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A commentary by Thomas J. Blumenfeld, MD, is linked to the online version of this article at jbjs.org.

The Fate of Spacers in the Treatment of Periprosthetic Joint Infection

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Background: Two-stage exchange arthroplasty remains the preferred method to treat periprosthetic joint infection. The aim of this study was to investigate the clinical course of periprosthetic joint infection following resection arthroplasty and insertion of a spacer.

Methods: Our institutional database was used to identify 504 cases of periprosthetic joint infection (326 knees and 178 hips) treated with resection arthroplasty and spacer insertion as part of a two-stage exchange arthroplasty. A review of the patient charts was performed to extract information relevant to the objectives of this study that included the details of the clinical course following resection arthroplasty.

Results: The mean follow-up duration after initial spacer implantation was 56.2 months. Reimplantation occurred in the joints of 417 (82.7%) of 504 cases. Of these 417 cases, 329 (78.9%) had a minimum one-year follow-up, and 81.4% of these had successful treatment. The mean duration from resection arthroplasty to reimplantation was 4.2 months (range, 0.7 to 131.7 months). Sixty (11.9%) of the 504 joints required interim spacer exchange(s). Of the eighty-seven cases that did not undergo reimplantation, six (6.9%) required amputation, five (5.7%) underwent a Girdlestone procedure, four (4.6%) underwent arthrodesis, and seventy-two (82.8%) underwent spacer retention. Thirty-six patients died in the interstage period.

Conclusions: The commonly held belief that two-stage exchange arthroplasty carries a high success rate for the eradication of periprosthetic joint infection may need to be reexamined. A considerable number of patients undergoing the first stage of a two-stage procedure do not undergo a subsequent reimplantation for a variety of reasons or require an additional spacer exchange in the interim. Reports on the success of two-stage exchange should account for the mortality of these patients and for patients who never undergo reimplantation.

Level of Evidence: Therapeutic Level IV. See Instructions for Authors for a complete description of levels of evidence.

Peer Review: This article was reviewed by the Editor-in-Chief and one Deputy Editor, and it underwent blinded review by two or more outside experts. It was also reviewed by an expert in methodology and statistics. The Deputy Editor reviewed each revision of the article, and it underwent a final review by the Editor-in-Chief prior to publication. Final corrections and clarifications occurred during one or more exchanges between the author(s) and copyeditors.

The treatment of periprosthetic joint infection continues to pose challenges for the orthopaedic community¹. The preferred surgical treatment of chronic periprosthetic joint infection in North America is two-stage exchange arthroplasty that involves removal of the prosthesis and spacer placement, followed by reimplantation of new components during the second stage.

The reported success of two-stage exchange arthroplasty has varied in the literature, with some studies showing a 100% rate for infection control²⁻⁵. However, the majority of those studies focused on the clinical outcomes following successful reimplantation and thus may not accurately reflect the overall success rate of two-stage exchange for periprosthetic joint

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TABLE 1 Patient Demographic Characteristics

Variable	All Periprosthetic Joint Infections (N = 504)	Knee (N = 326)	Hip (N = 178)
Age at the time of infection* (yr)	66.3 ± 11.3	67.3 ± 10.2	64.6 ± 13.0
Age of men* (yr)	66.9 ± 10.8	67.5 ± 10.0	63.2 ± 13.9
Age of women* (yr)	65.7 ± 11.9	67.1 ± 10.4	66.2 ± 11.6
Body mass index* (kg/m ²)	31.4 ± 2.4	32.1 ± 2.4	30.2 ± 2.5
Musculoskeletal Infection Society classification†			
Infected	438 (86.9)	279 (85.6)	159 (89.3)
Non-infected	66 (13.1)	47 (14.4)	19 (10.7)
Previous operation before infection†			
Primary	254 (50.4)	180 (55.2)	74 (41.6)
Revision	98 (19.4)	46 (14.1)	52 (29.2)
No data	152 (30.2)	100 (30.7)	52 (29.2)
Comorbidities†			
Diabetes mellitus	115 (22.8)	84 (25.8)	31 (17.4)
Rheumatoid arthritis	44 (8.7)	29 (8.9)	15 (8.4)
Charlson Comorbidity Index*‡	4.4 ± 2.4	4.6 ± 2.4	4.2 ± 2.5
ASA score*	2.8 ± 0.5	2.8 ± 1.4	2.8 ± 1.4
Type of spacer†			
Dynamic	139 (27.6)	100 (30.7)	39 (21.9)
Static	365 (72.4)	226 (69.3)	139 (78.1)

*The values are given as the mean and the standard deviation. †The values are given as the number of cases, with the percentage in parentheses.
‡This category was adjusted for age.

infection. Furthermore, there is considerable variability in the literature with regard to how these studies define the success of periprosthetic joint infection treatment, which could result in an overestimation of the outcome measures. In addition, the study populations often consist of a small cohort⁶.

