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Twelve-Year Dynamics of Leading Pathogens Spectrum Causing Orthopedic Infection: A Retrospective Study

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Abstract

Background. The number of surgeries on the musculoskeletal system is increasing every year. Along with the increasing access to orthopedic care, the number of patients with orthopedic infection, the etiological agents of which can be from various taxonomic groups, is also increasing. *Staphylococcus aureus* and different types of coagulase-negative staphylococci (CoNS), including *S. epidermidis* and *S. lugdunensis*, together are the causative agents in 70% of cases.

Aim of the study — to analyze the dynamics of the leading pathogens spectrum isolated from patients of the septic surgery department for the period from 2011 to 2022.

Methods. We performed a retrospective analysis of the microbial spectrum isolated from patients who were treated in the septic surgery department from January 1, 2011 to December 31, 2022. The leading pathogens were microorganisms whose share in the spectrum exceeded 3.5%. Of all the isolated pathogens, 48.8% were the only etiological agents, and microbial associations were detected in 51.2% of the isolated pathogens.

Results. A total of 10,327 bacteria strains were identified over the 12-year period. The leading microorganisms causing orthopedic infection were *Staphylococcus* spp., *Enterococcus* spp., *Propionibacterium* spp., *Pseudomonas aeruginosa*, *Corynebacterium* spp., *Streptococcus* spp., *Klebsiella* spp. and *Acinetobacter* spp. In the dynamics of isolated pathogens during the analyzed period, several trends were determined: a decrease in the shares of *S. aureus, Enterococcus* spp., *P. aeruginosa*, *Acinetobacter* spp. and an increase in the shares of CoNS and *Corynebacterium* spp.

Conclusion. During 12 years, in the microbial spectrum of orthopedic infection in the patients of the septic surgery department of our Center, Gram-positive bacteria (in the majority representatives of the genus *Staphylococcus)* prevailed. At the same time, a significant decrease in the share of *S. aureus* strains and an increase in the frequency of isolation of various species of CoNS were registered. A significant decrease in the number of non-fermenting Gram-negative bacteria was also revealed.

Keywords: orthopedic infection, *Staphylococcus aureus*, microbial spectrum, periprosthetic infection, osteomyelitis.

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Двенадцатилетняя динамика спектра ведущих возбудителей ортопедической инфекции: ретроспективное исследование

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Реферат

Актуальность. Количество хирургических вмешательств на опорно-двигательном аппарате возрастает с каждым годом. Одновременно с ростом доступности ортопедической помощи увеличивается и количество пациентов с ортопедической инфекцией, этиологическими агентами которой могут быть представители различных таксономических групп. *Staphylococcus aureus* и различные виды коагулазонегативных стафилококков (CoNS), включая *S. epidermidis* и *S. lugdunensis*, в совокупности являются возбудителями в 70% случаев.

Цель исследования — проанализировать динамику спектра ведущих патогенов, выделенных от пациентов отделения гнойной остеологии, за период с 2011 по 2022 г.

Материал и методы. Выполнен ретроспективный анализ спектра микроорганизмов, изолированных от пациентов, находившихся на лечении в отделении гнойной хирургии с 1 января 2011 г. по 31 декабря 2022 г. К ведущим возбудителям относили микроорганизмы, доля которых в спектре превышала 3,5%. Из выделенных возбудителей 48,8% были единственными этиологическими агентами, в 51,2% определяли наличие микробных ассоциаций.

Результаты. За 12-летний период идентифицировано 10 327 штаммов различных видов бактерий. Ведущими микроорганизмами, выделенными от пациентов с ортопедической инфекцией, были *Staphylococcus* spp., *Enterococcus* spp, *Propionibacterium* spp., *Pseudomonas aeruginosa*, *Corynebacterium* spp., *Streptococcus* spp., *Klebsiella* spp. и *Acinetobacter* spp. В динамике выделенных возбудителей за анализируемый период определено несколько трендов: сокращение долей *S. aureus, Enterococcus* spp., *P. aeruginosa, Acinetobacter* spp. и увеличение доли CoNS и *Corynebacterium* spp.

