Genij Ortopedii. 2023;29(4):402-409.

Original article

https://doi.org/10.18019/1028-4427-2023-29-4-402-409

The role of culture-negative infection among infectious complications after total knee arthroplasty

L.V. Lyubimova[1]✉, S.A. Bozhkova[2], N.N. Pchelova[1], E.V. Preobrazhenskaya[1], E.A. Lyubimov[1]

[1] Federal Center for Traumatology, Orthopedics and Arthroplasty, Cheboksary, Russian Federation
[2] Vreden National Medical Research Center of Traumatology and Orthopedics, Saint-Petersburg, Russian Federation

Corresponding author: Lyudmila V. Lyubimova, borisova-80@mail.ru

Abstract

Introduction Diagnosis of chronic periprosthetic joint infection (PJI) is difficult with the clinical signs of periprosthetic inflammation showing no growth of microorganism in the biomaterial. The frequency of culture-negative infection can reach 42.1 %. The objective of the study was to analyze outcomes of two-stage treatment of chronic PJI of the knee joint depending on the etiology of the infectious process. **Material and methods** A retrospective analysis of outcomes was produced for 103 patients: group I (n=30) showing no growth of microorganisms and group II (n = 73) demonstrating positive growth of pathogens. Knee PJI was diagnosed according to the 2018 ICM criteria. A favorable outcome suggested absence of recurrence for at least two years after reimplantation of endoprosthesis, arthrodesis, "life with a spacer" without signs of infection. **Results** Culture-negative infection was detected in 29.1 % (n = 30). Patients in the group were 1.5 times more likely to receive antibiotic therapy prior to admission and had average levels of CRP, ESR and articular leukocyte count being 1.5-2 times less than those in group II. Staphylococci (69.8 %) including MRSE (75 %) was the leading pathogen in group II. Recurrence of infection was 3.4 % in group I and 16.9 % in group II (p = 0.0928), the two-stage treatment was successful in 96.7 % and 74 %, respectively (p = 0.0064). **Discussion** Causes for the lack of growth of microorganisms in biological materials included previous antibiotic therapy, wound drainage, violations of the rules for sampling of biological material, absence of media for the growth of atypical microorganisms and the ability of microorganisms to form biofilms on implant surfaces. An emergency histological examination of the affected tissues was practical during surgery in doubtful situations for adequate surgical approach. The results of a meta-analysis (2023) showed that the replacement of an infected endoprosthesis was more effective for the treatment of a culture-negative infection compared to debridement and preservation of implant. **Conclusion** The culture-negative infection group in our series showed better success rate of a two-stage treatment of PJI using implant replacement and broad-spectrum empiric antibiotic therapy at a two-year follow-up period. The negative microbiological result in the group could be caused by antibacterial drugs administered prior to diagnosis of PJI.

Keywords: periprosthetic joint infection, culture-negative infection, culture-positive infection, revision arthroplasty, inflammation markers, knee joint

For citation: Lyubimova L.V., Bozhkova S.A., Pchelova N.N., Preobrazhenskaya E.V., Lyubimov E.A. The role of culture-negative infection among infectious complications after total knee arthroplasty. *Genij Ortopedii*. 2023;29(4):402-409. doi: 10.18019/1028-4427-2023-29-4-402-409

INTRODUCTION

Diagnosis of chronic periprosthetic joint infection (PJI) does not cause difficulties in the presence of wound dehiscence, sinous tract communicating with the joint space or prosthesis, phenotypically identical microorganisms isolated from two or more samples of biological material in combination with clinical and laboratory signs of inflammation. However, in some cases, the clinical presentation of prosthetic joint infection is not confirmed by the growth of the microorganism in the biological material. The infection is called culture-negative with the prevalence ranging from 7 to 42.1 % [1-4]. A particular interest in culture-negative infection (CNI) is associated with the problems of pathogen verification, selection and duration of antibiotic therapy.

The results of treatment of infection depending on the presence or absence of the pathogen growth are controversial. Mortazavi S.M. et al. (2011) reported the incidence of recurrence after two-stage reimplantation was 4.5 times greater in the CNI group as compared with cases of PJI treatment in patients with an established etiology of the infectious process [5]. However, in their systematic review, M. Reisener, C. Perka (2018) concluded that CNI PJI had the same or even better outcomes than culture-positive infection. The rate of succesfully treated infections varied from 85 % to 95 % in all included studies. The two-stage exchange arthroplasty had the best outcome, based on the infection-free survival rate of 95 %, five years after treatment. [1]. Choi H.R. et al. (2013) reported higher success rate of infection control in the culture-negative group (p = 0.006, n = 40) in comparison with positive culture results (n = 135) [6]. By contrast, Huang R., Hu C.C. (2012) reported no differences in outcomes for both types of PJI.

The authors retrospectively analyzed 55 cases of CNI and 295 cases of culture-positive infection (CPI) and found an overall infection control rate in both groups beings 73 % at minimum 1-year followup after two-stage exchange arthroplasty and postoperative vancomycin therapy [7]. The conflicting data on the outcomes of culture-negative PJI and the lack of domestic publications on the topic were the reason for this study.

