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DOI: <https://doi.org/10.22141/2224-0586.20.3.2024.1689>V.A. Korsunov¹ , M.A. Georgiyants¹ , N.I. Zozulia², I.Yu. Odynets¹ , M.B. Pushkar¹ ,
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The role of aztreonam in rational antibacterial therapy of resistant nosocomial gram-negative infections. The new life for a well-known β -lactam

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Abstract. Background. The situation regarding the prevalence of resistant pathogens, types of β -lactamase products, and, accordingly, the justification of rational approaches to antibacterial therapy in Ukraine remains insufficiently studied. **Objective:** based on the determination of the etiological structure of the causative agents of hospital infections in the Kharkiv region and the state of their resistance due to the production of β -lactamases, to propose rational approaches to antibacterial therapy and assess the feasibility of using aztreonam as a potentially effective mean of treating infections caused by resistant bacteria. **Materials and methods.** In 251 patients, samples of biomaterials were tested by the polymerase chain reaction for the presence of the following gram-negative pathogens: *P.aeruginosa*, *Enterobacter*, *E.coli*, *K.pneumoniae*, *Proteus spp.* and *A.baumannii*. A molecular genetic study was also conducted to identify certain types of β -lactamases. **Results.** In the structure of hospital pathogens, the absolute majority of gram-negative bacteria belong to the enterobacteria family. When determining the profile of β -lactamases, we found that in 59.38 % of cases, *E.coli* was able to produce metallo- β -lactamases, which makes the therapy with carbapenems or ceftazidime-avibactam impossible. An alternative in such cases is a combination of aztreonam and ceftazidime-avibactam. When the causative agent *K.pneumoniae* is detected, in some cases there may also be a need for combined therapy with the use of aztreonam. It was found that *Enterobacter spp.* in most cases is sensitive to carbapenems. *A.baumannii* is completely insensitive to carbapenems and requires alternative approaches to antibacterial therapy, including aztreonam, ceftazidime-avibactam, and polymyxins. *P.aeruginosa* was found only as part of polymicrobial associations, so it was impossible to analyze its β -lactamase production profile. **Conclusions.** The results of the conducted study demonstrate an extremely high detection of gram-negative antibiotic-resistant pathogens in patients of the intensive care units in the Kharkiv region. Microorganisms such as *E.coli* and *A.baumannii* have the most unfavorable profile of antibiotic resistance, which is due to the high frequency of production of serine carbapenemases and metallo- β -lactamases, whose presence makes the effective use of carbapenems impossible.

Keywords: gram-negative infection; β -lactamase; antibiotic resistance; antibacterial therapy; intensive care unit

Introduction

The rate of diseases caused by polyresistant pathogens has accelerated dramatically in recent years. Previously, it was believed that bacterial antibiotic resistance was encountered mainly in hospital patients, especially in the intensive care units. However, there is now increasing reports of resistant strains in patients with community-acquired infections. For

instance, there is a rapid spread of fluoroquinolone-resistant strains of *Salmonella spp.* and *Shigella spp.*, polyresistant *S.pneumoniae*, methicillin-resistant *S.aureus* [1, 2]. There are even reports that polyresistant *P.aeruginosa*, *K.pneumoniae*, *A.baumannii*, and methicillin-resistant *S.aureus* could be the cause of 3.3 to 7.6 % community-acquired pneumonia cases in some European countries [3]. These microorganisms,

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resistant to carbapenems and producing extended-spectrum β -lactamases, are classified by WHO as critical in terms of danger. In particular, these bacteria are among the so-called ESKAPE pathogens.

The current state of antibiotic resistance has three gradations of severity, namely:

- multidrug resistant — acquired nonsusceptibility to at least one agent in three or more antimicrobial categories;
- extensive drug resistant — nonsusceptibility to at least one agent in all but two or fewer antimicrobial categories;
- pandrug resistant — nonsusceptibility to all agents in all antimicrobial categories.

Carbapenem-resistant *Enterobacteriaceae*, as defined by the US Centers for Disease Control and Prevention, are pathogens that non susceptible to at least one of the following antibiotics: meropenem, imipenem, doripenem, or ertapenem. Also, they are resistant to all third-generation cephalosporins; associated with high mortality (up to 40–50 %); resistant to other groups of drugs; pandrug-resistant strains of *K.pneumoniae* are registered.