Заключение. Выполненное исследование показало, что в течение 12 лет в спектре возбудителей ортопедической инфекции у пациентов отделения гнойной хирургии нашего Центра основными были грамположительные бактерии, в большинстве представители рода *Staphylococcus*. При этом регистрировали значимое снижение доли штаммов *S. aureus* и рост частоты выделения различных видов CoNS. Также выявлено значимое снижение количества неферментирующих грамотрицательных бактерий.

Ключевые слова: ортопедическая инфекция, *Staphylococcus aureus*, спектр возбудителей, перипротезная инфекция, остеомиелит.

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BACKGROUND

Nowadays, the frequency of primary and revision orthopedic interventions is increasing due to population aging and will keep on increasing in future. Infection control and adequate pathogen-specific therapy are particularly important in orthopedic surgery because of extensive operations, risks associated with implant placement, severe consequences for a patient and healthcare system if an orthopedic infection develops, which requires additional surgeries in the vast majority of cases.

Orthopedic infection includes both processes affecting the native musculoskeletal system (osteomyelitis, arthritis) and those associated with hardware installation. Risk of infection increases with hardware implantation. According to the literature, the incidence of implant-associated infection ranges from 2.5% after primary arthroplasties to 20% after revision surgeries, and the mortality rate for this complication reaches 2.5% [1]. In case of revision surgery for an existing infection, relapses develop in 25-67% of cases and are largely determined by the type of infectious agent [2]. In 2020, J. Akindolire et al. showed that infectious complications in total hip arthroplasty increase the cost of treatment fivefold compared to primary uncomplicated hip replacement [3].

Representatives of various taxonomic groups can be etiological agents in the development of orthopedic infection [4]. *Staphylococcus aureus* and various species of coagulase-negative staphylococci (CoNS), including *S. epidermidis* and *S. lugdunensis*, together are the causative agents in 70% of cases [5]. In addition, their antibiotic resistance remains a major problem for clinicians. In turn, *Cutibacterium acnes* is the most common biofilm-forming pathogen of upper extremity infections leading to osteomyelitis. *C. acnes* was isolated in 5% of periprosthetic joint infection (PJI) cases of the lower extremities and in more than 50% of shoulder PJI cases [6, 7].

Even though the most common causative agents of infection of bones and joints, including those associated with orthopedic implants, are staphylococci, involvement of Gram-negative pathogens such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* in the etiology is a prognostically unfavourable sign [8]. This is caused by an extremely low efficacy of treatment of orthopedic infection caused by *K. pneumoniae* and *P. aeruginosa*, which, as a rule, are characterized by high antibiotic resistance [9]. Various mechanisms of resistance to beta-lactams and fluoroquinolones make it impossible to prescribe prolonged etiotropic antibiotic therapy, which is a standard treatment for bone and joint infection due to the lack of other oral drugs active against Gram-negative pathogens.

In addition to the "classical", most frequently detected pathogens, the spectrum of etiological agents of orthopedic infection is currently expanding with the development of bacteriologic identification methods. Moreover, according to various studies, in 6-46% of PJI cases, several microorganisms are isolated from a single patient's biomaterial [10, 11]. *S. aureus* is the most frequently registered in case of polymicrobial etiology of osteomyelitis, while coinfecting bacteria can be both opportunistic and obligate pathogens. Contamination from the skin most often occurs by various CoNS, in case of ingress from the environment: *S. aureus, E. coli, Enterobacter* spp., *P. aeruginosa, A. baumannii* and *Enterococcus* spp. and others [5]. Polymicrobial infections are often associated with more unfavourable outcomes and characterized by greater severity of disease [12], which can be explained by microbial synergism that provides resistance of different bacterial species to adverse factors — antibiotics, antiseptics, immune cells, etc.

Aim of the study — to analyze the dynamics of the leading pathogens spectrum isolated from the patients of the septic surgery department for the period from 2011 to 2022.

METHODS

Study design

Type of the study: retrospective, single-center, observational.

We analyzed the spectrum of microorganisms isolated from more than 6,000 patients treated in the septic surgery department of the Vreden National Medical Research Center of Traumatology and Orthopedics (hereinafter referred to as the Center) from January 1, 2011 to December 31, 2022. The leading pathogens were considered to be microorganisms, whose share in the spectrum exceeded 3.5%.