To accurately depict the clinical course of two-stage exchange, an enhanced understanding of the interstage period is needed. Although there are many studies that investigated the role of spacer selection (static or dynamic) in either functional outcomes or infection control⁷⁻¹¹, very few, if any, to our knowledge, have investigated the clinical course following the first stage of a two-stage exchange arthroplasty. Furthermore, little is known with regard to the fate of spacers in these patients undergoing a two-stage exchange arthroplasty.

The aim of this study was to investigate the natural history of resection arthroplasty and spacer implantation in patients undergoing the first stage of a planned two-stage exchange arthroplasty for treatment of periprosthetic joint infection.

Materials and Methods

Patient Demographic Characteristics

Following institutional review board approval, our institutional joint arthroplasty database was queried to identify 647 periprosthetic joint infections in patients who underwent resection arthroplasty and spacer insertion as part of an intended two-stage exchange arthroplasty for suspected periprosthetic joint infection. The period of study was from 1999 to 2013 and, during this time, 32,417 patients had undergone joint arthroplasty at our institution. Patients with a megaprosthesis, prior native septic arthritis, prior two-stage exchange, or failed

one-stage exchange, or those who underwent spacer placement for reasons unrelated to periprosthetic joint infection were excluded. After exclusion of 143 cases on the basis of the above criteria, a total of 504 periprosthetic joint infections (326 knees and 178 hips) in 482 patients were included in the final cohort (Table 1).

Component Specifications

At the time of initial spacer implantation, 365 periprosthetic joint infections (72.4%) were treated with nonarticulating spacers and 139 periprosthetic joint infections (27.6%) were treated with articulating spacers. The articulating spacers were intraoperatively constructed primarily from prefabricated molds with endoskeleton implants (StageOne; Biomet, Warsaw, Indiana). The use of articulating spacers increased during the study period from 0.0% in 1999 to 26.9% in 2013. Dual antibiotics were in 97.6% of spacers, consisting almost entirely of 1 to 4 g per pack (range of total grams, 1 to 12 g), to ensure activity against gram-positive and gram-negative organisms; vancomycin was in 99.1% of spacers and tobramycin was in 96.4% of spacers. In 2.4% of cases, the antibiotic utilized was an antifungal or cephalosporin, which was based on the suspected organism or used if an allergy to the standard antibiotic was present. The dosages increased during the time course of the study, with the recent spacers regularly using 3 g of vancomycin and 2.4 to 3 g of tobramycin. Reimplantation was scheduled to occur following a minimum of four weeks, but the duration of the interstage period was not otherwise designated. The timing of reimplantation was based on laboratory values and clinical improvements. The erythrocyte sedimentation rate and C-reactive protein values were examined for progressive sequential decreases. Prior to reimplantation, aspiration was not routinely performed. In addition, clinical signs and improvement were monitored as a proxy for infection control, particularly during the antibiotic-free period. At the time of reimplantation, spacers were removed and repeat debridement was performed, followed by insertion of routine revision-type prosthetic components utilizing antibiotic-loaded cement in total knee arthroplasties and uncemented total hip arthroplasties. When cemented components were used in the hip, antibiotic-loaded bone cement was utilized.