The main mechanisms of inactivation of antibacterial drugs in gram-negative pathogens are considered to be efflux pumps, modification of porin proteins, and production of various β -lactamases. According to WHO, in the European Union and the USA, antibacterial resistance leads to more than 20,000 fatal cases and costs the economies of these regions from 1.5 to 20 billion in direct losses annually [4].

The most accessible for clinical assessment of resistance of pathogens are β -lactamases. It is known that they can belong to four groups — A, B, C, D [5]. The most concern worldwide is caused by the spread of carbapenemases, which are increasingly found in gram-negative bacteria, namely: *P.aeruginosa*, *Enterobacteriaceae* spp. and *A.baumannii*. The presence of such enzymes in pathogens makes them resistant to any carbapenems. Carbapenemases include class A serine enzymes (KPC — *Klebsiella pneumoniae* carbapenemase; imipenem-hydrolyzing β -lactamase; GES — Guiana extended-spectrum β -lactamase), class D OXA enzymes and metallo- β -lactamases (MBL) of class B (NDM — New Delhi metallo- β -lactamase; VIM — Verona integron-borne metallo- β -lactamase; IMP — imipenem-resistant *Pseudomonas* carbapenemase, etc.) (according to Ambler) [5]. The problem of treating infections caused by serine carbapenemase producers was solved by introducing into clinical practice beta-lactam antibiotics protected by new β -lactamase inhibitors (avibactam, vaborbactam, relebactam), which also protect antibacterial agents from extended-spectrum β -lactamases [6]. The only such drug available in Ukraine is ceftazidime-avibactam. However, the situation is much worse with producers of class B metallo- β -lactamases, as none of the new and old β -lactamase inhibitors can protect neither penicillins, nor cephalosporins, nor carbapenems from hydrolysis by enzymes of this class. Therefore, until recently, in the treatment of patients infected with bacteria-producing metallo- β -lactamases, it was only possible to rely on the use of tigecycline and polymyxins whose effectiveness is quite limited. Thus, Kagami K. et al. (2020) state that therapy of resistant gram-negative infections with colistin had clinical success in only 60 % of patients, and microbiological eradication was achieved in only 42.9 % of cases.

It is worth noting that in 47.6 % of patients, nephrotoxicity developed [7]. According to Garg S.K. et al. (2017), the effectiveness of monotherapy with polymyxin B in patients with infections caused by extensive drug-resistant *A.baumannii* was 33.3 %, and with tigecycline — 28.6 % [8]. The effectiveness of monotherapy with polymyxin B in patients with infections caused by carbapenem-resistant *K.pneumoniae* is also unsatisfactory, as the 30-day mortality was 48.7 % [9]. So, we are forced to conclude about the unsatisfactory effectiveness of these drugs. However, in the difficult situation associated with the treatment of infections caused by metallo- β -lactamase-producing pathogens, a new hope has appeared for the well-known monobactam antibiotic aztreonam. Widely used in the 1980s and 1990s, this drug began to lose clinical significance due to instability to hydrolysis by extended-spectrum β -lactamases, AmpC β -lactamases, and serine carbapenemases. But this antibiotic has a unique property, a resistance to metallo- β -lactamases and even the function of their inhibitor, that is, the ability to protect other β -lactam antibiotics from the influence of these enzymes. The editorial comment “Aztreonam Combination Therapy: An Answer to Metallo- β -Lactamase-Producing Gram-Negative Bacteria?” states that aztreonam has the ability to unproductively bind to metallo- β -lactamase molecules and is a promising tool for solving the problem of this type of resistance [10]. The condition for conducting effective therapy of infections caused by gram-negative bacteria — metallo- β -lactamase producers is the protection of aztreonam by a new inhibitor avibactam, which led to the release of a new combined antibiotic aztreonam-avibactam, which is unfortunately not registered in Ukraine. A systematic review and meta-analysis of 35 *in vitro* and 18 *in vivo* studies of the combination of aztreonam and avibactam for the treatment of infections caused by gram-negative MBL-producing pathogens demonstrated that the high antibacterial activity of aztreonam-avibactam was observed at a minimum inhibitory concentration of 4 mg/l in relation to 80 % of *Enterobacteriaceae* MBL producers, 85 % of *Stenotrophomonas*, and 6 % of *Pseudomonas* MBL producers. Clinical data on the treatment of 94 patients, 83 % of whom had bacteremia, demonstrated the 30-day survival of 80 % [11]. But the possibility of using combined therapy with aztreonam and ceftazidime-avibactam, imipenem-relebactam, or meropenem-vaborbactam is also being considered. Of the listed combinations, only the combination of aztreonam and ceftazidime-avibactam is available in Ukraine. Falcone M. et al. (2020) report on the treatment of 102 patients with bloodstream infections, which in 82 cases were caused by β -lactamase NDM producers (79 *K.pneumoniae* and 3 *E.coli*), in 20 — by β -lactamase VIM producers (14 *K.pneumoniae*, 5 *Enterobacter* spp., 1 *M.morganii*). The 30-day mortality was 19.2 % in patients treated with the combination of ceftazidime-avibactam and aztreonam and 44 % in the comparator group (colistin, tigecycline, fosfomicin, gentamicin, and meropenem) ($p = 0.007$) [12]. It is also reported that the combination of ceftazidime-avibactam and aztreonam provides a synergistic effect against carbapenem-resistant *Enterobacteriaceae* in 97.5 % of cases [13].

