

Original Study Article

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Characterization of the molecular genetic properties of epidemic strains of *Klebsiella pneumoniae* and *Staphylococcus aureus*, the pathogens of healthcare-associated infections circulating in the Nizhny Novgorod region

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Abstract

Introduction. Molecular epidemiological monitoring is aimed at obtaining up-to-date information on the genetic variants of healthcare-associated infections (HAIs) circulating in the region. Currently, special attention is being paid to monitoring representatives of the ESKAPE group, as they are a frequent cause of HAIs, complicate the course of the underlying disease, and are becoming an increasingly serious threat to the health and lives of patients due to their complex pathogenicity genes and diverse antibiotic resistance mechanisms.

The aim of the study is to analyze the results of whole-genome sequencing of epidemic strains of pathogens of HAIs — *Klebsiella pneumoniae* ssp. *pneumoniae* and *Staphylococcus aureus* — circulating in the Nizhny Novgorod region.

Materials and methods. Classical bacteriological methods, MALDI-TOF mass spectrometry, whole-genome sequencing, and bioinformatics methods were used.

Results. In-depth analysis revealed the circulation of a population of classical *K. pneumoniae* strains of sequence type (ST) 3-K type (K) 3 in the neonatal intensive care unit, containing a number of virulence genes and the *bla*_{SHV-1} beta-lactamase. Circulation of a population of *K. pneumoniae* strains of the convergent pathotype ST395 and K39 was detected in a multidisciplinary hospital, and strains of the convergent pathotype *K. pneumoniae* ST395-K2, K47, as well as strains of the classical pathotype *K. pneumoniae* ST5209-K35, ST441-K62, ST147-K64, containing a spectrum of pathogenicity genes and beta-lactamases in their genome, including New Delhi metallo-beta-lactamase *bla*_{NDM-1}, were identified. *S. aureus* strains associated with catheter-associated bloodstream infections have significant pathogenic potential, belonging to 13 different STs and 19 spa types (t). Circulation of methicillin-resistant (SCCmec IV, ST8, t008) and methicillin-susceptible (ST1, t127) staphylococcal strains has been detected in hemodialysis centers and departments.

Conclusion. The data obtained indicate the circulation of convergent and classical strains of *K. pneumoniae* and virulent strains of *S. aureus* in medical and preventive organizations, which justifies the need for molecular epidemiological monitoring.

Keywords: *Klebsiella pneumoniae*, *Staphylococcus aureus*, healthcare-associated infections, whole-genome sequencing, microbiological monitoring

Ethics approval. The study was conducted with the informed consent of the patients or their legal representatives. The research protocol was approved by the Ethical Committee No. 1 on conducting scientific research with human subjects as a research object of Privolzhsky Research Medical University, Nizhny Novgorod (protocol No. 7, May 7, 2018).

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Характеристика молекулярно-генетических свойств эпидемических штаммов *Klebsiella pneumoniae* и *Staphylococcus aureus* — возбудителей инфекций, связанных с оказанием медицинской помощи, циркулирующих на территории Нижегородской области

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Аннотация

Введение. Молекулярно-эпидемиологический мониторинг направлен на получение актуальной информации о генетических вариантах возбудителей инфекций, связанных с оказанием медицинской помощи (ИСМП), циркулирующих в регионе. В настоящее время особое внимание уделяется слежению за представителями группы ESKAPE, т. к. они являются частой причиной ИСМП, осложняют течение основного заболевания и становятся всё более серьёзной угрозой здоровью и жизни пациентов, поскольку обладают комплексом генов патогенности и разнообразными механизмами антибиотикорезистентности.

Цель работы — анализ результатов полногеномного секвенирования эпидемических штаммов возбудителей ИСМП — *Klebsiella pneumoniae* ssp. *pneumoniae* и *Staphylococcus aureus*, циркулирующих на территории Нижегородской области.

Материалы и методы. Использованы классические бактериологические методы, MALDI TOF масс-спектрометрия, полногеномное секвенирование, биоинформатические методы.

Результаты. Углублённый анализ показал циркуляцию в отделении новорождённых популяции классических штаммов *K. pneumoniae* сиквенс-типа (ST) 3-K-типа (K) 3, содержащих ряд генов патогенности и бета-лактамазу *bla*_{SHV-1}. В многопрофильном стационаре обнаружена циркуляция популяции штаммов конвергентного патотипа *K. pneumoniae* ST395-K39, а также выявлены штаммы конвергентного патотипа *K. pneumoniae* ST395-K2, K47 и штаммы классического патотипа *K. pneumoniae* ST5209-K35, ST441-K62, ST147-K64, содержащие в геноме спектр генов патогенности и бета-лактамаз, в том числе Нью-Дели металло-бета-лактамазу *bla*_{NDM-1}. Штаммы *S. aureus*, связанные с катетер-ассоциированными инфекциями кровотока, обладают выраженным патогенным потенциалом, относятся к 13 различным ST и 19 spa-типам (t). В гемодиализных центрах и отделениях гемодиализа выявлена циркуляция штаммов метициллин-резистентных (SCCmec IV, ST8, t008) и метициллин-чувствительных (ST1, t127) стафилококков.

