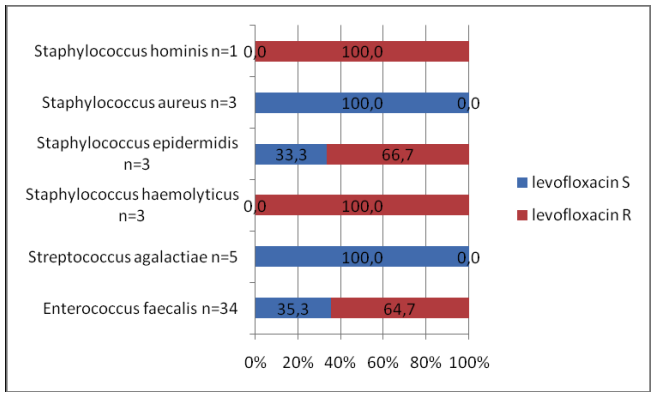

Figure 6: Sensitivity of gram-positive bacteria to levofloxacin in men with BPH.

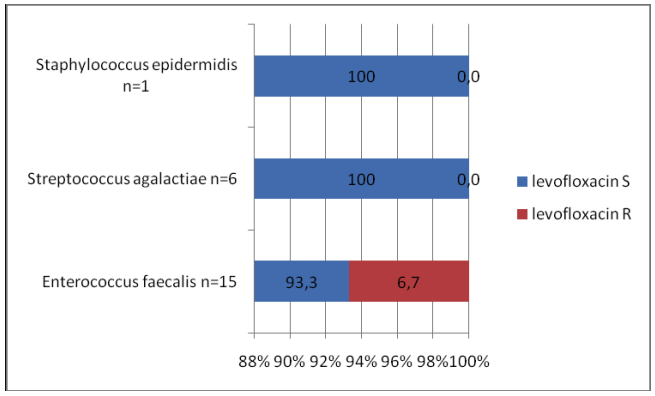

Figure 7: Sensitivity of gram-positive bacteria to levofloxacin in men without BPH.

Statistical analysis showed that gram-positive bacteria isolated from urine of men with BPH were significantly more resistant to levofloxacin compared to gram-positive bacteria isolated from urine of men without BPH ($\chi^2 = 17.98$, $p < 0.01$). Also, the statistical analysis confirmed that predominantly isolated *E. faecalis* was significantly more resistant to levofloxacin in men with BPH compared to *E. faecalis* isolated from men without BPH ($\chi^2 = 14.07$, $p < 0.01$).

In men with BPH, dominant were gram-negative bacteria strains resistant to levofloxacin (80.4%). Also, two most frequently isolated bacteria in men with BPH showed resistance to levofloxacin: 89.7% strains of *K. pneumoniae* and 73.3% strains of *E. coli* (Figure **8**). In men without BPH, gram-negative bacteria and their strains showed a high level of *in vitro* sensitivity to levofloxacin (75%), and the most frequently isolated *E.*

coli showed sensitivity to levofloxacin in over 2/3 strains (76.3%) (Figure **9**). Other isolates of gram-negative bacteria and their sensitivity to levofloxacin are shown in Figures **8** and **9**.

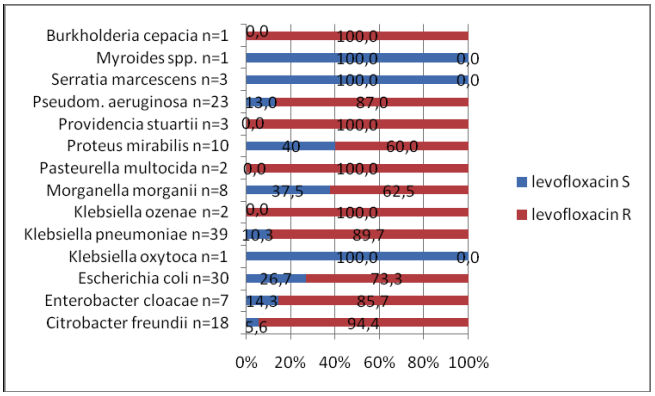

Figure 8: Sensitivity of gram-negative bacteria to levofloxacin in men with BPH.

