



Analysis of existing approaches to determine culture-negative periprosthetic infection of the hip and knee joints and assessment of its treatment outcomes

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Abstract

Introduction Periprosthetic infection is one of the most frequent and devastating complications after total hip replacement. The effectiveness of infection management depends on possibility of prescribing etiotropic antibiotics after the operation and the rational choice of a surgical technique. In 5–30 % of all patients the etiology of the infectious process remains unknown throughout the entire treatment period. Such cases are described by the term "culture-negative periprosthetic joint infection". Nowadays, there is no single definition for culture-negative PJI in the professional community.

The **aim** of this study is to evaluate the treatment results of patients with culture-negative periprosthetic infection, depending on the approach to its detection, as well as formulate possible ways to reduce its rates.

Methods Literature search was performed in electronic databases eLIBRARY, PubMed (MEDLINE), ScienceDirect, Google Scholar according to PRISMA recommendations. The study included articles in Russian and English, original articles and case series on the treatment of chronic culture-negative periprosthetic infection of the hip joint and/or knee joints in patients over 18 years of age using any surgical operations and in which there was at least one indicator of treatment effectiveness. The existing approaches to detection of culture-negative periprosthetic joint infection of the knee and hip and the outcomes of treatment of patients with this pathology were analyzed, as well as possible ways to reduce the number of patients with an unknown etiology of the infectious process were formulated.

Results and Discussion Our analysis of scientific publications revealed no clear difference in the effectiveness of infection control depending on the approach to detection of culture-negative PJI. For the first time, the effectiveness of treatment for patients with culture-negative PJI is examined depending on the approach to detection of this pathology. Significant heterogeneity was identified in both the interpretation of culture-negative PJI and the choice of surgical techniques. The high rate of successful outcomes indicates the importance of appropriate selection of drugs for empirical antibiotic therapy (ABT) and regular monitoring of the spectrum of nosocomial pathogens. Potential ways to reduce the incidence of negative microbiological test results are proposed.

Conclusion The efficacy of treatment of culture-negative PJI did not differ significantly depending on the interpretation of this term. Ways to reduce the incidence of this pathology are aimed at modifying the factors that cause negative results of MBI of biomaterial samples and removed structures.

Keywords: chronic periprosthetic infection, pre-operative examination, microbiological test, revision arthroplasty

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INTRODUCTION

Periprosthetic joint infection (PJI) is considered one of the most devastating complications of total hip arthroplasty (THA) that impairs quality of life and overall life expectancy of patients [1, 2]. Infectious complications in arthroplasty pose a heavy socioeconomic burden on the healthcare system [3, 4], while the risk of failure remains quite high, ranging from 10–29 % in two-stage revision arthroplasty, which is still considered the “gold standard” [5, 6].

One of the key factors that significantly affect the success of treatment is the etiology of the infectious process, or the type of microbial pathogen and its antibiotic sensitivity [7]. The proportion of patients in whom microbiological diagnosis was not made based on the results of preoperative studies, and in some cases, based on the results of intraoperative cultures, has been grown. This phenomenon is known as culture-negative PJI, the incidence of which reaches 5–30 % [8, 9]. The main causes of culture-negative PJI are the use of antimicrobial drugs within less than two weeks before microbiological tests, presence of low-virulent or difficult-to-cultivate PJI pathogens [10], as well as the peculiarities of the pathogenesis of the infectious process associated with orthopedic implants (a bacterial depot in patient's body which includes biofilms, intracellular bacteria and colonized osteocyte-lacunar tubules) [11]. All these factors make it practically impossible to routinely prescribe etiotropic antibiotic therapy (ABT) at the time of performing a sanitizing operation on a patient with PJI.

There is no consensus within the professional community regarding this phenomenon. Some authors define culture-negative PJI as the absence of pathogen growth based on preoperative microbiological studies (PMS), although the pathogen may be detected in intraoperative specimens [12–17]. Other authors define this term as a complete lack of pathogen data [18–22]. These differences explain the wide range of this pathology rates and, consequently, the impossibility of developing uniform treatment recommendations for these patients.

The **aim** of this study is to evaluate the treatment results of patients with culture-negative periprosthetic hip and knee joint infection, depending on the approach to its determination, as well as formulate possible ways to reduce its rates.

MATERIALS AND METHODS

This systemic analysis was conducted according to the international requirements PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [23].

The search for literature sources was performed in the electronic databases eLIBRARY, PubMed (MEDLINE), ScienceDirect, Google Scholar.

