TRAUMATOLOGY

MICROBIOLOGICAL PROFILE OF PATIENTS WITH ORTHOPEDIC IMPLANT-ASSOCIATED INFECTION IN THE POST-COVID PERIOD

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ABSTRACT

Background. *The etiological structure of implant-associated infection and antibiotic resistance of pathogens are important when choosing empirical antibiotic therapy. COVID-19 pandemic and increased consumption of antibiotics by the population could provoke an increase in antibiotic resistance.*
The aim of the work. *To compare the spectrum of leading pathogens of implant-associated infection in the pre- and post-Covid period and to assess antibiotic resistance.*
Materials and methods. *A continuous retrospective study of biomaterial samples from traumatology and orthopedic patients with implant-associated infection was carried out for 2018–2019 and 2021–2022. The sample consisted of 548 microorganism strains (n = 237 and n = 317, respectively) in 442 cases of infectious complications. The antibiotic resistance of all isolated microorganisms, including those from microbial associations, was assessed.*
Results. *The leading pathogen of monomicrobial implant-associated infection in both study periods was Staphylococcus epidermidis (33–37 %). In 2021–2022, the proportion of microbial associations increased (from 12.5 to 17.5 %; p = 0.147) with the appearance of fungi in the microbial landscape. In the post-Covid period, the increase in Staphylococcus aureus resistance to tetracycline and doxycycline was revealed; the isolation of methicillin-resistant strains among Staphylococcus aureus decreased from 4 cases (out of 187) to 3 (out of 232); 100 % sensitivity to rifampicin and co-trimoxazole was maintained. An increase in Staphylococcus epidermidis resistance to all tested antibiotics was detected (statistically significant increase in resistance to fluoroquinolones; p = 0.002–0.003) with the isolation of methicillin-resistant strains in 80.5 % and 80.9 % of cases, respectively. All staphylococcal isolates were susceptible to vancomycin and linezolid. Enterobacteriaceae representatives showed a decrease in resistance to carbapenems and an increase in resistance to co-trimoxazole; in Pseudomonas aeruginosa and Acinetobacter baumannii, there is an increase in resistance to carbapenems and fluoroquinolones. All gram-negative microorganisms were sensitive to colistin.*
Conclusion. *The high frequency of isolation of methicillin-resistant staphylococci determines the choice of vancomycin for empirical therapy. Increasing resistance of staphylococci to fluoroquinolones may limit their use. Increasing resistance of gram-negative bacteria and a narrow spectrum of antibiotics acting on carbapenemase producers may reduce the effectiveness of therapy.*

Key words: *implant-associated infection, periprosthetic infection, antibiotic resistance, COVID-19, Staphylococcus epidermidis, microbial associations, carbapenemase producers, methicillin-resistant staphylococci*

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МИКРОБИОЛОГИЧЕСКИЙ ПРОФИЛЬ ПАЦИЕНТОВ С ОРТОПЕДИЧЕСКОЙ ИМПЛАНТАТ-АССОЦИИРОВАННОЙ ИНФЕКЦИЕЙ В ПОСТКОВИДНОМ ПЕРИОДЕ

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РЕЗЮМЕ

Введение. *Этиологическая структура имплантат-ассоциированной инфекции и антибиотикорезистентность патогенов важны при выборе эмпирической антибиотикотерапии. Пандемия COVID-19, увеличение потребления населением антибиотиков могли провоцировать рост антибиотикорезистентности.*

Цель работы. *Сравнить спектр ведущих возбудителей имплантат-ассоциированной инфекции в до- и постковидном периоде с оценкой антибиотикорезистентности.*

Материалы и методы. *Проведено сплошное ретроспективное исследование образцов биоматериала пациентов травматолого-ортопедического профиля с имплантат-ассоциированной инфекцией за 2018–2019 и 2021–2022 гг. Выборка составила 548 штаммов микроорганизмов (n = 237 и n = 317 соответственно) в 442 случаях инфекционных осложнений. Проводилась оценка антибиотикорезистентности всех выделенных микроорганизмов, в том числе из микробных ассоциаций.*

