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ORIGINAL ARTICLE

Eight years experience in treatment of prosthetic joint infections at a teaching hospital in Central Taiwan

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Background/Purpose: Prosthetic joint infection (PJI) has become an important issue in the management of patients who receive prostheses. We compared the clinical outcomes of PJIs caused by Gram-negative bacteria (GN PJIs) and Gram-positive bacteria (GP PJIs).
Methods: Patients with culture-proven PJIs admitted to China Medical University Hospital between March 2001 and March 2009 were included in this retrospective study.
Results: Fifty-nine patients were diagnosed with PJI during the study period. Nineteen patients had GN PJIs (mean age: 68 years) and 40 had GP PJIs (mean age: 61 years). The most common comorbid condition was diabetes mellitus (23.7%) and the most common presentation was joint pain (79.7%). *Staphylococcus aureus* was the most common pathogen, whereas *Klebsiella pneumoniae* was the most common Gram-negative pathogen. The GN PJI group included more cases of hematogenous infection (36.8% vs. 20%; $p < 0.001$), showed a shorter interval between onset of infection symptoms and surgical intervention (median: 8 days vs. 21 days; $p = 0.04$), and required longer medical treatment (median: 259 days vs. 161 days; $p = 0.04$). In comparison with patients whose prostheses were eventually removed, patients whose prostheses were not removed had a shorter interval between onset of infection symptoms and surgical intervention (median: 6 days vs. 90 days; $p = 0.004$ and median: 6 days vs. 44 days; $p = 0.04$) in the GP PJI and GN PJI groups, respectively.

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Conclusion: GN PJI was less common than GP PJI, but GN PJI was more complicated and required longer treatment. Prospective randomized clinical studies are needed to investigate whether prosthesis implantation should be reserved if the patient undergoes early surgical intervention for PJI.

Introduction

With the improvements in medical and surgical therapy, joint replacements are now being widely performed.[1,2] In Taiwan, an increasing number of patients are undergoing joint-replacement procedures for the lower extremities.[3–5] Patients who undergo joint replacement show improvement in the quality of life and wellbeing. However, they may also experience several complications, such as infection, aseptic loosening, periprosthetic fractures, all of which can lead to prosthesis dysfunction.[2,6] Infection, which occurs in 0.39–3% of cases,[7–10] is the most important and serious complication,[7,11] and increases the medical costs associated with joint replacement.[12]

Current strategies to manage prosthetic joint infection (PJI) include prosthesis removal with or without two-stage reimplantation, and prosthesis retention with adequate debridement and long-term antibiotic therapy.[13,14] Although it has been reported to be a mainstay of treatment,[15] prosthesis removal with or without two-stage reimplantation may cause immobilization and prolonged rehabilitation, and has a high surgical risk. Debridement with retention of the prosthesis, which has been suggested in selected cases,[16] may require prolonged antibiotic treatment and is associated with high rates of treatment failure. These two treatment strategies may be indicated in different clinical entities, such as PJIs caused by Gram-positive or Gram-negative bacteria. However, only a few studies have discussed the difference in treatment and clinical outcome between PJIs caused by Gram-positive bacteria (GP PJI) and those caused by Gram-negative bacteria (GN PJI). Therefore, with the aim of reporting our clinical experience of managing PJIs, with particular emphasis on the outcomes of different strategies for treating GP PJI and GN PJI, we initiated this retrospective study in a teaching hospital in Taiwan.

Materials and methods

Patient selection

Patients who were diagnosed with their first episode of monomicrobial PJI and were treated at China Medical University Hospital (a 2000-bed tertiary teaching hospital in Central Taiwan) between March 2001 and March 2009 were included in our study. Using the electronic system of medical records and charts, we included the information of all patients who, according to the *International Classification of Diseases, Ninth Revision, Clinical Modification,* matched the criteria for PJI (code 996.66). We excluded cases with incomplete charts, no postoperative follow-up data, or poor drug compliance. We recorded demographic data for each patient, including information about comorbidity, disease presentations, laboratory findings, and clinical management. Cases of GP PJI and GN PJI were compared for risk of treatment failure and clinical outcome. All patients were followed up from the diagnosis of PJI until the last outpatient visit or admission to our hospital.

