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Debridement, Antibiotics, and Implant Retention Is a Viable Treatment Option for Early Periprosthetic Joint Infection Presenting More Than 4 Weeks After Index Arthroplasty

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Background. The success of debridement, antibiotics, and implant retention (DAIR) in early periprosthetic joint infection (PJI) largely depends on the presence of a mature biofilm. At what time point DAIR should be disrecommended is unknown. This multicenter study evaluated the outcome of DAIR in relation to the time after index arthroplasty.

Methods. We retrospectively evaluated PJIs occurring within 90 days after surgery and treated with DAIR. Patients with bacteremia, arthroscopic debridements, and a follow-up <1 year were excluded. Treatment failure was defined as (1) any further surgical procedure related to infection; (2) PJI-related death; or (3) use of long-term suppressive antibiotics.

Results. We included 769 patients. Treatment failure occurred in 294 patients (38%) and was similar between time intervals from index arthroplasty to DAIR: the failure rate for Week 1–2 was 42% (95/226), the rate for Week 3–4 was 38% (143/378), the rate for Week 5–6 was 29% (29/100), and the rate for Week 7–12 was 42% (27/65). An exchange of modular components was performed to a lesser extent in the early post-surgical course compared with the late course (41% vs 63%, respectively; $P < .001$). The causative microorganisms, comorbidities, and durations of symptoms were comparable between time intervals.

Conclusions. DAIR is a viable option in patients with early PJI presenting more than 4 weeks after index surgery, as long as DAIR is performed within at least 1 week after the onset of symptoms and modular components can be exchanged.

Keywords. joint arthroplasty; early prosthetic joint infection; DAIR; failure; time interval.

Total joint arthroplasty (TJA) is a widely used treatment modality for advanced osteoarthritis of the hip and knee [1]. Although this procedure is highly successful, in 1–2% of total joint arthroplasties a periprosthetic joint infection (PJI) develops, which is a major complication with a large impact on a patient's well-being [2]. When PJI develops within 3 months after index arthroplasty, the infection is classified as early PJI [3–8].

The preferred surgical treatment for early PJI is debridement, antibiotics, and implant retention (DAIR). DAIR is considered as a less invasive surgical treatment option than revision

surgery, due to the preservation of bone stock, shorter duration of the surgical procedure, decreased risk of intraoperative fractures, and faster postoperative rehabilitation [9, 10]. The success rates for DAIR vary widely, from 30% to 80% [11–15]. Although there are no absolute contraindications for performing a DAIR procedure in patients with PJI, it is accepted that DAIR should be performed in patients with an acute PJI, defined as a symptom duration of less than 3 weeks [16].

Multiple factors influence the outcome of DAIR, including host- and implant-related factors, clinical presentation, intraoperative variables, causative microorganisms, and the applied antimicrobial regimen [15, 17–20]. Moreover, several studies have demonstrated that the DAIR failure rate increases when the infection exists for a longer time period [17, 18, 21–24]. This finding can be explained by the fact that once a mature biofilm has developed, the infection cannot be cured without removing the implant [25, 26]. For this reason, the Infectious Diseases Society of America guideline published in

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2013 recommends removing the implant when a PJI develops more than 30 days after the index arthroplasty [27]. An important limitation of this approach is that it does not take into account the fact that the process of biofilm formation varies substantially based on the type of causative microorganism, the inoculum size that contaminates the wound during surgery, and host-related factors [28, 29]. Therefore, performing a DAIR merely based on a short time interval from the index arthroplasty may lead to unnecessary removals of implants in a large subset of patients.

This multicenter study was designed to evaluate the influence of important variables on the outcome of DAIR: in particular, the time interval from index surgery to DAIR. The study sought to determine whether DAIR is still a viable option for patients with PJI occurring more than 30 days after index arthroplasty.

