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Course and medium-term outcomes of implant-associated infection caused by leading gram-negative pathogens

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Abstract

Introduction Implant-associated infection (IAI) caused by gram-negative pathogens is characterized by a more severe, recurrent course and higher mortality than the one caused by gram-positive ones. The main reason is growing antibiotic resistance of these pathogens and the complexity of choosing drugs for inpatient and outpatient therapy.

Purpose To evaluate the influence of various factors and compare the features of the course of implant-associated infection caused by *P. aeruginosa, K. pneumoniae, A. baumannii* in patients with positive and poor treatment outcomes

Methods A retrospective analysis of the medical records of 172 patients treated at the Department of Purulent Osteology between January 1, 2017 and December 31, 2022 for implant-associated infection caused by *P. aeruginosa, K. pneumoniae, A. baumannii* was conducted. Based on the results of a telephone survey or examination, patients were divided into 2 groups: positive and poor treatment outcomes by Delphi criteria. The impact of various factors in the anamnesis, laboratory and microbiological analysis, features of surgical intervention, antibacterial therapy and the course of the early postoperative period on the outcomes was analyzed in the IBM SPSS STATISTICS (version 26).

Results Among patients with IAI caused by gram-negative bacteria, the rate of poor outcomes was 45 %, with fatality rate of 10 %. During the comparative study, a statistically significant effect on the development of a poor outcome was shown by the postoperative level of serum albumin ($p = 0.002$), the sensitivity of the isolated isolate to the tested antibacterial drugs ($p = 0.011$), the isolation of the pathogen from patients' biomaterial in the postoperative period ($p = 0.001$), a more frequent need for intravenous administration of albumin and iron ($p = 0.003$ and $p = 0.056$, respectively) and the need for repeated surgical intervention in the early postoperative period ($p = 0.001$).

Discussion IAI caused by gram-negative bacteria is characterized by a prolonged recurrent course and high mortality, primarily associated with the overall growing antibiotic resistance of pathogens which requires an individual approach to both surgical treatment and drug therapy, as well as the development of new tactical approaches to therapy.

Conclusion The rate of poor outcomes was 45 %. Hypoalbuminemia and antibacterial resistance of isolates of *P. aeruginosa, K. pneumoniae, A. baumannii*, detection of the pathogens in the postoperative material, as well as the need for surgical reoperation in the early postoperative period, are risk factors for poor outcomes.

Keywords: implant-associated infection, periprosthetic joint infection, osteomyelitis, enterobacteria, *K. pneumoniae, P. aeruginosa, A. baumannii*, antibacterial therapy, fluoroquinolones, co-trimoxazole

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INTRODUCTION

As the population ages and the incidence of osteoarthritis grows, the number of large joint replacements will increase. By 2040, 2.8 million hip replacements (HRs) and one million knee replacements (KRs) are expected to be performed [1]. Although these interventions are generally successful, joint replacements can be complicated by periprosthetic joint infection (PJI) with a two-year incidence of 1.63 % for HRs and 1.55 % for KRs [2]. The incidence of fracture-associated infection (FAI) ranges from 1.8 % to 27 % and depends on the location and type of fracture [3].

In the majority of cases, implant-associated infection (IAI) develops in the first two years after joint replacement, but thereafter the risk of this complication continues to exist, and its number increases annually by 0.04–0.06 % [4]. Given the widespread growth of primary arthroplasty, the rate of revisions caused by infectious complications has also been growing.

Despite the fact that the leading causative agents of bone and joint infections, including those associated with orthopedic implants, are staphylococci, the participation of Gr(–) pathogens in the etiology, including *K. pneumoniae, P. aeruginosa, A. Baumannii*, is a prognostically unfavorable sign [5, 6]. The rate of Gr(–) bacteria in the structure of causative agents of orthopedic infection varies from 10 % to 23 % [5, 7], but the ever-increasing rate of isolation of strains with resistance to various antibiotics is particularly challenging due to the limited choice of antibacterial drugs, both at the inpatient and outpatient stages of treatment. In this regard, many authors indicate the participation of Gr(–) bacteria in the etiology of IAI as an independent factor in the possible failure of treatment in 50 % of cases of such patients [8, 9].

Currently, there are very few published scientific papers (mainly foreign ones) devoted to the study of treatment outcomes of patients with IAI caused by Gr(–) bacteria. According to researchers, risk factors in the treatment of such patients include, first of all, the wrong choice of the type of surgical intervention [10], and the key error is retention of the infected implant [8, 11, 12]. At the same time, the effectiveness of exclusively conservative therapy is only 10 % [13]. In addition, the factors of poor outcomes include female gender, detection of microbial associations, obesity [11, 12], history of repeated surgical debridements[8, 14], antibiotic resistance of the infectious agent [15], and others.

