

2-stage revision of 120 deep infected hip and knee prostheses using gentamicin-PMMA beads

Results after 5 (2–20) years

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Background and purpose — A 2-stage revision is the most common treatment for late deep prosthesis-related infections and in all cases of septic loosening. However, there is no consensus about the optimal interval between the 2 stages.

Patients and methods — We retrospectively studied 120 deep infections of total hip (n = 95) and knee (n = 25) prostheses that had occurred over a period of 25 years. The mean follow-up time was 5 (2–20) years. All infections had been treated with extraction, 1 or more debridements with systemic antibiotics, and implantation of gentamicin-PMMA beads. There had been different time intervals between extraction and reimplantation: median 14 (11–47) days for short-term treatment with uninterrupted hospital stay, and 7 (3–22) months for long-term treatment with temporary discharge. We analyzed the outcome regarding resolution of the infection and clinical results.

Results — 88% (105/120) of the infections healed, with no difference in healing rate between short- and long-term treatment. 82 prostheses were reimplanted. In the most recent decade, we treated patients more often with a long-term treatment but reduced the length of time between the extraction and the reimplantation. More reimplantations were performed in long-term treatments than in short-term treatments, despite more having difficult-to-treat infections with worse soft-tissue condition.

Interpretation — Patient, wound, and infection considerations resulted in an individualized treatment with different intervals between stages. The 2-stage revision treatment in combination with local gentamicin-PMMA beads gave good results even with difficult prosthesis infections and gentamicin-resistant bacteria.

dence is, since arthroplasty registries appear to miss one-third of the infections, and complex linkages with other databases are necessary to obtain reliable data (Witsø 2015).

Successful eradication of deep prosthesis infection has been reported using 1-stage and 2-stage revision, with comparable infection-free rates of approximately 90% (Lange et al. 2012, Leonard et al. 2014, Puhto et al. 2014). Even so, in most countries the preferred treatment for infection-related prosthesis loosening and late infections is a 2-stage revision: repeated debridements and antibiotic treatment for a prolonged period are possible before reimplantation or other reconstruction is performed. Stepwise decisions can be made for a particular patient and infection during treatment. There is, however, no evidence in the literature concerning the optimal length of time between extraction of the prosthesis and reimplantation (Zimmerli et al. 2004, Puhto et al. 2014).

At our institution, early and delayed deep prosthetic infections (joint age < 2 years) are preferentially treated in situ with retention of the prosthesis if there is no loosening. The results in 90 patients have been published (Geurts et al. 2013). We treat the remaining cases (where extraction of the infected prostheses is indicated) with a 2-stage revision and use local antibiotic carriers in the form of gentamicin-PMMA beads. During the course of the present study, some changes in the treatment protocol were introduced, but the cornerstone of the treatment remained unchanged: the use of a local antibiotic carrier in the form of gentamicin beads to give a high local antibiotic concentration in exudate and tissues (Walenkamp et al. 1986).

■ The main goal of this study was to determine the results of treatment of the infection of prostheses with a 2-stage revision using gentamicin-PMMA beads, with either a short interval or a long interval between the first-stage operation and the second-stage operation.

The incidence of prosthetic joint infection is 1–2%, and it may be increasing. It is difficult to ascertain what the “true” inci-

Patients and methods

In this retrospective observational study, we analyzed a cohort of all proven deep postoperative and hematogenous infections of total hip prostheses (THR) and total knee prostheses (TKR) that had been treated with extraction of the prosthesis at our center from January 1986 through December 2010. This covered early or delayed deep infections in cases of loosening, all late infections (> 2 years after implantation), all patients with poor soft-tissue conditions (fistula, gross indurations, large abscesses), patients who were significantly immunocompromised, and patients with persistent infections after previous treatment with debridement, antibiotics, and implant retention (DAIR) at another hospital.

Baseline characteristics (Table 1)

Over a period of 25 years, we treated 312 THR and TKR prosthesis infections. The results of the treatments in which 89 prostheses were not extracted but treated in situ with DAIR have already been described by us (Geurts et al. 2013). In 167 infections the prosthesis was extracted including all late infections (> 2 years after implantation), and infections with loosening (< 2 years). We excluded 47 prostheses as follows: in 18 patients, the Mayo criteria (Berbari et al. 1998) for deep infection were not met, 6 patients had already undergone an extraction at another center, 23 patients had been treated with a 1-stage revision because a low grade infection had not been diagnosed prior to the operation (but only afterwards from intraoperative cultures). We included the remaining 120 infected prostheses in 120 patients (51 men and 69 women). The age of the patients at the extraction was 62 (30–82) years. There were 95 THR infections (34 primary THRs and 61 septic or aseptic revisions) and 25 TKR infections (10 primary TKRs and 15 septic or aseptic revisions). 6 of the infections were hematogenous: 5 THR and 1 TKR. We considered deep infections as being hematogenous infections when there was no sign of prosthes-

