Translated by E.V. Trushina

Research Article

https://doi.org/10.23934/2223-9022-2024-13-1-22-28

Carbapenemases Produced by Multidrug-Resistant Strains of Klebsiella Pneumoniae Isolated from Intensive Care Patients

T.V. Chernenkaya ✉***, L.A. Borisova, T.Yu. Vorobieva, M.A. Godkov, A.K. Shabanov***

Scientific Laboratory of Clinical Microbiology
N.V. Sklifosovsky Research Institute for Emergency Medicine
3, Bolshaya Sukharevskaya Sq., Moscow 129090, Russian Federation

✉ **Contacts:** Tatyana V. Chernenkaya, Candidate of Medical Sciences, Head, Scientific Laboratory of Clinical Microbiology, N.V. Sklifosovsky Research Institute for Emergency Medicine.

Email: chernenkayat@rambler.ruu

RELEVANCE *Klebsiella pneumoniae* is one of the main pathogens of nosocomial infections. Hospital strains of this pathogen are characterized by a high frequency of resistance to many antibiotics, including carbapenems. The main mechanism for the formation of resistance to carbapenems is the production of carbapenemases by bacteria. To date, *K. pneumoniae* is considered one of the main "distributors" of clinically important antibiotic resistance genes.

AIM OF THE STUDY To study the frequency of occurrence of the most common carbapenemase genes in multiresistant *K.pneumoniae* strains isolated from patients of intensive care units in an emergency hospital.

MATERIAL AND METHODS 4708 samples of various types of clinical material from patients of 5 intensive care units of the N.V. Sklifosovsky Research Institute for Emergency Medicine were analyzed. Microbiological studies were carried out using standard generally accepted methods. For the purposes of this study, unique sequential *K.pneumoniae* strains resistant to imipenem and/or meropenem were selected. DNA isolation was carried out using the RIBO-prep kit (Russia). Carbapenemase genes were detected by real-time PCR using the kits of reagents "AmpliSens MDR-MBL-FL" and "AmpliSens MDR-KPC/OXA-48-FL" on a "Rotor Gene" device (Corbett Research, Australia).

RESULTS Etiologically significant microorganisms were detected in 64.7% of the studied samples. *K. pneumoniae* was isolated in a quarter of the samples. 194 unique carbapenem-resistant strains of *K.pneumoniae* were selected. Of these, 11.3% of the genes of the studied carbapenemases were not detected. In 38.1% of strains, 1 carbapenemase was detected, in 29.9% — two and in 20.6% — three or more. Among the strains with one carbapenemase gene, OXA-48 (19.1%) and CATTLE (13.4%) producers prevailed. Strains producing only NDM betalactamase were found in 5.7% of cases. Isolated allocation of VIM and IMP was not detected. In 34%, metallobectalamases were isolated in combination with serine carbapenemases. The production of serine carbapenemases alone was detected in 48.5% of the strains. Depending on the specialization of the intensive care unit, there are differences in the frequency of detection of serine and metallobetalactamases in strains of carbapenem-resistant *Klebsiella*.

CONCLUSION *K. pneumoniae* is the causative agent of nosocomial infections in 25% of cases. In 11.3% of carbapenem-resistant strains, the production of KPC, OXA-48, NDM, VIM and IMP genes was not detected. When developing algorithms for antibacterial therapy, it is necessary to take into account that from 25.7% to 60.6% of *K. pneumoniae* strains in different intensive care units are the producers of metallobetalactamases.

Keywords: *Klebsiella pneumoniae*, multiresistant strains, carbapenemases, serine beta-lactamases, metallo-betalactamases

For citation Chernenkaya TV, Borisova LA, Vorobieva TYu, Shabanov AK, Godkov MA. Carbapenemases Produced by Multidrug-Resistant Strains of Klebsiella Pneumoniae Isolated from Intensive Care Patients. *Russian Sklifosovsky Journal of Emergency Medical Care*. 2024;13(1):22–28. https://doi.org/10.23934/2223-9022-2024-13-1-22-28 (in Russ.)