The search phrases in the PubMed (MEDLINE), ScienceDirect, Google Scholar, Ovid, as recommended by Aromataris and Riitano [24], included combinations of key words: "periprosthetic joint infection" or "prosthetic joint infection" or PJI) and ("single-stage" or "one-stage" or "two-stage" or "2-stage" or "revision" or "revisions") and ("culture negative" or "negative") and ("culture positive" or "positive").

The eLIBRARY database search query included the following combination of keywords: "culture-negative infection," "culture-negative periprosthetic joint infection," and "chronic hip periprosthetic joint infection OR chronic knee periprosthetic joint infection." The search was not retrospectively restricted; the last query date was February 4, 2025. Various combinations of search queries were used in the listed databases as a preliminary option.

At the first stage, the criteria for inclusion and exclusion of articles in the study were determined.

Inclusion criteria:

- articles in the Russian and English languages;
- original articles and case series including five or more observations devoted to the treatment of chronic culture-negative periprosthetic infection of the hip and/or knee joints, infectious complications after hip and/or knee arthroplasty;
- age of patients: older than 18 years;
- at least one indicator of treatment effectiveness (proportion of positive and negative outcomes, survival rate);
- any surgical intervention for PJI.

Exclusion criteria:

- articles in veterinary field;
- studies that depict coxitis consequences;
- literature reviews, meta-analyses, text books, book chapters, letters to editors, expert opinions;
- articles devoted to the treatment of acute PJI only;
- articles devoted to the diagnosis of PJI;
- case reports;
- absence of comparison groups in the study (culture-negative and culture-positive groups);
- lack of a clearly defined definition of culture-negative PJI in the publication.

A manual search for references in the identified articles was conducted to find additional publications that could be included in the study. Abstracts of the publications were then reviewed for inclusion and exclusion criteria, and duplicate studies were identified and eliminated. Finally, full-text articles were reviewed.

During the analysis of the included works the following indicators were assessed:

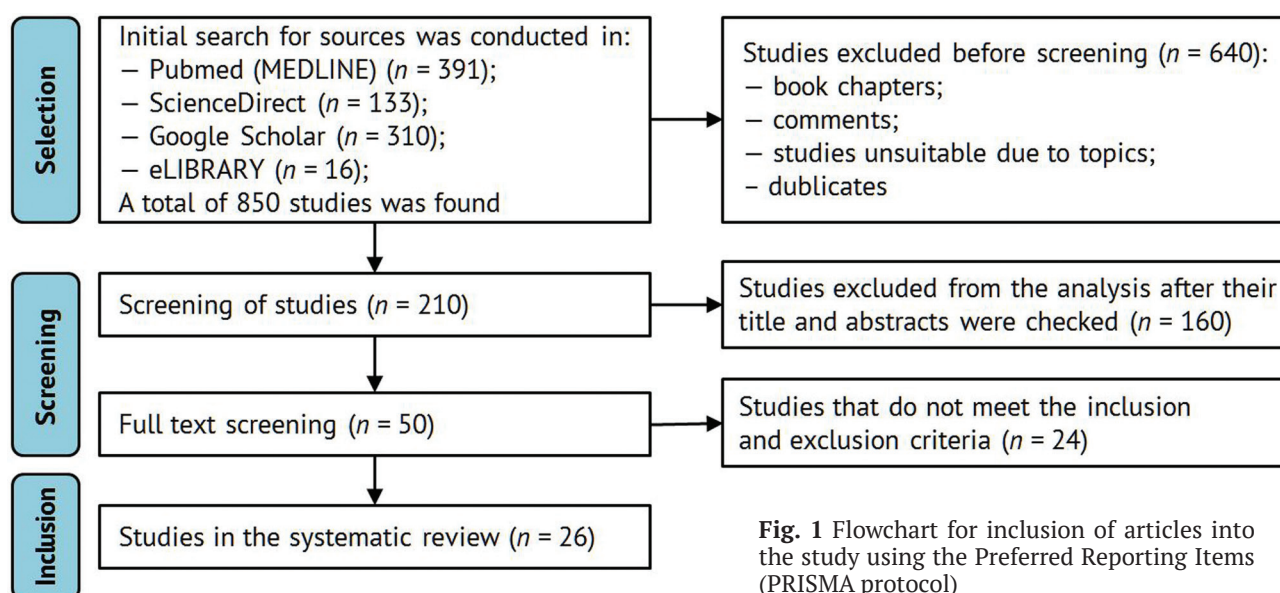
- general information about the study (authors, country and year of publication, type and duration of study, duration of follow-up, diagnostic criteria, number of clinical groups, joints involved, types of surgical interventions and antibiotic therapy);
- study results that included the rates of positive and negative treatment outcomes.

