Microbiology and antibiotics after second-stage revision of periprosthetic joint infections: A two-year follow-up cohort

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Highlights

- Unknown optimal antibiotic duration after PJI management by two-stage procedures
- Two-year follow-up after reimplantation
- Factors associated with positive reimplantation microbiology assessed by logistic regression
- Time-to-positivity of 48 hours in case of positive microbiology at reimplantation
- Relapse not associated with reimplantation microbiology or antibiotic duration

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Declaration of Interest

We declare no conflict of interest related to this work.

Abstract

Background Optimal duration of antimicrobial regimen after reimplantation of two-stage procedures for periprosthetic joint infection (PJI) is poorly standardized. The aim of this study was to assess the characteristics of reimplantation microbiology with 6 weeks (2nd stage positive culture) or 10 days (2nd stage negative culture) of antibiotics in patients with complex chronic PJI and factors associated with microbiology at reimplantation.

Patients and Methods We performed a retrospective single-center study including all consecutive complex PJI recipients managed by two-stage surgery in a referral centre, from 2015 to 2018. Outcome was assessed at a minimum 2-year follow-up. Logistic regression analysis was performed to assess predictors of reimplantation microbiology.

Results Fifty patients (median age 69 [62-77] years) were included. PJI predominantly involved the hip (48%). The most common microorganisms were *Staphylococcus aureus* (36%), and coagulase-negative staphylococci (24%). At the second stage, reimplantation microbiology was positive for 10 patients (20%). Documentation was obtained within 48 hours. With median follow-up of 41 [30-50] months after reimplantation, treatment failure occurred in 4 patients (8%). Using log-rank to compare Kaplan-Meier survival curves, no difference in the probability of treatment failure was found according to reimplantation microbiology (*P*=0.34).

After adjustment, relapse was not associated with positive reimplantation microbiology (*P*=0.53).

Conclusions In this work, positive microbiology at reimplantation did not predict treatment failure. Rapid growth at post-reimplantation suggests that antibiotic use should not exceed 10 days when cultures are negative. Additional studies are needed to determine the optimal duration of antibiotic therapy in case of negative microbiology.

Keywords: arthroplasty; prosthesis-related infections; surgical revision; antibiotic

Introduction

Periprosthetic joint infection (PJI) is a serious complication after arthroplasty, associated with major morbi-mortality and economic burden [1]. PJI accounts for 2 and 2.7% of hip and knee arthroplasty respectively, in the United States [2].

PJI management involves both surgery and antimicrobial therapy. The treatment strategy depends on the delay between arthroplasty and the first signs of infection, the time elapsed between the onset of symptoms and the diagnosis of PJI, the type of implant, the type of pathogen and host comorbidities [3,4]. In the United States, two-stage exchange arthroplasty remains the most common approach for chronic PJI [5], despite longer hospital stay and medical complications compared to one-stage procedures [6]. In France, most chronic PJIs are

currently managed with one-stage procedure. The use of two-stage procedures is highly variable among institutions [7]. Two-stage revision procedure remains the standard for complex chronic PJI [8–14], as it allows a window period with no prosthetic material and a success rate over 90% [13,15,16]. Positive cultures at reimplantation, due to persistent infection or reinfections with another microorganism [17], may be associated with treatment failure [18–22]. In addition to the surgical procedure, antibiotic therapy is based on expert recommendations [23–25]. However, few studies have evaluated the appropriate antibiotic duration required in case of PJI in association with surgery. Recently, Bernard and colleagues showed that 6 weeks of antimicrobial regimen in PJI was not noninferior to 12 weeks and resulted in a higher number of unfavourable outcomes [26]. However, this study included different two-stage surgical procedures, and was focused on antibiotics prior to reimplantation.

Antibiotic regimen after the second-stage revision is not consensual. After the 2nd stage, recent clinical practice tends to shorten the duration of the antibiotic therapy to 10-14 days when per-operative cultures are negative, based on the time of microbial growth.

We conducted a single-center retrospective study to assess the characteristics of the reimplantation microbiology of two-stage revision with 6 weeks (when the 2nd stage cultures are positive) or 10 days (when the 2nd stage cultures are negative) of antibiotics post-reimplantation in patients with complex chronic PJI and the factors associated with microbiology at reimplantation.

