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ORIGINAL STUDY

Investigation of the changing etiology and risk factors of prosthetic joint infections : a university hospital surveillance study from 2011-2017

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We sought to characterize the causative pathogens of prosthetic joint infections (PJIs), evaluate the trends in microbial etiologies, and identify potential risk factors for PJI. This was a retrospective study analyzing 70 patients with PJI following 3,253 total joint arthroplasties between 2011 and 2017. Staphylococci were the most common cause of infection (52.9%). There was a significant trend in the percentage of carbapenem-resistant gram-negative bacilli (GNB) (increased to 66.7% in 2016 from 0.0% in 2011) (p=0.021). GNB and polymicrobial etiology were found at significantly high levels in cases involving early PJIs (p=0.005 and p=0.048, respectively). While staphylococci were significantly higher in PJIs after total knee arthroplasty (75%), GNB were significantly higher in PJIs after total hip arthroplasty (49.1%) (p<0.001 and p=0.001, respectively). Binary logistic regression analysis showed that the risk of PJI was significantly higher in cases with fracture and diabetes mellitus (odds ratio [OR], 4.3, 95% confidence interval [CI], 1.78-10.5 ; OR, 4.1, 95% CI, 1.66-10.5, respectively). These results suggest that the empirical and targeted antimicrobial treatment of PJIs may become more difficult in the future.

Keywords : arthroplasty ; prosthetic joint infections ; microbial etiology ; case-control.

INTRODUCTION

Total joint arthroplasties (TJAs) are cost-effective procedures that improve quality of life in patients with degenerative joint disease resistant to nonoperative treatment *(27,32).* Unfortunately, prosthetic joint infection (PJI) continues to be a major cause of patient morbidity after TJA, with a prevalence of 0.5% to 3% *(9,25,18).* PJI is the leading cause of failure in total knee arthroplasty (TKA) and the third most common cause of failure in total hip arthroplasty (THA) *(20)*. PJI extends hospitalization time, increases the re-hospitalization rate, requires one or more reoperations, and increases the cost of care by more than 300% *(13,33)*. Obesity and the total number of medical conditions are associated with a higher risk of infection in patients undergoing arthroplasty *(15,10,7)*. In particular, revision surgery, diabetes mellitus, tobacco abuse, methicillin-resistant *Staphylococcus aureus* (MRSA) colonization or infection, and current or prior bone cancer have

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been identified as independent risk factors for PJI. (*9*)

The microbial etiology of PJI has important implications for empirical antimicrobial therapy and surgical antibiotic prophylaxis. *Staphylococcus aureus* and coagulase-negative staphylococci (CNS) are the most common causes of PJI, with CNS accounting for 30-41% and *S. aureus* for 12-39%. Gram-negative bacilli (GNB) are less common than gram-positive organisms, causing around 10% of cases *(24)*. In recent years, the rates of GNB in PJI have been steadily increasing and account for 5% to 23% of cases *(29)*. While infections caused by multidrug-resistant organisms are increasing worldwide *(8,21)*, very little is known about their role in PJIs. Studies investigating the various microbial agents of PJI are scarce in our country.

This study aimed to characterize the causative pathogens of PJIs, assess the trends in microbial etiology, and determine the independent preoperative predictors of PJI among patients who underwent TJA in our hospital.

MATERIAL AND METHODS

Study design and data collection

This study was conducted at the Bezmialem Vakıf University, Medical School Hospital with 550 beds in Istanbul. Our Orthopedics Department serves as an important arthroplasty center with an average of 500 TJA performed annually, with the number gradually increasing to 800 in recent years. In this surveillance study, we included all patients who underwent TJA at our hospital from January 2011 through December 2017. Only episodes of PJI diagnosed for the first time during the study period were included. Exclusion criteria included patients who could not be followed-up, whose medical data could not be accessed, or who were aged less than 18 years. In addition, late PJIs (after one year) and another hospital-acquired PJIs were excluded since it was a surveillance study. Cefazolin is the main antibiotic used for surgical prophylaxis in these procedures ; vancomycin is used in penicillin-allergic patients. During the study period, there were no changes in the surgical procedures performed for THA and TKA. Infection control measures for surgical site infections (SSIs) in our hospital are based on prevention guidelines from the CDC.