Due to the relatively small number of publications on the topic of IAI caused by Gr(–) bacteria and the complexity of treating patients with IAI, this problem requires a more detailed study.

Purpose To evaluate the influence of various factors and compare the features of the course of implant-associated infection caused by *P. aeruginosa, K. pneumoniae, A. baumannii* in patients with positive and poor treatment outcomes

MATERIALS AND METHOD

A continuous single-center retrospective study included patients diagnosed with IAI who were treated at the Department of Purulent Osteology from January 1, 2017 to December 31, 2022.

Inclusion criteria:

— Detected IAI;

— Surgical debridement in the infection focus (index surgery);

— Isolation of *P. aeruginosa, K. pneumoniae, A. baumannii* strains (both as isolated strains and in the microbial association) from one or more samples harvested for microbiological study before the intervention and in the intraoperative material (tissue biopsy, removed implant, synovial fluid).

Exclusion criteria:

— reoperation due IAI recurrence caused by *P. aeruginosa, K. pneumoniae, A. baumannii*;

— infection located exclusively within soft tissues;

— spinal IAI;

— amputation (exarticulation) performed during a sanitizing operation,

The exclusion criterion was the lack of information on the two-year outcome (including impossible telephone communication with the patient).

Patients were selected for the study using the Mikrob-2 microbiological monitoring program (2017–2020) and the Across-Engineering LIS (2021–2022) based on the analysis of the results of MBI of the biomaterial of patients treated in 2017–2022 at the Department of Purulent Osteology. Isolation of clinical strains of *P. aeruginosa, K. pneumoniae, A. baumannii* was performed in accordance with international MBI standards (Standards for microbiology investigations, UK SMI). Species identification was carried out on Microlatest panels using iEMS Reader MF (2017–2020), and since 2021 with the MALDI-TOF-MS (Matrix Assisted Laser Desorption Ionization Time of Flight Mass-Spectrometry) method using the FlexControl system. The sensitivity of isolated cultures of Gr(–) bacteria to antibacterial drugs was assessed in accordance with the EUCAST criteria (2017–2022).

After the medical records of patients who met the inclusion criteria (n = 172) had been selected, a telephone survey was conducted, during which patients were asked standard questions about whether they had had clinical or laboratory signs of recurrent infection within two years after the index surgery, and whether repeated debridement operations had been performed. In case of a patient's death, the patient's relatives were interviewed. All included patients were divided into two groups by outcomes according to the Delphi criteria [16]: positive outcome (group 1) and poor outcome (group 2). A positive outcome was absence of clinical and laboratory signs of recurrent infection and debridement surgery within two years from the date of the index surgery.

According to the inclusion and exclusion criteria, 172 individuals were included in the study.

Group 1 comprised 95 subjects (55 %), of whom 37 (22 %) did not undergo surgical interventions either due to the lack of indications or due to dissatisfaction with the quality of life. Surgical interventions, during which no data on infection were found (no growth of microorganisms was obtained during the MBI of the intraoperative material) were performed in 58 patients (34 %).

Group 2 included 78 patients (45 %), of whom 59 patients (34 %) underwent another sanitizing operation due to recurrent infection, both at our Center or at other clinics. In addition, 18 deaths (10 %) were registered in this group.

Based on the medical records and the results of a telephone survey, a database was created, which included:

— anthropometric information (age, gender, body mass index (BMI);

— anamnesis data (infection location, time since the time of the primary surgical intervention or the intervention after which the IAI developed until the manifestation of the infection, duration of the infectious process, number of debridements in the anamnesis, duration since the last debridement until the index operation);

— results of laboratory blood tests at the time of admission and before discharge from the hospital: leukocytes, ESR, CRP level, hemoglobin, total protein, albumin, creatinine;

— results of microbiological investigation (MBI) of biomaterial samples (fistula biopsies, synovial fluid, wound discharge, tissue biopsies, removed implants, hematoma) obtained in the pre-, intra- and postoperative periods;

— type of surgical intervention, its duration, intraoperative blood loss, volume of drained discharge;

— medication therapy at the inpatient (antibacterial therapy (ABT), intravenous infusion of albumin, iron preparations) and outpatient stages;

— re-debridement or its absence in the early postoperative period after the index operation;

— retained implant at the time of discharge from hospital.