Table 1. Baseline characteristics of patients and infections, with results of infection treatment

	Total n = 120	Success n = 105	Failure n = 15
Patient characteristics			
Age	62 (30–82)	62 (30–82)	62 (44–80)
Sex: M / F	51 / 69	42 / 63	9 / 6
ASA-1	35	63	2
ASA-2	61	57	4
ASA-3	24	15	9
Morbidities			
Smoking	24	22	2
Alcohol abuse	12	10	2
Diabetes mellitus	18	13	5
Inflammatory disease	4	3	1
Malignancy	9	8	1
Immunosuppression	1	1	0
Renal failure (dialysis)	7	3	4
Heart failure	22	18	4
Host score according to McPherson			
A - Uncompromised	60	55	5
B - Compromised	54	47	7
C - Significantly compromised	6	3	3
Host score according Cierny			
Uncompromised	43	39	4
Compromised	77	66	11
Prosthesis and infection characteristics			
Total hip	95	84	11
Total knee	25	21	4
Indication index prosthesis			
Primary arthroplasty	44	39	5
Aseptic revision	49	41	8
Septic revision	27	25	2
Infection period			
Postoperative infections, n	114	100	14
joint age, weeks	108 (2–1,407)	117 (2–779)	46 (3–1,407)
Hematogenous infections, n	6	5	1
symptoms, days	41 (7–48)	46 (7–84)	(48)
Soft tissue			
Not involved	73	63	10
Induration	2	2	0
Abscess or fistula	45	40	5
Infection score according to McPherson			
Early postoperative (< 4 weeks)	4	2	2
Hematogenous infections	5	4	1
Late postoperative (> 4 weeks)	111	99	12
Local score according to McPherson			
Grade 1 - Uncompromised	37	34	3
Grade 2 - Compromised	66	57	9
Grade 3 - Significantly compromised	17	14	3
Infection type according to Zimmerli			
Early postop. + hematogenous ^a	9	4	5
Delayed exogenous ^b	45	37	8
Delayed hematogenous ^b	1	1	0
Late exogenous ^c	61	59	2
Late hematogenous ^c	4	4	0
Preoperative blood markers			
ESR > 20 mm/h	103	88	15
CRP > 10 mg/L	91	79	12
Leucocytes > 11 x 10 ⁹ /L	16	13	3
Temperature ≥ 38.0°	24	21	3
Systemic antibiotics			
Preoperatively, n	34	27	7
i.v. postoperatively, days	35 (2–132)	32 (2–132)	51 (20–125)
Oral postoperatively, days	76 (21–221)	76 (21–221)	78 (38–166)
Total days of postoperative therapy	104 (32–251)	101 (29–251)	128 (65–203)

a < 3 months; b 3–24 months; c > 2 years

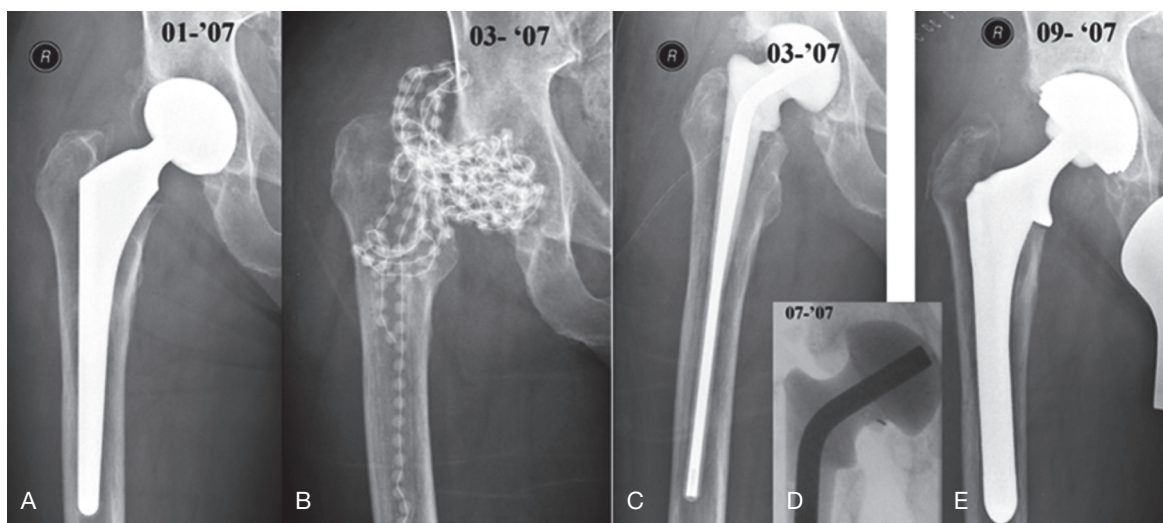


Figure 1. 2-stage revision. A. Infected hip prosthesis in a 68-year-old woman. After extraction of the prosthesis, implantation of 360 gentamicin-PMMA beads for 2 weeks (B), then exchange to a spacer for 2 months (C). D. Puncture for culture, after 2 weeks of “antibiotic holiday”. E. After re-admission, extraction of the spacer and reimplantation of a total hip.

tion, in combination with a distant focus of infection (Chen et al. 2014).