MATERIAL AND METHODS

Study Design

All patients with early PJI of the hip or knee treated with DAIR from 1999 to 2016 in 6 hospitals in 4 different countries (the United States, Spain, Portugal, and The Netherlands) were included and retrospectively analyzed. Early PJI was defined as an infection occurring within 90 days of index arthroplasty [30]. The diagnosis of PJI was determined according to the criteria of the International Consensus Meeting, published in 2013 [31]. Patients who underwent arthroscopic debridement, those with positive blood cultures, and those with a follow-up of less than 1 year were excluded. The start date of symptoms was defined as the onset of fever, redness of the wound, progressive wound leakage (or recurrence of wound leakage after an initial dry wound), worsening of pain, or swelling of the prosthetic joint and/or an increase in serum C-reactive protein (CRP) that could not be explained by the normal post-operative course or by another source of infection.

Surgical Treatment

The details of how DAIR was performed were retrieved from the clinical records. The DAIR procedure involved an arthrotomy, extensive synovectomy, and irrigation of the joint with 3 to 6 liters of irrigation fluid. The modular components were exchanged in some cases and retained in others. Empirical, broad-spectrum, intravenous antibiotic treatment was started after obtaining multiple deep tissue biopsies for culture and, if necessary, was adjusted according to the culture results. Intravenous antibiotics were continued for at least 2 weeks before switching to an oral regimen, which was continued for an additional 10 weeks. Rifampin was added to the antibiotic treatment regimen in infections caused by rifampin-susceptible staphylococci. DAIR was performed as soon as a clinical suspicion of infection arose, consisting of infective symptoms such as fever, redness of the wound, persisting or recurrent wound leakage, and/or elevated inflammatory serum parameters.

Definition of Outcome

The main outcomes were treatment failure and implant failure. Treatment failure was defined as 1 of the following events within 1 year after DAIR: (1) the need for any further surgical procedure related to infection (ie, a second DAIR, implant removal, or amputation); (2) PJI-related death; or (3) the need for administration of long-term suppressive antimicrobial treatment, due to persistent clinical or biochemical signs of infection. Implant failure was defined as the need for implant removal at any time point after DAIR.

Statistical Analysis

Categorical variables were expressed in absolute frequencies and percentages. Continuous variables were presented as a mean and standard deviation or as a median and interquartile range when not normally distributed according to the Kolmogorov-Smirnov test of normality. The Chi-square test was used to compare categorical variables. Parametric continuous variables were compared using the Student's *t* test or a 1-way analysis of variance. Non-parametric continuous variables were compared with the Mann-Whitney U test. Failure rates were calculated for each 2-week time interval from index surgery to DAIR. Subsequently, a logistic regression analysis was performed to identify the independent risk factors for treatment failure. Variables with a difference between groups, defined as a *P* value <.15 in the univariate analyses, were included in the multivariate analysis. Statistical significance was defined as a 2-tailed *P* value <.05. Statistical analyses were performed using IBM SPSS Statistics (version 24.0; Chicago, IL).

RESULTS

Patient Characteristics

The study cohort consisted of 769 patients with early PJI who were treated with DAIR. Data were collected from 981 patients, but 212 patients were excluded due to a time interval more than 90 days from index arthroplasty to DAIR (*n* = 122), positive blood cultures (*n* = 42), or a follow-up of less than 1 year (*n* = 48). There were 463 patients (60%) with a PJI of the hip and 306 patients (40%) with a PJI of the knee. The mean age was 70 years (standard deviation ± 12; range 24–97 years) and 57% (*n* = 431) of patients were female. The PJI occurred after primary TJA in 622 patients (82%) and after revision TJA in 140 patients (18%). The median follow-up time was 3.2 years (range 1–15 years), with significant differences in follow-up times between intervals: 3.2 years (range 1–14) for Weeks 1–2, 3.0 years (range 1–14) for Weeks 3–4, 4.0 years (range 1–14) for Weeks 5–6, and 4.0 years (range 1–15) for Weeks 7–12 (*P* = .008).