The obtained data were recorded in the form of spreadsheets in MS Office Excel, 2007 (Microsoft, USA); the data structure was visualized and analyzed using IBM SPSS STATISTICS (version 26). Quantitative indicators were assessed for compliance with the normal distribution using the Kolmogorov – Smirnov test. In the absence of a normal distribution, quantitative data were described using the median (Me) and the lower and upper quartiles (Q1–Q3). Categorical data were described indicating absolute values and percentages. Comparison of two groups by a quantitative indicator whose distribution differed from normal was performed using the Mann–Whitney U test. To assess the risk in the comparison groups, the odds ratio (OR, 95 % CI) was calculated. Comparison of percentages in the analysis of four-field contingency tables was performed using the Pearson chi-square (χ^2) test (for expected event values greater than 10) or the Fisher exact test (for expected event values less than 10); the relationship was assessed using the Cramer test. Differences in indicators between groups were considered statistically significant at $p < 0.05$.

RESULTS

Anthropometric and anatomical data

The analyzed groups were comparable by gender, age and BMI (Table 1). The dominant IAI location were the joints and bones of the lower limb (*n* = 164, 95 %) in the area of the hip joint (*n* = 94, 55 %) or knee joint (*n* = 33, 19 %). No statistically significant impact of infection location on the outcome of treatment was found (*p* = 0.948).

Table 1

Comparison of groups in gender, age and BMI

Factors	Group 1, *n* = 95	Group 2, *n* = 77	*p*
Males, *n* (%)	47 (49)	33 (43)	*p* = 0.443
Age, years, Me [IQR]	63.0 [49.0–68.0]	58.0 [45.0–66.0]	*p* = 0.114
BMI, weight/height W/H^2, Me [IQR]	27.5 [24.2–31.6]	27.8 [23.7–33.0]	*p* = 0.838

Table 2

Comparison of groups in IAI history

Factors	Me [IQR]		*p*
	Group 1, *n* = 95	Group 2, *n* = 77	
Interval between implant installation* and infection manifestation (days)	153.5 [30–1247]	95 [23–730]	*p* = 0,331
Duration of infection (days)	610 [161–1410]	493 [121–1226]	*p* = 0,345
Interval between previous and index debridement (days)	241 [81–862]	135 [28–455]	*p* = 0,095

Note: * — after primary and revision surgeries

Despite the lack of statistical significance, the manifestation of infection or its relapse developed earlier in group 2 patients, and the duration of the infectious process was shorter than in the comparison group (Table 2).

The proportion of patients with the first debridement intervention was 24 % in group 1 and 14 % in group 2, and two or more debridements in the anamnesis were performed in 40 % and 52 % of patients, respectively (*p* = 0.173). The median number of debridements in the anamnesis was 1 [1.2] in the group with positive outcomes and 2 [1.3] in the comparison group (*p* = 0.112).

Laboratory findings

Table 3

Results of laboratory tests before surgery and before discharge from hospital

Parameter		Me [IQR]		*p*
		Group 1, *n* = 95	Group 2, *n* = 77	
Before surgery	Leucocytes, 10^9/l	7.6 [6.5–9.7]	8.3 [6.0–9.9]	*p* = 0.625
	ESR, mm/h	44 [26–63]	53 [29.5–63]	*p* = 0.430
	CRP, mg/l	25 [10.5–40]	33 [9–75]	*p* = 0.121
	Hemoglobin g/l	117 [104–131]	111 [97.5–132]	*p* = 0.246
	Albumin g/l	**40 [35.5–43]**	**35 [33–43]**	***p* = 0.068**
Before discharge from the hospital	Leucocytes, 10^9/l	6.6 [5.7–8,2]	6.8 [5.2–8.0]	*p* = 0.749
	ESR, mm/h	35 [22–52.5]	39 [22–55.5]	*p* = 0.926
	CRP, mg/l	23.5 [12–42]	25.5 [13–52]	*p* = 0.284
	Hemoglobin g/l	99 [95–114.5]	100 [91–108.5]	*p* = 0.250
	Albumin g/l	**34 [32–41]**	**32 [28–35]**	***p* = 0.002***

On admission, patients in Group 2 tended to have higher levels of inflammation (white blood cell count, CRP, and ESR) and lower levels of hemoglobin and albumin, with no significant differences between the groups (Table 3). Before discharge, laboratory test results were similar in both groups and reflected the normal course of the postoperative period. It is worth noting that there was a statistically significant increase in albuminuria in the patients with poor outcome ($p = 0.002$).

