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ORIGINAL ARTICLE

Clinical characteristics, microbiology, and outcomes of prosthetic joint infection in Taiwan

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Background: Prosthetic joint infection (PJI) after total knee or hip replacement is a devastating complication associated with substantial morbidity and economic cost. The incidence of prosthetic joint infection is increasing as the use of mechanical joint replacement increases. The treatment approach to prosthetic joint infection is based on different clinical situations such as a patient's comorbidities, epidemic microbiology data, and surgical procedures. The aim of our study was to understand clinical characteristics of prosthetic joint infection, the microbiology of the prosthetic joint infection, and the outcomes of different treatment strategies during 2006–2011.
Methods: We retrospectively collected cases of prosthetic joint infection in the National Taiwan University Hospital between January 1, 2006 and December 31, 2011. The patients' characteristics, microbiology, outcomes, and factors associated with treatment success were recorded.
Results: One hundred and forty-four patients were identified as having PJI. Of these, 92 patients were entered into per-protocol analysis. *Staphylococcus aureus* was the most common causative organism (29.9%), followed by coagulase-negative *Staphylococci* (16.7%), and *Enterococci* (9.7%). The overall treatment success rate was 50%. Patients who received a two-stage revision had a better outcome, compared to patients who underwent other types of surgeries (70% vs. 32.7%, respectively; $p < 0.001$). In multivariate analysis, the two-stage

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revision was significantly associated with treatment success (odds ratio = 3.923, 95% confidence interval = 1.53–10.04).
Conclusion: Our study demonstrates that *Staphylococcus aureus* was the most common causative organisms in PJI. Performing two-stage revisions was significantly associated with a better outcome.

Introduction

Because of changing lifestyles and prolonged longevity, there is an increasing prevalence of osteoarthritis among the elderly.[1] The symptoms of osteoarthritis affect a patient's normal activity and may reduce a person's function. Arthroplasty improves a patient's quality of life and is highly cost effective.[2,3] However, prosthetic joint infection (PJI) after total knee or hip replacement is a devastating complication associated with substantial morbidity and economic cost.[4] The frequency of PJI is increasing as the use of mechanical joint replacement increases. The incidence of PJI of these arthroplasties is between 1% and 2%.[5] Management of infection in arthroplasty poses the challenge of eradicating the infection. The two-stage revision is the most common approach to PJI in many countries.[6,7] A recent meta-analysis including—926 two-stage knee joint revisions—report an 82%–100% success rate.[8] The treatment success rates described for two-stage revisions for hip prostheses ranges from 75% to 90%.[9–12] However, the approach to management is based on different clinical situations, a patient's comorbidities, and surgical risks.[13] In this study, we analyzed the clinical characteristics, microbiology, and the outcomes of different treatment strategies for PJI in a medical center during 2006–2011.

Materials and methods

Study design

This was a retrospective chart review of all cases of PJI in the National Taiwan University Hospital between January 1, 2006 and December 31, 2011. The study was approved by the ethics committee of NTUH.

By using hospital activity coding databases (*International Classification of Diseases-edition 9*; code 996.66)[14] Patients were managed by infectious disease physicians and orthopedic surgeons in a multidisciplinary team. We included all patients with PJI. PJI was defined as the clinical syndrome of arthroplasty infection (i.e., any persistent inflammation in the tissues around the implant, wound discharge, or implant loosening) with one or more of the following: bacterial growth of an indistinguishable organism from two or more deep periprosthetic tissue samples; histology of the periprosthetic tissues indicative of infection; or a persistent sinus tract.[15] Excluded from analysis were patients who were <20 years old, who experienced an open reduction with internal fixation (ORIF) infection, or who had missing data after reviewing the charts.