Recurrent infection was defined as the presence of general or systemic signs of PJI, repeated debridement surgeries on the same joint for the infectious process, and a fatal outcome resulting from PJI. International guidelines based on the Delphi-based international multidisciplinary consensus were used to determine a successful outcome for patients with PJI [25].

Study design

The initial search identified 850 publications, of which 640 (commentaries, book chapters, articles irrelevant to the topic, and duplicates) were excluded. After reviewing the titles and abstracts for relevance to the search topic, 50 publications were selected. After checking the availability of full-text articles in the public domain and their compliance with the inclusion and exclusion criteria, 26 studies were included in the final analysis (Fig. 1).

The selected studies were published between 2007 and 2024 and included 7,713 cases of PJI. The follow-up period ranged from 12 to 120 months. For the diagnosis of PJI, the MSIS (Musculoskeletal Infection Society) criteria [26] were used in 17 studies, the ICM (International Consensus Meeting) criteria [27] in five studies, the IDSA (Infectious Diseases Society of America) criteria [28] in one study, and the EBJIS (European Bone and Joint Infection Society) criteria [29] in one study. Four studies used criteria developed by authors, and three other publications did not provide data.



Risk of systemic error

Each study was methodologically assessed for quality according to the Oxford Center for Evidence-Based Medicine (CEBM) criteria to determine its level of evidence. For both case series and cohort studies, the Joanna Briggs Institute Critical Appraisal Tools (JBI) checklist, consisting of 11 questions, was applied (Fig. 2).

Statistical analysis

Data from all 26 articles were included in the statistical analysis. The analysis was performed using IBM SPSS Statistics v.26 (IBM Corporation). To describe quantitative indicators, we tested for normality of distribution using the Shapiro-Wilk and Kolmogorov-Smirnov tests. The median (Me) was used to describe quantitative variables, and the lower (Q1) and upper (Q3) quartiles (25–75 % IQR) were used as measures of dispersion. Comparisons within the study groups were performed using the Mann–Whitney test. Differences between the groups were considered statistically significant at $p < 0.05$.

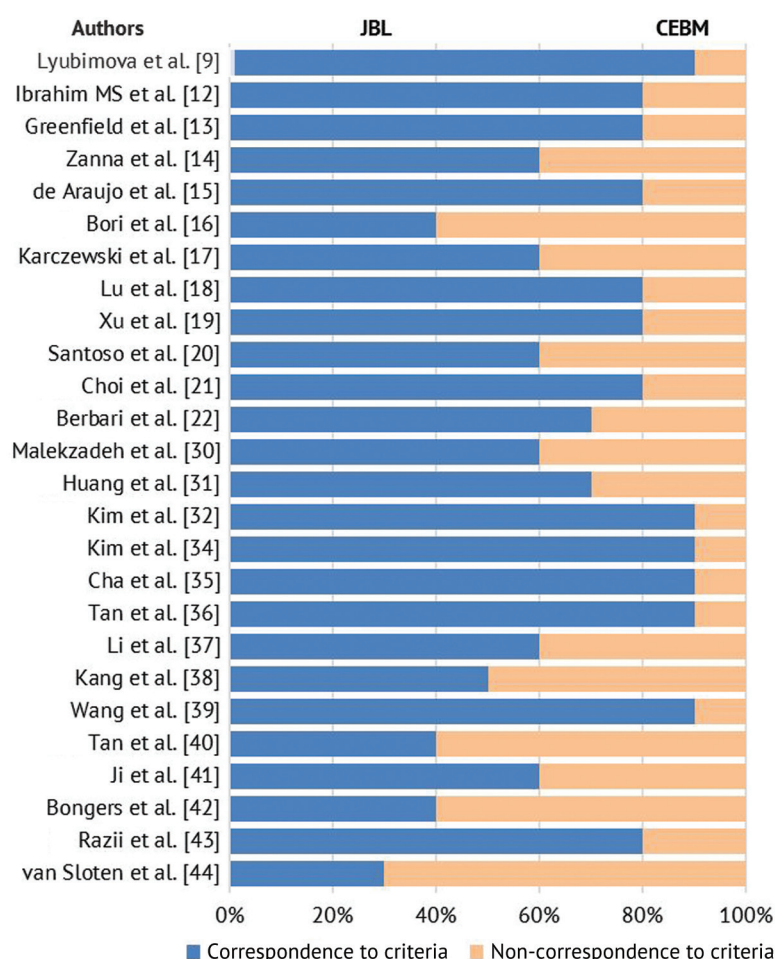


Fig. 2 Results of methodological evaluation of the quality of articles included in the study

All studies were divided into two groups based on their approach to detection CNI. The first group, in which the authors defined CNI as the absence of pathogen growth in all samples, included 20 publications. The second group, which considered the absence of microbial growth only in preoperative studies, included six publications. For each study, the proportion of successful CNI

treatment outcomes was calculated. The mean infection resolution rate (MIR) in each group was then calculated. The Mann-Whitney test was used to test for statistically significant differences between the groups.