Features of surgical intervention

In the studied cohort of patients, the most common types of surgical intervention were the installation of an antimicrobial spacer ($n = 112$, 65 %), resection arthroplasty with muscle grafting ($n = 16$, 9 %), and revision surgery with implant retention ($n = 11$, 6 %). However the type of surgical intervention did not have a significant impact on the outcome ($p = 0.487$). To fabricate the antimicrobial spacer, gentamicin-containing bone cement was used, which was additionally impregnated with a heat-stable antibacterial drug at a dose of 4 g per 40 g of cement. In this type of surgical intervention, vancomycin was added to the bone cement in 53 % of cases, meropenem in 15 %, and fosfomycin in 10 %. Moreover, only in 23 % of cases was the antibiotic active against the microorganism isolated from the intraoperative material.

The volume of intraoperative blood loss was Me: 600 [400–800] ml, there were no statistically significant differences in the groups for this parameter ($p = 0.133$). In group 1, drainage blood loss was slightly lower than in group 2: 450 [340–600] and 500 [380–750] ml, respectively ($p = 0.091$).

MB findings

According to the MBI results of the biomaterial, K. pneumoniae was isolated in 55 % of cases, *A. baumannii* in 18 % and in 27 % of cases it was *P. aeruginosa*. The distribution of isolated cultures in the compared groups is shown in Fig. 1.

K. pneumoniae in group 2 as the causative agent of IAI was 1.3 times more frequent and *P. aeruginosa* was 1.7 times less frequent but there were no significant differences between the groups ($p = 0.097$).

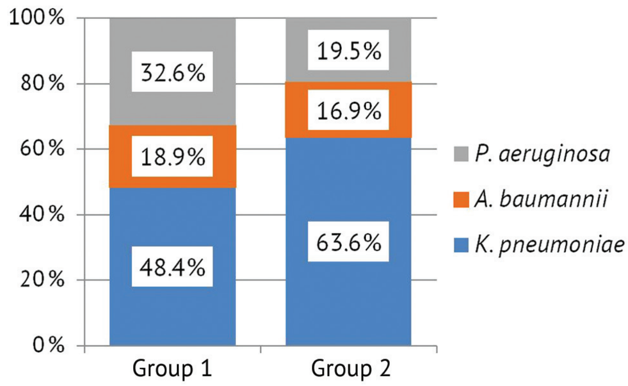

Fig. 1 Distribution of patients in the groups according to the isolated microbes detected

At the preoperative stage, the microbiological study of the biomaterial from the implantation area, monocultures of *K. pneumoniae, A. baumannii* or *P. aeruginosa* were isolated in 58 % of cases. However, no statistically significant impact of the infection etiology, the information about which was obtained at the preoperative stage, on the treatment outcome was found ($p = 0.895$). *K. pneumoniae, A. baumannii* or *P. aeruginosa* were also isolated from other loci in 9.3 % of cases (urine — 7.6 %, blood — 0.6 %, sputum — 0.6 %), which indicates the potential hematogenous spread of the causative IAI agent.

In 94 % of cases ($n = 172$), the pathogen was isolated from intraoperative tissue biopsies. Despite the absence of statistically significant differences between the groups ($p = 0.192$), it is noteworthy that the median number of tissue biopsies from which the microorganism was isolated was 4 [2–5] in group 1 and 5 [3–5] in group 2. *K. pneumoniae, A. baumannii*, or *P. aeruginosa* strains were isolated from the material on the implant surface in 73 % of cases.

The incidence of polymicrobial infection in the compared groups did not differ and was 66 % and 69 %, respectively, in groups 1 and 2 ($p = 0.871$) (Table 4). In both groups, the microbial associations with the leading Gr(−) pathogens also contained Gr(+) bacteria without significant impact of the composition on the treatment outcome ($p = 0.570$).

Table 4

Microbial associations detected in the biomaterial of the patients in the compared groups

Состав микробных ассоциации	Группа 1, *n* = 63		Группа 2, *n* = 53	
	n	%	*n*	%
Contains only Gr(−) bacteria, including *E. coli, Enterobacter spp.* and others	9	14	5	9
Contains only Gr(+) bacteria, including *S. aureus, S. epidermidis* and others	54	86	48	91

The proportion of patients in whom isolated strains of *P. aeruginosa, K. pneumoniae, A. baumannii* were sensitive to fluoroquinolones was 5.25 times higher in group 1 than in group 2, while the proportion of patients with extremely resistant strains, on the contrary, was 1.3 times higher in group 2 (Fig. 2). At the same time, a statistically significant impact of sensitivity to antibacterial drugs on the outcome was observed ($p = 0.011$, Cramer's V = 0.254).

