Prosthetic joint-associated infections treated with DAIR (debridement, antibiotics, irrigation, and retention)

Analysis of risk factors and local antibiotic carriers in 91 patients

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Background and purpose **For prosthetic joint-associated infection (PJI), a regimen of debridement, antibiotics, irrigation, and retention of the prosthesis (DAIR) is generally accepted for acute infections. Various risk factors associated with treatment success have been described. The use of local antibiotic carriers (beads and sponges) is relatively unknown. We retrospectively analyzed risk factors in a cohort of patients from 3 hospitals, treated with DAIR for PJI.**

Patients and methods **91 patients treated with DAIR for hip or knee PJI in 3 Dutch centers between 2004 and 2009 were retrospectively evaluated. The mean follow-up was 3 years. Treatment success was defined as absence of infection after 2 years, with retention of the prosthesis and without the use of suppressive antibiotics.**

Results **60 patients (66%) were free of infection at follow-up. Factors associated with treatment failure were: a history of rheumatoid arthritis, late infection (> 2 years after arthroplasty), ESR at presentation above 60 mm/h, and infection caused by coagulase-negative *Staphylococcus.* Symptom duration of less than 1 week was associated with treatment success. The use of gentamicin sponges was statistically significantly higher in the success group, and the use of beads was higher in the failure group in the univariate analysis, but these differences did not reach significance in the logistic regression analysis. Less surgical procedures were performed in the group treated with sponges than in the group treated with beads.**

Interpretation **In the presence of rheumatoid arthritis, duration of symptoms of more than 1 week, ESR above 60 mm/h, late infection (> 2 years after arthroplasty), and coagulase-negative *Staphylococcus* PJI, the chances of successful DAIR treatment decrease, and other treatment methods should be considered.**

Prosthetic joint-associated infection (PJI) occurs in around 1–2% of primary total hip arthroplasties (THAs) and total knee arthroplasties (TKAs) (Trampuz and Zimmerli 2005, Kurtz et al. 2008, Del Pozo and Patel 2009). Infected artificial joints are often unresponsive to antibiotic treatment, due to poor vascular supply and biofilm formation. Generally, PJIs are classified in 3 groups, based on duration of symptoms and time after surgery: (I) early postoperative: symptoms less than 4 weeks after surgery; (II) late chronic: a gradual, indolent onset of symptoms; or (III) acute hematogenous: acute onset in a previously well-functioning prosthesis (Tsukayama et al. 1996, Toms et al. 2006). A similar classification describes early (3 months), delayed/low-grade (3–24 months), and late infection (> 24 months) (Trampuz and Zimmerli 2005).

Various risk factors have been described that are associated with occurrence of PJI, such as rheumatoid arthritis, diabetes mellitus, malignancy, obesity, and use of immunosuppressant drugs (Choong et al. 2007, Bongartz et al. 2008, Jamsen et al. 2009, Azzam et al. 2010, Lora-Tamayo et al. 2013). Revision surgery also increases the risk of PJI (Bongartz et al. 2008, Byren et al. 2009, Jamsen et al. 2009). Factors that have been associated with a worse outcome of PJI treatment include: infections caused by *Staphylococcus* spp. (Azzam et al. 2010), and more specifically by *Staphylococcus aureus* (Marculescu et al. 2006, Soriano et al. 2006, Byren et al. 2009, Cobo et al. 2011), polymicrobial PJI (Lora-Tamayo et al. 2013), intra-articular purulence (Azzam et al. 2010), retention of exchangeable components (Lora-Tamayo et al. 2013), and longer time between initial arthroplasty and PJI diagnosis (Brandt et al. 1997, Barberan et al. 2006, Marculescu et al. 2006, Lora-Tamayo et al. 2013).

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Most PJIs are caused by coagulase-negative *Staphylococcus* (30–41%) and *S. aureus* (12–47%). *Streptococcus* spp. and *Enterococcus* spp. are less common causes, both at around 10% of the total, as are gram-negative bacteria such as *Escherichia coli* (< 5%) (Moran et al. 2007, Sharma et al. 2008, Byren et al. 2009). A prevalence of 5–39% has been described for polymicrobial infections (Moran et al. 2007, Azzam et al. 2010, Cobo et al. 2011, Westberg et al. 2012, Lora-Tamayo et al. 2013).