As part of routine surveillance at our hospital, an infection control team consisting of an infectious disease specialist and three infection nurse prospectively identifies patients with PJI within a year after surgery. Patient data are recorded manually on surveillance forms prepared by the Ministry of Health. This surveillance is performed by monitoring all inpatient and outpatient medical records and wound and blood culture reports for up to one year. The surveillance definition of PJI is based on the CDC's definition of organ or space SSIs *(10)*.

The microbiologic etiology of PJI was established when two or more intraoperative cultures or a combination of preoperative aspiration and intraoperative cultures yielded the same organism *(22)*. When the diagnostic criteria for PJI were met, a virulent microorganism (e.g., *S. aureus*) isolated in a single specimen of a tissue biopsy or synovial fluid was also considered significant *(22)*. The term "polymicrobial infection" was used when different bacterial species were simultaneously identified from the samples *(3)*. We calculated the annual proportion of PJIs, accounted for each of the most common organisms, and evaluated temporal trends. Microbiological agents of PJI were also analyzed according to the PJI type (THA, TKA) and duration of PJI (early, within 90 days after index arthroplasty ; delayed, within 90-360 days after index arthroplasty).

A control group was established to identify patient populations at increased risk of PJI. The controls were selected from among the patients in the study population who did not develop PJI. Controls were matched 1:1 to cases by age, sex, and prosthesis location and to cases by date of implantation to check for changes in clinical practices during the study period. The medical records of the case and control groups were abstracted for data on potential risk factors previously reported in the literature *(9,15,10,7)*.

Data on demographics, preexisting conditions, comorbidities, possible risk factors (host and arthroplasty risk factors), physical examination findings, reason for and date of PJI, type of PJI, laboratory

findings [white blood cell (WBC) count, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR)], microbial etiology, and antimicrobial susceptibility were obtained from surveillance forms and the patients' electronic medical records.

Microbiological identification

Surgical and biopsy samples sent from the clinics to the microbiology laboratory were inoculated on blood agar (Becton Dickinson, USA), eosin-methylene blue (EMB) agar (Becton Dickinson, USA), and chocolate agar (Becton Dickinson, USA) and incubated aerobically for 24-48 hours in a CO2 incubator at a temperature range of 35± 2°C. Hemoculture tubes (Becton Dickinson, USA) sent to the microbiology laboratory were put into the BACTEC FX (Becton Dickinson, USA) device and programmed for an incubation period of 5 days. In samples with positive signals during this period, a gram staining was done from the bottle first, after which incubations were done in blood agar (Salubris, Turkey), EMB agar (Salubris, Turkey), and chocolate agar (Salubris, Turkey) at 37 °C for 18-24 hours. The bacteria that had grown were identified using the Vitec® MS (using Matrix Assisted Laser Desorption Ionization Time-of-Flight [MALDI-TOF]) (BioMérieux, France) device, and antimicrobial susceptibility results obtained with the VITEK® 2 Compact (BioMérieux, France) were evaluated according to Clinical and Laboratory Standards Institute (CLSI) criteria).

Statistical analysis

Distribution of data was analyzed by the Shapiro-Wilk test. The Kruskal-Wallis test was used for the comparison of three groups that did not show normal distribution. Fisher's exact, Pearson Chi-square, and Fisher-Freeman-Helton tests were used to compare categorical data. We determined the annual incidence of PJIs following THA and TKA, the annual percentage of polymicrobial infections, and the annual number of microbial isolates. Descriptive statistics of the data are given as frequency (percentage) and median (min-max). A binary logistic regression ("backwards : LR" method) model was developed to predict the risk of PJI. All statistical tests were analyzed and reported in IBM SPSS Statistics 22.0 program at a level of $\alpha = 0.05$ and a confidence level of 95%.