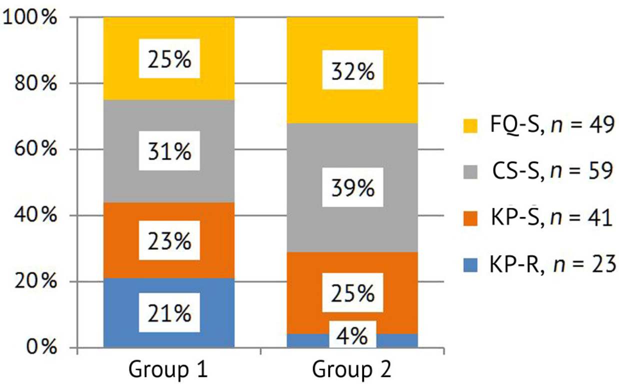

Fig. 2 Analysis of sensitivity of Gr(−) strains to the main antibacterial drugs in comparison groups. Strains: FQ-S — fluoroquinolone-sensitive, CS-S — sensitive to cephalosporins, but resistant to fluoroquinolones, KP-S — sensitive to carbapenems, but resistant to fluoroquinolones and cephalosporins, KP-R — carbapenem-resistant

Postoperative period

Systemic antibacterial therapy was administered to all patients. In 10 % of cases, it was necessary to start antibacterial therapy before the ndex surgery due to either a life-threatening septic condition or a previous sanitizing surgical intervention. Empirical antibacterial therapy with vancomycin and with the fluoroquinolone group agent (cipro- or levofloxacin) from the day of surgery was received by 9 % of patients, and with vancomycin and cefoperazone-sulbactam by 29 %. In the rest of the cases, antibacterial therapy was prescribed based on the results of preoperative cultures. Etiotropic antibacterial therapy from the day of surgery was prescribed to 61 % of patients, while this did not have a statistical impact on the outcome ($p = 0.120$). A tendency towards a shorter inpatient course of antibacterial therapy was noted in the patients of group 1 compared to group 2: 13 [10–15] and 16 [11–24] ($p = 0.096$), respectively.

In 86 % of cases, oral antibacterial drugs were prescribed at the outpatient stage. Among patients with these recommendations, adverse outcomes were somewhat less common (*p* = 0.077, OR 0.443, 95 % CI: 0.178–1.052). At the outpatient stage, fluoroquinolones were recommended in 55 % of cases, co-trimoxazole in 13 %, and both fluoroquinolones and co-trimoxazole in 9 %. Despite the fact that the very fact of prescribing these drugs did not have a statistically significant impact on the outcome (*p* = 0.446, *p* = 0.665 and *p* = 0.300, respectively), it was confirmed that in the case where the isolated microorganism was sensitive to the drug prescribed at the outpatient stage, the probability of a positive outcome increased significantly (*p* = 0.001) by 7.87 times (95 % CI: 2.26–27.03).

Patients in group 2, compared to group 1, required the administration of albumin solution infusion (26 % and 2 % of cases, *p* = 0.003) and iron preparations (27 % and 15 % of cases, *p* = 0.056) more frequently. Moreover, the duration of prescribed symptomatic therapy in group 2 was also longer (Table 5).

Table 5

Frequency of administration of drugs for symptomatic therapy

Infusion	Me [IQR]		*p*
	Group 1, *n* = 63	Group 2, *n* = 53	
Abumin solution	5.0 [5.0–5.0]	10.0 [5.0–11.0]	*p* = 0.101
Iron preparations	4.0 [3.0–5.0]	5.0 [5.0–10.0]	*p* = 0.286

In the postoperative period, 40 patients (23 %) showed a re-growth of the studied pathogens in the intraoperative material, hematoma contents or wound discharge, which increased the risk of an unfavorable outcome in the future by 3.4 times (95 % CI 1.61–7.2; *p* = 0.001). Revision surgery in the early postoperative period was required in 38 cases (22 %), which increased the likelihood of an unfavorable outcome in the future by 4.86 times (95 % CI 2.18–10.84; *p* = 0.001), of which postoperative wound debridement was performed in 19 patients (10.9 %), implant removal and muscle grafting in 8 patients (4.6 %), antimicrobial spacer reinsertion in 7 patients (4 %), implant removal in 3 cases (1.7 %) and arthrodesis in one (0.6 %) patient. Finally, at the time of discharge, reimplantation was used in 133 patients (77 %); however, the insertion of a new implant did not have a statistically significant impact on the likelihood of a poor outcome (*p* = 0.101).