The **objective** was to conduct a comparative analysis of the outcomes of two-stage treatment of PJI of the knee joint, depending on the known or unknown etiology of the infectious process.

MATERIAL AND METHODS

Outcomes of 103 patients with chronic PJI after primary or revision total knee arthroplasty were retrospectively reviewed berween 2017 and 2021 based on data from the medical information system. The study included patients who underwent the first stage of a two-stage treatment with the removal of the prosthesis and placement of a spacer impregnated with an antibiotic. A diagnosis of PJI relied on the criteria developed by the 2018 International Consensus Meeting (ICM) [8]. Synovial fluid culture yielded no growth of pathogenic bacteria in 35 cases out of 103 outpatients with PJI.

Positive growth of microorganisms with intraoperative biological material was seen in 5 cases out of 35 inpatients. The cases were divided into two groups. Group I (n = 30) included cases of PJI with no growth of microflora (CNI), group II (n = 73) consisted of cases with a positive growth of pathogens (CPI) in synovial fluid sample by preoperative aspiration, surgical specimens of tissue biopsy and/or swabs from the construct removed. Patients were examined by gender, age, proportion of patients with systemic conditions and BMI (Table 1).

A synovial fluid sample was collected from the knee joint in a sterile syringe under aseptic conditions without the use of local anesthetics. Delivery of the biomaterial was performed within 05-60 minutes. A quantitative calculation of the cellular composition with differentiation of leukocytes was produced in the laboratory and the punctate was bacteriologically examined. The aspirate was added to the aerobic and anaerobic vials of the Bact/Alert 3D analyzer. With the punctate volume being less than 1 ml, inoculation was produced in pediatric analyzer bottles or in broths prepared in a routine way.

Reseeding on solid nutrient media (Columbian, chocolate, Shedler, Saburo agars) was performed with culture growth detected in analyzer vials or broth after 5-10 days. To isolate microorganisms from microbial biofilms, the prosthetic components obtained intraoperatively were processed in a BRANSON 8510 ultrasound machine (USA) for 5 min. at a frequency of 40 ± 2 kHz, followed by inoculation of swabs on nutrient media and on analyzer flasks. The cultures were incubated for 14 days creating conditions for the culturing aerobes, anaerobes, capnophiles and fungi. Species identification of pathogens and sensitivity was performed using an automatic bacteriological analyzer Vitec 2-compact (Bio Merieux, France) and semi-automatic analyzer Multiskan FC [9].

The duration of antibiotic therapy at the stage of debridement and reimplantation was at least 6 weeks (2 weeks intravenously, 4 weeks orally). CPI patients received etiotropic therapy and CNI patients received empiric antibiotic therapy (vancomycin and cefoperazone/sulbactam administered intravenously for 2 weeks, levofloxacin orally for 4 weeks at the stage of debridement and the therapy was combined with rifampicin after reimplantation) [10]. The database was based on medical records including:

– concomitant pathology (systemic diseases);

– the history of previous treatments of PJI including courses of antibacterial drugs;

– signs of generalized infection: septicemia, multiple organ failure, fever;

– local manifestations of edema, hyperemia, hyperthermia, fistula on admission to the first stage of debridement including individual symptoms and in combination.

Table 1

Characteristics of patients in the groups

		Group I, abs. number (%)	Group II, abs. number (%)	P < 0.05
Age, years		66.1 (95 % CI: 62.6-69.2)	64.1 (95 % CI: 62.3-65.6)	0.2251
Gender	male	7 (23.3)	28 (38.4)	0.1737
	female	23 (76.7)	45 (61.6)	
BMI (kg/m^2)		32.9 (95 % CI: 30.9-34.1)	32.9 ± 5.2 (95 % CI:31.7-34.0)	0.9116
Patients receiving antibiotic therapy before admission, %		16 (53.3)	26 (35.6)	0.1845
Systemic diseases (rheumatoid arthritis, undifferentiated arthritis)		3 (10.0)	9 (12.3)	1.0000

Laboratory blood tests (leukocyte count, ESR, CRP and D-dimer), articular aspirate (leukocyte count, stab neutrophils (SNF), bacteriological examinations (from 1 to 3 consecutive samples of joint fluid taken preoperatively, intraoperative biopsy specimens, joint fluid if any, swabs from metal constructs removed) were evaluated. I n 3 cases in group I and in 9 cases in group II, the results of a Sterility blood test was performed for 3 patients of Group I and 9 patients of Group II with signs of a systemic inflammatory reaction with increased blood procalcitonin over 1.0 ng/ml. Effective debridement suggested absence of clinical and laboratory signs of an infectious and inflammatory process at the time of admission to the second stage of treatment. A favorable outcome of the two-stage treatment suggested no recurrence of PJI for at least 2 years after implantation of the prosthesis or arthrodesis or "life with a spacer" without signs of infection.