RESULTS

A total of 3,253 total arthroplasties (1,768 TKAs and 1,485 THAs) were performed at our institution during the study period. Eight patients with PJI were excluded from the study due to a lack of data and lack of follow-up. PJI was diagnosed in 70 patients (2.1% of the total TJAs). The overall annual incidence of PJIs (range, 0.9-3.6%) did not change significantly during the study period (p=0.304). The annual incidence of PJIs following THA increased significantly over the years and peaked in 2015 (p=0.036). The annual incidence of PJIs after TKA decreased significantly during the study period (p=0.036) (Table I).

Staphylococci were the most common cause of PJI (52.9%), followed by GNB (45.7%). The most commonly identified microorganisms were : *S. aureus* (28.6%), CNS (24.3%), *Klebsiella* spp. (12.9%), *Pseudomonas aeruginosa* (11.1%), and *Enterococcus* species (11.1%). Among the patients with PJIs, 31.3% had extended spectrum beta lactamase (ESBL)-producing GNB and 18.7% had carbapenem-resistant GNB. The percentage of methicillin-resistant staphylococci in patients with PJI was 24.3% (17/70). Among the patients with PJI, 20% (n=14) had polymicrobial etiology. The number and percentage of microorganisms in polymicrobial PJIs were 12 (85.7%) GNB, 11 (78.6%) staphylococci, and three (21.4%) *Enterococcus* species.

Over the years, there were no significant trends in either the proportion of PJIs caused by gram-positive cocci or the proportion of GNB (p=0.902 and p=0.634, respectively). There was an increase in the percentage of GNB (increased to 61.5% in 2017 from 36.4% in 2012), but it was not statistically significant (p=0.634). There were significant trends in the percentage of carbapenem-resistant GNB (increased to 66.7% in 2016 from 0.0% in 2011) (p=0.021 for trend) and the proportion of PJI caused by *Acinetobacter* spp. over time (decreased to 7.7%

Table I. — Demographic characteristics and microbiological results of patients with PJI from 2011 to 2017