Definitions

We defined treatment success as a patient being free of symptoms and discontinuing antibiotics after the management of a PJI for more than 1 year. Treatment failure was defined as one of the following: (1) the recurrence of the same PJI because of the original microorganism at any time after the first intervention (i.e., relapse of infection); (2) the recurrence of the same PJI because of a different strain of a microorganism or a different microorganism (i.e., reinfection) at any time after the first intervention; (3) the presence of an acute inflammation in the periprosthetic tissue on histopathological examination or at any subsequent surgery on the joint; (4) the development of a sinus tract to the joint; or (5) death from PJI. A PJI-related death was defined as death directly caused by sepsis due to active PJI symptoms and without other infection focus detected by an infectious disease specialist.[16] Recurrent infection (relapse and reinfection) or persistent infection was defined as swelling and pain of the joint or sinus tract drainage, elevated C-reactive protein (CRP), persistent positive culture after interventions during follow-up examinations at the clinic. Patients who were followed up for at least 1 year were included in the per-protocol analysis (Fig. 1). Prosthetic joint infection has been characterized as "early" (i.e., developing within the first 3 months after surgery), "delayed" (i.e., occurring 3–24 months after surgery), and "late" (i.e., occurring >24 months after surgery).[17]

Data collection

From the medical records, we collected data on patient demographics, comorbidities (e.g., diabetes, chronic kidney disease, liver disease, hypertension, chronic lung disease, rheumatoid arthritis, and malignancy), the site of arthroplasty, date of surgical intervention, different interventions (e.g., debridement and retention of prosthesis, debridement with removal of the implant, one-stage revision, two-stage revision, and medical treatment only), antibiotic treatment duration, and microbiology data (obtained from synovial fluid culture, deep tissue culture, and blood culture).[18]

Statistical analysis

All statistical hypothesis testing was assessed with 0.05 level of significance. The outcome was analyzed by using the Chi-square test or the Fisher's exact test. Descriptive

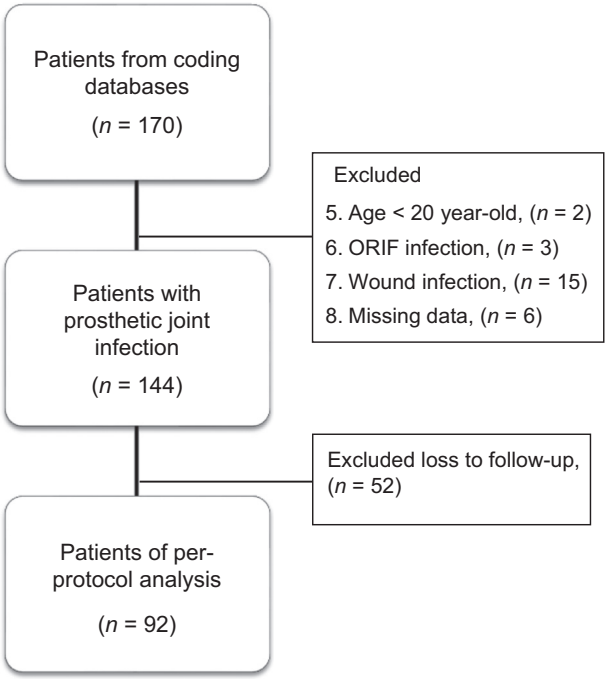

Figure 1. Diagram of patients with infected prosthetic joint, based on per-protocol analysis.

statistics such as the mean, standard deviation, and 95% confidence interval was used for the continuous variables. Categorical variables were summarized by counts and percentage in the frequency table. Variables in the univariate analysis with $p < 0.2$ were entered in the multivariate analysis by using the multiple logistic regression method. The data were censored from follow-up after the infection recurred or when the patient was lost to follow-up. All statistical analyses were performed by using the software SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Demographic characteristics

One hundred and forty-four patients were included in the study. The mean age was 68 years (standard deviation, 13.1 years). There were 81 (56.2%) female patients. The knee was the most commonly infected site (61.1%). Half (56.9%) of the patients had hypertension, 34% of the patients had diabetes, 11.1% of the patients had chronic lung disease, 11.8% of the patients had liver disease, and 13.9% of the patients had chronic kidney disease. In addition, 6.3% of the patients had a malignancy and 5.6% of the patients had rheumatic arthritis. One hundred and sixteen (80.6%) patients had primary revision prosthesis and 28 (19.4%) patients had a secondary revision prosthesis. Most (59.02 %) patients had a late prosthesis joint infection (i.e., the time since the first prosthesis joint infection was >1 year), followed by 18.8% of patients with delayed PJI, and 19.4% of patients with early PJI. Fifty-eight (40.3%) patients received a two-stage revision. A total of 33.3% patients did not receive antibiotics after reimplantation during follow-up. The median duration of intravenous or oral antibiotic use after reimplantation was 6.1 weeks (range, 1—114 weeks; Table 1).