Microbiological examination of biomaterials was performed in accordance with international standards (Standards for microbiology investigations — UK SMI). Tissue and bone biopsy samples, synovial fluid, wound and fistula discharge, hematomas, as well as removed hardware were used for the study. Positive microbial growth was obtained in 66.9% of analyzed samples. Bacterial identification until 2021 was performed on Microlatest panels (Erba Lachema) using iEMS Reader MF (Labsistems, Finland), from 2021 — by MALDI-TOF-MS (Matrix Assisted Laser Desorption Ionization Time of Flight Mass-Spectrometry) using FlexControl system and MBT Compass 4.1. software (Bruker Daltonics, Germany), Score ≥2.0. The sensitivity of staphylococci to cefoxitin was studied according to EUCAST (v.1-12) (2011-2022).

Epidemiological analysis of the study results was performed using the Microbiological Monitoring System 'Microb-2' (MedProject-3, 2002-2020) software and the Across-Engineering (2021-2022) laboratory information system. Comparative analysis of the changes in the microbial spectrum was carried out for two-year periods: 2011-2012, 2013-2014, 2015-2016, 2017-2018, 2019-2020 and 2021-2022.

Statistical analysis

The obtained data were recorded in the form of spreadsheets and analyzed using MS Office Excel, 2007. Absolute values (n) and shares (%) were used to describe the data. The trend hypothesis for categorical data was tested using the Cochran-Armitage test for trend with a multinominal outcome. Correction for multiple hypotheses testing was made by the Holm-Sheffer correction. Linear trend for time series was estimated by the bootstrap version of t-test for time series (Bootstrap-Based Tests for Trends in Hydrological Time Series). The null hypothesis was rejected at $p<0.05$. The calculations were performed using the R 4.2.3 programming language.

RESULTS AND DISCUSSION

A total of 10,327 strains of various bacterial species were identified from 7,323 patients over the studied 12-year period. The leading microorganisms isolated from the patients with orthopedic infections were *Staphylococcus* spp., *Enterococcus* spp., *Propionibacterium* spp., *Pseudomonas aeruginosa, Corynebacterium* spp., *Streptococcus* spp., *Klebsiella* spp. and *Acinetobacter* spp. (Table 1). The share of these pathogens in the microbial spectrum amounted to 88.2% (n = 9,108). Microorganisms of other taxonomic groups, the so-called rare pathogens of orthopedic infection, were identified in 11.8% of cases. At the admission to the septic surgery department of the Center, the chronic course of the infectious process is diagnosed in the vast majority of patients, of whom about 75% are non-resident, which allows us to extrapolate the results obtained to the entire population of relevant patients in the country.

Table 1

Leading pathogens of orthopedic infection isolated from 2011 to 2022

Microorganism	n	%
S. aureus	3.272	31.33
S. epidermidis	1.950	18.67
CoNS, except *S. epidermidis*	605	5.79
Enterococcus spp.	579	5.54
Propionibacterium spp.	515	4.93
P. aeruginosa	499	4.78
Corynebacterium striatum	467	4.47
Streptococcus spp.	435	4.17
Klebsiella spp.	405	3.88
Acinetobacter spp.	381	3.65
Others	1.219	11.80

The microbial spectrum of orthopedic infection pathogens remained stable throughout the analyzed period. Among all isolated pathogens, 77.5% were Gram-positive bacteria, 21.6% were the Gram-negative ones. The share of strict anaerobic bacteria was 5%.

Out of 10,327 strains isolated, 48.8% (n = 5,043) were the only etiologic agents, and in 51.2% of cases (n = 5,284) the presence of microbial associations was determined. The share of associations of two strains of different bacterial species was 32.7% (n = 3376), three strains — 13.4% (n = 1,388), four strains — 5.0% (n = 520).

According to scientific reports, these values vary greatly. For example, S. Sebastian et al. showed that only 8.3% of 106 cases of PJI were caused by several pathogens [13]. In a single-center study by Chinese authors during 5 years of follow-up, simultaneous isolation of two or more microorganisms of different species was reported in 28.3% of cases [14]. Other studies with different previous treatment reported 34% [15] and 46.6% [11] of cases of polymicrobial etiology of orthopedic infection. In general, there is a trend towards an increase in the frequency of polymicrobial infection in observational studies. This may be related both to the true increase in the number of polymicrobial associations and to the changing methods of microorganism identification due to the introduction of modern equipment in diagnostic laboratories and the development of new progressive diagnostic methods. Also, most researchers have noted a direct correlation between the number of previous surgical interventions and the risk of polymicrobial infection [14, 15].