Failure Rates According to Time Interval After Index Surgery

Overall, 294 patients (38%) had treatment failure within 1 year after DAIR. More than half of the patients (161 patients, 55%) required a second DAIR, 82 patients (28%) required

revision surgery for infection, 42 patients (14%) were placed on long-term suppressive antimicrobial treatments, 8 patients (3%) died due to PJI, and 1 patient (0.3%) required an amputation. There were no statistically significant differences in types of failure between time intervals ($P = .414$). The treatment failure rates per time interval from index arthroplasty to DAIR were 39% (11/28) for Week 1, 42% (84/198) for Week 2, 41% (104/255) for Week 3, 32% (39/123) for Week 4, 30% (21/71) for Week 5, 28% (8/29) for Week 6, and 42% (27/65) for Weeks 7–12 (Figure 1A; Figure 2). Analyzing additional intervals from Weeks 7 to 12, no differences in treatment failure rates were observed between Weeks 7–8 and Weeks 9–12 (40% [12/30] vs 43% [15/35], respectively; $P = .816$). The implant failure rates per time interval from index arthroplasty to DAIR were 21% (6/28) for Week 1, 15% (30/198) for Week 2, 17% (42/255) for Week 3, 20% (25/123) for Week 4, 17% (12/71) for Week 5, 10% (3/29) for Week 6, and 23% (15/65) for Weeks 7–12 (Figure 1B). Analyzing additional intervals from Weeks 7 to 12, there were no differences in implant failure rates between Weeks 7–8 and Weeks 9–12 (30% [9/30] vs 17% [6/35], respectively; $P = .220$). Using a univariate binary logistic regression analysis, the time interval from index arthroplasty to DAIR was not a statistically significant factor for predicting treatment failure using time interval either as a continuous variable (odds ratio [OR] 0.99, 95% confidence interval [CI] 0.98–1.00; $P = .266$) or as a categorical variable (with 4 time-interval categories; OR 0.58, 95% CI 0.30–1.10; $P = .154$). These results were in agreement with the outcome

of the univariate binary regression on implant failure in relation to time interval (OR 1.00 [95% CI 0.99–1.01; $P = .899$] and OR 0.54 [95% CI 0.25–1.19; $P = .499$], continuous variable and categorical variable, respectively). The multivariate binary logistics regression analysis showed that several preoperative variables were independent predictors for treatment failure: a high CRP as a continuous variable (OR 1.01, 95% CI 1.00–1.01; $P < .001$), revision arthroplasty (OR 4.34, 95% CI 1.62–11.64; $P = .004$), arthroplasty indicated for a fracture (OR 2.36, 95% CI 1.25–4.48; $P = .008$), and female gender (OR 1.89, 95% CI 1.14–3.13; $P = .013$). Cases where the modular components were not exchanged (OR 1.70, 95% CI 0.96–3.00; $P = .067$) and cases with cemented arthroplasties (OR 1.84, 95% CI 0.96–3.52; $P = .074$) showed a trend towards worse outcomes.

Preoperative Variables According to Time Interval After Index Surgery

The general patient characteristics were comparable among patients in different time intervals for DAIR (Table 1). The mean CRP value and the duration of symptoms of PJI were also the same in patient groups divided based on the interval from index arthroplasty to DAIR. The leukocyte count was higher in patients undergoing DAIR within 2 weeks or later than 6 weeks after index arthroplasty ($P < .001$). When the time interval from index arthroplasty to DAIR increased, the number of patients experiencing pain increased ($P = .004$), as well as the number of patients with red wounds ($P = .002$). Patients who were treated in the late post-surgical course

Figure 1. Failure rates according to time interval from index arthroplasty to DAIR ($n = 769$). The definitions of treatment failure and implant failure are described in the Material and Methods section of the paper. A, Treatment failure. B, Implant failure. Abbreviation: DAIR, debridement, antibiotics, and implant retention.