Statistical methods. The data were recorded in the form of spreadsheets, the visualization of the data structure and analyzed using the MS Office Excel, 2007 software (Microsoft, USA) and the Graf Pad program. A normality test using the Kolmogorov-Smirnov criterion was performed to determine quantitative parameters. The mean and standard deviation with 95 % CI were used to describe a parameter with a normal distribution. The Mann–Whitney test was employed to compare quantitative parameters between the groups. Categorical data (gender, type of PJI, outcome) were described using conditional codes of categories that could not be measured and were not subject to ranking. Fisher's exact test was used to assess the effectiveness of the treatment in the groups. Differences in the parameters between groups were considered statistically significant at $p < 0.05$.

RESULTS

The proportion of CNI in the sample was 29.1 % (n = 30). Despite the absence of statistically significant differences (p = 0.1845), patients with negative cultures were 1.5 greater more those in group II receiving antibiotic therapy at the preadmission stage. PJI developed in 93.3 % (n = 28) in group I and in 87.7 % (n = 64) in group II (p = 0.5025) after primary TJR. The rest of the patients developed the complication after revision procedures for non-infectious causes. The diagnosis of PJI was confirmed (Fig. 1) in 98.6 % of patients in group II and in 76.7 % in group I (p = 0.0006) using the ICM diagnostic criteria (2018). The data for the diagnosis of PJI were not demonstrative (n = 6) or negated an infectious process (n = 1) in another 23.3 % of cases with CNI. There was 1.4 % (n = 1) of such cases in the comparison group.

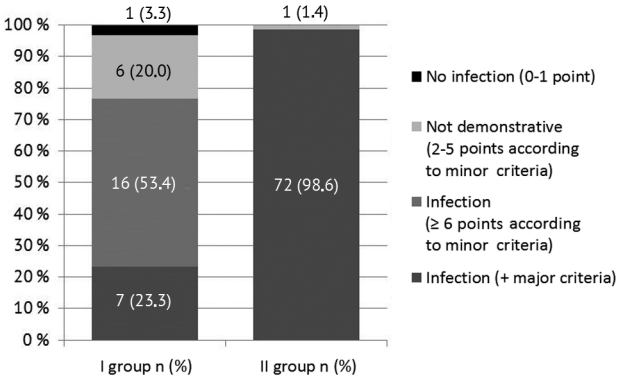

Fig. 1 PJI detected with ICM diagnostic criteria (2018)

The clinical presentation of PJI was comparable in both study groups. All patients included in the study had pain. Edema and hyperemia were observed in 51.8 % and 43.9 % of cases in group I and in group II, respectively. The fistulous form of PJI was diagnosed in 22.2 % group I and in 26.8 % of cases group II; general hyperthermia up to febrile numbers was observed in 48.1 % and 53.7 % of patients in group I and in group II, respectively. Septicemia was detected in 2 out of 9 cases in group II and there was no positive growth in blood culture among 3 patients in group I (p = 1.0000). Patients of both groups showed increased levels of inflammatory markers in the preoperative period (Table 2). The level of blood CRP, ESR and leukocyte count in the synovial fluid in patients of group II were statistically higher than those in group I ($p < 0.05$).

According to the ICM diagnostic algorithm (2018), 23.3 % (n = 7) of patients with CNI scored less than 5 points at the time of admission with laboratory markers of inflammation being lower than the reference values, and the average parameters were significantly lower than in patients with verified PJI (Table 3). However, radiological signs of early instability of the implant with pronounced osteolysis, resorption, R-lucency were revealed in these cases.

Staphylococci (69.8 %) were the leading pathogen among causative CPIs. Although no MRSA strains were isolated in the cases, a high proportion of MRSE was identified in the total number of coagulase-negative staphylococci (Fig. 2).

The species of gram-negative microorganisms were presented in the form of a monoculture of *E. coli*, *Achromobacter xylosoxidans, Burkholderia cepacia, Enterobacter cloacae*, in microbial associations – *Acinetobacter baumannii*.

Table 2

Preoperative laboratory measurements in groups

Parameter			Group I (n = 30)	Group II (n = 73)	p
Blood serum	ESR (mm/h)		45.9 ± 26.7	64.2 ± 29.2	0.0029
	SRP (mg/l)		33.6 ± 40.9	76.1 ± 64.1	0.0002
	D-dimer (ng/ml)		2672.8 ± 1663.8	2392.6 ± 1383.7	0.4231
Synovial fluid	Leukocyte (cells/μL)	aspiration 1 aspiration 2 aspiration 3	16221.4 ± 25920.0 12885.8 ± 27912.7 18876.5 ± 25286.1	40492.5 ± 63337.1 21310.6 ± 33027.3 48550.0 ± 76314.7	0.0075 0.3178 0.0366
	SNP 1 (%)	aspiration 1 aspiration 2 aspiration 3	88.6 ± 7.6 88.8 ± 6.8 80.1 ± 22.0	89.1 ± 12.6 88.3 ± 9.0 90.8 ± 6.8	0.8169 0.8545 0.1069

Table 3

Mean laboratory measurements of patients with CNI (n = 30) with confirmed and non-confirmed PJI according to ICM criteria (2018)

