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Periprosthetic Joint Infection Surrounding Lower-Extremity Endoprostheses After Tumor Resection

Causative Microorganisms, Effectiveness of DAIR, and Risk Factors for Treatment Failure

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Background: Periprosthetic joint infection (PJI) surrounding an endoprosthesis after reconstruction of a lower extremity following tumor resection is a common complication, and the treatment of these infections is challenging and often requires multiple surgical interventions or even implant removal. Because there has been limited evidence to support treatment strategies and understanding of the epidemiology of the causative microorganisms, we analyzed the effectiveness of debridement, antibiotics, and implant retention (DAIR), risk factors for the failure of DAIR, and causative microorganisms in patients with a PJI surrounding a lower-extremity endoprosthesis after tumor resection.

Methods: A retrospective cohort study was conducted in a tertiary referral center for orthopaedic oncology. All patients treated between 2000 and 2018 for PJI surrounding a lower-extremity endoprosthesis after tumor resection were included. Treatment outcomes and risk factors for failure were analyzed in patients primarily treated with DAIR. Causative microorganisms were recorded. The minimum follow-up period was 2 years.

Results: Of the 337 patients who underwent endoprosthetic reconstruction of a lower extremity after tumor resection, 67 patients (20%) developed a PJI surrounding the endoprosthesis. Of those patients, 55 were primarily treated with DAIR. The functional cure rate of DAIR was 65% (36 of 55). A median of 2 debridements per patient was needed. Chemotherapy (odds ratio [OR], 3.1 [95% confidence interval (CI), 1.0 to 9.3]) and an erythrocyte sedimentation rate of >50 mm/hr at diagnosis (OR, 4.5 [95% CI, 1.3 to 15.4]) were associated with treatment failure. Nineteen patients (28%) had a polymicrobial infection.

Conclusions: Although sequential procedures are often needed, DAIR has acceptable clinical outcomes and should be considered, dependent on expected survival and the risk factors for treatment failure noted in this study.

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

Modular endoprosthetic reconstruction is the preferred reconstructive technique after tumor resection of a lower extremity in most orthopaedic oncology centers. A periprosthetic joint infection (PJI) remains one of the major challenges, with reported incidences of up to 15%. These infections can be devastating, as they regularly necessitate multiple surgical debridements, removal of implants, or, rarely, amputation[1,2]. The treatment of infection often results in a delayed start of chemotherapy and possibly deterioration of oncologic outcomes. Patients undergoing tumor resection and subsequent reconstruction surgery may have an increased risk of PJI due to disseminated malignancy, the use of neoadjuvant chemotherapy, and/or radiation therapy[3]. Tumor resection and reconstruction are usually lengthy and result in large wound beds with extended soft-tissue removal, and possibilities for adequate soft-tissue coverage are often limited, requiring vascularized muscle flaps. These factors

Disclosure: No external funding was received for this work. The Article Processing Charge for open access publication was funded by the LUMC Hospital. The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJSOA/A741).

may contribute to the marked differences of infection risk (9% to 15%) when compared with conventional arthroplasty (<1%)[4,5].

Surgical treatment of a PJI surrounding an endoprosthesis after tumor resection consists of debridement, antibiotics, and implant retention (DAIR) or a 1-stage or 2-stage exchange of the implant. For PJI after conventional arthroplasty, the indications for the type of surgical strategy are well defined, and the clinical outcomes of these strategies have been reported on extensively[6]. However, there has been a lack of data on clinical outcomes of surgical strategies for PJI surrounding an endoprosthesis after tumor resection that can guide the decision to perform either DAIR or 1-stage or 2-stage revision procedures. Therefore, we analyzed the causative microorganisms, clinical outcome of DAIR, and risk factors for treatment failure in a cohort of patients who had undergone tumor resection and then had a PJI surrounding the lower-extremity endoprosthesis.

Materials and Methods

Study Design and Population

Institutional databases were queried to identify all patients who underwent endoprosthetic reconstruction of a lower extremity following tumor resection between 2000 and 2018 in a tertiary referral center for orthopaedic oncology. Patients who subsequently developed a PJI surrounding the endoprosthesis after tumor resection were included. Microorganisms isolated during the first surgical procedure for infection were recorded, as were the number of reoperations for persistent infection or secondary superinfection, antimicrobial treatment strategy, and outcome of treatment. A nested case-control study was performed to identify risk factors for treatment failure after the initial DAIR. Sex, age, American Society of Anesthesiologists (ASA) classification, cementation, silver coating, revision surgery, number of revisions, reconstruction length, adjuvant therapies, laboratory parameters, and characteristics of causative microorganisms were analyzed as risk factors. The minimum follow-up was 24 months, calculated from the moment that the infection was diagnosed.

