CLINICAL RESEARCH STUDY

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Clinical Presentation, Risk Factors, and Outcomes of Hematogenous Prosthetic Joint Infection in Patients with *Staphylococcus aureus* Bacteremia

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ABSTRACT

BACKGROUND: *Staphylococcus aureus* bacteremia is a life-threatening condition that may lead to metastatic infection, including prosthetic joint infection.

METHODS: To assess clinical factors associated with hematogenous prosthetic joint infection, we retrospectively reviewed all patients with a joint arthroplasty in place at the time of a first episode of *S. aureus* bacteremia over a 5-year period at our institution. Patients with postsurgical prosthetic joint infection without hematogenous prosthetic joint infection were excluded.

RESULTS: There were 85 patients (143 arthroplasties) with either no prosthetic joint infection (n = 50; 58.8%) or hematogenous prosthetic joint infection in at least one arthroplasty (n = 35; 41.2%). The odds of hematogenous prosthetic joint infection was significantly increased among patients with community-acquired *S. aureus* bacteremia (odds ratio [OR] 18.07; 95% confidence interval [CI] 2.64-infinity; $P = .001$), as compared with nosocomial *S. aureus* bacteremia, in which there were no patients with hematogenous prosthetic joint infection. After adjusting for *S. aureus* bacteremia classification, the presence of ≥3 joint arthroplasties in place was associated with a nearly ninefold increased odds of hematogenous prosthetic joint infection as compared with those with 1-2 joint arthroplasties in place (OR 8.55; 95% CI 1.44-95.71; $P = .012$). All but one joint with prosthetic joint infection demonstrated at least one clinical feature suggestive of infection. There were 4 additional *S. aureus* prosthetic joint infections diagnosed during a median of 3.4 years of follow-up post hospitalization for *S. aureus* bacteremia.

CONCLUSION: Prosthetic joint infection is frequent in patients with existing arthroplasties and concomitant *S. aureus* bacteremia, particularly with community-acquired *S. aureus* bacteremia and multiple prostheses. In contrast, occult *S. aureus* prosthetic joint infection without clinical features suggestive of prosthetic joint infection at the time of *S. aureus* bacteremia is rare.

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KEYWORDS: Arthroplasty; Bacteremia; Osteomyelitis; Prosthetic joint infection; *Staphylococcus aureus*

INTRODUCTION

Staphylococcus aureus bacteremia is the second leading cause of nosocomial-onset[1] and community-acquired bloodstream infection.[2] Complicated *S. aureus* bacteremia occurs in over 40% of the cases, with osteoarticular infection among the leading sites of metastatic infection.[3] Complications of *S. aureus* bacteremia that are unrecognized at the time of *S. aureus* bacteremia diagnosis may lead to inadequate therapy, increased morbidity, and relapse of infection.

Joint replacement is one of the most successful and frequently performed medical procedures. Over 1 million total hip and knee arthroplasties were performed in 2010 in the United States,[4] a number that is anticipated to top 4 million annually by 2030.[5] An estimated 4.2% of Americans older

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than 50 years currently have a knee replacement.[6] While the majority of prosthetic joint infections occur in the first 2 years after implantation,[7] joint arthroplasties remain vulnerable to hematogenous seeding throughout the lifespan of the prosthesis.

Several smaller studies have suggested that prosthetic joint infection occurs in 30% to 40% of patients with joint prostheses in place at the time of *S. aureus* bacteremia.[8-10] These studies suggested trends toward increased risk of prosthetic joint infection among patients with diabetes mellitus, community-acquired *S. aureus* bacteremia, knee arthroplasty, and methicillin-susceptible *S. aureus* bacteremia, but did not provide detailed analyses of the clinical presentations and orthopedic characteristics of patients with and without prosthetic joint infection. The purpose of this study was to identify clinical predictors of prosthetic joint infection in patients presenting with *S. aureus* bacteremia.

CLINICAL SIGNIFICANCE

- Community-acquired *Staphylococcus aureus* bacteremia and 3 or more arthroplasties are associated with increased risk of prosthetic joint infection during *S. aureus* bacteremia.
- Joint-specific associations with prosthetic joint infection include knee arthroplasty and prior revision surgery.
- While active investigation for prosthetic joint infection should be pursued in any symptomatic patient, occult prosthetic joint infection is rare.

METHODS

Study Setting and Participants

Patients hospitalized from June 1, 2006 to June 30, 2011 with *S. aureus* bacteremia at our institution were included in this analysis. Methodology for identification of *S. aureus* bacteremia cases, and inclusion and exclusion criteria are described in an earlier publication from this *S. aureus* bacteremia cohort.[11] The medical records of all patients in this database were reviewed, and all adults with a knee, hip, shoulder, or elbow arthroplasty in place at the time of their first episode of *S. aureus* bacteremia at our institution were included in this analysis. All patients provided consent to participate in research studies at Mayo Clinic. The study was approved by the Mayo Clinic Institutional Review Board.