Заключение. Полученные данные свидетельствуют о циркуляции в лечебно-профилактических медицинских организациях конвергентных и классических штаммов *K. pneumoniae* и вирулентных штаммов *S. aureus*, что обосновывает необходимость молекулярно-эпидемиологического мониторинга.

Ключевые слова: *Klebsiella pneumoniae*, *Staphylococcus aureus*, инфекции, связанные с оказанием медицинской помощи, полногеномное секвенирование, микробиологический мониторинг

Этическое утверждение. Исследование проводилось при добровольном информированном согласии пациентов или их законных представителей. Протокол исследования одобрен Этическим комитетом № 1 по проведению научных исследований с участием человека в качестве объекта исследования Приволжского исследовательского медицинского университета (протокол № 7 от 05.07.2018).

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Introduction

Molecular epidemiological monitoring is becoming an integral task in organizing a system for epidemiological surveillance of infectious diseases, as it allows for tracking the circulation of opportunistic microorganisms and timely identification of signs of potential outbreaks, which include: isolation of a homogeneous spectrum of microorganisms from examined individuals; an increase in the incidence of infectious diseases caused by a single species or group of species of pathogens; and an increase in the detection rate of hospital strains. The objectives include monitoring the population structure of infectious agents, including healthcare-associated infections (HAIs), MLST typing of strains, analysis of pathogenicity genes and antibiotic resistance determinants, detection of new variants of hospital strains, and observation of their variability to assess epidemiological forecasting and justify timely intervention in the course of the epidemic process [1].

ESKAPE pathogens are a frequent cause of healthcare-associated infections, complicate the course of the underlying disease, and pose a serious threat to the health and life of patients, as they are able to quickly adapt and find new ways to resist the effect of drugs, disinfectants and antiseptics, and also transmit this ability to other pathogens at a genetic level [2, 3].

Among the bacteria that cause hospital infections, *Klebsiella pneumoniae* and *Staphylococcus aureus* are the leading causes, with an increasing proportion of carbapenem-resistant *K. pneumoniae* and the widespread prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) belonging to the MRSA group, which can cause outbreaks and lead to catheter-associated bloodstream infections (CABSI) [4,5].

The aim of the study is to analyze the results of whole-genome sequencing of epidemic strains of pathogens of healthcare-associated infections — *K. pneumoniae* ssp. *pneumoniae* and *S. aureus*, circulating in the Nizhny Novgorod region.

Materials and methods

Strains under study

55 epidemic strains of pathogens were studied: 17 strains of *K. pneumoniae* ssp. *pneumoniae* and 38 strains of *S. aureus*. Based on their place of isolation, the strains were divided into three groups:

The 1st group consisted of 7 *K. pneumoniae* strains isolated from sick children (gastric contents) ($n = 4$) in the neonatal intensive care unit of a pediatric hospital, and from equipment and care items (swabs from suction tubing, feeding syringe) ($n = 3$);

The 2nd group – 10 strains of *K. pneumoniae* isolated from patients in the multidisciplinary hospital departments (wound discharge) ($n = 9$) and from the department's external environment (swab from the intensive care unit sink faucet) ($n = 1$);

The 3rd group – 38 strains of *S. aureus*, including 31 strains from patients with CABSI who were receiving outpatient treatment at hemodialysis centers in the city and region and were hospitalized in medical organizations in the city (blood, wound at the catheter site, peritoneal fluid, nasal swab); 3 strains isolated from medical personnel (nasal swab), and 4 from the medical organization environment (equipment swabs).

Cultivation and identification of bacteria

Isolation of strains of conditionally pathogenic microorganisms was carried out using the classical bacteriological method, and identification was performed by MALDI-TOF mass spectrometry using an Autoflex mass spectrometer (Bruker Daltonics). The susceptibility of bacteria to antibiotics was studied using the disk diffusion method on "Nutrient Medium for Determining the Susceptibility of Microorganisms to Antibacterial Drugs — Mueller-Hinton II Agar (State Research Center for Applied Microbiology and Biotechnology of Rospotrebnadzor) using extended sets of disks for enterobacteria (set No. 7) and staphylococci (set No. 14) (Pasteur Research Institute of Epidemiology and Microbiology). The susceptibility of the strains to ceftazidime-avibactam was studied using ceftazidime + avibactam 10/4 mcg disks (Mast Group), and to tigecycline using tigecycline 15 mcg disks (Mast Group). The assessment was conducted in accordance with the clinical guidelines "Determination of the Susceptibility of Microorganisms to Antimicrobial Drugs"¹.

Whole-genome sequencing

Libraries were prepared using the TrueSeq kit (Illumina Inc.), and sequencing was performed on the MiSeq platform (Illumina Inc.). The raw reads were processed using the Trimmomatic utility, while the SPAdes v. 3.11.1 and Prokka v. 1.12 programs were used for *de novo* read assembly [6, 7]. All nucleotide sequences were deposited in the international GenBank database.

