Delay in Diagnosis of Invasive Surgical Site Infections Following Knee Arthroplasty Versus Hip Arthroplasty

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Background. The timing of diagnosis of invasive surgical site infection (SSI) following joint replacement surgery is an important criterion used to determine subsequent medical and surgical management.

Methods. We compared time to diagnosis of invasive SSI following hip vs knee arthroplasty. SSIs were included in the analysis if they occurred within 365 days following procedures performed from 1 January 2007 through 31 December 2011 at 36 community acute care hospitals and 1 ambulatory surgery center in the Duke Infection Control Outreach Network. A Cox regression model was fitted to estimate the association between procedure type and time to diagnosis of SSI, adjusted for age, pathogen virulence, American Society of Anesthesiologists’ score, and hospital surgical volume.

Results. Six hundred sixty-one invasive SSIs were identified; 401 (61%) occurred following knee arthroplasties. The median time to diagnosis of SSI was 25 days (interquartile range [IQR], 17–48 days) following hip arthroplasty vs 42 days (IQR, 21–114 days) following knee arthroplasty (unadjusted hazard ratio [HR], 1.60; 95% confidence interval [CI], 1.37–1.87; P < .001). Time to diagnosis of invasive SSI remained significantly shorter for hip than for knee arthroplasties after adjusting for age, pathogen virulence, and hospital surgical volume (HR, 1.51; 95% CI, 1.28–1.78; P < .001).

Conclusions. The diagnosis of invasive SSI was delayed following knee arthroplasty compared with hip arthroplasty. We hypothesize that differences in symptom manifestation and disparities in access to care may contribute to the observed differential timing of diagnosis. Our findings have important implications for the management of prosthetic joint infections, because treatment strategies depend on the timing of diagnosis.

Keywords. prosthetic joint infection; surgical site infection; hip arthroplasty; knee arthroplasty.

Prosthetic joint infection is a serious complication of joint replacement surgery. Treatment typically requires aggressive surgical debridement and prolonged courses of antibiotics [1–3]. Many patients require removal of the prosthesis, and some patients will develop recurrent infections despite surgical and medical management [4, 5]. Overall, 1%–2% of patients who undergo hip and knee arthroplasties will develop a joint infection in the subsequent year [6, 7]. Because nearly 1 million people undergo knee and hip arthroplasties each year in the United States [8], the absolute number of patients who go on to develop postoperative infection is large.

The timing of the onset of infection in relation to the original arthroplasty is an important criterion used to direct subsequent surgical and medical management of prosthetic infections. Traditionally, prosthetic joint infections are categorized as early (occurring <3 months after arthroplasty), delayed (occurring between 3 months and 2 years following arthroplasty), and late (occurring >2 years after arthroplasty) [1]. This classification is thought to correlate with pathogen type. Early infections are more likely caused by more virulent pathogens.
(eg, Staphylococcus aureus or enteric gram-negative bacilli), and delayed infections are more likely caused by less-virulent pathogens (eg, coagulase-negative staphylococci) [1]. As a result, consensus recommendations for surgical debridement may be appropriate for some early infections, whereas prosthesis removal is usually required for treatment of delayed infections [2, 9].

We previously reported that approximately 25% of surgical site infections (SSIs) following knee arthroplasty and 9% of SSIs following hip arthroplasty were identified >90 days after the index surgical procedure in our large cohort of community hospitals [10]. Whether the differential timing of SSI diagnosis is fully explained by differences in pathogen type, baseline patient characteristics, anatomical differences, or differential symptom manifestation between the 2 surgical sites is unknown. Therefore, the primary objective of this investigation was to explore and characterize the relationship between arthroplasty site and timing of diagnosis of SSI.

METHODS

Design and Setting
We conducted a retrospective cohort study using prospectively collected surveillance data from the Duke Infection Control Outreach Network (DICON). DICON is a network of community acute care hospitals and ambulatory surgery centers in North Carolina, South Carolina, Virginia, Georgia, and Florida that has been described previously [11]. All DICON-affiliated hospitals have active infection control and surveillance programs that collect surveillance data on SSIs following joint arthroplasty and surveillance procedures for quality improvement, benchmarking, and reporting purposes. The study was conducted in 2 parts: (1) a time-to-event analysis using SSI surveillance data from a large hospital network and (2) a descriptive analysis of cases of SSI from a subset of the large cohort to elucidate additional predictors that were not captured during routine surveillance.