Microbiology results

The causative pathogens included Gram-positive cocci, (64.6%), Gram-negative bacilli (21.5%), *Candida* species (0.7%), and *Mycobacterium tuberculosis* (0.7%). The most common causative organisms were *Staphylococcus aureus* (29.9%), coagulase-negative staphylococci (16.7%), and enterococci (9.7%). The rate of culture negative infection was 18.8%. Concomitant positive blood culture was 7.6% (Table 2). *S. aureus* was cultured less frequently from the knee joint than from non-knee joints (23.9% vs. 39.3%, $p = 0.049$). However, this microorganism was not associated with primary or secondary revision prosthesis.

Outcomes

In the per-protocol analysis, 46 (50%) patients were treated successfully. Only patients who received the two-stage revision surgery had a better treatment outcome [65.2% (success) vs. 28.3% (failure); $p < 0.001$]. Patients who received debridement while retaining the implant had a higher treatment failure rate [13% (success) vs. 41.3% (failure); $p = 0.002$]. There was no significant differences in age, sex, comorbidities, steroid or immunosuppressive therapy, prosthetic location, type of prosthesis, or other infective organisms (Table 3). There was no difference in the treatment failure group with or without methicillin-resistant *Staphylococcus aureus* (MRSA; $p = 0.536$). Positive blood culture was 15.2% in the treatment failure group and 4.3% in the treatment success group; however, there was no significant difference ($p = 0.207$). The mean age tended to be older in the non—two-stage revision group (71.4 years) than in the two-stage revision group (67.9 years); however, there was no significant difference ($p = 0.081$).

The two-stage revision group most frequently had a primary type prosthesis, but the non—two-stage group more frequently had the secondary type prosthesis. Twenty-nine (51.7%) patients needed repeated debridement and were predominantly in the debridement with retention of prosthesis group. Only 3 (10.3%) patients in the medical treatment group received repeated debridement. However, all positive blood cultures were in the non—two-stage revision group (18.4%). There was no positive blood culture in the two-stage revision group (0%; $p = 0.008$; Table 4).

On multivariate analysis, only the two-stage revision was significantly associated with treatment success [odds ratio (OR) = 3.923, 95% confidence interval (CI): 1.53—10.04; Table 5]. On follow-up at 2 years, 34 patients had experienced a recurrent infection. Of these patients, 9 (26.5%) patients in the two-stage revision group and 25 (73.5%) patients developed a recurrent infection ($p = 0.036$). The Kaplan-Meier plot also demonstrated a recurrent infection rate of PJI over time, which was significantly increased in the non—two-stage revision group during follow-up in our study period ($p = 0.003$; Fig. 2).