Whole-genome sequence analysis was performed using VFDB² [8], ResFinder³ [9], the BIGSdb-Pasteur web platform⁴ [10], the PubMLST resource⁵ [11], and the Spa-typer and SCCmecFinder programs [12, 13]. Dendrograms were constructed using the maximum likelihood method to determine the genetic distance between microbial strains using the parsnp v. 1.7.4 program. The FastTree 2.1.1 algorithm and the Shimodaira–Hasegawa test [14] were used to assess the

¹ MACMACH Recommendations version 2024. URL: <https://www.antibiotic.ru/minzdrav/category/clinical-recommendations>

² Virulence factor database. URL: <http://www.mgc.ac.cn/VFs>

³ ResFinder. URL: <http://genepi.food.dtu.dk/resfinder>

⁴ Institut Pasteur. *Klebsiella pneumoniae* species complex. URL: <https://bigsdb.pasteur.fr/klebsiella>

⁵ PubMLST. MLST Database. *Staphylococcus aureus*. URL: <https://pubmlst.org/organisms/staphylococcus-aureus>

primary tree topology. Sequences from the GenBank database were used as references: GCF_000240185.1, GCA_000013425.1, and then the reference genome branch was removed. Phylogenetic trees were visualized using the iTol service [15].

Results

As a result of studying the molecular genetic properties of *K. pneumoniae* strains of group 1, it was found that all strains possess colibactin gene clusters, yersiniabactin genes, and genes responsible for the formation of type 3 fimbriae, and the *rmpA* gene, which regulates the hypermucoviscous phenotype, was detected in 3 strains (Table). A species-specific antibiotic resistance (ABR) determinant was identified in the genomes of all strains – the beta-lactamase *bla*_{SHV-1}, which confers natural resistance of microorganisms to aminopenicillins – ampicillin and amoxicillin. Phenotypically, the strains were susceptible to all antibiotics from other groups: 3rd–5th generation cephalosporins (cefazolin, cefotaxime, ceftriaxone, ceftazidime, ceftazidime/avibactam, cefepime, ceftaroline), aminoglycosides (gentamicin), fluoroquinolones (ciprofloxacin), carbapenems (ertapenem, imipenem, meropenem), monobactams (aztreonam), polymyxins (colistin), tetracyclines (tigecycline), and trimethoprim/sulfamethoxazole. As a result of the analysis of constitutional genes (housekeeping genes) and *wzi* gene alleles, the strains were identified as belonging to ST 3 and capsular type K 3 (Table).

K. pneumoniae strains of group 2 differed in their molecular genetic properties. Complete aerobactin siderophore gene clusters (*iucABCD* and *iutA*) were found in the genomes of *K. pneumoniae* strains 3254, 3260 and 3263, while *K. pneumoniae* strain 3263 was distinguished by the presence of the yersiniabactin gene cluster (*fyuA*, *irp1,2*, *ybtAEPQSTUX*) (Fig. 1). All strains were found to have a spectrum of ARGs – beta-lactamases and carbapenemases *bla*_{TEM-1}, *bla*_{CTX-M-15}, *bla*_{SHV-1}, *bla*_{OXA-1}, *bla*_{OXA-48} and the fosfomycin resistance determinant – *fosA*. This explains the fact that all 3 strains had an MDR phenotype and were resistant to penicillins, cephalosporins, aminoglycosides, fluoroquinolones, monobactams and carbapenems (ertapenem). Based on the analysis of constitutional genes and *wzi* gene alleles, the strains were identified as belonging to ST395 and K39.

The virulence gene spectrum of *K. pneumoniae* strains 3245 and 3251, like that of *K. pneumoniae* strains 3254 and 3260, was represented by the aerobactin gene cluster (*iucABCD* and *iutA*) (Fig. 1). *K. pneumoniae* strain 3245 was found to have an identical spectrum of antibiotic resistance genes (*bla*_{TEM-1}, *bla*_{CTX-M-15}, *bla*_{SHV-1}, *bla*_{OXA-1}, *bla*_{OXA-48}) in its genome, with the exception of *fosA*. This strain had the same antimicrobial susceptibility and resistance phenotypes as the strains described above. *K. pneumoniae* 3251 was characterized by the presence of the *bla*_{CTX-M-3} determi-

nant, the absence of the *bla*_{OXA-48} and *bla*_{CTX-M-15} genes, and was susceptible to carbapenems. *K. pneumoniae* 3245 and 3251 also belonged to ST395, but differed from *K. pneumoniae* strains 3254, 3260, and 3263 in their *wzi* gene alleles and belonged to K47.

K. pneumoniae strains 3255 and 3259 were characterized by the presence of complete aerobactin (*iucABCD* and *iutA*) and yersiniabactin (*fyuA*, *irp1,2*, *ybtAEPQSTUX*) gene clusters, with the salmochelin gene (*iro*) being detected in *K. pneumoniae* 3259. Their ABR gene spectrum was identical to the spectrum of determinants in *K. pneumoniae* 3254, 3260, 3263, 3245 (*bla*_{TEM-1}, *bla*_{CTX-M-15}, *bla*_{SHV-1}, *bla*_{OXA-1}, *bla*_{OXA-48}, *fosA*). *K. pneumoniae* 3255 and 3259 also had an MDR phenotype and were resistant to penicillins, cephalosporins, aminoglycosides, fluoroquinolones, carbapenems (ertapenem), and tigecycline. These strains also belonged to ST395, but to K2.

