MAJOR ARTICLE

Treatment of Joint Prosthesis Infection in Accordance with Current Recommendations Improves Outcome

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Background. Recently recommended treatment modalities for prosthetic joint infection (PJI) were evaluated.

Methods. A retrospective cohort analysis of 68 patients with PJI of hip or knee who were treated from 1995 through 2004 was conducted at the University Hospital Bern (Bern, Switzerland).

Results. A 2-stage exchange was the most frequent (75.0%) surgical strategy, followed by retention and debridement (17.6%), 1-stage exchange (5.9%), and resection arthroplasty or suppressive antimicrobial treatment (1.5%). The chosen strategy was in 88% agreement with the recommendations. Adherence was only 17% for retention and debridement and was 0% for 1-stage exchange. Most PJIs (84%) were treated with an adequate or partially adequate antimicrobial regimen. Recurrence-free survival was observed in 51.5% of PJI episodes after 24 months of follow-up. The risk of treatment failure was significantl higher for PJI treated with a surgical strategy other than that recommended (hazard ratio, 2.34; 95% confidenc interval, 1.10–4.70; $P = .01$) and for PJIs treated with antibiotics not corresponding to recommendations (hazard ratio, 3.45; confidenc interval, 1.50–7.60; $P = .002$). Other risk factors associated with lack of healing were a high infection score at the time of diagnosis (hazard ratio, 1.29; 95% confidenc interval, 1.10–1.40; $P < .001$) and presence of a sinus tract (hazard ratio, 2.35; 95% confidenc interval, 1.10–5.0; $P = .02$).

Conclusions. Our study demonstrates the value of current treatment recommendations. Inappropriate choice of conservative surgical strategies (such as debridement and retention) and inadequate antibiotic treatment are associated with failure.

Prosthetic joint infection (PJI) is a severe complication, causing significan morbidity and health care costs [1–3]. Much progress has been made in the prevention and management of PJI [4, 5]. Nevertheless, absolute numbers of PJIs are increasing because of a rise in the number of trauma and older patients requiring joint replacement [6]. Treatment of PJI includes surgical intervention(s) and antimicrobial therapy. Curative surgical strategies vary in their invasiveness from debridement and retention of the infected prosthesis to 2-stage exchange with or without the placement of a spacer or an extension device. Factors to be considered for the choice of the appropriate treatment modality are the conditions of the bone and soft tissue, the virulence and antimicrobial susceptibility of the pathogen, the general health status of the patient, and the experience of the surgeon [4]. To date, only 1 randomized study for the treatment of infection associated with orthopedic devices has been conducted [7]. This study was restricted to PJI and internal fixatio devices with short duration of symptoms, caused by *Staphylococcus aureus*, and amenable to an oral regimen of rifampicin and ciprofloxacin Recently, treatment recommendations have been published that cover a much broader spectrum of PJI [3]. The rationale of these guidelines was based on data from experimental and clinical studies, including animal experiments, case series, and the 1 randomized trial mentioned above [7]. Also, 2 prospective surveillance studies showed high success rates for PJIs treated in accordance with the suggested algorithm [8, 9]. However, these 2 studies were performed in the same center, and a relatively high proportion of PJIs was treated with debridement and retention or a 1-stage replacement strategy indicative of less severe PJI with lower risk of treatment failure.

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The applicability of this algorithm to other patient populations remains to be evaluated.

The aim of the present study was to evaluate the external clinical validity of this treatment recommendation and to analyze risk factors for treatment failure in a retrospective cohort study of 68 consecutive episodes of PJI.

METHODS

Study setting. The University Hospital of Bern (Bern, Switzerland) is an ~1000-bed tertiary care center with >30,000 admissions per year. The referral area covers the local region, with a population of ~1 million inhabitants, and includes a large number of smaller hospitals within and outside the Bernese region. The Clinic for Orthopedic Surgery performs ~140 hip and ~80 knee prosthesis implantations per year. Written perioperative infection control guidelines are employed. The operating theater has laminar flo ventilation, and cefuroxime is used routinely for perioperative prophylaxis. The clinic serves as the local reference center for difficult-to-t eat orthopedic conditions, including PJI. During the evaluation period, the choice of the treatment strategy for PJI was at the discretion of the surgeon, with or without consultation with the infectious diseases team.