Variables	**Overall**	2011	2012	2013	2014	2015	2016	2017	P*
Surgical procedure	3,253	219	300	351	375	471	737	800	
THA	1,485 (45.6)	158 (72)	164 (54.6)	173 (49.3)	167 (44.5)	223 (47.3)	312 (42.3)	288 (36)	<0.001
TKA	1,768 (54.4)	61 (28)	136 (45.4)	178 (50.7)	208 (55.5)	248 (52.7)	425 (57.7)	512 (64)	<0.001
Cases of PJI	70 (2.1)	2 (0.9)	11 (3.6)	6 (1.7)	9 (2.4)	13 (2.7)	16 (2.1)	13 (1.6)	0.304
PJI after THA	58 (3.9)	2 (1.3)	6 (3.6)	4 (2.3)	9 (5.4)	13 (5.8)	14 (4.5)	10 (3.4)	0.036
PJI after TKA	12 (0.7)	0 (0.0)	5 (3.7)	2 (1.1)	0 (0.0)	0 (0.0)	2 (0.5)	3 (0.6)	0.036
Age, median (min-max), years	71 (17-89)	78 (77-79)	72 (17-84)	76.5 (22-89)	66 (51-83)	63 (25-89)	72.5 (45-80)	71 (37-87)	0.498
Female	52 (74.3)	1 (50)	8 (72.7)	4 (66.7)	7 (77.8)	9 (69.2)	13 (81.3)	10 (76.9)	0.960
Microbiology results for PJI									
Gram-positive cocci[a]	50 (71.4)	1 (50)	9 (81.8)	4 (66.7)	7 (77.8)	10 (76.9)	10 (62.5)	9 (69.2)	0.902
Staphylococci	37 (52.9)	1 (50)	4 (36.4)	2 (33.3)	6 (66.7)	9 (69.2)	9 (56.3)	6 (46.2)	0.609
Staphylococcus aureus	20 (28.6)	1 (50)	1 (9.1)	1 (16.7)	4 (44.4)	6 (46.2)	4 (25)	3 (23.1)	0.370
MRSA[b]	3 (15)	0 (0.0)	0 (0.0)	1 (100)	1 (25)	1 (16.7)	0 (0.0)	0 (0.0)	0.539
Coagulase-negative staphylococci	17 (24.3)	0 (0.0)	3 (27.3)	1 (16.7)	2 (22.2)	3 (23.1)	5 (31.3)	3 (23.1)	0.995
-MRCNS[c]	14 (82.4)	0 (0.0)	2 (66.7)	1 (100)	1 (50)	2 (66.7)	5 (100)	3 (100)	0.468
Enterococcus spp.	12 (17.1)	0 (0.0)	3 (27.3)	2 (33.3)	2 (22.2)	2 (15.4)	1 (6.3)	2 (15.4)	0.665
Streptococcus spp.	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	0.771
Gram-negative bacilli[d]	32 (45.7)	2 (100)	4 (36.4)	3 (50)	4 (44.4)	5 (38.5)	6 (37.5)	8 (61.5)	0.634
Pseudomonas aeruginosa	10 (14.3)	0 (0.0)	1 (9.1)	3 (50)	1 (11.1)	2 (15.4)	1 (6.3)	2 (15.4)	0.361
Acinetobacter spp.	8 (11.4)	2 (100)	2 (18.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (18.8)	1 (7.7)	0.013
Klebsiella spp.	9 (12.9)	0 (0.0)	2 (18.2)	0 (0.0)	1 (11.1)	0 (0.0)	1 (6.3)	5 (38.5)	0.093
E. coli	6 (8.6)	0 (0.0)	1 (9.1)	0 (0.0)	2 (22.2)	1 (7.7)	1 (6.3)	1 (7.7)	0.805
Enterobacter spp.	5 (7.1)	0 (0.0)	1 (9.1)	1 (16.7)	0 (0.0)	1 (7.7)	2 (12.5)	0 (0.0)	0.755
Morganella morganii	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0.771
Citrobacter coseri	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0.771
Serratia spp.	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0.243
Candida spp.	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (6.3)	0 (0.0)	0.685
ESBL in gram-negative bacilli	10 (31.3)	0 (0.0)	1 (25)	0 (0.0)	2 (50)	1 (20)	2 (33.3)	4 (50)	0.737
Carbapenem resistance in gram-negative bacilli	6 (18.7)	0 (0.0)	1 (25)	1 (33)	0 (0.0)	0 (0.0)	4 (66.7)	0 (0.0)	0.021
Polymicrobial etiology	14 (20)	1 (50)	3 (27.3)	1 (16.7)	3 (33.3)	4 (30.8)	3 (18.8)	5 (38.5)	0.860

Data are number (%) of cases ; THA, total hip arthroplasty ; TKA, total knee arthroplasty ; PJI, prosthetic joint infection ; MRSA, methicilline resistant staphylococcus aureus ; MRCNS, methicilline resistant coagulase-negative staphylococci, ESBL, Extended spectrum beta lactamase ; a, number of patients with gram positive cocci ; b, Percentages of methicilin resistant S. aureus among the total number of isolated S.aureus ; c, Percentages of methicilin resistant coagulase-negative staphylococci among the total number of isolated coagulase-negative staphylococci ; d, number of patients with gram negative bacilli ; *p values indicate p for trend from 2011 through 2017.

in 2017 from 100% in 2011). Among isolated *S. aureus* strains, 15% were resistant to methicillin, and there were no significant trends over time either in the proportion of PJIs caused by *S. aureus* or in the percentage of MRSA. The methicillin resistance rate in CNS was 82%, and there were no significant trends in the proportion of PJIs caused by CNSs or methicillin-resistant CNSs. There were no significant trends for any of the other most commonly isolated organisms (Table I).