Only one aerobactin cluster determinant, *iutA*, was found in *K. pneumoniae* strains 3247, 3253, and 3256 (Fig. 1). *K. pneumoniae* isolate 3256 contained the beta-lactamases *bla*_{CTX-M-14}, *bla*_{OXA-244} and *bla*_{SHV-1} in its genome, exhibited phenotypic resistance to cephalosporins and aminoglycosides, and was susceptible to carbapenems. Its affiliation with ST5209 and K35 was established. *K. pneumoniae* 3253 was found to have 2 AMR determinants: *bla*_{SHV-168} and *fosA*. The strain was susceptible to all groups of antibacterial drugs except aminopenicillins and was classified as ST441 and K62. In the genome of *K. pneumoniae* 3247, the *bla*_{NDM-1}, *bla*_{TEM-1}, *bla*_{CTX-M-15}, *bla*_{SHV-1} and *bla*_{OXA-1} genes were detected. The strain was phenotypically resistant to penicillins, cephalosporins, aminoglycosides, fluoroquinolones, all carbapenem group drugs (ertapenem, imipenem, meropenem), and susceptible to colistin, tigecycline, and ceftazidime-avibactam, and was classified as ST147 and K64.

Adhesin genes, a type VII secretion system, and gamma-hemolysins were identified in the genomes of all group 3 *S. aureus* strains.

Strains *S. aureus* 2226, 3092, 3110, 2211, 3196, 3197, and 3198 were characterized by an identical spectrum of virulence genes, which included, in addition to those listed above, the serine protease genes *splABCDE*, the immune evasion genes *sak*, *scn*, enterotoxin A *sea*, exfoliative toxin *eta*, and leukotoxins *lukDE*. SCCmec type IV cassettes were detected in strains 3196, 3197, 3110 and 3092, the *blaZ* beta-lactamase gene was identified in *S. aureus* strains 3198, 2211 and 2226, and the erythromycin and chloramphenicol resistance genes *ermC* and *cat* were found (Fig. 2). The strains showed phenotypic resistance to oxacillin and cefoxitin, which may indicate their belonging to the MRSA group. As a result of MLST typing and analysis of the protein A gene sequence repeats, their belonging to ST8 and spa-type (t) t008 was established. Also belonging to ST8, but to t024, was the *S. aureus* strain

Molecular genetic characterization of *K. pneumoniae* strains isolated in the neonatal intensive care unit

Strain	Sequence type (ST)	Capsule type (K)	Pathogenicity genes				ABR genes
			hypermucoid phenotype regulator genes	colibactin synthesis gene	Yersiniabactin synthesis genes	type 3 fimbriae genes	
<i>n</i> = 3	3	3	<i>rmpA</i>	<i>clbABCDEFGHIJLMNOPQ</i>	<i>fyuA</i> , <i>irp1,2</i> , <i>ybtAEQPSTUX</i>	<i>mrkABCDHFIJ</i>	<i>bla_{SHV-1}</i>
<i>K. pn</i> 849 JAVGJO000000000							
<i>K. pn</i> 852 JAVHUD000000000							
<i>K. pn</i> 862 JAVBWS000000000							
<i>n</i> = 4	3	3	–	<i>clbABCDEFGHIJLMNOPQ</i>	<i>fyuA</i> , <i>irp1,2</i> , <i>ybtAEQPSTUX</i>	<i>mrkABCDHFIJ</i>	<i>bla_{SHV-1}</i>
<i>K. pn</i> 850 JAVCZJ000000000							
<i>K. pn</i> 854 JAVGJN000000000							
<i>K. pn</i> 863 JAVBWT000000000							
<i>K. pn</i> 893 JAVHUE000000000							