Data Collection

Clinical data were obtained by review of the electronic medical records for all patients by one of the investigators (AJT or BRP). The definitions used are described in **Table 1**.[12,13] Cases in which the classification of hematogenous prosthetic joint infection vs primary/indeterminate prosthetic joint infection was not clear were reviewed with an additional author (DRO).

Following *S. aureus* bacteremia, medical records were reviewed until the latest adequate clinical visit or death in order to assess for *S. aureus* prosthetic joint infection not diagnosed during the initial hospitalization. Duration of follow-up was the difference between first positive blood culture and last recorded follow-up. Visits with an orthopedic surgeon or infectious diseases provider, a full physical examination with a general or subspecialty medical provider, or mail-in questionnaires obtained as part of the Mayo Clinic Joint Arthroplasty Registry[14] were considered sufficient for follow-up information.

Statistical Analysis

Data were collected and entered into a secure REDCap Database (Vanderbilt University, Nashville, TN). Continuous features were summarized with medians and interquartile ranges (IQRs); categorical features were summarized with counts and percentages. Associations with hematogenous prosthetic joint infection among patients with *S. aureus* bacteremia and at least one joint arthroplasty were evaluated using logistic regression models. A multivariable model was developed using stepwise selection, with the *P*-value for a feature to enter or leave the model set to .05. Overall survival rates were estimated using the Kaplan-Meier method and compared between patients with and without hematogenous prosthetic joint infection using log-rank tests. The duration of follow-up for the survival analyses was calculated from the date of first diagnosis of *S. aureus* bacteremia to the date of death or last follow-up. Statistical analyses were performed using the SAS software package (SAS Institute, Inc, Cary, NC). All tests were 2-sided, and *P*-values $<.05$ were considered statistically significant.

RESULTS

Of the 678 patients with *S. aureus* bacteremia in the study period, 97 (14.3%) patients had 166 arthroplasties in place at the time of bacteremia and were included in the present study. Fifty patients (51.6%) had no prosthetic joint infection, 35 (36.1%) had hematogenous prosthetic joint infection in at least one joint arthroplasty, and 12 (12.4%) had only primary postsurgical or indeterminate prosthetic joint infection, without hematogenous prosthetic joint infection. The 12 patients with only primary or indeterminate prosthetic joint infection were excluded, and the remaining 85 patients (143 arthroplasties) who had either no prosthetic joint infection ($n = 50$) or hematogenous prosthetic joint infection in at least one arthroplasty ($n = 35$), were included for analysis (**Figure 1**).

There was one case of prosthetic joint infection that did not meet the modified MusculoSkeletal Infection Society (MSIS) criteria.[13] After treatment of a cellulitis surrounding a toe ulcer, this patient developed pain in the contralateral knee

Table 1 Definitions of Terms Used in this Study

Term	Definition
Definition of SAB	More than one peripheral blood culture positive for *Staphylococcus aureus* or one positive peripheral blood culture with signs and symptoms of infection.
Classification of SAB*	
Community-acquired SAB	SAB present or incubating at the time of admission to the hospital, or associated with the first positive blood culture obtained within 48 h of admission, in a patient who does not meet criteria for health care-associated infection.
Nosocomial SAB	SAB developing in a patient hospitalized for more than 48 h before the onset of signs/symptoms consistent with bacteremia.
Health care-associated, community-onset SAB	SAB diagnosed within 48 h of admission in an outpatient with any of the following criteria: (1) Received intravenous therapy, wound care, or specialized nursing care at home within the 30 d before the onset of SAB; or (2) Attended a hospital or hemodialysis clinic or received intravenous chemotherapy within the 30 d before the onset of SAB; or (3) Was hospitalized in an acute care hospital for 2 or more days in the 90 d before the onset of SAB; or (4) Resided in a nursing home or long-term care facility.
Duration of bacteremia	Based on the duration between date of first positive blood culture and first negative blood culture.
Immunocompromising condition	Active malignancy. HIV. Neutropenia (absolute neutrophil count <500 cells/μL at any time during SAB). Prior hematopoietic stem cell or solid organ transplant. Immunosuppressive therapy in the 3 months befpre SAB: Systemic corticosteroids (more than 30 d), Nonbiologic disease-modifying agents (cyclosporine, methotrexate, or azathioprine), Tumor necrosis-alpha inhibitors, or Cytotoxic chemotherapy.
Definition of PJI†	
	S. aureus isolated from one sterile synovial fluid or tissue culture with any of the following criteria: (1) S. aureus isolated from a second sterile synovial fluid or tissue culture; or (2) Sinus tract communicating with the prosthesis; or (3) 4 of: Elevated ESR/CRP, synovial fluid WBC, synovial fluid PMN%, joint purulence, or acute inflammation on periprosthetic histopathologic examination; or (4) Two-investigator review.
Classification of PJI	
Primary PJI	Clinical course suggesting direct inoculation from surgery or contiguous spread of infection.
Hematogenous PJI	Presence of an alternate source for the SAB or acute onset of symptoms of PJI in a previously asymptomatic joint not meeting definition of primary PJI.
Indeterminate PJI	PJI that could not be confidently classified as either hematogenous or primary PJI.
PJI treatment failure	
	(1) Death related to SAB or PJI; or (2) Additional debridement for PJI >30 d or resection arthroplasty <2 y after a DAIR strategy; or (3) Resection for any reason <2 y after reimplantation among patients undergoing 2-stage exchange; or (4) Nonreimplantation due to ongoing PJI or subsequent surgery for PJI after reimplantation among subjects treated with resection.

