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MICROBIOLOGICAL PROFILE AND ANTIMICROBIAL SUSCEPTIBILITY OF BACTERIA ASSOCIATED WITH URINARY TRACT INFECTIONS IN UKRAINIAN ADULTS

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Ключові слова: інфекція сечовивідних шляхів, сечокам'яна хвороба, антимікробна резистентність, бактерії, ускладнення, локальний профіль чутливості

Abstract. Microbiological profile and antimicrobial susceptibility of bacteria associated with urinary tract infections in Ukrainian adults. Barannik K.S., Ishchenko O.V., Duka R.V., Molchanov R.M., Stepanskyi D.O. The aim of the study was to analyse the microbial profile of the urinary tract infections (UTIs) due to urolithiasis and to study susceptibility to antibiotics in its causative agents. The main method of the research was bacteriological. Antimicrobial susceptibility testing was conducted by serial microdilution assay in accordance with recommendations of the European committee on antimicrobial susceptibility testing (EUCAST). For present study 128 unique urine samples were collected from patients with UTIs associated with urolithiasis. Among all collected specimens, 78% (n=100) gave clinically significant growth. Among all examined participants, 88.9% of women (64/72) and 64.3% of men (36/56) had confirmed UTI; in the study, female/male ratio was 1.4 ($\chi^2=9.76$; $p<0.05$). Microorganisms identified in our study predominantly belonged to Bacteria (93.4%), and yeasts of *Candida* genus comprised only 6.6%. Among all, 66.1% were representatives of Enterobacteriales (n=80), particularly, *Escherichia coli* (38.0%), *Klebsiella oxytoca* (15.7%), *Klebsiella pneumoniae* (2.5%), *Enterobacter cloacae* (5.8%), *Proteus mirabilis* (4.1%). Isolates of *Pseudomonas aeruginosa* comprised 3.3%. Among gram-positive isolates, *Staphylococcus spp.* (14.1%) and *Enterococcus spp.* (9.9%) were identified. Regarding female/male distribution, the biggest proportion of gram-positive bacteria were isolated from women, statistically significant results were obtained for sex distribution of *S. saprophyticus* ($p<0.05$). Antimicrobial susceptibility of Enterobacteriales was variable, and the best results were obtained for carbapenems, novel antibiotics (cefiderocol, ceftolozane-tazobactam and ceftazidime-avibactam), aminoglycosides and tigecycline. There were 9 isolates with production of carbapenemases and resistant to all relevant β -lactam antibiotics. All isolated *Staphylococcus spp.* were β -lactamase producers, one isolate of *S. saprophyticus* demonstrated methicillin-resistance. To summarise, there is an ongoing outbreak of multidrug-resistant infections in Ukraine and causative agents of UTIs are among the most important contributors. Availability of data on the local antimicrobial susceptibility profile may guide the informed decision making in etiologic treatment, therefore, contribute to global efforts in rational drug use and fight the resistance escalation.