Prostheses were considered to be infected when the Mayo criteria were fulfilled: growth of the same microorganism in 2 or more cultures from synovial fluid or periprosthetic tissue, pus in synovial fluid or at the implant site, histological evidence of acute inflammation in periprosthetic tissue, or a sinus tract communicating with the prosthesis (Berbari et al. 1998).

The interval between implantation of the prosthesis and the start of treatment of the infected prosthesis (i.e. joint age) in 114 postoperative infections was 25 (0.5–325) months. In the 6 hematogenous infections, the duration of symptoms was 41 (7–84) days (Table 1).

Surgical treatment

Our treatment consisted of extraction of the prosthesis, debridement, and implantation of gentamicin-PMMA beads for 2 weeks. If necessary, the debridement and implantation of beads for 2 weeks was repeated. Finally, we performed either a reimplantation, a girdlestone procedure, an arthrodesis, or an amputation. The gentamicin-PMMA beads had a diameter of 7 mm and contained 7.5 mg gentamicin sulfate per bead, in the form of chains (60 or 30 beads, Septopal; Merck GmbH, Darmstadt, Germany; Biomet GmbH, Berlin, Germany). We implanted as many beads as possible in all infected and contaminated tissues to create a high local concentration of gentamicin: median 296 (60–540) beads for THR and 228 (60–420) beads for TKR (Figure 1). The wound was tightly closed in layers, to keep the gentamicin containing exudate in the wound. To avoid leakage of a hematoma to the subcutaneous layers, a deep and a subcutaneous drain was left for a few days. The deep drain was passive, with just syphoning in the first day to avoid too much blood loss and with suction after 1

day to reduce the hematoma. The beads did not stick through the skin, but were removed in the second operation after 2 weeks. After they became available, we used antibiotic-loaded spacers, but never for primary infection treatment—only to make space between the articulating bones when patients were discharged for a long period of time between treatments, to improve stability and facilitate reimplantation.

2-stage procedure

After 1 or more treatment periods of debridement with 2 weeks of gentamicin beads, it was decided whether the final reimplantation or reconstruction should be performed during the same hospital stay (short-term treatment), or whether it would be better to postpone it and discharge the patient, observing the result at outpatient visits (long-term treatment).

With short-term treatment, we treated 63 patients (57 THRs and 6 TKRs). 35 patients had 1 single debridement and treatment with beads for 2 weeks, 22 had 2 debridements, and 6 had 3 or 4 debridements. In 30 of the 57 THRs and 2 of the 6 TKRs, a reimplantation after short-term treatment was performed, whereas in 31 patients no reimplantation followed (in 27 hips, a girdlestone; and in 4 knees, an arthrodesis) (Figure 2). For short-term treatment, the median interval between extraction and reimplantation or other reconstruction was 14 (11–47) days.

In long-term treatment, after extraction of the prosthesis, debridements, and the initial antibiotic therapy, patients were discharged without a prosthesis but with the availability of a spacer (since 2003), increasingly more often with a spacer. In these cases, full weight bearing was not allowed, but patients were encouraged to move the joint cautiously. Patients were discharged home for a median period of 5.5 (3–21) months. This period was used to finish the antibiotic treatment and

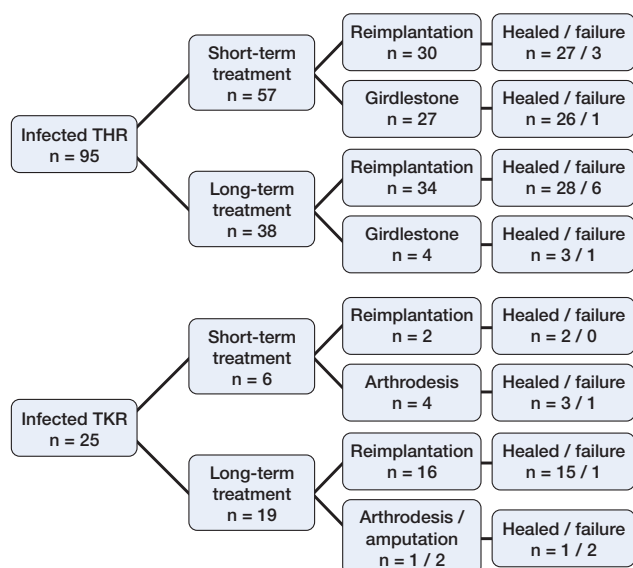


Figure 2. Diagram of treatments with data on reimplantation and healing of the infection.

to check that there was no recurrence of the infection over a period without systemic antibiotic treatment (the “holiday period”) (Sorli et al. 2012). When using spacers, an antibiotic-free period of at least 2 weeks was used before puncture of the joint for deep bacterial culture. After re-admission, the patients were reoperated. The spacer, if present, was removed, deep tissues were cultured, and the reconstruction was prepared, which in fact functioned as a final re-debridement. The reimplantation or arthrodesis was then performed, or—if healing of the infection was uncertain—gentamicin-PMMA beads were implanted again while waiting for the deep-tissue culture results.