Index Surgery

Tumor resection and reconstruction using a modular implant was performed in 1 surgical session. Proximal femoral, distal femoral, and proximal tibial modular endoprostheses (Kotz, Howmedica/Stryker; or MUTARS, Implantcast) were used. A first-generation cephalosporin was administered at least 30 minutes prior to skin incision in all patients and was repeated every 4 hours during the surgical procedure or in case blood loss exceeded 1.5 L. Prophylactic antibiotics were continued for 24 hours to 5 days, based on variables such as the duration of the surgical procedure, the extent of resection, wound-healing, and patient characteristics. Antibiotic-loaded cement, gels, and gentamicin beads were not used as local prophylaxis.

Surgical Treatment for PJI

Patients underwent either surgical debridement with retention of the implant (DAIR) or prosthesis explantation as part of a 2-stage revision. A DAIR was the preferred initial treatment strategy in patients with either acute postoperative or late acute hematogenous infection. A thorough debridement was performed with resection of all nonvital tissue, mechanical cleaning of the implant with chlorhexidine, disassembly of endoprosthetic parts, iodine pulse lavage, and exchange of polyethylene and mobile parts, whenever possible. During the surgical procedure, at least 5 tissue samples were obtained for culture. Gentamicin sponges were used at the surgeon's discretion. Primary wound closure without a surgical drain was preferred. Gastrocnemius muscle flaps were used to cover defects around the knee. Empiric antibiotic treatment was started immediately after surgical debridement and consisted of intravenous flucloxacillin and gentamicin. For patients treated with DAIR, rifampicin was added to empiric antibiotic treatment for 5 days, starting immediately postoperatively. Rifampicin was discontinued earlier if the cultures revealed gram-negative bacteria or enterococci. Antibiotic treatment was switched to targeted therapy, based on the antibiotic sensitivity of the cultured microorganisms, for at least 6 weeks. The decision to discontinue targeted therapy was made on the basis of the clinical response and infection parameters. All patients were regularly discussed in a multidisciplinary team meeting (orthopaedic surgeon, infectious disease physician, and microbiologist attending physician). The decision to treat with (repeated) DAIR, 2-stage exchange, amputation, or chronic suppressive antibiotic treatment was guided by the causative microorganisms, response to treatment, soft-tissue condition, anticipated survival, and quality of life.

Definitions

PJI was defined as the presence of ≥1 of the following criteria: the presence of pus around the prosthesis, a sinus tract communicating with the prosthesis, at least 2 positive perioperative cultures with the same microorganism, or at least 1 positive culture with a virulent microorganism[6,7]. Infection within 6 weeks was defined as an acute infection. Infection after 6 weeks but before 3 months was considered an early chronic infection. Infection after 3 months was considered a chronic infection[8]. Cure was defined as the endoprosthesis remaining in situ at the time of the latest follow-up, no draining fistula, and no antibiotic therapy. Patients were considered functionally cured when an endoprosthesis remained in situ at the time of the latest follow-up, with or without chronic suppressive antibiotic therapy or a draining fistula[2]. Implant removal or amputation was defined as treatment failure.

Statistical Analysis

Descriptive statistics using the count and/or percentage or the median with the interquartile range (IQR) were used for the reporting of baseline clinical characteristics, cultured microorganisms, and clinical outcomes. A nested case-control design was employed to determine which explanatory variables influenced treatment failure after the initial DAIR. Logistic regression was used to compare risk factors between patients with and without failure. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical analyses were

performed using SPSS (version 25.0; IBM). Significance was set at $p < 0.05$.

Results

A total of 337 patients with endoprosthetic tumor reconstruction surgery of a lower extremity were identified. The median follow-up after the index procedure was 9.5 years (95% CI, 6.2 to 12.8 years). Of the 337 patients, 67 (20%) developed a PJI. The baseline characteristics are summarized in Table I. The median age at reconstruction surgery was 52 years (IQR, 23 to 65 years). The median reconstruction length was 17 cm (IQR, 14 to 22 cm). PJI was diagnosed at a median of 1.4 months (IQR, 0.6 to 7.8 months) following the last surgical procedure preceding the infection. Fifty-five (82%) of the 67 patients with PJI were primarily treated with DAIR, 10 patients (15%) were treated with a 2-stage procedure, and 2 patients (3%) were treated with direct amputation (Fig. 1). The median follow-up after surgical debridement was 3.8 years (95% CI, 2.0 to 5.5 years).