Реферат. Мікробіологічний профіль та антимікробна чутливість бактерій, пов'язаних з інфекціями сечовивідних шляхів у дорослих українців. Бараннік К.С., Іщенко О.В., Дука Р.В., Молчанов Р.М., Степанський Д.О. Метою дослідження було вивчити мікробний профіль збудників інфекцій сечовивідних шляхів на фоні уролітіазу (ІСВШ) та їх чутливість до антибіотиків. Основним методом дослідження був бактеріологічний. Визначення чутливості до антибіотиків проводили методом мікросерійних розведень. Для цього дослідження було зібрано 128 унікальних зразків сечі від пацієнтів з ІСВШ на фоні сечокам'яної хвороби. Серед усіх зібраних зразків 78% (n=100) показали клінічно значущий ріст. Серед усіх учасників жінки з лабораторно підтвердженими ІСВШ становили 88,9% (64/72), а чоловіки – 64,3% (36/56), співвідношення за статтю становило 1,4 ($\chi^2=9.76$; $p<0.05$). Виявлені нами мікроорганізми переважно належали до бактерії (93,4%), а дріжджі роду *Candida* становили лише 6,6%. Серед отриманих ізолятів 66,1% становили представники порядку Enterobacteriales (n=80), зокрема *Escherichia coli* (38,0%), *Klebsiella oxytoca* (15,7%), *Klebsiella pneumoniae* (2,5%), *Enterobacter cloacae* (5,8%), *Proteus mirabilis* (4,1%). Ізоляти *Pseudomonas aeruginosa* становили 3,3%. Грампозитивні ізоляти були ідентифіковані як *Staphylococcus spp.* (14,1%) та *Enterococcus spp.* (9,9%). При порівнянні розподілу збудників за статтю виявлено, що найбільша частка грампозитивних бактерій була виділена саме від жінок; статистично значущі результати за розподілом за статтю отримано для *S. saprophyticus* ($p<0,05$). Чутливість Enterobacteriales до антибіотиків була різною, і найкращі результати були отримані для

карбапенемів, новітніх антибіотиків (цефідерокол, цефтолозан-тазобактам і цефтазидим-авібактам), аміноглікозидів і тайгецикліну. У нашому дослідженні виявлено 9 продуцентів карбапенемаз, резистентних до всіх відповідних β -лактамних антибіотиків. Усі культури *Staphylococcus spp.* були продуцентами β -лактамаз, один з ізолятів *S. saprophyticus* був метицилін-резистентним. Підводячи підсумок, варто зазначити, що в Україні триває спалах інфекцій, викликаних мультирезистентними збудниками, й етіологічні агенти ІСВШ відіграють важливу роль. Дані щодо локального профілю чутливості до антимікробних препаратів допоможуть у прийнятті обґрунтованого рішення щодо етіотропного лікування, а отже, сприятимуть глобальним зусиллям щодо раціонального використання ліків та боротьби з ескалацією резистентності.

Problem of urinary tract infections (UTIs) is constantly growing in the world and also in Ukraine [1]. UTIs have significant importance for public health and every year more than 150 million people are affected. From the economic point of view, its burden was estimated to be about \$6 billion worldwide each year [2]. The second to the respiratory tract infections, UTIs remain one of the most common infectious diseases. Furthermore, UTIs are among the most common causes of sepsis presenting in hospitals [3]. The problem is escalated by the global growth of antimicrobial resistance (AMR). In 2019 in Ukraine, there were 8.4 and 31.5 thousand deaths attributable and directly associated with AMR, respectively [4]. Pathophysiology of chronic UTIs is complicated by biofilm-formation, subsequent contributing to the resistance maintenance and dissemination [5]. Treatment of UTIs implies empirical administration of antibacterial drugs, and the choice should consider the local data of antibiotic resistance patterns [6].

The aim of the study was to analyze the microbial profile of UTIs associated with urolithiasis and to study susceptibility to antibiotics in its causative agents.

MATERIALS AND METHODS OF RESEARCH

The study was conducted in the cooperation of the department of surgery No. 1 and urology and the department of microbiology, virology, immunology, epidemiology and medico-biological physics and informatics of the Dnipro State Medical University from January 2023 to December 2023. Systematic sampling technique was employed. The inclusion criteria: patients with calcium urolithiasis complicated by urinary tract infections (UTI) and the absence of other chronic illnesses or pregnancy. Among these patients, there were 56 males and 72 females. The age of the patients ranged from 25 to 65 years, with an average age of 45 years. Patients enrolled in the study were trained to collect a midstream urine in the sterile container [7]. From a patient only one sample was taken for microbiological study.

The research work was approved by the Bioethics Committee of the Dnipro State Medical University protocol No. 3, of 16.11.2022 and was conducted in accordance with the written consent of the participants and in accordance with the principles of bioethics set forth in the Helsinki Declaration

“Ethical Principles of Medical Research Involving Humans” and the “General Declaration on bioethics and human rights (UNESCO)”.