The majority of PJIs developed within the first 90 days of index arthroplasty (75.7%). All PJIs caused by *E. coli* and MRSA presented within 90 days of joint replacement. Coagulase-negative staphylococci were found in significantly higher numbers in PJIs that developed within 90 days

Table II. — Distribution of the agents according to the timing of PJI development

	Time After Implantation of the Index Arthroplasty			
	0-30 days	31-90 days	91-365 days	P
Patients with PJI	30 (42.9)	23 (32.8)	17 (24.3)	0.072
Gram-positive cocci[a]	20 (66.7)	17 (73.9)	13 (76.5)	0.735
Staphylococci	13 (43.3)	14 (60.9)	10 (58.8)	0.381
Staphylococcus aureus	10 (33.3)	9 (39.1)	1 (5.9)	0.053
MRSA[b]	2 (20)	1 (11.1)	0 (0.0)	1.000
Coagulase-negative staphylococci	3 (10)	5 (21.7)	9 (52.9)	**0.004**
MRCNS[c]	2 (66.7)	5 (100)	7 (77.8)	**0.537**
Enterococcus spp.	5 (16.7)	5 (21.7)	2 (11.8)	0.785
Streptococcus spp.	0 (0.0)	1 (4.3)	0 (0.0)	NA
Gram-negative bacilli[d]	20 (66.7)	7 (30.4)	5 (29.4)	**0.005**
Pseudomonas aeruginosa	4 (13.3)	4 (17.4)	2 (11.8)	0.913
Acinetobacter spp.	6 (20)	1 (4.3)	1 (5.9)	0.195
Klebsiella spp.	7 (23.3)	1 (4.3)	1 (5.9)	0.124
E. coli	4 (13.3)	2 (8.7)	0 (0.0)	0.364
Enterobacter spp.	3 (10)	0 (0.0)	2 (11.8)	0.241
Serratia spp.	1 (3.3)	0 (0.0)	0 (0.0)	NA
Morganella morganii	1 (3.3)	0 (0.0)	0 (0.0)	NA
Citrobacter coseri	0	1 (4.3)	0 (0.0)	NA
Candida spp.	1 (3.3)	0 (0.0)	1 (5.9)	0.714
Polymicrobial PJI	13 (43.3)	5 (21.7)	2 (11.8)	**0.048**

Data are number (%) of cases ; PJI, prosthetic joint infection ; MRSA, methicilline resistant staphylococcus aureus ; MRCNS, methicilline resistant coagulase-negative staphylococci ; a, number of patients with gram positive cocci ; b, Percentages of methicilin resistant S. aureus among the total number of isolated S.aureus ; c, Percentages of methicilin resistant coagulase-negative staphylococci among the total number of isolated coagulase-negative staphylococci ; d, number of patients with gram negative bacilli ; NA : Not applicable.

after index arthroplasty (p=0.004). GNB and polymicrobial etiology were found to occur at a statistically higher rate in PJIs developing within 30 days after index arthroplasty (p=0.005 and p=0.048, respectively) (Table II).

Distribution of agents in PJIs after TKA and THA is shown in Table 3. While staphylococci occurred at significantly higher levels in PJI after TKA (75%), GNB occurred at significantly higher levels in PJI after THA (49.1%) (p<0.001 and p=0.001, respectively). Polymicrobial infections were also significantly higher in PJI after THA (p=0.048). *Acinetobacter* spp., *E. coli, Klebsiella* spp., *Enterococcus* spp., and *Candida* spp. were all detected in PJI after THA (Table III).

The clinical findings of the PJI patients were identified as follows : 80% (n=56) pain, 42.9% (n=30) discharge, 20% (n=14) heat increase, 18.6% (n=13) erytema, and 17.1% (n=12) edema. The mean values of the laboratory findings of the PJI patients were as follows : WBC 11,300±5,040/mL, CRP 8.86±7.4 mg/dL, and ESR 69.8±29.3 mm/h.

The host, index arthroplasty, and preoperative variables analyzed as potential risk factors for PJI are listed along with the results of the univariate analysis in Table IV. Independent risk factors such as TJA due to degenerative joint disease, fracture and joint infection, presence of malignancy and type II diabetes mellitus, and pyuria and bacteriuria in the preoperative urine analysis were included in the binary logistic regression model for the development of PJI. The binary logistic regression analysis showed that the risk of PJI was significantly higher in cases with fracture and type II diabetes mellitus (OR, 4.3, 95% CI, 1.78-10.5 ; OR, 4.1, 95% CI, 1.66-10.5, respectively) (Table V).