Table 1 Demographic features of 144 patients with prosthetic joint infection

Demographic characteristics	$N = 144$	%
Age, mean (SD)	68.9 (13.1)	
Sex		
Male	63	43.8
Female	81	56.2
Joint		
Hip	52	36.1
Knee	88	61.1
Elbow	4	2.8
Comorbidities		
Diabetes	49	34
Hypertension	82	56.9
Chronic lung disease	16	11.1
Liver disease	17	11.8
Chronic kidney disease	20	13.9
Malignancy	9	6.3
Rheumatic arthritis	8	5.6
Immunosuppressive therapy or steroid use	9	6.3
Prosthesis		
Primary	116	80.6
Secondary	28	19.4
Time from first prosthesis joint replacement to prosthetic joint infection[a]		
Early (≤3 mo)	28	19.4
Delayed (>3 mo to ≤1 y)	27	18.8
Late (>1 y)	85	59
Missing data	4	2.8
Procedure		
Debridement with retention of the prosthesis	35	24.3
Debridement with removal of the implant	25	17.4
One-stage revision	2	1.4
Two-stage revision	58	40.3
Medical treatment only	24	16.7
Gap between the two stages		
<2 mo	23	39.7
2–4 mo	21	36.2
>4–12 mo	11	19
>1–2 y	2	3.5
>2 y	1	1.7
Outcome		
Success	46	31.9
Failure	98	68.1
Antibiotic treatment duration after reimplantation (1 and 2 stage)[b]		
None	19	33.3
<1 wk	0	0
≥1–<6 wk	15	26.3
≥6 wk–<6 mo	14	24.6
≥6 mo–<1 y	8	14
≥1 y	1	1.8

[a] The time interval is described as the first time of prosthetic joint replacement to the onset of prosthetic joint infection.
[b] The antibiotic treatment duration is calculated as the time after discharge.
SD = standard deviation.

Table 2 The microbiology of prosthetic joint infection

	N (%)
Aerobic Gram-positive	
Staphylococcus aureus	43 (29.9)
MSSA	28 (19.4)
MRSA	15 (10.4)
Coagulase-negative staphylococci	24 (16.7)
Streptococci	12 (8.3)
Enterococci	14 (9.7)
Aerobic Gram-negative	
Escherichia coli	4 (2.8)
Klebsiella pneumoniae	3 (2.1)
Pseudomonas aereginosa	8 (5.6)
Acinetobacter baumannii	6 (4.2)
Enterobacter cloacae	2 (1.4)
Serrratia marcescens	3 (2.1)
Other Gram-negative bacilli	5 (1.7)
Polymicrobial infection	16 (11.1)
Candida spp.	1 (0.7)
Mycobacterium tuberculosis	1 (0.7)
Culture negative	27 (18.8)
Concomitant positive blood culture	
MRSA	3 (27)
MSSA	3 (27)
Escherichia coli	2 (18.2)
Samonella choleraesuis	1 (9.1)
Aeromonas sorbia	1 (9.1)
Streptococcus gordonii	1 (9.1)

MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*.

Discussion

To our knowledge, our study is one of several large case series of PJI in the medical literature.[15,19–21] Our results agree with another report that the two-stage revision resulted in a better outcome in PJI.[19] In Taiwan, the most common causative organism of PJI is *S. aureus*. Staphylococci account for nearly half of PJI cases. This finding is similar to the finding of a study by Trampuz et al.[20] However, Bejon et al[15] reported coagulase-negative staphylococci as the most commonly isolated organism in their study. Different studies have different culture negative rate. In the current study, the culture negative rate was 18.8% and often in the context of previous antimicrobial therapy. Bejon et al[15] report a surprisingly high culture negative rate of 41%. However, only a 7% culture negative rate was noted in a study by Berbari et al.[21] Prosthetic joint infection by *Candida* and *Mycobacterium* were noted in our respective review of one patient. Fungal cultures, mycobacterial cultures, or both may be considered (e.g., if bacterial cultures are negative in a patient with an apparent infection).[22] Similar to findings of a previous report,[23] we found that fungi or *Mycobacterium* were uncommon pathogens. Concomitant positive blood cultures were identified in 11 patients. There was no difference between the treatment success and failure group.