Figure 2. Treatment success of DAIR during follow-up, according to time interval from index arthroplasty to DAIR ($n = 769$). Abbreviation: DAIR, debridement, antibiotics, and implant retention.

(Weeks 7–12) had a lower rate of wound leakage than patients who were treated earlier ($P = .003$). DAIR was performed at an earlier time point in patients with PJI of the hip, compared with patients with PJI of the knee ($P < .001$), and patients with PJI of the hip experienced wound leakage more often than patients with PJI of the knee (84% vs 67%, respectively; $P < .001$). Subanalyses comparing PJI of the hip and knee showed no statistically significant differences in treatment failure and

implant failure rates (39% vs 38% [$P = .737$] and 16% vs 19% [$P = .237$], respectively).

Intraoperative Variables According to Time Interval After Index Surgery

Exchanges of modular components were performed to a lesser extent in the early post-surgical course (Weeks 1–2), compared to the late course (Weeks 7–12; 41% vs 63%, respectively; $P < .001$; Table 2). The predominant microorganisms causing PJI were *Staphylococcus aureus* (44%), *Staphylococcus epidermidis* (34%), *Enterococcus* species (15%), and *Streptococcus* species (11%). PJI was polymicrobial in 286 patients (37%). There were no major differences in causative microorganisms per time interval. Only methicillin-resistant *Staphylococcus aureus* was cultured more often when DAIR was performed more than 6 weeks after index arthroplasty, compared to the early post-surgical course (≤ 6 weeks; $P = .032$). The number of positive cultures gradually decreased when DAIR was performed at a later time point ($P < 0.001$). The failure rates per causative microorganism were comparable for different time intervals (Table 3). There were no statistical differences in the use of correct “antibiofilm” antibiotic treatment between time intervals, either for rifampicin based regimens in cases of infections caused by staphylococci

Table 1. Patient Characteristics According to Time Interval

Variables	Week 1–2, $n = 226$	Week 3–4, $n = 378$	Week 5–6, $n = 100$	Week 7–12, $n = 65$	P Value
Age in years, mean (SD)	69.5 (11.8)	70.5 (11.8)	67.3 (13.3)	69.6 (13.2)	.149
Gender, male	108 (48.0%)	153 (40.7%)	39 (39.8%)	31 (48.4%)	.220
BMI in kg/m^2 , mean (SD)	31.0 (7.1)	31.2 (6.2)	31.3 (5.8)	30.7 (6.5)	.920
Comorbidities					
Diabetes mellitus	41 (18.1%)	77 (20.4%)	16 (16.0%)	13 (20.0%)	.757
COPD	46 (20.4%)	62 (16.4%)	10 (10.0%)	8 (12.3%)	.095
Malignancy	30 (13.3%)	57 (15.1%)	17 (17.0%)	12 (18.5%)	.695
Renal failure	16 (7.1%)	20 (5.3%)	7 (7.0%)	10 (15.4%)	.032
Liver cirrhosis	8 (3.5%)	9 (2.4%)	7 (7.0%)	3 (4.6%)	.154
Rheumatoid arthritis	11 (4.9%)	23 (6.1%)	10 (10.0%)	3 (4.6%)	.321
Type of arthroplasty					
Primary	179 (80.6%)	315 (83.8%)	79 (79.0%)	49 (76.6%)	.414
Revision	43 (19.4%)	61 (16.2%)	21 (21.0%)	15 (23.4%)	
Site of arthroplasty					
Hip	164 (72.6%)	228 (60.3%)	38 (38.0%)	33 (50.8%)	<.001
Knee	62 (27.4%)	150 (39.7%)	62 (62.0%)	32 (49.2%)	
Indication for arthroplasty					
Osteoarthritis	151 (68.6%)	281 (74.7%)	84 (84.8%)	47 (73.4%)	.108
Fracture	42 (19.1%)	54 (14.4%)	7 (7.1%)	10 (15.6%)	
Days of symptoms, mean (SD)	6.0 (4.7)	7.3 (6.6)	6.7 (5.2)	6.1 (6.6)	.135
Type of symptoms					
Fever	29 (12.2%)	43 (14.2%)	11 (14.7%)	11 (26.2%)	.235
Pain	48 (32.2%)	98 (37.0%)	25 (44.6%)	25 (62.5%)	.004
Redness	65 (43.6%)	138 (52.1%)	30 (53.6%)	31 (77.5%)	.002
Wound leakage	115 (77.2%)	220 (82.7%)	42 (75.0%)	23 (57.5%)	.003
Leukocyte count in $\times 10^9/\text{L}$, mean (SD)	11.4 (6.3)	9.7 (3.9)	9.0 (3.4)	9.8 (4.0)	<.001
CRP value in mg/L , mean (SD)	101.6 (98.4)	93.6 (95.5)	88.7 (92.7)	86.2 (93.4)	.567
KLIC score, mean (SD)	2.9 (1.9)	2.9 (1.7)	2.8 (1.6)	2.8 (2.0)	.947