Definition

Diagnosis of PJI was based on: (1) isolation of the same microorganism from two or more joint aspirates; (2) detection of inflammation in histopathological examinations and the presence of at least one positive culture in the intraoperative specimens; or (3) infectious symptoms such as a discharging sinus tract communicating with the prosthesis, or a purulent joint space observed during surgery.[14,17–20]

Relapse of infection was defined as PJI caused by the same microorganism that was isolated previously. Reinfection was defined as PJI caused by a microorganism different from that isolated from the previous PJI. Treatment failure was considered to be unsuccessful under the following conditions: (1) relapse of infection; (2) reinfection; (3) histopathological evidence of periprosthetic tissue inflammation; (4) purulent joint or occurrence of a sinus tract; and (5) death due to prosthesis-related infection.[14,17–20]

Hematogenous route of infection was considered if the patient had no history of direct bacterial invasion (invasive procedure or penetrating trauma) or local spread (osteomyelitis, cellulitis, and abscess) in the prior 3 months.[21,22]

Statistical analysis

We used SPSS for Windows version 12.0 (SPSS, Chicago, IL, USA) for analyzing the clinical comparisons. The χ^2 or Fisher's exact test was used to analyze categorical data, and Student's *t* test was used to analyze continuous variables. A two-tailed *p* value <0.05 was considered statistically significant.

Results

We followed all patients in our study group for at least 24 months (range: 25–96 months). Fifty-nine patients with PJI, including 19 (32.2%) with GN PJI and 40 (67.8%) with GP PJI, were included in our study. The demographic characteristics of the patients are listed in Table 1. The median ages of the GN PJI and GP PJI patients were 68 years and 61 years, respectively. Twenty-six patients (44%) had underlying diseases: diabetes mellitus was the most common

Table 1 Demographic characteristics of patients with GN PJI and GP PJI

Characteristics	GN PJI ($n = 19$)	GP PJI ($n = 40$)	p value
Age (yr), median age (range)	68 (27–84)	61 (34–85)	0.92
Male sex	14 (73.6)	21 (52.5)	0.34
Hematogenous route	7 (36.8)	8 (20)	<0.001
Prosthesis age, median days (range)			
Symptom duration[a]	91 (7–2880)	100 (7–2160)	0.04
median days (range)	8 (2–155)	21 (1–120)	0.04
Clinical symptoms			
pain	14 (73.6)	33 (82.5)	0.12
swelling	12 (63.1)	29 (72.5)	0.82
limited range of motion	3 (15.7)	19 (47.5)	0.59
local heat	3 (15.7)	15 (37.5)	0.59
fever (≥38.3°C)	1 (5.2)	7 (17.5)	0.80
discharge sinus	7 (36.8)	17(42.5)	0.51
Comorbidity			
DM	3 (15.7)	11 (27.5)	0.42
ESRD	1 (5.2)	3 (7.5)	NA
gouty arthritis	1 (5.2)	4 (10)	NA
liver cirrhosis	0 (0)	3 (7.5)	NA
Laboratory finding, median (range)			
ESR (mm/hr)	67.1 (7–140)	71.4 (16–140)	0.72
WBC ($\times 10^3$ cells/μL)	8.1 (3.90–19.10)	9.1 (4.23–38.67)	0.24
hsCRP (mg/dL)	5.8 (0.07–29.55)	8.8 (1.50–43.58)	0.18
Treatment			
hospital stay, median days (range)	31 (15–107)	22 (14–80)	0.07
total treatment days,[b] median days (range)	259 (109–1979)	161 (60–877)	0.04
debridement, median times (range)	1 (0–4)	2 (0–5)	0.81

Number (%) of patients, unless indicated. Data with $p < 0.05$ were considered to be statistically significant.
DM = diabetes mellitus; ESR = erythrocyte sedimentation rate; ESRD = end-stage renal disease; GN PJI = Gram-negative prosthetic joint infection; GP PJI = Gram-positive prosthetic joint infection; hsCRP = high sensitivity C-reactive protein; NA = not applicable; WBC = white blood cells.
[a] Duration of infectious symptoms prior to surgical intervention.
[b] Duration included medical and surgical treatment.

comorbid condition and was reported in 14 cases (23.7%). The most common symptoms of PJI were pain (47 cases, 79.6%) and swelling (41 cases, 69.5%), while fever was present in eight (13.6%).

The interval between onset of infection symptoms and surgical intervention was shorter in the GN PJI group than in the GP PJI group (median: 8 days vs. 21 days; $p = 0.04$). Moreover, the duration of hospital stay tended to be longer in GN PJI patients than in GP PJI patients (median: 31 days vs. 22 days; $p = 0.07$). The total treatment duration, including the time required for surgical and antibiotic treatment, was also longer in GN PJI patients (median: 259 days vs. 161 days; $p = 0.04$).

