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The Fate of Periprosthetic Joint Infection Following Megaprosthesis Reconstruction

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Background: A megaprosthesis may be used for reconstruction in patients with massive bone loss or a periprosthetic fracture. Periprosthetic joint infection (PJI) may occur after a megaprosthesis reconstruction and may pose a major challenge. The outcomes of managing PJI in patients with a megaprosthesis is relatively unclear. The aim of this study was to investigate the clinical course and outcomes of PJI in patients with a megaprosthesis in place.

Methods: From a total of 219 patients who underwent megaprosthesis replacement for non-oncologic conditions, 38 (17.4%) developed subsequent PJI. A retrospective review of the medical record was performed to ascertain the course of the PJI and treatment outcomes. Kaplan-Meier analysis was performed to evaluate the survival function, and the log-rank test was used to assess differences in outcome measures.

Results: The surgical management of 33 patients with PJI included debridement, antibiotics, and implant retention (DAIR) (82%), consisting of DAIR with modular component exchange (19 patients) and DAIR without component exchange (8 patients); 2-stage exchange arthroplasty (9%); resection arthroplasty (6%); and a single-stage revision arthroplasty (3%). The Kaplan-Meier survivorship analysis demonstrated that the overall survival rate was 65.1% at 2 years. The mortality rate was 15%, with many patients undergoing salvage procedures including amputation (18%), arthrodesis (6%), and resection arthroplasty (6%).

Conclusions: The rate of PJI after megaprosthesis reconstruction, 17% in this study, appears to be very high. The management of PJI in these patients is challenging, with 1 of 3 patients undergoing failed treatment. Despite the limited options available, DAIR seems to be an appropriate treatment strategy for some of these patients. Further data on a larger cohort are needed to assess the success of various surgical procedures and predictors of failure in this challenging patient population.

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

Massive bone loss or periprosthetic fracture is often encountered in revision arthroplasty that may necessitate the use of a megaprosthesis. However, the use of a megaprosthesis is not without complications. One of the most devastating complications following a megaprosthesis implantation is periprosthetic joint infection (PJI), which occurs at a significantly higher rate than following other primary or revision procedures[1,2]. This increased propensity for infection often occurs because of the associated longer operative time and larger soft-tissue dissection and because the patient who undergoes multiple revisions and has massive bone loss is more likely to be a poor host.

PJI is a serious complication after total joint arthroplasty and is associated with remarkable morbidity and mortality. However, PJI following a megaprosthesis introduces several new challenges given the morbidity associated with revision or explantation of a megaprosthesis. Given the relative rarity of the use of a megaprosthesis, little is known with regard to the fate of a patient with a PJI occurring after a megaprosthesis is implanted. Outcomes after arthroplasty using non-megaprostheses are far from optimal, with high rates of reinfection, mortality, and need for subsequent salvage procedures. Thus, it is expected that outcomes following PJI involving a megaprosthesis may be even worse. Due to the lack of literature on an infection involving megaprostheses, it is difficult for surgeons to recommend the most appropriate treatment option and manage patient expectations without knowing the associated complication profile.

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJSOA/A345).

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This study was designed to investigate the success of treating patients with PJI after megaprosthesis placement and to determine the survival rate of megaprostheses with and without PJI.

Materials and Methods

After institutional board review approval, a retrospective review of medical records and our institutional database was performed between 2000 and 2018. A total of 219 megaprostheses were implanted in this time period for non-oncologic etiologies, including 73 proximal femoral replacements (PFRs) and 146 distal femoral replacements (DFRs) (Fig. 1). The protocol for antibiotic prophylaxis, anticoagulation, and rehabilitation was similar or the same for all patients. Weight-based (15 mg/kg), first-generation cephazolin was administered for 24 hours. All distal femoral replacements were cemented, and some of the proximal femoral replacements were cemented. When used, cement was antibiotic-impregnated. All patients with a megaprosthesis who subsequently developed PJI and had a minimum follow-up of 1 year were included in this study. A total of 38 megaprosthesis cases (17.4%) developed subsequent PJI after megaprosthesis placement according to recent International Consensus Meeting (ICM) criteria[3]. The initial indication of those megaprosthesis replacements was prior PJI (20 [32%] of 63 cases), periprosthetic fracture (10 [12%] of 81 cases), and aseptic loosening (8 [12%] of 67 cases). Five additional patients who developed PJI were excluded because they did not have a minimum of 1-year follow-up, but no complication, reoperation, or death occurred in this group of 5 patients. The final analyses were on 33 infected megaprostheses, including 15 PFRs (46%) and 18 DFRs (55%) (Fig. 1, Table I).