CRP = C-reactive protein; DAIR = debridement and implant retention; ESR = erythrocyte sedimentation rate; HIV = human immunodeficiency virus; PJI = prosthetic joint infection; PMN% = neutrophil percentage; SAB = *Staphylococcus aureus* bacteremia; WBC = white blood cell count.

*Classification system from reference.[12]

†Definition modified from reference.[13]

arthroplasty and presented with *S. aureus* bacteremia and signs of prosthetic joint infection. This patient underwent debridement, from which a single operative specimen was sent. This sample grew *S. aureus* with identical susceptibility results to the blood culture isolate. No preoperative aspiration was performed. Operative histopathology demonstrated acute inflammation, and the patient had a high erythrocyte sedimentation rate and C-reactive protein, but lacked enough supporting criteria to fulfill the MSIS criteria for prosthetic joint infection. This was felt to be consistent with prosthetic joint infection based on 2-investigator review.

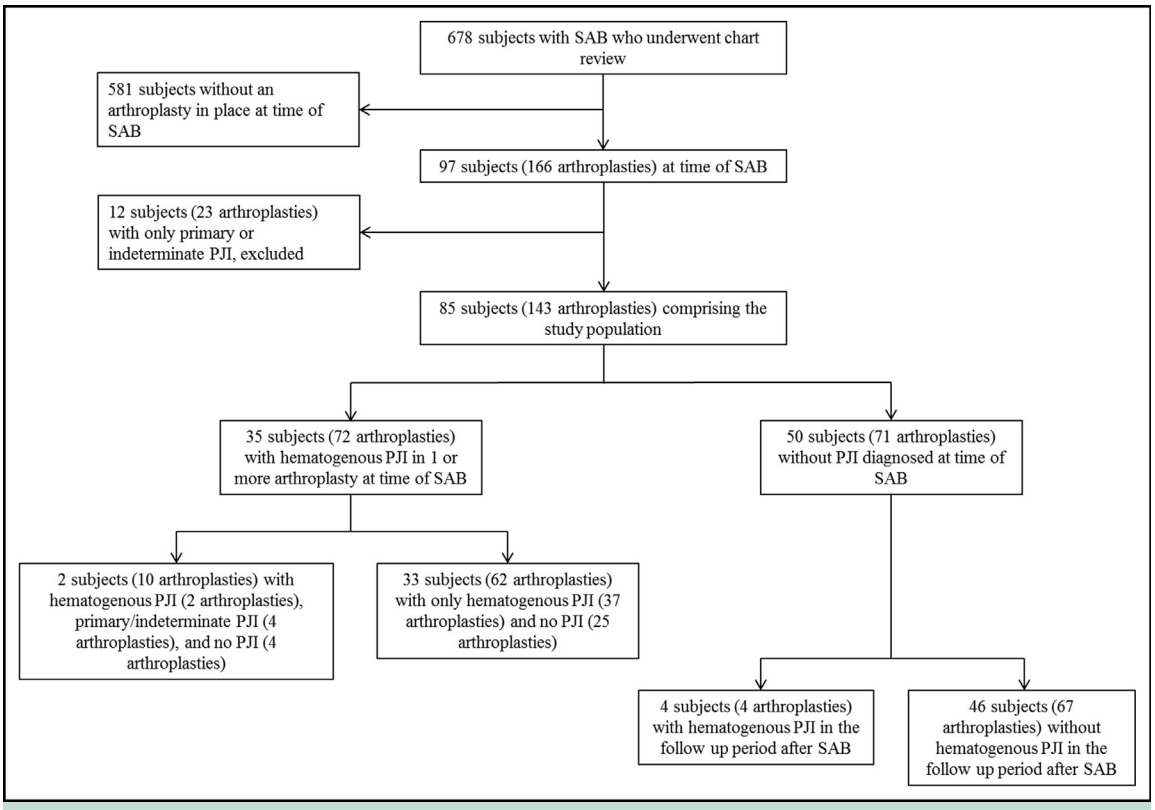

Figure 1 Flowchart of the study cohort. PJI = prosthetic joint infection.

