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Preliminary trial of 24 vs 72 hour perioperative meropenem in patients with ESBL-producing *Enterobacterales* bacteriuria scheduled for urological procedures

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Introduction Antimicrobial prophylaxis is an important issue in positive urine culture patients undergoing endourological procedures or extracorporeal shock wave lithotripsy (ESWL). It is especially recognized in asymptomatic bacteriuria patients of alarm pathogen etiology. We designed a preliminary study to determine optimal duration of antibiotic prophylaxis in patients undergoing endourological procedures or ESWL with asymptomatic bacteriuria caused by *Enterobacterales* with extended spectrum beta-lactamase positive (ESBL+) type resistance.

Material and methods A total of 60 patients with confirmed ESBL+ *Enterobacterales* bacteriuria were admitted for endourological procedures or ESWL. The patients were randomized into two groups – a one-day (n = 33) and a three-day (n = 27) period of perioperative antibiotic prophylaxis with meropenem. In both groups on the following day after the procedure (24 hours after the procedure) and 7 days after the procedure serum inflammation markers were assessed.

Results Values of white blood count, C-reactive protein and procalcitonin prior to, 24 hours and seven days after the procedure clearly showed no statistically significant differences between groups that have received a one-day and three-day antibiotic regimen.

Conclusions In patients with ESBL+ *Enterobacterales* asymptomatic bacteriuria undergoing endourological procedures or ESWL a 72-hour perioperative meropenem prophylaxis showed no superiority over a 24-hour regimen. Further studies will be carried out to establish optimal prophylaxis for specific endourological procedures and to test safety of a single dose regimen.

Key Words: asymptomatic bacteriuria ‹› prophylaxis ‹› extracorporeal shock wave lithotripsy ‹› ureteroscopy ‹› extended spectrum beta-lactamase ‹› meropenem

INTRODUCTION

Introduction of antibiotics to medicine gave many patients a chance to recover 'miraculously' from infections that were considered fatal. Application of the principles of antiseptics and antibiotic prophylaxis alongside with anesthesia allowed the development of modern surgical procedures. Since the discovery of antibiotics in 1928 by Alexander Fleming, the enormous power of antimicrobial substances has become a widely available and often an overused method of treatment. Antibiotics became a double-edged sword, as over time specific bacteria became resistant to their action. Despite the efforts of the scientific world and invention of new generations of antibiotics, pathogens have learned to defend themselves against the effects of these substances. In recent decades, easy access and excessive use of antibiotics in both medicine and agriculture has led to the production of bacterial strains resistant to all cur-

rently available antimicrobial agents. These multi-drug resistant pathogens, with high epidemiological potential are vastly spreading and are responsible for many nosocomial infections.

In the current era of rising antibiotic resistance pathogens, such as Vancomycin Resistant Enterococcus (VRE), High Level Aminoglicoside Resistant Enterococcus (HLAR) or *Enterobacterales* with Extended-Spectrum Beta-Lactamases (ESBL) and New Delhi Metallo-β-lactamase (NDM) are becoming more frequent [1]. We found that previously used recommendations for the management of patients, including the principles of antibiotic prophylaxis were often inadequate in those with a colonized urinary tract that had no symptoms of urinary tract infection – which is commonly known as asymptomatic bacteriuria (ABU) [2, 3, 4].

Antimicrobial prophylaxis is aimed at ensuring safety and minimizing infectious complications in patients undergoing surgical procedures. Prophylaxis is especially valid in procedures entering the urinary tract. Prolonged use of antibiotic prophylaxis is unjustified, increases the risk of producing strains with a higher degree of resistance (e.g. strains producing cephalosporinases or carbapenemases – ESBL, AmpC, NDM, OXA-48, KPC), the occurrence of unwanted side effects, and additionally increases the healthcare costs and the length of hospitalization of the patient [5]. To date, it has not been determined how peri-procedural antibiotic prophylaxis should be performed in patients with asymptomatic bacteriuria caused by multi-drug-resistant bacteria [6]. So far there are no specific guidelines for handling this group of patients undergoing endourological procedures or extracorporeal shock wave lithotripsy (ESWL) for urolithiasis. This is especially valid currently where presence of alarm pathogens is so frequent [7, 8].