A regimen of debridement, antibiotics, irrigation, and retention of the prosthesis (DAIR) is generally accepted for acute infections without complicating factors such as significant comorbidity or loosening of the prosthesis. DAIR has shown varying success rates: as low as 14% (Crockarell et al. 1998) and as high as 100% (Zimmerli et al. 1998). Success can be achieved in over 70% of the cases when patients with favorable factors are selected, such as those with short duration of symptoms (less than 3–4 weeks), a stable implant, and healthy soft tissues surrounding the prosthesis (Soriano et al. 2006, Byren et al. 2009, Vilchez et al. 2011, Sukeik et al. 2012, Osmon et al. 2013). In the case of chronic infections, implant retention is rarely successful. Implant removal leaves the patient disabled for weeks or even months (Osmon et al. 2013).

Local antibiotic treatment, with aminoglycosides in beads or sponges, could theoretically reach high local concentrations without exposing the patient to toxic serum levels. Beads have a prolonged release compared to sponges but do not reach such high concentrations (Diefenbeck et al. 2006). These can also act as foreign bodies, to which bacteria might adhere (Barth et al. 2011). We evaluated the outcome of DAIR for total hip and knee PJI in 3 Dutch hospitals, to study factors associated with successful outcome and to study the outcomes of the use of local antibiotic carriers.

Patients and methods

Study design

This was a retrospective cohort study, with a follow-up of at least 2 years or until the patient died. Prosthetic joint-associated infection was defined according to Crockarell et al. (1998), and required 1 or more of the following criteria:

(I) growth of the same microorganism in at least 2 culture specimens (preoperative joint aspiration and/or intraoperative, intracapsular specimen); (II) 1 positive culture, and intracapsular purulence during debridement procedure, acute inflammation on histopathological examination of intraoperative specimen, and/or an actively draining sinus tract; (III) culture-negative infection: negative culture results and at least 2 of intracapsular purulence during debridement procedure, acute inflammation on histopathological examination of intraoperative specimen, and an actively draining sinus tract.

The study population consisted of 91 patients who were treated with DAIR for PJI of total hip arthroplasty (THA) or total knee arthroplasty (TKA) at 3 Dutch hospitals between January 2004 and December 2009. 34 of the patients with PJI of the hip have already been described (Kuiper et al. 2013) and they were also included.

Treatment

The decision for or against DAIR treatment was made by the treating surgeon, in consultation with the orthopedic team. It was based on clinical signs and symptoms, type of infection, and absence of radiographic loosening. DAIR was repeated after 2 weeks if clinical symptoms and laboratory signs did not improve. The decision to remove the implant was made individually by the surgeon in consultation with the patient.

The decision to use local antibiotic carriers was made by the treating surgeon. Carriers were either gentamicin beads (Septopal; gentamicin sulfate in polymethylmethacrylate, 225 mg per chain; Biomet, Germany) or gentamicin sponges (Garacol; gentamicin sulfate in equine collagen, 130 mg per sponge; EusaPharma, UK). Antibiotic therapy, based on bacterial susceptibility and in consultation with either an infectious diseases specialist or a medical microbiologist, was administered for at least 6 weeks.

The joint was opened through the old scar or wound, and after tissue collection for multiple cultures (at least 3) from synovium, capsule, and interfaces, was thoroughly debrided—including synovial resection. Exchangeable components were replaced in most cases, but this was not standard procedure. After debridement, the joint and wound were meticulously irrigated with saline using pulsed lavage, and primarily closed. No drains or vacuum systems were used. Removal of gentamicin beads was always combined with debridement, and was therefore counted as a procedure. Postoperatively, antibiotic treatment was started, either with a broad range agent such as vancomycin (Vancomycin; Xellia Pharmaceuticals ApS, Denmark), or—when the causative species was known—an agent based on susceptibility. A thromboprophylactic agent (Nadroparine) was administered during the hospital stay.