Therefore, numerous literature data demonstrate the presence of a complex problem of resistance to carbapenems in the world, which is further growing in the context of

the COVID-19 pandemic [14]. A series of studies shows that infections caused by carbapenem-resistant gram-negative bacteria are characterized by a 2–3 times higher mortality rate than those caused by carbapenem-sensitive pathogens [15, 16]. However, the situation regarding the prevalence of resistant pathogens, types of β -lactamase production, and, accordingly, the justification of rational approaches to antibacterial therapy in Ukraine remains inadequately studied. This fact was the basis for conducting our study.

The purpose. Based on determining the etiological structure of pathogens of hospital infections in the Kharkiv region and the state of their resistance assessed by β -lactamase production, to propose rational approaches to antibacterial therapy and the appropriateness of using aztreonam as a potentially effective mean of treating infections caused by resistant bacteria.

Materials and methods

To achieve the set goal, we have examined data from 251 patients with clinical-laboratory signs of sepsis. They were treated in the intensive care units of Kharkiv hospitals (Kharkiv Regional Clinical Infectious Hospital, Kharkiv Regional Children’s Clinical Infectious Hospital, Kharkiv Regional Clinical Hospital, Kharkiv Regional Children’s Clinical Hospital, Kharkiv Regional Oncology Center, Kharkiv City Clinical Hospital, and other municipal hospitals) during 2020–2021. We conducted laboratory studies of material samples (blood, tracheobronchial content, pus from the pleural and joint cavities, cerebrospinal fluid, wound content, urine) using the polymerase chain reaction method for the presence of the following gram-negative pathogens: *P.aureginosa*, *Enterobacter*, *E.coli*, *K.pneumoniae*, *Proteus* spp., and *A.baumannii*. The diagnosis of sepsis was made based on the consensus criteria of the Surviving Sepsis Campaign 2021 [17]. Molecular genetic research was also carried out to determine the following types of β -lactamases: DHA-AmpC, KPC, GES, VIM, NDM, IMP, OXA-10 like, OXA-23 like, OXA-40 like, OXA-48 like. All studies were conducted on the CFX96 Real-Time PCR Detection System (Bio-Rad, USA) using the appropriate resistomes.

Results

The material under study was obtained from 218 blood samples, 15 tracheobronchial content samples, 10 joint fluid samples, 6 urine and pleural content samples, 1 cerebrospinal fluid sample, and postoperative wound content.

The structure of hospital pathogens is presented in Table 1. From it, the absolute majority of DNA of gram-negative bacteria belongs to the *Enterobacteriaceae* family. The total number of DNA samples obtained (360) is greater than the number of patients examined (251) due to the presence of polymicrobial associations in some cases. In 24 patients, the material obtained did not contain DNA of gram-negative pathogens. Polymicrobial associations were identified in 124 samples.

To determine the profile of β -lactamase production, a study of their structure was conducted in those samples where DNA of one of the *Enterobacteriaceae* pathogens was detected, but not a polymicrobial association. Regarding *E.coli*, such samples were found in 32 cases. The structure of β -lactamase resistomes of *E.coli* is presented in Table 2.

From the Table 2, it is evident that in 56.25 % of cases, *E.coli* was a producer of AmpC β -lactamases, which excludes the possibility of using cephalosporins not protected by inhibitors. Class A serine carbapenemases were produced in 87.5 % of cases, which excludes the possibility of effective use of carbapenems but gives reason to rely on effective therapy with ceftazidime-avibactam. However, we must state that in 59.38 % of cases, *E.coli* was capable of producing metallo- β -lactamases, which makes the use of both carbapenems and ceftazidime-avibactam impossible. The only alternative therapy in such cases is the combination of aztreonam and ceftazidime-avibactam.