RESULTS AND DISCUSSION

Investigation of treatment outcomes by different approaches to detection of culture-negative PJI does not reveal any significant differences in the effectiveness of infection control. In the first group (CNI, no pathogen growth in all samples), infection eradication was achieved in an average of 91.5 % of cases (IQR = 78.0–95.5 %); the data distribution was not normal ($p = 0.03$). In the second group (no microbial growth in preoperative tests only), the rate of successful CNI treatment outcomes averaged 92.0 % of cases (IQR = 86.0–97.0 %); the distribution of results did not differ from normal ($p = 0.326$).

No statistically significant difference in the effectiveness of PJI treatment was found between the two study groups ($p = 0.582$). It is noteworthy that studies in which the authors described CNI as the absence of pathogen growth only before surgery included a small number of cases and did not always include a comparison group. A number of studies did not specify the criteria used to confirm the PJI diagnosis (Table 1). All studies analyzed were retrospective.

Table 1

Characteristics of studies on the treatment of patients with culture-negative PJI based on the approach to its detection

Authors [reference number]	Joint, %		Analysys (period)	PJI criteria	CNI detection	Total cases	KHI		Surgery
	knee	hip					n	%	
Lubimova et al. [9]	100		2017–2021	ICM (2018)	preop + intra	103	30	29.1	2-stage revision
Ibrahim MS et al. [12]		100	2007–2012	Berbari EF et al. [22]	preop + intra	100	50	50	2-stage revision
Greenfield et al. [13]		100	2006–2015	MSIS (2011)	preop	105	28	26.7	1-stage revision
Zanna et al. [14]	45.5	54.5	2016–2018	HJI	preop	640	22	3.4	1-stage revision
de Araujo et al. [15]	50.0	50.0	2003–2020	ICM (2018)	preop + intra	53	6	11.1	DAIR, 2-stage revision, 1-stage revision, RA, amputation, disarticulation, arthrodesis
Bori et al. [16]	100		1998–2007	HJI	preop	24	6	15.8	1-stage revision
Karczewski et al. [17]		100	2011–2021	EBJIS (2021)	preop	30	10	33.3	1-stage revision
Lu et al. [18]	34.5	65.5	2008–2020	MSIS (2013)	preop + intra	87	24	27.6	2-stage revision
Xu et al. [19]	41.6	58.4	2012–2017	ICM (2018), MSIS (2011)	preop + intra	77	24	31.2	DAIR, 2-stage revision, 1-stage revision
Santoso et al. [20]		100	2010–2015	MSIS (2011)	preop + intra	84	27	32.1	2-stage revision
Choi et al. [21]	50.0	50.0	2000–2009	MSIS (2013)	preop + intra	175	40	23	2-stage revision
Berbari et al. [22]	55.0	45.0	1990–1999	HJI	preop + intra	897	60	7	DAIR, 2-stage revision, PA
Malekzadeh et al. [30]	50.0	50.0	1985–2000	HJI	preop + intra	270	135	50	DAIR, 2-stage revision, 1-stage revision, RA, amputation
Huang et al. [31]	44.0	56.0	2000–2007	MSIS (2011)	preop + intra	250	48	19.2	DAIR, 2-stage revision
Kim et al. [32]	100		1991–2008	McPherson et al. [33]	preop + intra	191	51	26.7	DAIR, 2-stage revision
Kim et al. [34]	100		2001–2008	MSIS (2011)	preop + intra	242	102	42.1	DAIR, 2-stage revision
Cha et al. [35]	100		1998–2011	MSIS (2011)	preop + intra	76	22	29.0	2-stage revision
Tan et al. [36]	62.9	37.1	2000–2014	MSIS (2013)	preop + intra	1045	159	15.2	2-stage revision
Li et al. [37]	100		2003–2014	MSIS (2011)	preop + intra	129	18	13.9	1-stage revision, 2-stage revision
Kang et al. [38]		100	1996–2015	MSIS (2011)	preop + intra	85	15	17.6	2-stage revision
Wang et al. [39]		100	2003–2006	MSIS (2011)	preop + intra	58	19	32.7	2-stage revision

Table 1 (continuation)