Outcome

A successful treatment outcome was defined as the absence of clinical and laboratory signs of inflammation (C-reactive protein blood serum levels of < 10 mg/L) at a follow-up of 2 years. Patients who required chronic, suppressive antibiotic treatment, who underwent prosthesis removal, or who died within this 2-year period were considered to be cases of treatment failure.

Statistics

The assumption of normality was checked by visual inspection of the histograms, q-q plots, and box plots of the data. A Kolmogorov-Smirnov test was also performed on the data. For continuous variables with a normal distribution, mean and standard deviation (SD) are given, whereas variables that were not normally distributed are given as median and interquartile

range (IQR). To determine whether patients with successful treatment differed significantly from patients with unsuccessful treatment, independent t-tests were performed for continuous variables with normal distribution and the non-parametric Mann-Whitney U-test was used for continuous variables without normal distribution. For categorical variables, chi-square tests were performed for large groups and Fisher's exact test was used for small groups. Variables that were statistically significantly different between success and failure groups were subsequently analyzed with logistic regression to correct for confounding. Kaplan-Meier analysis was used to describe the infection-free survival (with treatment failure as endpoint).

All statistical analyses were performed with IBM SPSS Statistics 20.0 and p-values < 0.05 were considered statistically significant.

Results

Population and patient characteristics

91 patients with prosthetic joint-associated infection (62 hips, 29 knees) were treated with DAIR, 60 of whom were free of infection without resection arthroplasty or use of suppressive antibiotics at follow-up: a 66% success rate. Factors analyzed for the success and failure groups are summarized in Table.

16 patients died during follow-up. 9 had a follow-up of at least 2 years, 8 of whom were treated successfully and 1 of whom died 32 months after revision surgery. 7 patients died within 2 years of follow-up and they were considered treatment failures. 2 of these patients were free of symptoms when they died. 2 deaths were infection-related: 1 patient died of sepsis and 1 patient refused further treatment, both within 3 months of the start of symptoms (Figure 1). No other permanent complications were seen. 7 patients developed high creatinine levels during treatment, but renal function normalized in all 7 in the months that followed.

Mean duration of follow-up was 35 (0–79) months. See Figure 1 for a flow chart of surgical treatment in this study, and Figure 2 for infection-free survival.

Factors associated with outcome

In univariate analysis, 8 factors were statistically significantly associated with treatment failure (Table). After logistic regression analysis, 5 factors were associated with failure: rheumatoid arthritis, late infection, ESR at presentation above 60 mm/h, symptom duration of more than 7 days before the start of treatment, and PJI caused by coagulase-negative Staphylococcus (Table). Revision arthroplasty was not associated with either treatment failure or success.

Surgical treatment

The mean number of procedures was similar in successfully and unsuccessfully treated patients (Table). No difference in success rate was seen between patients who underwent 1 DAIR procedure and patients who underwent multiple procedures.

The use of gentamicin sponges was statistically significantly higher in the success group, and the use of beads was significantly higher in the failure group. These differences were not significant in the logistic regression analysis. The mean number of procedures was lower when sponges were used (2.0, SD 0.8) than when beads were used (2.8, SD 1.4) (p = 0.006).

Microbiology

Preoperative aspiration was performed in 65 patients, and a causative microorganism was found in 60 of them. Intraoperative samples were collected from all 91 cases, which yielded at least 1 positive result in 87 patients. For the other 4 patients, aspiration fluid yielded positive cultures. No culture-negative infections were seen.

Most infections were caused by *S. aureus* (Table). MRSA was responsible for only 2 cases of PJI, both of which were treated successfully. PJI caused by coagulase-negative *Staphylococcus* was associated with a low success rate and streptococcal infections were associated with a high success rate. All streptococcal infections were treated within 1 week of onset of symptoms. 5 patients had a polymicrobial prosthetic joint-associated infection; all were treated successfully.

Discussion

Demographics and comorbidity

Of the 91 patients included in this study, 60 were treated successfully with DAIR. Revision arthroplasty has been described by others as a risk factor for PJI (Bongartz et al. 2008, Byren et al. 2009, Jamsen et al. 2009), but it was not associated with treatment failure in this cohort. Of all comorbidities described, only rheumatoid arthritis was found to be associated with PJI; this was also found in 1 other study (Bongartz et al. 2008). Only 2 patients with rheumatoid arthritis were using immunosuppressive drugs (1 in the success group and 1 in the failure group).