Результаты. *Ведущим возбудителем мономикробной имплантат-ассоциированной инфекции в оба периода исследования был Staphylococcus epidermidis (33–37 %). В 2021–2022 гг. увеличилась доля микробных ассоциаций (с 12,5 до 17,5 %; p = 0,147) с появлением в микробном пейзаже грибов. В постковидном периоде отмечен рост резистентности Staphylococcus aureus к тетрациклину и доксициклину; выделение метициллин-резистентных штаммов среди Staphylococcus aureus снизилось с 4 случаев (из 187) до 3 (из 232); сохранялась 100%-я чувствительность к рифампицину и ко-тримоксазолу. Выявлен рост резистентности Staphylococcus epidermidis ко всем тестируемым антибиотикам (статистически значимый – к фторхинолонам; p = 0,002–0,003) с выделением метициллин-резистентных штаммов в 80,5 % и 80,9 % случаев соответственно. Все выделенные изоляты стафилококков были чувствительны к ванкомицину и линезолиду. У представителей семейства Enterobacteriaceae выявлено снижение резистентности к карбапенемам и её рост к ко-тримоксазолу; у Pseudomonas aeruginosa и Acinetobacter baumannii – рост резистентности к карбапенемам и фторхинолонам. Все грамотрицательные микроорганизмы были чувствительны к колистину.*

Заключение. *Высокая частота выделения метициллин-резистентных стафилококков определяет выбор ванкомицина для эмпирической терапии. Рост резистентности стафилококков к фторхинолонам может способствовать ограничению их использования. Рост резистентности грамотрицательных бактерий, узкий спектр антибиотиков, действующих на карбапенемазопродуцентов, могут снижать эффективность терапии.*

Ключевые слова: *имплантат-ассоциированная инфекция, перипротезная инфекция, антибиотикорезистентность, COVID-19, Staphylococcus epidermidis, микробные ассоциации, карбапенемазопродуценты, метициллин-резистентные стафилококки*

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INTRODUCTION

In the last decade, medicine has seen a trend towards increasing the use of various implants during surgical interventions. Despite the constant improvement of the biomechanical properties of structures, the development of implant-associated infections (IAI) remains a pressing issue.

This term implies a broad concept, including the development of infection in the area of installation of any implants, including orthopedic ones. Their presence in the body leads to the emergence of a lifelong risk of infection. The frequency of infectious complications varies depending on the type of surgical intervention: after primary endoprosthetics of the hip or knee joint, it is low and amounts to 0.3–2 %; after revision endoprosthetics, it increases to 20 % [1–4]; after osteosynthesis of fractures, it ranges from 1.8 to 27 % [5–9]; after external transpedicular fixation of the spine, it occurs in 0.7–20 % of cases [10].

According to a study conducted by the R.R. Vreden National Medical Research Center of Traumatology and Orthopedics of the Ministry of Health of the Russian Federation (St. Petersburg) in 2018, a decrease in the frequency of *Staphylococcus aureus* isolation was noted in the structure of the leading gram-positive pathogens of IAI – from 34.5 % in 2012-2013 to 28.6 % in 2016-2017 – with its leading position maintained and a parallel increase in the share of *Staphylococcus epidermidis* (from 18.4 % to 22.5 %), however, the increase in the isolation frequency of methicillin-resistant strains was insignificant [11].

The prevalence of pathogens causing infectious complications and their resistance to antibiotics in healthcare facilities may vary. In cases where the pathogen has not yet been verified, local epidemiological data can be used to determine the optimal tactics for choosing empirical antibacterial therapy, influencing the success of treatment. According to foreign authors, the recent COVID-19 pandemic has created a predisposition to the development of concomitant diseases and coinfections in those who have recovered, which may be a manifestation of the immune burden that this virus creates for the host [12]. Increased consumption of antibacterial drugs by the population could also change the microbiological etiology of IAI and provoke an increase in antibiotic resistance.

THE AIM OF THE STUDY

To compare the spectrum of leading pathogens of implant-associated infection in the pre- (2018–2019) and post-COVID (2021–2022) period and to assess antibiotic resistance.

MATERIALS AND METHODS

A continuous retrospective comparative study was conducted at the Federal Center for Traumatology, Orthopedics and Endoprosthetics of the Ministry of Health of Russian Federation (Cheboksary).