Characteristics of studies on the treatment of patients with culture-negative PJI based on the approach to its detection

Authors [reference number]	Joint, %		Analysys (period)	PJI criteria	CNI detection	Total cases	KHI		Surgery
	knee	hip					n	%	
Tan et al. [40]	37.0	63.0	2000–2014	MSIS (2013)	preop + intra	996	219	22	DAIR, 2-stage revision, 1-stage revision
Ji et al. [41]		100	2009–2016	McPherson et al. [33], MSIS (2011)	preop + intra	243	51	21	1-stage revision
Bongers et al. [42]	100		2003–2013	MSIS (2013)	preop	113	53	46.9	2-stage revision
Razii et al. [43]	100		2006–2016	MSIS (2011), IDSA, ICM (2013, 2018)	preop	84	16	19	1-stage revision
van Sloten et al. [44]	74.3	25.7	2013–2018	EBJIS (2021), ICM (2018), MSIS (2013)	preop + intra	1556	70	4.5	DAIR, 2-stage revision, 1-stage revision

Notes: DAIR — wound debridement, antibiotics and implant retention; RA — resection arthroplasty

Existing approaches to defining culture-negative PJI

Currently, there is no consensus in the orthopaedic trauma community regarding the specific cases in which periprosthetic joint infection can be considered culture-negative. The term "culture-negative PJI" was first described by Berbari et al. as the absence of growth of aerobic or anaerobic pathogens in microbiological tests of tissue samples harvested around the endoprosthesis. The authors listed the following diagnostic criteria: pus in the area of the implants, elevated number of leukocytes ($> 1.7 \times 10^3/\text{ml}$) and/or the percentage of polymorphonuclear neutrophils ($> 65\%$) in the synovial fluid, acute inflammation according to histological study, and a fistula tract communicating with the implant [22]. The rate of culture-negative PJI in that study was 7 % (60/897), with more than half (53 %) of patients having a history of preoperative intake of antibacterial drugs. Palan et al. point out the need to differentiate between a "true negative" preoperative MBI result (7–15 % of cases) when it is more likely to be aseptic loosening, and a "false negative" result, when for a number of reasons it is impossible to isolate the causative agent of the infectious process but its presence is beyond doubt [45]. Accordingly, all cases of presumed culture-negative PJI can be divided into two large groups. The first group includes patients with evident periprosthetic infection, the etiology of which cannot be determined at the moment. The authors propose to include patients with suspected periprosthetic joint infection in the second group if the results of MBI of tissue from the affected joint are negative but there are no clear signs of infection (visible suppuration or a functioning fistula). The described clinical picture may indicate the presence of low-virulence or atypical pathogens, such as fungi or bacteria of the genus *Mycobacterium spp.*, *Propionibacterium spp.* and others. This division appears reasonable and appropriate, as patients in both groups differ significantly in the severity of symptoms and infection nature. It should be noted that not all publications on culture-negative PJI clearly define the CNI criteria for inclusion in the study.

The term "culture-negative PJI" is often understood as the absence of growth of aerobic and anaerobic pathogens in all samples taken both preoperatively and intraoperatively [9, 17–22]. In studies in which the authors used the described above approach, the incidence of culture-negative PJI was 7–30.8 % of cases. Thus, in the study by Lu et al. the incidence of infection of unknown etiology was 27.6 %, while in 25.0 % of cases a functioning fistula tract was described. However, in 91.7 % of cases the presence of inflammation was confirmed histopathologically and in 70.8 % of cases pus was detected in the area of the endoprosthesis during surgery [19]. In the work of Lyubimova et al., the proportion of patients without pathogen growth was 29.1 %, while only 76.6 % of patients had an infectious process confirmed according to the ICM criteria (2018), while in the culture-positive PJI group it was 98.6 % ($p = 0.0006$) [9]. Although the clinical picture was comparable in the groups, blood tests for ESR, CRP and the leukocyte level in the synovial fluid were

significantly higher in the preoperative period in the group where the causative agent of PJI was identified ($p < 0.05$). These data are consistent with the results of Choi et al., according to which the proportion of patients with CNI was 23 % in the analyzed sample, while their ESR levels were significantly lower than in the group of patients with positive cultures [19]. Prior hospitalization, treatment with antibacterial drugs was significantly more common in the group without pathogen growth ($p = 0.005$).