Aim of the study

The rising frequency of presence of *Enterobacterales* ESBL+ among patients in our department aroused fear and uncertainty. Lack of literature on choice of treatment combined with awe towards ABU of *Enterobacterales* ESBL+ origin lead in many cases to prolonged use of antibiotic regimen. Doubting the significance of such antimicrobial prophylaxis, we designed a preliminary study for the purpose of determining the optimal duration of antibiotic regimen. We selected patients treated with endourological procedures or ESWL for urolithiasis who presented with ABU caused by *Enterobacterales* with ESBL+ resistance mechanism. In this parallel-group, prospective, randomized control trial we compared the effectiveness of 24-hour and 72-hour peri-procedural antimicrobial prophylaxis in patients undergoing these procedures.

In the trial we enrolled 60 patients with asymptomatic bacteriuria of *Enterobacterales* ESBL+ origin who underwent endourological procedures or ESWL at the Department of General, Functional and Oncological Urology of the Military Institute of Medicine in Warsaw (WIM), Poland. Patients were randomized into two groups – a one-day (n = 33) and three-day (n = 27) treatment period of perioperative antibiotic prophylaxis with meropenem (Fresenius Kabi) 500 mg i.v. TID.

MATERIAL AND METHODS

Ethical statement

The study design was approved by the institutional Bioethical Committee (24/WIM/2016 of April 20, 2016).

An informed consent has been obtained from the patients that participated in the study.

Patients

During the period of time from October 2016 to June 2020 we enrolled 60 patients with asymptomatic bacteriuria of *Enterobacterales* ESBL+ origin who underwent endourological procedures or ESWL at the Department of General, Functional and Oncological Urology of the Military Institute of Medicine in Warsaw, Poland. Chronic and concomitant diseases were not taken into account. The inclusion criteria are shown in Table 1.

Upon admission, patients underwent the following laboratory tests: white blood count (WBC), C-reactive protein (CRP), procalcitonin (PCT). After confirming the occurrence of asymptomatic bacteriuria, the patients were randomized into one of two groups – a one-day (n = 33) and three-day (n = 27) prolonged antibiotic prophylaxis with meropenem (Fresenius Kabi) 500 mg i.v. TID.

In both groups on the following day after the procedure (24 hours after the procedure) and after 7 days following the procedure, laboratory tests (control urine culture, blood count, CRP, procalcitonin) measurements were performed. We compared data accordingly between the two groups.

Methods

A total of 60 patients were enrolled in the study (28 female, 32 male) and gave their written informed consent to participate. The enrolled patients were

subject to endourological procedures or ESWL, e.g.: Bricker's conduit distention (n = 1), cystolithotripsy (n = 2), JJ-stent removal (n = 3), urethrocystoscopy (n = 3), transurethral resection of bladder tumor (TURBT, n = 4), nephrostomy tube replacement (n = 8), URSL (ureteroscopic lithotripsy) (n = 8), JJ-stent replacement (n = 10), UPG (uretero-pyelography) (n = 2), ESWL (n = 19) (Table 2).
The patients were randomized to one of two groups, independently of the procedure:
Group I – 24-hour antimicrobial prophylaxis (n = 33) – the total time of perioperative antibiotic prophylaxis lasted 24 hours. Meropenem 500 mg administered one hour before the procedure and every 8 hours on the day of the procedure (accordingly to the dosage suggested by the manufacturer).
Group II – 72-hour antimicrobial prophylaxis (n = 27) – the total time of perioperative antibiotic prophylaxis lasted 72 hours. Meropenem 500 mg administered on a day prior to the procedure and every 8 hours for a duration of 72 hours, i.e. also on the following day after the procedure.
The patients received antimicrobial prophylaxis effective against ESBL producing pathogens according to the supplied antibiogram – meropenem (Fresenius Kabi) (n = 60).
Randomization was confirmed by Mann-Whitney test.
In both groups (prior to the administration of the first dose of meropenem 500 mg) blood samples were taken to determine the values of inflammatory parameters (WBC, CRP, PCT) before the procedure, and again 24 hours after the procedure.
On day 7 after the procedure, urine and blood samples were collected again in both groups for urine culture and blood tests to determine WBC, CRP and PCT values.
The dynamics of the inflammatory parameters – WBC, CRP and PCT were compared in both groups. The results were analyzed statistically.
During the study, symptoms of urinary tract infection were observed in only one patient who was randomized to Group II, i.e. receiving meropenem for 72 hours. This patient developed fever and increased inflammatory parameters on day 5 after TURBT, which resulted in re-admission and extension of the full course of meropenem treatment. No other inflammatory complications were observed in any other patients.
The CRP level was determined on a Roche Diagnostics COBAS c501 analyzer. PCT concentration was determined on the COBAS e601 or e411 analyzer by Roche Diagnostics, and WBC values using the Sysmex XN-1000 analyzer. Diagnostic reference levels are presented in Table 3.