57 patients had long-term treatment (38 THRs and 19 TKRs). 1 debridement was performed for 37 infections and 2 or more debridements were performed for 20 infections. Before the introduction of spacers in our clinic in 2003, we had discharged 16 patients without a prosthesis (15 girdlestone hips and 1 knee pseudarthrosis) for an interval of 5–21 months. After the introduction of spacers, we could more often give long-term treatment, since the joint, especially in knees, was more stable. We used spacers in 23 of 38 THR treatments and in 18 of 19 TKR treatments. After long-term treatment, reimplantation of a prosthesis was performed in 34 of 38 hips and in 16 of 19 knees. A girdlestone procedure was performed in 4 THR patients; in the knee patients, 1 arthrodesis and 2 amputations were performed (Figure 2). Altogether, in long-term treatment the median interval between extraction and reimplantation of the prosthesis was 7 (3–22) months. Patients with negative culture results received amoxicillin/clavulanate as broad-spectrum antibiotic treatment.

Systemic antibiotics

The surgical treatment was combined with systemic antibiotics—intravenously during hospitalization and continued,

Table 2. Causative microorganisms

Microorganism	Total	Success	Failure
CNS (β-lactamase positive)	32	27	5
CNS (β-lactamase negative)	14	14	0
<i>Staphylococcus aureus</i> (β-lactamase positive)	18	14	4
<i>Staphylococcus aureus</i> (β-lactamase negative)	8	8	0
MRSA	1	1	0
<i>Streptococcus</i> spp.	7	7	0
<i>Enterococcus</i> spp.	3	1	2
<i>Enterobacter</i> spp.	4	4	0
<i>Pseudomonas aeruginosa</i>	5	3	2
<i>Propionibacterium acnes</i>	4	4	0
Negative culture without antibiotics	8	8	0
Negative culture with antibiotics	2	2	0
Polymicrobial	14	12	2
Total	88	78	10

if possible, orally after discharge from hospital. The choice of antibiotic was based on the resistance pattern of the deep-tissue cultures and after consulting a microbiologist with an interest in orthopedic infections.

We stopped the oral antibiotic treatment at the outpatient clinic when clinical and laboratory parameters had been normal for at least 4 weeks. The intravenous antibiotic treatment was given for a median period of 35 (2–132) days, followed by oral treatment for 76 (21–221) days. Median total antibiotic treatment was 105 (21–251) days.

Microbiology

Swabs and synovial fluid were taken for bacterial culture and multiple tissue cultures. Cultures were taken preoperatively and peroperatively in antibiotic-free patients, so antibiotics were given peroperatively after all the samples had been taken. The samples were cultured in the microbiology laboratory for at least 3 weeks to detect slow-growing microorganisms, and minimal inhibitory concentrations (MICs) of gentamicin were determined for all bacteria detected. We found a beta-lactamase producing coagulase-negative staphylococcal strain to be the most frequent causative microorganism (32 of 120 infections) (Table 2). In 10 patients, the peroperative cultures showed no growth. 2 of these patients had ongoing antibiotic therapy.

Mixed flora caused 14 infections, with bacterial species in many combinations and coagulase-negative staphylococcal species and streptococcal species being the most frequent. The MIC of gentamicin for the causative bacteria was ≤ 2 $\mu\text{g/mL}$ in 62 infections, 2–15 $\mu\text{g/mL}$ in 15 infections, 16–64 $\mu\text{g/mL}$ in 21 infections, and ≥ 64 $\mu\text{g/mL}$ in 7 infections (Table 3). In 31 of the 120 cases, a change in the original causative bacterium to another bacterium occurred during treatment.

Follow-up

During the hospital stay, we checked the infection parameters ESR, CRP, and leukocyte differentiation twice a week,

Table 3. Minimal inhibitory concentrations (MIC) of gentamicin with results of treatment

MIC gentamicin ($\mu\text{g/mL}$)	Total	Success	Failure
< 2	62	53	9
2–15	17	15	2
16–64	24	21	3
> 64	7	6	1
Negative cultures	10	10	0
	120	105	15

and also liver and kidney function once a week, to monitor infection healing and possible toxicity of the antibiotic treatment. The follow-up period started at the first operation for deep infection and the end of the follow-up period was either the date of the last outpatient clinic visit or the date of death, whether or not it was related to the infection. We extended the follow-up by contacting the family doctor when possible. Mean follow-up was 5 (2–20) years, with the exception of 8 patients who had died before the 2-year follow-up.