Table III. — Distribution of agents in PJIs after total hip and knee arthroplasty

Agent	Hip PJI 58	Knee PJI 12	P
Gram-positive cocci[a]	39 (68.4)	11 (91.7)	<0.001
Staphylococci	28 (49.1)	9 (75)	<0.001
Staphylococcus aureus MRSA[b]	16 (28.1) 2 (12.5)	4 (33.3) 1 (25)	0.007 0.007
Coagulase-negative staphylococci MRCNS[c]	12 (21.1) 10 (83.3)	5 (41.7) 4 (80)	0.073 0.077
Enterococcus spp.	12 (21.1)	0 (0.0)	NA
Streptococcus spp.	0 (0.0)	1 (8.3)	NA
Gram-negative bacilli[d]	28 (49.1)	3 (25)	0.001
Pseudomonas aeruginosa	8 (14)	2 (16.7)	0.022
Acinetobacter spp.	7 (12.3)	1 (8.3)	0.125
Klebsiella spp.	9 (15.8)	0 (0.0)	NA
E. coli	6 (10.5)	0 (0.0)	NA
Enterobacter spp.	2 (3.5)	2 (16.7)	NA
Morganella morganii	1 (1.8)	0 (0.0)	NA
Citrobacter coseri	1 (1.8)	0 (0.0)	NA
Serratia spp.	1 (1.8)	0 (0.0)	NA
***Candida* spp.**	2 (3.5)	0 (0.0)	NA
Polymicrobial etiology	18 (31)	2 (16.6)	0.005

NA : Not applicable ; PJI, prosthetic joint infection ; THA, total hip arthroplasty ; TKA, total knee arthroplasty ; MRSA, methicilline resistant staphylococcus aureus ; MRCNS, methicilline resistant coagulase-negative staphylococci ; a, number of patients with gram positive cocci ; b, Percentages of methicilin resistant S. aureus among the total number of isolated S.aureus ; c, Percentages of methicilin resistant coagulase-negative staphylococci among the total number of isolated coagulase-negative staphylococci ; d, number of patients with gram negative bacilli.

DISCUSSION

PJI remains a serious and devastating complication of TJA, leading to expensive and prolonged treatments. Despite the routine use of perioperative antibiotics and modern medical care, the overall incidence of PJI remains approximately 0.3-1.7% for TKA and 0.8-1.9% for THA *(5,14)*. In accordance with the aging population, the incidence of PJI is expected to increase continuously, with a concomitant increase in THA and THA implantation. Thus, new therapeutic approaches and further clinical trials are required. In our patients, the overall incidence of PJI was 2.1%, and the incidence of PJI after THA increased over time with a fluctuating course, while the incidence of PJI after TKA decreased. Our study population had a typical demographic risk profile for PJI with older age (66±15.8 years) and a high proportion of comorbidities such as diabetes mellitus (35.7%), malignancy (7.1%), and chronic obstructive pulmonary disease (7.1%).

This study provides information about the etiological agents of PJIs in our hospital from 2011 to 2017. Staphylococci (52.9%) were the most common cause of infection, with *S. aureus* being the most commonly cultured microorganism, as previously reported *(24,3,12)*. There was an increase in the percentage of GNB over time in our patients, consistent with the literature *(16)*. However, we found a significant increase in the number of carbapenem-resistant GNB during the study period. This result parallels other recent reports from our hospital that have also shown an increase in resistant GNB in infections in the intensive care unit *(8)*. Moreover, in the last decade, several previous studies that have characterized the microbial agents of primary healthcare-associated bloodstream infections *(19,6)* and PJIs *(24,3,2)* reported consistent increases in infections due to GNB.