Clinical Presentation at *S. aureus* Bacteremia Diagnosis

Table 2[15,16] includes the comparative analysis among patients with hematogenous prosthetic joint infection and those with no prosthetic joint infection. There were several nonstatistically significant differences among patients with hematogenous prosthetic joint infection, as compared with those without prosthetic joint infection. There was no difference in the presence of endocarditis between the 2 groups. Other observed complications of *S. aureus* bacteremia included vertebral osteomyelitis/diskitis (n = 9) and cardiac implantable electronic device infection (n = 7). Seven patients had a central venous catheter in place at the time of *S. aureus* bacteremia, none of whom developed a hematogenous prosthetic joint infection ($P = .041$). The catheter was the likely source of *S. aureus* bacteremia in 6 of 7 patients and was removed in all 7 patients. The classification of *S. aureus* bacteremia appeared to correlate with diagnosis of hematogenous prosthetic joint infection, as there were no patients with nosocomial *S. aureus* bacteremia diagnosed with hematogenous prosthetic joint infection. In contrast, patients with community-acquired *S. aureus* bacteremia had an 18-fold increased odds of being diagnosed with hematogenous prosthetic joint infection, compared with those with nosocomial *S. aureus* bacteremia (odds ratio [OR] 18.07; 95% confidence interval [CI], 2.64-infinity; $P = .001$). Community-onset health care-associated *S. aureus* bacteremia was associated with nonstatistically significant increased odds of hematogenous prosthetic joint infection, compared with nosocomial *S. aureus* bacteremia (OR 6.15; 95% CI, 0.86-infinity; $P = .075$). The number of prostheses in situ also correlated with hematogenous prosthetic joint infection, as the presence of 3 or more arthroplasties was associated with a greater than fivefold increased odds of hematogenous prosthetic joint infection, compared with 2 or fewer arthroplasties (OR 5.42; 95% CI, 1.35-21.81; $P = .017$). Multivariable logistic regression analysis demonstrated that both the classification of *S. aureus* bacteremia and the number of joint arthroplasties in place were jointly significantly associated with hematogenous prosthetic joint infection (Table 3). After adjusting for the classification of *S. aureus* bacteremia, the presence of 3 or more joint arthroplasties in place was associated with nearly ninefold increased odds of hematogenous prosthetic joint infection, compared with patients with only 1-2 joint arthroplasties in place (OR 8.55; 95% CI, 1.44-95.71; $P = .012$).

Arthroplasty Characteristics

Overall, 85 patients had 143 arthroplasties in place: 47 patients had 1, 26 patients had 2, 7 patients had 3, 3 patients had 4, 1 patient had 5, and 1 patient had 6 arthroplasties. The arthroplasty locations were knee (n = 73), hip (n = 59), shoulder

Table 2 Univariable Associations with Hematogenous PJI

	No PJI (n = 50)	Hematogenous PJI (n = 35)	*P*-Value
Baseline features			
Female sex	19 (38%)	11 (31.4%)	.53
Age, in y	75.5 (65-83)	69 (63-80)	.34
Diabetes mellitus*	14 (28%)	7 (20%)	.4
Rheumatoid arthritis†	3 (6%)	6 (17.1%)	.11
Active malignancy	11 (22%)	3 (8.6%)	.11
Immunocompromising condition‡	18 (36%)	11 (31.4%)	.61
Chronic skin condition§	8 (16%)	3 (8.6%)	.32
Central venous catheter	7 (14%)	0	.041
Number of arthroplasties in place per subject	1 (1-2)	2 (1-3)	.008
Subjects with three or more arthroplasties in place	3 (6%)	9 (25.7%)	.017
Clinical SAB presentation			
ESR, in mm/h‖	61 (40-70)	78 (32-91)	.13
CRP, in mg/L¶	193 (67-252)	240 (133-310)	.12
Time to positive blood cultures, in h	13.4 (10.5-16.7)	14.5 (12-21.5)	.6
Duration of bacteremia based on symptoms, in d	5 (3-10)	7 (5-8)	.7
Duration of bacteremia based on cultures, in d	4 (2-8)	4 (3-7)	.48
Endocarditis**	8 (16%)	3 (8.6%)	.32
Classification of SAB			
Nosocomial	10 (20%)	0	
Community acquired	17 (34%)	24 (68.6%)	.001††
Community onset health-care associated	23 (46%)	11 (31.4%)	.075††
Oxacillin susceptible	32 (64%)	29 (82.9%)	.062

Categorical variables expressed in absolute number and (percentage); continuous variables expressed in median and (interquartile range).
CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; PJI = prosthetic joint infection; SAB = *Staphylococcus aureus* bacteremia.
*Based on the recorded medical history.
†Based on review of the medical record using the 2010 American College of Rheumatology classification criteria.[15]
‡Immunocompromising conditions included immunosuppressive medications (n = 22), active malignancy (n = 14), or neutropenia (n = 2). Patients could have more than one cause for immunocompromise.
§Includes vascular or decubitus ulcers, chronic dermatitis, or psoriasis.
‖ESR was known in 56 patients.
¶CRP was known in 58 patients.
**Definite cases using the modified Duke Criteria.[16]
††*P*-values were calculated through logistic regression modeling. In the presence of a 0 count, odds ratios were estimated using exact logistic regression.