The time interval was from index arthroplasty to DAIR ($n = 769$). Bold values indicate statistically significant differences.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DAIR, debridement, antibiotics, and implant retention; KLIC, chronic renal failure (K); liver cirrhosis (L), index surgery (I), cemented prosthesis (C), and C-reactive protein $>115 \text{ mg}/\text{L}$; SD, standard deviation.

Table 2. Intraoperative Variables According to Time Interval

Variables	Week 1–2, n = 226	Week 3–4, n = 378	Week 5–6, n = 100	Week 7–12, n = 65	PValue
Exchange of modular components	85 (40.7%)	158 (44.4%)	56 (59.6%)	36 (63.2%)	<.001
Percentage of positive cultures, mean (SD)	88.6% (22.4)	86.5% (24.5)	75.1% (33.8)	63.2% (39.3)	<.001
All of the obtained cultures positive	141 (74.2%)	228 (69.5%)	46 (52.9%)	22 (43.1%)	<.001
Polymicrobial	79 (35.0%)	157 (41.5%)	32 (32.0%)	18 (27.7%)	.066
Gram-positive microorganisms	196 (86.7%)	334 (88.4%)	82 (82.0%)	50 (76.9%)	.054
<i>Staphylococcus aureus</i>	94 (41.6%)	174 (46.0%)	50 (50.0%)	21 (32.3%)	.101
MRSA	15 (6.6%)	17 (4.5%)	8 (8.0%)	9 (13.8%)	.032
<i>Staphylococcus epidermidis</i>	80 (35.4%)	134 (35.4%)	26 (26.0%)	19 (29.2%)	.257
<i>Enterococcus</i> species	36 (15.9%)	52 (13.8%)	15 (15.0%)	11 (16.9%)	.852
<i>Streptococcus</i> species	28 (12.4%)	44 (11.6%)	5 (5.0%)	8 (12.3%)	.224
Other Gram-positives	26 (15.4%)	64 (21.1%)	12 (16.0%)	7 (16.7%)	.412
Gram-negative micro-organisms	57 (25.2%)	99 (26.2%)	26 (26.0%)	13 (20.0%)	.765
<i>Escherichia coli</i>	16 (7.1%)	26 (6.9%)	9 (9.0%)	2 (3.1%)	.536
<i>Pseudomonas</i> species	14 (8.3%)	20 (6.6%)	7 (9.3%)	3 (7.1%)	.831
<i>Enterobacter cloacae</i>	11 (4.9%)	15 (4.0%)	4 (4.0%)	3 (4.6%)	.957
<i>Proteus</i> species	7 (3.1%)	24 (6.3%)	4 (4.0%)	3 (4.6%)	.329
Other Gram-negatives	18 (8.0%)	33 (8.7%)	9 (9.0%)	5 (7.7%)	.978
Anaerobe micro-organisms	2 (0.9%)	9 (2.4%)	1 (1.0%)	2 (3.1%)	.437
<i>Candida</i> species	2 (0.9%)	1 (0.3%)	0 (0.0%)	2 (3.1%)	.054

The time interval was from index arthroplasty to DAIR (n = 769). Bold values indicate statistically significant differences.