Table 2 lists the microorganisms that caused PJI in our study. *Staphylococcus aureus* was the most common causative pathogen. Furthermore, most of the GN PJIs were caused by *Klebsiella pneumoniae* (4 cases, 21.1%), followed by *Pseudomonas aeruginosa* (3 cases, 15.8%) and *Escherichia coli* (3 cases, 15.8%). When the cases of PJI were divided into three time-based groups: after implantation to early infection (<3 months); delayed infection (3–24 months); and late infection (>24 months), GP PJIs accounted for 17 (42.5%), 17 (42.5%), and six (15%) cases, and GN PJI accounted for nine (47.4%), three (15.8%), and seven (36.8%) cases, respectively. Virulent Gram-positive bacteria such as *S. aureus* (28 cases in total) tended to occur in early (16 cases, 57.1%) and late (5 cases, 17.9%) infection, whereas Gram-negative bacterial infections were also relatively common in these two stages. Compared to GP PJIs, GN PJIs showed a higher degree of correlation with a hematogenous route of infection (36.8% vs. 20%; $p < 0.001$).

Patients with GP PJIs received intravenous antibiotic treatment for at least 3–4 weeks; 29 patients (72.5%) received antibiotic monotherapy, and 11 patients (27.5%) received combined antibiotic therapy. One patient who was treated with intravenous antibiotics for 2 weeks died from PJI during the follow-up period. The antibiotic monotherapy regimen included treatment with vancomycin or teicoplanin in nine cases (22.5%), oxacillin in 17 cases (42.5%), (3) cefazolin in two cases (5%), and moxifloxacin in one case (2.5%). The combined antibiotic therapy regimen included treatment with vancomycin or teicoplanin combined with rifampicin in 11 cases (27.5%). Fusidic acid and rifampicin were used to treat methicillin-resistant *S. aureus*, and cloxacillin or fusidic acid was used to treat

Table 2 Microbiological findings in cases of GN PJI and GP PJI

Microorganism	Case number (%)
Gram-positive bacteria	40 (100%)
Staphylococcus aureus	
methicillin-sensitive *S. aureus*	15 (37.5%)
methicillin-resistant *S. aureus*	13 (32.5%)
Coagulase-negative staphylococci	5 (12.5%)
Streptococcus spp.	5 (12.5%)
Enterococcus faecalis	1 (2.5%)
Peptostreptococcus prevotii	1 (2.5%)
Gram-negative bacteria	19 (100%)
Enteral bacteria	
Klebsiella pneumoniae	4 (21.1%)
Escherichia coli	3 (15.8%)
other species[a]	5 (26.2%)
Nonenteral bacteria	
Pseudomonas aeruginosa	3 (15.8%)
other species[b]	4 (21.1%)

GN PJI = Gram-negative prosthetic joint infection; GP PJI = Gram-positive prosthetic joint infection.
[a] included *Enterobacter cloacae* (2 cases), *Salmonella choleraesuis* (2 cases), and *Proteus mirabilis* (1 case).
[b] included *Stenotrophomonas maltophilia* (1 case), *Acinetobacter baumannii* (2 cases), and *Acinetobacter lwoffii* (1 case).

other microorganisms; these antibiotics were selected for oral antibiotic switch in cases of GP PJI.

Among patients with GN PJI, 17 (89.5%) received intravenous antibiotic monotherapy and two (10.5%) received combined antibiotic therapy (1 with imipenem plus sulbactam, and 1 with ciprofloxacin plus amikacin). All but one patient with GN PJI received at least 4 weeks of intravenous antibiotic therapy. The antibiotic monotherapy regimen included treatment with fluoroquinolones in seven cases (36.8%), carbapenem in three cases (15.8%), extended-spectrum cephalosporins in six cases (31.6%), and amikacin in one case (5.2%). Fluoroquinolones were selected for oral antibiotic switch in patients with GN PJI.

Fig. 1 summarizes the management of PJI in the follow-up period. The treatment outcomes of GP PJIs and GN PJIs are listed in Table 3.

In comparison with the GP PJI patients whose prostheses could not be preserved, GP PJI patients whose prostheses could be preserved during the follow-up period had a shorter interval between onset of infection symptoms and surgical intervention (median: 6 days vs. 90 days; $p = 0.004$), shorter total treatment duration, including the duration of surgical and antibiotic treatment (median: 120 days vs. 303 days; $p = 0.068$), and required less debridement (median: 0 vs. 2, $p = 0.013$). Among 28 cases of *S. aureus* infection, 12 (42.9%) showed preserved prosthesis after debridement and antibiotic treatment.

