Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2023;12(3):700-9

Very late periprosthetic joint infection: Etiological agents and outcomes of two stage revision

Osman Cimen[1], Alper Koksal[2]

Metin Sabanci Baltalimani Bone and Joint Diseases Training and Research Hospital, Department of Orthopedics and Traumatology, İstanbul, Türkiye

Received 01 June, 2023; Accepted 18 July, 2023
Available online 19.08.2023 with doi: 10.5455/medscience.2023.05.075

Abstract

The main aim of the current study is to evaluate the success of two-stage revision surgery in very late periprosthetic joint infection (PJI). The second aim was to identify the causative etiological agents and to rank these pathogens according to their incidence. Twenty-seven patients (16 THA and 11 TKA) who were operated on with two-stage revision arthroplasty due to very late PJI (>60 months after primary arthroplasty) were included in our study. Demographic information of the patients, operation site, follow-up period, time from the first spacer application to the second stage revision, number of spacer replacement surgeries, duration of infection, presence of fistula, presence of recurrence after second stage arthroplasty and complications were noted. Preoperative and last follow-up Knee Society and Harris Hip Scores were calculated. The success of two-stage revision surgery was evaluated statistically. The causative etiological agents were ranked according to their incidence. The age of the patients at the time of first stage revision ranged from 24 to 94 years, with a mean age of 57.9±15.7. Infection recurrence was 18.75% in the very late hip and 27.3% in the very late knee PJI group. There was a statistically significant increase in postoperative Knee Society and Harris Hip Scores ($p<0.05$). Staphylococcus epidermidis was the first and Staphylococcus aureus was the second in the ranking of isolated pathogens according to their frequency (37% and 18.5%, in total, respectively). There were 2 patients infected with Pseudomonas aeruginosa in the very late hip and one patient infected with Escherichia Coli in the very late knee PJI group. Two-stage revision is an effective and safe surgical procedure to treat PJI and achieve better functional outcomes. Staphylococcus epidermidis was the pathogen with the highest incidence, while Staphylococcus aureus was the pathogen with the second highest incidence in very late PJI.

Keywords: Knee prosthesis, hip prosthesis, infection, revision surgery, staphylococcus epidermidis, staphylococcus aureus

Introduction

Periprosthetic joint infection (PJI) is an unwanted and devastating complication of total joint arthroplasty. This rare complication may lead to removal of the existing prosthesis, and rarely may cause loss of limb or even life [1]. It has been presented that, subcutaneously implanted foreign bodies in animals can be selectively infected with 100-1000 colony-forming units of Staphylococcus aureus per milliliter of blood [2]. The presentation by Murdoch et al. of the development of PJI in 15 of 44 patients with prosthetic implants during Staphylococcus aureus bacteremia proves that this observation holds true for humans as well [3]. In other words, an implant can be infected not only during surgery, but at any time in the human body. Infection can be exogenous or hematogenous [4]. Various studies have reported that most PJIs are diagnosed after the first year after surgery [5,6].

Periprosthetic joint infections had previously been classified in the literature, and infection that occurred more than 60 months

CITATION
Cimen O, Koksal A. Very late periprosthetic joint infection: Etiological agents and outcomes of two stage revision. Med Science. 2023;12(3):700-9.

Corresponding Author: Osman Cimen, Metin Sabanci Baltalimani Bone and Joint Diseases Training and Research Hospital, Department of Orthopedics and Traumatology, İstanbul, Türkiye
Email: osmancimen44@gmail.com

DOI: 10.5455/medscience.2023.05.075

after primary arthroplasty was also classified as very late PJI [7]. There is no internationally accepted standard treatment method in the management of very late PJI. Therefore, the main aim of this study is to evaluate the success of two-stage revision arthroplasty by sharing our results in the treatment of very late PJI. The second aim of the study was to identify the causative etiological agents of very late PJI and to rank these pathogens according to their incidence.

Material and Methods

Patient information

After our institution's local ethical committee approval received on 8 May 2023 with IRB number 7/67, this study was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients included in the study. The radiological and clinical data of 171 patients who underwent revision knee and 178 patients who underwent revision hip surgery due to PJI between 2005 and 2017 were obtained retrospectively from the online database of our tertiary referral hospital. Thirty-eight patients (20 total hip arthroplasties (THA) and 18 total knee arthroplasties (TKA)) were identified, who underwent two-stage revision arthroplasty because of developing very late PJI. Eleven patients (4 THA and 7 TKA) who did not come for the final follow-up were excluded from the study. Eventually, as seen in the flowcharts in the figure 1 and 2, the remaining 27 (16 THA and 11 TKA) patients were included. Seventeen (9 TKA, 8 THA) of these patients were referred from other hospitals with a diagnosis of PJI. All patients with very late PJI were infected after primary total knee or hip arthroplasties.

A standard protocol was used for the management of PJI in all patients. Joint aspiration was routinely performed before the operation. The consensus guidelines of the workgroup of Musculoskeletal Infection Society were followed for the diagnosis of PJI [8] (Table 1).