Methods

Study design

All consecutive adult subjects with PJI having been treated between January 2015 and December 2018 with a two-stage revision, according to the French guidelines for osteoarticular infections on materials (SPILF), in the academic hospital of Rennes, a referral centre for complex bone and joint infections in France, were retrospectively included.

The type of revision procedure was decided on during a weekly multidisciplinary meeting at the complex bone and joint infection referral centre (CRIOAC). The team included at least an infectious disease physician, a microbiologist, a surgeon and a specialist in medical imaging.

This study was approved by an institutional review board of the CRIOGO research group. Given the observational study design, need for informed consent was waived. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Population

Patients with PJI treated with a two-stage revision procedure underwent complete removal of the prosthesis, debridement and implantation of a gentamicin-based spacer. All patients received antibiotic prophylaxis with cefazoline. Explantation of the spacer was followed by debridement and implantation of a new joint prosthesis.

After the first-stage surgery, all patients received standardized empirical treatment. The antibiotic regimen was reassessed and tailored to culture and susceptibility data when available. Both empirical and definitive therapies were selected in accordance with the guidelines of Société de Pathologie Infectieuse de Langue Française [27] after discussion during the multidisciplinary meeting.

In case of signs of poor tolerance of infection, antibiotics were initiated before the first-stage surgery according to pre-operative documentation after needle punction or biopsy.

After the first stage, antibiotics were administered for 6 or 12 weeks at the physician's discretion, IV or by oral route depending on the pathogen. Clinical and biologic follow-up was performed regularly during treatment between the first and the second-stage.

Discontinuation before prosthetic reimplantation usually lasted 2 weeks.

After the second stage, when microbiology was positive, patients received antibiotics for 45 days (6 weeks) and when bacterial cultures were negative, antibiotics were discontinued at day 10. No maintenance or suppressive antibiotic therapy was administered at the end of the second-stage antibiotic regimen. After the second stage, standard follow-up included consultations with an infectious disease specialist at 15 days and 6 weeks and then at 3, 6, 12 and 24 months.

Definitions

PJI was identified by at least one clinical symptom including pain, fever, fistula, outflow around the scar, erythema, or swelling, and microbiological documentation. PJI was considered when criteria for infected periprosthetic joint, according to the major criteria of the Musculoskeletal Infection Society (MSIS) score [28], were fulfilled.

The definition of **complex PJI** is not consensual. In the multidisciplinary meeting, PJIs were considered as complex when infection was caused by virulent or highly resistant bacteria, when the host was immunocompromised or with multiple comorbidities, or in case of recurrent PJI septic failure and complex revision procedures pertaining to bone and soft tissues defects.

Positive microbiology was considered when at least one bacterial culture was positive, yielding a virulent pathogen. At least two cultures of the same pathogen or one culture with high suspicion of infection (previous infection with the same pathogen, clinical signs of infection, rapid growth…) were required if the identified pathogen corresponded to skin bacteria such as coagulase negative staphylococci (CNS), *Cutibacterium acnes*, *Corynebacterium*, *lactobacillus*, or *Micrococcus.*

Negative microbiology was defined as negative intraoperative specimens for aerobic and anaerobic bacterial cultures at 10 days on agar media and in Schaedler broth medium.

Contamination was defined as one positive perioperatory sample without sufficient evidence to pursue antibiotic therapy for more than 10 days.

Rapid-growth was defined as positive culture within 48 hours.

Short-course antibiotic regimen was defined when patients received fewer than 14 days of antibiotic therapy after the second-stage revision and was based on the time required to obtain definitive microbiological documentation, while **long-course** corresponded to of 6-week antibiotic therapy.

The time interval between first and second-stage surgery corresponded to the duration of spacer implantation. **The antibiotic-free period** was defined as the time period off antibiotics before reimplantation.

Treatment failure was defined as the persistence or recurrence of infection with the initial causative bacteria, with an antibiotic susceptibility pattern that was phenotypically indistinguishable; or infection with a new bacterium, with or without the presence of the initial causative bacteria at any time during follow-up after the second stage.