Several trends were determined in the dynamics of isolated pathogens during the analyzed period: a decrease in the shares of *S. aureus, Enterococcus* spp.*, P. aeruginosa, Acinetobacter* spp. and an increase in CoNS and *Corynebacterium* spp. (Table 2).

The main trends identified coincide with the global data. In the majority of studies analyzing the microbial spectrum of orthopedic infection, Gram-positive bacteria take the leading place, their share varying from 65 to 77% [14, 15, 16]. However, there are scientific publications that show the leading role of Gram-negative bacteria. For instance, S. Sebastian et al. report that, contrary to the existing opinion on the prevalence of Gram-positive bacteria in the etiology of implant-associated infection, they more often isolated Gram-negative bacteria (in 61% of cases) in their center.

Interregional differences in the leading pathogens may be due to different clinical approaches to the diagnosis of orthopedic infection, technical resources of local diagnostic centers, and methods used to identify the pathogen and the microbial spectrum circulating in the region. In addition, long periods from the infection onset to the patient's admission to the hospital for a complex treatment and attempts of conservative treatment with antibiotics without surgical sanation of the infection site play a significant role.

In our Center, *S. aureus* remained in the first place by the frequency of isolation during 12 years of observation. However, a stable decrease in its share in the overall spectrum was noted from 41.1 to 29.4% during 10 years of observation (up to and including 2020), including methicillin-resistant strains. In 2021-2022, an increase in *S. aureus* to 33.6% was recorded again. The general trend over 12 years of observation can be characterized as a decrease (see Table 2).

Table 2

Main trends in the spectrum of orthopedic infection pathogens from 2011 to 2022

Microorganism	2011–2012 (*n* = 1074)	2013–2014 (*n* = 1556)	2015–2016 (*n* = 1420)	2017–2018 (*n* = 1398)	2019–2020 (*n* = 1365)	2021–2022 (*n* = 3514)	Trend	p
S. aureus	41.1%	32.1%	27.4%	28.9%	29.4%	33.6%	Decrease	0.066
MSSA/MRSA ratio	3.49	3.41	3.89	5.16	4.35	5.72	Increase	**0.010**
Enterococcus spp.	8.2%	5.9%	6.6%	6.8%	5.9%	4.5%	Decrease	**0.002**
CoNS (except *S. epidermidis*)	2.2%	4.1%	5.5%	3.5%	4.2%	12.1%	Increase	**0.001**
P. aeruginosa	5.2%	6.2%	4.9%	4.2%	5.2%	3.8%	Decrease	**0.040**
Corynebacterium spp.	3.9%	4.0%	4.5%	4.0%	5.5%	5.0%	Increase	0.275
Acinetobacter spp.	5.8%	3.3%	3.6%	3.5%	4.0%	2.8%	Decrease	**0.033**

Statistically significant values are highlighted in bold font.

The key importance of *S. aureus* as a causative agent of orthopedic infection has also been shown in other studies from different medical centers. A retrospective analysis of the PJI microbial spectrum performed at the Center for Medical Care in Germany from 2012 to 2016 showed that *S. aureus* was isolated from patients with PJI in 26.6% [17]. According to the data of S. Sebastian et al., *S. aureus* was also the leading causative agent of orthopedic infection (19.5%), despite the predominance of Gram-negative pathogens in the spectrum [13].

Against the background of a decrease in the overall frequency of *S. aureus* isolation, a change in its sensitivity to methicillin was observed. When comparing the frequency of isolation of methicillin-sensitive (MSSA) and methicillin-resistant S. aureus (MRSA) strains, a significant decrease in the share of MRSA (from 22 to 15%) and an increase in the share of MSSA (from 78 to 85%) were registered ($p = 0.01$) (Fig. 1). The MSSA/MRSA ratio ranged from 3.49 to 5.72 throughout the whole follow-up period.