A comparative analysis of changes in the spectrum of pathogens of intravascular inflammatory infections and antibiotic resistance was conducted in 2018–2019 and 2021–2022. The inclusion criterion in the study was the pathogen detection in a microbiological study of 4–6 samples of biomaterial from each patient (intraoperative tissue biopsies, aspirate from removed metal structures after ultrasonic treatment, synovial fluid) obtained intraoperatively and in outpatient settings in the presence of a deep or superficial infection of the surgical site. One, the most informative, of the 4–6 results was included in the analysis. Pathogens in microbial associations were not included in the analysis of monomicrobial infection.

The sample size was 548 isolated strains of microorganisms (n = 237 in 2018–2019 and n = 317 in 2021–2022) in 442 cases of infectious complications (n = 208 and n = 234, respectively).

The majority of subjects were female (52.8 %) with an average age of 58.5 ± 13.6 years (4–88 years; over 65 years – 37.5 %). According to localization, deep and superficial IAI was detected after arthroplasty – in 70.4 % (n = 311), after reconstructive plastic surgery on bones, joints (in 17.6 % of cases; n = 79) and spine (12 % of cases; n = 53).

The crops were incubated for up to 14 days with the creation of conditions for the cultivation of aerobes, anaerobes, capnophiles and fungi. Species identification of pathogens with sensitivity determination to antibacterial drugs was performed on an automatic bacteriological analyzer Vitec 2 Compact (Bio Merieux, France) and on a semi-automatic analyzer Multiskan FC (Thermo Fisher Scientific, USA) using kits and test systems Erba Lachema (Czech Republic).

Antibiotic susceptibility testing was performed in accordance with clinical guidelines[1, 2]. The disk diffusion method was used when there were criteria for assessing the inhibition zones of pathogen growth. Susceptibility determination of gram-negative bacteria to colistin and staphylococci to doxycycline and vancomycin was determined by serial dilutions in Mueller – Hinton broth or using the E-test. When resistant strains were identified by the disk diffusion method, the results were confirmed by the same methods. Despite the changes in the EUCAST (European Committee on Antimicrobial Susceptibility Testing) 2021 criteria for assessing the diameter of the inhibition zones of microorganisms with the transition from category S (susceptible) to category I (susceptible with increased exposure), we classified cases of sensitivity I of staphylococci

1 Antimicrobial susceptibility testing: clinical guidelines (version 2018-03). 2018. URL: https://www.antibiotic.ru/files/321/clrec-dsma2018.pdf [date of access: November 02, 2023].

2 Antimicrobial susceptibility testing: clinical guidelines (version 2021-01). 2021. URL: https://www.antibiotic.ru/files/321/clrec-dsma2021.pdf [date of access: November 02, 2023].

to ciprofloxacin and levofloxacin, enterobacteria – to imipenem to category S.

To obtain the production of extended emission beta-lactamases (ESBL) in the *Enterobacteriaceae* family isolates, the "double disk" method and the electronic cefazidime/clavulanate test were used. Identification of carbapenemase-producing isolates of gram-negative blasts occurs using the double disk method with ethylenediaminetetraacetic acid (EDTA) and the Hodge test.

Microbial associations included cases of isolation of more than one type of microorganism in the studied biomaterials. Antibiotic resistance was assessed taking into account all isolated pathogens, including pathogens in microbial associations. A positive result of growth of the same microorganism in two or more samples was considered diagnostically significant. The microbiological study results of the biomaterial from the fistula tract were not analyzed separately in the work.

Among gram-positive and gram-negative pathogens, an antibiotic resistance analysis of the most significant isolates (with an isolation frequency of more than 4 %) was conducted.

Statistical data processing

The sample size was determined by the type of study (continuous). The obtained data were recorded in the form of spreadsheets, the data structure visualization and data analysis were carried out using MS Office Excel 2007 (Microsoft Corp., USA). The distribution normality was determined using Kolmogorov – Smirnov test. For the categorical data analysis in the GraphPad program (GraphPad Software, USA), Fisher's exact test was used to check the relationship ($p < 0.05$). Quantitative data were assessed using frequency distribution analysis (in percent).

RESULTS

The leading causative agent of monomicrobial IAI in both study periods was *Staphylococcus epidermidis* – 37 % in 2018–2019, and 33 % in 2021–2022 (fig. 1).