(n = 10), and elbow (n = 1). Among the 35 patients with at least one hematogenous prosthetic joint infection, there were 39 arthroplasties that were hematogenously infected, one arthroplasty that was a primary prosthetic joint infection, and 3 others that were indeterminate (**Figure 1**). After excluding the 4 primary or indeterminate prosthetic joint infections, there were 139 joint arthroplasties in 85 patients (**Table 4**). Previously revised joints were significantly more likely to develop hematogenous prosthetic joint infection (OR 3.35; 95% CI, 1.36-8.23; $P = .01$). When analysis was limited to only hip and knee arthroplasties, hematogenous prosthetic joint infection occurred in 25 (35.2%) of 71 knee arthroplasties and 11 (18.6%) of 59 hip arthroplasties ($P = .036$). Of the 8 shoulder arthroplasties, 3 (37.5%) developed hematogenous prosthetic joint infection. There was one elbow arthroplasty that did not develop infection.

The most common signs and symptoms of prosthetic joint infection were joint pain (97.4%), periarticular swelling or effusion (61.5%), and periarticular warmth (46.2%). In one patient, there was bilateral knee prosthetic joint infection, although there were no symptoms in one knee. This patient presented with *S. aureus* bacteremia secondary to post-thoracotomy *S. aureus* pleural empyema and a painful right

Table 3 Associations with Hematogenous PJI on Multivariable Analysis

Characteristic	Odds Ratio (95% CI)	*P*-Value
Classification of SAB		
Nosocomial	1.0 (reference)	
Community onset health-care associated	5.91 (0.77-infinity)	.095
Community acquired	21.39 (2.92-infinity)	.001
Number of arthroplasties in place		
1-2	1.0 (reference)	
3 or more	8.55 (1.44-95.71)	.012

P-values were calculated through logistic regression modeling. In the presence of a zero count, odds ratios were estimated using exact logistic regression.
CI = confidence interval; PJI = prosthetic joint infection; SAB = *Staphylococcus aureus* bacteremia.

Table 4 Orthopedic Characteristics of the Joint Arthroplasties in Place at Time of SAB

	No PJI (n = 100)	Hematogenous PJI (n = 39)	*P*-Value*
Location of joint arthroplasty			
Knee	46 (46%)	25 (64.1%)	.12
Hip	48 (48%)	11 (28.2%)	
Shoulder	5 (5%)	3 (7.7%)	
Elbow	1 (1%)	0	
Revision surgery before SAB†	13 (18.3%)	15 (42.8%)	.01
Time from arthroplasty implantation to SAB, in y	7.9 (3.3-14.4)	11.3 (3.0-16.0)	.47
Time from last surgery to SAB, in y	7.3 (3.0-12.2)	5.7 (2.5-11.3)	.35
Joint symptoms and examination‡			
Joint pain	14 (14%)	38 (97.4%)	<.001
Periarticular erythema	2 (2%)	7 (17.9%)	.002
Drainage	0	0	
Periarticular warmth	0	18 (46.2%)	<.001
Swelling/effusion	3 (3%)	24 (61.5%)	<.001
Decreased range of motion	1 (1%)	8 (20.5%)	<.001
None of the above	83 (83%)	1 (2.6%)	<.001

Categorical variables expressed in absolute number and (percentage); continuous variables expressed in median and (interquartile range).
PJI = prosthetic joint infection; SAB = *Staphylococcus aureus* bacteremia.
**P*-values were calculated using chi-squared or Fisher's exact test for categorical variables and Wilcoxon Rank-Sum test for continuous variables.
†Previous revision status was known for only 71 and 35 joints without and with hematogenous PJI, respectively.
‡Each arthroplasty may be associated with more than one sign/symptom.

knee arthroplasty. Orthopedic surgery evaluation noted effusion and warmth about the right knee, but there were no abnormalities in the left hip or left knee arthroplasty. While performing debridement of the right knee, aspiration of the asymptomatic left knee confirmed the presence of *S. aureus* prosthetic joint infection.

Treatment of *S. aureus* Bacteremia

All patients received intravenous antimicrobial therapy for *S. aureus* bacteremia (Table 5). Nine (18%) patients without prosthetic joint infection and 4 (11.4%) patients with prosthetic joint infection died before completion of parenteral antimicrobial therapy. Among patients who completed

