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DISTRIBUTION OF METALLO-β-LACTAMASE PRODUCING STRAINS AMONG POLY-DRUG RESISTANT NON-FERMENTING GRAM-NEGATIVE BACILLI IN THE MODERN PERIOD IN UKRAINE

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Among poly-drug resistant non-fermenting gram-negative bacilli (NFGNB), isolated from patients of surgical departments of hospitals located in different regions of Ukraine, 54.0-56.0 % of strains were detected as producers of metallo-β-lactamases (MβL) – enzymes that induce high-level resistance to carbapenem antibiotics. All strains were resistant to cephalosporins and had low susceptibility to non-β-lactam antibiotics. The most active antibiotic against polyresistant Acinetobacter baumannii was netillin (68 %), polyresistant strains of Pseudomonas aeruginosa maintained susceptibility only to imipenem (29.6 %).

Key words: *metallo-β-lactamases, antibiotic resistance, non-fermenting Gram-negative bacilli, Pseudonomas, Acinetobacter.*

The group of nonfermenting gram-negative bacilli (NFGNB) every year becomes more clinical significant [1, 2]. In 2013 MDR NFHNB infections were outlined in CDC USA report as a «serious threat» due to the mortality level of 6 % [3]. The most dangerous is the worldwide distribution of NFGNB strains, that are resistant to the antibiotics of last resort – carbapenems.

Carbapenems are a group of critically important β-lactam antibiotics because of their broad spectrum of activity against most aerobic and anaerobic microorganisms and high-level stability to most known β-lactamases [4]. Due to these properties carbapenems are used as the last-line drugs used for treatment of infections that don`t respond to therapy with other penicillins and cephalosporins, including infections caused with poly-drug resistant strains. In fact, nowadays we don't have any alternative group of antibiotics, that would be comparable with carbapenems in efficiency.

Therefore extremely dangerous is the process of rapid spreading of the resistance enzymes – carbapenemases that is gathering pace in all countries over the world. The most dangerous features of carbapenem resistance acquisition is a quick gene exchange between strains belonging not only to different species, but to different genera. Furthermore, there occurs the circulation of genetically different types of carbapenemases. Currently carbapenemases are classified in 5 main families, including 3 families (IMP-imipenem-active carbapenemase, VIM (Verona integrones-mediated metallo-β-lactamase), NDM-1 (New Delhi metallo-β-lactamase) that belong to the metallo-β-lactamase group (zinc-depending enzymes), and 2 families – KPC (*K. pneumonia* carbapenemases) and OXA (oxacillinases) belonging to molecular classes A and D, respectively (enzymes with serine-dependent mechanism). General mechanism of resistance to carbapenems in NFGNB is the production of metallo-β-lactamases of IMP and VIM families; OXA production is also common, especially in *Acinetobacter* genus [5].

The most significant pathogen among NFHNB is *Pseudomonas aeruginosa*, which causes 8 % of all nosocomial infections [3]. *P. aeruginosa* is the most frequent causative agent of ventilator-associated pneumonia in ICU patients (16.6 %); in addition, it causes 8.2 % of infections in blood flow, 14.1 % of urinary tract infections and 7 %, surgical wounds infections [2].

According to recent national monitoring (2006-2007), level of resistance to carbapenems in *P. aeruginosa* in Russia was 20.3 %, and even then was valued as «national disaster». [6] According to a recent study carried out in Ukraine (2010) [7] the number of carbapenem-resistant isolates of *P. aeruginosa* was 24.7 %. *Acinetobacter* spp., which is less common NFGHB genus than *Pseudomonas*, has gained much more clinical significance in recent years.

In 2013 data on infections caused by *Acinetobacter baumannii* were for the first time included in the annual report of European Centre for Disease Prevention and Control (ECDC) [2], indicating the huge increase in the number of infections caused by this pathogen in the world. Special at-

tention is paid to the role of *A. baumannii* as a nosocomial infections causative agent. Although the overall percent of *A. baumannii* in nosocomial infections comparing with other agents is less than 2 %, strains of this pathogen, isolated from ICU, were found to show extremely high level of resistance to carbapenems – 68.8 % [2]. According to MYSTIC study, conducted in Europe in 2002-2004, 23,9-25,3 % isolates of *A. baumannii* were resistant to carbapenems, in 2006 the level of resistance was already 42,5-43, 4 % [8-9]. In Russian Federation the number of carbapenem-resistant isolates in *A. baumannii* increased from 2,7-14,5 % in 2006-2008 (REVANSH study, IACMAC [10]) to 78,6-83,3 %. [local research data, 11]. Another important concern is the role of *A. baumannii* in the transfer of resistance genes. If previously it was assumed that the main source of carbapanemases is *P. aeruginosa*, modern molecular studies has identified *A. baumannii* as MβL genes reservoir in NFGNB species. In addition, this species was shown to serve as an intermediate in the carbapenem-resistance genes exchange between NFHNB and *Enterobacteriaceae* [12].