Abbreviations: DAIR, debridement, antibiotics, and implant retention; MRSA, methicillin-resistant *Staphylococcus aureus*; SD, standard deviation.

($P = .676$) or ciprofloxacin in cases of infections caused by Gram-negative microorganisms ($P = .543$).

DISCUSSION

This multicenter, multinational study consisting of a large group of patients with early PJI of the hip and knee is among the first studies to refute the importance of the time interval from index arthroplasty to DAIR on the outcome of DAIR. The results demonstrated that, although failure rates were highest when DAIR was performed 7–12 weeks after the index arthroplasty, DAIR was still successful in approximately 60% of patients and the implant could be retained in 75% of patients. Moreover, within the first 6 weeks after index arthroplasty, failure rates tended to gradually decrease, instead of increase, which may be due to the lower bacterial inoculum observed in these cases. The higher failure rate observed when DAIR was performed more than 6 weeks after the index arthroplasty may be explained by the presence of a more mature biofilm and, within this time frame, the bacterial inoculum *per se* is probably not a trivial factor anymore for a better outcome. Our results not only question the current guidelines stating that DAIR is not recommended when PJI develops more than 30 days after index arthroplasty [27], but clearly demonstrate that DAIR is still a viable surgical treatment option in a large proportion of these patients. Our results do not imply or justify postponing DAIR, though. In fact, based on the recommendation of the second International Consensus Meeting, DAIR should be performed as soon as symptoms of infection arise [16]. These findings are in agreement with existing literature, demonstrating that each day of delaying DAIR decreased the chance of treatment success by approximately

10%, depending on the affected joint [17]. Indeed, in our study, the average symptom durations were short (ie, less than 1 week) and comparable between time intervals.

Although we expected differences in the types of microorganisms causing the infection for each time interval—that is, virulent microorganisms (eg, *Staphylococcus aureus* and Gram negatives) in the early post-surgical course (ie, ≤ 6 weeks) and low-virulent microorganisms (eg, coagulase-negative staphylococci and enterococci) in the late post-surgical course (ie, >6 –12 weeks)—no major differences were observed. Only a higher rate of methicillin-resistant *Staphylococcus aureus* was observed when DAIR was performed more than 6 weeks after index arthroplasty. Our observations that treatment failure and implant failure rates slightly increased when DAIR was performed more than 6 weeks after index arthroplasty are supported by in vivo studies evaluating the time to develop a mature biofilm [32–34]. Carli et al [34] demonstrated in a mouse model with a proximal tibial implant that although a biofilm was evident 2 weeks after injection with *Staphylococcus aureus*, it matured and was covered by fibrinous tissue and multiple host cells after 6 weeks. However, the fact that treatment was still successful in approximately 60% of patients when DAIR was performed in the late post-surgical course and remained equally successful between 6 and 12 weeks after index arthroplasty illustrates that the development of a biofilm is a variable process, which not only depends on time, but also on the causative microorganism, the inoculum size, and the host [28, 29]. In addition, microorganisms could enter the joint cavity during the post-surgical course, causing uncertainty as to when the process of biofilm formation started.