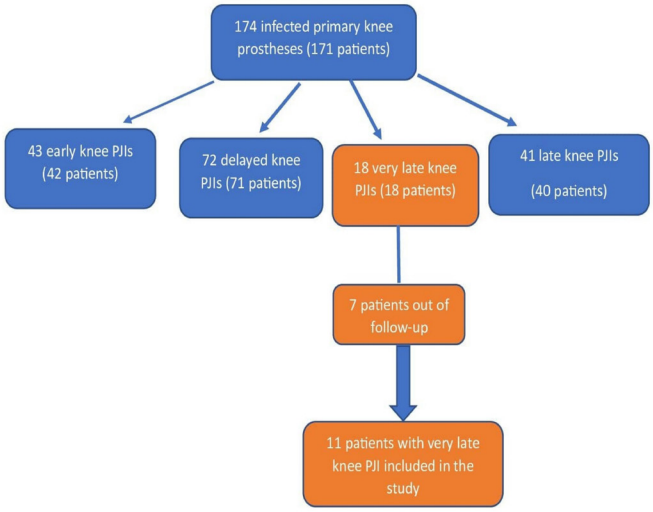

Figure 1. Flowchart showing the patient selection process for the very late knee PJI patients

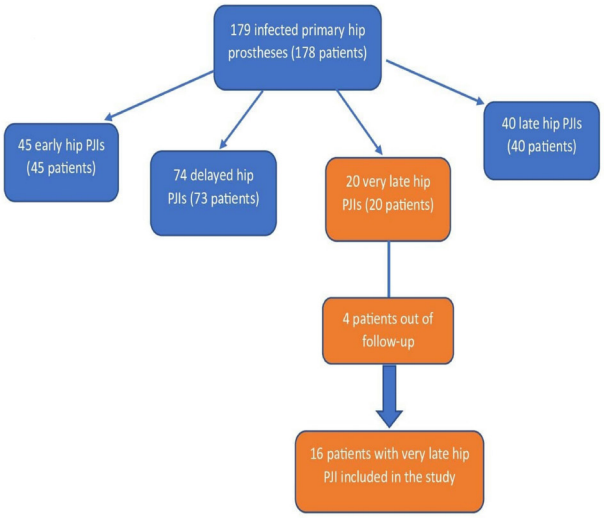

Figure 2. Flowchart showing the patient selection process for the very late hip PJI patients

Table 1. Definition of periprosthetic joint infection

Major criteria (One of the following enough for diagnosis)				
Visualization of prosthesis or evidence of a sinus				
Two positive cultures with the same organism				
		Minor criteria	**Score**	**Decision**
Preoperative diagnosis	**Serum**	Elevated CRP or D-dimer	2	≥6 infected
		Elevated ESR	1	
	Synovial	Elevated synovial WBC count or LE	3	2-5 possibly infected
		Positive alpha-defensin	3	
		Elevated synovial PMN (%)	2	0-1 not infected
		Elevated synovial CRP	1	
Inconclusive pre-op score or dry tap				
Intraoperative diagnosis		Preoperative score	-	≥6 infected
		Intraoperative purulent material	3	4-5 inconclusive
		Positive culture with an organism	2	
		Positive frozen biopsy	3	≤3 not infected

LE: leukocyte esterase, PMN: polymorphonuclear, WBC: white blood cell. For the patients who had 2-5 scores based on the intraoperative minor criteria or who had dry tap, intraoperative diagnostic criteria can be used

DOI: 10.5455/medscience.2023.05.075

Surgical information

First-stage revision and follow-up

All very late knee PJI patients were operated in supine position. An anterior midline longitudinal incision with medial parapatellar arthrotomy was performed. In the first stage, the components of the prosthesis and cement were removed. All infected and non-viable soft and osseous tissues were debrided. Samples were taken from joint fluid, intra-articular soft and osseous tissue for microbiological culture and pathological examination. Teicoplanin or vancomycin with gentamicin impregnated bone cement spacer (Figure 3, 4) which was fashioned intraoperatively in an articulating form was placed following the debridement.

Figure 3. AP radiograph of a handmade articulating type antibiotic impregnated knee cement spacer

Figure 4. Lateral radiograph of a handmade articulating type antibiotic impregnated knee cement spacer

Lateral decubitus position and posterolateral approach was preferred in all very late hip PJI patients. While making the skin incision, the draining sinus and scar tissue are removed. The external rotator tendons of the hip are cut to reach the pseudocapsule. Samples were taken from pseudocapsule, joint fluid and infected soft tissue for microbiological culture and pathologic examination. After hip joint luxation, all implants, cement, infected and necrotic tissues were debrided. Teicoplanin or vancomycin with gentamicin impregnated bone cement spacer which is prepared by molding into a partial hip prosthesis form, which a titanium vertebrae rod was placed in the stem to prevent breakage, was placed in the articular space following the debridement.