TABLE II Outcomes and Complications Following Initial Spacer Implantation

Outcome Measure	All Periprosthetic Joint Infections (N = 504)	Knee (N = 326)	Hip (N = 178)
Follow-up* (mo)	56.2 (1.1 to 186.9)	59.7 (1.9 to 167.0)	49.1 (1.1 to 186.9)
Duration of spacer* (mo)	4.2 (0.7 to 131.7)	4.1 (0.7 to 131.7)	4.4 (1.1 to 73.3)
Spacer complications and outcomes†			
Amputation	6 (1.2)	6 (1.8)	0 (0.0)
Girdlestone	5 (1.0)	0 (0.0)	5 (2.8)
Arthrodesis	4 (0.8)	4 (1.2)	0 (0.0)
Spacer retention	72 (14.3)	38 (11.7)	34 (1.9)
Dislocation	6 (1.2)	5 (1.5)	1 (0.6)
Wound complications	30 (6.0)	24 (7.4)	6 (3.4)
Requirement for a second spacer	60 (11.9)	40 (12.3)	20 (11.2)
Persistent infection	44 (73.3)	27 (67.5)	17 (85.0)
Spacer dislocation	6 (10.0)	5 (12.5)	1 (5.0)
Wound problems	9 (15.0)	7 (17.5)	2 (10.0)
Tibial fracture	1 (1.7)	1 (2.5)	0 (0.0)
Reimplantation	417 (82.7)	280 (85.9)	137 (77.0)
Treatment success after reimplantation	268 (81.4)	179 (81.4)	89 (81.7)
Treatment success after spacer retention	17 (23.6)	8 (21.1)	9 (26.5)
Mortality after implantation of spacer†			
Thirty days	6 (1.2)	3 (0.9)	3 (1.7)
Ninety days	13 (2.6)	8 (2.5)	5 (2.8)
One year	33 (6.5)	20 (6.1)	13 (7.3)
Two years	52 (10.3)	38 (11.7)	14 (7.9)

*The values are given as the mean, with the range in parentheses. †The values are given as the number of cases, with the percentage in parentheses. Percentages for the four requirements for a second spacer were determined from the number of cases that required a second spacer. Percentages for the two treatment success categories were determined from the number with reimplantation or the number with spacer retention with a minimum of one year of follow-up.

TABLE III Organism Profile at Initial Spacer Implantation*

Microorganism	All Periprosthetic Joint Infections (N = 504)	Knee (N = 326)	Hip (N = 178)
Coagulase-negative Staphylococcus	84 (16.7)	60 (18.4)	24 (13.5)
Methicillin-sensitive <i>Staphylococcus aureus</i>	73 (14.5)	43 (13.2)	30 (16.9)
Streptococcus species	36 (7.1)	27 (8.3)	9 (5.1)
Enterococcus species	9 (1.8)	5 (1.5)	4 (2.2)
Gram-negative bacilli	33 (6.5)	23 (7.1)	10 (5.6)
Antibiotic resistant (vancomycin-resistant Enterococcus or methicillin-resistant <i>Staphylococcus aureus</i>)	75 (14.9)	37 (11.3)	38 (21.3)
Other organism	19 (3.8)	16 (4.9)	3 (1.7)
Polymicrobial	39 (7.7)	24 (7.4)	15 (8.4)
Negative cultures	136 (27.0)	91 (27.9)	45 (25.3)

*The values are given as the number of cases, with the percentage in parentheses.

TABLE IV Reimplantation Rate by Organism and Comorbidity*

Factor	No. of Cases	Overall Reimplantation Rate (%)	P Value	Knee Reimplantation Rate (%)	Hip Reimplantation Rate (%)
Gram-negative			0.002		
No	459	84.5		87.2	79.6
Yes	33	64.4		72.4	50.0
Missing data	12	NA		NA	NA
Antibiotic-resistant			>0.05		
Yes	76	76.3		77.7	72.5
No	428	83.9		86.9	78.3
Charlson Comorbidity Index			<0.0001		
0	14	NA		NA	NA
1	26	84.6		83.3	85.7
2	55	96.4		100.0	92.0
3	97	90.7		93.2	86.8
4	121	88.4		96.2	74.4
5	79	79.7		81.4	75.0
6	43	65.1		56.4	66.7
≥7	69	63.8		50.0	72.1
Rheumatoid arthritis			0.0347		
Yes	44	70.5		69.0	73.3
No	447	83.9		87.8	77.0
Missing data	13	NA		NA	NA
Diabetes mellitus			>0.05		
Yes	115	81.9		84.5	71.0
No	375	82.9		86.6	78.0
Missing data	14	NA		NA	NA

*NA = not applicable.