Microbiological specimens

Four different per-operative samples (tissue, bone, or joint fluid specimens) were collected during first and second-stage surgery. Each sample was collected with dedicated instruments, and sampling tools were changed between each specimen site. Samples were sent rapidly to the laboratory. Samples were crushed using bead mill processing and enriched in aerobic (BD BACTEC® Plus Aerobic/F) and anaerobic (BD BACTEC® Lytic/10 Anaerobic/F) flasks incubated for 10 days, cultured on agar media incubated for 7 days, and in Schaedler broth medium kept until the 14th day, as previously described [29].

Bacterial identification was performed by MALDI-TOF/MS technique (Biotyper, Bruker Daltonics).

Data

Patients' demographic and medical data were retrospectively retrieved from a computerized database. All antibiotic therapy received before and after the first and second-stage revision procedure, microbiological documentation before the first-stage revision and from perioperative samples collected during the first and second-stage revision were collected from paper records, electronic records, and laboratory data. Time-to-positivity were collected when cultures from samples collected at the second-stage revision were positive.

Statistical analysis

The primary objective was to assess the characteristics of the reimplantation microbiology of two-stage revision with 6 weeks (when the 2nd stage cultures were positive) or 10 days (when the 2nd stage cultures were negative) of post-reimplantation antibiotics in patients with

complex chronic PJI. The secondary objective was to define factors associated with microbiology at reimplantation.

Data are described as median and interquartile range (IQR) for continuous variables and number and percentage for categorical variables. Categorical variables were compared using Chi-square or Fisher's exact test and continuous variables using Wilcoxon test or 2-sample t test as appropriate. Treatment failure is reported as incidence density for 1000 days. Kaplan-Meier survivorship curves were constructed to determine the overall rate of treatment failure according to reimplantation microbiology. Curves were compared using Log-Rank test. Logistic regression analysis was used to identify risk factors associated with reimplantation microbiology. Preplanned clinically relevant variables (*Staphylococcus aureus* PJI and treatment failure) were forced into the final model, if not previously selected. Sensitivity analyses were performed to assess risk factors associated with antibiotic regimen duration at reimplantation. In addition, sensitivity analysis was performed using competing risk analysis to assess cumulative risk of treatment failure using competitive risk analysis according to reimplantation microbiology with mortality as a competing risk.

Statistical significance was considered on two-sided tests with a critical alpha risk of 0.05. Statistical analyses were performed using R version 3.4.4 (R Foundation for Statistical Computing), 'survival' packages.

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Results

We retrospectively included 50 patients with PJI treated by a two-stage revision procedure between 2015 and 2018. **Table 1** shows patients and PJI characteristics. Patients had median age of 69 [62-77] years and 32 (64%) were male. The most frequently found comorbidities were cardiovascular disease (40%) followed by obesity (26%). Fourteen (28%) patients were receiving immunosuppressive drugs. PJI predominantly involved the hip for 24 (48%) patients and the knee for 22 (44%) patients. Half of the study cohort (54%) had at least one previous septic failure. All patients had pre-operative needle punction. Initial microbial identification was present in 92% of the cases and was polymicrobial in 12%. *S. aureus* was identified in 18 (36%) patients followed by CNS in 12 (24%) patients (**Figure 1a)**. Twenty-three (46%) patients received antibiotic therapy before first-stage surgery for signs of poor tolerance of infection. After first-stage revision, patients had antibiotics for a median of 10 [6-12] weeks and an antibiotic-free period lasted a median of 14 [12-18] days.

At the second-stage revision, 40 (80%) patients had negative reimplantation microbiology. Patients with positive microbiology had prosthesis implant less often for arthrosis (50% versus 90%), and more frequently for inflammatory diseases (50% versus 10%). When microbiology was positive (n=10; 20%), CNS (n=4, 40%) and *S. aureus* (n=4, 40%) were the predominant bacteria **(Figure 1b).** Documentation was similar to the initial microbiology for 6 patients and different for 4. Bacterial documentation was given within 2 [1-2] days (**Supplementary Table 1**). All *S. aureus* grew within 72 hours. One sample culture came positive at 12 days with *C. acnes*. All patients with positive microbiology, as defined above (method section), received a

long-course antibiotic regimen. One patient received a long-course antibiotic regimen (91 days) despite negative microbiology at the 2nd stage, due to implantation of a massive knee prosthesis in a context of recurrent infections on neoplastic bone disease.