The most common mechanism of resistance to carbapenems in NFNHB is synthesis of metallo-β-lactamases (MβL). [4]. Today there occur 13 main types of MβL and more than 100 variants of these enzymes [13]. Molecular studies have shown that these enzymes had evolved independently, i.e. various groups of MβL had originated from different bacterial strains [14]. The result is that enzymes of different types may not have structural similarities between them, excepting the presence of metal cations in the active center. Therefore, it is imposible to create a universal MβL inhibitor that could be applied to clinical practice.

Rapid spreading of these enzymes and their interspecies and interstrain transfer is possible due to the overwhelming localization of resistance genes in mobile genetic elements – integrones and gene cassettes. Besides MβL genes, such elements often carry resistance factors to several groups of antibiotics, such as aminoglycosides and fluoroquinolones [15].

Aim of study to investigate the distribution of metallo-β-lactamase producing strains among poly-drug resistant non-fermenting gram-negative bacilli (NFGNB) isolated from surgical patients and to determine the susceptibility levels to main clinically important antibiotics groups.

Materials and methods

The strains of microorganisms used for this study were isolated in 2013-2015 from biological material obtained from patients with surgical inflammatory processes in the postoperative period, that were undergoing therapy in hospitals located in different regions of Ukraine. Multiresistant strains isolated during bacteriological study were sent to the DSB «Ukrainian center for disease control and monitoring of the Ministry of Health of Ukraine» in accordance with Decree N167 of Ministry of Health of Ukraine «On Approval of guidelines «Determination of the sensitivity of microorganisms to antibiotics» [16].

For this study there were selected 256 poly-drug resistant strains of opportunistic pathogenic bacteria, from whose 152 strains were isolated from wounds, 49 – from blood, 32 – from urine, 22 – from sputum and 1 strain – from cerebrospinal fluid. Nonfermenting gram-negative bacilli (NFGNB) constituted 39 % of all isolated strains and were presented with genera *Pseudomonas* and *Acinetobacter* that were distributed in equal parts.

Identification of NFGNB species was performed with use of test systems NEFERMtest24 and API 20 NE (BioMerieux, France) or with automatic microbiological analyzer VITEK 2 Compact System (BioMerieux, France). Sensitivity to antibiotics was tested with disc diffusion method on Mueller-Hinton agar (BioMerieux, France) according to the 9.9.5-143-2007 methodological guidelines [17]. In some cases, antibiotic sensitivity was determined with microbiological analyzer VITEK 2 Compact. Analysis of antibiotic resistance of investigated strains was performed using the computer program WHONET 5.1. Strains that showed resistance to at least 5 groups of antibiotics were considered as poly-drug resistant.

Strains of NFHNB that showed resistance or reduced susceptibility to carbapenems (imipenem and meropenem), were studied for the production of metallo-β-lactamase (MβL) using double-disk synergy test with EDTA (ethylene diamintetraacetic acid) (Reahim, Russia) [18]. The presence of metallo-β-lactamases was detected based on presence/absence of synergism of carbapenem with EDTA which is an inhibitor (chelating agent) for MβL. Test was considered positive if presence of EDTA increased the sensitivity of strains to carbapenems, that was manifested in greater inhibition zone around disk impregnated with combination of carbapenem: EDTA. All obtained results were statistically analyzed with Student's t-test considering the level of significance (p) with use of «Biostat» program.

Results and discussion

We have investigated for MβL production polyresistant strains of *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, isolated in different regions of Ukraine. It was found that 54.0 % of *P. aeruginosa* and 56.0 % of *A. baumannii* strains produce MβL (Figure 1). Such distribution of metallo-β lactamase level in Ukraine can be consumed as very high, but, unfortunately, national data on carbapenemases from other European countries and CIS are absent, and comparisons can be made only using literature data on NFHNB sensitivity to carbapenems.