Surgical Technique

The surgical treatment selected was largely based on the surgeon's preference and acuity of infection. Moreover, the fixation status of the components, patient comorbidity, and intraoperative findings influenced the choice of surgical option. For patients who underwent debridement, antibiotics, and implant retention (DAIR), debridement of all devitalized osseous and soft tissues was performed in all cases. At least 6 L of various irrigation solutions were used depending on the surgeon's preference. The decision to perform a modular component exchange was also made by the treating surgeon. It is customary that all modular parts of a megaprosthesis are exchanged during a DAIR procedure unless the prosthesis is custom-made or modular parts are not available off the shelf. In the latter circumstance, the modular part is usually scrubbed physically by a brush and/or immersed in an antiseptic solution. During DAIR, surgeons also utilized many liters of antiseptic solution for irrigation that includes dilute povidone iodine (0.5%) and dilute hypochlorite solution (0.125%). A total of 3 to 5 tissue samples were collected for culture and were sent for routine aerobic and anaerobic bacterial, fungal, and acid-fast cultures. For patients with a 2-stage exchange, components were explanted and a static spacer was placed after debridement of bone and soft tissues. The spacers included dual antibiotics containing both 3 g of vancomycin and 3.6 g of tobramycin per 40-g package of bone cement if there is no contraindication. The decision to undergo reimplantation was based on numerous metrics that included suitability of the patient, serum markers, and other parameters. Following the surgical procedure, parenteral antibiotic therapy was introduced for 6 weeks and was followed by oral antibiotics for 6 months to 1 year, which was initiated on the basis of consultation with an infectious disease specialist and followed the treatment response, clinical follow-up, laboratory markers, and radiography per the institute protocol.

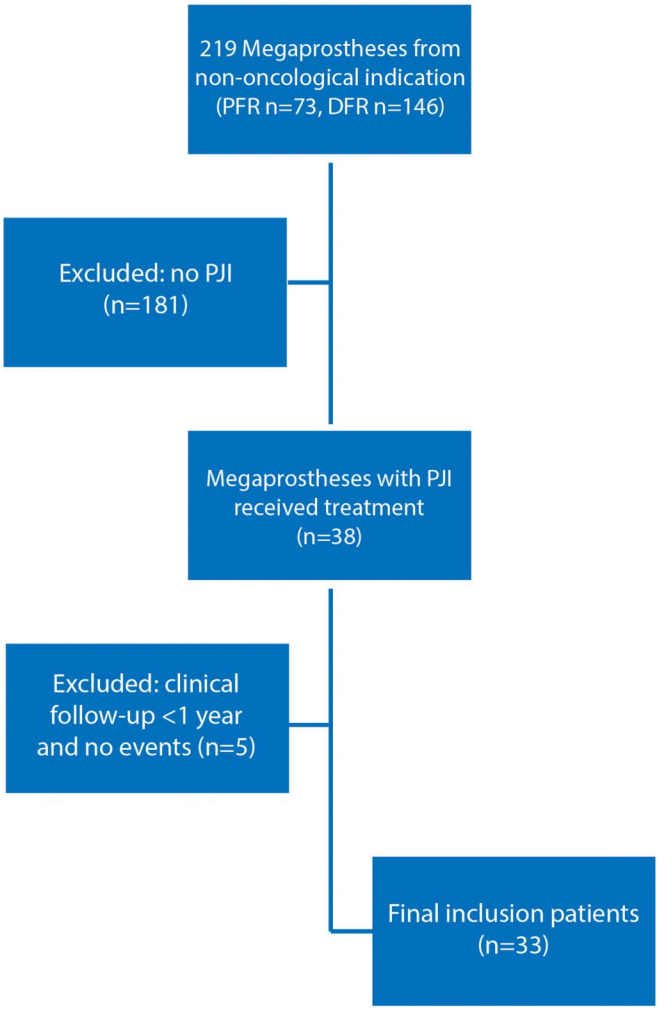

Fig. 1
Flowchart of patient inclusion.