Out of the 50 patients, 4 (8%) presented treatment failure within a follow-up period of 41 [30-50] months. Incidence density of treatment failure was 0.07 [0.02 – 0.18] events per patient-1000 days. Similar incidence density was found using competing risk analysis (**Supplementary Figure 1**).

Characteristics of patients with treatment failure are presented in **Supplementary Table 2**. Among patients with treatment failure, two had positive reimplantation microbiology and had received a long-course antibiotic, and 2 had negative microbiology and had received a short-course antibiotic regimen. Among patients with negative microbiology at reimplantation, one relapsed with the same microorganism as initially isolated (*Streptococcus agalactiae*) and one had *de novo* infection (*S. aureus* followed by *Enterococcus faecalis*). Two patients with positive microbiology to CNS and *S. aureus* relapsed, one with *Streptoccocus dysgalactiae* and *S. aureus* and the other with *S. aureus*.

Using a log-rank test to compare Kaplan-Meier survival curves, no difference in probability of treatment failure was found according to reimplantation microbiology (p=0.34; **Supplementary Figure 1**). Similar results were obtained with antibiotic duration.

On multivariate analysis after adjustment on confounders, treatment failure was not independently associated with reimplantation microbiology (aOR 0.35 [0.008-8.12]; P=0.53). Osteoarthritis (aOR 0.09 [0.01-0.65]; P=0.02), and inflammatory diseases (aOR 12.4 [1.46-

153]; *P*=0.03) were independently associated with positive cultures at the time of reimplantation (**Table 2**). Sensitivity analysis showed similar factors associated with second-stage antibiotic duration (**Supplementary Table 3**).

Discussion

In this work and in agreement with recently published data on PJI [7], complex chronic PJI infections managed by two-stage revision procedure were due mainly to *S. aureus* and CNS. At reimplantation, consistent with other reports [20,21], cultures were positive for 20% of patients. We found incidence density of treatment failure after the two-stage revision of 0.07[0.02-0.18] at 1000 days. At two years, the proportion of treatment failure was 2%, in line with previous studies [30–32,1,33]. Interestingly, the proportion of treatment failure, when reimplantation microbiology was positive, was null at 2 years but reached 20% at 4 years (**Figure 2 and supplementary Figure 1**), which is consistent with other studies [34,35]. Larger scale studies should pursue investigation of delayed treatment failure in patients with positive microbiology compared to patients with negative microbiology at the time of reimplantation, one objective being to assess whether long-course antibiotic regimen after the second stage could modify occurrence of treatment failure. After adjustment and in line with previous reports [18,19], positive reimplantation microbiology was not associated with increased risk of treatment failure in patients with complex chronic PJI. In sensitivity analysis, short-course antibiotic regimen for negative reimplantation microbiology was not predictive of treatment failure. Patients with positive microbiology more often had inflammatory diseases than patients with negative cultures at reimplantation. In our study, the antibiotic free-period when microbiology was positive was longer than when microbiology was negative (9[4 - 15] versus 5[3-7]; P=0.07) and was close to significance. However, in the multivariate analysis, increased

antibiotic free-period duration was not associated with the risk of positive reimplantation microbiology. The absence of association could also be due to the low statistical power of our study. Comparing two groups of patients from two different orthopaedic centers [36], Asciane *et al.* reported that continuous antibiotic therapy instead of 2 weeks of antibiotic free-period pre-implantation was associated with better outcome. However, Tan and colleagues reported no association between the duration of antibiotic-free period and reinfection [37].

Herein, the overall treatment success rate for complex chronic PJI treated by a two-stage revision procedure reached 92% with mean follow-up of 41 [30-50] months, a result consistent with published data. Wolf and colleagues reported an overall success rate with eradication of prosthetic infection of 94.5%, but with high morbi-mortality [13]. In our work, 27 (54%) patients had previous septic failure before the two-stage revision procedure and 3 displayed treatment failure requiring further treatment for PJI. Khan and colleagues reported higher treatment failure after two-stage revision in patients with recurrent septic failure [38]. Moreover, Brown *et al*. reported survival free from any revision of 74% at two years, which decreased over time with high complication and failure rates [39].