The treatment of infection was considered to be successful when the infection was healed at follow-up, that is, when there were no clinical or radiological signs of recurrence after the treatment of the infection with or without a prosthesis in situ. We considered that laboratory parameters had normalized when CRP and WBC counts were normal at 2 subsequent controls, and when the ESR was less than 30 mm/h in patients without systemic diseases. Failure was assumed if the patient never became infection-free, if there was relapse of the infection, or if amputation was necessary.

Data analysis and statistics

Data are presented as either median (range) or mean (SD). All patients and types of infections were scored according to classifications by ASA, Cierny, McPherson, and Zimmerli (Cierny and DiPasquale 2002, McPherson et al. 2002, Zimmerli et al. 2004). Success and failure rates were analyzed according to these stagings and classifications.

We analyzed the influence on infection healing of the characteristics of patients and infections, the index operation, blood markers, and the pathogen (including the MIC value for gentamicin). 8 patients died within 24 months of the start of the treatment for infection, 3 of them without healing of the infection. 5 other patients died within 24 months because of poor health, but this was not related to the infection and there were no symptoms of infection.

Survival analysis of healing of infection was performed with Kaplan-Meier curves (Figure 3). In this analysis, the event of healing was considered to be the moment when the patient had been free of infection for 6 months after termination of surgical and antibiotic treatment. This period was chosen as a clinically relevant period when the diagnosis of healing could be considered to be a safe one. It corresponds well with the

time after the treatment when any relapse of infection in any of the patients had already occurred: 5.5 months.

Right-censored observations were included: this indicated, for example, patients who left the study before becoming infection-free, or that the end of the observation period had been reached. The ASA classification and the infection classification according to Zimmerli are represented as Kaplan-Meier curves, also with censoring (Figures 4 and 5).

A log-rank test was performed to determine the influence on the outcome of the characteristics of patients and infections, the index operation, blood markers, and the pathogen (including the MIC value for gentamicin). Any p-value of less than 0.05 was considered to be significant. In determining differences between the short-term and long-term treatment groups, chi-square test was used to analyze categorical variables and the Mann-Whitney U-test was used for analysis of continuous variables. Cox regression analysis was used to analyze confounding factors. We used SPSS version 22.0 for Windows.

Results

Successful treatment of the infections was achieved for 105 of 120 prostheses (88%). 15 treatments failed: 3 of the failures were never infection-free, and in 12 failures a relapse of the infection occurred (after apparent healing) between 15 and 156 days after completing the antibiotic treatment (Figure 2). 8 of the 15 failures became free of infection after another treatment regimen, in 2 of the patients with re-extraction of the reimplanted prosthesis, increasing the healing rate for infection to 94%.

In THRs, 84 of 95 infections healed. Reimplantation was performed in 64 of these 95 THRs: after 30 short-term treatments and after 34 long-term treatments, and for these reimplanted prostheses infection was resolved in 55 of the 64 patients.

In TKRs, 21 of 25 infections healed. Reimplantation was performed in 18 of the 25 patients: after 2 short-term treatments and 16 long-term treatments. The 5 arthrodeses consolidated and the infection healed.

6 hematogenous infections are included in the above results. Of these, one TKR treatment failed, and 5 hematogenous THR infections were successfully treated.

We analyzed the effect on resolution of the infection of Zimmerli classification, ASA classification, primary or revision prosthesis, and whether the infected revision itself was performed for aseptic loosening or because of infection. We found similar age and sex distributions in the success group and the failure group. There was similar outcome for infections of primary and revision prostheses. Irrespective of the original indication for the infected revision (aseptic or septic cause), there was also similar outcome. We found a higher risk of failure for ASA score 3 than for ASA score < 3 ($p = 0.01$) (Figure 4), and for early postoperative infections according

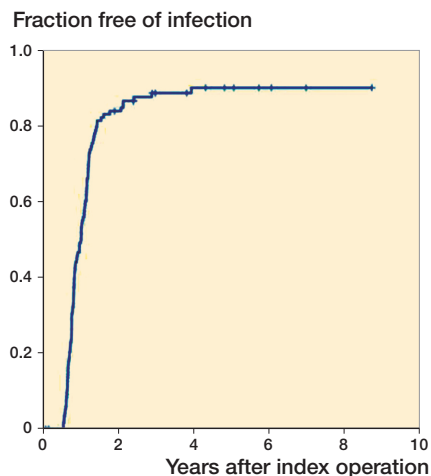


Figure 3. Kaplan-Meier curve depicting the time-to-event analysis with right-censoring, for healing of the infection. The event is healing for 6 months since the completion of the operative and antibiotic treatment.