There are no significant changes in the structure of IAI pathogens during the studied periods, however, an increase in the proportion of microbial associations was found – from 12.5 to 17.5 % ($p = 0.147$) – with the fungi appearance in the microbial landscape in 2021–2022.

The sample size of microbial associations was 173 isolates (49 isolates in 2018–2019, 124 isolates in 2021–2022). The most common pathogens among gram-positive microorganisms were corynebacteria (18.2 %), isolated in two or more biomaterial samples, *Staphylococcus aureus* (17.5 %) and MRSE (12.4 %); among gram-negative bacteria – *Acinetobacter baumannii* (8.7 %) and *Enterobacter cloacae* (8.0 %). At the same time, about 2/3 of cases were associations of two microorganisms ($n = 48$) and 1/3 were associations of three or more microorganisms ($n = 19$). Microbial associations were isolated from intraoperative biomaterial in 92.3 % of cases in patients with fistula infection.

The microbial spectrum, including pathogens of poly- and monomicrobial infections, is represented mainly by gram-positive bacteria with an isolation frequency of 81.0 % (2018–2019) and 73.2 % (2021–2022), respectively ($p = 0.041$) (table 1).

Despite the continuing leading role of gram-positive microorganisms in the study periods (in particular, *Staphylococcus epidermidis*), in 2021–2022 a tendency was revealed towards an increase in the number of gram-negative pathogens from 12.1 % to 16.1 % ($p = 0.219$) and other microorganisms from 6.9 % to 10.7 % ($p = 0.136$) with a decrease in the proportion of gram-positive pathogens from 81.0 % to 73.2 % ($p = 0.041$). Among