It is difficult to determine whether this reduction in the share of methicillin-resistant strains in the structure of *S. aureus* is a worldwide trend. It is known that there are territorial differences in the sensitivity of *S. aureus*. For example, a review of 12 studies demonstrates that the prevalence of MRSA in Nigeria increased from 18.3% in 2009 to 42.3% in 2013. However, even within the same country, different trends were highlighted: there was a decrease in MRSA prevalence in the north-east (from 12.5 to 8.0%) and an increase in the south-west (from 20.2 to 47.4%) between 2006 and 2010 [18]. The researchers from Sudan and Nepal provide similar data on the increase in the number of patients with MRSA infections [19, 20].

Even though CoNS are less virulent than *S. aureus*, the number of sequenced types of CoNS is constantly increasing, along with the number of virulence factors detected in these cultures. In addition, the presence of antibiotic resistance genes in CoNS leads to difficulties in treating infections caused by them in accordance with generally accepted therapeutic strategies [21]. Currently, different CoNS (especially *S. epidermidis, S. haemolyticus, and S. lugdunensis*) are becoming increasingly important in the etiology of infection in patients after insertion of various constructs [21]. In the study by T. Winkler et al., the leading pathogens in PJI were coagulazonegative *staphylococci* (30-43%), followed by *S. aureus* (12-23%) [22].

The frequency of isolation of different CoNS during the analyzed period in our study had an undulating dynamics. Methicillin-resistant *S. epidermidis* (10.6-13.1%) predominated in the overall CoNS structure, methicillin-sensitive *S. epidermidis* was in the second place (6.8-8.3%), other CoNS accounted for 2.2 to 5.4% and were often not identified to species due to the complexity of biochemical differentiation. The proportion of *S. epidermidis* among all the pathogens remained stable throughout

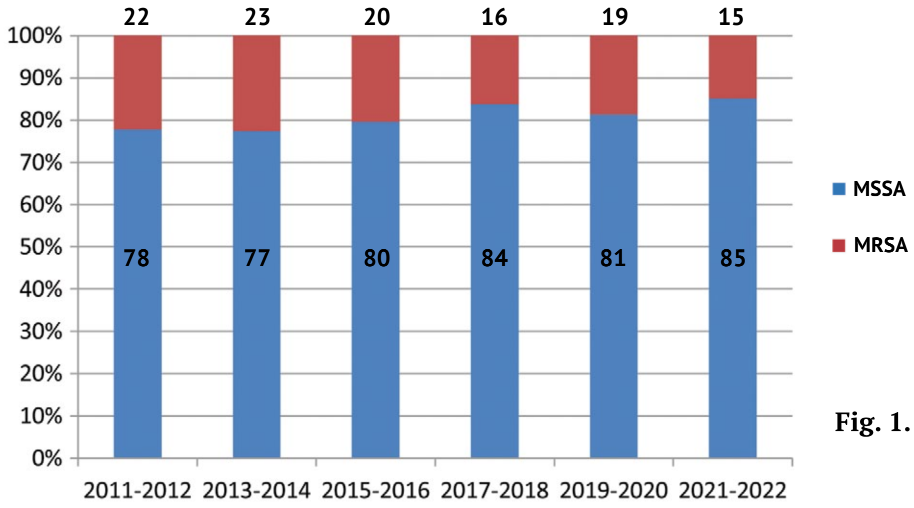

Fig. 1. Ratio of MSSA/MRSA isolation

the analyzed period (p>0.999). The MSSE/MRSE ratio showed a decrease during the 10 years of follow-up (2011-2020), indicating predominance of methicillin-resistant strains. The total proportion of *S. epidermidis* was decreasing due to methicillin-resistant strains (Fig. 2).

Expansion of the species spectrum of CoNS isolated from the patients with orthopedic infection in 2021-2022 is noteworthy. Introduction of the new MALDI-TOF-MS method of microorganism identification into practice allowed to perform microbiological diagnosis of orthopedic infection with greater accuracy and speed, so that the strains previously registered as *S. epidermidis* were classified also as other CoNS (*S. haemolyticus, S. hominis, S. lugdunensis, S. pettenkoferi, S. piscifermentans*, etc.). The share of MRSE in the total decreased to 9.2%, while the share of other CoNS increased sharply to 12.1% (p<0.001). A slight decrease in the frequency of *S. epidermidis* isolation was also observed in 2021-2022.

