Genij Ortopedii. 2022. Vol. 28, no. 6. P. 842-851.

Review article

https://doi.org/10.18019/1028-4427-2022-28-6-842-851

Analysis of the economic and clinical effectiveness of one- and two-stage revisions in the treatment of periprosthetic infection of the hip joint (literature review)

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Abstract

Introduction Infection is a devastating complication of joint replacement surgery and is associated with significant medical costs of treatment and rehabilitation. This review is based on the analysis of modern domestic and foreign literature and demonstrates the problem of periprosthetic joint infection (PJI) in terms of etiology, pathogenesis, diagnosis and surgical treatment options for PJI, as well as economic costs in different countries. Currently, two-stage revision arthroplasty is the most used treatment method in the world. At the same time, the number of publications on the effectiveness of one-stage revision arthroplasty in PJI has been increasing every year. **Purpose** Analysis of the clinical and economic efficiency of one- and two-stage revision arthroplasty interventions for suppression of the purulent inflammatory process and their medical costs. **Materials and methods** The literature search was carried out in open electronic databases of scientific literature PubMed, eLIBRARY and Scopus. The search depth was 22 years. Sixteen articles were selected for economic analysis in which the expenditures on PJI management in developed and developing countries were reported. Also, there were 15 studies on evaluating the effectiveness of two-stage revisions and 26 articles on evaluating the effectiveness of one-stage revisions and 15 articles on analyzing the functional state of the affected limb according to the Harris Hip Score. The following inclusion criteria were used: systematic reviews, literature reviews, cohort studies on the topic of periprosthetic infection. **Results** The rate of PJI arrest with one-stage method was 89.5 % (Me-88.6; Q1-86 Q3-94) and the average mortality was 2.23 ± 2.24 (Me-1.2 Q1-0.8 Q3 -2.7). The rate of PJI suppression by two-stage method averaged 91.4 % (Me-93;Q1-88.2 Q3-96) with an average mortality rate of 3.2 %. The functional HHS after one-stage replacement averaged 81.8 points, and after two-stage revision arthroplasty it was 77.4 points. The economic cost of treating one patient with PJI, according to various authors, varies from 6,500 to 150,000 dollars. **Conclusions** One-stage revision is cost-effective, has better functional parameters and lower mortality with comparable results in PJI arrest if strict adherence to indications is followed.

Keywords: periprosthetic infection, one-stage revision, two-stage revision, arthroplasty, hip joint, economic costs

For citation: Rozhkov N.I., Ermakov A.M., Burtsev A.V., Triapichnikov A.S., Sazonova N.V., Malyuchenko L.I. Analysis of the economic and clinical effectiveness of one- and two-stage revisions in the treatment of periprosthetic infection of the hip joint (literature review). *Genij Ortopedii*, 2022, vol. 28, no. 6, pp. 842-851. DOI: 10.18019/1028-4427-2022-28-6-842-851.

INTRODUCTION

A hundredfold increase in the publications on the diagnosis and treatment of infectious complications after joint arthroplasty over the past 10 years underlines the interest of the orthopedic community in this problem.

The demographic trend towards an aging population in developed and developing countries, advances in surgical technologies and improvement of implants increased the number of large joint replacement surgeries worldwide [1, 2]. However, there is a growth in various complications, including instability of the endoprosthesis components, periprosthetic fractures, wear of materials in the friction pair, dislocations, and periprosthetic joint infection (PJI) [3].

PJI is a relatively rare but a devastating complication after total joint replacement. The risks of infectious complications after implantation of a primary endoprosthesis, according to the world literature, vary from 0.5 to 3 % and reach 15 % in cases of revision interventions [4].

Infection after arthroplasty is also one of the most expensive diseases, the treatment of which requires revision interventions with a prolonged course of antibiotic therapy, long-term inpatient and rehabilitation treatment with involuntary disability of the patient [5].

Two-stage revision is the most reliable strategy for the treatment of PJI in the world; however, more and more surgeons prefer to use one-stage revision [3, 6]. Both of the above methods provide high rates of infection eradication, reaching 85-95 % of cases according to various literature data.

Purpose Analysis of the clinical and economic efficiency of one- and two-stage revision arthroplasties in terms of infection suppression and medical costs for their implementation.

MATERIALS AND METHODS

The search for publications was carried out in open electronic sources of medical literature PubMed, eLIBRARY, Scopus with a search depth of 22 years (from 2000 to 2022).