Study design and study population. The study was performed according to local ethical guidelines. In a retrospective cohort design, all patients who underwent a hip or total knee arthroplasty and who received a diagnosis of PJI at our Orthopedic Clinic from 1 January 1995 through 31 December 2004 were included.

Study patients were identifie using the clinic's patient information system. Microbiological data were retrieved from the laboratory information system of the Institute for Infectious Diseases, University of Bern (Bern, Switzerland). Socioeconomic characteristics and clinical patients' data were collected from the clinical charts through use of a standardized questionnaire. The terms and definition that were used are presented in table 1.

Statistical analysis. All analyses were performed with StatView, version 5.0 (SAS Institute). Differences between means were tested by Student's t test or the Mann-Whitney U test, and proportions were compared using the χ^2 test or Fisher's exact test, as appropriate. The probability of prosthesis survival within 24 months after implantation was estimated using the Kaplan-Meier survival method. Risk factors for treatment outcome identifie by univariate statistics were entered into a Cox regression model. The fina model contained the largest number of variables with $P \leqslant .05$. A 2-tailed P value $\leqslant .05$ was used as the cutoff value for all statistical analyses.

Table 1. Definitions of terms for a study of prosthetic joint infection (PJI).

Term	Definition
PJI[a]	Presence of a sinus tract communicating with the joint space or a positive bacterial culture result for at least 2 intraoperative tissue specimens or a joint aspirate specimen or the presence of neutrophils in tissue specimens or intraoperative purulence
Timing of PJI	Relative to prosthesis implantation: (1) early, <3 months; (2) delayed, 3–24 months; (3) late, >24 months
Long-term PJI	Duration of symptoms ⩾3 weeks before diagnosis
Episode of PJI	Beginning with diagnosis of PJI at study center and ending at end of the follow-up time or treatment failure
Infection score	According to Zimmerli et al. [11], with the following adaptations (maximal score, 17): (1) a maximum of 1 point each for local redness and warmth and (2) no score for local induration
Comorbidity	Charlson Comorbidity Index [12]
Immunosuppression	(1) Steroid therapy (⩾20 mg of prednisone per day) during the 2 months before PJI onset, (2) chemotherapy or radiotherapy, (3) neoplastic disease, and (4) connective-tissue disease
Surgical strategy	(1) Debridement and device retention, (2) 1-stage exchange with removal of the infected prosthesis and reimplantation of a new prosthesis in the same procedure, (3) 2-stage exchange (interval between resection and reimplantation), (4) palliative (long-term suppressive oral antimicrobial therapy or permanent explantation or joint arthrodesis [girdlestone]) [3]
Antimicrobial treatment category	(1) Adequate (total duration of ⩾3 months, duration of therapy administered intravenously ⩾2 weeks, use of agent-appropriate drugs according to susceptibility testing and clinical studies, use of antibiotics with efficacy against surface-adhering bacteria, if possible), (2) partially adequate (duration of at least 2 but <3 months and/or <2 weeks of therapy administered intravenously), (3) inadequate (antimicrobial treatment not corresponding to the above or no antimicrobial treatment) [8]
Healing	Absence of clinical and radiological and, if applicable, intraoperative signs and symptoms of PJI and sterile culture samples from intraoperative specimens obtained at reimplantation of the prosthesis or any other surgical procedure involving the joint during the 24-month follow-up time; "probable healing" was defined as above, but with a follow-up period of close to 2 years (20-24 months) [8]

[a] Based on the definition of Berbari et al. [10].

Table 2. Sociodemographic characteristics and clinical history of patients with prosthetic joint infection.

Variable	Patients (n = 68)
All infection episodes	68 (100)
Age, mean years ± SD	67.1 ± 11.7
Male sex	47 (69.1)
Prosthesis implantation site[a]	
Study center	14 (20.6)
External center	49 (72.1)
Unknown	5 (7.4)
Duration of symptoms[b]	
<3 weeks	29 (42.6)
⩾3 weeks	37 (54.4)
Unknown	2 (3.0)
Type of infection	
Early	6 (8.8)
Delayed	30 (44.1)
Late	32 (47.1)
Treatment of PJI ⩾14 days before referral	28 (41.2)
Sinus tract	14 (20.6)
Infection score, mean score ± SD	8.1 ± 3.0
Surgical strategy	
Retention and debridement	12 (17.6)
1-Stage exchange	4 (5.9)
2-Stage exchange	51 (75.0)
Suppressive antimicrobial treatment	1 (1.5)

NOTE. Data are no. (%) of patients, unless otherwise indicated.
[a] Information on implantation site was lacking in 10 episodes.
[b] In 2 episodes, duration of symptoms was unknown.

