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Changes in Antibiotic Susceptibility of *Staphylococcus aureus* Between the Stages of 2-Stage Revision Arthroplasty

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ABSTRACT

Background: *Staphylococcus aureus* is the predominant cause of periprosthetic joint infection (PJI) and can persist at the time of planned second stage of 2-stage revision arthroplasty, despite antibiotic cement spacer insertion and parenteral antibiotic therapy. Given the rapid emergence of antibiotic resistance, it is important to determine whether the antibiotic susceptibility of microorganisms changes between the stages of a 2-stage revision.

Methods: A total of 1614 2-stage revision hip/knee arthroplasties performed for PJI at 2 academic institutions from 2000 to 2015 were identified. *S aureus* (methicillin susceptible and/or resistant) was isolated by culture in 402 (24.9%) cases during the first stage (resection arthroplasty). *S aureus* persisted and was cultured in 30 cases (knees = 18, hips = 12) during the second stage. Minimum inhibitory concentrations (MICs), demographics, antibiotic therapy, and surgical history were collected. The MICs at the time of the first-stage and second-stage surgeries were compared.

Results: Nine (30%) revisions had an increase in vancomycin MIC. Six had an increase from ≤0.5 to 1 μg/mL, 2 had an increase from ≤0.5 to 2 μg/mL, and 1 had an increase from 1 to 2 μg/mL. All of the 9 revisions with an increase in vancomycin MIC had vancomycin in spacer.

Conclusion: Increases in the MICs were observed for vancomycin, the antibiotic widely used in cement spacers, in about one-third of the revisions. Despite the small sample size, the data from this preliminary study raise concern about the potential for emergence of resistant organisms between the stages of a 2-stage revision.

Periprosthetic joint infection (PJI) is a serious complication of total hip and knee arthroplasty with an overall incidence of approximately 1.5 infections per 1000 person-joint-years [1,2]. Currently, 2-stage revision arthroplasty, which involves the removal of prosthesis, and the implantation of a temporary antibiotic cement spacer, is the most widely used treatment for PJI [3,4]. In addition to the local delivery of the high dose of antibiotics, patients are administered parenteral antibiotic therapy for 6 to 8 weeks before attempting prosthesis reimplantation. Despite the delivery of both parenteral and high local concentrations of antibiotics, the 2-stage revision surgeries have a reported success rate approaching 70% to 80%, with some suggesting that success rates of these procedures are on the decline [5–10]. The majority of failed 2-stage revisions is thought to be due to the inability to eradicate the original infection before proceeding with the second-stage reimplantation [11,12].

Staphylococcus aureus (methicillin-susceptible *S aureus* [MSSA] or methicillin-resistant *S aureus* [MRSA]) is the predominant microbial species causing PJI and is responsible for approximately 50% to 60% of the culture-positive PJIs [1,2,13]. The microorganisms isolated at the time of the second-stage surgery may or may not be the same species initially responsible for the PJI. Isolation of the same species of microorganism is most likely due to persistence of the original pathogen, while a different species might be isolated if it was acquired during the interim period (ie, between the first-stage and second-stage surgeries), or went undetected during the

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first-stage surgery. When the same species is isolated at the second-stage surgery, this may be related to its susceptibility to the antibiotics used in spacers and/or the antibiotic concentration that was delivered locally [14–17]. Previous studies have shown that spacers retain their eluting properties for long periods, suggesting that the latter (ie, susceptibility of these organisms to the antibiotics used in spacers) is the issue [14–17]. Furthermore, the antibiotic content of spacers usually differs from those administered systemically, which are based on the culture sensitivity [18]. This might expose the organisms to various concentrations of multiple antimicrobial agents, some of which may be subtherapeutic, thereby increasing the risk for emergence of resistant strains [19,20].

With an increased focus on antibiotic resistance, it is important to determine whether antibiotic spacers increase the minimum inhibitory concentrations (MICs) of microorganisms to the antibiotics that are commonly used in spacers, such as vancomycin [18,19]. Previous studies have examined the susceptibility patterns of microorganisms that cause PJI [21,22]. However, these studies were limited to those isolated at the time of first-stage surgery and did not evaluate the changes in the antibiotic susceptibility following the insertion of antibiotic spacers [21,22].

Therefore, we asked: (1) what proportion of the persistent *S aureus* shows an increase in the MIC of various antibiotics, especially vancomycin; and (2) what factors are associated with the increase in MICs?

Methods

This was a multicenter, retrospective study of patients who had a PJI caused by *S aureus* and underwent a 2-stage revision hip or knee arthroplasty between 2000 and 2015, but had persistence of *S aureus* at the time of their planned second-stage surgery. After obtaining approval from the institutional review boards, data, including microbiology information related to the MIC of organisms against various antibiotics at the time of first-stage and second-stage surgeries, were reviewed and collected from electronic medical records.