A different approach can be found in a number of scientific papers, where the term "culture-negative" is used in cases where the growth of the pathogen was not detected only in the preoperative tests. Thus, Ibrahim et al., based on the growth or absence of growth of pathogens before surgery, identified two equal groups of patients; periprosthetic infection was confirmed by the criteria of Berbari et al. [18]. At the same time, the authors indicate that the MBI of biomaterial samples from patients with culture-negative PJI were negative at all stages of treatment. According to the authors, the greatest influence on the probability of the absence of pathogen growth was exerted by the use of antibacterial drugs in the preoperative period ($p = 0.003$, OR 4.1) and if there was previous treatment of periprosthetic infection at other hospitals ($p = 0.001$, OR 3.1).

Greenfield et al. assessed the impact of preoperative pathogen identification on the effectiveness of single-stage revision arthroplasty. It should be noted that the authors did not introduce the concept of culture-negative infection per se, but divided patients into two groups based on whether the preoperative MBI tests were positive or negative [13]. Thus, the etiology of PJI was known at the time of surgery in only 27 % of cases.

A different approach to expanding the indications for a one-stage technique was demonstrated in the work of Zanna et al. The study sample included those patients whose MBI results were negative only in the preoperative period; their proportion amounted to 3.4 % [14]. The authors considered the absence of pathogen growth to be negative in two microbiological studies of synovial fluid and one open biopsy. It is noteworthy that in a half of the cases included in the study, microbial associations were detected in intraoperatively taken tissue biopsies. Bori et al. studied the effectiveness of one-stage revision arthroplasty using femoral components with cementless fixation and found that six (15.8 %) patients had no data on the pathogen at the time of surgery [16]. However, in subsequent five cases, growth of coagulase-negative staphylococci was found in from intraoperatively taken biopsies and growth of *Peptostreptococcus spp.* in one case.

A group of scientists from the Charité Clinic in Berlin put forward a more radical hypothesis in their study, suggesting that pathogen identification prior to single-stage revision arthroplasty is not mandatory [17]. According to the authors, the use of a single-stage technique may depend more on the condition of soft tissues and bone, patient's somatic status, and patient's medical history than on the specific pathogen. It should be emphasized that the authors do not introduce the concept of "culture-negative PJI," but they repeatedly reference studies on this condition in the discussion.

Current approaches to treating patients with culture-negative PJI

Currently, the professional community of trauma- and orthopedic surgeons has accumulated a certain experience in treating patients with culture-negative PJI, which allows them to analyze the outcomes of various surgical treatment methods, including the comparison with the results of treating patients with culture-positive infection. According to the results of a meta-analysis by Lai et al. that included 11 studies, the etiology of the infectious process was not determined in an average of 32.5 % of patients (9.9–73.3 %) [46]. Moreover, treatment outcomes in culture-negative and culture-positive PJI did not differ significantly (OR = 1.20, 95 % CI: 0.84–1.70). The effectiveness of two-stage revision arthroplasty was 82.5 % in each group, the effectiveness of one-stage revision arthroplasty was 90.6 % and 94.5 %, respectively. It is noteworthy that the meta-analysis included studies on the treatment of patients with acute PJI [32; 47], which implies perioperative antibiotic prophylaxis which may affect the results of the MBI of the joint fluid. In particular, in the work of Kim et al. more than a half (51 %) of the cases in the culture-negative

group were classified as acute (early) infection [32]. In addition, the effect of antibiotic-containing bone cement, which was used to fix the implant components, cannot be excluded. In addition to the above factors, the limitations include the predominantly retrospective nature of the included studies, the use of various diagnostic criteria for both the periprosthetic infection itself and the concepts of relapse and reinfection, as well as the inclusion of patients with pathology of both the knee and hip joints in the studied samples.

The data presented are consistent with the results of another meta-analysis of 30 studies devoted to the comparison of the effectiveness of treatment of patients with PJI of known and unknown etiology [48]. The treatment outcomes of patients with chronic PJI after two-stage revision arthroplasty were significantly better in patients with an unknown infectious agent than in cases with an identified pathogen: infection control was achieved in 83.9 % and 79.6 %, respectively ($p = 0.002$). The effectiveness of one-stage revision arthroplasty did not differ significantly between the compared groups: 88.5 % and 92.4 %, respectively ($p = 0.23$). It is noteworthy that the authors do not provide an unambiguous definition of the term "culture-negative" and do not select publications based on this principle, what may affect the reliability of the results obtained. Despite a number of limitations, this meta-analysis represents one of the most extensive studies on this topic.

