Prosthetic joint infections: new diagnostic and therapeutic strategies

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CHAPTER 5

Infected tumor prostheses of the lower extremities: causative micro-organisms, effectiveness of DAIR and risk factors for treatment failure

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Background

Infection of tumor endoprostheses after reconstruction of the lower extremities is a common complication and treatment of these infections is challenging and often requires multiple surgical interventions or even implant removal. Because there is limited evidence to support treatment strategies and knowledge of epidemiology of causative micro-organisms, we analyzed the effectiveness of Debridement, Antibiotics and Implant Retention (DAIR), risk factors for failure of DAIR and causative micro-organisms in patients with an infected tumor endoprosthesis of the lower extremity.

Methods

A retrospective cohort study was conducted. In a tertiary referral center for orthopedic oncology, all patients treated for prosthetic joint infection (PJI) between 2000 and 2018 with an infection of a tumor endoprosthesis of the lower extremities were included. Treatment outcomes and risk factors for failure were analyzed in patients primarily treated with DAIR. Causative micro-organisms were recorded. The minimum follow-up period was two years.

Results

Of 337 patients who underwent endoprosthetic reconstruction of the lower extremities, 67 patients (20%) developed an infection of a tumor endoprosthesis. Of them, 55 were primarily treated with DAIR. The cure rate of DAIR was 65% (36/55). A median of 2 debridements per patient was needed. Chemotherapy (OR=3.1,95%CI=1.0-9.3) and erythrocyte sedimentation rate >50 at diagnosis (OR=4.5,95%CI=1.3-15.4) were associated with treatment failure. Eighteen (27%) patients had a polymicrobial infection.

Conclusions

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

Background

Modular endoprosthetic reconstruction is the preferred reconstructive technique after tumor resection of the lower extremities in most orthopedic oncology centers. A prosthetic joint infection (PJI) remains one of the major challenges, with reported incidences of up to 15% (table 1). These infections can be devastating, as they regularly necessitate multiple surgical debridements, removal of implants, or, rarely, amputation[1,2]. Treatment of infection often results in 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 radiation therapy[3]. Tumor resection and reconstruction is usually lengthy, results 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 may contribute to the marked differences of infection risk when compared to conventional arthroplasty (9-15% vs <1%) (table 2)[4,5].

Surgical treatment of an infected tumor endoprosthesis consists of debridement, antibiotics and implant retention (DAIR) or a one- or two-staged exchange of the implant. For PJI after conventional arthroplasty, the indications for the type of surgical strategy are well defined and clinical outcomes of these strategies are reported on extensively [6]. However, there is a lack of data on clinical outcomes of surgical strategies for infected tumor endoprostheses that can guide in the decision to perform either DAIR, one-stage, or two-stage revision procedures. Therefore, we analyzed (1) causative micro-organisms, (2) clinical outcome of surgical treatment strategies and (3) risk factors for treatment failure in a cohort of patients with an infected tumor endoprosthesis of the lower extremity. In addition, we reviewed the literature regarding surgical management of infected tumor endoprostheses.

Table 1. Baseline characteristics of 67 patients with tumor endoprosthesis PJI.

	n	%
Gender (male)	43	64
Localization		
Proximal femur	21	31
Distal femur	32	48
Proximal tibia	10	15
Total femur	2	3
Intercalary femur	2	3
Diagnosed bone tumor		
Osteosarcoma	24	36
Chondrosarcoma	14	21
Ewing Sarcoma	3	5
Soft tissue sarcoma	6	9
Benign tumors	8	12
Metastasis	12	18
ASA classification[$]		
ASA 1	8	12
ASA 2	45	67
ASA 3	13	19
ASA 4	1	2
Chemotherapy (adjuvant)	33	49
Radiotherapy (adjuvant)	9	13
Silver coating	20	30
Cemented fixation	24	36
Prophylactic antibiotic mats	10	15
Infection after revision procedure	33	49
Implant loosening	4	6
Fistula	6	9
Acute PJI (<6w)	29	43
Early chronic PJI (6-12w)	13	19
Chronic PJI (>12w)	25	37
Late acute (hematogenous) PJI	0	-

[$]American society of anesthesiologists classification system

Table 2. Causative micro-organisms of 67 patient's tumor endoprosthesis PJI.