Table 5 Antimicrobial Therapy Used

	No PJI (n = 50)	Hematogenous PJI (n = 35)
Subject died during intravenous antimicrobial course	9 (18%)	4 (11.4%)
Median duration of intravenous antimicrobial therapy, in d (IQR)*	32 (22-40)	41 (40-47)
Type of intravenous antimicrobial†		
Anti-staphylococcal penicillin	9 (18%)	4 (11.4%)
Cephalosporin	21 (42%)	18 (51.4%)
Ertapenem	1 (2%)	0
Vancomycin	16 (32%)	9 (25.7%)
Daptomycin	2 (4%)	3 (8.6%)
Linezolid	1 (2%)	1 (2.9%)
Combination antimicrobial used		
None	47 (94%)	20 (57.1%)
Gentamicin	1 (2%)	0
Rifampin‡	1 (2%)	15 (42.9%)
Gentamicin and rifampin	1 (2%)	0
Oral antimicrobial(s) after intravenous antimicrobial§	8 (16%)	22 (62.9%)

Categorical variables expressed in absolute number and (percentage).
DAIR = debridement and implant retention; IQR = interquartile range; PJI = prosthetic joint infection.
*Among the 72 patients who survived to completion of intravenous antimicrobials.
†The definitive antimicrobial was the antimicrobial(s) used for ≥50% of the treatment course.
‡Rifampin was used in combination with DAIR procedure in patients with PJI and due to persistent bloodstream infection with multifocal soft tissue abscesses in the patient without.
§Reasons for subsequent oral antimicrobials include DAIR procedure (n = 17), spine infection (n = 7), concern for relapse after arthroplasty reimplantation (n = 3), retained spacer (n = 1), high risk of cardiac device seeding (n = 1), and vascular graft infection (n = 1).

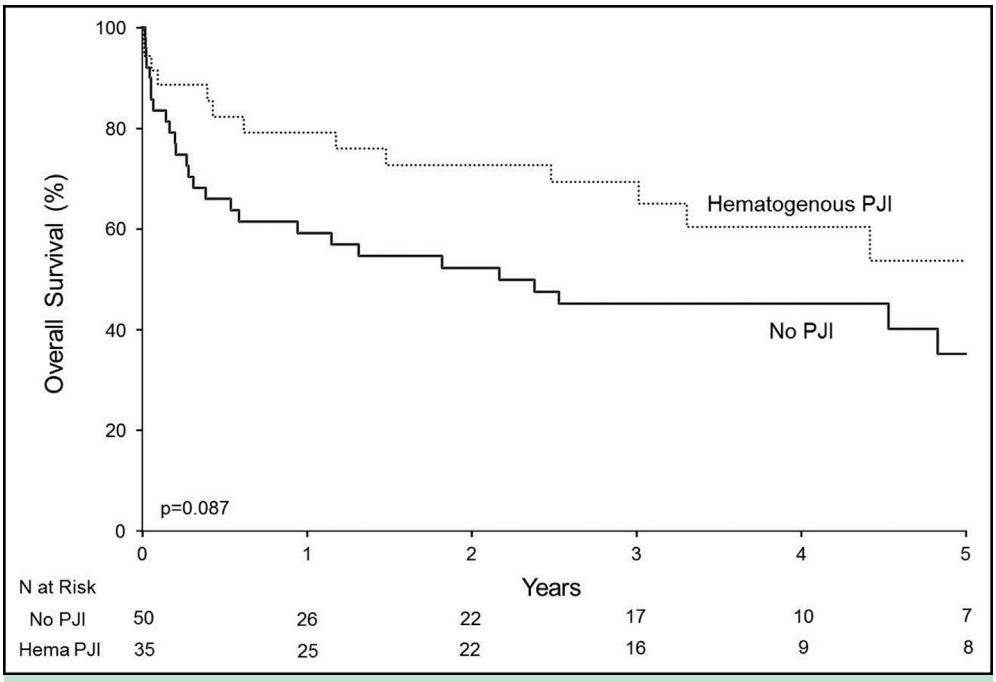

Figure 2 Overall survival among patients with and without hematogenous prosthetic joint infection. There was not a statistically significant difference in likelihood of mortality among patients with or without hematogenous prosthetic joint infection ($P = .087$). Dotted line = subjects with hematogenous prosthetic joint infection (n = 35); solid line = subjects without hematogenous prosthetic joint infection (n = 50). The rows below the Figure show the number of patients at risk of mortality at each year. PJI = prosthetic joint infection; SAB = *Staphylococcus aureus* bacteremia.

parenteral antimicrobial therapy, the median duration of intravenous antimicrobials was >4 weeks in both groups. Among the 35 patients with hematogenous prosthetic joint infection, 32 underwent either resection of the arthroplasty, or irrigation and debridement with implant retention (DAIR) for treatment of prosthetic joint infection. The remaining 3 patients had significant medical comorbidities and were managed with comfort-focused care rather than surgical treatment; all 3 died within 60 days. Among those with prosthetic joint infection who underwent DAIR (n = 17), 15 were treated with a rifampin-based regimen, and subsequent chronic oral antimicrobial suppression was given to 17 patients. Two patients without prosthetic joint infection at presentation received rifampin.