Table 3. Failure Rates According to Causative Microorganism and Time Interval

Variables	Week 1–2	Week 3–4	Week 5–6	Week 7–12	P Value
Polymicrobial infections	38/79 (48.1%)	57/157 (36.3%)	8/32 (25.0%)	9/18 (50.0%)	.080
Gram-positive micro-organisms	88/196 (44.9%)	126/334 (37.7%)	24/82 (29.3%)	19/50 (38.0%)	.094
<i>Staphylococcus aureus</i>	51/94 (54.3%)	77/174 (44.3%)	18/50 (36.0%)	10/21 (47.6%)	.185
MRSA	9/15 (60.0%)	4/17 (23.5%)	4/8 (50.0%)	6/9 (66.7%)	.102
<i>Staphylococcus epidermidis</i>	32/80 (40.0%)	37/134 (27.6%)	5/26 (19.2%)	8/19 (42.1%)	.094
<i>Enterococcus</i> species	16/36 (44.4%)	20/52 (38.5%)	5/15 (33.3%)	5/11 (45.5%)	.861
<i>Streptococcus</i> species	11/28 (39.3%)	16/44 (36.4%)	1/5 (20.0%)	3/8 (37.5%)	.877
Other Gram-positives	11/26 (42.3%)	15/64 (23.4%)	4/12 (33.3%)	3/7 (42.9%)	.286
Gram-negative micro-organisms	25/57 (43.9%)	38/99 (38.4%)	7/26 (26.9%)	4/13 (30.8%)	.479
<i>Escherichia coli</i>	8/16 (50.0%)	11/26 (42.3%)	4/9 (44.4%)	0/2 (0.0%)	.608
<i>Pseudomonas</i> species	4/14 (28.6%)	6/20 (30.0%)	1/7 (14.3%)	1/3 (33.3%)	.864
<i>Enterobacter cloacae</i>	5/11 (45.5%)	4/15 (26.7%)	1/4 (25.0%)	1/3 (33.3%)	.764
<i>Proteus</i> species	5/7 (71.4%)	9/24 (37.5%)	2/4 (50.0%)	2/3 (66.7%)	.388
Other Gram-negatives	7/18 (38.9%)	17/33 (51.5%)	1/9 (11.1%)	2/5 (40.0%)	.184
Anaerobe micro-organisms	1/2 (50.0%)	6/9 (66.7%)	1/1 (100.0%)	2/2 (100.0%)	.626
<i>Candida</i> species	2/2 (100.0%)	1/1 (100.0%)	0/0 (0.0%)	1/2 (50.0%)	.392

The time interval was from index arthroplasty to DAIR ($n = 769$).

Abbreviations: DAIR, debridement, antibiotics, and implant retention; MRSA, methicillin-resistant *Staphylococcus aureus*.

What could be perceived as a limitation of this study is the exclusion of patients with bacteremia. Nevertheless, since we could not be certain that the PJI was the cause of the bacteremia and not secondary to the bacteremia itself, we considered it more accurate to exclude this patient category. If a PJI occurs due to bacteremia by another focus (for example, via a central venous catheter), the joint will be contaminated/infected by bacteria at that particular time point, which precludes the possibility of solely evaluating the time interval after an index surgery in relation to the outcome. Nevertheless, the outcome of our analysis was not different when we included patients with bacteremia (data not shown). Another limitation is the difference in clinical variables between time intervals. For example, polymicrobial infections were less prevalent in the late post-surgical course and mobile components were exchanged at a higher rate. Nevertheless, neither polymicrobial infections nor the exchange of mobile components were significant predictors for treatment failure in the multivariate analysis. However, the importance of exchanging the mobile components has been demonstrated in many studies [16] and also trended towards better outcomes in our study. A final limitation is the statistically significant difference in follow-ups per time interval, although this difference is clinically irrelevant since all patients had a follow-up more than 1 year and had comparable ranges, such that the treatment failure rates are unbiased by this difference.

In conclusion, we believe the outcome of DAIR is affected by a number of factors that are in complex interplay. Basing a surgical decision solely on the time interval from index arthroplasty to DAIR is neither logical nor evidence based. Further studies are needed to examine the influences of all factors on the outcomes of DAIR, both in isolation and in combination. Machine learning and/or artificial intelligence may need to be used to

develop an algorithm that will better help surgeons decide when to perform DAIR in patients with early PJI. Until such an algorithm is developed, DAIR can be perceived as a viable treatment option in patients presenting more than 4 weeks after index surgery, as long as DAIR is performed within 1 week after the start of symptoms and modular components are exchanged.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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