The causative microorganisms are summarized in Table II. Staphylococci were the predominant causative microorganisms (*Staphylococcus aureus* [28%] and coagulase-negative staphylococci [36%]), followed by anaerobic bacteria (15%), enterococci (12%), streptococci (10%), and *Cutibacterium acnes* (10%). Nineteen patients (28%) had a polymicrobial infection. Of them, 13 patients had a polymicrobial infection with >2 microorganisms. Eleven patients (16%) remained culture-negative.

Treatment with DAIR

The 55 patients primarily treated with DAIR needed a median of 2 debridements, compared with a median of 3 procedures after the first stage of a 2-stage procedure. Each subsequent DAIR had a functional cure rate between 32% and 50% (Fig. 2). Thirty-six patients (65%) were functionally cured at the final follow-up. Of these 36 patients, 11 patients (31%) received chronic suppressive antibiotic treatment. None of these 11 patients had clinical signs of active infection or needed further surgical treatment at the latest follow-up. The decision to continue suppressive antibiotic treatment was based on uncertainty regarding complete surgical eradication of the biofilm, patient life expectancy, or patient reluctance to undergo an additional surgical procedure. Of the patients with treatment failure after ≥1 DAIR, 13 (24%) proceeded with a 2-stage exchange of the endoprosthesis, and 6 patients (11%) proceeded with an amputation or definitive explantation. Of the 13 patients who had undergone a 2-stage procedure after failed DAIR, the secondary implant could be retained in 10 patients (77%), with a complete cure in 7 patients and a functional cure in 10 patients. The remaining 3 patients (23%) eventually needed amputation or definitive explantation (Fig. 1).

Risk Factors for Failure

To evaluate risk factors for failure, a nested case-control was performed for the 55 patients initially treated with DAIR (Tables III and IV). Chemotherapy (OR, 3.1 [95% CI, 1.0 to 9.3]; $p = 0.05$) and the erythrocyte sedimentation rate (ESR) >50 mm/hr at diagnosis (OR, 4.5 [95% CI, 1.3 to 15.4]; $p = 0.02$) were significantly associated with treatment failure. There was a trend toward higher failure rates after DAIR with a non-silver coating on the prosthesis (OR, 4.0 [95% CI, 0.8 to 19.8]) and a history of <2 revisions prior to the onset of PJI surrounding the endoprosthesis (OR, 3.7 [95% CI, 0.9 to 15.2]). The time from the last procedure to surgical debridement (OR,

TABLE I Baseline Characteristics of 55 Patients Undergoing DAIR to Treat PJI Surrounding the Endoprosthesis After Tumor Resection*

Sex	
Male	35 (64%)
Female	20 (36%)
Endoprosthesis	
Proximal femur	18 (33%)
Distal femur	27 (49%)
Proximal tibia	6 (11%)
Total femur	2 (4%)
Intercalary femur	2 (4%)
Diagnosed bone tumor	
Osteosarcoma	21 (38%)
Chondrosarcoma	10 (18%)
Ewing sarcoma	2 (4%)
Soft-tissue sarcoma	2 (4%)
Benign tumors	8 (15%)
Metastasis	12 (22%)
ASA classification	
1	4 (7%)
2	37 (67%)
3	13 (24%)
4	1 (2%)
Adjuvant chemotherapy	28 (51%)
Adjuvant radiation therapy	2 (4%)
Silver coating†	20 (65%)
Cemented fixation	20 (36%)
Prophylactic antibiotic mats	10 (18%)
Infection after revision procedure	25 (46%)
Implant loosening	1 (2%)
Fistula	2 (4%)
PJI	
Acute (<6 weeks)	36 (65%)
Late acute (hematogenous)‡	4 (7%)
Early chronic (6 to 12 weeks)	5 (9%)
Chronic (>12 weeks)	14 (25%)

*The values are given as the number of patients, with the percentage in parentheses. †For a subset of patients, the use of silver coating was unclear. ‡Defined as PJI >12 weeks after the surgical procedure with a virulent microorganism that caused infection via a hematogenous route (e.g., *S. aureus,* hemolytic streptococci).