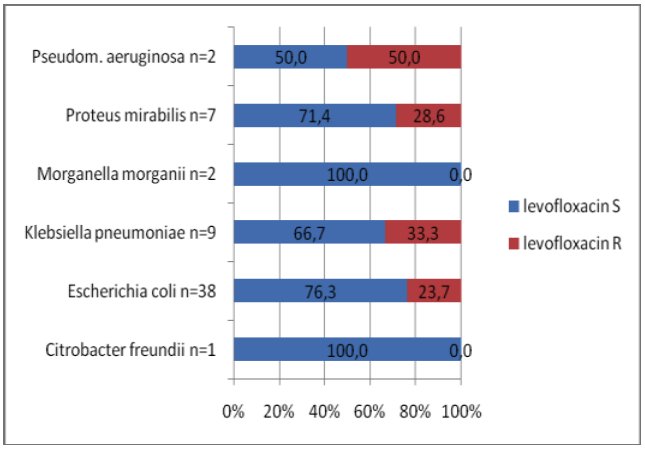

Figure 9: Sensitivity of gram-negative bacteria to levofloxacin in men without BPH.

Statistical analysis showed that gram-negative bacteria isolated from urine of men with BPH were significantly more resistant to levofloxacin compared to gram-negative bacteria isolated from urine of men without BPH (χ^2 = 57.29, p <0.01). Also, statistical analysis confirmed that two most frequently isolated bacteria in men with BPH, *K. pneumoniae* (χ^2 = 14:52, p <0.01) and *E. coli* (χ^2 = 14.91, p <0.01), showed statistically significant resistance to levofloxacin compared to the same bacteria isolated from urine of men without BPH.

b. Sensitivity to Carbapenems

In the examined group with BPH, gram-negative bacteria showed a relatively high sensitivity to carbapenems (93.2%), as out of 148 isolated bacteria only 10 strains showed resistance to carbapenems (Figure **10**). P*seudomonas aeruginosa* (2.7%) was the most resistant bacteria to carbapenems in the urine of patients with BPH, (Figure **10**). In men without BPH all 60 gram-negative bacteria showed sensitivity to carbapenems. However, statistical analysis proven statistical difference in the sensitivity to carbapenems in gram-negative bacteria isolated from urine of men with BPH compared to gram-negative bacteria isolated from urine of men without BPH (χ^2 = 4.79, p < 0.05).

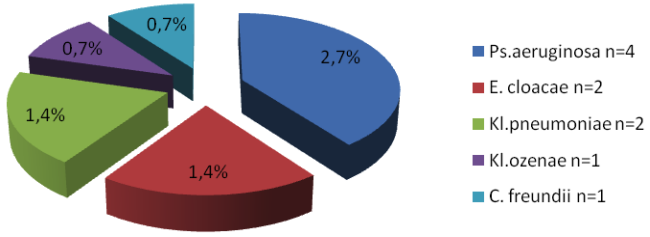

Figure 10: The resistance of isolated strains to carbapenems from urine of men with BPH.

c. The ESBL-Producing Bacteria

In urine of men without BPH there were few strains of gram-negative bacteria (6.7%), with the ability to synthesize hydrolytic ESBL enzymes, while in men with BPH, more than half (53.4%) of isolated strains of gram-negative bacteria had the ability to synthesize ESBL enzymes.

K. pneumoniae is a bacterium whose strains of both groups usually synthesize ESBL enzymes (79.2%). In men with BPH the most ESBL-producing species were: *K. pneumoniae* (with 89.7% strains), and *Citrobacter freundii* (with 88.9% strains) (Figure **11**). In the group of men without BPH only two species were with ESBL-producing strains: three strains (33.3%) of nine isolated *K. pneumoniae* and one strain (14.4%) of seven isolated *P. mirabilis*. The most commonly isolated *E. coli* in men without BPH did not show the ability to synthesize ESBL (Figure **12**).