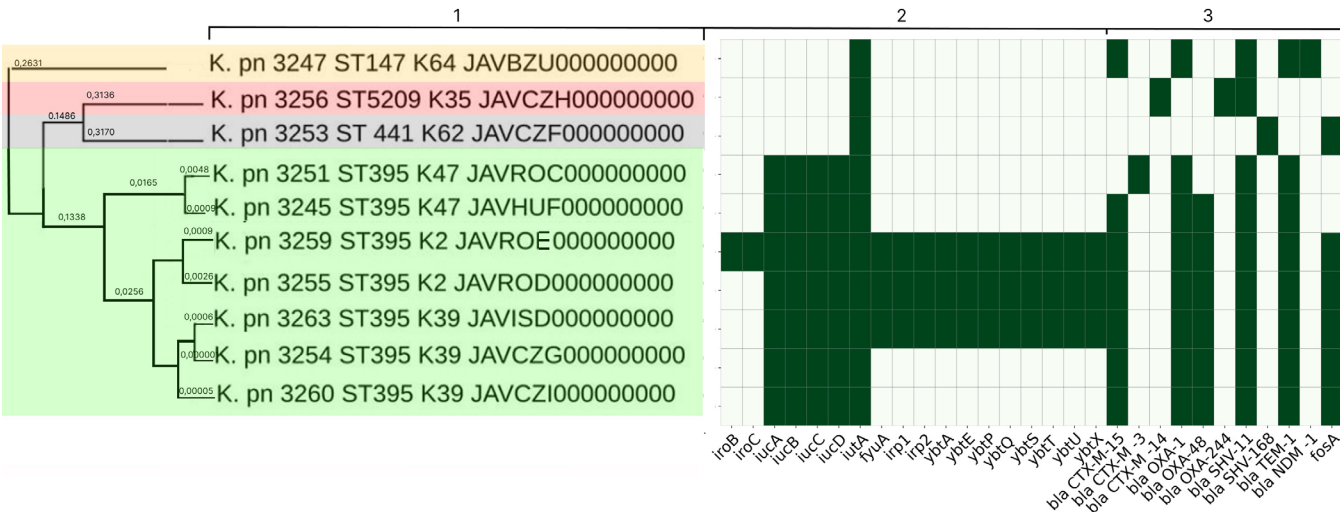


Fig. 1. Phylogenetic tree for genomes of *K. pneumoniae* strains of group 2.

1 — microorganism type, strain number, ST, K-type, GenBank database accession number; 2 — determinants of pathogenicity genes (green — presence of the trait, white — absence); 3 — determinants of ABR (green — presence of the trait, white — absence)

3107, which was distinguished by the absence of the *SCCmec* cassette.

Pathogenicity genes *splABCDE*, *eta* and *lukDE* were identified in the genomes of *S. aureus* strains 3086, 3087 and 3088, while *S. aureus* 2203 and 2213 were characterized by the presence of *sak* and *scn* genes (Fig. 2). The *blaZ* and *ermC* antibiotic resistance genes were found in *S. aureus* 3086, 3087, and 3088, while only *blaZ* was found in *S. aureus* 2213. All 5 isolates were resistant to amoxicillin, tetracycline and lincosamides. It was established that strains 3086, 3087, and 3088 belonged to ST1 t127, while *S. aureus* 2203 and 2213 belonged to ST1 t177.

As a result of analyzing the molecular genetic properties of *S. aureus* strains 3082, 3094, 3111, 3102, 2212, and 2204, the genes for exfoliative toxin *eta* and

staphylokinase *sak* were identified, and the absence of serine protease determinants (*spl*) and leukotoxins D and E (*lukDE*) was established. Enterotoxin genes *sec* and *sell* were found in *S. aureus* 3082; *sec*, *sell* and *selo* were found in 3094. The *blaZ* gene was present in *S. aureus* 3082, 3111, 3094, and 3082; the *blaZ* gene and the aminoglycoside resistance determinant *aph(3')-III* were present in strain 3094; and *aph(3')-Ia* was present in *S. aureus* 2212. All 5 isolates were phenotypically resistant to amoxicillin and amikacin. The strains were identified as belonging to ST45, but to different spa-types: t102, t362, t8416, t5599, t5132 (Fig. 2).

S. aureus strains 3084, 3085, and 2219 were characterized by the presence of the pathogenicity genes *splABCDE*, *eta*, *lukDE* and *blaZ*. Genes for enterotoxins *sei*, *sej*, *selo* and *selr* were detected in 3085 strains.