The following inclusion criteria were used: systematic reviews, literature reviews, cohort studies on the topic of periprosthetic infection. The selection was carried out using key phrases in Russian and English: hip arthroplasty, PJI (periprosthetic joint infection), two-stage revision or exchange, one-stage revision or exchange, medical expenses for treatment (economic burden).

Exclusion criteria: animal studies, case reports or case series, abstracts, republishing.

A total of 15,580 articles published between 2000 and 2022 were found. Of these, 16 publications on economic costs in various countries were selected and analyzed. Also, 41 studies were chosen that were related to one- and two-stage revision interventions with an analysis of the effectiveness and arrest of periprosthetic infection of the total hip arthroplasty (THA). The review also includes 15 articles on the analysis of the functional state of the operated limb according to the Harris Hip Score. The remaining sources of literature display general data on PJI.

RESULTS

Epidemiology of periprosthetic infection

Twelve percent of patients undergo revision surgery after primary knee and hip arthroplasty within 10 years after the installation of the primary implant [7, 8]. The Russian Register of the Vreden NMRC for TO ranks aseptic loosening of components among the first causes of revision THA with the incidence of 34 to 94 % of cases. This is followed by deep infection, dislocations, wear of implants, periprosthetic fractures. Kurtz SM et al. suggested that the annual increase in patients with periprosthetic infection by 2030 in the United States would be approximately 270 thousand cases, and, according to the findings of Schwartz AM et al., periprosthetic infection would dominate among the causes of revision surgery by 2030 [9, 10].

The number of large joint arthroplasty continues to increase in all countries of the world [3]. In the Russian Federation, 147,061 surgeries for primary knee and hip arthroplasty were performed in 2019, and 4,282 cases of PJI were registered [11]. According to the data of the register of the Vreden NMRC for TO, in the structure of revision interventions, infection accounts for 52.9 % of cases during the first years after surgery and 14.07 % of cases in later periods [11]. For comparison, revision interventions due to PJI occupy in foreign national registries from 18.5 to 25 %; 22.3 % in Australia, 18.5 % England and Wales [12, 13].

As reported by foreign authors, the incidence of PJI after primary hip arthroplasty varies from 0.5 to 3 % of cases [14], and according to Russian experts, it is 5-6 % [15]. At the same time, there is a significant increase in infectious complications after aseptic revision arthroplasty, reaching 35 % [8, 16] of cases, and a recurrence of a purulent process following PJI treatment is observed in 22 % of cases [17]. Due to the fact that the disease is chronic, the risks of relapse are life-long. Thus, the general economic costs of health care systems to solve them have been growing every year [18].

Despite the serious accumulated experience in the treatment of PJI, mortality in foreign countries (such as the USA, China, France and Spain) reaches 3.5 % [19, 20, 21]; in the Russian Federation, the mortality rate was 2.99 % after two-stage revision interventions [22].

Long-term surgical treatment of recurrent PJI and poor functional results in elderly patients often become the causes of disputes at the court between the surgeon and the patient [23].

Based on the foregoing, revision THA is becoming increasingly important. Due to the fact that repeated operations frequently cause the development of periprosthetic infection, orthopedic surgeons often face the question of choosing between the tactics of one- or two-stage revision arthroplasty.

Risk factors associated with PJI

Risk factors for PJI are usually divided into causes related to the patient's somatic condition, features of surgical intervention, and the nature of the postoperative period [3, 24].

In the current literature, there is evidence of patient-related factors that significantly contribute to the development of PJI, among them: smoking, drug use, diabetes mellitus, urinary tract infection, HIV infection, chronic viral hepatitis, oncological diseases, chronic kidney disease in stages of decompensation, obesity, glucocorticoids intake [3, 25].

Among the intraoperative reasons for the development of infectious complications after joint arthroplasty are the duration of surgery for more than 180 minutes, significant blood loss (more than 800 ml), blood transfusion, excessive tissue trauma, nosocomial strains of bacteria, as well as non-compliance with the rules of asepsis and antisepsis [26].

In the postoperative period, it is also recommended to observe the asepsis of medical manipulations, the sequence of dressings in patients with varying contamination of the surgical wound, and to monitor the patient's main laboratory parameters (hemoglobin levels, glycemia, and acute phase markers of inflammation) [3].

Through timely identification and management of patient-related risk factors along with patient compliance with appropriate medical recommendations, it is possible to improve the overall postoperative clinical outcomes of PJI treatment [6].