Conflict of interest Authors declare lack of the conflicts of interests

Acknowledgments, sponsorship The study had no sponsorship

Affiliations

Tatyana V. Chernenkaya	Candidate of Medical Sciences, Head of the Scientific Laboratory of Clinical Microbiology, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0002-6167-7117, chernenkayat@rambler.ru; 30%, concept of the article, analysis of the data obtained, text writing
Lyudmila A. Borisova	Head of the Bacteriological Laboratory, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0003-0691-4519, borisovala@sklif.mos.ru; 20%, conducting the experimental part of the study, analyzing the data obtained
Tatyana Yu. Vorobieva	Bacteriologist of the Bacteriological Laboratory, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0003-4469-3497, vorobievatj@sklif.mos.ru; 20%, conducting the experimental part of the study, analyzing the data obtained

ikhail A. Godkov — Doctor of Medical Sciences, Head of the Scientific Department of Laboratory Diagnostics, N.V. Sklifosovsky Research Institute for Emergency Medicine;
https://orcid.org/0000-0001-9612-6705, godkovma@sklif.mos.ru;
15%, editing of primary material, approval of the final version

Aslan K. Shabanov — Doctor of Medical Sciences, Deputy Chief Physician for Anesthesiology and Resuscitation, N.V. Sklifosovsky Research Institute for Emergency Medicine;
https://orcid.org/0000-0002-3417-2682, shabanovak@sklif.mos.ru;
15%, analysis of the received data, approval of the final version

BICU – burn intensive care unit
EICU – emergency intensive care unit
ESBLs – extended-spectrum beta-lactamases
HAI – healthcare-associated infections
IMP – IMiPenem - hydrolyzing beta-lactamase
KPC – *Klebsiella Pneumoniae Carbapenemase* - a strain of *K. Pneumoniae* that produces carbapenemase
MBLs – metallo-β-lactamases
NDM – New Delhi metallo-β-lactamase
NICU – neurological intensive care unit
NSICU – neurosurgical intensive care unit
OXA – OXAcillinase - group of carbapenemases
SHV – SulphHydryl Variable - chromosomal beta-lactamase
SICU – surgical intensive care unit
SME – Serratia Marcescens Enzyme – beta-lactamases
TEM – Temoneira – beta-lactamases
VIM – Verona Imipenemase - metallo-β-lactamase

INTRODUCTION

Klebsiella pneumoniae is a gram-negative bacteria that live in the environment, including soil and surface waters; is part of the normal intestinal microflora of humans and animals [1]. This microorganism was first described by Carl Friedländer in 1882 as an etiological agent of pneumonia, and for a long time was called the "Friedländer bacillus". Currently, *K. pneumoniae* is one of the main causative agents of nosocomial pneumonia, urinary tract and bloodstream infections. Hospital strains of this pathogen are characterized by a high incidence of antimicrobial resistance [2].

Carbapenems are β-lactam antibiotics that had the broadest spectrum of antimicrobial activity at the time of their introduction into clinical practice, and represented the last line of defense in the treatment of severe life-threatening infections. When imipenem, the first carbapenem antibiotic, entered clinical practice in 1985, about 98% of gram-negative pathogens were sensitive to it. However, since the early 1990s, reports began to appear about the spread of clinical strains resistant to imipenem [3]. Reports on carbapenem resistance were initially sporadic. This resistance was primarily explained by the high level of extended-spectrum AmpC type β-lactamase production in combination with modification of porin channels in the bacterial outer membrane. In extremely rare cases, the production of carbapenem-hydrolyzing β-lactamases (carbapenemases) by the bacteria was recorded.

At present, the spread of carbapenem-resistant microorganisms is considered one of the most pressing health problems worldwide. The main mechanism of carbapenem resistance of gram-negative pathogens is the production of carbapenemases by the bacteria. Most of the genes encoding carbapenemase production are distributed between different types of microorganisms using plasmids containing determinants of resistance to antibiotics of different groups. This is how the simultaneous transmission of the multidrug resistance phenotype occurs [4, 5].

K. pneumoniae is a microorganism in which several new carbapenem resistance genes (the most famous are KPC and NDM) were first discovered. Subsequently, these β-lactamases spread widely among other bacterial species.

K. pneumoniae has a significantly larger genome than other Enterobacteriaceae and is characterized by a high diversity of acquired antimicrobial resistance genes. Today, *K. pneumoniae* is considered one of the main "spreaders" of clinically important antibiotic resistance genes [6].