Outcome Variables

A manual review of medical records was conducted to collect pertinent information including medical comorbidities, operative information, organism information, subsequent surgical procedures, and mortality. The primary outcome was treatment failure, which was defined as unplanned revision or salvage surgical procedures or implant removal. All antibiotic treatment was given in consultation with an infectious disease specialist who determined the dose and duration of the antimicrobials.

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TABLE I Demographic Data, Etiology, and Prosthesis Type According to Type of PJI

	Acute Postoperative PJI Group (N = 12)	Acute Hematogenous PJI Group (N = 10)	Chronic PJI Group (N = 11)	P Value
Age* *(yr)*	68.3 ± 14.2	65.1 ± 12.4	64 ± 11.2	0.694
Female sex†	8 (67%)	6 (60%)	6 (55%)	0.837
Body mass index* *(kg/m²)*	32.8 ± 5.9	32.5 ± 7.6	34 ± 9	0.88
Charlson Comorbidity Index*	1 ± 1.7	1.1 ± 1.8	1.1 ± 1.3	0.986
Diabetes†	0	1 (10%)	0	0.305
Rheumatoid arthritis†	0	0	0	
Smoking†	5 (42%)	2 (20%)	5 (45%)	0.357
No. of previous operations*	4.3 ± 1.9	3.5 ± 2.6	5 ± 3	0.415
Estimated blood loss* *(mL)*	775 ± 711.5	518.8 ± 334.8	1,400 ± 1,444.8	0.165
Operative time* *(min)*	195.3 ± 88.1	179.6 ± 37.8	217.3 ± 74.5	0.582
Follow-up duration* *(mo)*	24.6 ± 17.6	49 ± 31.7	36.6 ± 26.5	0.1
Etiology for megaprosthesis†				0.404
Prior PJI	7 (58%)	4 (40%)	9 (82%)	
Fracture	3 (25%)	3 (30%)	2 (18%)	
Aseptic loosening	2 (17%)	3 (30%)	0 (0%)	
Type of prosthesis†				0.014
PFR	6 (50%)	1 (10%)	8 (73%)	
DFR	6 (50%)	9 (90%)	3 (27%)	

*The values are given as the mean and standard deviation. †The values are given as the number of patients, with the percentage in parentheses.

Statistical Analysis

This study used descriptive statistics for evaluation of categorical and continuous data. Categorical variables were analyzed using the chi-square test or the Fisher exact test, and continuous variables were analyzed using the independent t test or the Mann-Whitney U test. An alpha level of 0.05 was used to determine significance. Kaplan-Meier survivorship curves were generated using a revision surgical procedure or treatment failure as an end point. Differences in survivorship were evaluated based on the log-rank test. All analyses were performed using SPSS Statistics for Macintosh, version 26.0 (IBM).

Source of Funding

None.

TABLE II Operative Treatment of Subsequent PJI According to Type of PJI and Initial Etiology of the Megaprosthesis Reconstruction*

		Type of PJI			Prosthesis Etiology		
	No. of Patients	Acute Postoperative	Acute Hematogenous	Chronic	PJI	Fracture	Aseptic Loosening
Total no. treated	33 (11)	12 (2)	10 (5)	11 (4)	20 (8)	8 (2)	5 (1)
Operation							
DAIR	27 (10)	11 (2)	9 (5)	7 (3)	16 (7)	7 (2)	4 (1)
With modular component exchange	19 (6)	7 (1)	8 (4)	4 (1)	11 (4)	5 (2)	3 (0)
Without modular component exchange	8 (4)	4 (1)	1 (1)	3 (2)	5 (3)	2 (0)	1 (1)
2-stage exchange	3 (1)	0	1 (0)	2 (1)	2 (1)	1 (0)	0
1-stage exchange	1 (0)	0	0	1 (0)	1 (0)	0	0
Resection arthroplasty	2 (0)	1 (0)	0	1 (0)	1 (0)	0	1 (0)

*The values are given as the total number of patients, with the number of patients who underwent failed treatment in parentheses.