PJI etiology

According to various literature sources, isolated gram-positive microflora is the cause of PJI in 50-60 % [27, 28], of which there are strains of *Staphylococcus*

aureus in 20-50 % and in 30-43 % of *epidermal Staphylococcus* [29, 30], while resistant strains of *MRSE* and *MRSA* vary from 23 to 63 % of the total number of staphylococci [31]. It should be noted that bacteria of the staphylococci family have various pathogenicity factors in the form of protein toxins, adhesion factors, invasion and colonization, as well as the ability to form biofilms, which prevent the action of immune cells of the macroorganism and antibacterial drugs [32].

Isolated gram-negative microflora is diagnosed in PJI in 7 % of cases and is represented by *P. aeruginosa*, *Acinetobacter spp., K. pneumonia, Proteus spp., Enterobacter spp., E. Coli* [33].

Polymicrobial infection accounts for up to 37 % of the etiology of purulent inflammatory complications after arthroplasty of large joints [34], which is characterized by a severe and recurrent course of the disease, presence of resistant strains of microorganisms in its composition, and a high level of generalization of the infectious process [31]. The so-called difficult-to-treat microorganisms (DTT) are often detected in the microbial associations, including rifampicin-resistant staphylococci, fluoroquinolone-resistant gram-negative bacteria and fungi (*Candida sp*.) [34].

Contamination with subsequent adhesion of pathogenic microorganisms on the implant surface occurs either during the intervention or by hematogenous way from non-sanitized foci in the patient's body [31, 36]. Subsequently, microorganisms colonize on the endoprosthesis components and pass four stages of bacterial film maturation (primary and secondary adhesion, maturation, dissemination), actively forming a mucopolysaccharide matrix for a mature biofilm [37]. The process of biofilm formation is the basis of PJI pathogenesis [31]. Being in the biofilm, bacteria are protected from the effects of antimicrobial drugs and cells of the human immune system, what makes it difficult to treat the infection without radical surgical treatment with the forced removal of all elements of the endoprosthesis [31, 38].

Moreover, there is evidence of the ability of staphylococci to penetrate into target cells such as osteoblasts, macrophages and neutrophils. It is these properties of bacteria that allow them to persist for a long time in various target cells and in the body as a whole, often becoming the causes of recurrence of the pathological process [39].

PJI diagnosis

To date, there is no single diagnostic method that can 100 % confirm or exclude the presence of PJI [40]. Diagnosis of PJI is based on the analysis of clinical manifestations (including persistent pain in the joint) [41], the results of laboratory tests of peripheral blood and synovial fluid, as well as data from microbiological, histological and radiological examinations [3, 42].

Current guidelines for the diagnosis of PJI are the algorithms presented by the following bodies: ICM (International Consensus Meeting 2013 and 2018) [43], WAIOT (The World Association against Infection in Orthopedics and Trauma), EBJIS (The European Bone and Joint Infection Society 2018) [44]. Clinical and laboratory studies used in the above algorithms include the detection of fistulous tracts communicating with the joint cavity, purulent contents in the affected joint, elevated levels of ESR and CRP in the blood serum, a cytological examination of the aspirated joint fluid with the determination of leukocytes count and percentage of neutrophil content, including bacteriological and histological examination of joint tissues.

Blood biomarkers such as ESR and CRP have been well studied and recognized in the diagnosis of PJI, but they are indicative of general inflammation in the body and may not be elevated in low infection activity [45]. The low cost of studies of acute phase hematological markers allows them to be widely available in various medical hospitals [43]. The normal reference value of CRP does not exceed 10 mg/l, ESR 30 mm/h, while CRP has a slightly higher sensitivity and specificity [46]. Patients with high ESR and CRP should undergo a diagnostic puncture of the prosthetic joint to determine the number of leukocytes and neutrophils in the aspirated exudate. The level of leukocytes more than 3000 per μl and neutrophils more than 70 % indicates the presence of an infectious process [43]. Interleukin-6 (IL-6) is another hematological marker produced by monocytes and macrophages and is of interest for diagnosing PJI. According to the literature, this method has a sensitivity of 62.5-97 % and a specificity of 85.7-100 % [47], while the main disadvantage is its high cost [48].

Other new and promising serological tests, such as IL-6, calprotectin, adenosine deaminase, procalcitonin, α-defensin and D-dimer, synovial cytokines, are under active study and have economic and technical limitations in daily clinical practice [48, 49].