Parameters		PJI		p
		confirmed (n = 23)	Not confirmed (n = 7)	
Blood serum	ESR (mm/h)	53.8 ± 27.0	24.3 ± 7.0	0,0001
	SRP (mg/l)	43.7 ± 44.5	8.2 ± 6.3	0,0022
	D-dimer (ng/ml)	2753.7 ± 1687.8	2418.4 ± 1687.7	0,6569
Synovial fluid – aspiration 1	Leukocyte (cells/μL)	22532.1 ± 28420.8	444.6 ± 849.8	0,0026
	SNP 1 (%)	88.6 ± 7.6	–	–

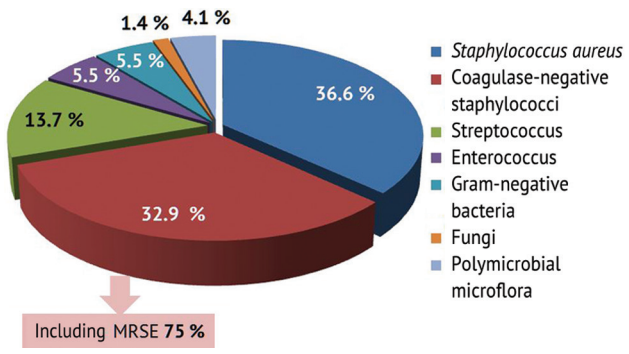

Fig. 2 Species spectrum of pathogens CPI

The pathogen isolated in 5 cases (6.8 %) group II only from the intraoperative material included *S. aureus* (n = 3), *E. faecalis* (n = 1) and *S. haemolyticus* (n = 1). The growth of strains obtained from preoperative aspiration, S. aureus (n = 2) and coagulase-negative staphylococci (n = 2) was not confirmed in four cases (5.5 %) by examination of intraoperative material.

The average interval between surgical stages of PJI treatment and II was 2.5 months (CI = 95 %; 1.2-4.9) in group I and 2.8 month (CI = 95 %; 0.2-17.5) in group II. Recurrence of PJI was detected in 12.3 % (9 out of 73) of patients in group II after debridement (Fig. 3).

There were 3.3 and 7.8 % patients in groups I and II who refused from the second stage of treatment. The reasons for "living with a spacer" included the patient's unwillingness to accept the treatment plan (arthrodesis after placement of a spacer block, n = 3), absolute contraindications to surgical treatment because of concomitant pathology (n = 2), patient's refusal from surgical treatment after coronavirus infection (n = 1). Indications for arthrodesis included large defects of the soft tissues and/or bones that form the knee joint due to previous operations, contractures.

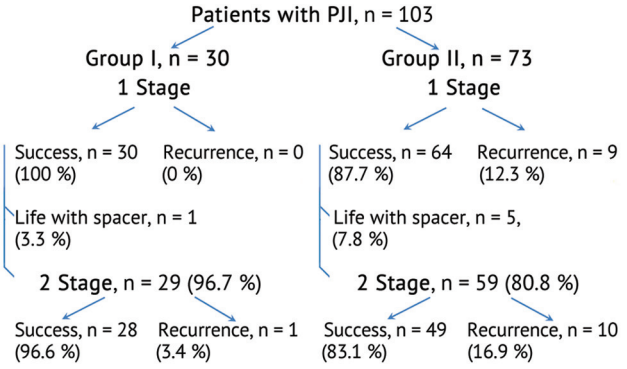

Fig. 3 Outcomes of each stage of treatment

Reimplantation was performed in 96.7 % and 80.8 % of patients in groups I and II, respectively. The average follow-up period after the second stage of re-arthroplasty was 40.1 months. (CI = 95 %; 6.2-77.7) in group I and 29.4 months (CI = 95 %; 0.5-57.5) in group II, p = 0.0197. Recurrent PJI with the need for repeated debridement were diagnosed in 3.4 and 16.9 % (p = 0.0928) of cases in groups I and II, respectively. The average period from implantation of the prosthesis to recurrent PJI was 20.8 months in patients with

CPI (CI = 95 %; 1.7-48.2) and 11.9 months (n = 1) in a patient with CNI.

Recurrent PJI was caused by *S. aureus* (n = 8 out of 20), coagulase-negative staphylococci (n = 4), streptococci (n = 3), gram-negative bacteria (n = 2), polymicrobial infection (n = 3). *Streptococcus agalactiae* was isolated in the one patient with CNI who showed a poor outcome. The etiology of recurrent CPI was similar to the etiology of PJI at the stage of debridement in 26.3 % of cases (5 out of 19): *S. aureus* was isolated in three cases and *E. coli* and *Streptococcus spp*. were isolated in 1 case. Inconsistent etiology of CPI in 9 cases was caused by absent growth of microorganisms at subsequent stages of debridement with present signs of PJI. Substitution of microflora during relapses occurred in 5 patients with CPI (Table 4).

The effectiveness of the two-stage treatment of PJI was 96.7 % (1 out of 30) and 74 % (19 out of 73) in groups I and II, respectively (p = 0.0064) (Fig. 3).