Clinical presentation

In most cases (60/91), treatment was started within 1 week of onset of infectious symptoms, which had a better outcome. The treatment success with early infections and infections of short duration of symptoms is commonly attributed to lack of biofilm formation (Del Pozo and Patel 2009), and it is strongly recommended (Osmon et al. 2013) that DAIR should only be used for patients with a short duration of symptoms (less than 3 weeks) or time after initial arthroplasty of less than 30 days (Osmon et al. 2013). We found that having symptoms for less than 1 week was associated with treatment success.

Although usually discouraged, 7 patients with a duration of symptoms of more than 4 weeks were treated with DAIR. In

Patient characteristics and variables of a cohort treated with debridement, antibiotics, irrigation, and retention of the prosthesis (DAIR), divided by success or failure of treatment

Variable	Success (n = 60)	Failure (n = 31)	p-value (univariate)	p-value (adjusted)	Odds ratio
Demographics					
Mean age in years (SD [a])	70 (11)	69 (13)	0.7		
Female sex	37	17	0.5		
Hip joint	38	24	0.2		
Knee joint	22	7	0.2		
Infection after revision surgery	12	8	0.5		
Cemented arthroplasty	22	20	0.01	0.7	0.3–7
Comorbidities					
Cardiac	31	16	1.0		
Pulmonary	5	6	0.2		
Renal insufficiency	6	0	0.09		
Diabetes	7	6	0.4		
Rheumatoid arthritis	3	7	0.03	0.03	1.2–84
Malignancy	4	3	0.7		
Clinical presentation					
Median duration of symptoms in days (IQR [b])	3 (5)	6 (7)	0.02		
Symptoms < 1 week	44	16	0.02	0.05	1.0–18
Symptoms < 3 weeks	54	25	0.1		
Median time from arthroplasty to presentation in days (IQR)	21 (51)	42.5 (266)	0.05		
Early infection (< 3 months)	48	19	0.06		
Delayed infection (3–24 months)	10	7	0.5		
Late infection (> 2 years)	2	5	0.04	0.04	1.1–366
Type 1 (early postoperative)	38	14	0.2		
Type 2 (chronic)	3	4	0.2		
Type 3 (acute hematogenous)	19	13	0.3		
Mean CRP [c] at presentation, in mg/L (SD)	164 (119)	155 (118)	0.7		
Mean ESR [d] at presentation, in mm/h (SD)	54 (26)	76 (27)	0.002		
ESR > 60 mm/h	19/47	20/24	0.001	0.005 [f]	2.2–98
Surgical treatment					
Mean number of procedures (SD)	2.0 (0.8)	2.4 (1.5)	0.1		
Single DAIR procedure	21	11	1.0		
Multiple DAIR procedures	39	20	1.0		
Gentamicin sponges used	48	16	0.005	0.4	0.05–3
Gentamicin beads used	4	8	0.02	1.0	0.06–18
Sponges and beads used	2	4	0.2		
No local antibiotic use	6	3	1.0		
Microbiology (including polymicrobial infections)					
CNS [e]	4	9	0.009	0.02	1.8–309
Staphylococcus aureus	34	16	0.6		
Streptococcus spp.	10	1	0.09		
Escherichia coli	3	1	1.0		
Enterobacter cloacae	2	2	0.6		
Enterococcus faecalis	5	0	0.2		
Other	7	2	0.7		

[a] SD: standard deviation.
[b] IQR: interquartile range.
[c] CRP: C-reactive protein.
[d] ESR: erythrocyte sedimentation rate.
[e] CNS: coagulase-negative *Staphylococcus.*
[f] ESR as a continuous value and ESR as a dichotomous value are the same variable: only the clinically more useful dichotomous ESR with a cutoff of 60 mm/h was analyzed by logistic regression.

all cases, the decision to use DAIR was made by the treating surgeon because of early PJI occurring within 3 months after initial surgery (Trampuz and Zimmerli 2005). We included these 7 patients nonetheless, because this might further identify factors associated with outcome. Duration of symptoms of more than 4 weeks was not a factor associated with treatment outcome.