The main method of the research was bacteriological. Collected urine *extempore* was inoculated on a set of growth mediums. For isolation of gram-negative non-fastidious bacteria, we used MacConkey agar; for selective isolation and fast identification of staphylococci, correspondent chromogenic agar was used; for selective isolation of fungi, we used Sabouraud dextrose agar with chloramphenicol. For non-selective cultivation, assessment of haemolytic activity and isolation of fastidious bacteria, blood agar with 5% sheep blood was used. The inoculated plates were incubated in thermostat for 24-48 h at 37°C aerobically. The quantitative evaluation of the bacteriuria was done using calibrated loop technique (10 μ L) giving a count of bacteria and yeasts above a threshold of about 10^2 CFU/mL of urine. When bacteriuria comprised $\geq 10^4$ CFU/mL, UTI was confirmed [7].

For differentiation of gram-negative bacteria growing on MacConkey agar we used Hugh-Leifson medium and oxidase test. On the further steps of microbial identification, a set of biochemical tests from API 20E, and API 20NE was used for Enterobacterales and *Pseudomonas*, respectively. Bacteria were tested for β -galactosidase activity; hydrolysis of L-arginine, urease, gelatine, esculin; production of lysine decarboxylase, ornithine decarboxylase, tryptophan deaminase, H₂S, indole, acetoin; Simmon's citrate utilization; fermentation of D-glucose, D-mannite, inositol, sorbitol, L-rhamnose, D-saccharose, D-melibiose, amygdaline, L-arabinose. Gram-positive cocci were tested for their ability to produce catalase, plasma coagulase, deoxyribonuclease, ornithine decarboxylase, pyrrolidinyl arylamidase; capacity to coagulase mannitol, split esculin, urease; novobiocin and bacitracin sensitivity; haemolytic characteristics.

Antimicrobial susceptibility testing was conducted by serial microdilution assay in accordance with the EUCAST recommendations with supplements and updates [8, 9, 10]. *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 29213 and *Pseudomonas aeruginosa* ATCC 27853 were used for quality control.

The Microsoft Office Excel 2010[®] with customizations was used for statistical data processing (version 14.0.7265.5000, license No. 02278-581-

0218935-38456). Categorical variables are expressed as percentages and were compared by the χ^2 two-tailed test. Incidence proportions of pooled combinations and probabilities were calculated, which established the corresponding 95% confidence intervals and the p -values <0.05 . The Kruskal-Wallis's test was used for multiplying comparisons of quantitative data; found differences further were assessed by the Mann-Whitney U-test. The results of the experiments were statistically significant at $p < 0.05$ [11].

RESULTS AND DISCUSSION

For the present study 128 urine samples were collected. Among all participants, there were 72 female and 56 male specimens. There were 28 negative samples, therefore, 78% ($n=100$) gave clinically significant growth. Among all examined participants, 88.9% of women (64/72) and 64.3% of men (36/56) had confirmed UTI; in the study, female/male ratio was 1.4 ($\chi^2=9.76$; $p < 0.05$). Among all, 21 specimens harboured mixed culture.

The list of pathogens causing UTIs associated with urolithiasis in Ukrainian adults is given in the Figure 1.

Microorganisms identified in our study predominantly belonged to Bacteria (93.4%); yeasts of *Candida* genus comprised only 6.6%. Among all, 66.1% was occupied by representatives of Enterobacterales ($n=80$), particularly, *E. coli* (38.0%), *K. oxytoca* (15.7%), *K. pneumoniae* (2.5%), *E. cloacae* (5.8%), *P. mirabilis* (4.1%). Isolates of *P. aeruginosa* comprised 3.3%. Among gram-positive isolates, *Staphylococcus spp.* (14.1%) and *Enterococcus spp.* (9.9%) were identified. *Staphylococcus spp.* was represented by *Staphylococcus saprophyticus* ($n=9$) and *S. aureus* ($n=8$). There were isolates of *Enterococcus faecalis* among *Enterococcus spp.* Therefore, gram-positive bacteria comprised 24.0%. Regarding female/male distribution, the biggest proportion of gram-positive bacteria were isolated from women, 14/17 of *Staphylococcus spp.* and 10/12 of *Enterococcus spp.* The most *C. albicans* also was isolated from women, 6/8. Usually, mixed culture contained association with *C. albicans* (8/8) or *S. aureus* (7/11).