The heterogeneous genetic structure of CoNS has been confirmed in the studies showing that phenotypically identical isolates can be identified as different species [23]. Larger systematic studies are needed to understand the clinical significance of these findings. The prevalence of methicillin-resistant strains over methicillin-sensitive CoNS over the years is also a common phenomenon [24, 25]. According to our data, the share of methicillin-resistant strains was increasing until 2020, and from 2021 an increasing share of MSSE has been observed (see Fig. 2).

The share of other Gram-positive bacteria in the overall microbial spectrum amounted to 19.1%. The dynamics of *Streptococcus* spp. isolation did not have a linear trend (p>0.999) throughout the 12-year observation. Until 2018, an increase in the share from 2.0 to 5.5% was determined, followed by a pronounced decrease to 3.68%. In the dynamics of other Gram-positive pathogens, a decrease in the share of *Enterococcus* spp. from 8.2 to 4.5% (p = 0.002) and a tendency to increase in the share of *Corynebacterium* spp. from 3.9 to 5.0% (p = 0.275) were noted.

The leading pathogens from the genus *Enterococcus* included only *E. faecalis*. From 2011 to 2016, a decrease in the number of *E. faecalis* was registered, and the opposite trend has been observed starting from 2017.

Comparing our results with the data from other studies on the changing trends in the etiology of orthopedic infection, we can affirm that over the past 20 years, the decrease in the frequency of isolation of Gram-positive pathogens has been a general trend. In a Spanish study based on a 10-year follow-up (from 2003 to 2012) in 19 centers, it was observed that different *Staphylococcus* spp. continue to be the most common cause of infection (65.2%). However, a significant linear upward trend in the registration of Gram-negative pathogens was shown, mainly due to their increased isolation in the last 2 years of the study (25% in 2003-2004, 33.3% in 2011-2012; p = 0.024 for trend). Though, no specific species contributed disproportionately to the overall increase in share [26].

In our Center, the spectrum of leading Gram-negative pathogens remained almost unchanged from 2011 to 2020 and ranged from 11.9 to 13.5% of the total number of identified bacteria, but