Instrumental methods such as radiography contribute to the diagnosis of PJI, identify the type of implanted endoprosthesis, the degree of its stability, the nature of bone defects in the prosthetic joint, and the presence of periprosthetic fractures and dislocations [50]. Visualization on radiographs of periosteal bone reaction, osteolysis at the interface with the implant, migration of endoprosthesis components, and accumulation of gas may indicate infection.

Most diagnostic algorithms do not recommend the widespread use of expensive methods in clinical practice, such as spiral, computed tomography, magnetic resonance imaging, three-phase bone scintigraphy, leukocyte-labeled scintigraphy, and positron emission tomography [43, 44].

Variants of PJI treatment and economic issues

The main tasks in the treatment of PJI are the eradication of the purulent inflammatory process and the maximum possible preservation of the limb

functionality. Moreover, the treatment process is a serious challenge for both the surgeon and the patient, and for the healthcare system as a whole [51].

The most used methods of surgical treatment of PJI are one-stage and two-stage revision interventions [52]. However, in the acute period of the disease, preference is given to the debridement technique (DAIR – Debridment, Antibiotics, Implant Retension), which is based on thorough surgical debridement with tissue irrigation and replacement of the modular components of the endoprosthesis (liner and head). Due to the fact that the debridement technique does not provide for the complete replacement of infected endoprosthesis components, the risks of possible complications such as bone fractures, dislocations, and loss of bone tissue during implant removal decrease [52]. Many studies reported variable success in eradication of infection after DAIR, with rates ranging from 26 % to 95 % [16]. Negative results of the DAIR method are associated with a high probability of recurrence and subsequent surgical intervention.

The one-stage technique is indicated for patients with a compensated somatic status, a satisfactory soft-tissue condition, an identified microorganism and its good sensitivity to oral antibiotics [54]. Further, Table 1 shows the main indicators of the technique of one-stage revision arthroplasty in 8,110 patients with an overall PJI arrest of 89.5 % (Me-88.6; Q1-86; Q3-94) and an average mortality rate of 2.23 ± 2.24 (Me-1.2; Q1-0.8; Q3-2.7).

One-stage revision has a number of advantages compared to two-stage revision, which include one surgical and anesthetic intervention, a total lower intra-operative blood loss, a low level of postoperative complications and a percentage of deaths, one hospitalization with a shorter rehabilitation period, cost-effectiveness with comparable results in infection eradication between the techniques [55].

Table 1

Summary of the data on the efficiency of one-stage revision THA

Authors and year of pulication	Number of cases	Follow-up (months)	Mortality rate, %	PJI recur-rence, %	Arrest of infection, %
Ermakov et al., 2019 [55]	14	30	–	14	86
Zahar et al., 2019 [56]	85	–	–	6	94
Buchholz et al., 1981 [57]	640	52	2.7	23	76.8
Wroblewski, 1986 [58]	102	38	–	9	91
Sanzén et al., 1988 [59]	102	–	–	25	80
Hope et al., 1989 [60]	72	–	–	13	87
Loty et al., 1992 [61]	90	47	1.1	10	79
Elson, 1994 [62]	235	–	–	14	86
Raut et al., 1994 [63]	57	88	7	14	86
Raut et al.,1996 [64]	15	120	–	7	87
Ure et al., 1998 [65]	20	120	0	0	100
Callaghan et al., 1999 [66]	24	120	–	8.3	92
Jackson & Schmalzried, 2000 [67]	1299	58	0.8	17	83
Vielpeau & Lortat-Jacob, 2002 [68]	127	36	–	16	84
Rudelli et al., 2008 [69]	32	103	–	6.2	94
Wolf et al., 2011[70]	576	–	0.5	28	72
Beswick et al., 2012 [71]	1225	24	–	9	91
Lange et al., 2012 [72]	375	–	–	13	87
Zeller et al., 2014 [73]	157	41.6	1.3	5	88
Kunutsor et al., 2015[74]	2536	35	–	8	92
Ilchman et al., 2016 [75]	39	24	–	–	100
Born et al., 2016 [76]	28	84	–	–	100
Ebied et al., 2016 [77]	72	72	–	–	97
Whiteside et al., 2017 [78]	21	63	–	1	95
Lange et al., 2018 [79]	56	24	–	8.9	96
Ji et al., 2019 [80]	111	58	–	17.4	89.2
Total	8,110	61.8 ± 33.3 Me – 55 Q1 – 35.5 Q3 – 86	2.23 ± 2.24 Me – 1.2 Q1 – 0.8 Q3 – 2.7	11.8 ± 7 Me – 10 Q1 – 7 Q3 – 15	89 ± 7.2 Me – 88.6 Q1 – 86 Q3 – 94