Causative micro-organisms	Monomicrobial (n=37, 55%)	Polymicrobial (n=19, 30%)	Culture-negative (n=11, 16%)
S. aureus	11 (20%)	8 (42%)	-
CNS	15 (41%)	9 (47%)	-
Streptococci[‡]	1 (3%)	6 (32%)	-
Gram-negative[^]	1 (3%)	4 (21%)	-
C. acnes	5 (14%)	2 (11%)	-
Corynebacteriae	0	2 (11%)	-
Enterococci	3 (8%)	5 (26%)	-
Anaerobic[#]	1 (3%)	8 (42%)	-

[^] *Proteus mirabilis, Enterobacter cloacae, Pseudomonas aeruginosa, Acinetobacter baumanni, Moraxella,* Klebsiella species, *Haemophilus parainfluenzae*

[#] *Peptoniphilus harei, Finegoldia magna, Clostridium paraputrificum, Lactobacillus, Clostridium perfringens, Clostridium disporicum,* Veillonella species, *Peptostreptococcus anaerobius*

[‡] *Streptococcus anginosus, Micrococcus luteus, Streptococcus oralis, Streptococcus vestibularis,* other Beta-hemolytic streptococci

Materials and Methods

Study design and population

A retrospective cohort study and a review of the literature was conducted. Institutional databases were queried to identify all patients who underwent endoprosthetic reconstruction of the lower extremities following tumor resection between 2000 and 2018 in a tertiary referral center for orthopedic oncology. Patients who subsequently developed a PJI of the tumor endoprosthesis were included. Micro-organisms 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 the outcome of treatment. A nested case-control study was performed to identify risk factors for treatment failure after initial DAIR. The minimum follow-up was 24 months, calculated from the moment the infection was diagnosed.

Index surgery

Tumor resection and reconstruction using a modular implant was performed in one surgical session. Proximal femur, distal femur and proximal tibia modular endoprostheses (Kotz, Howmedica/Stryker, Kalamazoo, Michigan, United States; MUTARS, Implantcast, Buxtehude, Germany) were used. A first-generation cephalosporin was administered at least 30 minutes prior to skin incision in all patients and repeated every 4 hours of surgery or in case blood loss exceeded 1.5 L. Prophylactic antibiotics were continued for 24 hours

to five days based on variables such as duration of surgery, 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 two-stage revision. A DAIR procedure was the preferred initial treatment strategy in patients with either acute postoperative or late acute hematogenous infections. A thorough debridement was performed with resection of all avital 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 surgery, at least five Prosthetic tissue samples were obtained for culture. Gentamicin sponges were used at surgeons discretion. Primary wound closure without a surgical drain was pursued. A primary two stage procedure was considered in patients with a chronic or low-grade PJI, a sinus tract or septic loosening of the implant. Following explantation in two stage procedures, re-implantation was considered if the inflammatory parameters normalized after a minimum of six weeks of antibiotic treatment and two weeks without antibiotics. Temporary use of gentamicin beads and spacers was considered in case of large dead spaces. 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 five postoperative days, starting immediately postoperative. Rifampicin was discontinued earlier if cultures revealed Gram-negative bacteria or enterococci. Antibiotic treatment was switched to targeted therapy for at least six weeks based on antibiotic sensitivity of cultured micro-organisms. The decision to discontinue targeted therapy was made based on clinical response and inflamatory parameters. All patients were regularly discussed in a multidisciplinary team meeting (orthopedic surgeon, infectious disease physician and microbiologist attending). The decision to treat with (repeated) DAIR, two-stage exchange, amputation or chronic suppressive antibiotic treatment was guided by the expected risk of treatment failure and survival, quality of life and patient preference.

Definitions

Prosthetic joint infection was defined as presence of one or more of the following criteria: presence of pus around the prosthesis, a sinus tract communicating with the prosthesis, at least two positive intraoperative cultures with the same microorganism or one positive culture with a virulent micro-organism. Infection within six weeks was defined as an acute infection. Infection after six weeks but before three months was considered an early chronic infection. Infection after three months was considered chronic infection. Cure

was defined as an endoprosthesis 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 was in situ at the time of the latest follow-up *with or without* chronic suppressive antibiotic therapy or a draining fistula. Implant removal or amputation were defined as treatment failure.

Statistics

Descriptive statistics were used for baseline clinical characteristics, cultured micro-organisms and clinical outcome. A nested case-control design was employed to determine which explanatory variables influenced treatment failure after initial DAIR. Logistic regression was used to compare risk factors between patients with and without failure. Results were reported as odds ratios (OR) with 95% confidence intervals (95%CI). Statistical analyses were performed using SPSS Statistics (version 25).