There was no significant difference in demographic characteristics or microbiology between the treatment

Table 3 Factors associated with treatment outcome by per-protocol analysis

Factors	Outcome		
	Success (n = 46)	Failure (n = 46)	p
Age, mean (SD)	69.4 (15.2)	70.1 (10.9)	0.571
Sex			
Male	19 (41.3)	21 (45.7)	0.674
Comorbidities			
Diabetes	14 (30.4)	16 (34.8)	0.656
Liver disease	5 (10.9)	7 (15.2)	0.536
Chronic kidney disease	7 (15.2)	6 (13)	0.765
Hypertension	32 (69.6)	25 (54.3)	0.133
Chronic lung disease	6 (13)	4 (8.7)	0.503
Malignancy	0 (0)	3 (6.5)	0.242
Rheumatic arthritis	3 (6.5)	4 (8.7)	0.694
Immunosuppressive therapy or steroid use	4 (8.7)	3 (6.5)	0.694
Prosthesis location			
Hip	14 (45.7)	16 (34.8)	0.656
Non-hip	32 (69.6)	30 (65.2)	
Type of prosthesis			
Primary	40 (87)	34 (73.9)	0.115
Secondary	6 (13)	12 (26.1)	
Procedure			
One stage revision	1 (2.2)	0 (0)	0.315
Two-stage revision	30 (65.2)	13 (28.3)	$<$0.001
Debridement with implant retention	6 (13)	19 (41.3)	0.002
Debridement with removal of implant	3 (6.5)	7 (15.2)	0.108
Medical treatment only	6 (13)	7 (15.2)	0.765
Microbiology			
MRSA	5 (10.9)	7 (15.2)	0.536
MSSA	10 (21.7)	11 (23.9)	0.804
Coagulase-negative Staphylococcus	9 (19.6)	9 (19.6)	$>$ 0.99
Enterococci	6 (13)	4 (8.7)	0.503
Streptococci	3 (6.5)	5 (10.9)	0.694
Gram-negative bacilli	7 (15.2)	11 (23.9)	0.293
Culture negative	8 (17.4)	5 (10.9)	0.369
Positive blood culture	2 (4.3)	7 (15.2)	0.207

Data are presented as n (%) unless otherwise indicated.
MRSA = methicillin-resistant *Staphylococcus aureus;* MSSA = methicillin-sensitive *Staphylococcus aureus;* SD = standard deviation.

success group and the failure group, except for the intervention by two-stage revision (Table 2). The two-stage revision was associated with a better outcome, compared to other interventions. Positive blood cultures were all isolated from the non-two-stage revision group. On multivariate analysis, however, a positive blood culture was not an independent factor for the treatment outcome. We revealed that the two-stage revision was the only factor that successfully eradicated PJI. Haleem et al[24] report that the success of the two-stage reimplantation of an infected total knee arthroplasty is well maintained and with a modest rate of late recurrent infection (9%) or mechanical implant failure (6%).

Wilson et al[25] showed that the risk of PJI is significantly increased in patients—particularly in males—who had rheumatoid arthritis, ulcers of the skin, and who had undergone a previous operation on the knee. However, our study did not show these risk factors. Zimmerli et al[26] showed that another important risk of PJI was undergoing revision of an existing prosthetic joint. However, most of our patients with PJI had a primary prosthesis revision. In our study, the distribution of time since the first prosthesis joint infection was predominantly the late PJI infection. Bejon et al[15] showed that 83% of the patients had a late PJI infection. In the two-stage revision, giving empirical systemic antibiotics after the first-stage operation while awaiting culture results was more widely accepted.[13] However, most of these patients did receive further antibiotics because of positive microbiological sampling of the joint space at the second stage.[15] The finding was similar in our study in that half of the patients received antibiotics within 6 months after reimplantations.

We found that patients who received the two-stage revision had better outcomes, based on univariate analysis or multivariate analysis. In several studies, there is a high failure rate in other interventions such as debridement with the retention of the prosthesis, debridement with removal of prosthesis, and the one-stage revision.[27–29] Our study

Table 4 Characteristics of the two-stage revision and the non-two-stage revision by per-protocol analysis