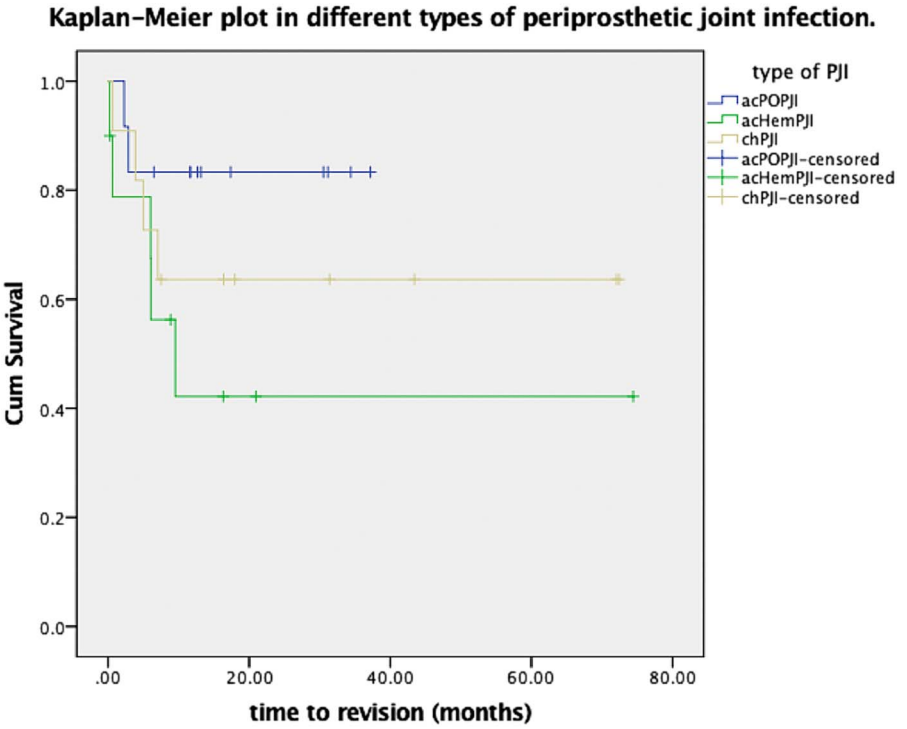

Fig. 2

Kaplan-Meier plot comparing survival functions in different types of PJI. Cum = cumulative, acPOPJI = acute postoperative PJI, acHemPJI = acute hematogenous PJI, and chPJI = chronic PJI.

Results

The mean follow-up duration (and standard deviation) for all patients was 36 ± 26.2 months. Of the 33 infected megaprostheses that were included in the final data, DAIR was the most commonly performed surgical procedure (82% [27 patients]). This consisted of 11 cases in the acute postoperative

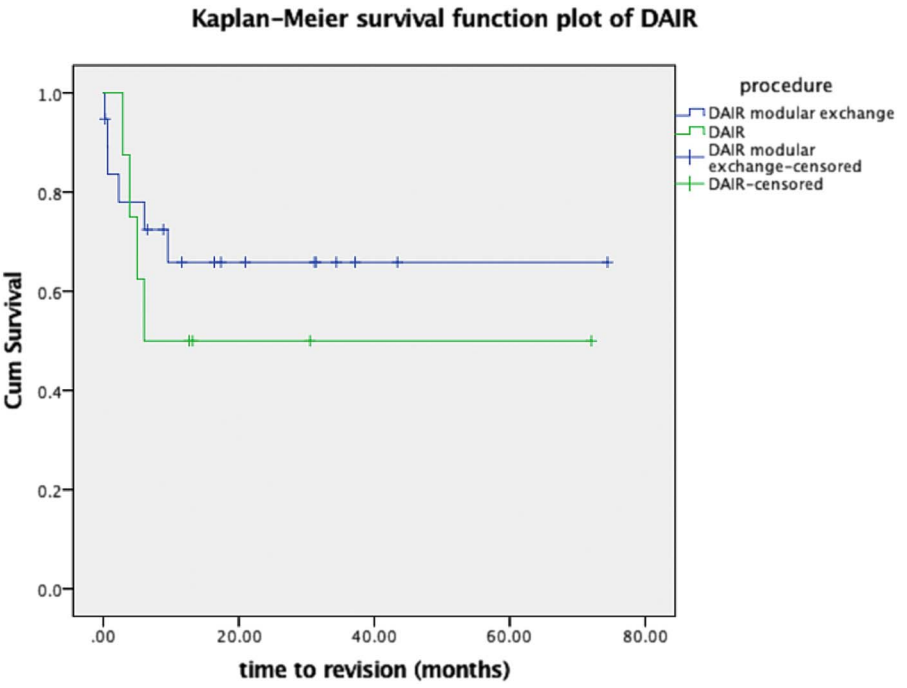

Fig. 3

Kaplan-Meier plot comparing survival functions between DAIR with and without modular-component exchange. Cum = cumulative.