Aim of the research: to study the prevalence of the most common carbapenemase genes in multidrug-resistant strains of *Klebsiella pneumoniae* isolated from patients in various intensive care units of an emergency hospital.

MATERIAL AND METHODS

For the period from January 1 to December 31, 2021, 4708 samples of various types of clinical material obtained from patients of 5 intensive care units of the N.V. Sklifosovsky Research Institute for Emergency Medicine were analyzed. In the surgical intensive care unit (SICU), patients with mediastinitis, generalized peritonitis, and open trauma to the chest and abdomen are treated. In the neurosurgical intensive care unit (NSICU), care is provided to patients with ruptured cerebral aneurysms, arteriovenous malformations at bleeding height, with isolated and combined traumatic brain injury; in neurological intensive care unit (NICU) - with hemorrhagic and ischemic strokes. Victims with severe combined trauma are treated in the emergency intensive care unit (EICU), and in the burn intensive care unit (BICU) - with severe thermal injury.

Indications for microbiological tests were determined by the patient's attending physician. Microbiological tests were carried out using standard generally accepted methods.

Primary seeding was performed, depending on the type of clinical material under study, on 5% blood, chocolate and mannitol salt agar, as well as on Endo and Sabouraud media. Blood culture was carried out in BactecTM Plus Aaerobic/F Culture Vials (for aerobic bacteria) and BactecTM Plus Anaerobic/F Culture Vials (for anaerobic microorganisms), which were incubated in a Bactec FX analyzer (BD, USA). The standard protocol for culturing vials in the device is 5 days. Pathogens were identified using a VITEK MS mass spectrometer (bioMérieux, France), sensitivity to antibiotics was determined on a VITEK-2 Compact analyzer (bioMérieux, France) or WalkAway-40 analyzer (Beckman Coulter, USA). For the purposes of this study, *Klebsiella pneumoniae* strains resistant to imipenem and/or meropenem were selected. When carbapenem-resistant *K. pneumoniae* was isolated from one patient in several samples, only the first strain obtained was selected for further studies.

DNA from microorganism strains was isolated according to the instructions for the "RIBO-prep" kit (Central Research Institute of Epidemiology, Russia). Metallo-β-lactamase (MBL) genes of the VIM, IMP, NDM groups and serine carbapenemases of the KPC and OXA-48 groups were detected by the real-time polymerase chain reaction using AmpliSens MDR-MBL-FL and AmpliSens MDR-KPC/OXA-48-FL reagent kits (Central Research Institute of Epidemiology, Russia) on a Rotor Gene device (Corbett Research, Australia).

RESULTS

4708 samples of various types of clinical material obtained from patients of the indicated intensive care units were studied. The growth of etiologically significant microorganisms was obtained in 64.7% of samples. The general structure of pathogens of healthcare-associated infections (HAIs) in intensive care patients is presented in Fig. 1. As can be seen from the figure, the main pathogens in intensive care patients are gram-negative bacteria, such as *Klebsiella pneumoniae* (25.05%), *Acinetobacter spp.* (14.71%) and *Pseudomonas aeruginosa* (14.65%).

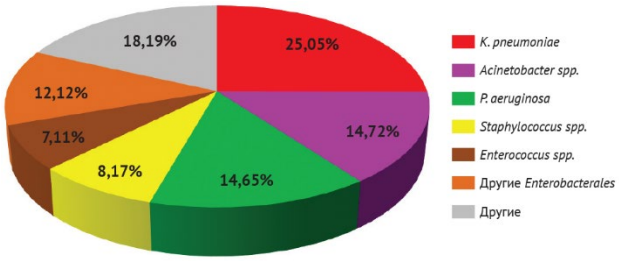

Fig. 1. Structure of the main nosocomial pathogens in intensive care patients in 2021

For the purposes of this research, we selected 194 consecutive unique carbapenem-resistant strains of *K. pneumoniae* isolated from intensive care patients at the N.V. Sklifosovsky Research Institute for Emergency Medicine: from NICU patients - 30; from BICU and EICU patients - 33 each; from SICU patients – 35, and from NSICU patients - 63 strains.