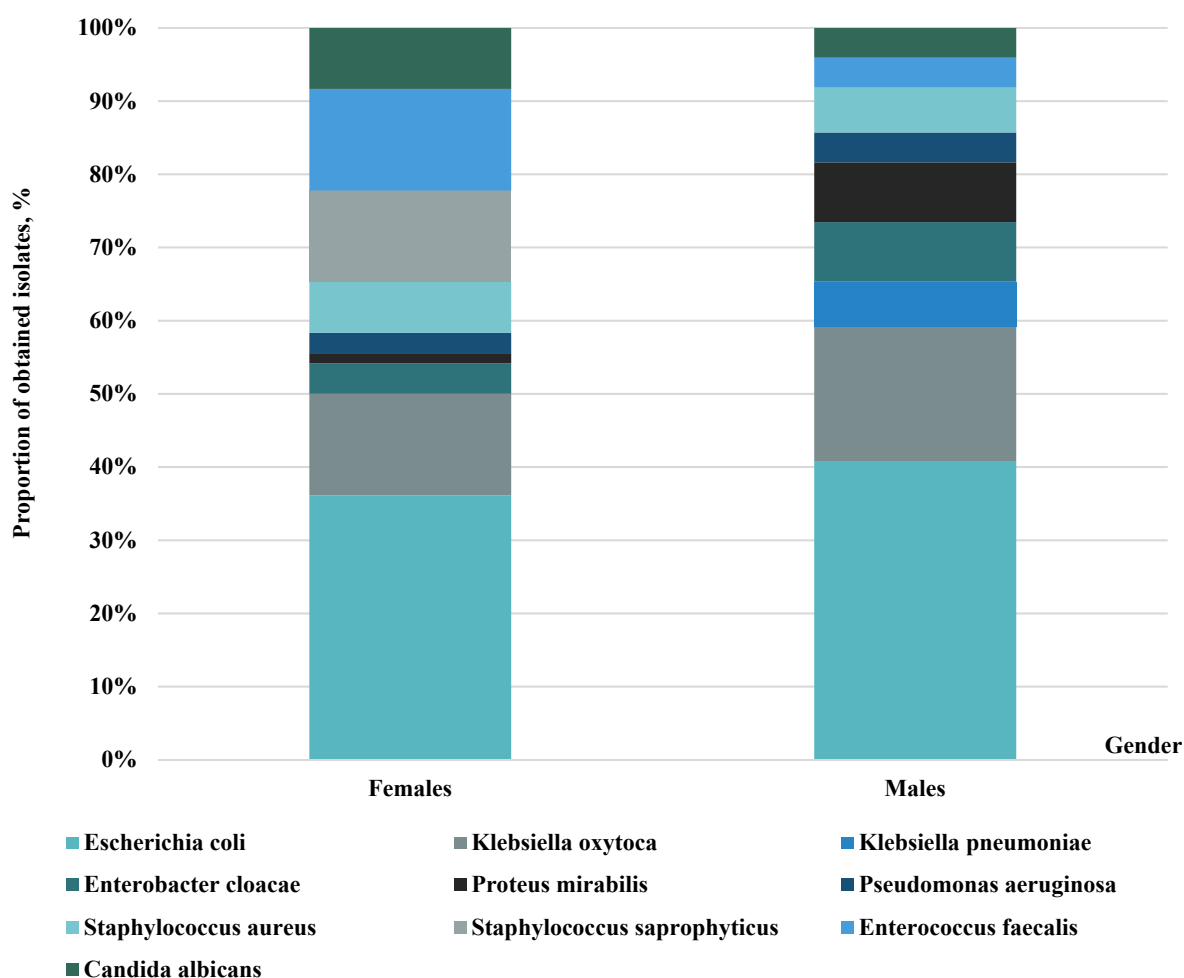