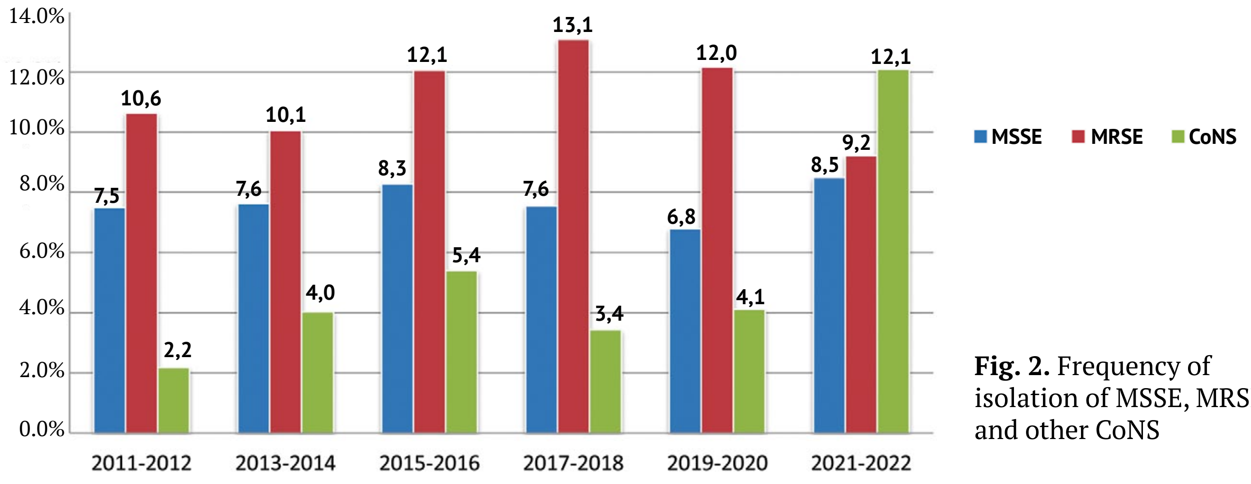

Fig. 2. Frequency of isolation of MSSE, MRSE and other CoNS

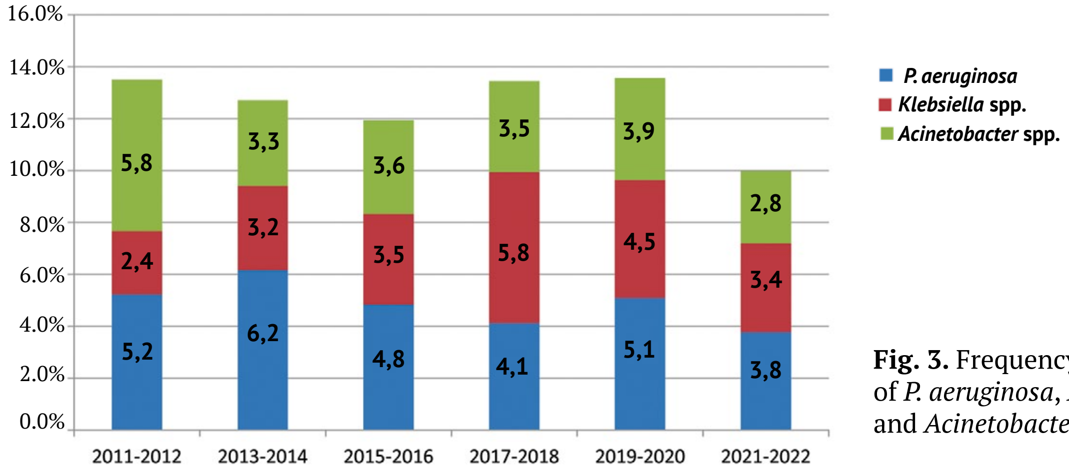

Fig. 3. Frequency of isolation of *P. aeruginosa*, *Klebsiella* spp. and *Acinetobacter* spp.

in 2021-2022, a decrease in the frequency of isolation of Gram-negative cultures to 9.9% was noted. Of these, the leading causative agents of orthopedic infection were *P. aeruginosa, Klebsiella* spp. and *Acinetobacter* spp. (Fig. 3).

During the 12-year observation period, a statistically significant decrease in the frequency of isolation of *P. aeruginosa* from 5.23 to 3.76% ($p = 0.040$) was registered, while in 2013-2014 and 2019-2020, an increase in the number of representatives of this species was recorded. The maximum number of *Acinetobacter* spp. was identified in the period 2011-2012 (5.84%), and further a significant decrease in the proportion of *Acinetobacter* spp. was observed up to 2.79% in 2021-2022 ($p = 0.033$). The dynamics of *Klebsiella* spp. isolation in the microbial spectrum of orthopedic infection was described by two linear trends. Thus, from 2011 to 2018, a stable increase in the frequency of isolation of bacteria of this genus was determined ($p<0.01$), and starting from 2019, the trend changed to a decrease. At the same time, there were no significant changes in the end-to-end trend analysis over 12 years of observation ($p>0.99$).

Limitations

During the analysis we did not distinguish between the localization of the infectious process (joints, soft tissues), type of infection, clinical diagnosis, type of performed treatment and etiological significance of the isolated pathogen, which may serve as a limitation of this study.

Perspectives

Due to the impossibility to present all the data of local monitoring for 12 years in one article, our further publications will be devoted to the analysis of antibiotic sensitivity dynamics of the leading pathogens of orthopedic infection and recommendations on the choice of antimicrobial agents.

CONCLUSIONS

The study showed that during 12 years the spectrum of the leading pathogens of orthopedic infection in the patients of the septic surgery department of our Center was dominated by Gram-positive bacteria, mostly belonging to the genus Staphylococcus. At the same time, a significant decrease in the share of *S. aureus* strains and an increase in the frequency of isolation of various CoNS were registered. A significant decrease in the number of non-fermenting Gram-negative bacteria was also detected. However, even though the authors of a number of published papers note an increase in the share of Gram-negative pathogens in orthopedics, a slight decrease in the frequency of isolation of these pathogens was noted in our study.

Currently, the identification of the etiologic agent remains a priority in the treatment of patients with infection of the musculoskeletal system. The choice of not only drugs for etiotropic antimicrobial therapy, but also surgical treatment tactics often requires an established microbiologic diagnosis with determination of antibiotic sensitivity of bacteria.

DISCLAIMERS

Author contribution

All authors have read and approved the final version of the manuscript of the article. All authors agree to bear responsibility for all aspects of the study to ensure proper consideration and resolution of all possible issues related to the correctness and reliability of any part of the work.

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