Table 4

Etiology of CPI in primary PJI and relapse

Primary PJI	Recurrent PJI
S. aureus	*S. aureus* + *S. epidermidis MRSE*
S. epidermidis	*S. aureus* + *Streptococcus oralis*
S. aureus	*Acinetobacter baumannii* + *E. faecalis*
S. epidermidis MRSE	*Staphylococcus lugdunensis*
Streptococcus pyogenes	*Corynebacterium jeikeium*

DISCUSSION

Researchers have been interested in studying outcomes of CNI of prosthetic joints and reasons behind the absent growth of pathogens in biological material, as evidenced by scientific publications for the key phrase "Culture-Negative Periprosthetic Joint Infection" in the PubMed that increased from 33 in 2012-2017 to 100 between 2018 and 2023. However, there are no publications on the topic in the Russian scientific literature.

One of the reasons behind the absent growth of a microorganism may include an infection caused by difficult-to-culture microorganisms, such as fungi, non-tuberculous mycobacteria (*Listeria monocytogens, Propionibacterium acnes, Brucella, Coxiella burnetii*) and others [11]. Culturing methods for diagnosing an infectious agent are currently available standard tests used in many areas of medicine. Detection of microorganisms in infected tissues and/or synovial fluid after total joint arthroplasty facilitates etiotropic therapy and increases the chances of a successful outcome of debridement. A wide range of negative results of microbiological examination with an established diagnosis of infection is reported in foreign studies. The frequency of CNI ranges from 7 % [10] to 42.1 % [12, 13].

The prevalence of suspected culture-negative PJI was reported by Huang et al. (2012) as 11.9 % [7], by Tan TL et al. (2018) as 22 % at an average of 15 years, ranging from 11.9 to 33.3 % [14], by Malekzadeh et al. (2010) as 35 % [15]. The present study showed the incidence of CNI in almost a third of all identified cases of PJI (29.2 %).

Common reasons for the lack of growth of microorganisms in the biological materials may include previous antibiotic therapy [16, 17], wound drainage [18], irrigation of the wound with antiseptic solutions before sampling [19], taking an insufficient number of tissue samples (at least 3-5 needed) or from non-infected tissue [20], increased sample transportation time, non-compliance with incubation periods, or lack of media for the growth of atypical microorganisms. In our series, the obvious reason for the lack of microorganism growth included the use of antibiotics prior to diagnosis of PJI, which was found in 50 % of cases in group I. Collection of biomaterial for bacteriological culture is standardized in our medical organization, prosthetic components are treated with ultrasound and incubated for at least 14 days providing conditions for culturing aerobes, anaerobes, capnophiles and fungi.

The ability of microorganisms, such as staphylococci and *Pseudomonas aeruginosa* to form a biofilm on the surface of implants from planktonic forms to be a barrier to the detection is an important problem in identifying PJI pathogens [21, 22]. The presence of the viable but not cultivated forms in biofilms is another factor hindering identification of bacteria. Such cells temporarily lose their ability to grow on conventional bacteriological media, but can restore their metabolic activity under certain conditions [23, 24].

In addition to that, *S. aureus* can exist intracellularly when internalized into osteoblasts and osteocytes leading to a failure in identifying the pathogen. Molecular diagnostic methods using DTT technologies and PCR sequencing have evolved in addition to cultural methods for identifying pathogens. The latter allows the identification of organisms by highly efficient parallel sequencing of all microbial DNA present and comparison of the generated sequence scanning with a bioinformatic database of all known microorganisms [25]. The statistics with the number of PJI in the absence of microorganism growth can change with the introduction of new technologies in the near future. Disadvantages

of molecular diagnostic methods include the high cost and impossibility of detecting sensitivity to antibiotics. Repeated sampling for microbiological research can be offered to improve identification of pathogens in the absent microorganism growth through incubation of cultures for at least 14 days, ultrasonic treatment of implants refraining from antibiotics prior to sampling [26].

Despite the improvement of PJI diagnostic criteria (ICM, 2018), demonstrating high sensitivity (97.7 %) and specificity (99.5 %) [8] with the possibility of verifying the infectious process in the absence of microorganism growth in the biological materials, diagnosis of CNI is still difficult. In our series, the total ICM score was less than 5 in 7 cases with an established diagnosis of CNI. Statistically significant differences in the level of inflammatory markers (ESR, CRP, and cytosis) were found in comparison with cases of unconfirmed CNI; there were no differences in the level of D-dimer. The diagnosis of PJI in the group of patients was based on radiological criteria for early instability of the prosthesis with zones of osteolysis or resorption. An emergency histological examination of the altered tissues can help to verify the diagnosis during surgery and decide on the optimal surgical strategy (one-stage rather than two-stage revision). The method offered by L. Morawietz et al. for determining more than 23 neutrophilic granulocytes in 10 high-power fields allows differential diagnosis of aseptic and infectious endoprosthesis loosening [27]. According to the literature, an emergency histological examination has a sensitivity of 95-98 %, a specificity of 98-99 %.

An automating technique using the CD15 focus score and the CD 15 quantifier computer program has been described with the sensitivity of 83 %, specificity of 86.4 % and an accuracy of 84.6 % [28]. This method allows for the diagnosis of PJI caused by low-virulence pathogens to be verified within a short period of time, in contrast to microbiological examination. Immunohistochemical examination of the CD15 antigen on the surface of neutrophils significantly increase the accuracy of PJI diagnosis, as reported by Silantieva T.A. et al. in 2021 exploring infected periprosthetic membranes [29]. Li H., Yang R., Geng L. (2014) suggested describing CNI that the infectious process with a negative culture was characterized by a slow onset and a moderate inflammatory response. In our series, the average levels of CRP, ESR and the leukocyte count in the joint fluid were reduced by 1.5 to 2 times in the CNI group than in the comparison group, which confirms the hypothesis of foreign colleagues.