Participants/Study Subjects

A total of 1614 2-stage revision hip/knee arthroplasties performed at 2 large academic institutions were identified from the infection databases at these institutions. *S aureus* (MSSA or MRSA) was isolated at the time of antibiotic spacer insertion (first-stage surgery) in 402 (24.9%) cases. These revisions were screened to determine those in which *S aureus* persisted at the time of antibiotic spacer removal (ie, second-stage surgery), which identified 30 cases (knees = 18, hips = 12) to be included in the study cohort.

During the first-stage revision surgery, all patients had their implants removed followed by irrigation and debridement. An antibiotic cement spacer was then implanted; the cement spacers were composed of tobramycin plus vancomycin (n = 23), tobramycin alone (n = 4), vancomycin alone (n = 2), or tobramycin plus daptomycin (n = 1). The second stage of the 2-stage revision was usually attempted after at least 6-8 weeks of parenteral antibiotic therapy, and an antibiotic holiday of approximately 2 weeks. The median duration between the first-stage and second-stage surgeries was 101 days (interquartile range, 73 to 137 days). The decision to reimplant or to perform a spacer exchange was made on the basis of clinical features, preoperative laboratory parameters, and intraoperative findings. At the planned second stage, a total of 4 revisions underwent reimplantation, whereas the remaining 26 revisions had a spacer exchange or a similar procedure due to concerns of persistent infection. The antibiotic selection was based on culture sensitivity reports and the respective institutions' guidelines. All patients were initially on broad-spectrum antibiotics based on the recommendations of infectious disease specialist, and the regimen was altered in 17 patients after intraoperative culture results were obtained. In the remaining 13 patients, the same antibiotic was continued. Intravenous (IV) antibiotics used after first stage were vancomycin 15 mg/kg q12 h (n = 12), daptomycin 6 mg/kg IV q24 h (n = 11), cefazolin 1-2 g IV q8 h (n = 4), nafcillin 1.5-2 g IV q4-6 h (n = 1), ampicillin-sulbactam 3 g IV q6 h (n = 1), and ceftaroline 200 mg IV q12 h (n = 1). The dose of vancomycin was adjusted to maintain a trough level between 10-20 mg/L. In addition to the IV therapy, some patients also received oral antibiotics (rifampin = 6, ciprofloxacin = 2, doxycycline = 1, metronidazole = 1) based on the infectious disease specialists' recommendations.

Cultures were obtained preoperatively (synovial fluid) and intraoperatively (synovial fluid and multiple tissue specimens from different areas) based on the surgeons' preferences. The median number of cultures taken at the first stage was 4 (range = 2 to 8), while that at the second stage was 4 (range = 1 to 10). We did not have any predefined number of positive cultures for a revision to be considered as truly infected. However, all the patients in the study had more than one positive cultures with *S aureus* at the first stage, and all expect 4 patients had more than one positive cultures with *S aureus* at the second stage. As *S aureus* is a virulent pathogen and is rarely considered to be a contaminant, we believe that it is reasonable to assume *S aureus* as a true pathogen even if only 1 culture was positive. Moreover, as patients who had a single positive culture at second stage had established infection with the same organism, this is unlikely to have been a contaminant.

MICs, which are the lowest concentrations of antibiotics that prevent growth of the microorganisms, were obtained from laboratory reports [23]. The MIC values were reported over a predetermined range that was specific for each antibiotic, based on the Clinical and Laboratory Standards Institute susceptibility testing guidelines [24]. For example, the vancomycin MICs of susceptible *S aureus* are reported as $\leq$ 0.5 μg/mL, 1 μg/mL, or 2 μg/mL [25]. The MICs were tested using commercially available automated systems routinely used at the respective institutions (VITEK at institution 1 and Pheonix at institution 2); however, MIC measurements are expected to have a measurement error of 1 dilution [26]. The MICs of all antibiotics were not usually assessed for every specimen. The choice of antibiotics to be tested for each specimen was based on the laboratory guidelines at the 2 institutions.

The MICs of the organisms isolated at the time of planned second-stage surgery were compared with the MICs of the corresponding first-stage surgery to see whether there was any increase in the MICs. All antibiotics whose MICs were recorded in the culture reports were analyzed. A comparison between the first-stage and second-stage surgery MICs was only possible when the MIC data were available for both specimens. With the exception of vancomycin and oxacillin, the MICs of other antibiotics were not routinely evaluated. The proportion of revisions in which there was an observed increase in the MICs was noted. To account for the lack of data in certain specimens, the number of revisions with complete data were used as the denominator when calculating proportions for different antibiotics (Table 1). Due to the limited sample size, only the factors (age, gender, body mass index (BMI), Charlson comorbidity score, joint type, culture results, and relevant surgical history including number of prior surgeries on the joint and previous spacer use) associated with increase in vancomycin MIC were evaluated. Fisher exact tests were used to detect differences between categorical variables, and Wilcoxon rank sum tests were used to compare continuous variables. The threshold for statistical significance for all analyses was set at less than 0.05. Statistical analysis was performed using R software (version 3.1.3, Vienna, Austria) [27].