DOI: 10.5455/medscience.2023.05.075

An antibiotic-impregnated spacer was produced using 4 g antibiotics with each package (40 g) of polymethyl methacrylate bone cement.

Intravenous cefazolin was continued postoperatively until the microbiological cultures resulted. Subcutaneous low molecular weight heparin was administered to very late knee PJI patients for ten days and to very late hip PJI patients for three weeks for thromboembolism prophylaxis. On the first postoperative day, all patients were allowed to bear as much weight as the operated extremities could tolerate. Intravenous antibiotic treatments of the patients were adjusted according to the culture antibiogram results. Fifteen days after the surgery wound was checked and sutures were removed. Successive follow-ups were planned once in every month. Patients were received parenteral antibiotic therapy for about 6 weeks. In the presence of normalized CRP (C-reactive protein) and ESR (erythrocyte sedimentation rate) values at the end of six weeks, intravenous antibiotic treatment was terminated and treatment was continued with oral antibiotics. Oral antibiotic treatment was continued for 4 weeks. The patients were re-evaluated for spacer replacement, when CRP and ESR elevations were detected in the postoperative period.

Second-stage revision and follow-up

C-reactive protein and ESR levels were evaluated once a week for three weeks after discontinuation of oral antibiotic therapy. Three weeks later, patients with normal ESR and CRP values and no clinical signs of infection underwent a second-stage revision.

The second stage revision for very late knee PJI was performed in the supine position using an anterior midline longitudinal incision. Medial parapatellar arthrotomy was performed in all patients following the skin incision. Articulating type cement spacer was removed. All infected and non-viable soft and osseous tissues were debrided. Samples were taken from joint fluid, intra-articular soft and osseous tissue for microbiological culture and pathological examination. A revision knee prosthesis was implanted by using the hybrid cementation technique.

The lateral decubitus position and posterolateral approach were preferred for the second stage revision in all very late hip PJI patients. Cement spacer was removed. All infected and non-viable soft and osseous tissues were debrided. Joint fluid, intra-articular soft and osseous tissue samples were taken for microbiological culture and pathological examination. Finally, a cementless revision hip prosthesis was implanted.

Intravenous cefazolin was continued postoperatively until the microbiological cultures resulted. If these microbiological cultures were found negative, antibiotic therapy was discontinued. All patients were allowed to bear weight as early as they could tolerate on the first postoperative day. Fifteen days after the surgery wound was checked and sutures were removed. Successive follow-ups were planned on the first, third, and sixth months postoperatively. Patients' ESR levels, CRP levels, standing AP and lateral radiographs were checked at each visit.

Sample collection for bacterial culture

Before prophylactic antibiotics were given in the operating room, joint fluid, intra-articular soft and osseous tissue samples were taken for microbiological culture and pathological examination. Samples were transferred in dry, sterile, plastic containers for gram staining and culture. They were inoculated directly onto a conventional blood agar plate (5% of bovine blood) or liquid thioglycolate medium. Blood agar and thioglycolate medium cultures were incubated at 37°C. Blood agar cultures were incubated in 5% CO_2 atmosphere and thioglycolate medium cultures were incubated in an air atmosphere. Cultures were checked daily for 7 days. If any growth was suspected in the thioglycolate medium, it was cultivated on a Schadler agar medium with 5% sheep blood and incubated in an anaerobic atmosphere. Cultures were accepted negative if no growth was seen within 7 days. Isolated microorganisms were identified by conventional and metabolic tests (catalase, oxidase etc). Antibiotic susceptibility was evaluated by using disc-diffusion susceptibility test. ARB and mycobacteria cultures were also performed if a previous history or suspicion of tuberculosis.

Data evaluation

Patients' demographics (age, gender), operation site, follow-up time, time from first spacer application to second stage revision, time until signs of periprosthetic infection appear, presence of fistula, presence of recurrence after second stage arthroplasty operation, the number of spacer replacement and complications were noted from our medical records. The preoperative and the last follow-up Knee Society (KSS) and Harris Hip Scores (HHS) were calculated for all knees. The laboratory and clinical findings were evaluated at the final follow-up to decide whether the infection has completely been eradicated. Isolated microorganisms were analyzed retrospectively and noted to rank according to their incidence.

Statistical analysis

Statistical analyses were performed using the IBM SPSS Statistics for Windows v.22 software (IBM Corp., Armonk, NY, USA). Fisher's exact test was used as appropriate for the analysis of the categorical data. The Wilcoxon rank-sum test was used for comparing preoperative and postoperative functional scores (KSS, HHS). The chi-square test was used to compare frequencies of bacteria species isolated from very late knee or hip PJI patients. Statistically significant difference was considered for p-values less than 0.05.

Results

Demographics and clinical results of the patients are presented in Table 2. Age of the patients at initial surgery was ranged from 24 to 94 years with a mean age of 57.9±15.7.