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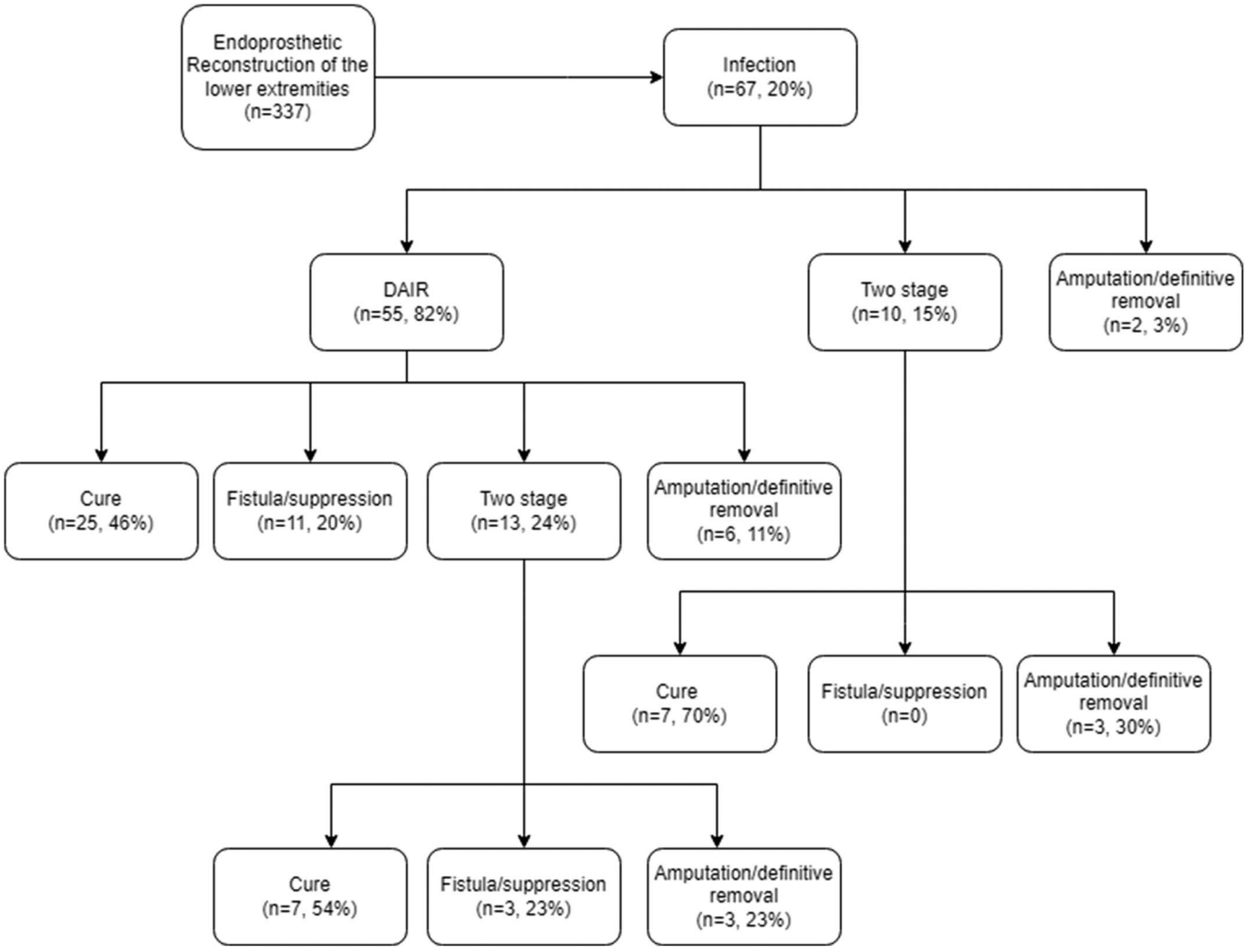

Fig. 1

Outcomes of 67 patients with PJI surrounding a lower-extremity prosthesis after tumor resection.

1.0 [95% CI, 0.9 to 1.0]), resection length (OR, 1.0 [95% CI, 0.99 to 1.01]), leukocyte count at diagnosis (OR, 1.0 [95% CI, 0.9 to 1.2]), and C-reactive protein (CRP) at diagnosis (OR, 1.0 [95% CI, 0.99 to 1.00]) were not associated with treatment failure.