Similarly, we also observed that GN PJI patients whose prostheses could be preserved during the follow-up period had a shorter interval between onset of infection symptoms and surgical intervention (median: 6 days vs. 44 days; $p = 0.04$), shorter treatment period, including surgical and antibiotic treatment (median: 247 days vs. 383 days; $p = 0.48$), and required less debridement (median: 0 vs. 2, $p < 0.001$) than GN PJI patients whose prostheses could not be preserved. In 16 cases (40%) of GP PJI and 10 cases (52.6%) of GN PJI, the prostheses could be preserved during the follow-up period, despite two GP PJI patients having a relapse of infection.

Two patients with GP PJI died during PJI treatment: one patient died from hospital-acquired pneumonia and one died from PJI. Furthermore, two patients with GN PJI died during treatment, including one who died because of the PJI.

Discussion

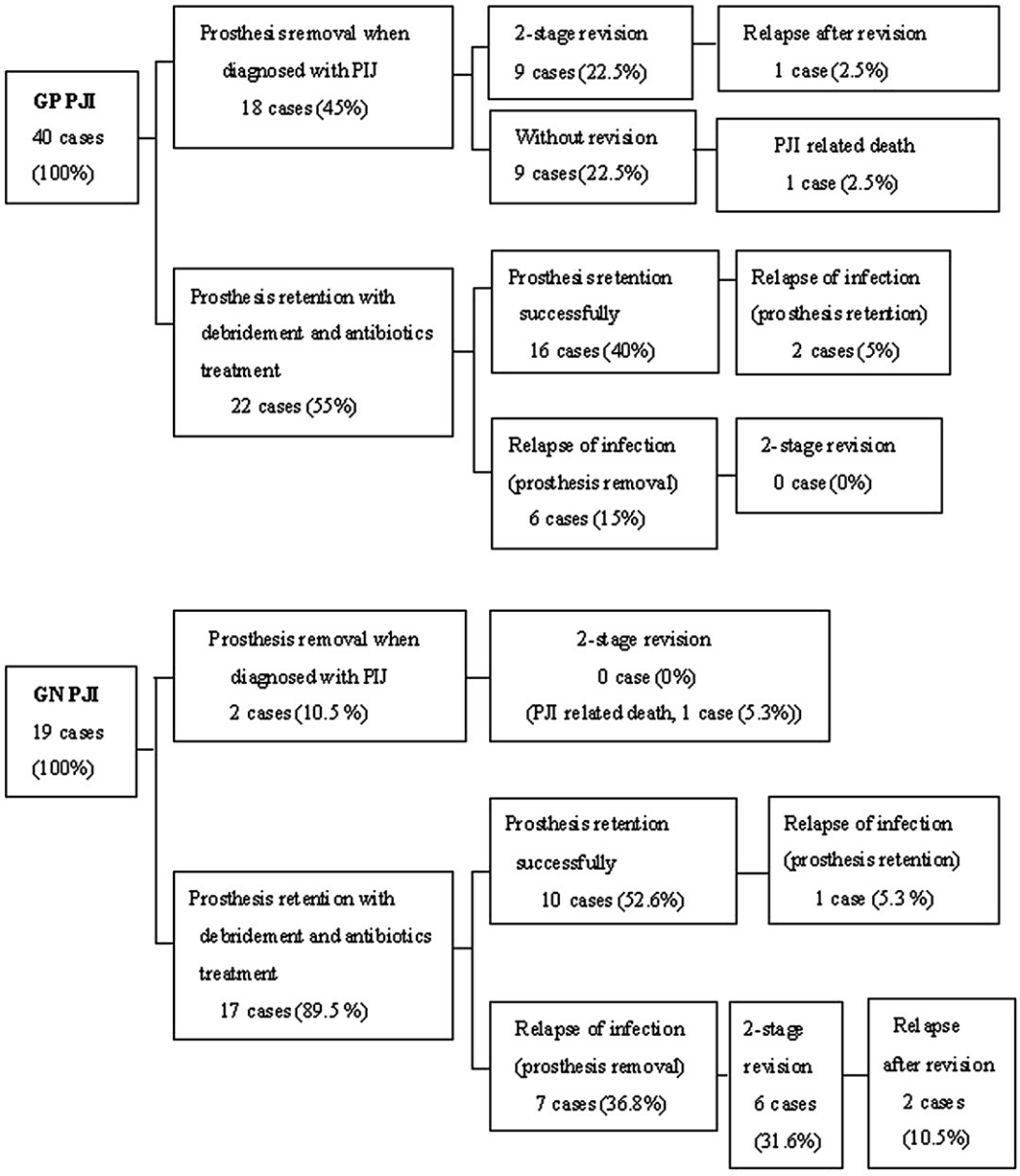
With the increasing number of joint replacements in Taiwan, over 40,000 patients are expected to receive a replacement joint in 2011.[3–5] On the basis of the reported occurrence rates of PJIs (0.98%), at least 400 cases of PJI are estimated to occur annually.[23] PJI can increase the cost of medical treatment[12] and may necessitate complicated and long-term treatment.