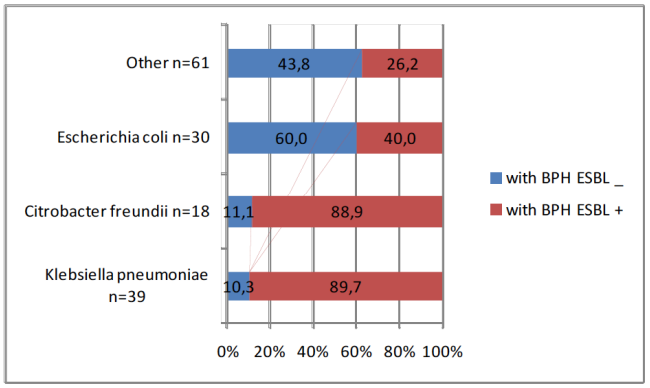

Figure 11: ESBL-producing entero bacteria strains isolated from urine of men with BPH.

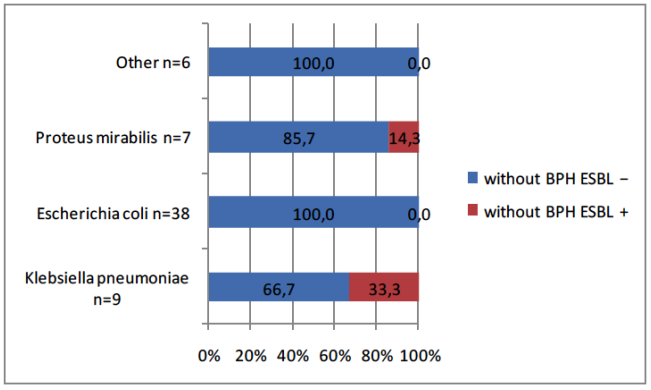

Figure 12: ESBL-producing entero bacteria strains isolated from urine of men without BPH.

Statistical analysis proven that ESBL-producing bacteria was significantly more common in men with BPH compared to men without BPH (χ^2 = 56.83, p < 0.01) and may represent a risk factor for unsuccessful treatment of UTI.

Statistical analysis proven that *K. pneumonia,* as the most frequently isolated bacteria from the urine of men with BPH, significantly more often contained ESBL-producing strains compared to the same type of bacteria in men without BPH (χ^2 = 12.38, p < 0.01).

Multi Drug Resistance of Gram-Positive and Gram-Negative Bacteria

Out of the total 279 isolated bacteria from the urine of men with and without BPH, 60.6% of bacteria showed MDR, out of which 9.7% were gram-positive bacteria and 50.9% were gram-negative bacteria. This high percentage of the overall presence of MDR was the result of large number of MDR strains of bacteria isolated in the urine of men with BPH. Thus, out of total 197 bacteria isolated from the urine of men with BPH even 155 (78.7%) showed MDR, 53.1% in gram-positive bacteria and 87.2% in gram-negative bacteria.

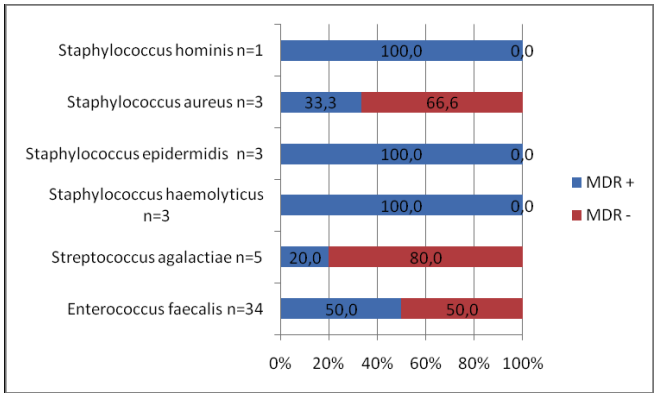

Figure 13: MDR gram-positive bacteria isolated from the urine of men with BPH.