Discussion

Study Limitations

There were several limitations to this study. This was a retrospective analysis, with its inherent shortcomings. The sample size was relatively small. Because of limited patient numbers, only univariate analyses could be performed. Therefore, the outcomes of this study should be interpreted with care. Although we only reported on infections of the lower extremities, there was heterogeneity in our study group because of the inclusion of a number of anatomic sites. The numbers were too small to detect significant differences in infection treatment outcomes based on anatomic site. Because of the relatively long inclusion period, implants and treatment strategies changed over time, causing heterogeneity in our study group.

Long-Term Risk of Infection

Twenty percent of our patients developed a PJI, which is high compared with the literature (range, 9% to 15%). However, most studies have reported the risk of infection during the first months after implantation, whereas the follow-up after the index surgical procedure in this cohort was >9 years. Also, many studies have shown the incidence of implant removal for infection rather than the true incidence of PJI. Many infections (49%) in our cohort occurred after revision procedures for mechanical complications. In a study on long-term outcomes of endoprosthetic reconstruction of tumor defects, Grimer et al. reported that 21 patients (9%) developed a PJI following the primary procedure, whereas 39 patients (14%) developed a PJI after revision procedures. They reported that the risk of PJI persists during follow-up, at a mean of 1% per year[9]. The high

TABLE II Causative Microorganisms in 67 Patients with PJI Surrounding the Endoprosthesis After Tumor Resection

Causative Microorganisms	Monomicrobial* (N = 37 [55%])	Polymicrobial* (N = 19 [28%])	Culture-Negative (N = 11 [16%])
S. aureus	11 (30%)	8 (42%)	—
Coagulase-negative staphylococci	15 (41%)	9 (47%)	—
Streptococci†	1 (3%)	6 (32%)	—
Gram-negative‡	1 (3%)	4 (21%)	—
C. acnes	5 (14%)	2 (11%)	—
Corynebacteria	0 (0%)	2 (11%)	—
Enterococci	3 (8%)	5 (26%)	—
Anaerobic§	1 (3%)	8 (42%)	—

*The values are given as the number of patients, with the percentage in parentheses. †*Streptococcus anginosus, Streptococcus oralis, Streptococcus vestibularis,* and other beta-hemolytic streptococci. ‡*Proteus mirabilis, Enterobacter cloacae, Pseudomonas aeruginosa, Acinetobacter baumannii,* Moraxella species, Klebsiella species, and *Haemophilus parainfluenzae*. §*Peptoniphilus harei, Finegoldia magna, Clostridium paraputrificum,* Lactobacillus species, *Clostridium perfringens, Clostridium disporicum,* Veillonella species, and *Peptostreptococcus anaerobius*.

risk of secondary infection following revision surgery for mechanical complications stresses the importance of fixation and durability of implant designs.

Surgical Treatment Strategy

The cure rate in this study (65%) is comparable with those of other studies on PJI surrounding endoprostheses after tumor resection (45% to 93%) and studies that show outcomes for conventional PJI (on average, 60%)[4-6,10-14]. However, as a result of the heterogeneity of definitions of treatment success and the length of follow-up, outcomes were difficult to compare. We observed a higher mean number of operations in patients initially planned for 2-stage revision compared with DAIR, which can be attributed to the scheduled reimplantation. Our results showed that DAIR was successful in 65% of the patients treated with ≥1 DAIR. A 2-stage procedure could be prevented in these patients. However, 19 patients treated with ≥2 debridements, with associated hospital admissions and long-term antibiotic therapy, had to proceed to a 2-stage procedure, amputation, or definitive removal of the implant. Although the numbers were limited, the chance of a functional cure was 32% to 50% after each subsequent DAIR. The literature has shown conflicting evidence regarding the outcome of sequential DAIRs in conventional arthroplasty. Some authors have identified the number of DAIRs as an independent risk factor for treatment failure[15-17]. However, other studies showed favorable outcomes of sequential DAIRs[18-20].