After the second-stage surgery, antibiotics were discontinued after approximately 10 days for 39 (78%) patients who had negative reimplantation microbiology. This practice is justified when definitive microbiological culture is provided at day 10. In sensitivity analysis, short-course antibiotic was not associated with increased treatment failure (**Supplementary Table 3**). Consequently, given that all positive intraoperative samples, except for one, showed time-to-positivity of 2 [1-2] days, one could be tempted to stop antibiotics at 48 hours. The lack of data on antibiotic duration after the second stage in case of negative microbiology warrants further studies, of which one objective would be to limit unnecessary antibiotic exposure.

This work has some limitations. First, the retrospective and single-centered design may have limited the external validity of our findings. Our small population sample (n=50) included complex cases; 54% were recurrent septic failures and 28% were immunocompromised. In addition, PJIs were heterogeneous insofar as our cohort included all types of joints. Nevertheless, all patients were surgically managed by the same team and antibiotic regimen was standardized according to the guidelines. We could not assess risk factors associated with treatment failure, as the number of events was too low. Moreover, we did not provide the functional outcome upon two-stage revision; after all, the aim of this study was to focus on the microbiological outcome.

In our study, to conclude, positive microbiology at reimplantation did not predict treatment failure. Our findings suggest that with proper microbiological techniques (including automated grinding), cultures grow rapidly, and consequently, that post-reimplantation antibiotic should not exceed 10 days. Additional studies are needed to determine the optimal duration of antibiotic therapy in case of negative microbiology, which could potentially be reduced to 72 hours.

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Authors' contributions

AS, JMU and DLP collected the data. AS, JMU and DLP analysed the data. AS, PT, AJG, MB, PT and CA interpreted patient's data. AS, JMU, DLP, PT and CA wrote the paper. CH and MR provided surgical expertise. All authors reviewed the manuscript. All authors read and approved the final manuscript.

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Figure 1. **Initial and second-stage microbiological documentation of prosthetic joint infection. A)** Initial microbial documentation obtained from joint suction. **B)** Microbial documentation of perioperative samples collected at the second-stage surgery. Data are given as percentage (n=50).