Of the 194 tested carbapenem-resistant *Klebsiella* strains, the genes of the studied carbapenemases were not detected in 22 (11.3%). In 38.1% of strains, one carbapenemase was detected, in 29.9% - two, and in 20.6% - three or more carbapenemases. At the same time, in different intensive care units, the frequency of isolation of various carbapenemase genes from resistant *Klebsiella* strains differs (Fig. 2). As can be seen from the figure, the tested carbapenemase genes were detected in all *Klebsiella* strains isolated from EICU patients. In the strains isolated from BICU patients, the studied genes were absent in 21.2%; and in SICU, NSICU and NICU

patients - in 8.6%; 14.3% and 10% of cases, respectively.

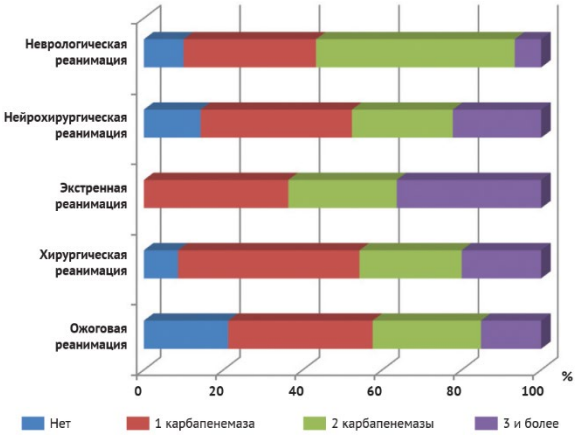

Fig. 2. The percentage of *Klebsiella pneumoniae* carbapenemase genes isolated from patients of various intensive care units of the N.V. Sklifosovsky Research Institute for Emergency Medicine in 2021 (%)

Among the strains in which one carbapenemase gene was detected, producers of OXA-48 (OXAcillinase) (19.1%) and KPC (*Klebsiella Pneumoniae Carbapenemase*) (13.4%) predominated. Strains producing only NDM beta-lactamases were found in 5.7% of cases. Isolated production of VIM and IMP in carbapenem-resistant *Klebsiella* strains was not detected. Most often, genes encoding metallo-β-lactamase production (NDM, VIM and IMP) were isolated in combination with genes of serine carbapenemases (34%). The production of serine carbapenemases alone was detected in 48.5% of the studied *K. pneumoniae* strains resistant to carbapenems. The production of metallo-beta-lactamases was recorded in 40.2% of cases. Depending on the specialty of the intensive care unit, there were differences in the frequency of detection of serine and metallo-beta-lactamases in the strains of carbapenem-resistant *Klebsiella* (Fig. 3). In SICU, NSICU and NICU, serine carbapenemases predominate and were isolated in 65.7%; 47.6% and 60% cases, respectively. Strains isolated from EICU and BICU patients were more often the producers of metallo-beta-lactamases (60.6% and 48.5%, respectively).

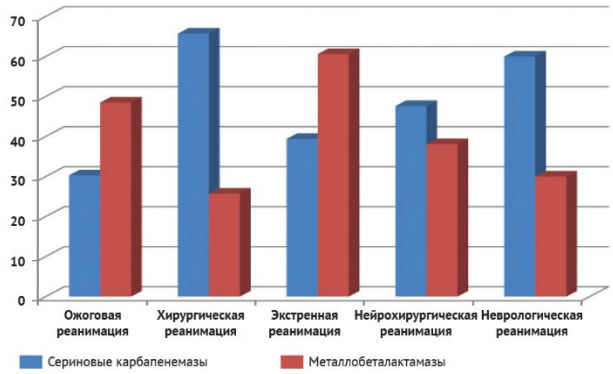

Fig. 3. Frequency of production of various types of betalactamases by carbapenem-resistant *K. pneumoniae* isolated from patients of various intensive care units

DISCUSSION OF THE RESULTS

β-lactam antibiotics are the most numerous class of antimicrobial drugs for the treatment of infectious and inflammatory diseases, and their complications. The history of the creation of new drugs of this class is inextricably linked with the history of the emergence of beta-lactamases which are the main reason for the resistance of pathogens to beta-lactam antibiotics. Benzylpenicillin was the first β-lactam to be widely used in clinical practice since 1944. The spread of penicillinase-producing staphylococcal strains stimulated scientists to create methicillin, oxacillin, and first-generation cephalosporins that were resistant to staphylococcal β-lactamases.