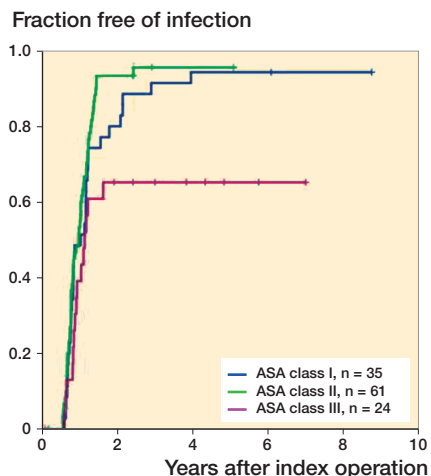


Figure 4. Kaplan-Meier curves for infection healing with strata for ASA classifications.

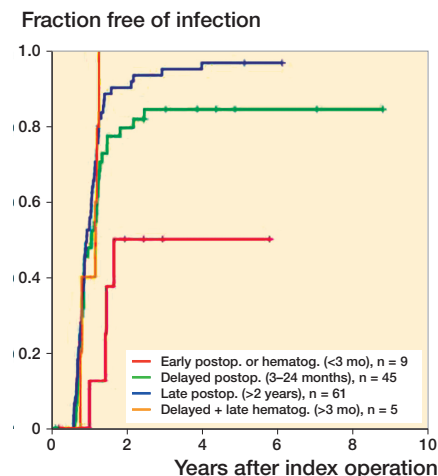


Figure 5. Kaplan-Meier curves for infection healing with strata for the classification of type of infection according to Zimmerli.

to Zimmerli ($p = 0.006$) (Figure 5). The influence of patient characteristics on these effects was analyzed but it was not statistically significant (i.e. had no confounding effect).

In the 114 surgical site infections (SSIs), the earlier the infection was treated postoperatively (i.e. the shorter the joint age), the more the treatment failed ($p = 0.001$). In the 6 hematogenous infections, the duration of the symptoms (7–84 days) had no influence on the outcome. Other patient and wound scores, other comorbidities, and preoperative infection parameters (fever, laboratory values) had no influence on the outcome.

We found no association between the result of the treatment and the primary causative bacterial species, no difference between the group of gram-positive and gram-negative bacteria, no difference between *Staphylococcus* species and *Streptococcus* species, and not more failures in beta-lactamase producing bacteria. In the last 5 years of the study period, more causative bacteria had a MIC value for gentamicin of $\geq 16 \mu\text{g/mL}$ compared to the previous 20-year period, but the success rate for resolution of the infection was the same for high and low MIC values ($p = 0.08$). During 31 of 120 treatments, the causative microorganism changed to other bacteria, and these treatments failed more often than treatments where no shift in causative bacteria occurred. The therapeutic use of antibiotics just before the start of treatment of the infection had no influence on the outcome (Table 1). The length of the intravenous antibiotic treatment postoperatively and the total length of postoperative antibiotic treatment was shorter in the successfully treated patients than in the failures ($p = 0.02$ and $p = 0.05$).

The long-term treatment group included more difficult-to-treat infections: more acute infections with a shorter prosthetic joint age and less loosening of the prosthesis ($p = 0.03$). The

causative bacteria more often had a MIC value of $\geq 16 \mu\text{g/mL}$ ($p = 0.007$). In THR, in the long-term treatment group the wound score was worse, with more fistulae ($p < 0.001$). More debridements were necessary ($p < 0.001$). TKRs were given long-term treatment more often than THR ($p = 0.001$). Despite the more difficult-to-treat infections being given long-term treatment, these cases were reimplanted more frequently than those in the short-term treatment group ($p < 0.001$).

If success was defined as the combination of resolution of infection and successful reimplantation, the treatment was successful in 71 of 120 patients (60%), and failed in 49 patients. The failure rate was higher in patients with an ASA score of 3 than in those with an ASA score of 1 or 2 ($p = 0.01$), in more compromised patients according to McPherson ($p = 0.02$), and in those with more compromised soft tissue according to Cierny ($p = 0.009$). Other covariates had no influence on the risk of failure.

Discussion

In our long study period of 25 years, the treatment of infected prostheses has gradually changed worldwide. In the 1960s, the common therapy for osteomyelitis or prostheses infections after debridement was suction-irrigation for 4–6 weeks (Willemegger et al. 1970). The development of gentamicin-PMMA beads in the 1970s, a better alternative to suction-irrigation systems, made it possible to close the wound and mobilize the patient. The main advantage was a high antibiotic delivery locally without systemic toxicity (Walenkamp et al. 1986). The introduction of spacers improved the technical possibilities for the 2-stage approach (Haddad et al. 2000). They largely facilitate the reimplantation but have an inferior release of antibiot-

Table 4. Results in the literature of treatment of infected THR and TKR with hand-made or commercial antibiotic-loaded PMM beads