An ESR at presentation of more than 60 mm/h was associated with treatment failure. A low ESR at presentation could indicate a shorter duration of infection, and might therefore be predictive of a higher chance of success. Other studies have focused on the ability of these blood infection markers (CRP and ESR) to establish a diagnosis of PJI (Greidanus et al. 2007, Muller et al. 2008), and 1 study found that high CRP

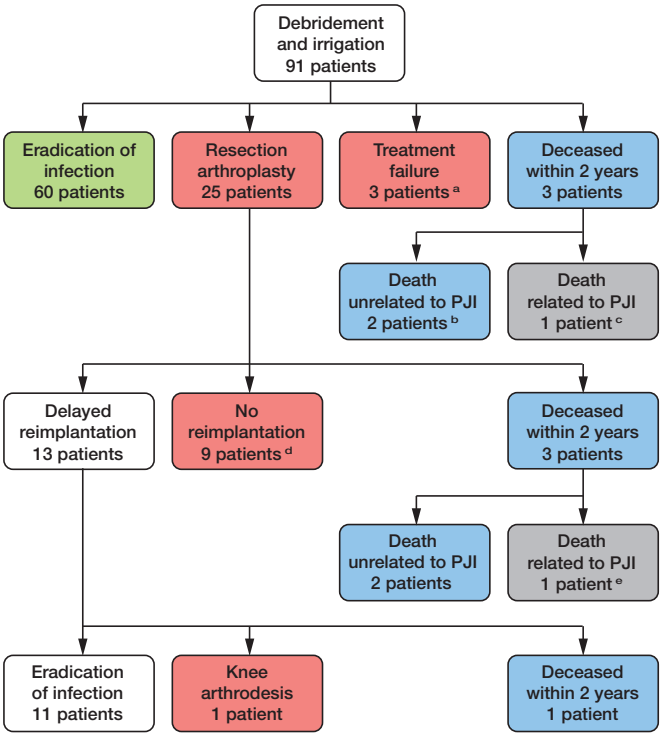

Figure 1. Flow chart of surgical treatment of patients included in the study.
[a] 3 patients chronic lowgrade infection, of which 1 chronic use of antibiotics.
[b] 2 patients had no infectious symptoms (but were assigned to 'failure' as adequate follow-up was not possible).
[c] 1 patient refused further surgical and antibiotic treatment and died 19 days after DAIR procedure.
[d] 2 arthrodesis knee; 1 above knee amputation after failed arthrodesis; in 6 patients the resection situation was accepted.
[e] 1 patient died 14 days after prosthesis removal due to sepsis.

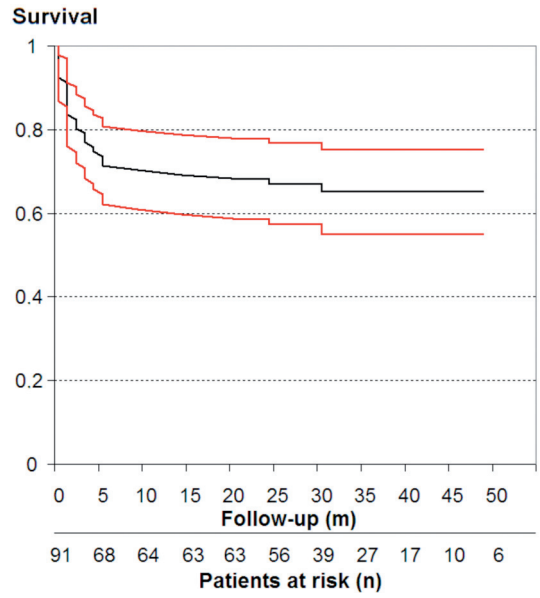

Figure 2. Kaplan-Meier survival analysis (patients free of infection) of 91 patients treated with debridement, antibiotics, irrigation, and retention (DAIR). Red lines show 95% confidence intervals.

was predictive of failure (Lora-Tamayo et al. 2013), but to our knowledge ESR has never been described as a factor associated with treatment outcome.