Results

337 patients with endoprosthetic tumor reconstruction surgery of the lower extremities were identified. Median follow-up following the index procedure was 9.5 years (95%CI=6.2-12.8). Of them, 67 (20%) patients developed a PJI. Baseline characteristics are summarized in table 1. The median age at reconstruction surgery was 52 years (IQR 23 to 65 years). Median reconstruction length was 17cm (IQR 14-22). Prosthetic joint infection (n=67) was diagnosed at a median of 1.4 months following the last surgical procedure preceding infection (IQR 0.6-7.8 months). Fifty-five (82%) patients were primarily treated with DAIR, ten (15%) patients with a two-stage procedure and two (3%) patients with direct amputation. Median follow-up after surgical debridement was 3.8 years (95%CI=2.0-5.5) (figure 1). The causative micro-organisms are summarized in Table 2. Staphylococci were the predominant causative microorganisms (*Staphylococcus aureus* 28%, Coagulase-negative staphylococci (CNS), 36%), followed by anaerobic bacteria (15%), enterococci (12%), streptococci (10%) and *Cutibacterium acnes* (10%). Eighteen (27%) patients had a polymicrobial infection. Of them, 13 patients had a polymicrobial infection with more than two micro-organisms. Nine patients (13%) remained culture negative.

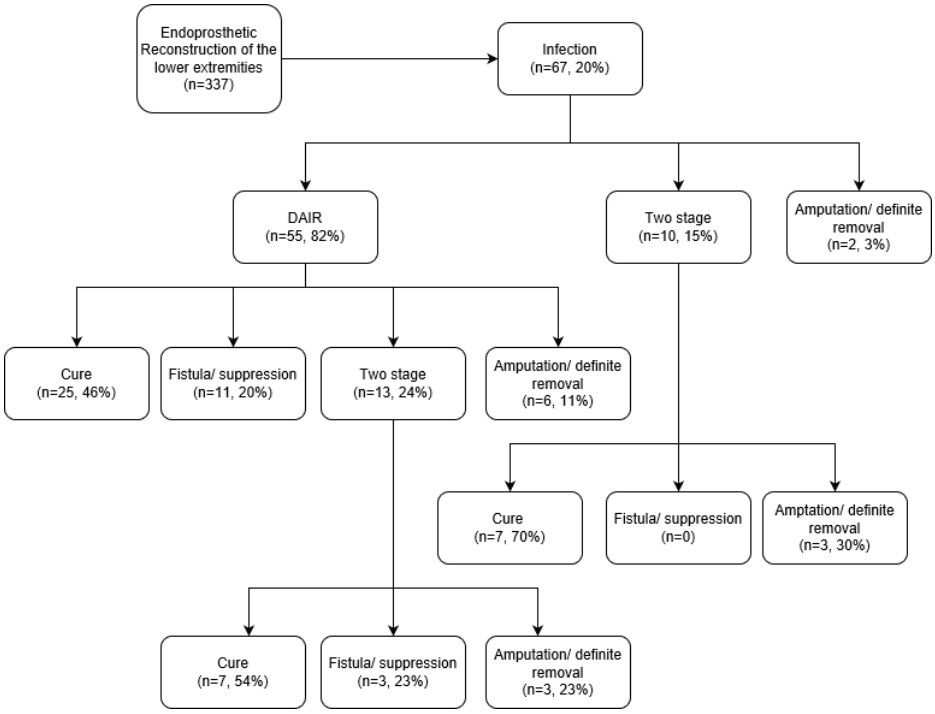

Figure 1. Outcome of 67 patients with tumour prostheses PJI of the lower extremities.

Of the 55 patients primarily treated with DAIR, a median of 2 debridements per patient was needed. Each subsequent DAIR procedure had a functional cure rate between 32 and 50% (figure 2). Thirty-six patients (65%) were functionally cured at final follow up. Of these 36 patients, 11 (31%) patients received chronic suppressive antibiotic treatment. Of these eleven patients, none had clinical signs of active infection or needed further surgical treatment at the time of latest follow-up. The decision to continue suppressive antibiotic treatment or to leave a fistula untreated was based on uncertainty of complete surgical eradication of the biofilm, patient life expectancy or patient reluctancy towards additional surgery. Of the patients with failure after one or more DAIR procedures, thirteen (24%) proceeded with a two-stage exchange of the endoprosthesis, six patients (11%) proceeded with an amputation or Girdlestone procedure. Of thirteen patients with a two-stage procedure after failed DAIR, the secondary implant could be retained in ten patients (77%) with complete cure in seven and functional cure in three patients. Three patients (23%) eventually needed amputation or a Girdlestone procedure (Figure 1).