TABLE III Descriptive Data for Patients Who Underwent Failed Treatment*

Patient No.	Prosthesis	Etiology of Megaprostheses	Former Culture Results	Important Clinical Notes	Type of PJI	First Operation for PJI Treatment	Organism(s)	Second Operation for Treatment	Time from First Operation to Final Operation *(mo)*	Final Operation
1	PFR	Prior PJI	MRSA	Sinus tract	Chronic	DAIR	Mixed	Resection	5	Girdlestone
2	PFR	Prior PJI	Negative	Sinus tract	Chronic	DAIR modular component exchange	*Serratia marcescen*	2-stage exchange revision, then amputation	0.7	Hip disarticulation
3	PFR	Prior PJI	NA	—	Chronic	2-stage exchange revision	*Proteus mirabilis*	Resection	7.1	Girdlestone
4	DFR	Prior PJI	MSSA	Tooth extraction	Acute hematogenous	DAIR modular component exchange	Coagulase-negative Staphylococcus	Amputation	9.5	Above-the-knee amputation
5	DFR	Fracture	—	MSSA bacteremia	Acute hematogenous	DAIR modular component exchange	MSSA	Resection, then amputation	0.23	Above-the-knee amputation
6	DFR	Prior PJI	MSSA	Previous pain 1 week	Acute hematogenous	DAIR modular component exchange	Coagulase-negative Staphylococcus	2-stage exchange revision	0.6	DFR and lifelong antibiotic
7	DFR	Prior PJI	MSSA	Postoperative day 21	Acute postoperative	DAIR modular component exchange	*Enterococcus faecalis*	Resection, then arthrodesis	2.3	Intramedullary knee arthrodesis
8	DFR	Fracture	—	Heel ulcer	Acute hematogenous	DAIR modular component exchange	Group B Streptococcus	Amputation	6.1	Above-the-knee amputation
9	DFR	Aseptic loosening	—	Cardiac procedure	Acute hematogenous	DAIR	NA	Resection, then fusion	6	Intramedullary knee arthrodesis
10	DFR	Prior PJI	Coagulase-negative Staphylococcus	Postoperative day 80	Acute postoperative	DAIR	Culture-negative	Amputation	2.9	Above-the-knee amputation
11	DFR	Prior PJI	Mixed	—	Chronic	DAIR	Mixed	Amputation	3.9	Above-the-knee amputation

*MRSA = methicillin-resistant *Staphylococcus aureus,* MSSA = methicillin-sensitivity *Staphylococcus aureus,* and NA = not available.

group, 9 cases in the acute hematogenous group, and 7 cases in the chronic PJI group. Other surgical treatments included 2-stage exchange arthroplasty (9% [3 patients]), resection arthroplasty (6% [2 patients), and a single-stage exchange (3% [1 patient]) (Table II). Treatment failure occurred in 11 patients (33%). The mean time to revision after the first PJI treatment was 1.3 ± 0.9 months for acute postoperative PJI, 36.7 ± 40.5 months for acute hematogenous PJI, and 17.9 ± 34.7 months for chronic PJI. The infection rate based on the indication for a megaprosthesis was 40% for the prior PJI group, 25% for the fracture group, and 20% for the aseptic loosening group ($p = 0.592$).