Microbiological diagnostics

Mid-stream urine samples were obtained from properly instructed patients. Handling of the obtained material was in accordance with standard microbiological procedures.
Samples were transferred to standard microbial media (Columbia agar, MacConkey agar, bioMérieux,

Table 1. *Inclusion criteria for the study*

Inclusion criteria
>18 years of age informed consent signed by a patient clinical confirmation of asymptomatic bacteriuria diseases of the urinary system requiring the use of endourology or ESWL
Exclusion criteria
<18 years of age impossibility to obtain informed consent symptomatic UTI other active infections

UTI – urinary tract infection; ESWL – extracorporeal shock wave lithotripsy

Table 2. *Types of interventions performed in the study, divided into study groups*

Procedure	Total	Group I 24h meropenem	Group II 72h meropenem
ESWL	19	11	8
DJ replacement	10	7	3
PCN replacement	8	4	4
UPG + URS	6	4	2
TURBT	4	0	4
Ureteroscopic lithotripsy	4	2	2
DJ removal	3	2	1
Cystoscopy	3	3	0
Cystolithotripsy	2	0	2
Bricker's conduit distention	1	0	1
Total	60	33	27

DJ – double-J ureteral stent; ESWL – extracorporeal shock wave lithotripsy; UPG – ureteropyelography; URS – ureteroscopy; PCN – percutaneous nephrostomy; TURBT – transurethral resection of bladder tumor

Table 3. *Diagnostic reference levels adopted for the trial*

Procedure	Diagnostic reference levels
WBC	4.0–10.0 x 10^9/l
CRP	≤0.8 mg/dL
PCT	≤0.046 ng/mL – 95th percentile in the population of healthy people (upper limit of reference values) <0.5 ng/mL: low-risk of severe sepsis and / or septic shock >2.0 ng/mL: high-risk of severe sepsis and / or septic shock

WBC – white blood count; CRP – C-reactive protein; PCT – procalcitonin

France; CPS Elite chromide, bioMérieux), then incubated at 37°C for 24 h.
Detailed microbiological identification was performed with the VITEK 2 automated system (bioMérieux, France).
An automated microdilution method using VITEK 2 AST cards was used to determine the susceptibility of pathogens to antibiotics.
Microbiological analyses were performed in accordance with the guidelines of the European Committee on Antimicrobial Susceptibility Testing (EUCAST), as well as the recommendations of the National Reference Center for Antimicrobial Susceptibility of Microbials, Warsaw, Poland (KORLD).
In the control of susceptibility tests, reference strains of *Pseudomonas aeruginosa* ATCC 27853, *Klebsiella pneumoniae* ATCC 700603, *Staphylococcus aureus* ATCC 29213 and ATCC 43300, *Enterococcus faecium* ATCC 27270, and *Enterococcus faecalis* ATCC 29212 were used.
The analysis of bacterial resistance mechanisms was performed in accordance with the EUCAST guidelines [9].
Enterobacterales which produce β-lactamases with an extended spectrum of action.
A double disc synergy test (DDST) using discs with amoxicillin / clavulanate (20/10 μg) and 30 μg ceftazidime and 30 μg cefotaxime) was performed. A clear enlargement of the growth inhibition zone around the ceftazidime or cefotaxime disc on the side of the clavulanic acid disc was read as a positive result, confirming the production of ESBL.