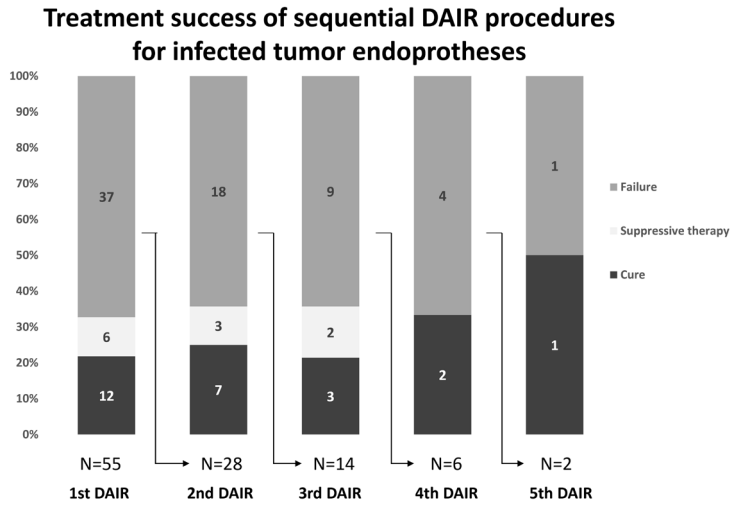

Figure 2. Outcome of sequential DAIR procedures for tumor endoprostheses PJI.

Patients in the second DAIR group consists of patients with a failure after the first DAIR who were subsequently treated with a second DAIR.

In ten patients primarily treated with a two-stage procedure, three patients (30%) did not need additional surgery, while 5 patients (50%) needed two to five extra debridements between implant removal and reimplantation. A mean of 3.1 debridements were performed per patient including reimplantation surgery. Eventually, seven patients were completely cured (70%) while three patients needed an amputation or a Girdlestone procedure (30%).

To evaluate risk factors for failure, a nested case-control was performed for the 55 patients initially treated with DAIR (Table 3). Chemotherapy (OR=3.1,95%CI=1.0-9.3, p=.05) and erythrocyte sedimentation rate (ESR) >50mm/hour at diagnosis (OR=4.5,95%CI=1.3-15.4, p=.02) were significantly associated with treatment failure. A silver coating on the prosthesis and a history of less than two revisions prior to the onset of an infected endoprosthesis showed a trend towards improved success rates after DAIR (OR=4.0,95%CI=0.8-19.8 and OR=3.6,95%CI=0.9-15.2, respectively). Time from last procedure to surgical debridement (OR=1.0,95%CI=0.9-1.0), resection length (OR=0.9,95%CI=0.99-1.01), leukocyte count at diagnosis (OR=1.0, 95%CI 0.9-1.2) and C-reactive protein at diagnosis (OR=1.0,95%CI=0.99-1.00) were not associated with treatment failure.

Table 3. Risk factors for treatment failure[$]

	Success (n = 25 cases)	Failure (n = 30 controls)	OR	95% CI	p-value
Male gender	15	20	0.75	0.25-2.26	0.61
Age (mean)	47	52	0.99	0.97-1.02	0.51
ASA (mean)	2.11	2.24	1.00	0.40-2.48	1.00
Cemented fixation	6	1	1.28	0.42-3.83	0.68
Non-silver coated implant	10	14	4.00	0.81-19.82	0.09
Gentamicin mats	5	6	1.00	0.27-3.77	1.00
Secondary infection			2.03	0.69-6.02	0.20
Revisions prior to infection (>1)	9	16	3.67	0.88-15.25	0.07
Reconstruction length: (mm)	203	195	1.00	0.99-1.01	0.75
Chemotherapy	9	19	3.07	1.02-9.26	0.05
Radiotherapy	1	1	0.81	0.18-3.62	0.78
Leukocyte count at diagnosis (mean)	9.96	12.12	1.04	0.92-1.17	0.53
CRP at diagnosis (mean)	124	70	1.00	0.99-1.00	0.26
ESR >50 at diagnosis (mean)	8/22	18/28	4.50	1.31-15.42	0.02
Polymicrobial infection	8/25	9/29	1.05	0.33-3.31	0.94
Gram negative infection	4/25	2/29	0.39	0.07-2.33	0.30

In this analysis, patients with successful outcome are regarded as cases, patients with a failure as controls. Dichotomous variables are presented as number of patients, from continuous variables, mean is shown. Univariate logistic regression analysis was used for continuous variables, Odds Ratios were calculated for dichotomous variables.