DAIR treatment demonstrated an overall success rate of 63% (Table II). Treatment success was higher when modular components were exchanged (68% for DAIR with a modular component exchange compared with 50% for DAIR without a modular component exchange). However, this difference did not reach significance with the given number of patients in the cohort. A single DAIR treatment was successful in 30% of cases, and a second DAIR operation was performed in 53% of patients and achieved treatment success in 44% of these patients. If ≥3 DAIRs were performed, the treatment success was only 25%. Treatment success with DAIR was the highest in patients with acute postoperative PJI (82% [9 of 11]). However,

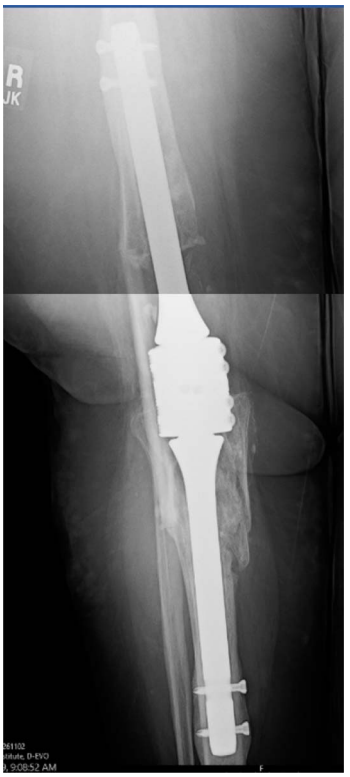

Fig. 4

Anteroposterior radiograph of a right knee that underwent intramedullary knee arthrodesis at 2 years after megaprosthesis placement. This patient had had subsequent PJI after the megaprosthesis placement and treatment failure following DAIR; resection arthroplasty was performed, but the patient was a poor candidate for distal femoral replacement reimplantation.

treatment success was only 44% in patients with acute hematogenous PJI (p = 0.212). When DAIR was performed for patients with chronic PJI, the success rate was 57%.

The overall survivorship, being defined as free of failure, was 65% at 2 years. All failures occurred within the first year after the surgical intervention. Survivorship was higher, but not significantly (p = 0.211), for patients with acute postoperative PJI (83%) than patients with acute hematogenous PJI (42%) or chronic PJI (63.6%) (Fig. 2).

When stratified by PJI treatment, survivorship at 2 years was 61% for patients who underwent DAIR and 67% for patients who underwent 2-stage exchange arthroplasty (p = 0.739). Patients who underwent DAIR with a modular component exchange had a higher survival rate at 2 years (66%) than patients who underwent DAIR without a modular component exchange (50%) (p = 0.511) (Fig. 3).

Uncontrolled infection occurred in 11 patients, requiring several salvage and subsequent surgical procedures (Table III). One patient was given lifelong antibiotic suppression treatment, and 6 patients required amputation that included 1 hip disarticulation and 5 above-the-knee amputations. Two patients needed knee arthrodesis and 2 patients underwent permanent resection arthroplasty of the hip (Fig. 4, Table III). Reinfection treatment failure was found in 40% (8 of 20) in the prior PJI group: acute postoperative PJI for 2 cases, acute hematogenous PJI for 2 cases, and chronic PJI for 4 cases. Four of 8 patients from this group later underwent lower-limb amputation (Table III).

The overall mortality rate was 15% (5 patients), with a mean time to mortality of 15.4 ± 13 months. The microorganism isolation is demonstrated in Table IV, in which the most common organisms were mixed organisms at 27% and coagulase-negative Staphylococcus at 18%.

Discussion

The management of PJI after megaprosthesis reconstruction is extremely challenging, especially given the paucity of literature with regard to outcomes of a PJI after megaprosthesis placement. To our knowledge, this is the first reported

TABLE IV Organisms Isolated in Cases of PJI After Megaprosthesis Implantation*

Organism(s)	Patients†
Coagulase-negative Staphylococcus	6 (18%)
Staphylococcus aureus	
MSSA	2 (6%)
MRSA	1 (3%)
Streptococcus species	4 (12%)
Serratia marcescens	2 (6%)
Proteus mirabilis	2 (6%)
Culture-negative	4 (12%)
Mixed organisms	9 (27%)
Actinomyces species, *Bacteroides fragilis,* Gemella species	
Corynebacterium species, *Staphylococcus epidermidis*	
Cutibacterium acnes, coagulase-negative Staphylococcus	
Coagulase-negative Staphylococcus, *Klebsiella pneumoniae, Pseudomonas aeruginosa*	
S. epidermidis, Candida lusitaniae	
MSSA, Streptococcus species	
Enterococcus faecalis, K. pneumoniae, S. epidermidis	
Corynebacterium species, Candida species	
C. acnes, coagulase-negative staphylococcus, *E. faecalis*	
Other	3 (9%)