RESULTS

Demographic and clinical characteristics. This retrospective study identifie a total of 68 PJI episodes in 68 patients treated at our center from 1996 through 2004 (table 2). Most PJIs (60 PJIs; 88%) affected hip prostheses. The mean age ± SE of patients was 67 ± 12 years, the patients were predominantly male (47 men; 67.6%) and had a mean ± SE of 1–2 ± 1.6 comorbidities. The incidence of drug abuse (in 1 patient; 1.4%) and immunosuppression (among 6 patients; 8.8%) was low. In 14 (20.6%) of the episodes, the prosthesis was implanted at our center. Therefore, the surgical infection rate was 1.2% (for 60 patients) for hip and 0.4% (for 8 patients) for knee prosthesis implants during the 10-year study period.

In 28 episodes (41%), the PJI had been treated for >14 days at another institution before referral to our center; the duration of previous treatment was <3 months in 7 (25%) of these episodes and was ⩾3 months in the remaining 21 (75%) episodes. The mean infection score ± SE at the time of PJI diagnosis was 8 ± 3 points (table 2).

Microbiology. Sixty-seven of the 68 PJIs were microbiologically confi med. In 52 episodes (76%), culture revealed a single microorganism. *S. aureus* was the most common pathogen, followed by a polymicrobial flora streptococci, and coagulase-negative staphylococci (table 3). In all polymicrobial episodes, staphylococci were involved. In 4 of the 15 episodes of polymicrobial PJI, there was a sinus tract.

Treatment strategy. A 2-stage exchange was the most commonly (51 episodes; 75%) pursued surgical strategy (table 2); the 2-stage strategy was in 88% (44 of 51 episodes) agreement with the recommendations by Zimmerli et al. [3]. Adherence was lower for the less invasive strategies: 17% (2 of 12 episodes) for retention and debridement and 0% (0 of 4 episodes) for 1-stage exchange. One course of suppressive therapy was in agreement with recommendations. A high number of episodes (57 episodes; 84%) of PJIs was treated with an adequate or partially adequate antimicrobial regimen (table 4).

Outcome. Thirty-nine (57%) of 68 patients with PJI had a successful outcome at 24 months of follow-up. Two patients with a follow-up time of 21 months were classifie as having probably been healed. Figure 1*A* shows the Kaplan-Meier curve for treatment failure–free survival. The probability of survival without treatment failure was 54% after 1 year and was 52% after 2 years. The 29 treatment failures comprised persisting infection or a new infection in 12 episodes (41%) each; in 5 episodes (17%), death occurred as a consequence of PJI. Success rates were 50% after retention and debridement, 0% after 1-stage exchange, and 65% after 2-stage exchange. The healing rate was 55% (6 episodes) for the 11 streptococcal infections, 100% (2 episodes) for the 2 enterococcal infections, and 53% (8 episodes) for the 15 PJIs due to a polymicrobial flora

Table 4 summarizes the characteristics of the antimicrobial treatment administered. When antimicrobial treatment was ad-

Table 3. Microbiological characteristics of 68 episodes of prosthetic joint infection.

Microbiological characteristic	No. (%) of episodes (n = 68)
Single microorganism[a]	52 (76.5)
Staphylococcus aureus	26 (38.2)
Coagulase-negative staphylococci	9 (13.2)
Streptococcus species	11 (16.2)
Enterococcus species	2 (2.9)
Gram-negative rods	2 (2.9)
Anaerobes	1 (1.5)
Propioni species	1 (1.5)
Polymicrobial	15 (22.0)
Microorganism unknown	1 (1.5)

[a] Methicillin resistance was observed in 1 isolate of *S. aureus* and in 13 of 19 isolates of coagulase-negative staphylococci (including isolates from polymicrobial infections).

Table 4. Outcome of 68 episodes of prosthetic joint infection according to antimicrobial treatment.