DNA of *K.pneumoniae* without combination with other pathogens was found in 25 patients. The structure of β -lactamase resistomes of *K.pneumoniae* is presented in Table 3.

Table 3 demonstrates that in 32.0 % of cases, *K.pneumoniae* was a producer of AmpC β -lactamases. Class A serine carbapenemases were produced in 20.0 % of cases. Only in 8.0 % of cases, *K.pneumoniae* was capable of produ-

Table 1. Etiological structure of hospital pathogens

Pathogen	<i>K.pneumoniae</i>	<i>E.coli</i>	<i>Enterobacter</i>	<i>A.baumannii</i>	<i>P.aeruginosa</i>
Amount	125	120	90	14	11

Table 2. Structure of β -lactamase production in *E.coli*

	AmpC	Class A serine carbapenemases		Class D serine carbapenemases				Class B metallo- β -lactamases		
		KPC	GES	OXA-10 like	OXA-23 like	OXA-40 like	OXA-48 like	NDM	VIM	IMP
The resistome	DHA	KPC	GES	OXA-10 like	OXA-23 like	OXA-40 like	OXA-48 like	NDM	VIM	IMP
Amount	18	16	12	1	0	0	0	5	14	0

Table 3. Structure of β -lactamase production in *K.pneumoniae*

	AmpC	Class A serine carbapenemases		Class D serine carbapenemases				Class B metallo- β -lactamases		
		KPC	GES	OXA-10 like	OXA-23 like	OXA-40 like	OXA-48 like	NDM	VIM	IMP
The resistome	DHA	KPC	GES	OXA-10 like	OXA-23 like	OXA-40 like	OXA-48 like	NDM	VIM	IMP
Amount	8	2	3	1	0	0	0	0	2	0

Table 4. Structure of β -lactamase production in *Enterobacter* spp.

	AmpC	Class A serine carbapenemases		Class D serine carbapenemases				Class B metallo- β -lactamases		
		KPC	GES	OXA-10 like	OXA-23 like	OXA-40 like	OXA-48 like	NDM	VIM	IMP
The resistome	DHA	KPC	GES	OXA-10 like	OXA-23 like	OXA-40 like	OXA-48 like	NDM	VIM	IMP
Amount	5	1	0	0	0	0	0	0	0	0

Table 5. Structure of β -lactamase production in *A.baumannii*

	AmpC	Class A serine carbapenemases		Class D serine carbapenemases				Class B metallo- β -lactamases		
		KPC	GES	OXA-10 like	OXA-23 like	OXA-40 like	OXA-48 like	NDM	VIM	IMP
The resistome	DHA	KPC	GES	OXA-10 like	OXA-23 like	OXA-40 like	OXA-48 like	NDM	VIM	IMP
Amount	4	3	0	1	2	4	4	1	1	0

cing metallo- β -lactamases. Thus, it can be thought that this pathogen has a better profile of sensitivity to carbapenem group antibiotics, but in individual cases may also require combined therapy using aztreonam.

DNA of *Enterobacter* spp. without combination with other pathogens was found in 12 patients. The structure of β -lactamase resistomes of *Enterobacter* spp. is presented in Table 4.

From the Table 4, it is evident that in 41.7 % of cases, *Enterobacter* spp. were producers of AmpC β -lactamases. Class A serine carbapenemases were found in only one case (8.3 %). Production of metallo- β -lactamases was not detected at all. Thus, it can be thought that this pathogen is predominantly sensitive to carbapenems.

DNA of *A.baumannii* without combination with other pathogens was found in 4 patients. The structure of