Outcome Variables

A retrospective chart review was performed to extract patient demographic characteristics and all of the relevant data, which included the following variables: surgical procedure details and the type of spacer placed, microbiological data related to the infecting organism(s), and the clinical course of the patients after resection arthroplasty and spacer placement. Details pertinent to subsequent operations, including the reimplantation, were also extracted.

From the institutional database, queries were performed to obtain information on patient comorbidities including body mass index, diabetes mellitus, rheumatoid arthritis, Charlson Comorbidity Index, and American Society of Anesthesiologists (ASA) classification¹². The Charlson Comorbidity Index provides a method of quantifying overall health and is predictive of mortality¹³. Data related to mortality were ascertained from the clinical records and the status of each patient was checked using the Social Security Index, a governmental mortality search engine based on Social Security number; however, this tool does not provide the cause of death. Treatment success was judged according to criteria based on the Delphi international multidisciplinary consensus: infection eradication characterized by a healed wound without drainage, fistula, or pain and no infection recurrence; no occurrence of periprosthetic joint infection-related mortality (e.g., sepsis, necrotizing fasciitis); and no subsequent surgical intervention for infection after reimplantation surgery¹⁴. Given that the Delphi criteria do not account for patients who do not undergo the reimplantation phase of the two-stage exchange, treatment success also included no subsequent surgical intervention for infection after spacer implantation in patients with a retained spacer and no mortality related to the infection.

Statistical Analysis

Differences in the reimplantation rate between gram-negative and gram-positive organisms and between resistant and susceptible organisms were calculated with use of the Fisher exact test. A logistic regression was used to assess the correlation between the Charlson Comorbidity Index and the reimplantation rate. The number of surgeries and spacers were analyzed with use of the Wilcoxon test for binary comparison. The total number of surgeries was compared with the patient's comorbidities, including ASA score, Charlson Comorbidity Index, and body mass index. Significance was set at $p < 0.05$.

Source of Funding

There was no external funding source for this study.

Results

Reimplantation occurred in 417 (82.7%) of 504 cases. The mean duration from resection arthroplasty to reimplantation was 4.2 months (median, 2.7 months [range, 0.7 to 131.7 months]) (Table II). The mean follow-up duration after spacer insertion was 57.4 months for patients who underwent reimplantation and 42.7 months for those who did not undergo reimplantation. Sixty (11.9%) of 504 cases required a mean of 1.1 spacer exchanges (range, one to six spacer exchanges) in the interstage period between initial resection arthroplasty and eventual