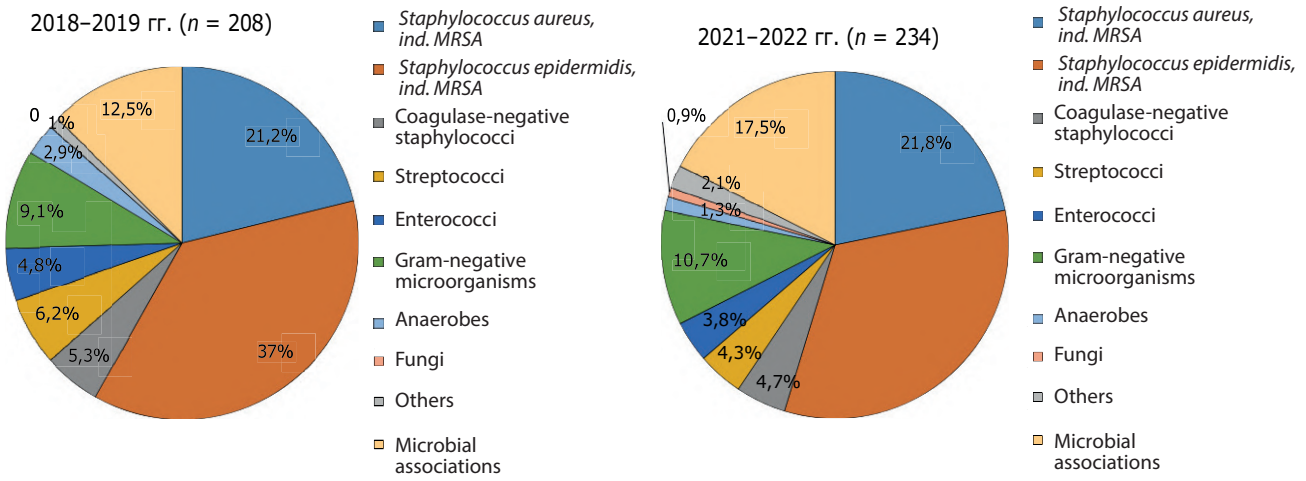

FIG. 1.
The structure of culture-positive implant-associated infection

TABLE 1

THE NUMBER OF ISOLATES OF POLY- AND MONOBACTERIAL INFECTIONS, 2018–2019 AND 2021–2022

Types of microorganisms	2018–2019, *N* (%)	2021–2022, *N* (%)	*p*
Gram-positive microorganisms	**187 (81.0)**	**232 (73.2)**	0.041
Staphylococcus aureus MSSA	51 (22.0)	70 (22.1)	1.000
Staphylococcus aureus MRSA	4 (1.7)	3 (0.9)	0.462
Staphylococcus epidermidis MSSE	17 (7.4)	18 (5.7)	0.481
Staphylococcus epidermidis MRSE	70 (30.3)	76 (24.0)	0.117
Staphylococcus lugdunensis	1 (0.4)	12 (3.8)	0.010
Staphylococcus capitis	1 (0.4)	4 (1.3)	0.403
Staphylococcus hominis	0 (0.0)	3 (0.9)	0.267
Staphylococcus haemolyticus	8 (3.5)	3 (0.9)	0.060
Staphylococcus caprae, Staphylococcus warneri, Staphylococcus xylosus	3 (1.3)	5 (1.6)	1.000
Streptococcus spp.	13 (5.6)	25 (7.9)	0.395
Enterococcus faecalis	18 (7.8)	11 (3.5)	0.033
Enterococcus facium	1 (0.4)	2 (0.6)	1.000
Gram-negative microorganisms	**28 (12.1)**	**51 (16.1)**	0.219
*Burkholderia cepacia**	10 (4.3)	5 (1.6)	0.064
Pseudomonas aeruginosa	4 (1.7)	6 (1.9)	1.000
Achromobacter xylosoxidans	1 (0.4)	2 (0.6)	1.000
Acinetobacter baumannii	5 (2.2)	8 (2.5)	1.000
Escherichia coli	1 (0.4)	10 (3.2)	0.029
Enterobacter cloacae	5 (2.2)	11 (3.5)	0.448
Klebsiella pneumoniae	1 (0.4)	5 (1.6)	0.322
Klebsiella oxytoca	1 (0.4)	1 (0.3)	1.000
Citrobacter braakii	0 (0.0)	1 (0.3)	1.000
Proteus mirabilis	0 (0.0)	1 (0.3)	1.000
Serratia marcescens	0 (0.0)	1 (0.3)	1.000
Others	**16 (6.9)**	**34 (10.7)**	0.136
Anaerobes	6 (2.6)	13 (4.1)	0.479
Corynebacterii	8 (3.5)	16 (5.0)	0.406
Candida albicans	0 (0.0)	2 (0.6)	0.511
Micrococcus spp.	1 (0.4)	1 (0.3)	1.000
Macrococcus caseolyticus	0 (0.0)	1 (0.3)	1.000
Listeria spp.	1 (0.4)	1 (0.3)	1.000
Total	**231 (100)**	**317 (100)**	

Note. * – the pathogen was isolated from patients who had undergone primary surgery in the same medical facility in another region.

gram-negative pathogens, *Burkholderia cepacia* was the leader in 2018–2019, and *Enterobacter cloacae* was the leader in 2021–2022.

In the post-COVID period, an increase in the number of *Staphylococcus aureus* resistant to tetracycline and doxycycline and an increase in sensitivity to fluoroquinolones and gentamicin were recorded; the isolation frequency of methicillin-resistant strains decreased from 4 cases (out of 187) to 3 (out of 232); 100 % sensitivity to rifampicin and cotrimoxazole remained. The isolation frequency of methicillin-resistant *Staphylococcus epidermidis* remained: 80.5 % in 2018-2019 and 80.9 % in 2021-2022. An increase in *Staphylococcus epidermidis* resistance to all tested antibiotics was revealed, including a statistically significant increase in resistance to fluoroquinolones (p = 0.002–0.003). Among coagulase-negative staphylococci in 2018–2019, resistance to methicillin was determined in 64.5 %, in 2021–2022 – in 81.0 %. All isolated staphylococcal strains remained sensitive to vancomycin and linezolid (table 2).

In the structure of gram-negative microorganisms in the post-COVID period, the frequency of *Escherichia coli* detection increased from 0.4 % to 3.2 % (p = 0.029), *Klebsiella pneumoniae* – from 0.4 % to 1.6 %, *Enterobacter cloacae* – from 2.2 % to 3.5 %. In 2018-2019, one case of *Klebsiella pneumoniae* and *Escherichia coli* was recorded, and if the first pathogen was characterized by a multidrug-resistant resistance phenotype, the second was sensitive to all tested antibiotics. In the post-COVID period, the *Enterobacteriaceae* family representatives in most cases were producers of extended-spectrum beta-lactamases with increasing resistance to co-trimoxazole. *Enterobacter cloacae* remained sensitive to fluoroquinolones, *Escherichia coli* and *Klebsiella pneumonia* were resistant from 40 to 80 %. *Enterobacter cloacae* and *Escherichia coli* remained sensitive to carbapenems and aminoglycosides in both study periods (table 3).