To make appropriate empirical antimicrobial decisions, the common microbiological causes of PJIs should be known. This is particularly important for patients with acute PJIs treated with debridement

Table IV. — Univariate analysis of risk factors for PJI in patients with PJI and the matched control group

	PJI group – n (%)	Control group – n (%)	P
Female Male	52 (74.3) 18 (25.7)	55 (74.3) 19 (25.7)	0.99
Age, mean±SD, years	66±15.8	62.1±9.8	0.08
THA TKA	58 (82.9) 12 (17.1)	56 (75.7) 18 (24.3)	0.28
Degenerative joint disease	30 (42.9)	59 (79.7)	0.0001
Fracture	29 (41.4)	9 (12.2)	0.0001
Congenital hip dysplasia	0	6 (8.1)	0.02
Malignancy	5 (7.1)	0	0.02
Type II diabetes mellitus	25 (35.7)	11 (14.9)	0.004
Coronary artery disease	7 (10)	2 (2.7)	0.09
Chronic obstructive pulmonary disease	5 (7.1)	0	0.02
Chronic renal failure	1 (1.4)	1 (1.4)	1
Malignancy	5 (7.1)	1 (1.4)	0.1
Rheumatoid arthritis	2 (2.9)	1(1.4)	0.6
Obesity	2 (2.9)	1(1.4)	0.6
Immunosuppression	3 (4.3)	3 (4.1)	1
Bacteriuria	2 (2.9)	1 (1.4)	0.6
Pyuria	1 (1.4)	6 (8.1)	0.1
Chronic liver disease	2 (2.9)	2 (2.7)	1
Blood transfusion	68 (98.6)	31 (41.9)	0.0001
Smoking	2 (2.9)	4 (5.4)	0.6
WBC median (min-max)	8,900 (3,400-20,000)	7,500 (3,200-14,300)	0.01
CRP median (min-max)	1.78 (0-31)	0.4 (0-11.3)	0.0001
ESR median (min-max)	36.5 (7-96)	27 (5-86)	0.6

PJI, prosthetic joint infection ; THA, total hip arthroplasty ; TKA, total knee arthroplasty ; a, number of patients with gram positive cocci ; b, Percentages of methicilin resistant S. aureus among the total number of isolated S.aureus ; c, Percentages of methicilin resistant coagulase-negative staphylococci among the total number of isolated coagulase-negative staphylococci ; d, number of patients with gram negative bacilli ; WBC, white blood cell ; CRP, c-reactive protein ; ESR, eritrosit sedimentation rat.

Table V. — Binary logistic regression analysis of risk factors for PJI

	B	P	OR	95% CI (Lower-Upper)
Fracture	1.467	0.001	4.3	1.78-10.5
Type II diabetes mellitus	1.431	0.002	4.1	1.66-10.5

PJI, prosthetic joint infection

and implant retention without a microbiological diagnosis before surgical treatment. Recent studies in different geographic areas have reported a higher frequency of gram-negative agents in surgical site infections following TJAs, ranging from 17% to 42% *(24,3,16,2,17)*. In our study, about half (45.7%) of the patients with PJI had GNB, while the other half (50%) had resistant agents (ESBL-positive and carbapenem-resistant). Empirical treatment is increasingly complicated by the increase in gram-negative agents and especially antibiotic resistance. As a recent study suggests, additional concerns have been raised about the appropriateness of currently recommended antibiotic prophylaxis for TJA that primarily addresses staphylococci *(24)*. However, our study was designed to assess trends within our hospital, and our results may not be generalizable to other hospitals in our country. The results of other centers are needed to make a thorough assessment.

While *S. aureus* infections are more common in the United States centers than in the European centers, the incidence of CNS infections is higher

in the European centers *(12,1)*. In a previous study, the incidence of MRSA in patients with PJI was significantly greater in the United States centers than in the European centers *(1)*. In our study, methicillin-resistant staphylococci were isolated in 24% (17/70) of all PJIs, among which only 4% was MRSA. In our country, methicillin-resistant CNS is isolated more frequently than MRSA in most of infections, in line with the findings of our study *(23)*.

Explanations for the observed microbial trends remain unclear. The use of preoperative prophylactic antibiotics with only gram-positive coverage may lead to a shift in microbiological etiology. However, the overuse of prophylactic antibiotics may increase the risk of infection caused by multidrug-resistant pathogens and alteration of intestinal flora *(31)*.

In delayed PJIs, the infecting organisms are generally less virulent, such as *Propionibacterium acnes*, enterococci, and CNS, and delayed PJIs may present similarly to aseptic failures *(16)*. In our study, CNS were commonly associated with PJIs and with delayed onset infections in particular, as reported in the literature *(16)*. However, GNB and polymicrobial etiology were associated with early onset PJIs in our patients.