RESULTS

Statistical analysis

Raw data was uploaded to Excel sheets, Microsoft Office version 2010 (Microsoft Corporation, Redmond, WA, USA). The data was analyzed using Statistica version 13.3 (TIBCO Software Inc, Palo Alto, CA, USA).
In the 24-hour group, mean WBC count [x10^9/L] upon admission was 7.92 (Figure 1), day after the procedure 7.07 and 8.3 at 7 days after the procedure. Standard deviation (SD) values were: 3.15; 2.58 and 3.6 respectively. In the 72-hour group, mean WBC count [x10^9/L] upon admission was 7.30 (Figure 1), day after the procedure 7.1 and 7.1 at 7 days after the procedure. SD values were: 1.98; 2.2 and 2.16 respectively.
In the 24-hour group mean CRP upon admission was 0.38 mg/dl (Figure 2), day after the procedure 0.58 mg/dl and 0.7 mg/dl at 7 days after the procedure. SD values were: 0.54; 0.51 and 1.1 respectively.
In the 72-hour group mean CRP upon admission was 0.58 mg/dl (Figure 2), day after the procedure 0.92 mg/dl and 0.63 mg/dl at 7 days after the procedure. SD values were: 0.90; 1.06 and 1.18 respectively.
In the 24-hour group mean PCT values upon admission were 0.05 ng/ml (Figure 3), day after the procedure 0.08 ng/ml and 0.04 ng/ml at 7 days after the procedure. SD values were: 0.036; 0.093 and 0.03 respectively.
In the 72-hour group mean PCT values upon admission were 0.07 ng/ml (Figure 3), day after the procedure 0.16 ng/ml and 0.06 ng/ml at 7 days after the procedure. SD values were: 0.13; 0.56 and 0.11 respectively (Table 4).

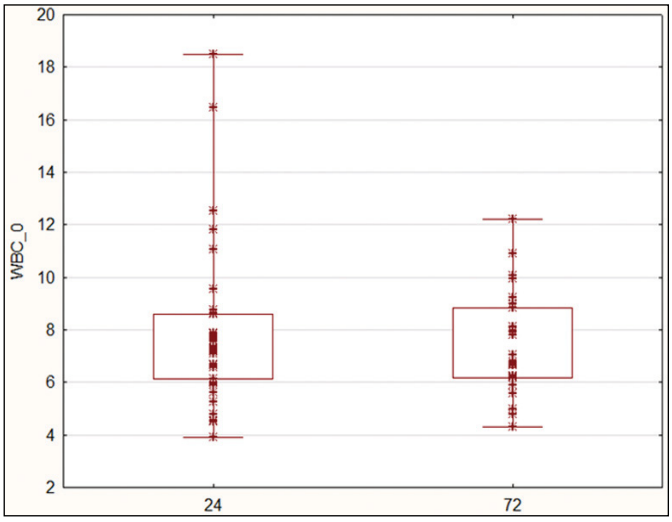

Figure 1. *White blood counts (x109/L) upon admission in 24-hour and 72-hour group. Boxes represent interquartile ranges.*
WBC – white blood count

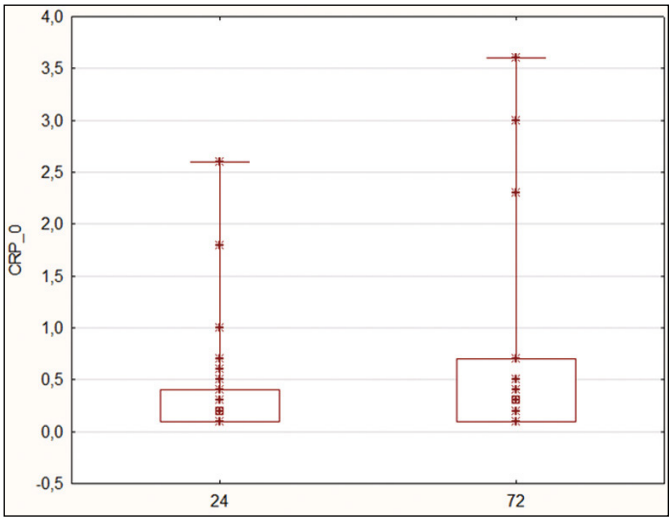

Figure 2. *C-reactive protein levels in mg/dL upon admission in 24-hour and 72-hour group. Boxes represent interquartile ranges.*
CRP – C-reactive protein