A systematic meta-analysis of CNI outcomes including a review of 8 English-language articles was published in 2018 [30]. The pooled culture-negative infection rate was 11 % (n = 504) with a success rate of 85-95 % with no difference in success rates with CPI. The results of a recent meta-analysis, which included 30 studies, demonstrated a similar or better efficacy in the treatment of CNI in comparison with the culture-positive PJI group with success rate of 81 % and 76.4 %, respectively [30]. One of reasons for the success of CNI treatment may include absence of infection in the prosthetic joint or presence of low-virulence microorganisms that are easier to treat than highly virulent gems, such as methicillin-resistant *Staphylococcus aureus* [6].

S. aureus is reported in the literature as playing a leading role in the development of PJI [31-34]. Tan TL (2018) reported 219 cases of CNI with methicillin-susceptible *S. aureus* accounting for 38.5 % (10/26) of recurrent PJI with positive microbiological growth [14]. The results of our study also confirm the leading role of *S. aureus* in the etiology of CPI, both newly diagnosed (32.9 %) and relapsed (50 %). MRSE staphylococci that account for 75 % of all isolated coagulase-negative staphylococci are essential for etiology of PJI. With *S. aureus* and methicillin-resistant coagulase-negative staphylococci being the leading causative agents of PJI in our series the rationale for the mandatory use of vancomycin as part of the initial empirical antibiotic therapy in combination with cefoperazone / sulbactam was essential for expanding the spectrum of antimicrobial activity. Bejon P. et al. (2010) described 62 cases of CNI with a two-stage debridement success rate of 83 % over 5.75 years of follow-up [31]. In our series, a successful treatment outcome was achieved in 96.7 % and 74 % of cases ($p = 0.0064$) with culture-negative and culture-positive PJI, respectively at a two-year follow-up.

Most studies have shown the advantage of two-stage revision arthroplasty over radical surgical debridement with preservation of the endoprosthesis in patients with CNI. Tan TL et al. (2018) reported the infection arrested in 71.2 % and 55.6 % of cases, respectively [14]; Berbari E.F. et al. (2007) described success in 94 and 71 % of cases, Huang R. et al. (2012) could achieve efficient treatment in 70 % and 50 % of observations, respectively. Only Malekzadeh D. et al. (2010) reported comparable results in the treatment of 135 cases of CNI with 78 % cumulative incidence free of treatment failure at 5 years followup being similar for CNI and CPI PJI regardless of the implant retention or removal [15]. The results of a recent meta-analysis (2023) suggested that surgery with the replacement of an infected endoprosthesis with one-stage or two-stage revision was more effective for the treatment of CNI compared with debridement and implant retention with the recurrence rate of 11.5, 16.1 and 22.2 % of cases, respectively [30].

CONCLUSION

In our series, the use of antibacterial drugs prior to diagnosis of PJI was the most obvious reason for the lack of growth of microorganisms. The findings indicated the high efficiency of two-stage revision arthroplasty, broad-spectrum empiric antibiotic therapy administered for culture-negative infection of the knee joint, which amounted to 96.7 % success at a 2-year follow-up, which statistically significantly exceeded outcomes with culture-positive infection with an established etiology with success rate of 74 %.

Conflict of interest *The authors declared no potential conflicts of interest with respect to the authorship and/or publication of this article.*