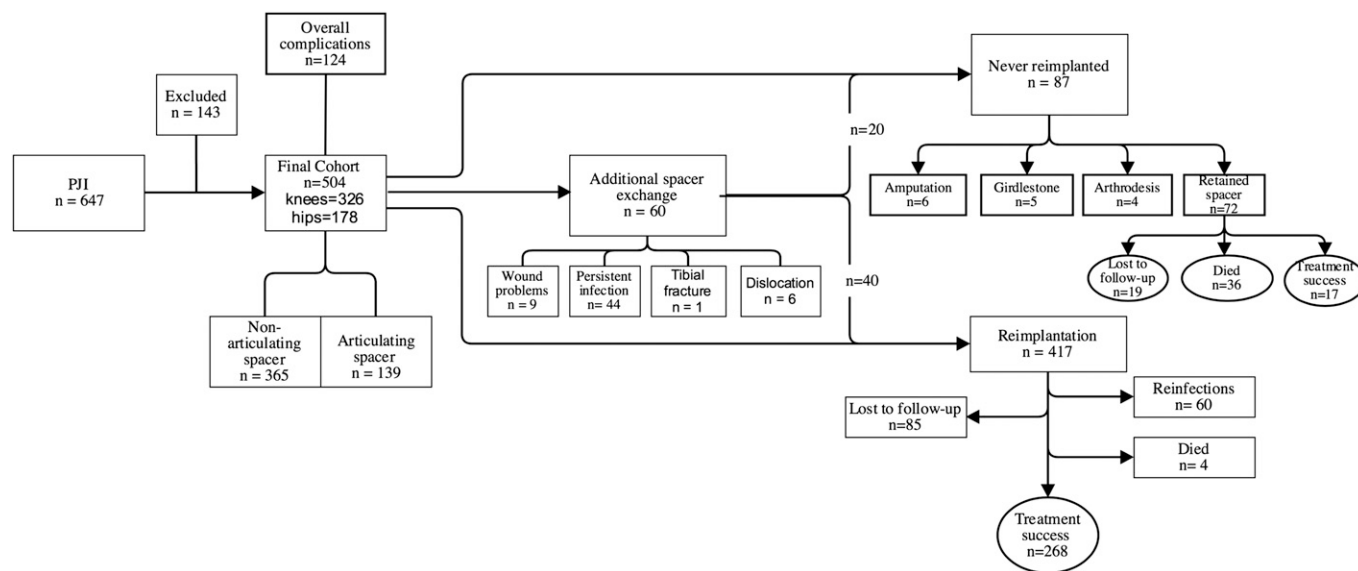


Fig. 1
Flowchart depicting the outcomes of the final cohort. PJI = periprosthetic joint infection.

reimplantation (Fig. 1). The reasons for requiring additional spacer exchanges included persistent infection (forty-four cases [73.3%]), spacer dislocation (six cases [10%]), wound-related problems (nine cases [15%]), and fracture of the tibia (one case [1.7%]). The reimplantation rate was 87.1% for articulating spacers and 81.2% for static spacers, and the duration to reimplantation was 4.3 months for articulating spacers and 4.0 months for static spacers. There was no difference in the reimplantation rate ($p = 0.146$) or treatment success rate ($p = 0.730$) between the types of spacers.

Of the cases undergoing reimplantation, 329 joints (78.9%) had a minimum one-year follow-up. Treatment success was 81.4% for the entire cohort, 81.4% for knees, and 81.7% for hips (Fig. 2). Following reimplantation, the mean follow-up duration was 57.0 months in cases with treatment success and 50.4 months in cases with failure. The mean number of surgeries between the resection arthroplasty with spacer insertion and the reimplantation was 1.3 surgeries (range, one to six surgeries), which included additional spacer exchanges, irrigation and debridement, and reoperation for wound-related complications. Of those eighty-seven cases that did not undergo second-stage reimplantation, six required amputation (6.9%), five (5.7%) underwent a Girdlestone procedure, four (4.6%) underwent arthrodesis, and seventy-two (82.8%) retained the spacer. Of the seventy-two cases that retained the spacer, treatment success was 23.6% (seventeen cases) at a minimum one-year follow-up (Fig. 1).

Of the seventy-two cases of retained spacers, nineteen (26.4%) were lost to follow-up after the decision was made to use the retained spacer as the definitive treatment, leaving fifty-three cases. When excluding cases lost to follow-up, treatment success was 32.1% (seventeen cases). In thirty-six cases (50.0%) with retained spacers, the patients died before the second stage at a mean time of 38.3 months (range, 0.4 to 127.5 months), with five of those deaths occurring during the initial hospitalization for spacer in-

sertion; we confirmed that mortality in the latter five cases was related to the infection. The major reasons for a retained spacer among the seventy-two cases were no desire for reimplantation (2.8% [two cases]) or being unfit for the surgical procedure (20.8% [fifteen cases]) for a variety of reasons (e.g., severe bone loss and non-healing ulcers).