First author	Year	No. of prostheses	THR/TKR	Follow-up (years)	Healed (%)	Weeks to reconstruction	Beads
Hovellius	1979	3	THR	1.5	100	3–4	Septopal®
Walenkamp	1983	41	THR/TKR	1.1	85	2–4	Septopal®
Scott	1993	7	TKR	?	100	6	hand-made
Garvin	1994	16	THR	5.7 (2–10)	100	?	hand-made
Lenoble	1995	32	THR	5 (2–11)	92	45–82	Septopal®
Haddad	2000	50	THR	5.8	92	3–52	hand-made
Taggart	2002	33	THR/TKR	5.8 (5–9.3)	97	40 (9–156)	hand-made
Hsieh	2004	70	THR	4.9 (2–8)	93	?	hand-made
Hoad-Reddick	2005	38	TKR	4.7 (2–10)	89	?	hand-made
Stockley	2008	114	THR	6.2 (0.2–15)	88	28 (9–96)	hand-made
Chen	2009	48	THR	5.6 (2–14)	96	23 (9–104)	both
This series	2015	120	THR/TKR	5 (2–20)	88	4 (1.6–102)	Septopal®

ics compared to beads, due to a largely reduced surface area and different composition of the gentamicin-loaded carrier (Greene et al. 1998, Mooijien et al. 2008). We therefore used spacers not as a tool for local antibiotic therapy, but only to make space between the articulating bones when patients were discharged during the time interval between stages in the long-term treatment group (to facilitate reimplantation) and, like other authors, continued the therapeutic application of antibiotic-loaded PMMA beads (Hovellius and Josefsson 1979, Taggart et al. 2002, Chen et al. 2009) (Table 4). Hsieh et al. (2004) compared 2 consecutive groups of patients treated with either antibiotic-loaded spacers or beads, and found that the treatment of 58 infected hip prostheses with spacers did not result in more persistent infection than in treatment of 70 prostheses with beads, despite the inadequate antibiotic elution. Patients had better function in the intervening period, but not any more at the final review after eventual reimplantation.

In this study, we excluded the infected prostheses that could be treated in situ with DAIR (Geurts et al. 2013). Thus, the more difficult infections remained; these would be more likely to have a lower success rate (Bejon et al. 2010, Joulie et al. 2011). In spite of this, the success rate is comparable to that in the literature in unselected cases: 67–95% (Beswick et al. 2012, Lange et al. 2012, Leonard et al. 2014, Sabry et al. 2014).

In most studies on revision of infected prostheses, there is an important surgical selection bias: the easy infections are treated more and more with 1-stage revision and the difficult infections with 2-stage revision (Langlais 2003, Zimmerli et al. 2004, Beswick et al. 2012, Lange et al. 2012). Most algorithms show a trend of having a less aggressive reimplantation strategy in cases with more difficult-to-treat bacteria, worse immune capacity, more complex reconstruction, or more failed treatments in the past (Zimmerli et al. 2004, Osmon et al. 2013). In our 2-stage revision approach, comparable choices are made by us in an individualized treatment approach, based on the seriousness of the infection, but taking into account the physical and psychological condition of the patient.

We preferred long-term treatment in the difficult cases to give the greatest chance that the infection would be resolved prior to reimplantation. Long-term treatments were made easier because we could use spacers to improve the function during the long discharge period and to facilitate reimplantation. Especially in TKR, the longer interval with spacers is helpful in recovering soft tissue before reimplantation can be safely performed.

We performed more long-term treatment procedures in the last decade of the study period (Figure 6), but at the same time reduced the interval between the first and last stages (Figure 7), as also described by Hansen and Spangehl (2004). The interval between extraction and reimplantation of the prosthesis, as used in 2-stage treatments, has some advantages: soft tissue has more time to recover, the systemic antibiotic therapy can be completed, and the result of treatment be observed in an antibiotic-free period. At the outpatient check-ups during the treatment, some patients appear to be insufficiently fit for reimplantation—invoking the risk of failure—or they refrain from further treatment. So we agree with other authors who have also used such a stepwise approach (Hansen and Spangehl 2004, Burnett et al. 2007, Osmon et al. 2013, Leonard et al. 2014).

Some authors have reported that treatments with an interval between extraction and reimplantation of less than 1 year have a better functional outcome than with longer intervals (Lenoble and Goutallier 1995, Joseph et al. 2003). However, the intervals might probably be reduced for both hips and knees: good results were described for a 2-stage approach with an interval of not more than 2–6 weeks for a selected population without any antibiotic resistance of the pathogen or significant compromise regarding the patient (Zimmerli et al. 2004, Trampuz and Zimmerli 2005).

The higher risk of failure that we found in patients with an ASA score of 3, high McPherson score, or renal failure has been confirmed by other authors (Sabry et al. 2014). We also found that preoperative laboratory values and body tempera-

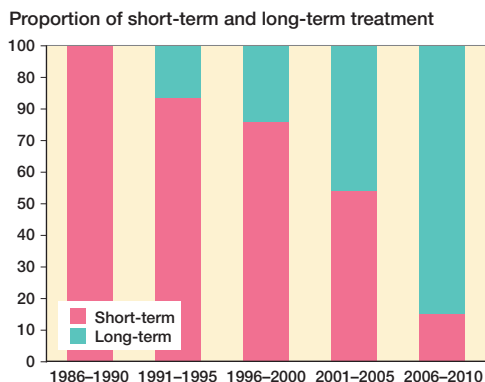


Figure 6. Proportions of short-term and long-term treatment in each 5-year period: increase in long-term treatment with time.