Time-to-Event Analysis
The time-to-event analysis included surveillance data from all DICON-affiliated facilities that performed knee and/or hip arthroplasties from 1 January 2007 to 31 December 2011, which included 36 acute care hospitals and 1 ambulatory surgery center. Trained infection preventionists at each hospital prospectively identified cases of SSI using standardized surveillance methods and definitions per the Centers for Disease Control and Prevention (CDC) [12]. All adult (>18 years of age) cases of invasive (ie, deep-incisional or organ/space) SSI identified within 365 days following primary or revision knee or hip arthroplasty procedures were included in the analysis. The primary aim was to estimate the relationship between arthroplasty procedure type and time to diagnosis of invasive SSI, defined as the number of days from the date of surgery to the date that all criteria to satisfy the CDC surveillance definition of invasive SSI were met. Age, sex, pathogen, American Society of Anesthesiologists’ score, and hospital procedure volume were evaluated as potential confounders of this relationship.

Univariable analysis was performed to assess patterns and distribution of data. Bivariable comparisons were performed to examine relationships between potential confounders and procedure type. Continuous variables were compared using medians and interquartile ranges (IQRs), and categorical variables were compared using proportions. Relationships between potential confounders and time to diagnosis of SSI were visualized using Kaplan–Meier plots and formally tested using the Wilcoxon test. A Cox regression model was fitted to estimate the association between procedure type and time to diagnosis of SSI, adjusted for confounders. All covariates with P < .1 in 1 or more bivariable comparisons were included in the initial multivariable model. Age was modeled as a dichotomous variable, defined as age ≤70 years or age >70 years. Pathogen was modeled as a dichotomous variable; S. aureus and enteric gram-negative organisms were considered more-virulent pathogens, whereas other pathogens (eg, coagulase-negative staphylococci or Propionibacterium acnes) or negative cultures were considered less virulent. Hospital procedure volume was divided into 3 categories—low (<500 hip and knee arthroplasties annually), medium (500–1000 hip and knee arthroplasties annually), and high (>1000 hip and knee arthroplasties annually)—and modeled using indicator variables. Effect measure modification was first assessed by comparing nested models with and without interaction terms between procedure type and pathogen virulence and between procedure type and age. A likelihood ratio test P < .2 was considered significant. A change-in-estimate method was used to drop covariates from the model that did not impact the estimated hazard ratio (HR) by >10% when a covariate was removed from the model.

Descriptive Analysis
We performed in-depth electronic medical record reviews on patients with invasive SSI following arthroplasty surgery from 2 DICON-affiliated community hospitals from 1 January 2008 through 31 December 2011. The primary aim of this analysis was hypothesis generation, not hypothesis testing. Specifically, we aimed to identify additional risk factors for delayed diagnosis of SSI, to distinguish time of symptom onset from time of diagnosis of SSI, and to determine if any cases of delayed diagnosis of SSI were more likely due to hematogenous seeding from an alternate primary infection rather than primary SSIs. Details about the patients’ risk factors, operative course, postoperative course, and infectious presentation were abstracted by a single reviewer using a standardized case report form. Additionally, 2 infectious
disease physicians independently reviewed the medical records of all patients whose SSI diagnosis occurred >90 days postoperatively to determine whether there was evidence of probable hematogenous seeding, defined as a concurrent positive blood culture with the same pathogen and a suspected or confirmed alternate primary site of infection. The reviewers also noted cases when the microbiologic diagnosis of SSI was delayed beyond the onset of clinical signs or symptoms of infection (eg, a nonhealing surgical incision or receipt of prolonged or repeated courses of antibiotics). Categorical variables were reported using proportions; continuous variables were reported using medians and IQRs.

Statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, North Carolina). This study was approved by the Duke University Institutional Review Board.

RESULTS

Time-to-Event Analysis
Six hundred sixty-one invasive SSIs were included in the analysis; 260 (39%) occurred following hip arthroplasties and 401 (61%) occurred following knee arthroplasties (Table 1). The overall rates of invasive SSIs during the study period were 1.15 per 100 hip arthroplasties and 0.90 per 100 knee arthroplasties. Three hundred thirty-one (57%) of the case patients were female; there was no significant difference in sex among the 2 procedure types (\(P = .4\)). The median age was 64 years (range, 21–97 years). One hundred sixty-six (41%) patients with SSI following hip arthroplasty, compared with 98 (24%) patients with SSI following knee arthroplasty, were aged >70 years (\(P < .001\)). Patients with SSIs following knee arthroplasty were more likely to have had surgery at low-volume facilities than patients with SSIs following hip arthroplasty (159 [40%] vs 62 [24%], respectively; \(P = .001\)).

Staphylococcus aureus was the most common pathogen to cause SSI (Tables 1 and 2). The proportion of SSIs due to \(S. \text{ aureus}\) was similar among the 2 procedure types (146 [56%] after hip arthroplasty and 209 [53%] after knee arthroplasty). Less-virulent pathogens were less common following hip arthroplasty (50 [19%]) than knee arthroplasty (115 [29%]; \(P = .02\)).