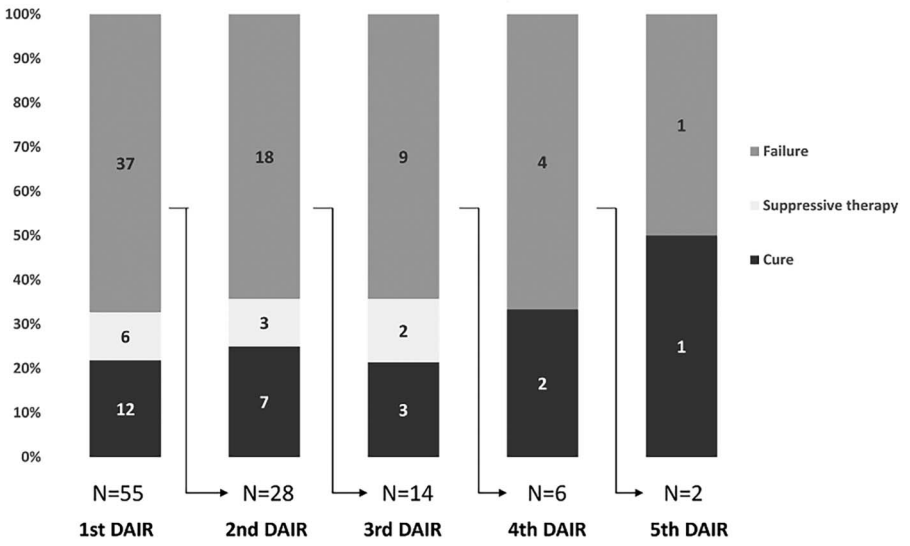

Fig. 2

Outcomes of sequential DAIRs for PJI surrounding an endoprosthesis after tumor resection. Patients in the second DAIR group had a treatment failure after the first DAIR and then were treated with a second DAIR.

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TABLE III Risk Factors for Treatment Failure*

	Success (N = 25 Cases)	Failure (N = 30 Controls)	OR†	P Value
Male sex	15	20	0.75 (0.25 to 2.26)	0.61
Mean age in yr	47	52	0.99 (0.97 to 1.02)	0.51
Mean ASA classification	2.11	2.24	1.00 (0.40 to 2.48)	1.00
Cemented fixation	6	1	1.28 (0.42 to 3.83)	0.68
Non-silver-coated implant‡	10	14	4.00 (0.81 to 19.82)	0.09
Prophylactic antibiotic mats	5	5	1.00 (0.27 to 3.77)	1.00
Secondary infection	9	16	2.03 (0.69 to 6.02)	0.20
>1 revisions prior to infection	9	16	3.67 (0.88 to 15.25)	0.07
Mean reconstruction length *(cm)*	203	195	1.00 (0.99 to 1.01)	0.75
Chemotherapy	9	19	3.07 (1.02 to 9.26)	0.05
Radiation therapy	1	1	0.81 (0.18 to 3.62)	0.78
Mean leukocyte count at diagnosis *(10^9/L)*	9.96	12.12	1.04 (0.92 to 1.17)	0.53
Mean CRP at diagnosis *(mg/L)*	124	70	1.00 (0.99 to 1.00)	0.26
ESR >50 mm/hr at diagnosis	8 of 22	18 of 28	4.50 (1.31 to 15.42)	0.02
Polymicrobial infection	8 of 25	9 of 29	1.05 (0.33 to 3.31)	0.94
Gram-negative infection	4 of 25	2 of 29	0.39 (0.07 to 2.33)	0.30

*In 55 patients primarily treated with DAIR. In this analysis, patients with successful outcomes are regarded as cases, and patients with treatment failure were regarded as controls. The values for dichotomous variables are given as the number of patients. The values for continuous variables are given as the mean. Univariate logistic regression analysis was used for continuous variables. †The values are given as the OR, with the 95% CI in parentheses. ‡For a subset of patients, the use of silver coating was unclear.

Risk Factors for Treatment Failure

The identification of risk factors for failure of successive DAIRs may guide the decision between sequential DAIRs and a 1-stage or 2-stage revision. Our study shows that chemotherapy is associated with an inferior outcome in patients treated with DAIR. This might be explained by a deficient innate and/or adaptive immune response secondary to chemotherapy and/or the effects of chemotherapy on vascularization[21]. A baseline ESR of >50 mm/hr was also significantly associated with an inferior outcome after DAIR. This might be explained by the fact that the ESR is a marker of chronic infection, which may lead to inferior outcomes. Other authors also identified elevated ESR as an independent risk factor for infection treatment failure after conventional hip or knee arthroplasty[20].