Two-stage revision arthroplasty using an antimicrobial spacer is the "gold standard" in the treatment of chronic PJI with an efficiency rate within 80 to 95 % [31] (Table 2). However, compared to one-stage revision, it has a number of disadvantages: the need to perform two surgical interventions, a longer rehabilitation period and hospital stay, a higher mortality rate [56, 79], and medical costs for treatment [9]. A two-stage treatment technique is indicated for patients with septic conditions, significant bone and soft tissue defects, DTT infections and unknown etiology of PJI [81]. This procedure includes the removal of all elements of the implant, a thorough surgical debridement of infected tissues and installation of a cement spacer with its subsequent conversion to a permanent endoprosthesis. Some authors are of the opinion that it is the antimicrobial effect of the spacer that ensures the high efficiency of two-stage revision arthroplasty [82]. Moreover, the spacer allows movements in the affected joint, provides the length and limb supportability [17, 22, 81].

The treatment results of 2,162 patients with PJI showed the effectiveness of the technique of two-stage revision arthroplasty in terms of infection arrest that averaged 91.4 % (Me-93; Q1-88.2; Q3-96) with an average mortality rate of 3.2 %.

Further, we considered it necessary to compare the functional state of the affected joint after the use of one- and two-stage replacement of the infected endoprosthesis. The results are shown in Table 3.

Table 2

Summary of the data on the efficiency of two-stage revision THA

Authors and year of pulication	Number of cases	Follow-up (months)	Mortality rate, %	PJI recurrence, %	Arrest of infection, %
Sanzen et al., 1988 [59]	102	24	1,8	25	75
Hsieh et al., 2004 [83]	42	55.2	–	7	93
Hofmann et al., 2005 [84]	27	76	0	6	94
Masri et al., 2007 [85]	29	24	6.9	14	86
Biring et al., 2009 [86]	99	144	–	11	89
Chen et al., 2009 [87]	48	66	–	4	96
Oussedik et al., 2010 [88]	39	60	–	5	95
Engesaeter et al., 2011[89]	283	24	–	8	92
D'Angelo et al., 2011 [90]	28	53	–	4	96
Klouche et al., 2012 [91]	46	24	–	3	97
Lange et al., 2012 [92]	929	–	–	10	90
Berend et al., 2013 [93]	205	53	4	24	76
Shen et al., 2014 [94]	33	60	–	0	100
Babis et al., 2015 [95]	31	30	–	0	100
Total	2,162	57.7 ± 33.2 Me – 55.2 Q1 – 24 Q3 – 72	3.2	10.08 ± 7.4 Me – 7.5 Q1 – 4.5 Q3 – 12.5	91.4 ± 7.5 Me – 93 Q1 – 88.2 Q3 – 96

Table 3

Summary of functional assessment with Harris Hip Score in the treatment variants

Authors and year of publication	One-stage revision		Two-stage revision	
	HSS before surgery (points)	HSS after surgery (points)	HSS before surgery (points)	HSS after surgery (points)
Ermakov et al., 2019 [55]	44.14	77.71		
Zahar et al., 2019 [56]	43	75		
Ji et al., 2019 [80]	–	79.6		
Hofmann et al., 2005 [84]			53	92
Masri et al., 2007 [85]			38	70
Chen et al., 2009 [87]			26	83
Oussedik et al., 2010 [88]	–	87.8	–	75.5
D'Angelo et al., 2011 [90]			43	82
Berend et al., 2013 [93]			–	65
Shen et al., 2014 [94]			42	89
Cabrita HB et al., 2007 [97]			19.7	75
Fink B et al., 2009 [98]			41	69
Fehring TK et al., 1999 [99]			–	81
Yoo JJ et al., 2009 [100]	53.5	88.9		
Total	46.8 ± 7.5 Me – 43	81.8 ± 6.2 Me – 79	37.5 ± 10.3 Me – 39,5	77.4 ± 8.5 Me – 77,5

The data obtained from the table demonstrate the advantage of the functional state of the limb according to HHS after one-stage replacement of the endoprosthesis (average 81.8 points) over the results after two-stage revision arthroplasty (average 77.4 points). The same finding was confirmed by Oussedik et al. who report significant differences in the functional results of the replaced joint after one-stage (HSS, 87.8 points) and two-stage (HSS, 75.5 points) treatment methods [88]. Moreover, one-stage revision may improve joint function by 35 HSS points after surgery, as reflected in a retrospective study [100].