DOI: 10.5455/medscience.2023.05.075

Table 2. Demographic and clinic results of the patients

	Hip (n: 16)	Knee (n: 11)	Total (n: 27)
Age (range), years	49.8±14 (24-66)	67.5±9.4 (61-94)	57.9±15.7 (24-94)
Sex (female/male)	9/7	9/2	18/9
Operation site (right/left)	11/5	6/5	17/10
Mean follow-up time (range), months	53.25±28.5 (24-119)	54.2±39.9 (24-143)	53.6±32.9 (24-143)
Fistula, n	3	3	6
Mean PJI occurance time (range), months	86±26.6 (63-132)	65.5±7.2 (60-84)	72±24.9 (60-132)
First spacer to final treatment time (range), months	10.88±11.3 (3-46)	13.5±7.9 (3-29)	11.7±9.9 (3-46)
Number of spacer replacement (range), n	1.63±1.26 (1-5)	1.73±1 (1-4)	1.67±1.14 (1-5)
Infection recurrance, n	3	3	6

Diabetes mellitus was present in 4 patients with very late hip and 2 patients with very late knee PJI. In addition, in the very late hip PJI group, there were one patient with ankylosing spondylitis, one patient with nephrotic syndrome, and one another patient with autoimmune hemolytic anemia that required immunosuppressive medication.

Infection was found to be eradicated in 13 of 16 (81.25%) patients in the very late hip PJI group and 8 of 11 (72.7%) patients in very late knee PJI group at the final follow-up (77.8%, in total). Very late hip and knee PJI groups were evaluated with Fisher's exact test in terms of infection eradication and there was no statistically significant difference (p: 0.662). If we consider implant loosening and infection recurrence as treatment failure, we can assume that 3 patients (one of three re-infected patients had septic implant loosening) in the very late hip and 4 patients (3 infection recurrence and one aseptic failure) in the very late knee PJI group had treatment failure. So, it can be assumed that the treatment success was 81.25% in the very late hip PJI group and 63.6% in the very late knee PJI group. According to Fisher's exact test there was no statistically significant difference between the two groups in terms of treatment success (p: 0.826).

The mean KSS was improved from 41.9±8.1 points (ranges, 26-67) preoperatively to 82.1±6.4 points (ranges, 30-94) (p: 0.013) and the mean HHS was improved from 36.3±9.4 points (ranges, 22-65) preoperatively to 79.4±5.2 points (ranges, 28-96) at the last follow-up (p: 0.021).

Bacteria were detected in the preoperative aspiration fluid in 4 patients in the very late knee and in 4 patients in the very late hip PJI group. Etiological agents isolated from periprosthetic joint infection sites and p-values are presented in table 3. *Staphylococcus epidermidis* was the first and *Staphylococcus aureus* was the second in the ranking of isolated pathogens according to their incidence, (37% and 18.5%, in total, respectively). There were ten *Staphylococcus epidermidis* isolated patients and 6 of these bacteria were methicillin-resistant *Staphylococcus epidermidis* (*MRSE*). There were five *Staphylococcus aureus* isolated patients. Only one of these bacteria was methicillin-resistant *Staphylococcus aureus* (*MRSA*). According to chi-square test there were no statistically significant difference in the isolation frequency of pathogen microorganisms in the knee and hip very late PJI groups (Table 3).

Table 3. Etiological agents isolated from periprosthetic joint infection sites

	Hip n (%)	Knee n (%)	Total n (%)	P value*
Staphylococcus epidermidis	6 (37.5)	4 (36.4)	10 (37)	0.95
Staphylococcus aureus	3 (18.75)	2 (18.2)	5 (18.5)	0.97
Pseudomonas aeruginosa	2 (12.5)	-	2 (7.4)	0.5
Escherichia coli	-	1 (9.05)	1 (3.75)	0.41
Staphylococcus hominis	-	1 (9.05)	1 (3.75)	0.41
Negative culture	5 (31.25)	3 (27.3)	8 (29.6)	0.82

*hip versus knee isolates

There were implant loosening in 10 of the 16 hip (62.5%) and 6 of 11 knee (54.5%) prostheses, preoperatively. These patients complained of pain at rest and exacerbated with movement. There were no signs of loosening on preoperative radiographs in the remaining 6 hip and 5 knee prostheses patients. These 11 patients had shown acute onset with fever, effusion, joint pain, erythema and warmth at the implant site. Three of acute onset very late knee PJI patients were infected with *Staphylococcus epidermidis* (two *MRSE*) and two patients were infected with *Staphylococcus aureus* (one *MRSA*). Additionally, two of acute onset very late hip PJI patients were infected with *Staphylococcus epidermidis* (one *MRSE*), one patient was infected with methicillin-sensitive *Staphylococcus aureus* (*MSSA*) and another one was infected with *Pseudomonas aeruginosa*. No pathogen could be isolated in 2 of 6 patients in the very late hip PJI group.

DOI: 10.5455/medscience.2023.05.075

There were four patients more than one spacer implementation have been made in the very late hip and five patients in the very late knee PJI group. Infection recurrence was observed in 3 patients in very late hip and in 3 patients in very late knee PJI group. The clinical features, isolated microorganism and the final treatments of the patients with infection recurrence were presented in Table 4.