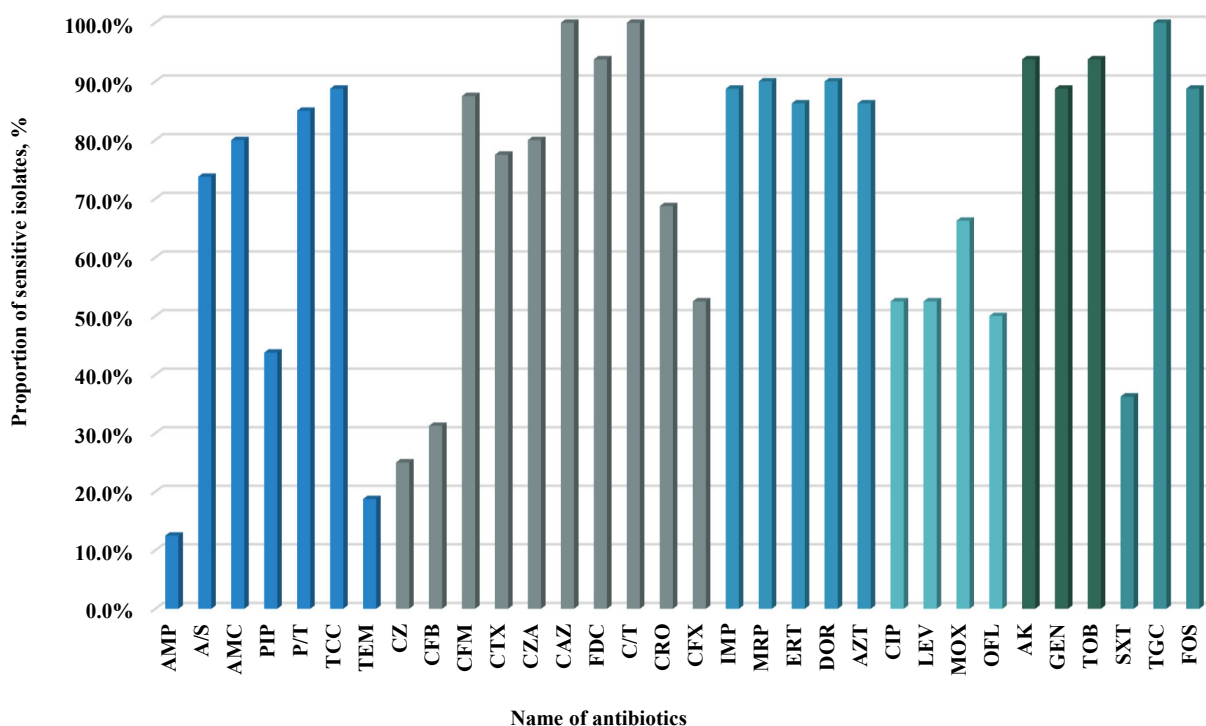