Financing *This study was not supported by any external sources of funding.*

Ethical expertise *Not applicable.*

Consent for publication *Not required.*

REFERENCES

1. Reisener M, Perka C. Do Culture-Negative Periprosthetic Joint Infections Have a Worse Outcome Than Culture-Positive Periprosthetic Joint Infections? A Systematic Review and Meta-Analysis. *Biomed Res Int*. 2018;2018:6278012. doi: 10.1155/2018/6278012
2. Yoon HK, Cho SH, Lee DY, et al. A Review of the Literature on Culture-Negative Periprosthetic Joint Infection: Epidemiology, Diagnosis and Treatment. *Knee Surg Relat Res*. 2017;29(3):155-164. doi: 10.5792/ksrr.16.034
3. Kalbian I, Park JW, Goswami K, et al. Culture-negative periprosthetic joint infection: prevalence, aetiology, evaluation, recommendations, and treatment. *Int Orthop*. 2020;44(7):1255-1261. doi: 10.1007/s00264-020-04627-5
4. Bozhkova SA, Kasimova AR, Tikhilov RM, et al. Adverse trends in the etiology of orthopedic Infection: results of 6-year monitoring of the structure and resistance of leading pathogens s. *Travmatologiya i ortopediya Rossii* [Traumatology and Orthopedics of Russia]. 2018;24(4):20-31. doi: 10.21823/2311-2905-2018-24-4-20-31
5. Mortazavi SM, Vegari D, Ho A, Zmistowski B, Parvizi J. Two-stage exchange arthroplasty for infected total knee arthroplasty: predictors of failure. *Clin Orthop Relat Res*. 2011;469(11):3049-54. doi: 10.1007/s11999-011-2030-8
6. Choi HR, Kwon YM, Freiberg AA, Nelson SB, Malchau H. Periprosthetic joint infection with negative culture results: clinical characteristics and treatment outcome. *J Arthroplasty*. 2013;28(6):899-903. doi: 10.1016/j.arth.2012.10.022
7. Huang R, Hu CC, Adeli B, Mortazavi J, Parvizi J. Culture-negative periprosthetic joint infection does not preclude infection control. *Clin Orthop Relat Res*. 2012;470(10):2717-23. doi: 10.1007/s11999-012-2434-0
8. Goh GS, Parvizi J. Diagnosis and Treatment of Culture-Negative Periprosthetic Joint Infection. *J Arthroplasty*. 2022;37(8):1488-1493. doi: 10.1016/j.arth.2022.01.061
9. Nikolaev NS, Pchelova NN, Preobrazhenskaya EV, Nazarova VV, Dobrovol'skaya N.Yu. "Unexpected" Infections in Revision Arthroplasty for Aseptic Loosening. *Travmatologiya i ortopediya Rossii* [Traumatology and Orthopedics of Russia]. 2021;27(3):56-70. doi: 10.21823/2311-2905-2021-27-3-56-70
10. Trampuz A, Renz N. *Pocket Guide to Diagnosis Treatment of Periprosthetic Joint Infection (PJI)*. PRO-IMPLANT foundation; 2017.
11. Berbari EF, Marculescu C, Sia I, et al. Culture-negative prosthetic joint infection. *Clin Infect Dis*. 2007;45(9):1113-9. doi: 10.1086/522184
12. Kim YH, Kulkarni SS, Park JW, Kim JS, Oh HK, Rastogi D. Comparison of infection control rates and clinical outcomes in culture-positive and culture-negative infected total-knee arthroplasty. *J Orthop*. 2015;12(Suppl 1):S37-43. doi: 10.1016/j.jor.2015.01.020
13. Kim YH, Park JW, Kim JS, Kim DJ. The outcome of infected total knee arthroplasty: culture-positive versus culture-negative. *Arch Orthop Trauma Surg*. 2015;135(10):1459-67. doi: 10.1007/s00402-015-2286-7
14. Tan TL, Kheir MM, Shohat N, Tan DD, Kheir M, Chen C, Parvizi J. Culture-Negative Periprosthetic Joint Infection: An Update on What to Expect. *JB JS Open Access*. 2018;3(3):e0060. doi: 10.2106/JBJS.OA.17.00060
15. Malekzadeh D, Osmon DR, Lahr BD, Hanssen AD, Berbari EF. Prior use of antimicrobial therapy is a risk factor for culture-negative prosthetic joint infection. *Clin Orthop Relat Res*. 2010;468(8):2039-45. doi: 10.1007/s11999-010-1338-0
16. Schinsky MF, Della Valle CJ, Sporer SM, Paprosky WG. Perioperative testing for joint infection in patients undergoing revision total hip arthroplasty. *J Bone Joint Surg Am*. 2008;90(9):1869-75. doi: 10.2106/JBJS.G.01255
17. Nikolaev NS, Borisova LV, Didichenko SN, et al. Optimal methods for treating infectious complications in endoprosthesis replacement of large joints in modern conditions. *Ural'skii meditsinskii zhurnal*. [Ural Medical Journal]. 2015;(10):51-56] (In Russ.)
18. Yoon HK, Cho SH, Lee DY, Kang BH, Lee SH, Moon DG, Kim DH, Nam DC, Hwang SC. A Review of the Literature on Culture-Negative Periprosthetic Joint Infection: Epidemiology, Diagnosis and Treatment. *Knee Surg Relat Res*. 2017;29(3):155-164. doi: 10.5792/ksrr.16.034
19. Goh GS, Parvizi J. Think Twice before Prescribing Antibiotics for That Swollen Knee: The Influence of Antibiotics on the Diagnosis of Periprosthetic Joint Infection. *Antibiotics* (Basel). 2021;10(2):114. doi: 10.3390/antibiotics10020114
20. Parvizi J, Erkocak OF, Della Valle CJ. Culture-negative periprosthetic joint infection. *J Bone Joint Surg Am*. 2014;96(5):430-6. doi: 10.2106/JBJS.L.01793
21. Trampuz A, Piper KE, Jacobson MJ, et al. Sonication of removed hip and knee prostheses for diagnosis of infection. *N Engl J Med*. 2007;357(7):654-63. doi: 10.1056/NEJMoa061588
22. Peterson BW, He Y, Ren Y, et al. Viscoelasticity of biofilms and their recalcitrance to mechanical and chemical challenges. *FEMS Microbiol Rev*. 2015;39(2):234-45. doi: 10.1093/femsre/fuu008
23. Oliver JD. Recent findings on the viable but nonculturable state in pathogenic bacteria. *FEMS Microbiol Rev*. 2010;34(4):415-25. doi: 10.1111/j.1574-6976.2009.00200.x
24. Lleò MM, Benedetti D, Tafi MC, Signoretto C, Canepari P. Inhibition of the resuscitation from the viable but non-culturable state in Enterococcus faecalis. *Environ Microbiol*. 2007;9(9):2313-20. doi: 10.1111/j.1462-2920.2007.01345.x