Variable	No. (%) of episodes
All infection episodes	68 (100)
Antimicrobial treatment[a]	
Adequate	32 (47.1)
Partially adequate	25 (36.8)
Inadequate	11 (16.2)
Antimicrobial treatment ⩾90 days	40 (58.8)
Intravenous treatment ⩾14 days	50 (73.5)
Type of oral treatment	
Rifampin combination	40 (58.8)
Clindamycin	7 (10.3)
Betalactam	7 (10.3)
Other	6 (8.8)
Intravenous treatment only	6 (8.8)
No antimicrobial treatment	2 (3.0)

[a] Based on Giulieri et al. [8].

equate or partially adequate, treatment success rates were 72% and 56%, respectively. Episodes treated with inadequate antimicrobial regimens had a very low (18%) success rate.

The success rate was highest (67%; 43 episodes) when the surgical strategy met current recommendations and antimicrobial treatment was adequate or partially adequate ($P < .001$, by log rank test) (figu e 1*B*). PJI treated with either a surgical strategy or an antimicrobial regimen as recommended ($n = 19$) still had a success rate of 52%. None of the 6 PJIs treated with neither a surgical strategy nor an antimicrobial regimen meeting recommendations was healed.

Risk factors for treatment failure. Table 5 presents univariate risk factors for treatment failure. Significan risk factors were the presence of a sinus tract (hazard ratio [HR], 2.3; 95% CI, 1.1–5.0; $P = .02$), a high infection score (HR, 1.30; 95% CI, 1.1–1.4; $P < .001$), a choice of surgical strategy different from those recommended (HR, 2.3; 95% CI, 1.1–4.7; $P = .01$) [3], and inadequate antimicrobial treatment (HR, 3.4; 95% CI, 1.5–7.6; $P = .002$). In the multivariate Cox regression analysis, the following factors were independent risks for therapy failure: a high infection score (HR, 1.24; 95% CI, 1.10–1.40; $P < .001$), choice of a surgical treatment strategy in disagreement with published recommendations (HR, 1.96; 95% CI, 0.97–3.95; $P = .05$) [3], and an inadequate antimicrobial regimen [5] (HR, 2.79; 95% CI, 1.21–6.45; $P = .01$).

DISCUSSION

This study found that treatment of PJI in accordance with currently recommended algorithms [3, 11] is associated with a significantl better outcome, compared with nonrecommended treatment. Both the choice of the surgical strategy and the antimicrobial treatment played an important role in the overall treatment success. Two earlier studies reported similar results, but both studies were conducted at 1 center and included a relatively high proportion of PJIs treated with less invasive surgical strategies. Our study demonstrates the applicability of the recommendations of Zimmerli et al. [3] to a patient population with relatively high proportions of treatment failures before referral to our center (41%), polymicrobial infection (22%), episodes involving a sinus tract (21%), and, consequently, 2-stage exchange procedures (75%).

The mean healing rate of 57% observed in our study was low in comparison with rates reported by Giulieri et al. (83%) [8], Trampuz et al. (90%) [13], Tsukayama et al. (91%) [14], and Meehan et al. (89%) [15]. However, this is likely explained by different characteristics of PJI episodes. As mentioned above, our study population included a high proportion of episodes