It should be noted that the lack of data on pathogens was long considered a contraindication for the use of a one-stage technique, since in this case the prescription of etiotropic antibiotic therapy immediately after surgery is impossible [49]. At the same time, this intervention is extremely attractive for both the physician and the patient, allowing for the avoidance of re-hospitalization, surgery, and, consequently, repeated courses of antibiotic therapy, and shortening the rehabilitation period so that the patient may return to the normal lifestyle faster. In this regard, an increasing number of studies have recently been published devoted to the successful expansion of indications for this intervention [19, 41, 50, 51]. Most authors report comparable results of using a one-stage technique in culture-negative and culture-positive PJI groups [17, 19, 41, 50, 51]. Extremely high efficacy was demonstrated by combining one-stage re-arthroplasty with intra-articular vancomycin administration in patients with unknown etiology of PJI: the infection was stopped in 90.2 % of cases [50]. According to the authors, intra-articular administration of antimicrobial drugs allows for high concentrations to be achieved at the site of infection in the absence of systemic toxic effects, which are characteristic of classical systemic high-dose therapy [52]. However, Xu et al. report lower efficacy of the one-stage technique in patients in the culture-negative group than in the culture-positive group, while the incidence of complications from systemic antibiotic therapy differs significantly: 58.3 % and 11.3 %, respectively ($p < 0.05$) [19]. Patients in the CNI group received a combination of vancomycin with a third-generation cephalosporin or carbapenem postoperatively, with intravenous antibiotic therapy lasting two to four weeks. Although the authors do not specify the antimicrobial dosing regimen, it can be assumed that such a high complication rate is related to the administration of significantly higher antibiotic doses than in patients in the culture-positive group.

Two-stage revision arthroplasty is considered the "gold standard" for treating patients with culture-negative PJI, since etiotropic antibiotic therapy is impossible in such cases, and detection of pathogens difficult to eradicate in intraoperative biopsies always remains possible. Furthermore, the advantages of staged treatment include the ability to prepare soft tissues and bone for subsequent reimplantation and reinsertion of a spacer with a long course of antibiotic therapy in the event of infection recurrence. Many publications devoted to this topic report good and even excellent results using a two-stage technique in patients with an unknown etiology of the infectious process, while the treatment efficacy is comparable, and in some cases even significantly higher, than that in patients with an identified pathogen [12, 18, 20, 21, 53]. Thus, in a study by Choi et al. failures were noted in 15 % of cases in patients without pathogen growth, while in the group with an identified pathogen it was 39 % ($p = 0.006$). However, in the first case, "desperation operations" (such as hip arthrodesis) were significantly more frequent during treatment ($p = 0.003$) [21].

We focused on existing approaches to defining culture-negative PJI. Treatment outcomes for patients with this condition were examined within the context of the term "culture-negative PJI." The rate of successful treatment outcomes in both the group that included only preoperative microbiological testing (MBT) and the group that included both preoperative and intraoperative cultures exceeded 90 % and showed no statistically significant differences ($p = 0.582$). It should be noted that such high infection control efficacy was achieved without the possibility of prescribing etiotropic antibiotics in the early postoperative period, highlighting the importance of timely and regular monitoring of the spectrum of nosocomial pathogens for the appropriate selection of drugs for empirical antibiotic therapy. Thus, a reduction in the rates of patients with CNJ can be achieved by modifying the factors that predict negative MBT results.

Possible ways to reduce the number of patients with unknown etiology of periprosthetic joint infection

Management of patients with infectious complications after large lower limb joint replacement is a complex task requiring the participation of a multidisciplinary team of specialists. The treatment process can be roughly divided into two major phases: the first includes the preoperative period and the surgical procedure itself, and the second, the postoperative period.

The results of microbiological cultures of biospecimens taken preoperatively significantly influence the choice of intervention. In most cases, patients receive empirical antibiotic therapy in the early postoperative period, while microbiological cultures of intraoperative samples determine the type of etiotropic antibiotic therapy that will be continued after the patient's discharge for outpatient treatment. Accordingly, several factors can be identified whose modification could help reduce the incidence of negative culture results (Fig. 3).