In the post-COVID period, an increase in resistance of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* to carbapenems and fluoroquinolones was noted. *Acinetobacter baumannii* isolates, previously sensitive to amikacin, acquired 57.1 % resistance to aminoglycosides (p = 0.018). All gram-negative microorganisms were sensitive to colistin (fig. 2, 3).

The identified increase in antibiotic resistance to fluoroquinolones may indicate unfavorable trends and further contribute to restrictions on the prescription of ciprofloxacin oral forms for long-term use.

TABLE 2

THE RESULTS OF ANTIBIOTIC RESISTANCE OF *STAPHYLOCOCCUS AUREUS* AND *STAPHYLOCOCCUS EPIDERMIDIS*, 2018–2019 AND 2021–2022

Medications	*Staphylococcus aureus* (n = 128), %			*Staphylococcus epidermidis* (n = 181), %		
	2018–2019 (n = 55)	2021–2022 (n = 73)	p	2018–2019 (n = 87)	2021–2022 (n = 94)	p
Cefoxitin	7.3	4.1	0.462	80.5	80.9	1.000
Gentamicin	12.7	4.1	0.098	32.2	42.6	0.169
Erythromycin	21.8	17.8	0.654	32.2	45.7	0.069
Clindamycin	18.2	17.8	1.000	28.7	27.8	1.000
Ciprofloxacin	10.9	5.5	0.325	29.9	52.1	0.003*
Levofloxacin	10.9	5.5	0.325	29.9	52.1	0.003*
Moxifloxacin	9.1	4.1	0.288	28.7	52.1	0.002*
Tetracycline	21.8	28.8	0.419	34.5	28.7	0.427
Fusidic acid	0	2.7	0.506	5.7	9.6	0.410
Doxycycline	1.8	11.0	0.077	13.8	20.2	0.324
Vancomycin	0	0	1.000	0	0	1.000
Rifampicin	1.8	0	0.430	2.3	8.5	0.102
Co-trimoxazole	1.8	0	0.430	16.1	26.6	0.104
Linezolid	0	0	1.000	0	0	1.000

Note. * – the differences are statistically significant at $p < 0.05$.

TABLE 3

ANTIBIOTIC RESISTANCE OF *KLESIELLA PNEUMONIA, ENTEROBACTER CLOACAE, ESCHERICHIA COLI*, 2018–2019 AND 2021–2022

Medications	*Klesiella pneumoniae* (*n* = 6)			*Enterobacter cloacae* (*n* = 16)			*Escherichia coli* (*n* = 11)		
	2018–2019 (*n* = 1)	2021–2022 (*n* = 5)	*p*	2018–2019 (*n* = 5)	2021–2022 (*n* = 11)	*p*	2018–2019 (*n* = 1)	2021–2022 (*n* = 10)	*p*
Ceftazidime	100	100	1.000	40	72.7	0.293	0	60.0	1.000
Ceftriaxone	100	100	1.000	40	72.7	0.293	0	60.0	1.000
Cefepime	100	100	1.000	40	72.7	0.293	0	60.0	1.000
Imipenem	100	40	1.000	0	0	1.000	0	0	1.000
Meropenem	100	60	1.000	0	0	1.000	0	0	1.000
Amikacin	100	60	1.000	0	0	1.000	0	0	1.000
Tobramycin	100	60	1.000	0	0	1.000	0	0	1.000
Ciprofloxacin	100	80	1.000	0	0	1.000	0	40.0	1.000
Levofloxacin	100	80	1.000	0	0	1.000	0	40.0	1.000
Co-trimoxazole	0	80	1.000	40	62.5	0.592	0	40.0	1.000
Aztreonam	100	75	1.000	20	33.3	1.000	0	40.0	1.000
Colistin	0	0	1.000	0	0	1.000	0	0	1.000