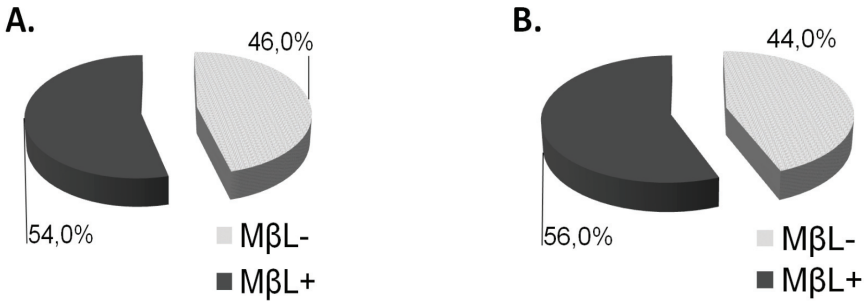

Figure 1. Frequency of isolation of MβL-producing strains among studied poly-drug resistant strains of *P. aeruginosa* (A); *A. baumannii* (B).

We determined the sensitivity of investigated polyresistant NFHNB strains to β-lactam and not β-lactam antibiotics (Figure 2). All strains showed low susceptibility to penicillin antibiotics (carbenicillin) and cephalosporin group, with percent of susceptible strains ranging from 2±1,97 % to 17,4±5,36 % for *P. aeruginosa* and from 2±1,97 % to 7,1±3,63 % for *A. baumannii*. Aminoglycoside antibiotics had low activity against *P. aeruginosa* and higher against *A. baumannii* but without significant differences between species. The most active antibiotics were netilmicin against the *A. baumannii* (68±6,59 % of susceptible strains), and imipenem for *P. aeruginosa* (38±6,86 %).

Separately there was analyzed the sensitivity to antibiotics of MβL-producing strains. As it can be seen from the diagram (Figure 3), all MβL-producing *P. aeruginosa* strains were resistant to cephalosporin antibiotics (cefepime, cefoperazone, ceftazidime) and ciprofloxacin. Aminoglycosides also showed low activity against these strains: percentage of *P. aeruginosa* strains susceptible to gentamicin and amikacin was 11,1±6,0 %, to netillin – 14,8±7,5 %. Most strains were resistant to carbapenems, sensitivity was maintained only in 29,6±8,8 % strains for imipenem and in 11,1±6,0 % strains to meropenem.

Among MβL-producing *Acinetobacter* spp. no strains were found susceptible to ciprofloxacin, ceftazidime, cefepime. The most effective antibiotic was netillin – 64,3±9,0 S% ($p<0.05$). Sensitivity to other aminoglycosides ranged from 10,7±5,8 % (to amikacin) to 33,3±8,9 % (to tobramycin). Very high resistance was determined to imipenem and meropenem – 96,2±3,6 % and 91,7±5,2 % of resistant strains, respectively.

Comparing the sensitivity of MβL-producers and overall sensitivity of polyresistant strains it can be concluded that synthesis of MβL notably reduces NFHNB susceptibility to carbapenems. Thus, susceptibility of MβL-producing *P. aeruginosa* to meropenem compared with overall level was 2.5 times lower; susceptibility of MβL-producing *A. baumannii* to imipenem – 3.2 times, and to meropenem – 9,3 times lower than overall NFGNB susceptibility level. Wherein statistically significant difference ($p<0.05$) in carbapenem susceptibility was only between MβL-producing/ all strains of *A. baumannii*, but not of *P. aeruginosa*.

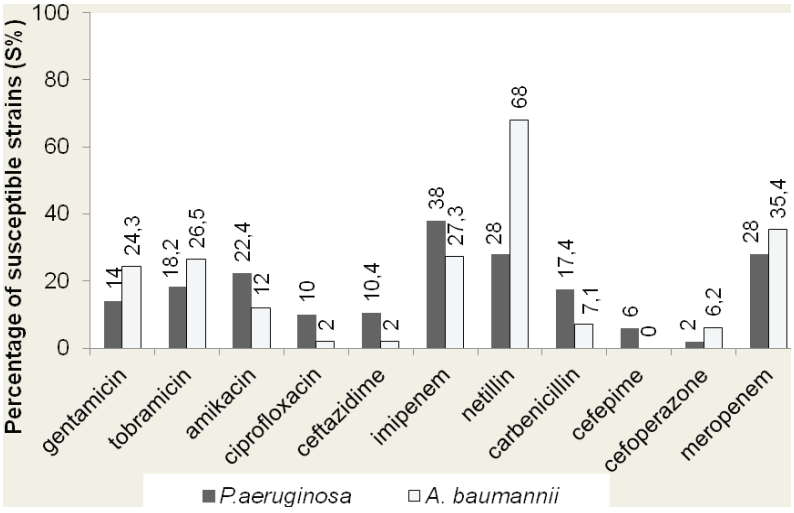

Figure 2. Antibiotic susceptibility of poly-drug resistant non-fermenting Gram-negative bacilli.