Table 4. The clinical features, isolated microorganism and the final treatments of the patients with infection recurrence after two stage revision surgery

Patient	Joint	Sex	Pathogen	Final treatment
1	Hip	M	Steril culture	Revision prosthesis loosening, awating for spacer implementation
2	Hip	F	*MSSE*	Spacer was placed after recurrence, awaiting for second stage revision
3	Hip	F	*MRSE*	Girdlestone procedure
4	Knee	F	*MSSA*	Spacer was placed after recurrence, awaiting for second stage revision
5	Knee	F	*MRSE*	Knee arthrodesis with custom made IMN
6	Knee	F	*Escherichia coli*	Knee arthrodesis with custom made IMN

M: male, F: female, *MSSE*: methicillin-sensitive *staphylococcus epidermidis*, *MRSE*: methicillin-sensitive *staphylococcus epidermidis*, *MSSA*: methicillin-sensitive *staphylococcus aureus*, IMN: intramedullary nail

There was a patient who was infected with MRSE and did not recover despite 5 spacer replacements after the second-stage revision in the very late hip PJI group. This patient was treated with Girdlestone procedure (Figure 5). Two different very late knee PJI patients who infected with *MRSE* and *Escherichia Coli*, developed infection recurrence after the second-stage revision, were treated with arthrodesis by using custom made intramedullary nails (IMN) after spacer implementation (Figure 6,7). Periprosthetic fracture developed two patients in the very late hip PJI group were treated with open reduction and internal fixation.

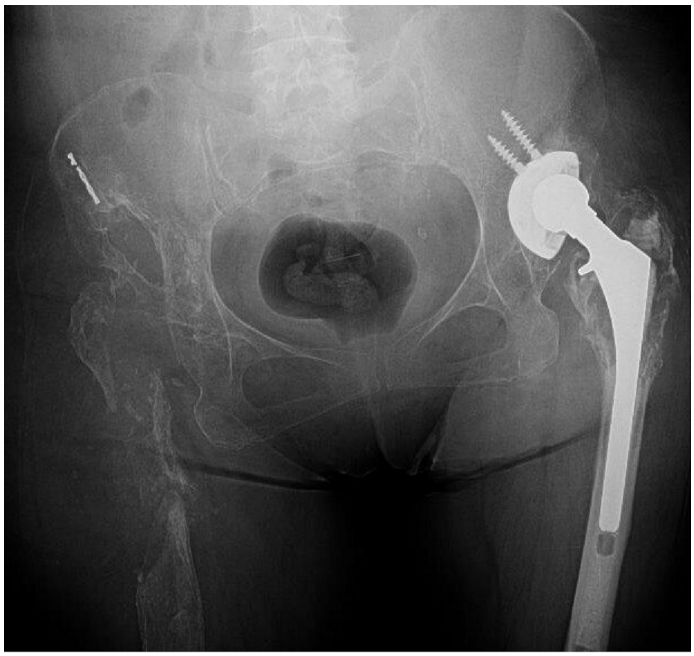

Figure 5. Radiograph of a patient treated with Girdlestone procedure because of persistent periprosthetic joint infection

Figure 6. AP radiograph of a very late knee PJI patient treated with arthrodesis because of infection recurrence after the second-stage revision

DOI: 10.5455/medscience.2023.05.075

Figure 7. Lateral radiograph of a very late knee PJI patient treated with arthrodesis because of infection recurrence after the second-stage revision

Discussion

The PJI was defined by Zimmerli et al as early (occurs less than 3 months after surgery), delayed (occurs within 3-24 months after surgery), and late (occurs more than 24 months after surgery) according to the onset of infection signs [9]. Late PJI is less common than early and delayed PJI, it can occur even years after primary arthroplasty [10]. A low-virulence bacterium can cause PJI more than 2 years after primary arthroplasty [11]. In the literature, to our knowledge, very late PJI (>60 months after primary arthroplasty) term was used by Huotari et al for the first time [7]. They showed that very late PJI is rarer than late PJI with an incidence of 0.044% in the hip and 0.058% in the knee prosthesis [7]. Patients with very late PJI basically have two different clinical presentation. First, acute infection, which accompanied by severe pain, fever, redness, increased temperature and swelling around the joint. Second, mild symptoms such as persistent joint pain and implant loosening (Figure 8) which can make the PJI difficult to distinguish from aseptic loosening.