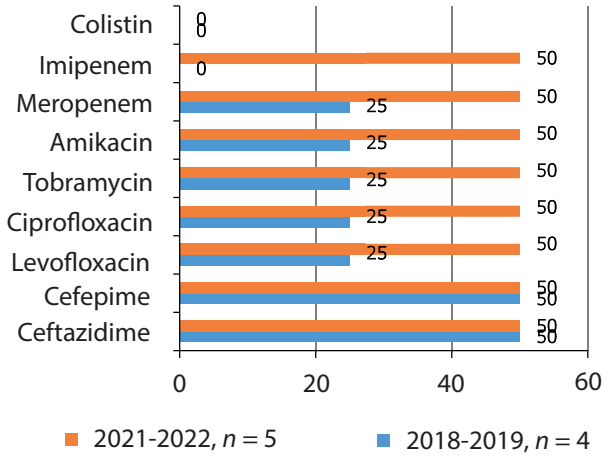

FIG. 2.
Antibiotic resistance of Pseudomonas aeruginosa, 2018–2019 and 2021–2022

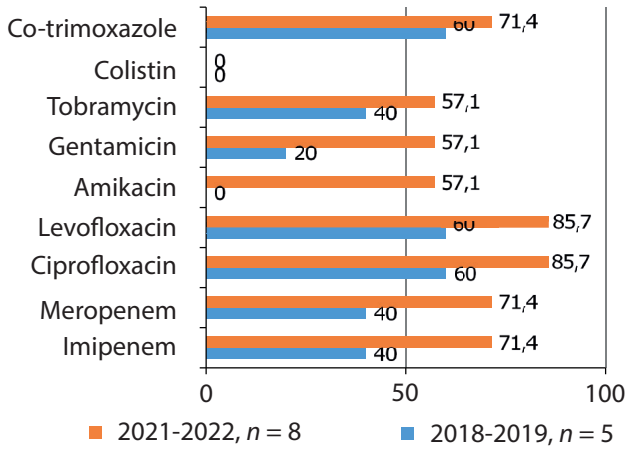

FIG. 3.
Antibiotic resistance of Acinetobacter baumannii, 2018–2019 and 2021–2022

DISCUSSION

Over the past four decades, there has been an increase in the number of antibiotic-resistant bacterial pathogens [13].

The study by F.S. Fröschen et al. (2022) shows that the most common causative agent of orthopedic implant-associated infection is coagulase-negative staphylococci, which could be detected in 44.61 % of cases, followed by *Staphylococcus aureus* (14.31 %) and enterococci (9.01 %) [3]. Our study confirms the leading role of *Staphylococcus epidermidis* in the IAI etiology with a detection rate of 37 % (2018–2019) and 33 % (2021–2022). Similar data were obtained by other foreign researchers – D.B.G. Tai et al. (2022) – for the observation period from 2010 to 2019 (2067 episodes of infection in 1651 patients), where it was demonstrated that coagulase-negative staphylococci (except *Staphylococcus lugdunensis*) were the leaders in the etiology of implant-associated infection (37 %; *n* = 761) [14].

In the work of B.T. Bjerke-Kroll et al. (2014), *Staphylococcus aureus* was indicated as the leading causative agent of IAI [15]. Similar data were published in the periprosthetic joint infection study by Y. Tsai et al. (2006–2014; *n* = 294), where the leading role in the development of hip and knee joint infection with a detection rate of up to 27 % (methicillin resistance – 21 %) belonged to *Staphylococcus aureus* [16], however, we could not confirm these results. Our study showed that in 2020–2021, only 4.1 % of *Staphylococcus aureus* isolates demonstrated methicillin resistance. The study, conducted by S.A. Bozhkova et al. (2018) at the R.R. Vreden National Medical Research Center of Traumatology and Orthopedics of the Ministry of Health of the Russian Federation (St. Petersburg), showed high activity against methicillin-resistant strains of *Staphylococcus aureus* fusidic acid and fosfomycin; in our study in the post-COVID period, we identified two strains resistant to fusidic acid [11].

In contrast to the coagulase-negative staphylococci methicillin resistance described in recent publications (76 % according to H.M. Peng et al. [17] and 60 % according to F.S. Fröschen et al. [3]), the resistance level identified in our study was even higher and amounted to 81.0 %.