Out of all isolated gram-positive bacteria, at least one bacterial strain was multi drug resistant, where *E. faecalis* was dominant with 50.0% of MDR (Figure **13**).

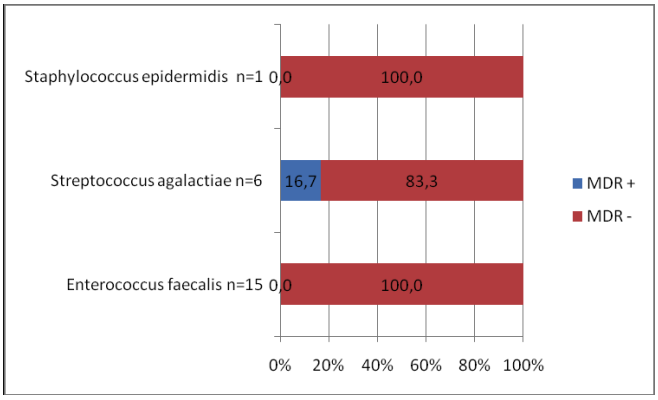

Figure 14: MDR gram-positive bacteria isolated from the urine of men without BPH.

Out of all isolated gram-negative bacteria, also, at least one strain showed MDR (except *K. oxytoca*), and *K. pneumonia* was dominant, with even 92.3% of MDR (Figure **15**).

In men without BPH, out of total 82 isolated bacteria, 17.1% of strains were MDR, predominantly in gram-negative bacteria (15.8%). Out of two dominantly isolated bacteria *E. faecalis* did not show MDR (Figure **14**), while *E. coli* in 6 (15.8%) strains showed MDR (Figure **16**).

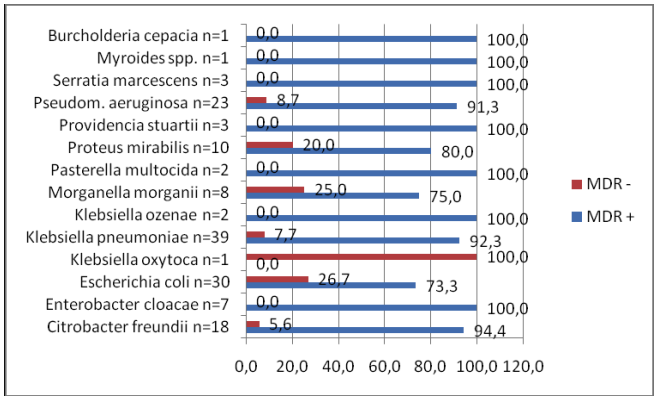

Figure 15: Gram-negative bacteria MDR strains isolated from urine of men with BPH.

Statistical analysis showed that MDR gram-positive bacteria (χ^2 = 15.67, p < 0.01) and MDR gram-negative bacteria (χ^2 = 77.15, p < 0.01) were significantly more often present in urine of men with BPH compared to men without BPH. Also, statistical analysis showed that MDR strains of *E. faecalis* (χ^2 = 11.48, p < 0.01), *K. pneumoniae* (χ^2 = 16.10, p < 0.01) and *E. coli* (χ^2 = 20.90, p <0.01) were significantly more often found in men with BPH compared to men without BPH.