The introduction of ampicillin into clinical practice in the 1960s made it possible to successfully treat diseases caused by enterobacteriaceae. But, at the same time, this contributed to the spread of *Escherichia coli* strains producing β-lactamase TEM-1 (named after the patient from whom it was isolated for the first time - Temoneira), which hydrolyzes ampicillin. The gene encoding the production of the TEM enzyme was localized on the bacterial plasmid. Concurrently, in the structure of pathogens of nosocomial infections, the proportion of *K. pneumoniae* strains began to increase, which were naturally resistant to aminopenicillins due to the natural production of the chromosomal SHV-1 beta-lactamase (SulphHydryl Variable). Subsequently, the isolation of TEM-1 and SHV-1 β-lactamases from other bacterial species (for example, *Haemophilus influenzae* and *Neisseria gonorrhoeae*)

was recorded. It is likely that chromosomally encoded endogenous antimicrobial resistance genes were translocated into plasmids and became easily transmitted between different bacterial species [7].

In the 1980s, the decrease in the clinical effectiveness of penicillins and cephalosporins of the first generation stimulated scientists to create and introduce into the clinic cephalosporins of the second and third generations, resistant to the hydrolysis of TEM-1 and SHV-1 β-lactamases. However, several years later, microorganisms were isolated that produced enzymes which destroyed beta-lactam antibiotics, including third-generation cephalosporins [8]. These new enzymes were named extended spectrum beta-lactamases (ESBLs).

The introduction of carbapenems into clinical practice in 1985 made it possible to effectively combat ESBL-producing microorganisms. But, back in 1982, before the introduction of imipenem into widespread clinical practice, SME-1 beta-lactamases (*Serratia Marcescens* Enzyme), hydrolyzing penicillins, cephalosporins and carbapenems, were isolated from two clinical isolates of *Serratia marcescens*. Since the early 1990s, publications began to appear on the isolation of clinical strains of microorganisms with acquired resistance to carbapenems due to various beta-lactamases. In 1991, metallo-beta-lactamase (IMiPenem—hydrolyzing beta-lactamase) was isolated from a clinical strain of IMP-1 *Serratia marcescens* in Japan. Then, in Italy, VIM-1 metallo-beta-lactamase (Verona Imipenemase) was isolated from a clinical strain of *Pseudomonas aeruginosa*. In 1996, a *Klebsiella pneumoniae carbapenemase* (KPC)-producing bacteria was described in the United States. KPC-producing bacteria soon spread rapidly in hospitals of the United States and subsequently in other countries around the world. In parallel with the spread of KPC producers in the United States in the 2000s, another group of carbapenemases, OXA-48, appeared and spread in Mediterranean countries. In 2008, a strain of *K. pneumoniae* producing a new metallo-beta-lactamase (New Delhi metallo-β-lactamase, NDM) was isolated from a Swedish citizen of Indian origin. Since then, NDM carbapenemase has spread throughout the world and been isolated from different types of bacteria [9].

Depending on the molecular structure of the active center of β-lactamase enzymes, they are divided into serine and metallo-beta-lactamases. The former use a serine residue to inactivate antibiotics. The active center of the latter contains zinc atoms. According to Ambler classification, serine beta-lactamases include enzymes from classes A, C and D. Metallo-beta-lactamases constitute class B. Carbapenemases are included in classes A, B and D. Currently, more than 50 types of different beta-lactamases capable of hydrolyzing carbapenems have been described. The most common enzymes from class A are KPCs; from class B - IMP, VIM, NDM; from class D - OXA.

Carbapenemases are not sensitive to traditional beta-lactamase inhibitors (clavulanic acid, tazobactam, sulbactam). At the same time, the effect of most serine carbapenemases can be suppressed by the inhibitor avibactam, and class A carbapenemases can be suppressed by vaborbactam and relebactam. The action of class B enzymes is not blocked by beta-lactamase inhibitors currently available in clinical practice. Therefore, for the correct selection of antibacterial therapy, information about the types of carbapenemases produced by pathogens is important.