Fig. 1. Etiological profile of UTIs associated with in urolithiasis

Although rough differences in relative quantities, statistically significant results were registered only in female/male distribution of *S. saprophyticus* ($\chi^2=3.98$; $p<0.05$).

Antimicrobial susceptibility testing was conducted for all bacteria isolated from patients with UTI and gave growth $\geq 10^4$ CFU/mL. Antimicrobial sus-

ceptibility of Enterobacterales was variable, and the best results were obtained for carbapenems, novel antibiotics (cefiderocol, ceftolozane-tazobactam and ceftazidime-avibactam), aminoglycosides and tigecycline. Patterns of antimicrobial susceptibility of Enterobacterales is demonstrated in the Figure 2.



AMP-Ampicillin, A/S-Ampicillin-sulbactam, AMC-Amoxicillin-clavulanic acid, PI-Piperacillin, P/T-Piperacillin-tazobactam, TCC-Ticarcillin-clavulanic acid, TEM-Temocillin, CZ-Cefazolin, CFB-Ceftibuten, CFM-Cefepime, CTX-Cefotaxime, CZA-Ceftazidime, CAZ-Ceftazidime-Avibactam, FDC-Cefiderocol, C/T-Ceftolozane-Tazobactam, CRO-Ceftriaxone, CFX-Cefuroxime, IMP-Imipenem, MRP-Meropenem, ERT-Ertapenem, DOR-Doripenem, AZT-Aztreonam, CIP-Ciprofloxacin, LEV-Levofloxacin, MOX-Moxifloxacin, OFL-Ofloxacin, AK-Amikacin, GEN-Gentamicin, TOB-Tobramycin, SXT-Trimethoprim-sulfamethoxazole, TGC-Tigecycline, FOS-Fosfomycin).

Fig. 2. Antimicrobial susceptibility of enterobacteria associated with UTI in Ukrainian adults

Susceptibility to penicillins comprised 12.5-88.5% with the lowest results for ampicillin and temocillin and the highest indexes for clavulanic acid combinations. Susceptibility to cephalosporins was between 25.0-100.0%, with the best results for the III and IV generation cephalosporins and novel antibiotics. According to results of the antimicrobial susceptibility testing, there were 9 isolates with production of carbapenemases and resistant to all relevant β -lactam antibiotics. Also, such cultures demonstrated multidrug-resistance profile and remain non-susceptible to fluoroquinolones, aminoglycosides, fosfomycin and trimethoprim-sulfamethoxazole. All isolates were collected from patients already exposed to several courses of antimicrobial treatment. Multidrug-resistant *K. oxytoca* is demonstrated on the Figure 3.

Antimicrobial susceptibility of Enterobacterales to fluoroquinolones was found to be 50.0-60.3%. Suscep-

tibility to aminoglycosides was 88.8-93.8%. Also, there were 88.8% isolates carrying sensitivity to fosfomycin. However, resistance to trimethoprim-sulfamethoxazole was high and comprised 71%. All tested isolates were susceptible to tigecycline and colistin.

All isolated *Staphylococcus spp.* were β -lactamase producers according to the test with benzylpenicillin or ampicillin. Among six tested, one isolate of *S. saprophyticus* demonstrated methicillin-resistance. Susceptibility to screening with norfloxacin comprised 3/6, however, resistant isolates tested susceptible to other fluoroquinolones. Susceptibility to screening with erythromycin was 2/6. Similar poor results also were found for trimethoprim-sulfamethoxazole. Susceptibility to aminoglycosides and nitrofurantoin (*S. saprophyticus*) was found to be 100%.