	Two-stage revision (n = 43)	Non-two-stage revision (n = 49)	p
Success rate	30 (70)	16 (32.7)	<0.001
Age, y (SD)	67.9 (12.9)	71.4 (13.4)	0.081
Sex			
Male	23 (53.5)	17 (34.7)	0.07
Comorbidities			
Diabetes	15 (34.9)	15 (30.6)	0.663
Liver disease	5 (11.6)	7 (14.3)	0.706
Chronic kidney disease	7 (16.3)	6 (12.2)	0.579
Hypertension	28 (65.1)	29 (59.2)	0.559
Pulmonary disease	3 (7)	7 (14.3)	0.261
Malignancy	1 (2.3)	2 (4.1)	0.636
Rheumatic arthritis	4 (9.3)	3 (6.1)	0.566
Prosthesis location			
Hip	12 (28)	18 (36.7)	0.367
Non-hip	31 (72)	31 (63.3)	
Type of prosthesis			
Primary	38 (88.4)	36 (73.5)	0.072
Secondary	5 (11.6)	13 (26.5)	
Microbiology			
MRSA	5 (11.6)	7 (14.3)	0.706
MSSA	9 (20.9)	12 (24.5)	0.685
Gram-negative bacilli	7 (16.3)	11 (22.4)	0.457
Positive blood culture	0 (0)	9 (18.4)	0.008

Data are presented as n (%) unless otherwise indicated.
MRSA = methicillin-resistant *Staphylococcus aureus;* MSSA = methicillin-sensitive *Staphylococcus aureus;* SD = standard deviation.

also demonstrated the same result. We also found that recurrent infection was less developed in patients who received the two-stage revision.

Our study had several limitations. First, this was a retrospective case collection; therefore, collection bias may have occurred. However, our results showed no significant differences in the basic demographic characteristics between the treatment success and treatment failure groups. Second, we excluded 52 patients whose follow-up was <1 year or who were lost to follow-up during the study period. For this reason, the power of our study was limited by the relative small case number. Third, important parameters such as debridement delay (i.e., the time from the onset of symptoms to debridement) and CRP level or the white blood cell count at the diagnosis of PJI were not analyzed in our study. Approximately 19.1 % patients who were diagnosed as having PJI were transferred from other hospitals with partial treatment. The definite laboratory data and debridement delay could not be calculated correctly.

In conclusion, the most common infective organisms were staphylococci. The two-stage revision was associated with a better outcome and it was also an independent

Table 5 Factors associated with treatment success, using the multivariate Cox regression

Factors	OR	95% CI	p
Type of prosthesis (secondary revision)	0.513	0.158—1.666	0.267
Two-stage revision	3.923	1.532—10.042	0.004
Positive blood culture	0.446	0.075—2.668	0.376

CI = confidence interval; OR = odds ratio.

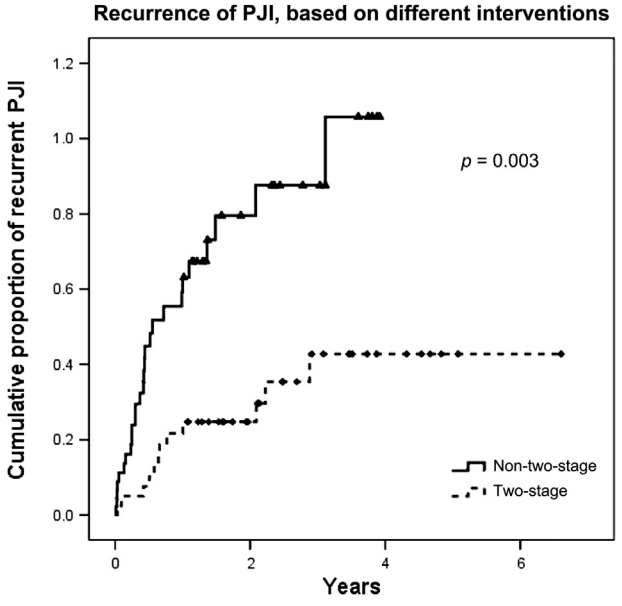

Figure 2. The Kaplan-Meier plot shows the cumulative recurrent infection rate, based on treatment.

factor in the multivariate analysis. Positive blood cultures were all found in the patients who had undergone the non-two-stage revision; however, this did not affect the treatment outcome. The recurrent infection rate was less frequent in the two-stage revision than in the other interventions during follow-up.

Conflicts of interest

The authors declare that they have no financial or nonfinancial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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