In 2 previous studies, treatment outcome after DAIR tended to be more successful with silver-coated implants[22,23]. Our numbers were too low to draw conclusions. However, it seems reasonable to continue the use of silver-coated implants, although larger randomized controlled trials are needed to address this issue. Other treatment strategies, such as iodine coatings, may have added value, but were not used in our cohort. In our study, the length of the reconstruction was not associated with the treatment outcome. Other factors, such as the quality of soft-tissue coverage, may be of more importance. Unfortunately, these factors are difficult to quantify.

Based on the data presented in our study, performing ≥1 DAIR in patients without risk factors for treatment failure seems to be a reasonable treatment strategy. When risk factors for failure are present, such as chronic PJI or recent chemotherapy, a 1-stage or 2-stage procedure should be considered. Although the numbers are limited, 2-stage revision as a salvage procedure after successive failed DAIRs showed reasonable success rates, justifying the choice for a step-up approach with the initial DAIR and a 2-stage replacement if the initial DAIR is unsuccessful. A major disadvantage of 2-stage revision is the loss of bone stock, complicating any future reconstruction. Furthermore, failed primary 2-stage procedures usually do not leave any limb-salvaging options.

TABLE IV Outcome of DAIR Stratified by the Endoprosthesis

Endoprosthesis	Treatment Success
Proximal femur	33% (6 of 18)
Distal femur	48% (13 of 27)
Total or intercalary femur	75% (3 of 4)
Proximal tibia	50% (3 of 6)

Epidemiology of Microorganisms

Most hip and knee infections were caused by *Staphylococcus aureus* (20%) and coagulase-negative staphylococci (36%), which

is comparable with the literature on conventional PJI[24]. The proportion of PJIs caused by polymicrobial flora (30%), including numerous anaerobic bacteria (42% of polymicrobial infections), in our cohort is higher than what is usually reported. Tande et al. reported 14% polymicrobial bacteria and 4% anaerobic bacteria in 1,979 patients with PJI after conventional hip or knee arthroplasty[6]. A larger wound area and reduced local immunity may explain the higher proportion of polymicrobial infections that we observed after tumor reconstruction surgery.

Prophylactic Antibiotic Strategy

The preoperative antibiotic prophylaxis strategy is determined by many factors, including local epidemiology, local resistance patterns, pharmacokinetic profile, bactericidal activity, cost, and safety. Infection prevention and antibiotic stewardship bundles during the surgical procedure may further reduce the risk of transmission of bacteria to the surface of the implant. Cefazolin prophylaxis did not prevent many *S. aureus* and streptococcal infections in this study, which totaled one-third of the PJIs in our cohort. Poor penetration of systemic antibiotics in the dead space after tumor resection may have played a role. Local prophylactic antibiotic treatment with gentamicin beads, cement, gels, and sponges is often used to achieve high local concentrations without systemic toxicity, but there has been no solid evidence to support this[20]. There is even a risk that bacteria can adhere to local gentamicin beads, causing secondary infections.

The high percentage of polymicrobial flora in this cohort may raise the question of whether a broader spectrum of antibiotic prophylaxis is needed. The use of prophylactic cefazolin could not prevent the 30% of PJIs that were caused by *S. aureus* and streptococci, possibly related to a reduced local concentration in large wound beds and other surgery-related factors. Larger observational studies are needed to define which specific patient groups are most likely to develop anaerobic and/or gram-negative infections and who may benefit from prophylactic antibiotics with an extended spectrum. The PARITY (Prophylactic Antibiotic Regimens in Tumor Surgery) cohort may contribute to answering this question[25].

Conclusions

This study shows that patients undergoing endoprosthetic reconstruction of a lower extremity have a high risk of PJI requiring multiple surgical interventions. A large proportion of infections are caused by revision procedures, stressing the importance of continuous innovation regarding PJI surrounding endoprostheses after tumor resection and surgical techniques to minimize revision procedures for mechanical reasons. Performing sequential DAIRs is a feasible treatment option when diligent patient selection is applied. Patients undergoing chemotherapy are less likely to be successfully treated with DAIR. Further research is needed to determine when to move from DAIR to more aggressive treatment options such as implant removal and exchange. We found more polymicrobial infections compared with the literature on conventional PJI, but we were unable to show an association with infection treatment outcomes. Larger observational studies are needed to identify patient groups who may benefit from additional prophylactic antibiotics with a broader spectrum. ■

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