Figure 8. AP radiograph of a patient with tibial component implant loosening

DOI: 10.5455/medscience.2023.05.075

There are many options for the treatment of chronic PJI occurred after hip and knee arthroplasty. These options can be listed as debridement and irrigation with component retention, antibiotic suppression, one or two-stage exchange arthroplasty, arthrodesis and amputation. One-stage exchange arthroplasty has advantages such as cost-effectiveness, better functional outcomes, and reduced morbidity [12]. However, in the literature, two-stage revision arthroplasty is accepted as the gold standard treatment modality [13-14]. Two-stage revision surgery involves removal of the infected prosthesis, debridement of surrounding soft tissues, and insertion of an antibiotic-releasing implant into the joint rather than replacing the prosthesis performed as in one-stage exchange arthroplasty [15]. It provides effective local and systemic antibiotic release and a second debridement if necessary. We routinely use two-stage revision at our center to manage very late PJI.

The main aim of the current study was to evaluate the success of two stage revision surgery in very late PJI. According to our literature review, current study is the first that evaluates outcomes and success of two-stage exchange arthroplasty for treatment of very late PJI. In some studies, with short and medium-term follow-up, two-stage replacement arthroplasty has been shown to be successful at a rate of 65-95% [16-19]. In the current study infection eradication was 81.25% in the hip and 72.7% in the knee very late PJI. It is well-known that infection recurrence increased as the follow-up period increased in PJI [20,21]. Although our results of two-stage exchange arthroplasty in the treatment of very late PJI seem successful, there is a possibility that infection recurrence may increase over time. The success of two-stage revision arthroplasty depends on many factors, such as the patient's general health, type of pathogen, and its antibiotic resistance [22,23]. It is well known that in general low-virulence microorganisms cause infection in late and very late PJI. The fact that low-virulence of the microorganisms isolated and the low number of immunocompromised patients in the current study may be the reason of our successful results.

In two-stage revision arthroplasty, the increase in the time between the first spacer application and the second stage revision surgery is associated with increased re-infection rates [21,24] because the local antibiotic concentration reaches below the threshold to prevent local bacterial growth and the spacer surface may become a suitable surface for adhesion and colonization of bacteria [25]. In the current study, period from the first spacer application to the second stage revision seems to be quite long (11.7±9.9 months, in total). Because of the comorbidities like diabetes and obesity, immunosuppressive medication and infection with resistant microorganisms some patients required more than one spacer implementation. Although more than one spacer application caused the prolongation of the inter-stage period, our infection recurrence rate is quite low. Consistent with present study, Aali Rezaie et al demonstrated that the increased interval between stages in two-stage revision arthroplasty did not have a statistically significant effect on implant failure [26].

Functional results are one of the most important criteria for measuring the effectiveness of treatment in arthroplasty. HHS is one of the most commonly used instruments for the hip, KSS is one of the most commonly used instruments for the knee arthroplasty. Although no studies have been conducted on the outcomes of two-stage revision surgery in patients with very late PJI, different studies and the current study demonstrated statistically significant improvement in the HHS and KSS following two-stage exchange arthroplasty. For example, Buyuk et al, demonstrated that KSS was increased from 40 to 77 points postoperatively following two-stage exchange arthroplasty [27]. Ibrahim et al demonstrated that the HHS was increased from 38 to 81.2 points after two-stage exchange arthroplasty [28]. In the present study there was a statistically significant increase. The mean KSS was improved from 41.9±8.1 to 82.1±6.4 points and the mean HHS was improved from 36.3±9.4 to 79.4±5.2 points at the final follow-up ($p<0.05$).

Evaluation of component stability of the revision prosthesis is an important criterion used to evaluate the success of arthroplasty. If we consider implant loosening as a treatment failure, in the current study, the treatment success should be reported 81.25% in the very late hip and 63.6% in the very late knee PJI group. Camurcu et al presented the success of their treatment as 87.9% in patients operated with two-stage exchange arthroplasty for hip PJI [15]. Castelli et al. reported greater than 92% success, in patients operated on with two-stage exchange arthroplasty for knee PJI [29]. Although the success of two-stage exchange arthroplasty in these two studies seems to be relatively better than the current study, there is a difference between the studies in terms of time of PJI presentation. The current study included very late onset PJI patients, while the other two studies included any time-onset PJI patients. This difference may be due to the fact that late PJI patients are frequently infected by resistant microorganisms such as methicillin-resistant *coagulase-negative staphylococcus species* (*CoNS*), and the fact that in very late PJI the implants remain longer in vivo.

The second aim of the current study was to identify the causative etiological agents and to rank these pathogens according to their incidence. In this study, the pathogen with the highest incidence in very late PJI was *Staphylococcus epidermidis*, and the pathogen with the second highest incidence was *Staphylococcus aureus*. The bacteria were resistant to methicillin in 60% of the *Staphylococcus epidermidis* isolated patients and in 20% of the *Staphylococcus aureus* isolated patients. Many studies have shown that the majority of patients underwent two-stage revision surgery are infected with gram-positive microorganisms [30,31]. Staphylococci (*CoNS* and *S. aureus*) are responsible for more than 50% of the cases in PJI [32], and gram-negative bacteria are also responsible for a significant proportion of cases, ranging between 5% and 23% [33]. In the current study, the most frequently isolated microorganisms were also *Staphylococcus* species. Consistent with previous studies, the most frequently isolated bacteria in this study were *CoNS*, especially *Staphylococcus*

DOI: 10.5455/medscience.2023.05.075

epidermidis, and the second most frequently isolated bacterium was S. aureus [34-35].