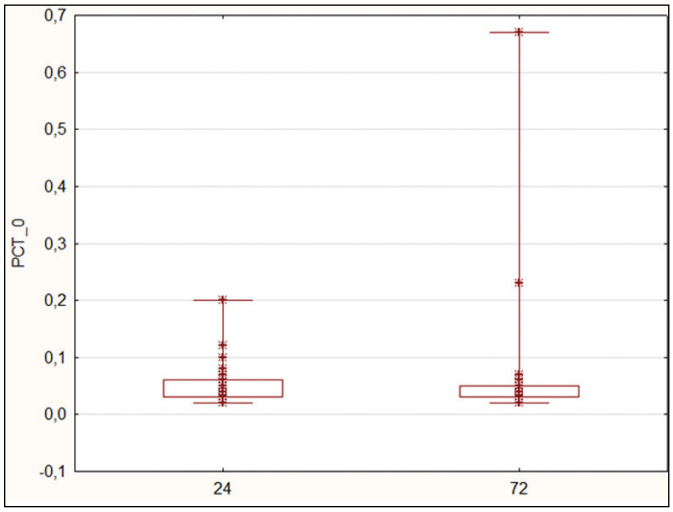

Figure 3. *Procalcitonin levels in ng/mL upon admission in 24-hour and 72-hour group. Boxes represent interquartile ranges.*

PCT – procalcitonin

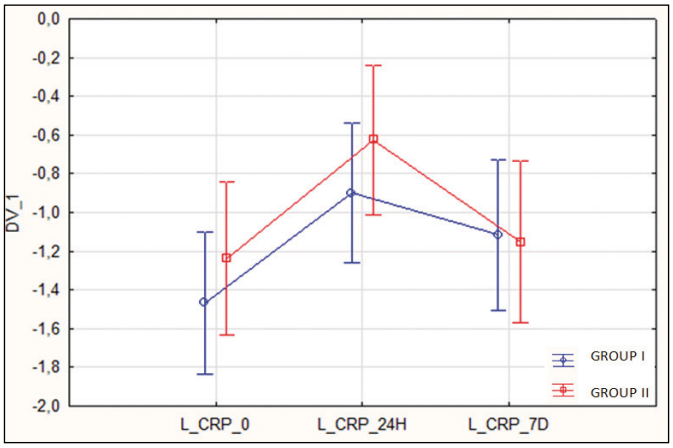

Figure 5. *C-reactive protein variability over time in 24-hour (Group I) and 72-hour (Group II) of perioperative meropenem. Mean values of logarithms are presented.*

L_PCT – logarithm of the PCT; L_CRP – logarithm of the CRP; DV – depended variable; CRP – C-reactive protein; L_CRP_0 – at admission; L_CRP_24H – 24h after procedure; L_CRP_7D – 7 days after procedure

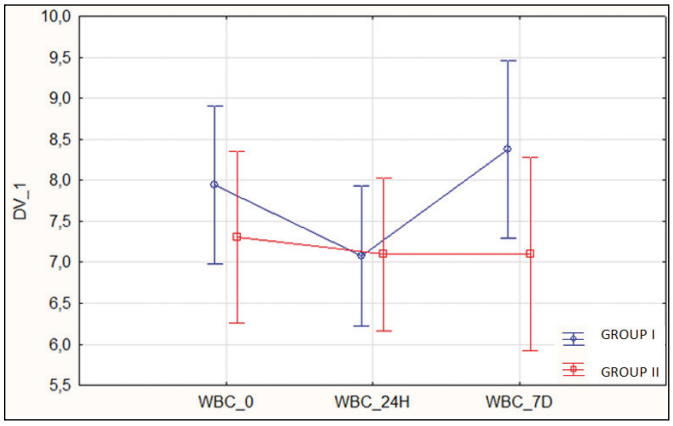

Figure 4. *White blood count variability over time in the study groups. Mean values are presented.*