25.Tarabichi M, Shohat N, Goswami K, Alvand A, Silibovsky R, Belden K, Parvizi J. Diagnosis of Periprosthetic Joint Infection: The Potential of Next-Generation Sequencing. *J Bone Joint Surg Am*. 2018;100(2):147-154. doi: 10.2106/JBJS.17.00434
26.Kurtz SM, Lau EC, Son MS, et al. Are We Winning or Losing the Battle With Periprosthetic Joint Infection: Trends in Periprosthetic Joint Infection and Mortality Risk for the Medicare Population. *J Arthroplasty*. 2018;33(10):3238-3245. doi: 10.1016/j.arth.2018.05.042
27.Morawietz L, Tiddens O, Mueller M, et al. Twenty-three neutrophil granulocytes in 10 high-power fields is the best histopathological threshold to differentiate between aseptic and septic endoprosthesis loosening. *Histopathology*. 2009;54(7):847-53. doi: 10.1111/j.1365-2559.2009.03313.x
28.Krenn V, Kölbel B, Wienert S et al. A new algorithm for histopathological diagnosis of periprosthetic infection using CD15 focus score and computer program CD15 QuantiFier. *Travmatologiya i ortopediya Rossii* [Traumatology and Orthopedics of Russia]. 2015;(3):76-85. (In Russ.) doi: 10.21823/2311-2905-2015-0-3-76-85
29.Silantieva TA, Ermakov AM, Tryapichnikov AS. Histological evaluation of periprosthetic infection using HOES and CD15 expression analysis in hip revision arthroplasty. *Travmatologiya i ortopediya Rossii* [Traumatology and Orthopedics of Russia]. 2021;27(2):84-98. doi: 10.21823/2311-2905-2021-27-2-84-98
30.Li F, Qiao Y, Zhang H, Cao G, Zhou S. Comparable clinical outcomes of culture-negative and culture-positive periprosthetic joint infections: a systematic review and meta-analysis. *J Orthop Surg Res*. 2023;18(1):210. doi: 10.1186/s13018-023-03692-x
31.Bejon P, Berendt A, Atkins BL, et al. Two-stage revision for prosthetic joint infection: predictors of outcome and the role of reimplantation microbiology. *J Antimicrob Chemother*. 2010;65(3):569-75. doi: 10.1093/jac/dkp469
32.Bozhkova SA, Bogdanova TYa, Krasnova MV, et al. Experimental and clinical study of phenotypic features of S. Epidermidis strains and their role in theemergenceand development of implant-associated infection after orthopaedic surgery. *Travmatologiya i ortopediya Rossii* [Traumatology and Orthopedics of Russia]. 2014;(2):68-77. (In Russ.) doi: 10.21823/2311-2905-2014-0-2-68-77
33.Botelho AMN, Nunes ZDG, Asensi MD, et al. Characterization of coagulase-negative staphylococci isolated from hospital indoor air and a comparative analysis between airborne and inpatient isolates of Staphylococcus epidermidis. *J Med Microbiol*. 2012;61(Pt 8):1136-1145. doi: 10.1099/jmm.0.035931-0
34.Nikolaev NS, Lyubimova LV, Pchelova NN, et al. Treatment of periprosthetic Infection with silver-doped implants based on two-dimensional ordered linear chain carbon. *Travmatologiya i ortopediya Rossii* [Traumatology and Orthopedics of Russia]. 2019;25(4):98-108. doi: 10.21823/2311-2905-2019-25-4-98-108

The article was submitted 11.04.2023; approved after reviewing 19.04.2023; accepted for publication 20.06.2023.

Information about the authors:

1. Lyudmila V. Lyubimova – Clinical Pharmacologist, borisova-80@mail.ru, https://orcid.org/0000-0002-5750-4459;
2. Svetlana A. Bozhkova – Doctor of Medical Sciences, Associate Professor, Head of Department, clinpharm-rniito@yandex.ru, https://orcid.org/0000-0002-2083-2424;
3. Nadezhda N. Pchelova – Doctor of Clinical Laboratory Diagnostics, nadyapchelova@mail.ru, https://orcid.org/0000-0001-9507-9118;
4. Elena V. Preobrazhenskaya – Head of Department, alenka_22@bk.ru, https://orcid.org/0000-0003-3556-145X;
5. Evgeniy A. Lyubimov – Anesthesiologist-resuscitator, fc@orthoscheb.com, https://orcid.org/0000-0001-5262-0197.

Contribution of the authors:

Lyubimova L.V. – conceptualization, research, data processing, writing the text of the article, project management.
Bozhkova S.A. – reviewing and editing the article, control.
Pchelova N.N. – conceptualization, research.
Preobrazhenskaya E.V. – methodology, validation, formal analysis, visualization.
Lyubimov E.A. – conceptualization, research.

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