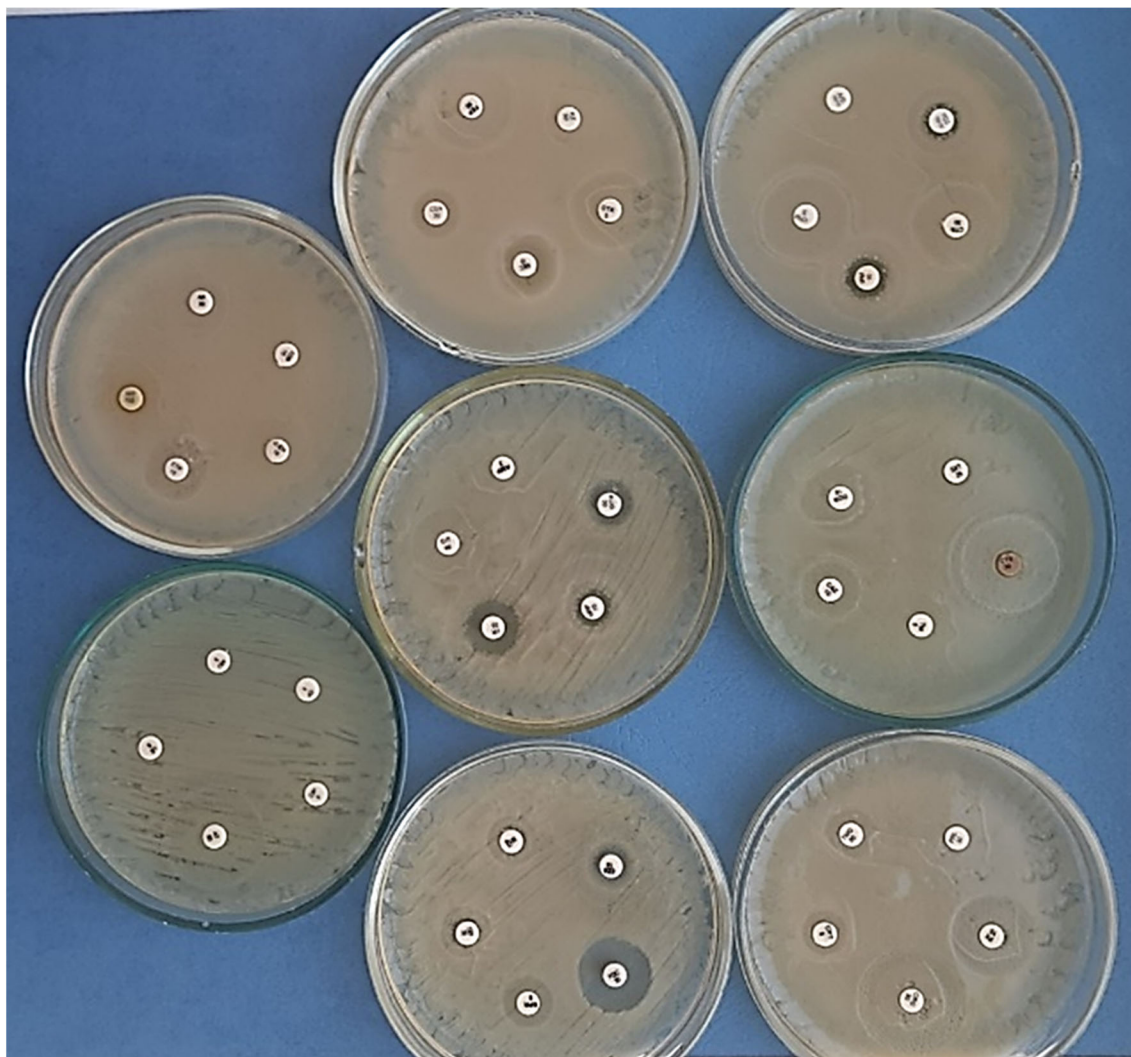


Fig. 3. Multidrug-resistant *K. oxytoca*. Antimicrobial susceptibility testing by the disc-diffusion method, Muller-Hinton agar, 18 hours

Antimicrobial susceptibility testing of *Enterococcus spp.* revealed that 8/12 tested isolates were non-susceptible to ampicillin, therefore, harboured resistance to ampicillin, amoxicillin, piperacillin with and without inhibitors. Such isolates also demonstrated non-susceptibility to gentamycin (indicates presence of high-level aminoglycosides resistance) and fluoroquinolones. All isolates tested susceptible to imipenem, vancomycin, tigecycline, linezolid and nitrofurantoin.