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<td>Knee Arthroplasty (n = 401)</td>
<td>(P) Value(^a)</td>
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<td>146 (56)</td>
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Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ASA, American Society of Anesthesiology; IQR, interquartile range; proc/year, average annual number of knee and hip arthroplasty procedures; Ref, referent group.

\(^{a}\) \(P\) value for age given by Wilcoxon rank-sum test. \(P\) value for categorical variables given by \(\chi^2\) test. For variables with \(>2\) categories, pairwise comparisons to a referent group were also made.

\(^{b}\) Gram-negative bacilli: \(E. \text{ coli}\) (20), \(E. \text{ enterobacter}\) species (19), \(P. \text{ aeruginosa}\) (16), \(P. \text{ species}\) (19), \(K. \text{ species}\) (9), \(S. \text{ species}\) (7), other gram-negative bacillus (10); note that some infections were caused by \(>1\) gram-negative bacillus.

\(^{c}\) Other less-virulent pathogens: coagulase-negative \(S. \text{ staphylococci}\) (77), enterococci (33), streptococci (35), \(C. \text{ diphtheroids}\) species (15), \(P. \text{ acnes}\) (3), other (19); note that some infections were caused by \(>1\) pathogen from this group.
cause SSI within 180 days of the surgical procedure. Less-virulent pathogens were more likely than S. aureus to cause SSI beyond 180 days from the surgical procedure (Table 2).

The median time to diagnosis of SSI was 33 days (range, 1–355 days). SSIs following hip arthroplasty were diagnosed earlier than SSIs following knee arthroplasty (median, 25 [IQR, 17–48] days vs 42 [IQR, 21–114] days, respectively; P < .001; Table 3). The time to diagnosis of SSI was also related to age, sex, pathogen type, and hospital surgical volume in bivariable analyses (Table 3).

The unadjusted HR comparing time to diagnosis of SSIs following hip vs knee arthroplasty was 1.60 (95% confidence interval [CI], 1.28–1.98). The time to diagnosis of SSI remained significantly shorter for hip arthroplasty than for knee arthroplasty (HR, 1.51 [95% CI, 1.28–1.78]). More than one-quarter of SSIs following knee arthroplasty were predicted to occur >90 days postoperatively, compared with approximately 15% of SSIs following hip arthroplasty (Figure 1).

### Descriptive Analysis

Fifty-five patients from 2 community hospitals were included in the descriptive analysis; 21 (38%) had SSI following hip arthroplasty and 34 (62%) had SSI following knee arthroplasty (Table 4). The majority of patients had osteoarthritis as opposed to fracture or inflammatory arthritis as an indication for arthroplasty. Fifteen (27%) SSIs occurred following revision procedures. Many patients had known risk factors for SSI including older age (>70 years; n = 14 [25%]), obesity (median body mass index [BMI], 35 [IQR, 28–41] kg/m²), and diabetes (n = 21 [38%]). *Staphylococcus aureus* was the most common pathogen (n = 35 [63%]).

As in the larger cohort, the median time to diagnosis of SSI was shorter for hip arthroplasty than for knee arthroplasty (23 days [IQR, 19–39] vs 33 days [IQR, 20–104], respectively). Larger proportions of patients undergoing hip prosthesis surgery were elderly, healthcare exposed prior to the procedure, and discharged to a rehabilitation or skilled nursing facility compared with knee prosthesis patients (Table 4). The median time to diagnosis of SSI in patients discharged to a rehabilitation or skilled nursing facility was 21 days (IQR, 16–25 days) vs 37 days (IQR, 21–113 days) for patients discharged home.
Two SSIs following hip arthroplasty and 9 SSIs following knee arthroplasty were diagnosed >90 days postoperatively. Seven of the infections diagnosed >90 days following knee arthroplasty were caused by *S. aureus*. In 5 of these 7 cases, the diagnosis of SSI was potentially delayed beyond the appearance of clinical symptoms suggestive of infection, as patients had received courses of antibiotics or undergone treatment for poor wound healing prior to their ultimate diagnosis. Other SSIs diagnosed >90 days after prosthesis surgery were caused by *Enterobacter aerogenes* (hip), *Bifidobacterium* species (hip), group B *Streptococcus* (knee), and coagulase-negative staphylococci (knee). Probable hematogenous seeding from a urinary source occurred in only 1 case of SSI diagnosed >90 days postoperatively (*E. aerogenes*, hip).