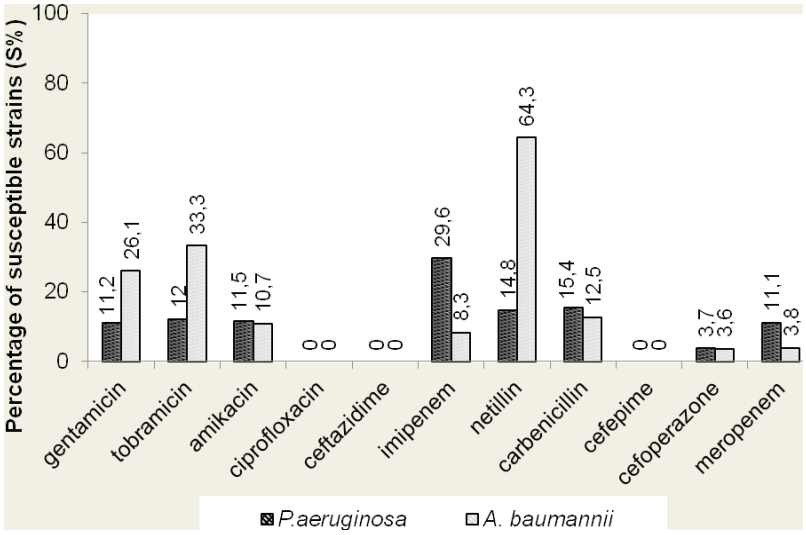

Figure 3. Antibiotic susceptibility of MβL-producing strains of poly-drug resistant non-fermenting Gram-negative bacilli.

Comparing the sensitivity of different NFGNB genera, it`s seen that sensitivity to aminoglycoside antibiotics (gentamicin, tobramycin, netillin) of *Acinetobacter* spp. was higher than of *P. aeruginosa*, with statistically significant difference only in case of netillin ($p<0.05$). Sensitivity to imipenem and meropenem was almost 3 times lower in strains of *P. aeruginosa*, than in *Acinetobacter* spp., without significant difference on the sensitive strains number of these species.

To study the dynamics of antibiotic resistance of *P. aeruginosa* and *A. baumannii* we conducted the retrospective analysis using obtained data on antibiotic susceptibility of MβL-producing NFGNB strains (Figures 4, 5). It was found that in recent years sensitivity of MβL-producing NFHNB strains has undergone significant changes. Thus, from 2010 to 2015 carbapenem resistance of MβL-producing *A. baumannii* strains has dramatically increased – in 8.2 times to meropenem and in 7.5 times to imipenem ($p<0.05$). For MβL-producing strains of *P. aeruginosa* high level of resistance to all groups of antibiotics was observed as early as 2010-2012, and in recent years has only slightly declined (in 3,7-9,1 %).

In recent years there is not observed any reliably significant changes in the number of MβL-producing NFHNB strains. Thus, according to our data for the period of 2010-2012, 60.6 % poly-drug resistant isolates of *P. aeruginosa* and 48,5 % of *A. baumannii* produced MβL, and in 2013-2015 the percent of MβL producers was 54.0 % and 56.0 % for strains and *P. aeruginosa A. baumannii* respectively [19].