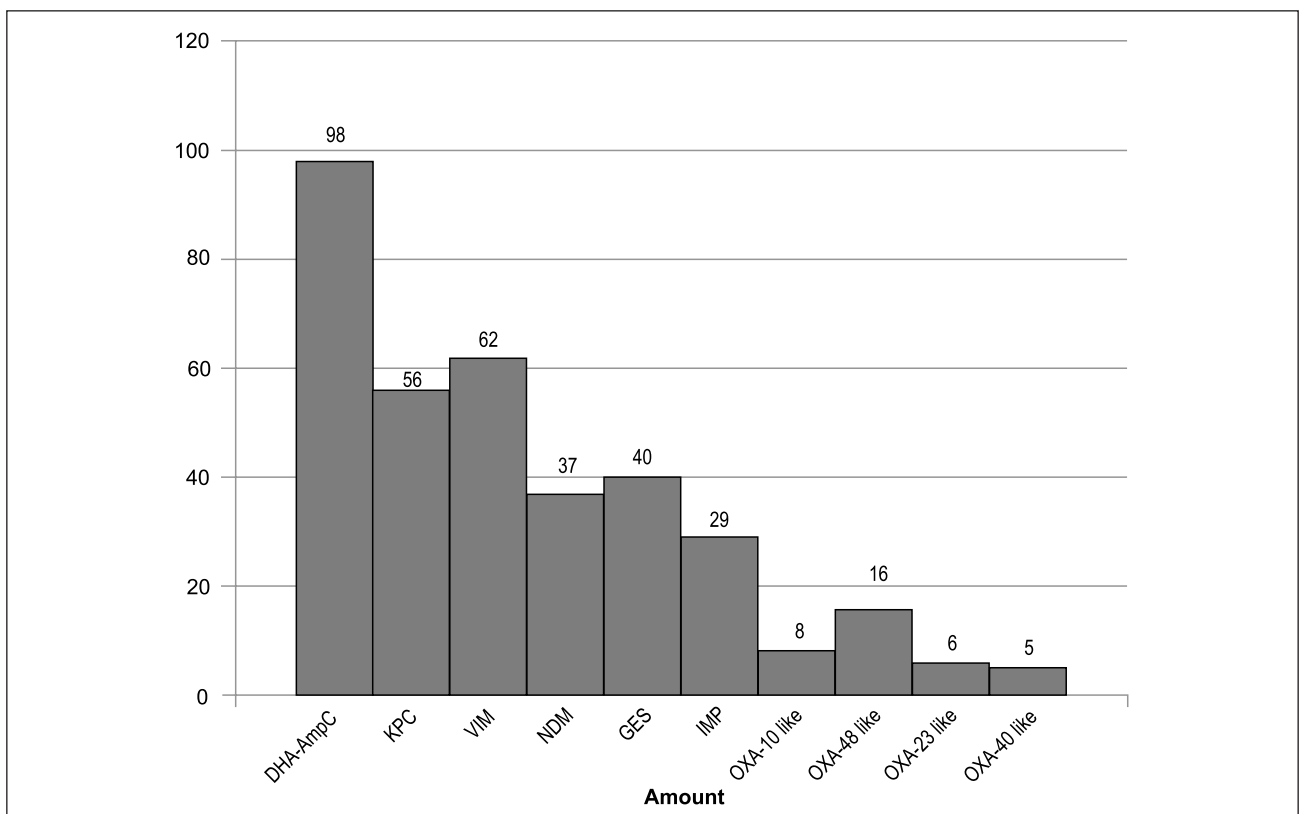
β -lactamase resistomes of *A.baumannii* is presented in Table 5.

Table 5 shows that *A.baumannii* in all cases was a producer of AmpC β -lactamases and class D serine carbapenemases. In 50 % of cases, it was also capable of producing metallo- β -lactamases.

Therefore, this pathogen is absolutely insensitive to carbapenems and requires alternative approaches to antibacterial therapy, including the use of aztreonam, ceftazidime-avibactam, and polymyxins.

P.aeruginosa was encountered only as part of polymicrobial associations, hence an analysis of its β -lactamase production profile was impossible.

In addition to assessing the resistance of individual gram-negative bacteria, we find it appropriate and useful to look at the general profile of β -lactamase production for

**Figure 1. General profile of β -lactamase production for all pathogens**

all pathogens (Fig. 1). From it, it is evident that in 39.0 % of cases, there was the production of AmpC β -lactamase, in 41.4 % — class A serine carbapenemases, in 51.0 % — class B metallo- β -lactamases, and in 14 % — class D serine carbapenemases. Therefore, an extremely unpleasant conclusion can be drawn about the end of the carbapenem era in the intensive care units of Kharkiv hospitals, which can probably be extrapolated to Ukraine as a whole. Chaotic antibacterial therapy, antibacterial therapy in patients who do not need it, indiscriminate abuse of third-generation cephalosporins and carbapenems, lack of adequate microbiological control and epidemiological surveillance have led to the critical spread of antibiotic-resistant strains.