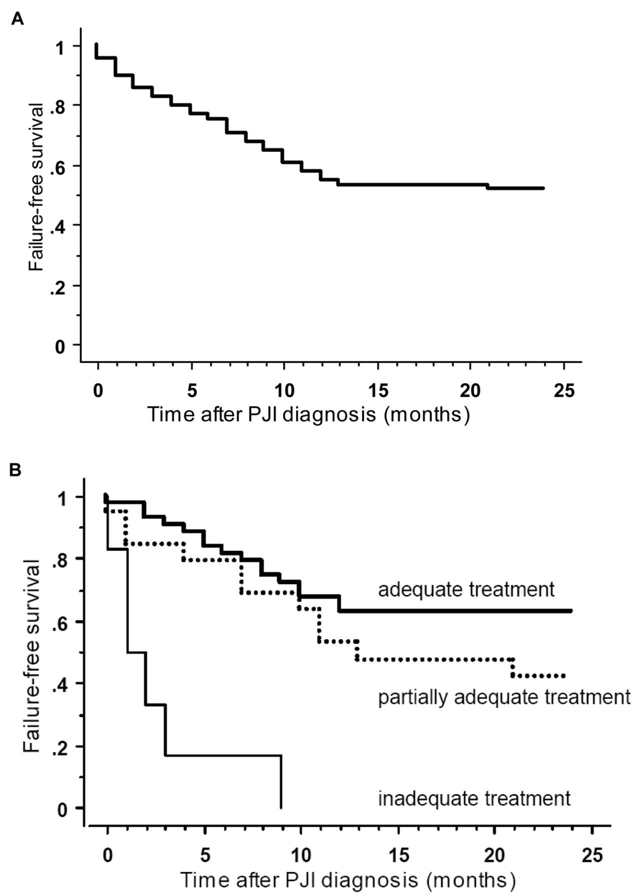

Figure 1. *A,* Kaplan-Meier curve of the proportion of patients whose prostheses remained treatment failure–free during follow-up. *B,* Kaplan-Meier curve by treatment group ($P < .001$, by log rank test). *Dark black line,* surgical strategy in agreement with recommendation and adequate or partially adequate antimicrobial treatment; *dotted line,* surgical strategy not aligned with recommendations or inadequate antimicrobial treatment; *light black line,* surgical strategy in disagreement with recommendations and inadequate antimicrobial treatment. PJI, prosthetic joint infection.

Table 5. Univariate analysis of risk factors for treatment failure among 68 patients with prosthetic joint infection.

Variable	Treatment failure (n = 29)	Healed (n = 39)	HR[a] (95% CI)	P
Age, mean years ± SD	70.6 ± 12.5	64.5 ± 10.4	1.03 (0.99–1.10)	.12
Charlson Comorbidity Index, mean score ± SD	1.9 ± 2.0	1.4 ± 1.3	1.09 (0.89–1.30)	.42
Immunosuppression	4 (13.8)	2 (5.1)	1.87 (0.66–5.30)	.24
Duration of symptoms <3 weeks	13 (44.8)	24 (61.5)	1.71 (0.80–3.40)	.14
Mean infection score ± SD	9.4 ± 2.8	7.1 ± 2.7	1.29 (1.10–1.40)	<.001
Sinus tract	10 (34.5)	4 (10.3)	2.35 (1.10–5.0)	.02
Inadequate antimicrobial treatment	9 (31.0)	2 (5.1)	3.45 (1.50–7.60)	.002
Surgical strategy not as recommended[a]	12 (41.4)	8 (20.5)	2.34 (1.10–4.70)	.01

NOTE. Data are number (%) of patients, unless otherwise indicated. HR, hazard ratio.
[a] Based on Giulieri et al. [8].

qualifying for a 2-stage procedure, which indicates more-advanced disease and/or more–difficult-to-t eat microorganisms. The healing rate after 2-stage exchange was 90% in the study by Giulieri et al. [8], 85% in the study by Laffer et al. [9], and 80% in the study by Trampuz et al. [13], compared with 68% in the present study.

A comparison of this study with other reports [1, 16, 17] is hampered by the fact that those studies included different patient populations and/or did not use similar algorithms for the choice of treatment strategies. Overall treatment success was 56% in a high-risk population with rheumatic disease, of whom 19% were treated with 2-stage exchange and 37% were treated with resection arthroplasty [16]. However, Marculescu et al. [17] showed a success rate of 60% with use of debridement and retention for patients with sinus tract and unstable prosthesis. The study by Brandt et al. [1] reported a success rate of 90% after a 2-stage exchange procedure, but that study was restricted to PJI due to *S. aureus,* and early treatment failures were excluded.

The present study also evaluated risk factors for treatment failure. Independent risk factors were advanced infection (i.e., a high infection score) at start of treatment and lack of adherence to the recommendations of Zimmerli et al. [3] for the choice of the surgical management and antimicrobial treatment. Among the studies compared, healing rates were highest for complete agreement in the present study (67%) and in the study by Giulieri et al. (88%) [8].

The choice of a surgical strategy in agreement with the algorithm increased healing rates from 40% to 60% in the present study, from 62% to 88% in the study by Giulieri et al. [8], and from 86% to 92% in the study by Laffer et al. [9]. The type of surgical treatment was also the most important predictor of treatment failure in the study by Berbari et al. [16]. Adherence to current antimicrobial treatment recommendations increased success rates from 18% to 65% in the present study, from 50% to 87% in the study by Giulieri et al. [8], and from 60% to 93%–100% in the report by Laffer et al. [9]. In our study, the assessment that there was a lack of adequate antimicrobial treatment was often because the duration of treatment was shorter than recommended. Compliance with long-term therapy after hospital discharge is often difficul to control and poses a challenge to improvement strategies. Overall, our study demonstrates the value of current surgical and antimicrobial treatment recommendations in an expanded patient population.

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