In our study, KPC, OXA-48, IMP, VIM, and NDM beta-lactamases were not detected in 11.3% of Klebsiella strains with phenotypic resistance to carbapenems. Moreover, in different intensive care units this figure ranged from 0 to 21.2%. Similar data were obtained in the works of other researchers [10]. This circumstance may be due to two reasons. First of all, in addition to the carbapenemases we are studying, the production of other, rarer enzymes is possible. In addition, enzymatic inactivation of betalactam antibiotics is considered the main, but not the only, reason for the development of bacterial resistance. More rare causes of resistance of gram-negative microorganisms to carbapenems are defects in the porin channels of the outer membrane of the bacteria, active removal of the drug from the bacterial cell, and overproduction of chromosomal enzymes (AmpC). These mutations are encoded by chromosomes. Therefore, these types of resistance spread very slowly and are detected in a small number of bacterial strains.

Carbapenemases, isolated from different genera of the bacteria and carried by plasmids, were initially associated with specific geographic regions. However, in an era of extensive international travel and medical tourism, the connection between a

specific resistance mechanism and the given region is quickly lost.

Initially, KPC-producing *Klebsiella pneumoniae* was widespread in the United States and some European countries such as Greece and Italy. OXA-48 producing strains were endemic in Turkey, Belgium, France and North Africa [11]. VIM and IMP metallo-β-lactamase enzymes were found most frequently in Spain, Italy and Hungary, and NDM – in India, Pakistan and Bangladesh [12]. Today, the isolation of all types of carbapenemases is recorded in many countries around the world.

In Russia, there are regional differences in the structure of the main mechanisms of bacterial resistance to carbapenems. Thus, according to several authors in St. Petersburg, in hospital strains of *K. pneumoniae*, a gene encoding the production of NDM beta-lactamase was isolated in most cases. Strains producing OXA-48 and KPC were much less common [10, 13]. And in Yekaterinburg, more than half of Enterobacter strains isolated from intensive care patients were carriers of the blaOXA-48 gene, and 21% - NDM [14]. In Moscow hospitals, *K. pneumoniae* strains that produce OXA-48 beta-lactamase also predominate [12, 15].

The results we obtained are comparable with data typical for Moscow hospitals. The main enzymes that destroy carbapenems are serine carbapenemases (found isolated in 48.5% of strains). However, the N.V. Sklifosovsky Research Institute for Emergency Medicine has its own local features: more than half of the *Klebsiella* strains simultaneously carried two or more different carbapenemase genes; and 40.2% of strains were producers of NDM metallo-beta-lactamase, and in most cases in combination with serine OXA-48 and KPC carbapenemases. Moreover, there are differences in the frequency of isolation of the studied carbapenemases in patients of different intensive care units of the Institute. Thus, in NICU, *K. pneumoniae* strains producing serine carbapenemases were found two times more often, and in SICU – almost 3 times more often than metallo-beta-lactamase producers. *Klebsiella* strains isolated from EICU and BICU patients produced metallo-beta-lactamases 2 times more often than serine ones. This may be due to both different populations of patients transferred to the intensive care units, and local features of compliance with the principles of infection control and antibacterial therapy tactics in each unit.

The data obtained indicate a difficult epidemiological situation in the hospital and the need for strict adherence to the principles of infection control.

When developing algorithms for antimicrobial therapy, it is necessary to take into account the fact that from 25.7 to 60.6% of strains of the leading pathogen of nosocomial infections – *K. pneumonia* – in different intensive care units are metallo-beta-lactamase producers and, as a result, resistant to all beta-lactam antibiotics, including modern beta-lactamase inhibitors.

CONCLUSION

Microbial resistance to antibiotics is a global problem and has enormous socio-economic significance. The emergence and spread of bacterial resistance is a natural biological response to the use of antimicrobial agents, which create selective pressures favoring the selection, survival and proliferation of resistant strains. Antimicrobials are an indispensable class of drugs, and without their use, modern medicine cannot exist. Therefore, “extending the lifespan” of antibiotics is an important task, the solution of which requires complex measures.

Understanding the causes and mechanisms of microbial resistance to antibiotics will allow us to develop the most effective ways to overcome the spread of bacterial resistance.

FINDINGS

1. *K. pneumoniae* is the causative agent of nosocomial infections in 25% of cases.
2. In 11.3% of carbapenem-resistant strains, the production of KPC, OXA-48, NDM, VIM and IMP genes was not detected.
3. When developing algorithms for antibacterial therapy, it is necessary to take into account that from 25.7% to 60.6% of *K. pneumoniae* strains in different intensive care units are producers of metallo-beta-lactamases.