Discussion

The data we obtained for the first time in Ukraine testify to the extremely high prevalence of gram-negative pathogens as agents of hospital infections and sepsis in the intensive care units. The most significant among them are enterobacteria, capable of producing various β -lactamases, including class A serine carbapenemases and non-fermenting pathogens — producers of class D serine carbapenemases. In every second patient, strains are found that have resistomes of class B metallo- β -lactamases. The results of our work demonstrate a much greater prevalence of critical antibiotic resistance associated with the production of all classes of carbapenemases than in the countries of the European Union. This situation can be considered catastrophic, which, including through the widespread and unjustified prescription of antibiotics for the treatment of patients with COVID-19, leads to the development of an antibiotic resistance pandemic in the intensive care units, an extraordinary increase in the cost of treating patients with hospital infections, and, very regrettably, to an increase in hospital mortality. The only direction to curb this catastrophe is to ensure strict monitoring of antibiotic prescriptions, create commissions with the participation of clinical pharmacologists, create passports of antibiotic resistance for each hospital institution, apply modern bacteriological analyzers to optimize the possibilities of antibacterial therapy, and establish control over the state of sepsis in the intensive care units. It should be noted that inadequate prescription of antibiotics is one of the main mistakes in the intensive care units [18]. The authors hope that finally domestic anesthesiologists and doctors of other specialties will also understand the importance of this problem.

Conclusions

Growing antibiotic resistance is a challenge for health care systems worldwide, and for a country like Ukraine, which suffers from constant underfunding of the medical system, it can become a real catastrophe.

The results of the study conducted demonstrate an extremely high detection of gram-negative antibiotic-resistant pathogens in patients of the intensive care units in the Kharkiv region.

The most unfavorable profile of antibiotic resistance is possessed by microorganisms such as *E.coli* and *A.baumannii*, which is determined by the high frequency of production of serine carbapenemases and metallo- β -lactamases, whose presence makes the effective use of carbapenems impossible.

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Роль азтреонаму в раціональній антибактеріальній терапії резистентних госпітальних інфекцій, викликаних грамнегативними бактеріями. Нове життя відомого β-лактаму

Резюме. Актуальність. Ситуація щодо поширеності резистентних збудників, типів продукції β-лактамаз та, відповідно, обґрунтування раціональних підходів до антибактеріальної терапії в Україні залишається недостатньо вивченою. **Мета:** на підставі визначення етіологічної структури збудників госпітальних інфекцій у Харківському регіоні та стану їх резистентності, обумовленої продукцією β-лактамаз, запропонувати раціональні підходи до антибактеріальної терапії та оцінити доцільність використання азтреонаму як потенційно ефективного засобу лікування інфекцій, викликаних стійкими бактеріями. **Матеріали та методи.** У 251 пацієнта методом полімеразної ланцюгової реакції було вивчено зразки біоматеріалів на наявність наступних грамнегативних збудників: *P.aeruginosa*, *Enterobacter*, *E.coli*, *K.pneumoniae*, *Proteus* spp. та *A.baumannii*. Також проводилося молекулярно-генетичне дослідження для визначення певних типів β-лактамаз. **Результати.** У структурі госпітальних збудників абсолютна більшість грамнегативних бактерій належить до родини ентеробактерій. При визначенні профілю β-лактамаз виявлено, що в 59,38 % випадків *E.coli* була здатна продукувати метало-β-лактамази, що унеможливує терапію карбапенемами або цефтазидимом-авібактамом. Альтернативою в таких випадках є комбі-

нація азтреонаму та цефтазидиму-авібактаму. При виявленні збудника *K.pneumoniae* в окремих пацієнтів також може бути потреба в комбінованій терапії з використанням азтреонаму. Установлено, що *Enterobacter* spp. у переважній більшості випадків є чутливим до карбапенемів. *A.baumannii* є абсолютно нечутливим до карбапенемів, що потребує альтернативних підходів до антибактеріальної терапії з включенням азтреонаму, цефтазидиму-авібактаму та поліміксинів. *P.aeruginosa* зустрічався лише в складі полімікробних асоціацій, отже, виконати аналіз профілю продукції β-лактамаз було неможливо. **Висновки.** За результатами проведеного дослідження продемонстровано надзвичайно високий процент виявлення грамнегативних антибіотикорезистентних збудників у пацієнтів відділення інтенсивної терапії Харківського регіону. Найбільш несприятливий профіль антибіотикорезистентності мають такі мікроорганізми, як *E.coli* та *A.baumannii*, що обумовлено високою частотою продукції ними серинових карбапенемаз та метало-β-лактамаз, наявність яких унеможливує ефективне використання карбапенемів.

Ключові слова: грамнегативна інфекція; β-лактамази; антибіотикорезистентність; антибактеріальна терапія; відділення інтенсивної терапії