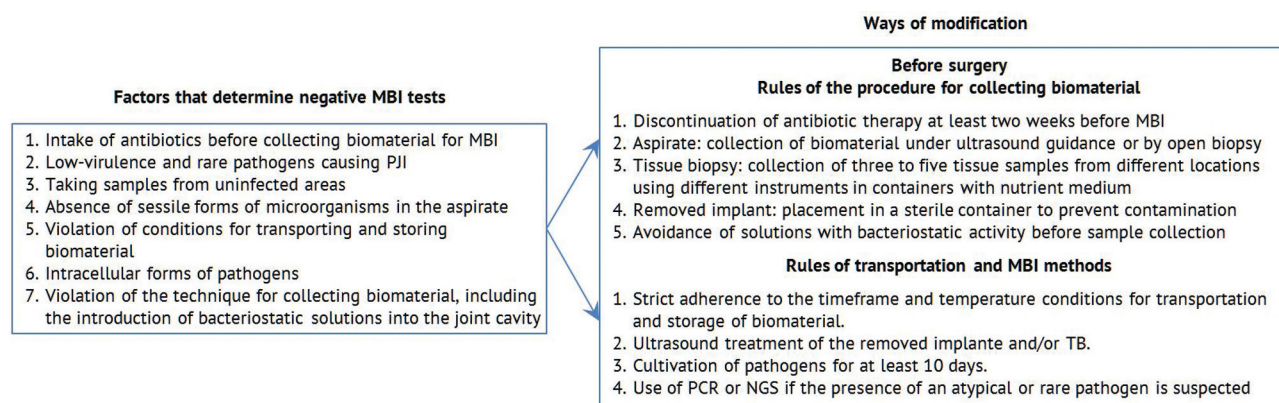


Fig. 3 Factors that have impact on identification of PJI agent and ways of their modification

Recommendations for microbiological diagnosis in the treatment of implant-associated infection are described in detail and summarized by Drago et al. [54]. Thus, in the preoperative period, a key role is given to the cancellation of antibiotic therapy before performing diagnostic tests, as well as an increase in the period of culture cultivation in cases of suspected low virulent pathogens or rare bacteria. For performing percutaneous biopsy, the use of ultrasound navigation is recommended since the probability of detecting a pathogen varies in different anatomical areas. According to Walker et al., the preferred locations for tissue sampling in the hip are the joint bursa (specificity, 100 %) and the joint capsule (sensitivity, 68 %), and the preferred tissue types are the synovial membrane (specificity, 93 %) and pus (sensitivity, 83 %) [55]. If a patient has a fistula tract leading into the joint cavity, fistula discharge collection for analysis is not recommended due to its contamination by skin microflora. A group of Russian scientists has developed and patented a technique for harvesting biopsies from deep within the fistula tract (RU 2 698 175 C1), which significantly improves the effectiveness of preoperative microbiological imaging. During surgery, it is recommended to collect tissue adjacent to the endoprosthesis or tissue with macroscopic signs of infection. Clean, sterile instruments should be used for sampling, avoiding contact with the skin. The biopsy volume

should be at least 1 cm³. Also, for extracting endoprosthesis components, gentle surgical techniques are recommended, avoiding contact with the skin, and placing each component in a separate container. If delivery of materials to the laboratory is delayed, tissue biopsies and metal components should be stored at 4 °C. Synovial fluid can be stored in specialized vials at room temperature for no longer than 48 hours. The use of sonication significantly increases the effectiveness of microbiological studies [56, 57], and if this is not possible, the use of dithiothreitol (DTT) [58] is an alternative.

Molecular methods such as polymerase chain reaction and next-generation sequencing (NGS) are indicated in cases where identification of the pathogen by conventional methods is ineffective (e.g., in cases of infection caused by *Abiotrophia defectiva*, *Granulicatella adiacens*), the clinical picture is not obvious, and the diagnosis of periprosthetic joint infection is questionable. According to the literature, the use of molecular methods enables identification of the pathogen in 4–13 % of patients with aseptic loosening [59]. Many publications on NGS demonstrated an extremely high sensitivity of the method compared to standard cultural studies [60–63]. According to Tarabichi et al., the use of next-generation sequencing allows establishing the etiology of the infectious process in 82 % of culture-negative PJI cases [63].

Limitations of this systematic review include retrospective nature of its material, the design of the included articles (case-control or cohort studies), and the lack of randomized controlled trials. Various studies used different criteria for PJI, its recurrence, and infection resolution. A number of studies failed to include a number of clinical parameters, such as duration of surgery, intraoperative blood loss, duration of antibiotic therapy, and others. Furthermore, a significant limitation is the small number and significant heterogeneity of studies that considered preoperative culture results only. For these reasons, the authors of the present study decided against conducting a meta-analysis. Thus, the obtained results can have only limited practical application; however, an increase in the number of studies devoted to this topic could enable the development of universal treatment guidelines for patients.

CONCLUSION

Based on the data obtained, no significant differences in the effectiveness of treatment in patients with CNI were found that depend on the approach to defining this term. The greatest challenge in treating patients with CNI is the inability to administer etiotropic antibiotics in the early postoperative period which can negatively impact the entire treatment process. The proposed approaches to reducing the incidence of CNI are aimed at modifying the factors that contribute to negative results in MBI tests of biomaterial samples and removed implants.

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