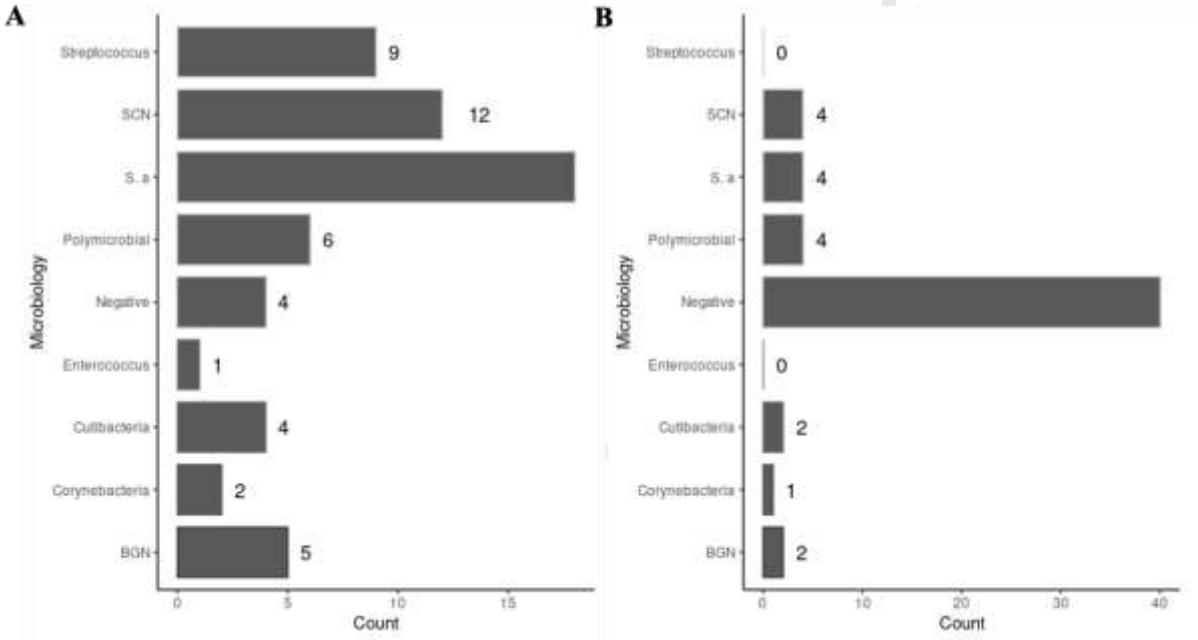

Figure 2. Kaplan-Meier survival curve representing the rate of treatment failure of two-stage total joint arthroplasty. A) Kaplan-Meier survival curve representing treatment failure of complex chronic PJI after two-stage total joint arthroplasty. B) Kaplan-Meier survival curve representing treatment failure of complex chronic PJI after two-stage total joint arthroplasty stratified on second-stage microbiological outcome. The red curve corresponds to the absence of documentation and the blue curve to positive microbiology. No difference was found between the absence and presence of documentation (p=0.34) in the treatment failure probability curves compared using a Log-Rank test. Time is given in months.

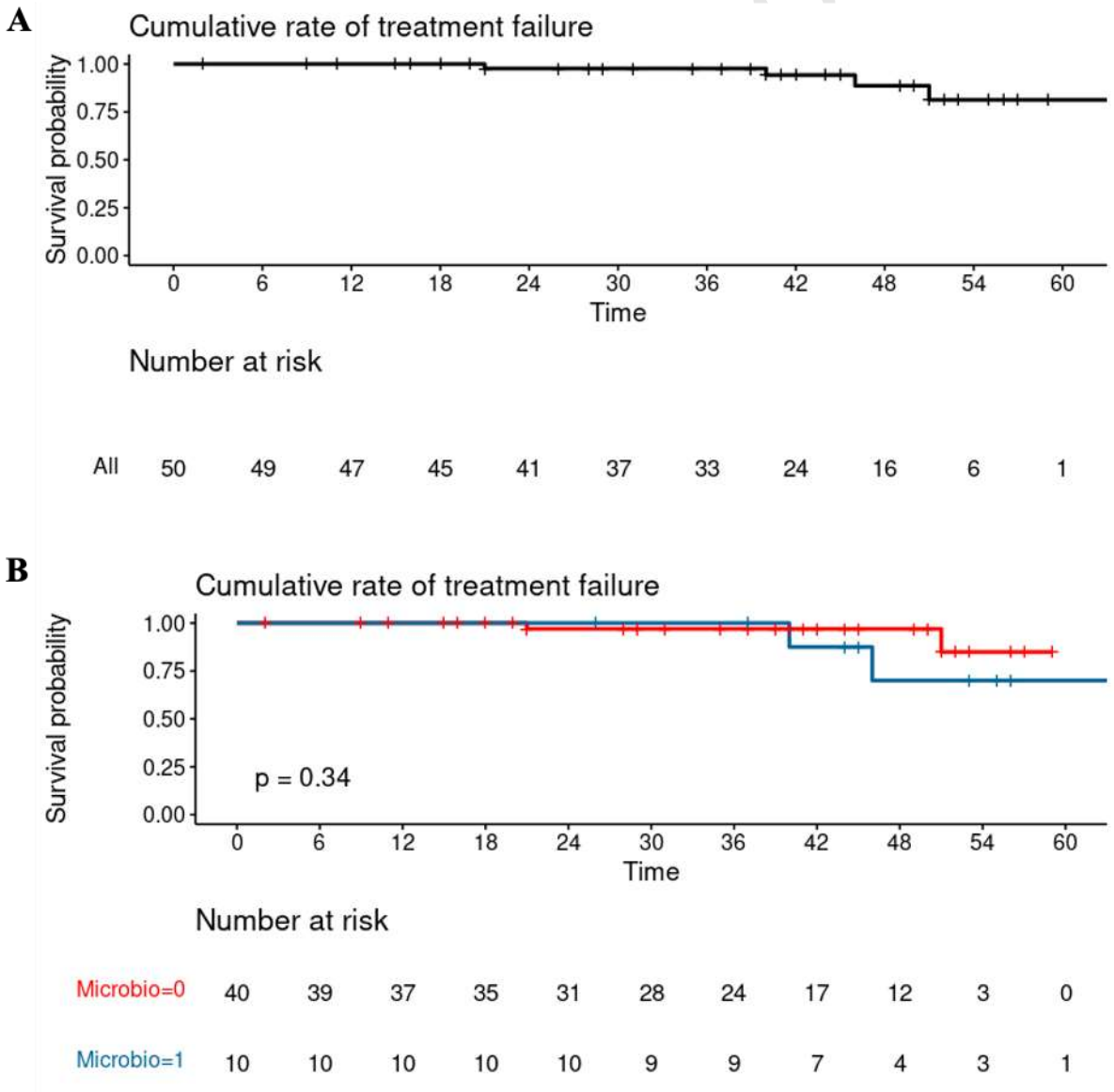

Table 1. Characteristics of the overall study population and according to the second-stage microbiology.