**DISCUSSION**

We observed that the time to diagnosis of SSI following hip arthroplasty was significantly shorter than the time to diagnosis of SSI following knee arthroplasty in our large community hospital cohort. This differential time to diagnosis was not fully explained by differences in pathogen virulence, patient characteristics, or facility surgical volume between the 2 procedure types. We believe that early identification of prosthetic infections is clinically important, as both the choice of surgical management and the overall treatment success are impacted by the duration of infection prior to intervention. Our findings therefore have notable implications for the diagnosis and treatment of prosthetic joint infections.

To our knowledge, this differential time to diagnosis of SSI between hip and knee arthroplasties has not been previously described or examined. However, our findings are corroborated by those of Miletic et al, who reported that 35% of rehospitalizations for SSI after hip replacement occurred within 30 days of the procedure, compared to approximately 22% of rehospitalizations for SSI after knee replacement surgeries in a large insurance cohort [7]. Additional studies are needed to determine if this finding is observed in other care settings such as academic or tertiary referral hospitals.

The reason for the difference in time to diagnosis of SSI between hip and knee infections remains unknown. Our findings contradict intuition. Because knee joints have less surrounding soft tissue and are more accessible for both examination and diagnostic testing, one might expect SSIs following knee surgeries to be recognized sooner than SSIs following hip surgeries. It is possible that the delayed time to identification reflects a diagnostic delay rather than a delay in symptom manifestation between the 2 surgical procedure types. We were unable to accurately and precisely determine the time of symptom onset in every case in our small, retrospective subcohort due to limited documentation. We did observe, however, several knee prosthesis patients diagnosed with SSI >90 days postoperatively who had prolonged symptomatology suggestive of infection prior to the definitive diagnosis of invasive SSI. This may reflect difficulty in differentiating expected from unexpected pain in knee arthroplasty patients during the early postoperative course. We also observed knee prosthesis patients who were initially treated for peri-incisional cellulitis or poor wound healing in...
the early postoperative course and were subsequently diagnosed with invasive SSI later in their postoperative course. Careful clinical follow-up including surveillance of inflammatory markers and arthrocentesis, if indicated, is warranted for such patients who are treated for early, superficial infections to avoid a delay in diagnosis of invasive SSI.

Patient mobility, social support, and access to medical care likely also play a role. Overall, time to diagnosis of infection was longer in small-volume facilities than in larger-volume facilities. Surgeon volume has been inversely correlated with risk of SSI following arthroplasty and other surgical procedures [13, 14]. Small-volume hospitals generally serve rural locations, where many patients have to travel greater distances to receive medical care. Distance from the hospital was inversely correlated with hospital readmission rates following hip and knee arthroplasties in 1 study [15]. Thus, the difference in time to diagnosis observed between small- and large-volume hospitals may, in part, reflect differences in access to medical care. Also, a larger proportion of patients who underwent knee arthroplasty were discharged to home rather than to a rehabilitation or skilled nursing facility. Trained nursing staff are expected to report concerning signs or symptoms of infection. On the other hand, patients at home may not have the expertise to recognize early signs and symptoms of infection and may defer follow-up until their next scheduled visit.

Our study has important limitations. First, surveillance data only allow us to comment on the differential time to diagnosis of infection rather than the differential time to manifestation of symptoms of SSI. Generally, the date of infection is assigned as the date on which all criteria were present to satisfy the surveillance definition which, in the case of SSI, is typically the date that cultures were obtained. We were unable to capture the actual date of symptom onset through surveillance. We attempted to examine this issue in our retrospective review of electronic medical records, but could not make any conclusions based on incomplete documentation. A prospective study comparing timing of symptom onset and duration of symptoms prior to diagnosis between hip and knee arthroplasty patients would provide additional valuable information. Second, our surveillance data contained information on only a small number of potential confounders. We were unable to fully examine the role of potentially important variables such as revision vs primary arthroplasty, need for subsequent surgeries in the postoperative period, and use of antibiotics in the postoperative period. Furthermore, we were unable to assess the impact of specific medical comorbidities, social support, socioeconomic status, and access to medical care on our findings. Still, we believe that the large size of our cohort adds validity to our observation and makes our results potentially generalizable to other community hospital settings. Additionally, our descriptive analysis provides 2 potential hypotheses to explain our observation.

In summary, patients with invasive SSI after hip replacement are diagnosed sooner than patients with invasive SSI after knee replacement. Importantly, the observed difference between the 2 groups is not driven solely by pathogen type or patient age. We believe that symptom manifestation and interpretation in hip and knee arthroplasties as well as certain social factors including mobility, access to care, and functional status may contribute to our observation. Early diagnosis and intervention are critical for the treatment of prosthetic joint infection. Therefore, our findings and hypotheses warrant validation and testing in other prospective cohorts.
**Notes**

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