DISCUSSION

Gr(–) microorganisms *K. pneumoniae, P. aeruginosa* and *A. baumannii* belong to a group of frequently encountered pathogens that are highly resistant to antibiotics, designated by the Infectious Diseases Society of America as “ESKAPE pathogens”. According to the WHO, the representatives of these species are classified as pathogens with a critically high priority level [17]. *K. pneumoniae, P. aeruginosa* and *A. baumannii* are characterized by the presence of a certain set of pathogenicity and persistence factors, including the ability to form biofilms and internalize into eukaryotic cells, including osteoblasts [18]. As the diversity of resistant strains steadily increases, the frequency of their spread not only among patients but also among the population increases, which causes high alertness among clinicians and the healthcare system [19].

Carbapenem-resistant enterobacterales (CRE) are of particular importance due to their high resistance to antibiotics, including broad-spectrum antibiotics [20]. According to the 2019 report of the Centers for Diseases Control, from 2012 to 2017, 210,500 cases of infections caused by Enterobacterales, producing broad-spectrum beta-lactamase or carbapenemases, were registered in the United States, resulting in 12,900 deaths annually [21]. The global spread of CRE pathogens is rapid, which restricts the choice of antimicrobial drugs during the infectious process to polymyxins, tigecycline, aminoglycosides, and in some cases high doses of carbapenems. However, these drugs may not be effective enough and cause many adverse reactions [22]. In addition, the resistance ability in these pathogens to beta-lactams and fluoroquinolones makes it impossible to prescribe prolonged etiotropic antibacterial therapy, which is standard for the treatment of bone and joint infections, due to the lack of other oral drugs active against Gr(–) pathogens.

Despite the low rates of IAI caused by Gr(–) pathogens [7], the treatment outcomes of such patients are significantly worse. In addition to rifampicin-resistant staphylococci and fluconazole-resistant *Candida* fungi, Gr(–) microorganisms resistant to fluoroquinolones are also classified as pathogens causing PJI that is difficult-to-treat (DTT), and for which a higher recurrence rate has been proven, requiring repeated sanitizing surgical interventions [23].

The results of a number of studies demonstrate that Gr(–) etiology of IAI is an independent predictor of poor outcome [8, 9, 12]. Thus, Kalbian et al. observed poor treatment results in patients with PJI caused by Gr(–) microorganisms and associations of Gr(–) and Gr(+) bacteria more frequently, compared to infection caused exclusively by Gr(+) pathogens (OR = 2.9, $p < 0.0001$; OR = 2.5, $p = 0.013$, respectively) [24]. And a meta-analysis showed that IAI caused by microbial associations involving Gr(–) bacteria caused treatment failures more frequently compared to monobacterial infection [12]. In our sample, the majority of IAI cases (67 %) were caused by bacterial associations, while the proportion of patients with poor outcomes after a two-year follow-up period was 45 %, which generally confirms global trends. Also, our cohort had a high mortality rate of 10 %, which is significantly higher than among patients with IAI that did not consider the etiology of the infectious process, about 3 % during the first year [25]. Depending on the type of Gr(–) pathogen involved in the IAI etiology, the rate of positive treatment outcome was 65 % for *P. aeruginosa*, 58 % or *A. baumannii* and 48 % for *K. pneumoniae*. No significant effect of the composition of microbial associations on the outcome of complex treatment was found ($p = 0.871$).

In our study, the groups were comparable in terms of gender, age, and BMI regardless of the treatment outcome. The data in scientific publications on this issue vary. Some authors claim that these parameters do not differ in groups with positive and poor outcomes [26], others believe that female gender and obesity are risk factors for failed outcomes [12], and others indicate old age as a predictor of poor outcome [15]. Hsieh et al. conducted a study of 346 patients and compared the influence of various factors on the course of IAI caused by Gr(+) and Gr(–) microorganisms. The authors concluded that patients with IAI caused by Gr(–) microorganisms were older (mean age 68 years versus 59 years; $p < 0.001$), and the period from primary JR to the manifestation of the infectious process was shorter (74 days versus 109 days; $p < 0.001$) [27].