Follow-up and Subsequent Prosthetic Joint Infection

At 30 days after the first positive blood culture, 32 (91.4%) of 35 and 42 (84%) of 50 patients with and without hematogenous prosthetic joint infection were alive, respectively ($P = .51$). During the follow-up period, 14 of 35 patients with hematogenous prosthetic joint infection and 29 of 50 patients without prosthetic joint infection died at a median of 11 and 4 months after *S. aureus* bacteremia diagnosis, respectively (Figure 2; $P = .087$). Among the surviving patients, the latest follow-up was a median of 3.3 years (IQR 2.6-5.3 years) and 3.4 years (IQR 1.4-4.5 years) after *S. aureus* bacteremia in those with and without hematogenous prosthetic joint infection, respectively. Prosthetic joint infection treatment was successful in 26 (74.3%) of 35 patients and 29 (67.4%) of 43 arthroplasties with prosthetic joint infection. Among the 9 patients with 14 prosthetic joint infections who failed treatment, reasons for treatment failure included arthroplasty resection/component resection after DAIR (n = 7 arthroplasties), death due to *S. aureus* bacteremia (n = 6 arthroplasties, 4 patients), and repeat debridement >30 days after DAIR (n = 1 arthroplasty). One patient with bilateral knee prosthetic joint infection was treated with bilateral DAIR, with successful treatment of the left knee and treatment failure of the right knee, despite ongoing suppressive antimicrobials. This patient experienced ongoing culture-positive right knee prosthetic joint infection and was treated with a one-stage exchange procedure 169 days after his *S. aureus* bacteremia episode.

There were 4 patients who had *S. aureus* prosthetic joint infection during the follow-up period, all occurring in the 50 patients without prosthetic joint infection during the initial hospitalization; these 4 had complicated *S. aureus* bacteremia at initial hospitalization (Table 6). Patient 4 is classified as a possible *S. aureus* prosthetic joint infection. Nearly 18 months after being treated for *S. aureus* bacteremia with multiple metastatic foci, this patient developed increasing left knee arthroplasty pain. Knee aspiration, performed while on

Table 6 Details of the 4 Patients Diagnosed with Subsequent *Staphylococcus aureus* PJI During Follow-up Period

Patient	Patient Age at SAB, in y	Duration From Last Joint Surgery to SAB, in y	Foci of Initial SAB	Classification of SAB	Duration of Bacteremia, in d	Intravenous Antimicrobial Duration for SAB, in d	Suppressive Oral Antimicrobials After Intravenous Antimicrobials	Duration Between SAB Clearance and PJI Diagnosis, in d	Susceptibilities at Subsequent PJI	Joint Infected	Recurrent SAB at PJI Diagnosis
1	67	6.4	MSSA, Septic thrombophlebitis	Nosocomial	3	Cefazolin, 15	None	316	Identical	THA	Yes
2	71	23.3	MRSA, Aortic graft infection	Community onset HCA	4	Vancomycin, 24	Minocycline	670	Identical	TKA	Yes
3	89	2.1	MRSA, native shoulder septic arthritis	Community onset HCA	4	Vancomycin, 42	Minocycline	174	Identical	THA	No
4*	59	0.7	VISA, native valve IE, psoas abscesses, vertebral osteomyelitis with epidural abscess	Community onset HCA	12	Linezolid, 94	TMP/SMX	503	Not available (see text)	TKA	No

HCA = health care associated; IE = infective endocarditis; MSSA = methicillin susceptible *S. aureus*; MRSA = methicillin resistant *S. aureus*; PJI = prosthetic joint infection; SAB = *Staphylococcus aureus* bacteremia; THA = total hip arthroplasty; TKA = total knee arthroplasty TMP/SMX = trimethoprim/sulfamethoxazole; VISA = Vancomycin intermediate *S. aureus*.

*Possible infection, see text for discussion.

suppressive trimethoprim/sulfamethoxazole, revealed >4500 nucleated cells with negative cultures. Repeat aspiration following antimicrobial discontinuation had a similar cell count and negative cultures. He underwent arthroplasty resection, and operative inspection was consistent with prosthetic joint infection. However, cultures were negative and no histopathology was obtained. The treating clinician felt that *S. aureus* prosthetic joint infection was likely.

DISCUSSION

This is the largest cohort to date to address hematogenous infection of prosthetic joints in patients with *S. aureus* bacteremia, and the first to analyze risk factors associated with prosthetic joint infection in *S. aureus* bacteremia patients using multivariable analysis. After excluding patients who had only primary prosthetic joint infection, we observed hematogenous prosthetic joint infection in 41% of patients and 27% of arthroplasties. This frequency is similar to that of previous smaller studies[8-10] and comparable with studies of *S. aureus* bacteremia in the setting of other types of implantable prosthetic devices.[17]