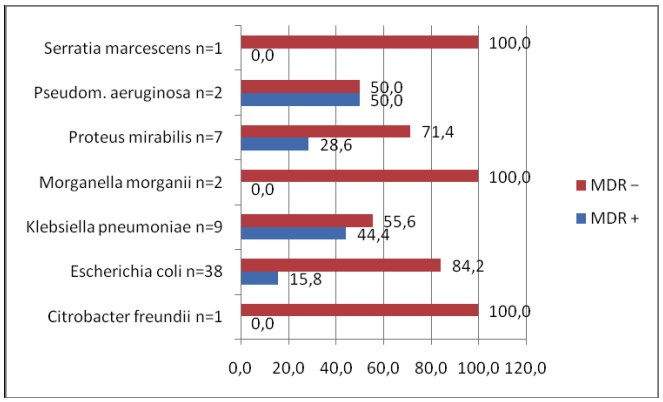

Figure 16: Gram-negative bacteria MDR strains isolated from urine of men without BPH.

DISCUSSION

In this study microbiological results showed that men with BPH in Podgorica, in almost a half of cases (47.5%) had positive urine culture, indicating to presence of UTI. UTI was by 21.9% more common in men with BPH compared to a group of men without BPH. Isolation of bacterium in urine culture and its further identification aims to show antimicrobial susceptibility. Determination of effective antibiotics is necessary because studies indicate that anti-inflammatory therapy is achieved by the combination of α-blockers, and antibiotics, which provides visible improvement of clinical symptoms [14].

The study found that a positive urine culture in men with BPH was continuously more common with aging of men. Thus, a positive urine culture and UTI in men with BPH reached its peak in the age group 71-80 years (49.1%). The men without BPH fairly have had a positive urine culture and UTI. Two slightly higher peak of incidence of urinary tract infections and positive urine culture in men without BPH occurred in age group from 31 to 40 years (25.9%) and 61-70 years (24.7%). Studies of other authors also suggest that due to the increased volume of the prostate, UTI are become more frequent with aging [15]. Thus, the study of Verhamme *et al.* 2002, found that men in the age group 45-49 years had BPH incidence of 3/1000, while in the period from 75 to 79 years of age, the incidence went up to 38/1000 [16]. Authors of this study recommend that often presence of UTI in men who were not diagnosed with BPH, should suggest the possible presence of BPH [16].

Study of Marberger *et al.* 2000, reported that those with larger prostates (>40 ml) and positive serum prostate-specific antigen were more likely to develop acute urinary retention and infection [17]. Similar results related to frequency of urinary infections at elderly population were also found by Jacobsen *et al.* 1993, they indicated that men aged 70 to 79 years were 4.6 times more likely to seek health care because of urinary symptoms (95% confidence interval, 2.1 to 10.1) compared to men aged 40 to 49 years [18].

Further, the study followed positive urine culture. Urine culture and their analysis showed that isolation of gram-negative bacteria was more common in both groups (men with BPH 75.2%; men without BPH 73.2%) compared to the gram-positive bacteria (men with BPH 24.8%; men without BPH 26.8%) and their mutual relationship (gram positive/gram negative) is fairly uniform. However, a difference was seen in relation to the number of isolated bacteria per sample. Thus, polyinfection was found in 14.2% of men with BPH, while in men without BPH it was found in only 1.2% of cases. Bacterial presence, associated with BPH has also been documented by other authors. For example, Gorlick *et al*., 1988, reported that 21% of prostatic tissue in patients undergoing prostatectomy yielded positive of bacterial grow [19]. An infection rate of 8.6% in men with BPH with no prior instrumentation has also been reported [20].

Regarding therapy, due to drug resistance of gram-positive bacteria to levofloxacin, failure of the treatment may occur in 57.1% of men with BPH, and in 4.5% of men without BPH. Analysis by type of gram-positive bacteria indicated that men in Podgorica in both study groups had mostly in their urine *E. faecalis* (men with BPH – 69.4%, men without BPH – 68.2%). However, when it is necessary to carry out treatment, there is a difference in sensitivity to levofloxacin. Thus, strains of enterococci in men with BPH were resistant to levofloxacin in 64.7% of cases, while in men without BPH it was negligible number of 6.7% of cases.