DV – depended variable; WBC – white blood count; WBC_0 – at admission; WBC_24H – 24h after procedure; WBC_7D – 7 days after procedure

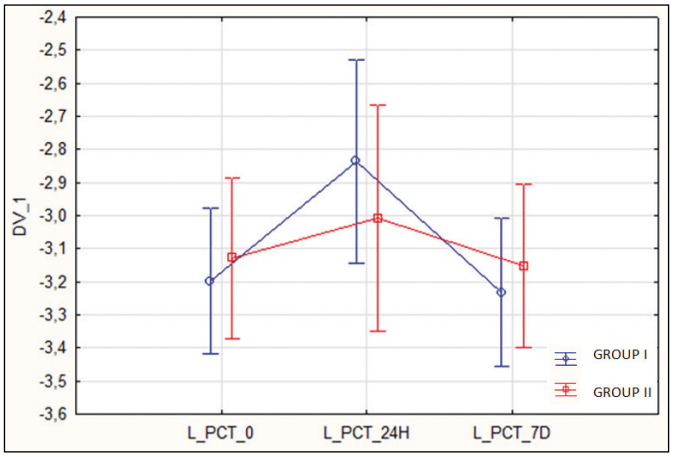

Figure 6. *Procalcitonin variability over time in 24-hour (Group I) and 72-hour (Group II) of perioperative meropenem. Mean values of logarithms are presented.*

DV – depended variable; L_PCT – logarithm of the PCT; L_PCT_0 – at admission; L_ PCT_24H – 24h after procedure; L_ PCT_7D – 7 days after procedure

Comparison of WBC, CRP and PCT at admission and 7 days after the procedure in two groups was then performed.

WBC: in both groups, the Wilcoxon test was used (for the reason of differences from the normal distribution) p = 0.127428 - no significant differences were found between in the number of WBC at admission and 7 days after the procedure.

CRP value: for Group II, the t-test was used (p = 0.851413), and for Group I, the Wilcoxon test was used (p = 0.107476). No statistically significant change in the CRP level was found between the time of admission and 7 days after the procedure (p = 0.580459).

For PCT values: as in the CRP analysis, in this case for Group II, the t-test was used (p = 0.624804), and for Group I, the Wilcoxon test was used (p = 0.602608). No statistically significant change in the level of PCT was found between the time of admission and 7 days after the procedure (p = 0.279458).

Multivariate analysis of variance

The obtained results indicate a statistically significant difference in changes in the WBC index val-

Table 4. *Inflammatory markers upon admission, 24-hours after procedure and 7-days after procedure – mean values with standard deviation*

Marker	Group I 24h meropenem		Group II 72h meropenem	
WBC	Mean	SD	Mean	SD
WBC at admission [x10^9/L]	7.92	±3.15	7.30	±1.98
WBC 24-hours post procedure [x10^9/L]	7.07	± 2.58	7.1	±2.19
WBC 7-days post procedure [x10^9/L]	8.31	±3.59	7.1	±2.16
CRP				
CRP at admission [mg/dl]	0.39	±0.54	0.59	±0.90
CRP 24-hours post procedure [mg/dl]	0.59	±0.50	0.92	±1.06
CRP at 7-days post procedure [mg/dl]	0.7	±1.098	0.63	±1.18
PCT				
PCT at admission [ng/ml]	0.05	±0.03	0.07	±0.13
PCT at 24-hours post procedure [ng/ml]	0.08	±0.09	0.16	±0.56
PCT at 7-days post procedure [ng/ml]	0.05	±0.03	0.06	±0.11

WBC – white blood count; CRP – C-reactive protein; PCT – procalcitonin

ue during subsequent measurements (test values p = 0.04629) and no significant differences in the case of CRP and PCT (p> 0.05). In the multivariate analysis taking into account the variables WBC, CRP and PCT in conjunction with the time variable, the Wilks test obtained the result p = 0.10882, which did not confirm the existence of significant differences between the antibiotic dosing procedures and the values of inflammatory markers. WBC values and logarithms of CRP and PCT indicators at admission, at 24 hours after the procedure and seven days after the procedure are shown on Figures 4, 5, 6.