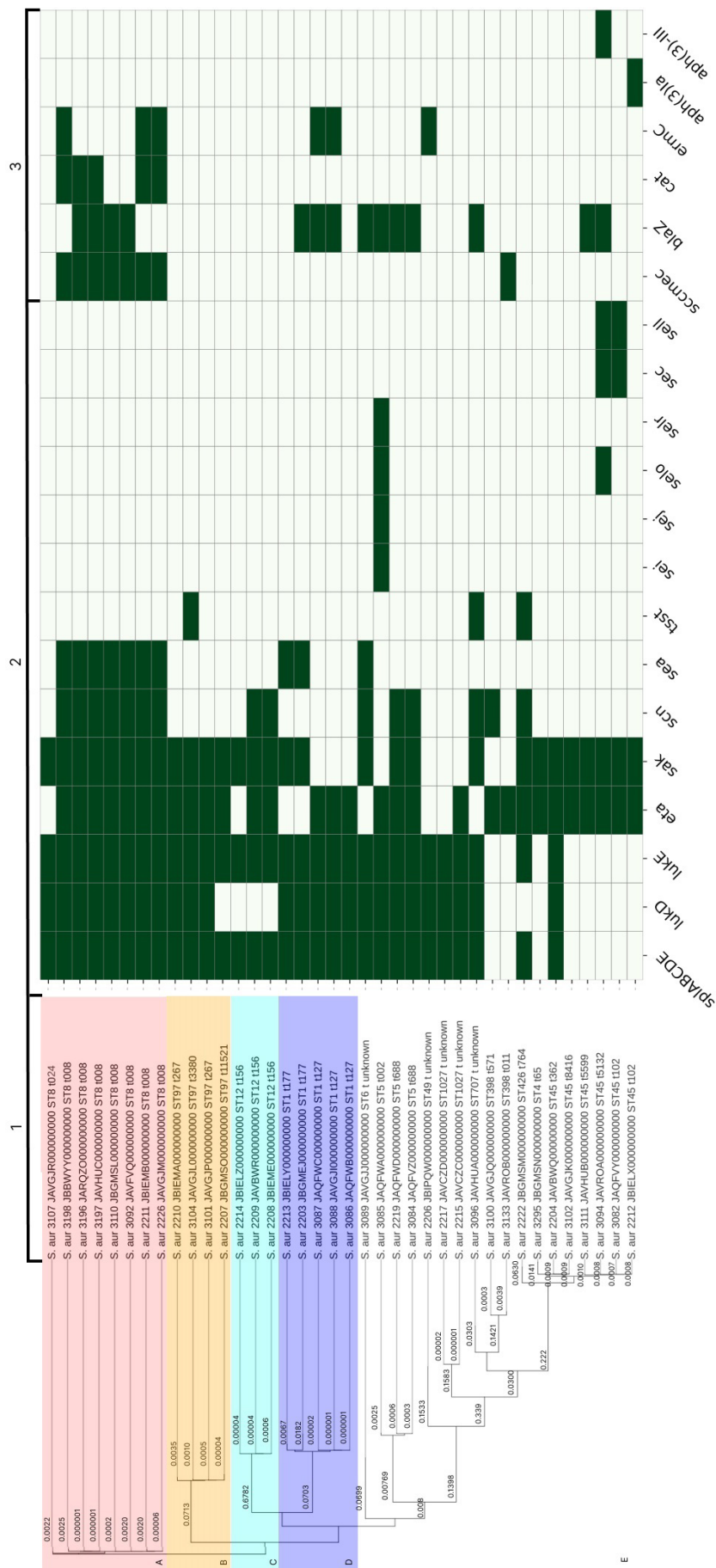


Fig. 2. Phylogenetic tree for genomes of *S. aureus* strains of group 3.
1 — microorganism type, strain number, GenBank database accession number, ST, spa type; 2 — pathogenicity gene determinants (green — presence of the trait, white — absence);
3 — antibiotic resistance determinants (green — presence of the trait, white — absence).

All strains were phenotypically resistant to amoxicillin and were identified as belonging to ST5, t002, and t688 (Figure 2). *S. aureus* strains 3096 and 3089 were characterized by the presence of the *splABCDE*, *lukDE*, *sak*, *scn*, and *blaZ* genes; strain 3096 contained the *tsst* gene, while strain 3089 contained the *sea* gene. They are also resistant to amoxicillin and were classified as ST707 and ST6, although the program used in the study did not allow their spa-type to be determined. *S. aureus* 3100 and 3133 were characterized by the absence of serine protease genes (*spl*) and leukotoxins D and E (*lukDE*); strain 3133 was resistant to oxacillin and cefoxitin, and a type IV SCCmec cassette was found in its genome. Both strains belonged to ST398, t571 and t011 (Fig. 2).

The remaining 12 strains belonged to different ST and spa-types. The genes *splABCDE*, *eta*, *lukDE* and *sak* were detected in *S. aureus* strains 2210, 3104, 3102 and 2207, and the toxic shock syndrome gene *tsst* was detected in *S. aureus* 3104. The strains belonged to ST97 and different spa types: t267, t3380, t11521 (Fig. 2). *S. aureus* strains 2208, 2209 and 2214 were characterized by the presence of the *splABCDE*, *lukDE*, *sak*, and *scn* genes and were assigned to ST12 and t156. Genes *splABCDE* and *lukDE* were identified in *S. aureus* 2206, 2217 and 2215, and their belonging to ST49 and ST1027 was established, but the program used in the study did not allow for the determination of their spa-types. Strain *S. aureus* 2222 was found to have the *splABCDE*, *lukE*, *sak*, *scn*, *eta* and *tsst* genes and was classified as ST426 and t764. *S. aureus* 3295 was characterized by the presence of *sak* and *eta* determinants and was classified as ST 4. All 12 strains lacked antibiotic resistance determinants and exhibited phenotypic susceptibility to antibacterial drugs from all groups.

In total, strains of *S. aureus* belonging to 13 different STs and 19 spa types were isolated from patients with CABSI, medical personnel and the external environment of the city and region.

Discussion

Circulation of the pathogen refers to its continuous and sequential transmission from one susceptible organism to another, ensuring its existence as a biological species, as well as the spread of the pathogen within healthcare facilities, characterized by the colonization of environmental surfaces and the involvement of patients and staff.