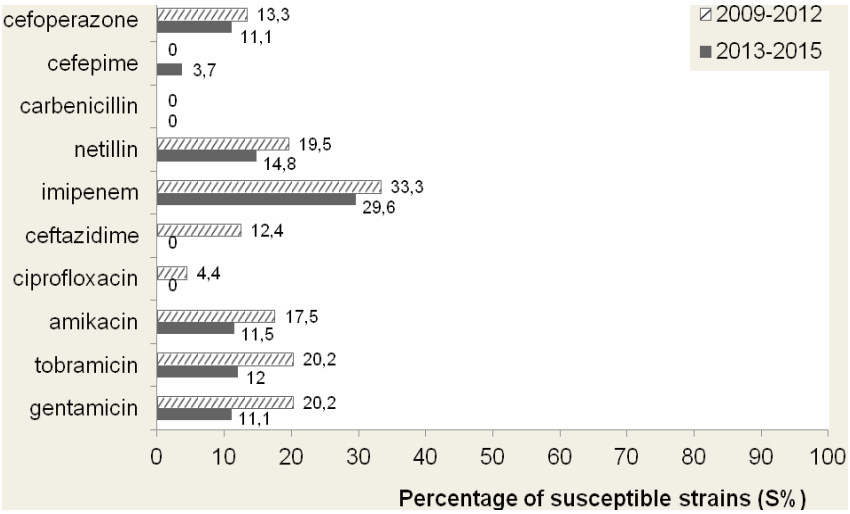

Figure 4. Antibiotic susceptibility of MβL-producing strains of *Pseudomonas aeruginosa* isolated in 2010-2012 and 2013-2015.

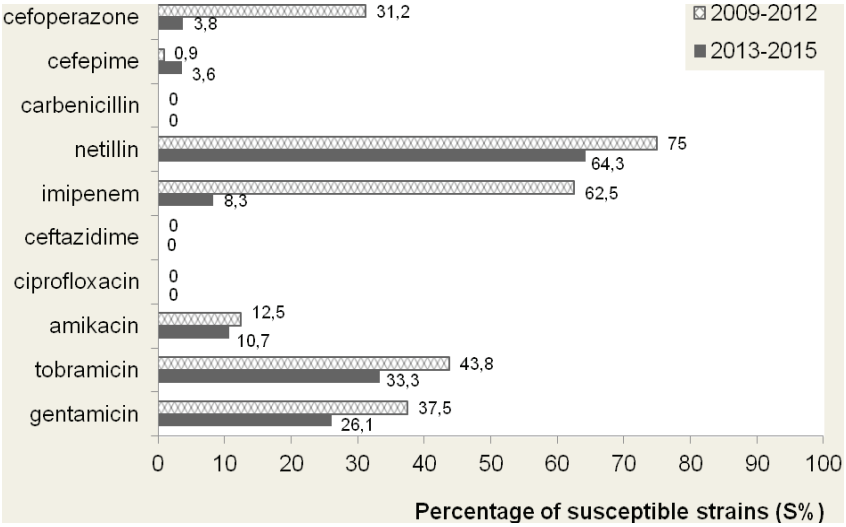

Figure 5. Antibiotic susceptibility of *Acinetobacter baumannii* MβL-producing strains isolated in 2010-2012 and 2013-2015.

Analysis of the antibiotic susceptibility shows that sensitivity of poly-drug resistant NFHNB to imipenem and meropenem has reduced in recent years: 6,2-6,09 % for *P. aeruginosa* and 13,1-53,5 % for *A. baumannii* respectively (Table 1).

Table 1

Susceptibility to carbapenems of investigated poly-drug resistant NFHNB strains and MβL-producing NFHNB strains isolated in different years

	Pseudomonas aeruginosa		Acinetobacter baumannii	
	Imipenem	Meropenem	Imipenem	Meropenem
All poly-drug resistant strains (S%)				
2010-2012	53,2±3,64	34,3±13,0	78,8±7,11*	48,5±7,02
2013-2015	38±6,86	28±6,54	27,3±6,30*	35,4±7,59
MβL-producing strains (S%)				
2010-2012	33,3±4,43	13,3±7,65	62,5±±12,1**	31,2±3,82***
2013-2015	29,6±8,78	11,1±6,04	8,3±5,21**	3,8±3,66***

*, **, *** – significant difference between (S%) values, p<0,05

Growing resistance of *Acinetobacter* spp. to carbapenems is a trend observed in recent years in different countries all over the world, and has been called «the resistance evolution». Thus, according to epidemiological data from China, the resistance of *A. baumannii* to imipenem and meropenem increased from 7,5-8,8 % resistant strains in 2003 to 40,3-41,9 R% in 2011 respectively [20]; similar resistance increase was registered in Korea: from 15,9-29,0 R% in 2003-2007 to 77.6 R% for both carbapenems in 2008-2010. [21]

An interesting trend in our data is the development of carbapenem resistance in a group of *Acinetobacter* strains that were identified as MβL producers, meaning they already had had at least one mechanism of resistance to carbapenems. However, if in 2010-2012 among MβL-positive *A. baumannii* 62,5±12,1 % were susceptible to imipenem, in 2013-2015 susceptibility lowered to 8,3±5,21 S%. This phenomenon may have several reasons. First of all, possible reason is the emergence of strains carriage high-expression plasmids or transposons that contain MβL genes, or strains with chromosomal localization of these genes [22]. Other reason could be an accession of new resistance mechanisms through migration of mutant *Acinetobacter* spp. strains and gene exchange between different strains. It is established that for *Acinetobacter* spp. it is possible the co-existence of several types of MβL [23] or carrying of combined phenotypes: MβL-ESβL (extended-spectrum β lactamase), MβL-AmpC (ampicillinase C) [24].