REFERENCES

1. Sneath PHA, Bergey DH, Holt J. *Bergey's manual of systematic bacteriology*. Williams&Wilkins; 1986. Vol. 2. p. 1165–1167.
2. Effah CY, Sun T, Liu S, Wu Y. Klebsiella pneumoniae: an increasing threat to public health. *Ann Clin Microbiol Antimicrob*. 2020;19(1):1. PMID: 31918737 https://doi.org/10.1186/s12941-019-0343-8
3. Queenan AM, Bush K. Carbapenemases: the versatile beta-lactamases. *Clin Microbiol Rev*. 2007;20(3):440–458. PMID: 17630334 https://doi.org/10.1128/CMR.00001-07
4. Walsh TR, Toleman MA, Poirel L, Nordmann P. Metallo-beta-lactamases: the quiet before the storm? *Clin Microbiol Rev*. 2005;18(2):306–325. PMID: 15831827 https://doi.org/10.1128/CMR.18.2.306-325.2005
5. Bennett PM. Integrons and gene cassettes: a genetic construction kit for bacteria. *J Antimicrob Chemother*. 1999;43(1):1–4. PMID: 10381094
6. Wyres KL, Holt KE. Klebsiella pneumoniae as a key trafficker of drug resistance genes from environmental to clinically important bacteria. *Curr Opin Microbiol*. 2018;45:131–139. PMID: 29723841 https://doi.org/10.1016/j.mib.2018.04.004
7. Arakawa Y. Systematic research to overcome newly emerged multidrug-resistant bacteria. *Microbiol Immunol*. 2020;64(4):231–251. PMID: 32068266 https://doi.org/ 10.1111/1348-0421.12781
8. Paterson DL, Bonomo RA. Extended-Spectrum β-Lactamases: a Clinical Update. *Clin Microbiol Rev*. 2005;18(4):657–686. PMID: 16223952 https://doi.org/10.1128/CMR.18.4.657-686.2005
9. Nordmann P, Poirel L. Emerging carbapenemases in Gram-negative aerobes. *Clin Microbiol Infect*. 2002;8(6):321–331. PMID: 12084099 https://doi.org/10.1046/j.1469-0691.2002.00401.x
10. Egorova SA, Lipskaya LV, Konovalenko IB, Oksema EV, Smirnova MV, Vedernikova NB, et al. Karbapenemazy, produtsiruemye shtammami K. pneumoniae – vozbuditelyami ISM v statsionarakh Sankt-Peterburga. *Russian Journal of Infection and Immunity*. 2016;6(3):22. (In Russ.)
11. Bonomo RA, Burd EM, Conly J, Limbago BM, Poirel L, Segre JA, et al. Carbapenemase-Producing Organisms: A Global Scourge. *Clin Infect Dis*. 2018;66(8):1290–1297. PMID: 29165604 https://doi.org/10.1093/cid/cix893
12. Yakovlev SV, Suvorova MP, Bykov AO. Infections Caused by Carbapenem-Resistant Enterobacterales: Epidemiology, Clinical Significance, and Possibilities for Antibiotic Therapy Optimization. *Antibiotics and Chemotherapy*. 2020;65(5–6):41–69. (In Russ.) https://doi.org/10.37489/0235-2990-2020-65-5-6-41-69
13. Bozhkova SA, Gordina EM, Schneider OV, Rukina AN, Shabanova VV. Resistance of carbapenemase-producing Klebsiella pneumoniae isolated from patients with orthopedic infection. *Clinical Microbiology and Antimicrobial Chemotherapy*. 2020;22(1):47–52. (In Russ.) https://doi.org/10.36488/cmac.2020.1.47-52
14. Rozanova SM, Beykin YaB, Kyrf MV, Perevalova EYu, Sheveleva LV, Vakalyuk AV et al. Rasprostranenie enterobakteriy, produtsiruyushchikh karbapenemazy, v reanimatsionnykh otdeleniyakh Ekaterinburga. *Clinical Microbiology and Antimicrobial Chemotherapy*. 2019;21(S1):55–56. (In Russ.)
15. Timofeeva OG, Polikarpova SV. Local microbiological monitoring of carbapenemases-producing Enterobacterales. *Laboratory Service*. 2019;8(3):14–19. (In Russ.) https://doi.org/10.17116/labs2019803114

Received on 09/12/2022
Review completed on 16/10/2023
Accepted on 16/10/2023