All of the hematogenous prosthetic joint infection cases in our patient cohort occurred with community-acquired or community-onset health care-associated *S. aureus* bacteremia, which supports existing literature that complicated *S. aureus* bacteremia is significantly more likely in these settings than in nosocomial *S. aureus* bacteremia.[3,18] Correspondingly, there were no cases of nosocomial *S. aureus* bacteremia or catheter-associated *S. aureus* bacteremia in which hematogenous prosthetic joint infection was diagnosed. This may have been due to rapid diagnosis and initiation of empiric antimicrobial therapy in nosocomial *S. aureus* bacteremia cases. This observation is consistent with an earlier smaller study where no episodes of hematogenous prosthetic joint infection were observed in nosocomial *S. aureus* bacteremia cases.[10] The presence of 3 or more arthroplasties remained significantly associated with hematogenous prosthetic joint infection, even after controlling for *S. aureus* bacteremia classification, a finding not previously observed. Similar to prior studies, we did not observe a significant association between hematogenous prosthetic joint infection and immunocompromising conditions.[8-10]

Hematogenous prosthetic joint infection was significantly more frequent in knee arthroplasty as compared with hip arthroplasty, occurring nearly twice as often. These findings expand on prior reports showing nonsignificant trends of increased hematogenous prosthetic joint infection in knee arthroplasty during *S. aureus* bacteremia[9] and remote infection with other organisms.[19] Native septic arthritis, which is typically hematogenous, also displays a predilection for the knee,[20,21] perhaps owing to the more complex mechanics of the knee joint as compared with the hip. Previous arthroplasty revision was also associated with an increased risk of hematogenous prosthetic joint infection, a novel finding. One postulated mechanism for this may be the increased prosthesis size sometimes required for revision arthroplasty to

compensate for previous bone loss. This may create more surface area for bacterial attachment during *S. aureus* bacteremia. There was no association between risk of hematogenous prosthetic joint infection and time from primary joint arthroplasty or prior surgery, similar to prior findings.[9,10]

A finding of this study that is highly clinically relevant and not previously reported, is that 97% of hematogenously infected arthroplasties had at least one sign or symptom suggestive of infection in the affected joint. While no single sign or symptom is present in all cases of prosthetic joint infection, pain is present in more than 75% of cases of prosthetic joint infection in other studies.[22] Similarly, all but one episode of prosthetic joint infection was associated with pain in this study. While a sinus tract communicating with the arthroplasty is considered definitive evidence of prosthetic joint infection,[23] this was not seen here, supporting the acute hematogenous nature of these prosthetic joint infections. Among the 100 arthroplasties that did not display signs or symptoms suggestive of prosthetic joint infection at the time of *S. aureus* bacteremia, treated with a median of 32 days of intravenous antimicrobials, 96 remained free of prosthetic joint infection until death or loss to follow-up. Although we believe that antimicrobial therapy alone has a low likelihood of success in treatment of unrecognized prosthetic joint infection,[24] we cannot exclude the possibility that the treatment provided for *S. aureus* bacteremia was sufficient to prevent subsequent overt prosthetic joint infection. These data suggest that while prosthetic joint infection associated with *S. aureus* bacteremia occurs frequently, there will typically be signs or symptoms suggestive of prosthetic joint infection at presentation. Accordingly, patients in whom a careful history and physical examination do not suggest prosthetic joint infection can be clinically monitored while undergoing treatment for *S. aureus* bacteremia.

There are several limitations to this study inherent to its retrospective nature. The study relied on data recorded in the medical record. Not every patient had the same evaluation for possible prosthetic joint infection, and misclassification bias is possible, particularly among patients with severe sepsis and early death from *S. aureus* bacteremia. However, some evaluation for prosthetic joint infection was performed in the majority of the 50 patients without hematogenous prosthetic joint infection, as evidenced by orthopedic surgery consultation (n = 25), plain radiograph (n = 14), or joint aspirate (n = 7). This suggests that the diagnosis of hematogenous prosthetic joint infection was at least considered and may lower the likelihood of misclassification. It is often difficult to differentiate hematogenous prosthetic joint infection from primary prosthetic joint infection initiated at the time of surgery. By using 2 investigator reviews and designating unclear cases as indeterminate, we attempted to minimize this. However, misclassification of the type of prosthetic joint infection is possible. Due to the relatively small sample size, our multivariable analysis was limited. Therefore, it is possible that there were unmeasured confounders underlying some of our observed findings. This may be true with patients with multiple arthroplasties, in whom an inflammatory joint disease might be more likely, and may partially contribute to a higher likelihood of prosthetic joint infection in this group. Finally, our large tertiary, referral center serves many patients with complicated orthopedic histories and multiple prostheses. Accordingly, the absolute frequency of prosthetic joint infection during *S. aureus* bacteremia may be lower in other settings. However, we suspect that the overall findings and implications of this study are valid.

In summary, these data indicate that hematogenous prosthetic joint infection is frequently seen among patients with *S. aureus* bacteremia, and that clinical signs or symptoms of prosthetic joint infection are typically present. Prosthetic joint infection is less common in patients with nosocomial *S. aureus* bacteremia, particularly when only a single arthroplasty is in place.

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