Also, analysis of the present antibiotic resistance has indicated that in 53.1% of men with BPH there was a problem of multidrug-resistance of gram-positive bacteria, while in men without BPH MDR was represented in 4.5% of cases. This leads to the fact that in the therapy of current UTI, caused by gram-positive bacteria, in more than a half of men with BPH in Podgorica, at least three groups of antibiotics will not be available.

Although men with and without BPH are more prone to gram-negative bacterial infections, they differ in the strains of bacteria. Thus, while in men with BPH there were two dominant strains of bacteria, *K. pneumoniae*

in more than 1/4 of examined men (26.4%) and *E. coli* in 1/5 of examinees (20.3%), in men without BPH infection caused by *E. coli* dominated convincingly in nearly 2/3 of men (63.3%). The importance of this consists is in the fact that *K. pneumoniae* is more prone to genetic changes and the acquisition of resistance to many antibiotics which directly affects the outcome of patient's treatment [21, 22, 23, 24].

Further analysis of the results confirmed the suspicion that the increasing presence of *K. pneumoniae* in a sample of men with BPH leads to infections which are often therapeutically extremely limited. Studies showed a mortality rate between 20 and 40% in patients with bacteremia caused by *K. pneumoniae* [25, 26, 27]. Tuon *et al.* 2011, showed that *K. pneumoniae* infection is high and more than 50% of patients were under inadequate treatment because of ESBL-producing strains, justifying the use of carbapenems as first choice in patients admitted to centers with high incidence of ESBL-producing strains [28].

A meta-analysis by Berry and Barratt, 2002, suggested that prophylaxis in men with BPH significantly decreased bacteriuria and septicemia, even in men with sterile urine preoperatively [29]. In their metaanalysis, effective agents included quinolones, aminoglycoside, sulfa-trimethoprim, and cephalosporin [29]. Such prophylaxis reduced septicemia rates from 4.4% to 0.7% in these low-risk patients. Short-course therapy was found to be more effective than single-dose regimens, regardless of the agent chosen [29]. However, the results of our study showed that treatment of men with BPH compared to men without BPH, in our society, is much more complicated due to the fact that week therapeutical effect was shown by following drugs: levofloxacin (resistance of gram-negative bacteria to levofloxacin at the level of 80.4% with 89.7% of resistant strains of *K. pneumoniae* and 73.3% of *E. coli* strains), β-lactam antibiotics (53.4% of isolated gram-negative bacteria synthesize ESBL enzymes out of which *K. pneumonia* even in 89.7% of strains), multi drug resistance has been present in 78.7% of strains (in gram-positive 53.1% of bacteria, in gram-negative 87.2% of bacteria, and in *K. pneumoniae* even 92.3% have been MDR) and resistance to carbapenems in 6.8% of cases. The fact that in men with BPH, gram-negative bacteria (and *K. pneumoniae* as the most commonly isolated bacteria) statistically significant frequent insensitive to levofloxacin, β-lactam antibiotics, carbapenems and have had MDR strains, is of practical importance as they represent a risk factor for failure in treatment of UTI in men with BPH.

The following fact raised by certain studies is of greater concern: prostatic inflammation is an extremely common histological finding in men with symptoms of BPH who have no symptoms of prostatitis [6]. On the other hand, how important is a good choice of antibiotics in treatment of prostate is well illustrated by the case of acute meningitis caused by multidrug-resistant *E. coli* after transrectal prostate biopsy presenting that antibiotic prevention with fluoroqinolons is not absolutely risk free [30].

CONCLUSION

The resistance of gram-negative bacteria, especially the most frequently isolated *K. pneumonia,* to levofloxacin, β-lactams and carbapenems, as well as the presence of MDR bacteria indicates the possible bad outcome in the antibiotic treatment of men with BPH in our community, thus it is advisable, when it is possible, to do microbiological analysis of sample before initiation of antibiotic therapy.

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