IAI caused by Gr(–) bacteria frequently has a long and wave-like course, combining periods of exacerbations requiring surgical intervention and antibacterial therapy, and remission. In our study, the duration of the infectious process in both groups was more than a year and did not differ significantly. The time interval from the day of surgery to the manifestation of infection and from the last debridement operation to the index operation was slightly shorter in the group of poor outcomes ($p = 0.331$ and $p = 0.095$, respectively). According to a meta-analysis of 11 clinical studies, including 593 patients with PJI caused by Gr(–) pathogens, acute infection had a more unfavorable course compared to chronic infection: the success rate after two-stage treatment was 66 % and 75 %, respectively, at a two-year follow-up [12]. Moreover, it was found that treatment outcomes when the infection was localized in the knee joint were significantly worse than in the hip joint (35 % versus 15 %, $p = 0.002$, respectively). In our study, these indicators did not differ: when the IAI was localized in the hip joint the failure outcome was 37 %, and in the knee joint 39 %.

Pfang et al. concluded that a history of a large number of debridement operations is an independent predictor of an poor outcome of IAI caused by species of the enterobacteria family [8]. Our previous study of the outcomes of IAI caused only by *K. pneumoniae* obtained similar results [14]. In the current study, no significant intergroup differences ($p = 0.112$) were found in the number of previously performed debridements, while in group 2 there were 30 % more patients with a history of two or more redebridements.

The levels of laboratory markers of inflammation in the studied groups were comparable in the pre- and postoperative periods. However, patients in group 2 showed a tendency toward more pronounced hypoalbuminemia upon admission, the level of which by the time of discharge was significantly different from group 1 ($p = 0.002$), despite the fact that they received albumin solution infusions more often ($p = 0.002$) and for a longer period ($p = 0.101$) after the operation. The obtained results are consistent with the data of Scarcella et al., who found that patients with reduced albumin levels were more likely to develop infection recurrence. The authors believe that a significant role in the development of hypoalbuminemia is played by chronic inflammation resulting in immunosuppression, which, in turn, complicates the elimination of the infectious process itself, closing this vicious circle [28]. In addition, hypoalbuminemia decreases the effectiveness of antibacterial therapy by reducing the amount of transport proteins. As a result, the fraction of the antibiotic unbound to albumin increases in the blood, which increases the risk of adverse reactions due to decreased antibacterial activity of the drug [29]. Thus, both foreign and domestic authors come to the conclusion that hypoalbuminemia increases the risk of infectious complications after orthopedic interventions. This allows us to consider this symptom as an independent predictor of failure of complex IAI treatment [30, 31]. Another possible predictor of failed outcomes in infectious diseases, including IAI, is considered to be anemia [32]. In our study, the need for intravenous iron preparations was also more frequently observed among the patients in group 2 ($p = 0.056$).

We have established a significant ($p = 0.011$, Cramer's V = 0.254) impact of the sensitivity of the isolated microorganisms to the tested antibacterial drugs on the outcome of complex treatment. Among patients in whom the etiology of IAI was strains of Gr(–) microorganisms sensitive to fluoroquinolones, there was the highest rate of successful outcomes — 87 %. And among patients in whom Gr(–) bacteria resistant to fluoroquinolones and cephalosporins and microorganisms with extreme resistance were isolated, the rate of positive outcomes was 49.2 and 49 %, respectively. Similar results were shown by Fantoni et al., whose study reported successful results of treatment in the patients with infection caused by carbapenem-resistant strains of Gr(–) microorganisms in only 50 % of cases [13].

The choice of drugs for ABT, both at the inpatient and outpatient stages, is the cornerstone in the treatment of patients with IAI caused by Gr(–) pathogens. The basis of ABT is considered to be parenteral administration of predominantly bactericidal antibiotics for 7–14 days from the day of surgery, followed by a transition to oral drugs up to 6–8 weeks after each stage of surgical treatment [33] or up to three months after a single-stage intervention [34]. All patients included in our study received systemic ABT with at least two drugs. Therapy was considered etiotropic if the strain of microorganism isolated was sensitive to at least one antibiotic received. Etiotropic ABT from the day of surgery, that considered the results of MBI of preoperative biomaterials, was received by 61 % of patients included in the study. Moreover, the median duration of ABT at the inpatient stage in group 2 was slightly longer than in group 1: 16 [11–24] and 13 [10–15] days, respectively ($p = 0.096$), which was due to a more frequent need to perform revision of the postoperative wound or impossibility of changing to etiotropic oral ABT of patients in group 2.