*MSSA = methicillin-sensitive *Staphylococcus aureus,* and MRSA = methicillin-resistant *Staphylococcus aureus*. †The values are given as the number of patients, with the percentage in parentheses.

study to reveal the surgical options for and outcomes of a PJI after megaprosthesis placement after a non-oncologic megaprosthesis reconstruction. This study demonstrates that the overall PJI rate after megaprosthesis reconstruction is high (up to 17.4%) even in the first megaprosthesis replacement, especially in the prior PJI group, in which one-third of patients developed reinfection after megaprosthesis replacement. We found that DAIR was a viable treatment option for acute postoperative PJI in patients with a megaprosthesis in place, with a success rate of 82%, and the overall success rate for treatment of PJI of any type was 63%, which compared favorably with the 67% overall success rate of 2-stage exchange, without the increased potential for surgical morbidity associated with complete implant removal. However, DAIR performed substantially worse for acute hematogenous PJI, with a failure rate of 56%, and chronic PJI, with a failure rate of 43%. Furthermore, if DAIR is to be performed, modular component exchange might improve the success rate, which was slightly higher but not significantly so in the current study. A high rate of salvage procedures and mortality was also observed in our study.

Although this is the first study on PJI after megaprosthesis placement, to our knowledge, there is some literature on the use of a megaprosthesis for a prior infection. Alvand et al.[4] reviewed 69 patients with megaprostheses for PJI management and reported an infection rate of 28%. Furthermore, Corona et al.[5] analyzed infection rates following the use of a megaprosthesis at reimplantation in patients with chronic PJI who demonstrated bone loss and reported an infection rate of 17%. The 2 aforementioned studies found that the 2 most commonly isolated pathogens were coagulase-negative staphylococcal and polymicrobial infections, which is also consistent with our findings (Table IV). When a megaprosthesis is used for fracture, a systematic review found that the infection rate was 29%[6]. However, the treatment outcomes after reinfection were not reported. Ercolano et al.[1] studied infection after megaprosthesis implantation for both oncologic and non-oncologic conditions in a series of 31 patients who developed infection after the megaprosthesis placement and found that the treatment failure rate was 52%. This higher failure rate may be attributed to the fact that 40% of treatment failure occurred in oncologic patients, who may have been poor hosts. The authors utilized DAIR, 1 and 2-stage revision, and amputation and found that no individual surgical method was preferred.

When evaluating the outcome of DAIR specifically, the current study found that it is a viable option with a relatively high success rate for patients who experience an acute PJI after the megaprosthesis is in place. A repeat DAIR in these patients appeared to improve the outcome only marginally. Our data add weight to the recent ICM recommendations that DAIR should be employed in patients with acute PJI after a megaprosthesis placement[2]. If DAIR is to be performed, our study advocates that modular component exchange should be performed, which is consistent with the recommendations of the ICM[2]. The indications for DAIR were likely expanded in the presence of a megaprosthesis given the morbidity of removing all components, massive bone loss and soft-tissue voids, and concern for instability. This also explains why DAIR was utilized in 64% of cases of chronic PJI, despite the propensity for increased failure rates.

There were several limitations to this study that should be considered. First, this study was a retrospective review and information was thus limited to the medical record. It was therefore difficult to determine the surgeon's individual rationale for choosing a particular surgical plan, which introduced the possibility of a selection bias. Second, because DAIR was the predominant surgical procedure chosen, we had only a few patients with 2-stage and 1-stage exchanges, which made it difficult for us to compare the different treatment options. Third, given the relatively low sample size, a multivariate analysis could not be performed, which made it difficult to control for potential confounding variables. Finally, we were unable to obtain information on postoperative functional outcomes.

In summary, patients with a megaprosthesis for non-oncologic conditions demonstrated a high rate of PJI and demonstrated high rates of subsequent reinfection after PJI treatment. DAIR was the most often performed procedure for infection following megaprosthesis placement, and success was most often achieved in patients with acute postoperative PJI and when modular exchange was performed. When failure of DAIR occurs, there may be a role for repeat DAIR. Surgeons should consider these factors when deciding on a surgical plan and counseling patients on expected outcomes. ■

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