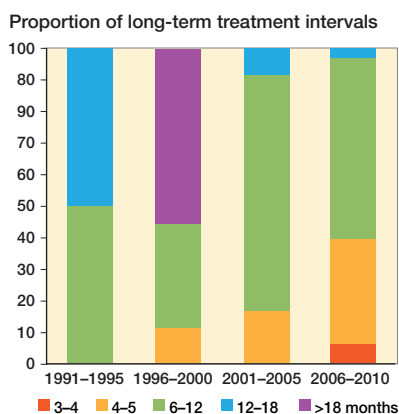


Figure 7. Intervals (months) of long-term treatment in four 5-year periods, with shorter intervals in more recent years.

ture were not predictive of failure of the infection treatment (Ghanem et al. 2009, Kusuma et al. 2011).

Our finding that there was a higher risk of failure in patients with a lower prosthetic joint age contrasts with some other reports (Zimmerli et al. 2004, Trampuz and Zimmerli 2005). But the early infections included in our study were subject to negative selection where extraction would be necessary, since the easier-to-treat infections were mainly treated in situ with a DAIR procedure, as already published (Geurts et al. 2013).

The most frequent causative microorganism in our series was coagulase-negative staphylococcus (CNS), as also published by others regarding late chronic infections (Trampuz and Zimmerli 2005, Puhto et al. 2014). If a shift in the causative bacteria cultured occurred during the treatment, the failure rate was higher—especially if a shift occurred to a more difficult-to-treat pathogen, for instance, MRSE or *Pseudomonas aeruginosa*. We have found no other data on the influence of the MIC value on the treatment of prosthesis infection in the literature, except Salvati et al. (1986), who described a patient where a treatment with gentamicin-PMMA beads was successful, despite a gentamicin MIC value of 250 µg/mL for *P. aeruginosa*.

The total length of antibiotic treatment following removal of the infected implant was between 4 weeks and 6 months, and substantially longer in the case of failures. There is no conclusive evidence regarding the ideal duration of antibiotic therapy; the recent literature recommends antibiotic therapy for between 2 and 6 weeks (Zimmerli and Ochsner 2003, Stockley et al. 2008, Osmon et al. 2013).

Discontinuation of antibiotic treatment prior to reimplantation (the “holiday” period) is used to ensure that the infection has been eradicated or to increase the reliability of a culture before or during reimplantation (Sorli et al. 2012). This antibiotic-free period, however, varies in the literature between only 2–4 days (Zimmerli and Ochsner 2003) and 6 weeks (Burnett et al. 2007). With easy-to-treat microorganisms, some authors have advised continuation of the antibiotic treatment up to the final reimplantation or reconstruction (Zimmerli et al. 2004).

Our study had some limitations. It was retrospective, and we did not study the functional outcome. Due to the long period covered, some changes in the treatment protocol were unavoidable, such as the introduction of spacers. Since our department functions as a tertiary referral center for orthopedic infections, patients were probably selected who were more often difficult to treat compared to other centers, which may have influenced the rate of reimplantation. The strength of our study was the consistent use of gentamicin-PMMA beads as a highly bactericidal tool used locally to achieve infection healing. Also, the 2-week stepwise treatment approach, inherent in proper use of the beads, was unaltered during the entire study period. The choice of interval between the 2 stages was based on surgical judgement of risk factors that did not change importantly in time, although the length of the interval gradually became shorter. This is the largest series in which the results of treatment of prosthesis infections with antibiotic-loaded PMMA beads have been studied, even more so when considered in combination with our previously published series of non-extracted prostheses: 210 prosthetic infections in total.

In conclusion, treatment of an infected prosthesis is a patient- and infection-dependent procedure where matching is important, in our case balancing between short-term treatment and long-term treatment. With our treatment, the healing of the infection is the first and main goal; reimplantation is only performed if infection healing is appropriate. As in other series, our results are based on a choice of therapeutic modalities without sound evidence from well-designed trials. The use of local antibiotics with gentamicin-impregnated PMMA beads is helpful, especially in bacteria with high gentamicin resistance. In our treatments, spacers are mainly useful to maintain better joint function with long interval periods, and they should preferably not be used for treatment of the infection itself, since they do not result in high exudate levels of gentamicin. In our approach, there was a tendency to give more high-risk infections long-term treatment, but with a shorter interval between the 2 stages.

GW and JG treated the patients. GW and DJ designed the study. DJ collected the data from the medical records and completed the follow-up. DJ and LJ performed the statistical analysis. All the authors contributed to interpretation of the data and to writing and revision of the manuscript.

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