One of the most important criteria for a hospital strain is its belonging to a homogeneous (uniform in composition) population of circulating microorganisms [16]. The homogeneity of a population can be most reliably assessed by studying the genetic characteristics of the strains, which involves identifying and analyzing virulence genes, antibiotic resistance genes, and determining the ST through the analysis of alleles of housekeeping genes. For the genetic typing of *K. pneu-*

moniae, determining their K-type, which depends on the sequence of the *wzi* gene encoding a surface protein involved in capsule assembly on the cell's outer membrane, is of significant importance. Establishing the belonging of strains to one of the known pathotypes is also important [17].

In recent years, the existence of three *K. pneumoniae* pathotypes has been recognized: hypervirulent (hvKp), classical (cKp), and convergent (hv-MDRKp). The hypervirulent pathotype is associated with the development of serious invasive infections in healthy immunocompetent individuals. Currently, the main characteristic correlated with hypervirulence is the secretion of the siderophores aerobactin, salmochelin, yersinia-bactin and the exotoxin colibactin [18]. The classical pathotype is globally widespread; these *Klebsiella* are representatives of the human microbiome, cause diseases in weakened patients, and are among the leading causes of nosocomial infections. Their genome invariably contains a complex of beta-lactamases and carbapenemases, and individual pathogenicity genes (excluding aerobactin and salmochelin) can also be detected. *K. pneumoniae* of the convergent pathotype combine the characteristics of hypervirulent and classical *Klebsiella*, meaning they have high pathogenic potential and multiple antibiotic resistance, and are capable of causing disease in both healthy immunocompetent individuals and immunocompromised patients [17, 18].

K. pneumoniae strains of group 1 isolated from sick children in the neonatal intensive care unit, as well as from equipment and care items, were similar in their virulence determinants and did not contain the aerobactin and salmochelin genes. However, the *rmpA* gene (hypermucoid phenotype) was detected in 3 strains, which was previously associated with hypervirulence. Currently, it is recognized that it is advisable to assess the entire complex of pathogenicity genes, and the presence of this determinant is not a significant indicator [5, 18]. The presence of the gene in only 3 out of the 7 strains studied (table) can be explained by its plasmid origin and high mobility within the microorganism population [19]. One beta-lactamase, *bla*_{SHV-1}, was identified in the genomes of all strains. Molecular typing revealed that the strain population belonged to a rare sequence type, ST3, and capsule type K3, which had not been previously isolated in Russia (only 16 isolates of this ST are registered in the BIGSdb-Pasteur database).

The homogeneity of the molecular-genetic and phenotypic properties of the strains isolated from patients and the external environment indicates the circulation of a population of classical *K. pneumoniae* strains within the hospital. The identification of this population is unfavorable from an epidemiological perspective and confirms the fact that cases of HAIs in the neonatal intensive care unit can be associated not only with hypervirulent strains of *K. pneumoniae* but also with classical strains that do not possess multiple antibiotic resistance

and a wide range of pathogenicity genes [20]. This necessitates continuous molecular-epidemiological monitoring of *K. pneumoniae* strains belonging to different pathotypes in the microbiota of newborns, mothers, medical personnel, and surrounding objects in neonatal units of pediatric hospitals and perinatal centers, studying their properties, as well as integrating the data into the VGARus Russian database.

Analysis of *K. pneumoniae* strains from group 2 isolated in a multidisciplinary hospital revealed that strains *K. pneumoniae* 3254, 3260, and 3263 had an identical pathogenicity and antibiotic resistance gene spectrum, as well as the same antibiotic resistance phenotype. These strains belonged to ST395-K39 and were classified as a convergent pathotype due to the presence of aerobactin and a spectrum of beta-lactamase and carbapenemase genes. The strains were isolated from both patients and the external environment, indicating the circulation of *K. pneumoniae* ST395-K39 strains within the hospital. The presence of the yersiniabactin gene cluster in *K. pneumoniae* 3263 can be explained by horizontal gene transfer processes associated with a transposon, which has high mobility [21]. *K. pneumoniae* strains 3255 and 3259 (ST395-K2) and *K. pneumoniae* 3245 and 3251 (ST395-K47) were isolated in single cases only from patients, contained the aerobactin gene and AMR determinants in their genomes, and were also classified as a convergent pathotype.

Thus, 7 out of 10 strains isolated in a multidisciplinary hospital belonged to ST395, which could be considered evidence of their circulation. This is consistent with scientific literature data on the widespread distribution of this ST, among which strains with significant pathogenic potential are frequently found, capable of causing severe systemic infections [5, 17]. However, in-depth analysis of the strains' molecular genetic properties revealed their heterogeneity even within a single ST and led to the conclusion that only the *K. pneumoniae* ST395-K39 strain populations were circulating in the hospital.

All other *K. pneumoniae* strains: 3256 (ST5209-K35), 3253 (ST441-K62), 3247 (ST147-K64) were classified as classical and were isolated only in isolated cases from patients. It should be noted that the *bla*_{NDM-1} gene for New Delhi metallo-beta-lactamase was found in the genome of the *K. pneumoniae* 3247 strain, which explains this strain's high degree of antibiotic resistance. It is known that this determinant is associated with plasmids and is capable of active horizontal transfer [17], so the detection of such a strain is unfavorable from an epidemiological perspective, as it can lead to the rapid global spread of a polyresistant population within medical facilities.