In our present study, advanced age was noted more often in GN PJI cases than in GP PJI cases; a finding similar to a previous study (median age: 68 years in GN PJI patients vs. 59 years in GP PJI patients).[14] Men accounted for the majority of the cases (35 cases; 59.3%) in our study; this finding was similar to the study by Willis-Owen et al.[23] Similar to the findings in previous studies,[22,24] Gram-positive bacteria (67.8%) were the dominant microorganisms causing PJIs in our study. *S. aureus* was the most common pathogen, consistent with the findings of previous studies[11,25] although other studies have reported *Staphylococcus epidermidis* as the most common pathogen causing PJI.[22]

The rate of GN PJIs in our study (32.2%) was higher than that reported previously (4–11%).[11,24] Polymicrobial infection accounted for 19% of PJIs in one study, and more cases of PJIs were due to Gram-positive bacteria.[26] However, we included only monomicrobial PJIs, which might explain the higher incidence of GN PJIs in our study.

In our study, the infections were classified as early (<3 months), delayed (3–24 months), and late (>24 months), according to the interval between prosthesis implantation and onset of infection symptoms.[27] The timing of infection [26 early (44.1%), 20 delayed (33.9%), and 13 late (22.0%)] in our study showed a trend similar to that observed in previous studies, which have reported that the infection incidence declined with time after joint replacement.[11,28] However, other studies have reported a higher incidence of late infections (32%) than delayed infections (23%), and 10% of the cases included in the study were cases of reinfection.[25]

In our study, cases of hematogenous infection were more common in GN PJIs than GP PJIs (36.8% vs. 20%, $p < 0.001$). Gram-negative bacterial infections were more common in the early stage (47.4%) and late stage (36.8%) after prosthesis implantation. Although previous articles have mentioned that hematogenous infection and Gram-negative bacteria infection tended to occur in the early



Abbreviation: PJI= prosthetic joint infection; GP PJI= prosthetic joint infection due to gram-positive bacteria; GN PJI= prosthetic joint infection due to gram-negative bacteria.

Figure 1. Clinical management in 59 patients with prosthetic joint infection.

and late stages,[13,27] a reasonable explanation for this phenomenon has not yet been obtained.

Management of Gram-negative bacteria-related bone and joint infection is complicated[29] because biofilms may form under the antibiotic-loaded bone cement[30] and drug-resistant microorganisms may cause infections, thereby restricting the available choices for oral antibiotics.[31] Furthermore, only a few studies have investigated Gram-negative bacteria-related bone and joint infection, especially PJIs.[14,32] Our study showed that patients with GN PJIs required longer treatment, including surgical and antibiotic treatment (median: 259 days vs. 161 days; $p = 0.04$), and longer hospital stay (median: 31 days vs. 22 days; $p = 0.07$) than those with GP PJIs. Legout et al have reported a similar trend, in which longer antibiotic therapy (6—9 months) was necessary to treat Gram-negative bacteria-related bone and joint infections.[32]

We found that a shorter interval (range: 1—10 days) between the onset of infection symptoms and surgical treatment was related to successful prosthesis retention in GN PJI and GP PJI patients. This was similar to two reports stating that prostheses were preserved when the cases

Table 3 22 GP PJI and 17 GN PJI patients treated with debridement and prosthesis retention