In this paper we discuss microbial spectrum of UTIs, and antimicrobial profile of bacteria related to infectious-inflammatory processes in the urinary tract with the background of urolithiasis. The main advantage of our study is sample size and systematic sampling approach of a chosen category of patients allowing us to evaluate microbial profile. Results describing the meaning of gram-negative bacteria is of special importance because depict the local profile of antimicrobial susceptibility. Our study provides

important new insights into the implications of antimicrobial treatment in complicated UTIs. Here we provide data on susceptibility to the novel antibiotics, in particular, cefiderocol, ceftazidime-avibactam and ceftolozane-tazobactam in cultured uropathogens. Even though increasing resistance rates in urinary isolates have been already published [12, 13, 14], Ukrainian data still needs to be extended. Our study complements the knowledge regarding the global trends of antimicrobial resistance.

In our study women occupied bigger proportion in comparison to men. The features of the female anatomy of urinary system predisposes to higher prevalence among this category. In the analytic domestic study, it was also found that morbidity and prevalence of chronic cystitis among the female population of Ukraine is more than 3 times higher than in male and is constantly growing [1]. Furthermore, the same figures on the age-sex UTIs rate were shown in the worldwide report and their data emphasize affection

of low- and middle-income countries [15]. In fact, the problem is not limited to the prevalence of pathological condition, but it is escalated by associated factors, in particular, antimicrobial resistance. Therefore, microbiological study is of special importance in chronic, recurrent and difficulty treated UTIs.

In our study, the main bacteria contributing to UTIs associated with urolithiasis were *E. coli* and *K. oxytoca*. These bacteria were equally distributed among men and women and, usually, they were isolated as monoculture, indicating the significance of the agents in infectious-inflammatory process. There were also some sex differences. Bacteria like *S. saprophyticus*, most *Enterococcus* and *Candida* fungi were found exactly in female samples. The meaning of *C. albicans* in pathogenesis of UTI is debatable, however, its presence in co-culture may either contribute to diseases severity or indicates local microbiota disturbances in adults with complicated UTI [16].

Antimicrobial resistance is of concern across the world and has been recognized as a rapidly growing challenge for the modern medical practice [1, 4, 17]. In our study, there were Enterobacterales resistant to the most clinically relevant antibiotics, including carbapenems, fluoroquinolones and aminoglycosides. In the prospective multicentre cohort study, which participants were pregnant Ukrainian women with UTIs, significant proportion of the main causative agents of UTIs (*E. coli*, *K. pneumoniae*, *P. mirabilis*, *P. aeruginosa*) were also found to be multidrug resistant [18]. Although here we didn't study genetic background of antimicrobial resistance, according to tests with meropenem and/or imipenem, carbapenemase producers were revealed. Even though other isolates were susceptible to carbapenems, they expressed extended-spectrum β -lactamases and demonstrated resistance to the III generation cephalosporins. The problem is existence of resistance genes coded in plasmids and the risk of horizontal genes transfer in hospital and, sub-

sequently, community sittings. Even more, simultaneous co-existence of other resistance mechanisms has also been documented [19, 20, 21]. It was shown in armed conflict on Ukrainian territory, patients of the domestic military hospitals harboured the same bacterial clones as our civilians who have fled to Germany and other European countries since the beginning of the ongoing war [22, 23, 24, 25].

CONCLUSIONS

1. There is an ongoing outbreak of multidrug-resistant infections in Ukraine, and causative agents of urinary tract infections are among the most important contributors.

2. Antimicrobial resistance is emerging problem and several ways have been proposed to impede its growth. Chronic infections are known to be associated with biofilm-formation and approaches for their eradications may require administration of multi-targeted compounds or their combination. Availability of data on the local antimicrobial susceptibility profile may guide the informed decision making in etiotropic treatment, therefore, contribute to global efforts in rational drug use and fight the resistance escalation.

Contributors:

Barannik K.S. – methodology, formal analysis, writing – original draft;

Ishchenko O.V. – formal analysis, validation, writing – original draft;

Duka R.V. – formal analysis, writing – review & editing;

Molchanov R.M. – software, supervision, project administration;

Stepanskyi D.O. – writing – review & editing, supervision.

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