Another difficulty in studying the resistance epidemiology of *Acinetobacter* spp. is the wide distribution of oxacillinase

(OXA) carbapenemases in this species. OXA-enzymes also have substrate specificity to carbapenems and sometimes can interfere the correct interpretation of the strain phenotype [25]. For example, in Russia, where is also observed an increase in resistance of *Acinetobacter* spp. to carbapenems (from 2,7-14,5 R% in 2006-2008 [12] to 25,2-62,5 R% in 2008-2012 [26]), no single strain gave a positive result the analysis of MβL; instead, all the strains were OXA-producers. The more probable origin of MβL-positive *Acinetobacter* spp. are the Eastern countries, in particular India, where in 2010 was discovered the most modern MβL – New Delhi NDM-1 (New Delhi metallo-β-lactamase). The genes of this enzyme have been widely distributed for the last 5 years in Europe between species and even genera of bacteria [27]. Threatable feature of metallo-β-lactamases, compared with oxacillinases is their much higher substrate specificity and efficiency in hydrolizing carbapenems (up to 100-1000 times higher activity) [28]. There are also reports on the emergence of *Acinetobacter* strains that produce both oxacillinases and metallo-β lactamases [27]. The combination of these two phenotypes may explain the rapid growth of resistance of *Acinetobacter* spp. to carbapenems in the past few years.

The threat of epidemiological situation that has developed in Ukraine and worldwide is that today we don`t have applicable alternatives for therapy of carbapenem-resistant infections . In clinical practice for treatment of such infection are used colistin and polymyxin B, rarely used before due to high renal toxicity and allergenicity of these drugs. Another possible option is a combination therapy or using the high doses of carbapenems [29,30]. However, the most important aspect today is the lack of rapid and regular monitoring of MβL-producing strains in Ukraine and CIS countries that leaves no possibility to adequately evaluate the level of threat on the hospital and region level and take steps to prevent the spread of resistant strains.

Conclusions

1. Among the studied strains of poly-drug resistant NFGNB 54.0 % of *P. aeruginosa* and 56.0 % of *A. baumannii* strains were identified as MβL-producers.

2. All MβL-positive strains of NFHNB were resistant to cephalosporin antibiotics and had low sensitivity to non-β-lactam antibiotics. The most active drug against the *A. baumannii* was netillin (68 S%), against *P. aeruginosa* – imipenem (29,6 S%).

3. In recent years it is observed the rapid growth of NFHNB resistance, especially fast-developing is the resistance of *A. baumannii* to carbapenems.

4. Since the most significant marker MβL production is the resistance to carbapenems, it is recommended to perform testing for MβL in all strains that exhibit reduced sensitivity or resistance to carbapenems, especially in *P. aeruginosa* and *Acinetobacter* spp.

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РОЗПОВСЮДЖЕННЯ ШТАМІВ-ПРОДУЦЕНТІВ МЕТАЛО-β-ЛАКТАМАЗ СЕРЕД МНОЖИННОСТІЙКИХ НЕФЕРМЕНТАЦІЙНИХ ГРАМ-НЕГАТИВНИХ БАКТЕРІЙ У СУЧАСНИЙ ПЕРІОД В УКРАЇНІ

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РЕЗЮМЕ. Серед множиннорезистентних до антибіотиків неферментаційних грам-негативних бактерій, виділених у хворих хірургічного профілю з різних стаціонарів України, у 54,0-56,0 % штамів виявлено продукцію метало-β-лактамаз, що зумовлюють стійкість до карбапенемів. Всі штами були резистентними до цефалоспоринових антибіотиків, мали низьку чутливість до не-β-лактамних антибіотиків. Найбільш активним препаратом до A. baumannii залишається нетилміцин.

Ключові слова: *метало-β-лактамази, резистентність, грам-негативні неферментуючі бактерії, Pseudomonas, Acinetobacter.*

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