[$] In 55 patients primarily treated with DAIR

Discussion

Long term risk of infection

Twenty percent of our patients developed a PJI, which is high compared to literature (range 9-15%, table 4). However, most studies report the risk of infection during the first months after implantation rather than the life-long risk. Also, studies report the incidence of implant removal for infection rather than the true incidence of PJI. The follow-up after index surgery in our study was long. 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 (9%) patients developed a PJI following the primary procedure, while 39 (14%) patients developed a PJI after successive revision procedures. They reported that the risk of PJI persists during follow-up, at a mean of 1% per year [7]. The high risk of secondary infection following revision surgery for mechanical complications stresses the importance of fixation and durability of implant designs.

Table 4. Outcome of DAIR stratified for location of infection.

Localization	Treatment success (%)
Proximal femur	6/18 (33)
Distal femur	13/27 (48)
Femur*	3/4 (75)
Proximal tibia	3/6 (50)

*Total femoral and intercalary reconstruction

Surgical treatment strategy

The cure rate in this study (65%) is comparable to other studies on tumor endoprostheses PJI (45-93%, table 2) and studies that report outcome for conventional PJI (on average 60%)[6]. However, as a result of heterogeneity of definitions of treatment success and length of follow up, outcomes are difficult to compare. We observed a higher mean number of operations in patients initially planned for two-stage revision (3.1) compared to DAIR (1.9), which can be attributed to the scheduled reimplantation. Our results show that DAIR was successful in 65% of the patients treated with one or more DAIR. A two-stage procedure could be prevented in these patients. On the other hand, 19 patients treated with two or more debridements, with associated hospital admissions and long-term antibiotic therapy, had to proceed to a two-stage procedure, amputation or definite removal of the implant. Although numbers were limited, the chance of eradicating the infection was 32-50% after each subsequent DAIR. Literature shows conflicting evidence concerning the outcome of multiple DAIR procedures in conventional arthroplasty. Some authors identified the number of sequential DAIR procedures as an independent risk factor for treatment failure [8-10]. However, other studies reported favorable outcomes of sequential DAIR [11-13].

Risk factors for treatment failure

The identification of risk factors for failure of successive DAIR procedures may guide in decision-making between repeat DAIR and a one or two-stage revision. Our study shows that chemotherapy is associated with 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[14]. Baseline ESR >50mm/hour was also significantly associated with 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 outcome. Other authors also identified elevated ESR as an independent risk factor for infection treatment failure after conventional hip or knee arthroplasty [13].

In two previous studies, treatment outcome after DAIR tended to be more successful with silver coated implants[15,16]. 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 was not used in our cohort. In our study, the length of reconstruction was not associated with 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 one or more DAIR procedures in patients without risk factors for treatment failure seems to be a reasonable treatment strategy. When risk factors for failure are present, like a chronic PJI or recent chemotherapy, a one- or two-stage procedure, should be considered. Although the numbers are limited, two stage replacement as a salvage procedure after successively failed DAIR procedures showed reasonable success rates, justifying the choice for a step-up approach with initial DAIR. A major disadvantage of two-stage revision is the loss of bone stock complicating any future reconstruction. Furthermore, failed primary two-stage procedures usually do not leave any limbsalvaging options.

Epidemiology of micro-organisms

Most hip and knee infections were caused by *Staphylococcus aureus* (20%) and coagulase-negative staphylococci (41%), which is comparable to the literature regarding conventional PJI[17]. The proportion of PJI caused by polymicrobial flora (30%) including numerous anaerobic bacteria (42%) in our cohort is higher than wat is usually reported. Tande et al. reported 14% polymicrobial and 4% anaerobic bacteria on 1979 patients with conventional hip or knee PJI. A larger wound area after tumor reconstruction surgery and reduced local immunity may explain the higher proportion of polymicrobial infections in these patients.