DISCUSSION

Our data showed that the effectiveness of one-day antibiotic prophylaxis with meropenem is no less effective than a three-day regimen. A 24-hour perioperative antibiotic prophylaxis with meropenem is safe and effective in patients with *Enterobacterales* ESBL+ urinary tract colonization undergoing endourological procedures. It can be indirectly inferred that this short-time prophylaxis minimizes the risk of producing strains with a higher degree of resistance, reduces the incidence of side effects, in addition, reduces the cost of treatment and shortens the duration of hospitalization [10].

These facts allow for substantive justification of the application of a short schedule of antibiotic prophylaxis. It remains to be hoped that similar patterns will also be explored in the future in carriers of bacterial strains with different resistance mechanisms.

The trial was designed to compare two antimicrobial prophylaxis regimens with meropenem in patients undergoing endourological procedures for urolithiasis or ESWL with colonization of urinary tract of *Enterobacterales* ESBL+. We compared the efficacy and safety of a short and prolonged antibiotic prophylaxis by using known inflammatory parameters. The idea of the study emerged when we noticed rising numbers of patients presenting asymptomatic bacteriuria caused by alarm pathogens, mostly *Enterobacterales* ESBL+ [7, 8]. Providing substantially safe and effective prophylaxis to patients with asymptomatic bacteriuria of ESBL+ origin who were awaiting urological procedures or ESWL seemed a questionable task. A Literature research provided us with no answer of how to proceed. To date, no recommendations have been developed for this emerging group of patients. Urological pathologies are more common in an ageing populations, thus we decided that other comorbidities, age or gender would be disregarded in order to simplify the method of the trial and avoid possible bias.

The study confirmed that short-term, targeted antibiotic prophylaxis is not associated with an increased risk of inflammatory complications, including sepsis as compared to prolonged prophylaxis. In the management of patients treated for urinary tract diseases, including urolithiasis, accompanied by asymptomatic bacteriuria caused by *Enterobacterales* ESBL+ strains, the use of meropenem at a dose of 3 x 500 mg on the day of surgery seems to be a safe and effective regimen of periprocedural antibiotic prophylaxis.

The lack of statistically significant differences

in inflammatory markers proves the equivalence and safety of short, 24-hour antibiotic prophylaxis. Potential additional benefits of shorter antibiotic prophylaxis for the above-mentioned group of patients include:

- reducing the risk of development of strains with a higher level of resistance [11];
- reduction of the risk of complications associated with the use of antibiotics: various forms of mycosis, incidence of nosocomial diarrhea of *Clostridioides difficile* etiology [12, 13];
- reducing the risk of acquiring other nosocomial infections;
- shortening the hospitalization period, and thus lowering healthcare costs [14].

CONCLUSIONS

As this is a preliminary, single-institute study we are aware of the limitations that the data provides especially due to the small number of patients and a wide spectrum of procedures that the patients underwent. To further investigate efficacy profiles of possibly even shorter than 24-hour antimicrobial prophylactic regimens, a confirmatory study with a larger number of patients and individual comparison per procedure is necessary.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DISCLOSURE

This work was carried out as part of the statutory project of the Military Institute of Medicine CSK MON entitled: "Comparison of the effectiveness of 24 and 72-hour perioperative antibiotic prophylaxis in patients with asymptomatic bacteriuria (colonization of the urinary tract) with *Enterobacterales* strains with the ESBL+ resistance mechanism subjected to endourological or ESWL procedures" and funded by the promoter grant for young scientist No. 495.

Approval of the research protocol by an Institutional Reviewer Board: the research protocol was approved by the institutional Bioethical Committee of Military Institute of Medicine, Warsaw, Poland (24/WIM/2016 of April 20, 2016).

An informed consent has been obtained from the patients that participated in the study.

Registration No. of the study: ClinicalTrials.gov Identifier: NCT04152369

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