Within the phylogenetic tree, all strains from group 2 clustered according to their ST and K-types. *K. pneumoniae* ST 395 strains formed 3 subclusters according to their K-types, and 3 *K. pneumoniae* ST395-K39

strains were included in a single cluster, uniting strains isolated from patients and the external environment of the medical organization (Fig. 1).

Analysis of pathogenicity gene spectra, antibiotic resistance profiles, MRSA or MSSA (methicillin-susceptible staphylococci) group affiliation, and ST and spa-typing [22] is crucial for studying the circulation of *S. aureus* strains. This is based on the analysis of the sequence of repeats in the gene for staphylococcal surface protein A (protein A) [4]. During investigations of local outbreaks of illness, determining the spa-type is an important step, as it allows for differentiation between strains belonging to the same ST.

Molecular genetic analysis of *S. aureus* group III strains associated with CABSИ revealed that the genomes of 7 strains of *S. aureus* 2226, 3092, 3110, 2211, 3196, 3197 and 3198 contained a type IV SCCmec cassette, they had identical virulence gene profiles, the same resistance phenotypes, and belonged to ST 8 t008.

The strains were isolated from both a healthcare worker and patients diagnosed with CABSИ who were receiving outpatient treatment at a hemodialysis center and inpatient treatment at medical institutions in the city, which confirms the fact of their circulation. The difference in strains based on the spectrum of *bla*_Z, *erm*C and *cat* determinants (Fig. 2) can be explained by the fact that these genes are located on plasmids and have high mobility [23–25]. According to scientific literature, *S. aureus* ST8 t008 SCCmec IV strains are common, often associated with HAIs, and have been identified in Russia since the 1990s [4].

Strains *S. aureus* 3086, 3087 and 3088 are also identical in their pathogenicity genes, determinants, and antibiotic resistance phenotype. They belonged to the MSSA group, were typed as *S. aureus* ST1 t127, and were isolated from 3 patients (peritoneal catheter exit site). At the same time, strains of *S. aureus* of other sequence types were isolated from the peritoneal fluid of these same patients — ST5 (t688), ST97 (t267), and ST45 (t8416). This indicates that the population of *S. aureus* ST1 t127 strains is circulating in this medical organization.

All other group III *S. aureus* isolates were heterogeneous in their determinant spectrum, antibiotic resistance phenotype, sequence types, and spa types, which prevents an assessment of their epidemiological significance in this study.

Phylogenetic analysis of whole-genome sequences of the strains revealed the presence of five clusters, grouping strains belonging to the same sequence types and clonal complexes (CCs), which are groups of genetically closely related sequence types. *S. aureus* strains ST8, 97, 12, and 1 formed independent groups (A, B, C, D), while strains of various sequence types: ST6 and ST5 belonging to clonal complex 5 (CC5), *S. aureus* ST4 and ST45 belonging to CC45, as well as strains ST49, ST1027, ST707, ST398 and ST426 not

belonging to specific clonal complexes but having phylogenetic relatedness to each other, were included in a single large cluster E (Fig. 2).

Thus, in the hemodialysis units of the city and region, 13 different sequence types and 19 spa-types of *S. aureus* strains were identified, and the circulation of populations of epidemic *S. aureus* MRSA (SCCmec IV) of molecular type ST8 t008 and *S. aureus* MSSA of molecular type ST1 t127 was demonstrated.

Conclusion

As a result of the study conducted in the Nizhny Novgorod region, a large genetic diversity of *K. pneumoniae* and *S. aureus* strains was identified. In-depth analysis revealed the circulation of a population of classical *K. pneumoniae* ST3-K3 strains in the neonatal intensive care unit of a pediatric hospital, isolated from the gastrointestinal tracts of children, from medical equipment and products, containing a number of virulence genes and the *bla*_{SHV-1} beta-lactamase.

The circulation of strains of the convergent *K. pneumoniae* ST395-K39 pathotype was detected in a multidisciplinary hospital, and strains of *K. pneumoniae* ST395-K2, ST395-K47, ST5209-K35, ST441-K62, ST147-K64 were identified, containing a spectrum of pathogenicity genes and beta-lactamases in their genome, including the New Delhi metallo-beta-lactamase *bla*_{NDM-1}, which could lead to the formation and spread of a polyresistant clone in the hospital, capable of replacing the circulating pathogen and causing outbreaks of healthcare-associated infections.

Circulation of *S. aureus* MRSA (SCCmec IV) ST8 t008 and *S. aureus* MSSA ST1 t127 populations was identified in the hemodialysis units of the city and region, and other *S. aureus* strains belonging to 11 different STs- and 17 spa-types, potentially capable of forming hospital clones and spreading widely within the medical facility, were also detected. In this regard, to prevent the occurrence and spread of healthcare-associated infections (HAIs), it is necessary to conduct mandatory continuous microbiological monitoring in hospitals, an integral part of which should be molecular epidemiological monitoring aimed at obtaining up-to-date information on the genetic variants of circulating pathogens, including *K. pneumoniae* and *S. aureus*.

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