Guo et al. reported in their study that *S. aureus* (38.3%) was primarily isolated bacteria in the late phase of PJI. They also reported that *MRSA* was the most isolated microorganism in the early phase and *MSSA* in the delayed and late phase [36]. Drago et al reported that the vast majority of microorganisms isolated in late PJI were *CoNS*, particularly *S. epidermidis* [37]. Unlike the study of Guo et al, *Staphylococcus epidermidis* was the primarily isolated microorganism in the present study, as in the study of Drago et al. However, consistent with the study of Guo et al *MSSA* was observed more than *MRSA*, in the current study. According to the literature, the incidence of *MRSE* in PJI has increased in the last two decades [34,38]. In the current study, the *MRSE* isolation rate in very late PJI was at a substantial level with 22.2%. The high isolation rates of *MRSE* in the current study and the gradual increase in these rates in PJI patients, as stated in the literature, indicate that using with more broad-spectrum in surgical prophylaxis and medical treatment of very late PJI patients may be a more rational way.

Persistent infection despite repeated staged revisions, severe bone and soft tissue loss, and irreparable damage to the extensor mechanism are the most common indications for arthrodesis in knee arthroplasty [39]. There were two very late knee PJI patients developed infection recurrence after second stage revision, in the current study. Because of massive bone loss and prolonged treatment time, we treated them with arthrodesis by using custom made IMNs.

The main limitation of this study is small patient population. Secondarily, it was a retrospective study. Third, the follow-up period was not long enough for such a study. However, we presented a single center experience of a very rare and devastating complication called very late PJI, which was managed following a standard treatment protocol.

Conclusion

In conclusion, two-stage exchange arthroplasty performed with an antibiotic cemented spacer application is a safe and effective method to eradicate very late PJI. In addition, two-stage revision is a surgical treatment that provides statistically significant improvement in postoperative functional scores. In very late PJI, the pathogen with the highest incidence was *Staphylococcus epidermidis*, and the pathogen with the second highest incidence was *Staphylococcus aureus*.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study

Ethical Approval
Written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo. Institutional review board (IRB) approval of the study was received on 08 May, 2023, with the IRB approval number 7/67.

References

1. Berbari EF, Hanssen AD, Duffy MC, et al. Risk factors for prosthetic joint infection: case-control study. Clin Infect Dis. 1998;27:1247-54.
2. Zimmerli W, Zak O, Vosbeck K. Experimental hematogenous infection of subcutaneously implanted foreign bodies. Scand J Infect Dis. 1985;17:303-10.
3. Murdoch DR, Roberts SA, Fowler VG Jr, et al. Infection of orthopedic prostheses after Staphylococcus aureus bacteremia. Clin Infect Dis. 2001;32:647-9.
4. Sendi P, Banderet F, Graber P, Zimmerli W. Periprosthetic joint infection following Staphylococcus aureus bacteremia. J Infect. 2011;63:17-22.
5. Pulido L, Ghanem E, Joshi A, et al. Periprosthetic joint infection: the incidence, timing, and predisposing factors. Clin Orthop Relat Res. 2008;466:1710-5.
6. Bongartz T, Halligan CS, Osmon DR, et al. Incidence and risk factors of prosthetic joint infection after total hip or knee replacement in patients with rheumatoid arthritis. Arthritis Rheum. 2008;59:1713-20.
7. Huotari K, Peltola M, Jämsen E. The incidence of late prosthetic joint infections: a registry-based study of 112,708 primary hip and knee replacements. Acta Orthop. 2015;86:321-5.
8. Parvizi J, Zmistowski B, Berbari EF, et al. New definition for periprosthetic joint infection: from the Workgroup of the Musculoskeletal Infection Society. Clin Orthop Relat Res. 2011;469:2992-4.
9. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. N Engl J Med. 2004;351:1645-54.
10. Zimmerli W. Infection and musculoskeletal conditions: prosthetic-joint-associated infections. Best Pract Res Clin Rheumatol. 2006;20:1045-63.
11. Portillo ME, Corvec S, Borens O, Trampuz A. Propionibacterium acnes: an underestimated pathogen in implant-associated infections. Biomed Res Int. 2013;2013:804391.
12. Parkinson RW, Kay PR, Rawal A. A case for one-stage revision in infected total knee arthroplasty? Knee. 2011;18:1-4.
13. Jämsen E, Stogiannidis I, Malmivaara A, et al. Outcome of prosthesis exchange for infected knee arthroplasty: the effect of treatment approach. Acta Orthop. 2009;80:67-77.
14. Moran E, Byren I, Atkins BL. The diagnosis and management of prosthetic joint infections. J Antimicrob Chemother. 2010;65:iii45-54.
15. Camurcu Y, Sofu H, Buyuk AF, et al. Two-stage cementless revision total hip arthroplasty for infected primary hip arthroplasties. J Arthroplasty. 2015;30:1597-601.
16. Akgün D, Müller M, Perka C, Winkler T. High cure rate of periprosthetic hip joint infection with multidisciplinary team approach using standardized two-stage exchange. J Orthop Surg Res. 2019;14:78.
17. Kuzyk PR, Dhotar HS, Sternheim A, et al. Two-stage revision arthroplasty for management of chronic periprosthetic hip and knee infection: techniques, controversies, and outcomes. J Am Acad Orthop Surg. 2014;22:153-64.
18. Berend KR, Lombardi AV Jr, et al. Two-stage treatment of hip periprosthetic joint infection is associated with a high rate of infection control but high mortality. Clin Orthop Relat Res. 2013;471:510-8.
19. Leonard HA, Liddle AD, Burke O, et al. Single- or two-stage revision for infected total hip arthroplasty? A systematic review of the literature. Clin Orthop Relat Res. 2014;472:1036-42.