Characteristics	GP PJI (n = 22)			GN PJI (n = 17)		
	Prosthesis retention[a] (*n* = 16)	Prosthesis removal[b] (*n* = 6)	*p* value	Prosthesis retention (*n* = 10)	Prosthesis removal (*n* = 7)	*p* value
Age (yr), median age (range)	63 (34–85)	62 (46–73)	0.93	56 (27–73)	63 (33–79)	0.38
Male sex	10 (62.5)	2 (33.3)	0.4	7 (70)	5 (71.4)	0.37
Clinical symptoms						
pain	13 (81.2)	5 (83.3)	0.66	7 (70)	6 (85.7)	0.25
swelling	12 (75)	5 (83.3)	0.61	6 (60)	5 (71.4)	0.10
limited range of motion	8 (50)	2 (33.3)	0.2	1 (10)	2 (28.5)	0.25
local heat	7 (43.7)	2 (33.3)	0.8	1 (10)	1 (14.2)	0.12
Fever ($\geq$38.3°C)	0 (0)	4 (66.6)	NA	1 (10)	0 (0)	NA
discharge sinus	7 (43.7)	3 (50)	0.5	3 (30)	3 (42.8)	0.71
Symptom duration[c] median days (range)	6 (1–10)	90 (30–120)	0.004	6 (2–8)	44 (31–155)	0.04
Laboratory finding median (range)						
ESR (mm/hr)	62 (25–140)	70 (18–108)	0.24	29 (7–140)	74 (22–140)	0.9
WBC ($\times 10^3$ cells/μL)	9.94 (4.3–18.2)	9.39 (4.2–38.6)	0.81	7.44 (4.1–19.1)	9.62 (4.5–10.7)	0.9
Comorbidity						
DM	2 (12.5)	2 (33.3)	0.66	1 (10)	2 (28.5)	0.75
ESRD	0 (0)	1 (16.6)	NA	0 (0)	1 (14.2)	NA
gouty arthritis	1 (6.2)	0 (0)	NA	0 (0)	0 (0)	NA
liver cirrhosis	0 (0)	1 (16.6)	NA	0 (0)	0 (0)	NA
Treatment						
total treatment days[d] median days (range)	120 (60–290)	303 (119–877)	0.068	247 (109–1100)	383 (120–1979)	0.48
debridement median times (range)	0 (0–1)	2 (1–5)	0.013	0 (0–1)	2 (1–4)	<0.001

Number (%) of patients, unless indicated. Data with $p < 0.05$ were considered to be statistically significant.
DM = diabetes mellitus; ESR = erythrocyte sedimentation rate; ESRD = end-stage renal disease; GN PJI = Gram-negative prosthetic joint infection; GP PJI = Gram-positive prosthetic joint infection; NA = not applicable; WBC = white blood cells.
[a] Successful debridement and prosthesis retention during the follow-up period.
[b] Failure of prosthesis retention due to relapse of infection during the follow-up period.
[c] Duration of infectious symptoms prior to surgical intervention.
[d] Duration included medical and surgical treatment.

showed a shorter interval between onset of infection symptoms and surgical intervention (4.85 days and 8 days, respectively).[17,33]

In this context, a few studies have discussed GN PJIs. In GN PJI patients with a median of 6 days (range: 2–8 days) between onset of infection symptoms and surgical intervention, the prostheses were preserved successfully, and these patients required shorter antibiotic treatment and less surgical debridement than patients with an extended period of infection symptoms. Hsieh et al also have observed that GN PJI patients who had a shorter interval between onset of infection symptoms and surgical intervention showed better outcomes.[14] However, long-term antibiotic treatment was needed in our GN PJI group (median: 247 days; range: 109–1100 days) for eradication of infection, compared to the 91 days of antibiotic treatment required in the study by Hsieh et al.[14] This difference in treatment time might have been due to different patient populations and treatment strategies. However, treatment success and failure in PJI might be related not only to early surgical intervention, but also to disease severity and underlying comorbid conditions; all these factors influence the surgical management and clinical outcome.

The limitation of the current study was that it was difficult to discern whether the effect of early or late surgical intervention was confounded by the disease severity per se. For patients who underwent early surgical intervention, the low disease severity might have helped the surgeons perform operations with less debridement, thereby ensuring shorter treatment duration. In contrast, patients whose prostheses were eventually removed might have experienced more comorbidity, requiring the surgeons to delay the surgery and perform it with more debridement. Thus, successful prosthesis retention might not be truly related to early surgical intervention; rather it may be related to disease severity and underlying condition. There was no standard treatment for PJI, therefore, differences between the findings of our study and other studies might have been due to different treatment regimens or patient populations. An ideal therapeutic strategy to achieve favorable outcomes could be identified from the results of further prospective multicenter studies.

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