	Overall n=50	**Negative microbiology** n=40	**Positive microbiology** n=10	***P***
Age (years)	69 [62-77]	70 [64-77]	61 [58-74]	0.21
Male	32 (64)	23 (58)	9 (90)	0.122
Comorbidities				
Smoking	8 (16)	7 (18)	1 (10)	0.92
Diabetes	7 (14)	6 (15)	1 (10)	1.00
Obesity	13 (26)	11 (28)	2 (20)	0.94
Cardiovascular disease	20 (40)	16 (40)	4 (40)	1.00
Osteoarthritis	41 (82)	36 (90)	5 (50)	**0.01**
Inflammatory disease	9 (18)	4 (10)	5 (50)	**0.01**
Immunosuppression*	14 (28)	10 (25)	4 (40)	0.58
Prosthesis characteristics				
Recurrent septic failure	27 (54)	21 (53)	6 (60)	0.94
Hip	24 (48)	18 (45)	6 (60)	0.62
Knee	22 (44)	20 (50)	2 (20)	0.18
Shoulder	4 (8)	2 (5)	2 (20)	0.36
Initial documentation				
Identification before surgery	46 (92)	38 (95)	8 (80)	0.36
Polymicrobial	6 (12)	6 (15)	0	0.45
MSSA	16 (32)	12 (30)	4 (40)	0.82
MRSA	2 (4)	2 (5)	0	1.00
CNS	12 (24)	10 (25)	2 (20)	1.00
Cutibacterium acnes	4 (8)	3 (8)	1 (10)	1.00
Corynebacterium striatum	2 (4)	2 (5)	0	1.00
Streptococcus	9 (18)	8 (20)	1 (10)	0.78

Enterococcus	1 (2)	1 (3)	0	1.00
GNB	5 (10)	5 (13)	0	0.56
	46 (92)	20 (50)	8 (80)	0.36
Antibiotic characteristics				
Antibiotic before surgery	23 (46%)	20 (50)	3 (30)	0.44
First-stage antibiotic duration (weeks)	10[6-12]	10 [6-12]	10 [7-12]	0.88
Time lapse between first and second-stage revision (weeks)	14 [12-18]	13 [12-16]	20 [13-24]	0.11
Antibiotic-free period duration (weeks)	6 [3-8]	5 [3-7]	9 [4-15]	0.07
Second-stage antibiotic duration (days)	10 [10-14]	10 [10-12]	42 [41-58]	<0.001
Outcome				
Treatment failure	4 (8)	2 (5)	2 (20)	0.36
Follow-up (months)	41 [30-50]	40 [29-49]	46 [41-55]	0.06
Mortality	4 (8)	4 (10)	0 (0)	0.70

MSSA: methicillin-sensitive *Staphylococcus aureus,* MRSA: methicillin-resistant *Staphylococcus aureus,* GNB: Gram-negative bacilli *(Salmonella enterica* Dublin, *Enterobacter cloacae Morganella morganii, Pseudomonas aeruginosa),* CNS: Coagulase-negative *Staphylococci.*

*Chemotherapy, monoclonal antibodies, immunotherapy or long-course corticosteroids.

Table 2. Factors independently associated with microbiological findings at reimplantation.

	aOR*	95%CI
Osteoarthritis	0.09	[0.01-0.65]
Inflammatory disease	12.4	[1.46-153]
Treatment failure	0.35	[0.01-8.12]
Antibiotic-free period	1.15	[0.99-1.37]
Initial documentation with *S. aureus*	0.63	[0.07-4.31]

*Adjusted odds ratios with 95% confidence intervals are given after adjustment on covariates using logistic regression.

aOR: adjusted odds ratio, 95%CI : 95% confidence interval.