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.

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