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. Antibiotic stewardship bundles during surgery may further reduce the risk of transmission of bacteria to the surface of the implant. Allegedly, cefazolin prophylaxis did not prevent many *S. aureus* and streptococcal infections in this study, together counting for a third of cases in our cohort. Poor penetration of systemic antibiotics in the dead space after tumor resection may have played a role here. Local prophylactic antibiotic treatment with gentamicin beads, cement, gels, and sponges is often used to achieve high local concentrations without systemic toxicity but there is no solid evidence to support this [13]. There is even a risk that bacteria can adhere to local gentamicin beads causing secondary infections. Despite the low level of evidence, application of local antibiotics to spacers which are inserted in infected wound areas after removal of the implant and debridement seems rational.

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 that 30% of PJIs were caused by *S. aureus* and streptococci, possibly related to reduced local concentration in large woundbeds 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 of prophylactic antibiotics with a more extended spectrum. The PARITY cohort may contribute answering this question[18].

To conclude, this study shows that patients undergoing endoprosthetic reconstruction of the lower extremities have a high risk of PJI requiring multiple surgical interventions. A significant proportion of infections is caused by revision procedures and stresses the importance of continuous innovation of tumor endoprostheses and surgical techniques to minimize revision procedures for mechanical reasons. Performing multiple DAIR procedures is a feasible treatment option when diligent patient selection is applied. Primary two-stage showed reasonable outcomes but has major drawbacks as noted in this study. In our series, we found more polymicrobial infections compared to conventional PJI. Larger observational studies are needed to identify patient groups who may benefit of specific additional prophylactic antibiotics.

Table 5. Review of studies reporting outcome of tumour prosthesis PJI.

Author	Year of surgery	N patients with reconstruction surgery	Location	Implant type	Cemented (%)
Mavrogenis[19]	1983 - 2010	1161	DF 64% PT 20% PF 13% TF 3% EAK 1%	KMFTR HMRS GMRS	8
Schmolders[20]	2008 - 2014	100	PF 52% DF 30% TF 14% EXP 3% PT 1%	N/R	N/R
Pala[21]	2003 - 2010	247	DF 76%, PT 25%	GMRS	9
Bus[4]	1995 - 2010	110	DF 81% PT 19%	MUTARS	10
Jeys[5]	N/R	1240	DF 37% PF 21% PT 20% HUM 14% PEL 4% FD 3% TF 1%	N/R	N/R
De Gori[22]	2001 - 2014	87	PF 46% DF 30% PT 10% KA 9% TF 5%	MSC	60
Sigmund[23]	1982 -2017	621	DF 51% PT 31% PF 15% EAK 2% TF 1%	KMFTR HMRS GMRS MUTARS	N/R
Morii[24]	1995-2009	388	DF 59% PT 41%	HMRS Kyocera	N/R
Peel[25]	1996-2010	121	PF/DF 74% PEL 9% PT 14 HUM 3	N/R	N/R

	Silver coating (%)	Infection (%)	Primary treatment strategy	Overall cause-specific failure risk (%)	Notes
	N/R	9	12% one-stage, 83% two-stage, 5% amputation	12% at 10 years, 16% at 20 years	Higher survival rate for uncemented implants; no influence of adjuvant treatments.
	100	10	40% implant removal, 20% two-stage, 30% DAIR, 10% amputation	7	50% of patients with an infection underwent no further reconstruction after implant removal.
	N/R	N/R	25% one-stage, 75% two-stage	9	87% of patients with an infection had a successful revision.
	3	14	N/R	9	33% of infected implants were retained.
	N/R	11	43% two-stage, 31% amputation, 24% one-stage, 1% implant removal	11	Patients treated over a 37-year period. Infection risk since 1996 dropped to 4%. Radiation therapy increased the risk of infection.
	14	12	67% two-stage, 33% one-stage	10	Patients treated for non-neoplastic conditions. 3% had an allograft-prosthetic composite reconstruction.
	N/R	13	73% one-stage, 19% two-stage, 5% amputation, 2% DAIR	13	In 44% of two-stage revisions, at least one well fixed stem was retained; these had a significantly higher re-infection rate (64%) than two-stage revisions in which the entire implant was removed (22%). No significant difference in re-infection rate between one- and two-stage revision procedures. No difference in re-infection risk between silver-coated and uncoated implants.
	N/R	15	N/R	55	Only total of procedures reported. Distribution of primary procedures not reported.
	N/R	14	53% DAIR 12% One-stage 24% Two-stage 12% Amputation	18	

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