Surgical treatment

In staged revision, gentamicin-loaded beads are often used to fill the dead space after arthroplasty removal, but evidence on their effectiveness is limited (Diefenbeck et al. 2006, Barth et al. 2011). To our knowledge, their use in DAIR has never been studied. The use of gentamicin sponges in treatment of PJI has only been described in a few studies (Swieringa and Tulp 2005, Diefenbeck et al. 2006, Swieringa et al. 2008, Kuiper et al. 2013). The report by Kuiper et al. (2013) includes 34 of the patients included in the present study.

A higher success rate for sponges and a lower success rate for beads was found in univariate analysis, but this was not confirmed in multivariate analysis. The use of gentamicin sponges was associated with fewer procedures.

The collagen-based gentamicin sponges used are biodegradable and do not need removal surgery, as opposed to beads. Furthermore, sponges reach higher local antibiotic concentrations than beads (Diefenbeck et al. 2006), and it has been suggested that beads are themselves foreign bodies and therefore maintain the infection (Barth et al. 2011). Our cohort may have been too small to allow us to find statistically significant differences between the 2 antibiotic carriers, but selection bias must be considered as well: one might argue that beads were used in cases of severe infection, where additional debridement procedures were anticipated and needed.

Microbiology

We found that CNS infection was associated with treatment failure. Other authors have also described staphylococcal or, more specifically, *S. aureus* infection to have a higher risk of failure (Marculescu et al. 2006, Soriano et al. 2006, Byren et al. 2009, Azzam et al. 2010). Possible explanations for this phenomenon are the ability of the species to form a biofilm, and the virulence of the causative microorganism: coagulase-negative *Staphylococcus* is known to be of low virulence, which may delay and impede the diagnosis.

Treatment of streptococcal infections had a high success rate, and they were all treated within 1 week after symptoms became apparent. That this was not a significant factor may be explained by sample size, but the high success rate might also be explained by the short duration of symptoms. 1 study also found a correlation between streptococcal infections and good outcome (Meehan et al. 2003).

Only 5 of 91 patients had an infection caused by multiple microorganisms, and all were free of infection at follow-up. Some authors have also found relatively few polymicrobial

infections, between 5 and 10% (Aboltins et al. 2007, Azzam et al. 2010), but others have described much higher rates of multi-organism PJI: between 19 and 39% (Moran et al. 2007, Cobo et al. 2011, Vilchez et al. 2011, Westberg et al. 2012, Lora-Tamayo et al. 2013). All of these studies used culture to identify microorganisms, and no DNA techniques. Whether this difference is a matter of culture method or whether some other (regional) factor might be involved remains uncertain. Only 1 study found higher failure for polymicrobial infection, with a hazard ratio of 1.8 (Lora-Tamayo et al. 2013).

Limitations

This was a retrospective study, with its inherent caveats for interpretation. The sample size may have been too small for identification of any weaker risk factors, and selection bias cannot be ruled out. Also, although comparable, the irrigation and debridement procedures and culture methods were not standardized in the different hospitals. The possible bias in the use of gentamicin beads and sponges has already been mentioned.

Conclusion

Several factors were associated with treatment failure: a history of rheumatoid arthritis, duration of symptoms of more than 1 week, late infection (more than 2 years after arthroplasty), ESR at presentation above 60 mm/h, and the presence of coagulase-negative *Staphylococcus.* When 1 or more of these factors is present in a patient, one should realize that the chances of successful DAIR treatment decrease. Furthermore, when local antibiotic carriers were used, gentamicin-loaded sponges—which do not require additional removal surgery—showed outcome results comparable to those with beads, but with fewer procedures. Prospective studies will be needed to evaluate their effect on PJI and biofilm formation.

All the authors contributed to interpretation of the data and to revision of the final manuscript. JK, SV, RS, HG, DV, and PN contributed to the conception and design of the study and to provision of the study patients. JK, SV, and RS collected data. JK wrote the protocol, analyzed data, and wrote the manuscript.

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No competing interests declared.

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