The small number of oral antibiotics active against the studied pathogens determines the difficulties in carrying out a prolonged etiotropic therapy in specialized patients. The choice of drugs is limited to the fluoroquinolone class and co-trimoxazole. Fluoroquinolones have the advantage of antibiofilm activity, good penetration into bone tissue and relatively good tolerability [35]. In the study by Rodríguez-Pardo et al., which included 242 patients with IAI, the rate of fluoroquinolone-sensitive isolates of Gr(–) bacteria was 81 %, which, when performing revision with implant retention and prescribing long-term etiotropic oral therapy, arrested infection in 79 % of cases observed at a two-year follow-up [36]. In our study, there was a similar group of patients that had the highest rate of success (87 %), which confirms the significant impact of pathogen sensitivity to antibiotics on treatment outcomes ($p = 0.011$). However, the high level of resistance of Gr(–) microorganisms to antibiotics of this group greatly limits the possibilities of their use [37]. In the sample we studied, 87 % of pathogens were resistant to fluoroquinolones, that, according to scientific publications, affects treatment outcomes for such patients [36].

To date, the question remains open as to whether it is advisable to prescribe fluoroquinolones at the outpatient stage of treatment if the isolates obtained are not sensitive to them. We have not found any studies on the efficacy of fluoroquinolone monotherapy for the treatment of infections caused by strains resistant to them. Grossi et al. showed that additional administration of fluoroquinolones to prolonged beta-lactam infusion throughout the entire treatment period (median 90 days) did not have an effect on the outcome of treatment of patients with IAI caused by strains resistant to fluoroquinolones [26]. In another study, 28 specialized patients received combination therapy with cefepime and fluoroquinolone after debridement. The efficacy over a two-year follow-up was 79 %, but the study did not analyze the effect of each antibiotic separately [38]. In our study, we did not obtain significant differences ($p = 0.446$) in the effectiveness of treatment depending on the presence or absence of a drug from the fluoroquinolone group in the extended antibiotic therapy in case of pathogen resistance to them.

Another drug that is theoretically active against the leading Gr(–) pathogens in orthopedic infection, with the exception of *P. aeruginosa*, which is naturally resistant to the drug, is co-trimoxazole. The antibiotic has a bactericidal effect and is able to penetrate into bone tissue [39]. However, co-trimoxazole does not have antibiofilm activity and about 70 % of *K. pneumoniae* and *A. baumannii* strains are resistant to it [37, 40]. Cisse et al. showed that the use of a combination of fluoroquinolones and co-trimoxazole for 8–12 weeks after surgical debridement in 30 patients with IAI caused by *E. cloacae* was effective in 80 % of cases [41]. The efficacy of co-trimoxazole in IAI caused by other Gr(–) pathogens has not yet been studied. In our study, the administration of co-trimoxazole or fluoroquinolone in the presence of sensitivity to them of isolates isolated from the patient statistically significantly ($p = 0.001$) increased the probability of a favorable outcome by 7.87 times (95 % CI 2.26–27.03), which once again confirms the critical role of antibiotic resistance in predicting the outcome of IAI treatment.

Revision of the surgical intervention area in the early postoperative period was required in every fifth patient, which increased the risk of a poor outcome by 4.86 times (95 % CI 2.18–10.84). Moreover, growth of Gr(–) bacteria in the early postoperative period increased the probability of poor outcomes by 3.4 times (95 % CI 1.61–7.21) (Cramer's V = 0.252). Culture isolation was recorded in 23 % of patients. In most cases, it was isolated from the intraoperative material during revision surgery, less frequently from a hematoma or wound discharge.

It is known that surgery with retention of the infected implant often leads to recurrence of IAI [8, 15]. In our study, in the majority of cases, the index surgery included complete removal or replacement of the infected implant with a new one. In the study sample, 77 % of patients were discharged with exchanged implants, most often antimicrobial spacers. As a result, we did not observe a significant impact of the presence of metal implants on the treatment outcome ($p = 0.101$).

CONCLUSION

Complex treatment of IAI caused by Gr(–) bacteria results in failure in 45 % of cases at a two-year follow-up, including a 10 % mortality rate. The leading gram-negative pathogens in most cases are found in mixed microbial associations with Gr(+) bacteria. IAI of this etiology is characterized by a long recurrent course. Significant risk factors for poor outcome within two years after the debridement operation are hypoalbuminemia, both initial and in the postoperative period, and early revision of the postoperative wound associated with positive growth of the pathogen from the biomaterial obtained from the surgical intervention area. Moreover, the prognosis in such patients is significantly influenced by the sensitivity of isolated Gr(–) pathogens to antibacterial drugs, which is of particular concern due to widespread growth of antibacterial resistance and requires the development of new tactical approaches to treatment.

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