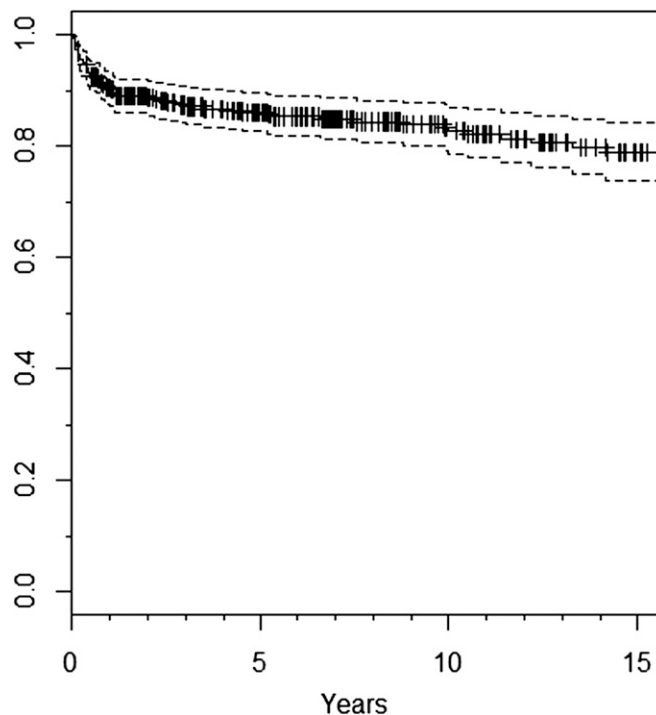


Fig. 2
Kaplan-Meier survivorship curve with treatment failure as an end point. The dashed lines indicate the 95% confidence interval.

The overall incidence of mortality for the cohort was 1.2% (six cases) within thirty days, 2.6% (thirteen cases) within ninety days, 6.5% (thirty-three cases) within one year, and 10.3% (fifty-two cases) within two years. In comparison, the death rate of patients who are sixty-five to seventy-four years of age in the United States is 2.0%¹⁵. The most common infecting organisms at the time of resection arthroplasty and spacer insertion were coagulase-negative *Staphylococcus* (16.7%) and methicillin-sensitive *Staphylococcus aureus* (14.5%) (Table III). For patients with reinfection, 22.5% were infected with the same organism as that identified at the time of initial resection arthroplasty. A significantly increased number of interim spacer exchanges were performed in the seventy-six patients who had periprosthetic joint infection by a resistant organism(s) ($p = 0.02$), but no difference in reimplantation rate was observed (Table IV). In addition, patients with gram-negative bacteria demonstrated a lower reimplantation rate than those infected with gram-positive bacteria ($p = 0.002$).

When stratified by comorbidities, increased Charlson Comorbidity Index ($p < 0.0001$) and presence of rheumatoid arthritis ($p = 0.03$) were associated with a lower reimplantation rate (Table IV). Furthermore, the total number of procedures was significantly higher when associated with higher body mass index ($p = 0.006$).

Discussion

The success of two-stage exchange arthroplasty for the treatment of chronic periprosthetic joint infection has been reported to approach or to exceed 80% in the majority of studies¹⁶⁻²². However, there is a widespread heterogeneity on the reporting of the clinical outcomes of two-stage exchange arthroplasty. The most important fact is that the definition of success has varied in these reports. The lack of consensus with regard to what constitutes a successful treatment outcome for periprosthetic joint infection makes it difficult to compare the outcomes between studies and ultimately between different treatment strategies. This has led to the development of a multidisciplinary consensus to better define success¹⁴. However, despite the availability of an acceptable definition for success, it is not known whether success should take into account patients who had a failure after the first-stage surgical procedure and never underwent reimplantation for a variety of reasons.

The majority of studies showing the outcome of two-stage exchange arthroplasty do not take into account the attrition that occurs between the two stages and arguably overestimate the success of this surgical procedure. Although there are a variety of reasons for the attrition between stages, one sobering recognition is that the proportion of patients who die after the initial resection arthroplasty is not small^{1,23}.

This study, specifically designed to evaluate the clinical course of patients in between two stages, demonstrated that almost one-fifth of patients who underwent resection arthroplasty and spacer insertion did not undergo a subsequent reimplantation. Within the literature, there is considerable variation in the reimplantation rates following explantation, ranging from 28.6%²⁴ to 100%²⁵⁻²⁹, and most studies have demonstrated reimplantation

rates above 80%^{1,2,5,30-34}. Failure to reimplant may occur for a variety of reasons, including mortality, medical comorbidity, patients lost to follow-up, patients satisfied with their current level of function in the setting of a retained spacer¹⁹, and persistent infection that may ultimately result in definitive treatment with amputation, arthrodesis, or lifetime antibiotic suppression. Therefore, the reimplantation rates within the literature and in the present study suggest that the number of patients who fail to undergo reimplantation is not inconsequential and that reported outcomes following completion of the second stage neglect the nearly 20% of treatment failures in the interstage period.