Medical costs for the treatment of large joint PJI significantly exceed the financial costs for primary and aseptic revision arthroplasty [101]. Economic expenses for the treatment of one patient with PJI, according to various authors, vary from 6,500 to 150,000 dollars (Table 4).

Such a wide range of costs is due to the peculiarities of the disease course, the diagnostics performed, and the choice of surgical treatment methods with different periods of rehabilitation [114]. According to Russian authors, in the Russian Federation, the average cost of PJI treatment using the one-stage revision technique is 324,531 rubles versus 683,328 rubles for two-stage revision [11].

Table 4

Summary of medical expenditures for PJI management

Authors and year of publication	Country	Expenditures per one PJI patient	
		One-stage	Two-stage
Kurz et al., 2012 [9]	USA	–	105, 463 $
Середа и др., 2021 [11]	Russia	4 406 $	9 278 $
Klouche et al., 2012 [91]	France	49 243 $	85, 568 $
Vanhegan IS et al., 2012 [101]	Great Britain	–	24 117 €
Bozic et al., 2005 [103]	USA	–	135, 554 $
Parvizi et al., 2010 [104]	USA	67 781 $	132, 921$
Romano et al., 2014 [105]	Italy	–	99, 079 $
Alp E et al., 2015 [106]	Turkey	–	16 999 $
Sousa A et al., 2018 [107]	Portugal	–	11 415 €
Puhto T et al., 2019 [108]	Finland	–	44 600 €
Peel.TN et al., 2013 [109]	Australia	–	19 469 €
K. Graf et al., 2011 [110]	Spain	–	2 342-38 554 $
J.L. Alfonso et al., 2007 [111]	Spain	–	10 232 $
Iqbal F et al., 2020 [112]	Pakistan	–	12 277 $
Kim HS et al., 2020 [113]	South Korea	–	6 016 $

DISCUSSION

An analysis of current medical literature shows a comparable level of success after one- and two-stage revision interventions in the treatment of infectious complications after joint arthroplasty. Whiteside L.A. and Roy M.E. reported 95 % success rate of infection arrest in the presence of resistant strains of microorganisms, using the simultaneous exchange of endoprosthesis components and the subsequent administration of antibacterial drugs into the joint cavity [78]. Artyukh V.A. et al. demonstrated good results in infection arrest using the one-stage revision technique (82.1 %) in patients with the fistulous PJI [115].

Berend K.R. et al. analyzed the use of two-stage revision arthroplasty for 15 years and reported the mortality rate of 7 % before the second stage of treatment [93]. According to the Danish Arthroplasty Registry, PJI recurrence after two-stage joint replacement reaches 14.6 % within 5 years [116]. Kildow B.J. and Chen S.Y. et al. report higher infection suppression rates (91.4-91.7 %) with a mortality rate of 16.1-41.1 % due to comorbidities [117, 118]. Petis S.M. et al. reported deaths in 56 % of patients treated for hip PJI over a 12-year follow-up period [119].

Most systemic reviews show close success rates for both revision techniques that overwhelmingly exceed 90 % [74, 120]. However, a number of specialists question the high efficiency of revision techniques, stating the recurrence rate of the purulent process in 16.8 and 32.3 % for one-stage and two-stage intervention, respectively [52]. Therefore, it is appropriate to conduct further comparative studies of one- and two-stage revision operations based on the results of infection control, function of the affected joint and medical expenses.

CONCLUSION

Two-stage revision arthroplasty with an antimicrobial cement spacer at the first stage is the most used technique for PJI treatment. However, more and more publications devoted to the analysis of the results of the technique of one-stage revision arthroplasty appear in the medical literature. This type of intervention demonstrates encouraging results of treatment in terms of infection arrest, high functionality of the operated joint, as well as minimal economic costs. At the same time, one-stage revision has significant limitations for use, including the septic condition of the patient, a history of failed revisions, bone and soft tissue deficit, resistant strains of microorganisms and/or polymicrobial infection.

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The article was submitted 07.06.2022; approved after reviewing 17.06.2022; accepted for publication 19.10.2022.

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