DOI: 10.5455/medscience.2023.05.075

20. Otten MR, Kildow BJ, Sayles HR, et al. Two-stage reimplantation of a prosthetic hip infection: systematic review of long-term reinfection and pathogen outcomes. J Arthroplasty. 2021;36:2630-41.

21. Kubista B, Hartzler RU, Wood CM, et al. Reinfection after two-stage revision for periprosthetic infection of total knee arthroplasty. Int Orthop. 2012;36:65-71.

22. Leung F, Richards CJ, Garbuz DS, et al. Two-stage total hip arthroplasty: how often does it control methicillin-resistant infection? Clin Orthop Relat Res. 2011;469:1009-15.

23. Zmistowski B, Tetreault MW, Alijanipour P, et al. Recurrent periprosthetic joint infection: persistent or new infection?. J Arthroplasty. 2013;28:1486-9.

24. Sabry FY, Buller L, Ahmed S, et al. Preoperative prediction of failure following two-stage revision for knee prosthetic joint infections. J Arthroplasty. 2014;29:115-21.

25. Kendall RW, Duncan CP, Smith JA, Ngui-Yen JH. Persistence of bacteria on antibiotic loaded acrylic depots. A reason for caution. Clin Orthop Relat Res. 1996:273-80.

26. Aali Rezaie A, Goswami K, Shohat N, et al. Time to reimplantation: waiting longer confers no added benefit. J Arthroplasty. 2018;33:1850-4.

27. Buyuk AF, Sofu H, Camurcu IY, et al. Can teicoplanin be an effective choice for antibiotic-impregnated cement spacer in two-stage revision total knee arthroplasty?. J Knee Surg. 2017;30:283-8.

28. Ibrahim MS, Raja S, Khan MA, Haddad FS. A multidisciplinary team approach to two-stage revision for the infected hip replacement: a minimum five-year follow-up study. Bone Joint J. 2014;96-B:1312-8.

29. Castelli CC, Gotti V, Ferrari R. Two-stage treatment of infected total knee arthroplasty: two to thirteen year- experience using an articulating preformed spacer. Int Orthop. 2014;38:405-12.

30. Tsai Y, Chang CH, Lin YC, et al. Different microbiological profiles between hip and knee prosthetic joint infections. J Orthop Surg (Hong Kong). 2019;27:2309499019847768.

31. Holleyman RJ, Baker P, Charlett A, et al. Microorganisms responsible for periprosthetic knee infections in England and Wales. Knee Surg Sports Traumatol Arthrosc. 2016;24:3080-7.

32. Del Pozo JL, Patel R. Clinical practice. Infection associated with prosthetic joints. N Engl J Med. 2009;361:787-94.

33. De Sanctis J, Teixeira L, van Duin D, et al. Complex prosthetic joint infections due to carbapenemase-producing Klebsiella pneumoniae: a unique challenge in the era of untreatable infections. Int J Infect Dis. 2014; 25:73-8.

34. Barnes R, Chetter I. Infection in prosthetic material. Surgery (United Kingdom). 2012;30:667-72.

35. Barrett L, Atkins B. The clinical presentation of prosthetic joint infection. J Antimicrob Chemother. 2014;69:i25-7.

36. Guo G, Wang J, You Y, et al. Distribution characteristics of Staphylococcus spp. in different phases of periprosthetic joint infection: a review. Exp Ther Med. 2017;13:2599-608.

37. Drago L, De Vecchi E, Bortolin M, et al. Epidemiology and antibiotic resistance of late prosthetic knee and hip infections. J Arthroplasty. 2017;32:2496-500.

38. Matsumoto T, Ishida K, Tsumura N, et al. Treatment of 50 deep infections after total knee arthroplasty. Orthopedics. 2015;38:e529-35.

39. Corona PS, Hernandez A, Reverte-Vinaixa MM, et al. Outcome after knee arthrodesis for failed septic total knee replacement using a monolateral external fixator. J Orthop Surg (Hong Kong). 2013;21:275-80.