We suggest that the success of two-stage treatment be considered from the point of initial spacer implantation rather than following reimplantation to account for failures that occur in the interstage period. For example, Berend et al. reported a success rate of 83% following reimplantation in a study of 205 hips. However, when accounting for a reimplantation rate of 92%, the rate of infection control following initial spacer implantation dropped to 77%¹. Another study of 130 patients with periprosthetic joint infection demonstrated a 95% rate of eradication following reimplantation, but only a 68% rate when taking into account a reimplantation rate of 84.6% and those who either had been lost to follow-up or had died²⁸. Despite having a lower reimplantation rate, the first stage as a starting point better represents the actual clinical course and explains the seemingly low infection eradication rates reported in the current study and previous reports from our institution³⁵⁻³⁸.

It is also important to point out that, even for patients in the present study who ultimately underwent reimplantation, many underwent spacer exchange or surgical intervention for wound-related problems in the interstage period, with all of the inherent risks of added surgical procedures^{19,39,40}. In nearly one of five patients, the intended two-stage exchange never occurred, with patients requiring arthrodesis or amputation or resorting to living with the implanted spacers. When taking into account the failures that occurred in the interstage period in addition to the patients who were reinfected after reimplantation, it becomes clear that the failure rate in the interstage period approaches the reinfection rate that is usually seen with the two-stage exchange, at around 17%.

Although several studies have investigated the impact of organism type and resistance profile on the eventual outcome of two-stage exchange arthroplasty, we are unaware of any studies investigating the role of microorganisms in the interstage period. We noted that patients with periprosthetic joint infection caused by resistant organisms and gram-negative organisms had a more complicated course requiring additional surgeries, and fewer of these patients underwent subsequent reimplantation (Table IV). The latter may relate to the fact that surgical management of patients with periprosthetic joint infection caused by more virulent organisms is more challenging^{32,36,41,42}. This is an important finding because patients with a culture-negative infection or resistant organisms are typically managed by two-stage exchange; however, our study demonstrates that these infections are still associated with a reduced reimplantation rate. In addition to the type of infecting organism, the overall medical comorbidity of the

patients also influenced the reimplantation rate and number of surgical procedures in the interstage period, with sicker patients having a more protracted interstage course. Surgeons should be aware that these factors, the type of infecting organism and comorbid medical conditions, might influence the likelihood of a patient completing both stages of a two-stage exchange.

There were limitations to the current study. The retrospective nature of the study, with all of the inherent limitations of such a study design, may have allowed for the introduction of bias. In addition, the current study intentionally did not include evaluation of radiographic or functional outcomes, which may be seen as a potential weakness. Furthermore, despite all our efforts, including calling all patients as part of another study, some patients were lost to follow-up or did not have long-term follow-up. However, all patients were included regardless of the follow-up to prevent an overestimation of the results and to allow a more realistic picture of the actual clinical course. In addition, some may argue that reinfection by a different organism than the initial infection, which happened in the majority (77.5%) of the cases of reinfection, should not be attributed to failure of the initial treatment. However, it is possible that the organisms cultured at the time of failure were in fact present at the time of the initial periprosthetic joint infection but were not captured by the culture technique, rather than representing a new infection. Because the latter possibility cannot be ruled out, we believe that an infection with a different organism may still be attributed to failure of the initial two-stage exchange. In addition, subsequent surgical procedure for infection and mortality were used to evaluate treatment success, and these do not require a recurrent organism to be present according to the Delphi consensus criteria¹⁴. Additionally, infection-related mortality was difficult to confirm in deaths that occurred outside of a hospital. Although the date of

death was known in these patients, the precise cause of death could not be determined. Lastly, it should be noted that there was not a clear reimplantation protocol and that some failures may potentially have been caused by variations in the reimplantation protocol, for example, returning to the operating room too soon or differences in an antibiotic-free period. This inconsistency can be attributed to the several surgeons involved in this study and the lack of current guidelines and literature for determining the optimal time for reimplantation.

Despite the aforementioned limitations, this study highlights the fact that the commonly held belief that two-stage exchange arthroplasty carries a high success rate for eradication of periprosthetic joint infection may need to be reexamined. A considerable number of patients undergoing resection arthroplasty and spacer insertion do not undergo subsequent reimplantation for a variety of reasons, and many are subjected to interim surgical procedures. Of those who undergo reimplantation, nearly one-fifth experience a failure later because of persistence of infection or reinfection. The future management of patients with periprosthetic joint infection needs to change as current strategies, which have a high burden on the patient and society, are far from perfect. ■

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