According to our data, in both study periods the proportion of methicillin-resistant strains was almost half of all isolated staphylococcal isolates. Due to the targeted action of vancomycin against methicillin-resistant staphylococcal strains in cases of an unknown pathogen, it can be recommended as the drug of choice for IAI empirical therapy. Given the patient's concomitant diseases, potential alternatives to vancomycin should not be forgotten – such as teicoplanin, daptomycin or linezolid; in our study, pathogens resistant to linezolid were not detected.

A retrospective review of implant-associated infection cases in two large infectious centers (Germany (*n* = 898) and the Rothman Institute in Philadelphia (*n* = 772)) showed a low frequency of polymicrobial infection (3.4 % and 7.4 %, respectively) [18]. In contrast, the work of T. Rosteius et al. (2018; *n* = 937) notes an increase in the number of microbial associations in the development of IAI of the hip or knee joint in the period from 2003 to 2011 with a polymicrobial infection detection rate of 23.6 % [19]. Our study also shows a high polymicrobial IAI frequency with growth dynamics in the post-COVID period.

According to the study by D.B.G. Tai et al. (2022), the presence of a fistula increased the likelihood of isolating more than one microorganism by almost three times (median – 2.6; 95% confidence interval: 2.0–3.3) [14], which correlates with the data of our study.

Infection caused by gram-negative bacteria and fungi more often leads to an unfavorable outcome after sanitation due to the high virulence of these microorganisms and growing antibiotic resistance. F.D. Wang et al. (2018) believe that the very fact of the gram-negative bacteria involvement in the IAI etiology greatly complicates and prolongs its treatment [20]. In our study in 2021–2022, along with an increase in the proportion of microbial associations in the IAI etiological structure, there is a tendency towards an increase in the frequency of gram-negative pathogens (of which *Enterobacter cloacae* took the leading position in the post-COVID period) and the fungi appearance in the microbial landscape, which may be associated with the high frequency of use of antibacterial drugs during the COVID-19 pandemic and a decrease in the general immunological status of patients.

Multidrug-resistant strains of gram-negative microorganisms currently retain sensitivity only to colistin. However, when choosing empirical antimicrobial therapy, the colistin use is limited by its high cost and insufficient effectiveness as monotherapy.

The results of the microbiological examination of the biomaterial from the fistula tract were not analyzed separately in the work, since patients with the fistula form of IAI are not recommended to undergo discharge bacteriological examination taken with a swab from the fistula tract [21, 22].

A limitation of this study is the small number of isolated strains of gram-negative bacteria, which prevents a full analysis of their antibiotic resistance.

CONCLUSION

According to the study, the microbial landscape has undergone minor changes in the post-COVID period. The leading causative agent of IAI is currently *Staphylococcus epidermidis* with a predominance of methicillin-resistant strains. However, it is worth paying attention to the increased role of microbial associations in the post-COVID period and, in particular, the increase in the gram-negative bacteria proportion in their composition (by 1.6 times). Timely analysis of the sensitivity of IAI pathogens is crucial for the treatment success. The high frequency of methicillin-resistant staphylococci isolation (especially among *Staphylococcus epidermidis*) determines the tactics of choosing vancomycin as an empirical therapy to ensure an optimal antimicrobial effect in the case of an unknown pathogen. In turn,

the growth of staphylococcal resistance to the fluoroquinolone series of antibiotics may further limit the use of levofloxacin as the drug of choice for IAI oral therapy. The growth of gram-negative bacteria resistance and the narrow spectrum of antibiotics acting on carbapenemase producers may reduce the therapy effectiveness, despite the fully performed surgical sanitation. Up-to-date information on the microbiological structure of pathogens is useful for optimal treatment of IAI.

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Conflicts of interest

No potential conflict of interest relevant to this article reported.

The Ethics Committee opinion regarding the study is not required, since it was carried out without providing personal data.

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Authors' contribution

Lyubimova L.V. – developed the concept, wrote the manuscript.

Pchelova N.N. – collected and analysed the data.

Nikolaev N.S. – developed the concept, carried out scientific editing of the manuscript.

Preobrazhenskaya E.V. – developed the study design, carried out a graphical representation of the data.

Lyubimov E.A. – collected and analysed the data.