In the current study, while staphylococci were present at significantly higher levels in PJI after TKA (75%), GNB occurred at significantly higher levels in PJI after THA (49.1%) ($p<0.001$ and $p=0.001$, respectively). In a previous study, the Bonferroni correction was performed for multiple comparisons of all organisms, and no difference was found between any of the species affecting TKA and THA *(5)*. In our study, polymicrobial infections were significantly higher in PJI after THA ($p=0.048$), as in a previous study *(28)*. *Acinetobacter* spp*., E. coli, Klebsiella* spp*., Enterococcus* spp., and *Candida* spp. were all detected in PJI after THA. Given the high rate of isolation of GNB and resistant GNB in the current study, carbapenem-resistant GNB should be considered when considering empirical antibiotic therapy for patients with PJI, especially in early onset PJI and PJI after THA.

Enterococcus species were isolated from 17% of PJI cases at our hospital. In a previous study, *Enterococcus* species were isolated from 5.2% of PJIs, with the majority of them isolated from infected THAs *(5)*. Given the challenging nature of enterococcal PJI, consideration should be given to empirical antibiotic treatment with *Enterococcus* coverage, especially for infected THAs. Coverage should be based on hospital-specific resistance profiles.

Fungal etiologies are rare in patients with PJIs *(5)*. In previous studies, fungal etiology was detected in 0.6-1.2% of the patients with PJIs *(24,3,5)*. In our study, fungal etiology was detected in two of the patients with PJI after THA (2/70, 2.9%), and it was *Candida* spp. in both cases. One of these patients had diabetes mellitus, while the other had a history of repeated surgery. Although we analyzed a small number of cases, the incidence of fungal etiology was slightly higher than that reported in previous studies.

Several studies have assessed the independent effect of multiple individual patient factors on preoperative infection risk *(9,15,4)*. In our study, the presence of various medical factors among patients with PJIs was compared with those without infection, and the following two independent risk factors for PJI were identified by multivariate analysis : diabetes mellitus and arthroplasty due to fracture. The mechanism by which diabetic patients are vulnerable to infection is not well understood, but it is very likely related to dysfunctional natural killer cells, which are responsible for infection control *(20)*. In our study, the presence of diabetes mellitus increased the odds of developing PJI by almost four-fold (OR, 4.1), as reported in the literature *(20)*. Several other studies have found PJI rates in diabetic patients to be higher than in nondiabetic patients *(15,30,34)*. In one previous study, fracture after trauma was found to be an independent predictor of surgical site infection in patients with total hip replacement *(26)*. Patients with pathological fractures or without a history of injury were excluded from the this study, and operation due to fracture was found to raise the odds of developing PJI by almost four-fold (OR, 4.3). This suggests that local and systemic reactions to trauma may predispose patients to an increased risk of infection.

Our study has some limitations. One such limitation is its retrospective and single-center design.

We included only patients with PJIs occurring within one year of TJA, and the etiological agents of PJIs presenting after one year may differ from the causative organisms of earlier infections. The power of our study was limited by the relatively small case number. Given the differences in patient characteristics as well as patient care and hospital factors, our results may not be generalizable to other institutions in our country. There is a need for further multi-center, prospective studies, especially on the incidence of GNB. Nevertheless, we believe that the results of this study are valuable owing to the large size of our center and the high number of arthroplasty cases performed per year.

CONCLUSIONS

According to our study, the most common infective organism in PJI was staphylococci. There was an increase in the percentage of GNB over time, especially carbapenem-resistant strains. GNB and polymicrobial etiology are associated with PJI after THA and early onset PJI. CNS are commonly associated with PJIs, especially delayed onset PJI, and methicillin resistance is more common in CNS than in *S. aureus*. Diabetes mellitus and arthroplasty due to fracture were independent risk factors for PJI in our patients. These results suggest that the empirical and targeted antimicrobial treatment of PJIs may become more difficult in the future. It may be necessary to reassess antimicrobial prophylaxis strategies and other preventive measures for patients undergoing joint replacement.

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