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Surgical Site Infections Following Total Joint Arthroplasty: An Examination of Microbial Isolates, Predisposing Patient Factors, and Diagnostic Delay

Brooke Beaulieu

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Surgical Site Infection Following Total Joint Arthroplasty : An Examination of Microbial Isolates, Predisposing Patient Factors, and Diagnostic Delay.

by

Brooke A. Beaulieu

B.S., Georgia Institute of Technology

A Thesis Submitted to the Graduate Faculty

of Georgia State University in Partial Fulfillment

of the

Requirements for the Degree

MASTER OF PUBLIC HEALTH

Atlanta, Georgia 30303

ABSTRACT

Background: Although device-associated total joint arthroplasty (TJA) has the potential to greatly improve recipient quality of life, the occurrence of surgical site infection (SSI) thereafter can render drastically debilitating and costly consequences.

Methods: A retrospective cohort design was used to analyze hospital discharge data from the State Inpatient Database (State of California, years 2009-2011). Descriptive statistics were conducted to establish microbial prevalence and multivariate logistic regression was conducted to examine associations between various patient-centric risk factors and the development of SSI. Interaction terms were evaluated for model inclusion. Finally, elapsed time from TJA operation to infection diagnosis was assessed according to site of TJA, pathogen virulence, and pre-existing comorbidities.

Results: During retrospective review, 1769 infections were detected. The incident rate of infection was 2.70 infections per 100,000 person-days. Staphylococci species were the most prevalent microorganisms (79%), including methicillin-resistant *S. aureus* (MRSA 24%) and methicillin-susceptible *S. aureus* (MSSA 40%). Polymicrobial aetiology was identified in 5% of infections. The multivariate logistic model revealed increased odds of infection were found for knee vs. hip operations (OR = 1.50; 95% CI = 1.41 – 1.60), for male sex (OR = 1.70; 95% CI = 1.60 – 1.80), for increasing length of hospitalization (OR = 1.10; 95% CI = 1.09 – 1.11), and for comorbidities including obesity (OR = 3.99; 95% CI = 3.16 – 5.04), diabetes (OR = 1.45; 95% CI = 1.29 – 1.63), and rheumatoid arthritis (OR = 1.49; 95% CI = 1.19 – 1.87). Diagnostic delay differed significantly according to pathogen virulence, but not with comorbid status and site of TJA.

<u>Conclusions:</u> Staphylococci species were the most prevalent microbes identified in infected patients. Anatomical site of TJA, male sex, length of hospitalization, and existing comorbidities were significantly associated with increased odds of surgical site infection following operative TJA. Surveillance networks continue to be fundamental for understanding and reducing the burden of SSI as a subset of healthcare-associated infections.

TABLE OF CONTENTS

CHAPTER 1: INTRODUCTION

CHAPTER 2: REVIEW OF THE LITERATURE

CHAPTER 3: ORIGINAL RESEARCH MANUSCRIPT

APPROVAL

Surgical Site Infection Following Total Joint Arthroplasty (TJA): An Examination of Microbial Isolates, Predisposing Patient Factors, and Diagnostic Delay.

by

Brooke A. Beaulieu

Approved:

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Committee Chair

_____

Committee Member

_____

Date

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I would like to express my genuine gratitude to the members of my thesis committee, Drs. Rothenberg and Lai, for all their helpful insight and feedback. Finally, I would like to dedicate this manuscript in its entirety to my parents, who possess perhaps more knowledge about the personal impact of surgical site infections than be communicated by the findings in the pages that follow.

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Brooke A. Beaulieu

800 Peachtree St. NE, #8309

Atlanta, GA 30308

The Chair of the committee for this thesis is:

Richard Rothenberg, MD, MPH

Division of Epidemiology and Biostatistics

School of Public Health

Georgia State University

Atlanta, Georgia 30302-3995

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CHAPTER I: Brief Introduction

1.1 Background

Modern surgical procedures provide avenues to considerably improve recipient quality of life. However, though benefits of surgery abound, there are inherent risks associated with all surgical procedures. One of the most common, and devastating, complications of surgery is the occurrence of surgical site infection (SSI). Encompassed under the broader categorization of healthcare-associated infections (HAI), SSI comprise almost one third of all infections associated with seeking healthcare and inflict significant burden unto both the patient and the healthcare system. Risk factors for contracting SSI vary according to patient attributes, hospital characteristics, and type of surgical procedure. Additionally, resulting morbidity and the severity thereof can fluctuate with the causative pathogenic agent, time at which the infection was detected, and the rectifying treatment. As such, an epidemiologic understanding of how various risk factors and interventions contribute to the overall risk of infection remains an imperative pursuit in the mitigation and reduction of postoperative infections.

1.2 Purpose of the study

The goal of the present study was to comprehensively and epidemiologically investigate the occurrence of and predisposition to SSI following total joint arthroplasty (TJA) operations. This goal was approached through three specific aims: 1) to determine the prevalence of microorganisms identified in cases of infection, 2) to examine the associations between various patient characteristics and the outcome of SSI in TJA recipients, and 3) to investigate the associations between procedure type, pathogen virulence, and existing comorbidities and the diagnostic delay from surgery to SSI detection.

CHAPTER II: Review of the Literature

2.1 A portrait of total joint arthroplasty in the United States.

Total joint arthroplasty (TJA) is an orthopedic operation that aims to increase mobility and relieve pain by reconstructing deteriorated joints in the musculoskeletal system. The vast majority of TJA operations comprise total hip arthroplasty (THA) and total knee arthroplasty (TKA). In the past decade, the cumulative number of TJA operations performed in the United States exceeded two million[1]. Further, due to the growth of both the aging and obese populations, the anticipated number of TJA operations is projected to skyrocket[1,2]. Therefore, the economic and personal burdens associated with complications resulting from TJA should be given considerable attention.

2.2 Aetiology of TJA surgical site infections.

Healthcare-associated infections (HAI) are infections that manifest as a result of receiving treatment within a healthcare setting. In 2011, 722,000 healthcare-associated infections occurred in the United States, resulting in roughly 75,000 deaths[3]. Approximately 20-30% of all health-care associated infections are categorized as surgical site infections (SSI), the occurrence of which results in increased patient morbidity, length of hospitalization, and augmented healthcare costs in estimation of $1.6 billion annually[4]. Therefore, infection as a postoperative complication remains a high priority for infectious disease surveillance and remediation.

2.2.1 *Classification of SSI*

Standardized definitions of surgical site infection are crucial to HAI surveillance efforts; such definitions heavily guide how infections are identified, and sequentially, how incident rates of SSI are determined. For TJA and other implant- or device-associated surgeries, an infection is defined as SSI if: it occurs within one year of surgery, it appears to be related to the initial arthroplasty operation, there is purulent drainage from the surgical site, and there is evidence of infection in either the deep soft tissue or organ/space[5]. Specific criteria for the diagnosis of SSI can be found in Figure 1.

Figure 1. Definition criteria for surgical site infection following implant-related operations.

Deep Incisional SSI	**Organ/Space SSI**
If within one year of surgery for implantation AND Infection appears to be related to the operation AND Infection involves deep soft tissues of the incisions and at least one of the following:	If within one year of surgery for implantation AND Infection appears to be related to the operation AND Infection involves any part of the anatomy (e.g., organs or spaces) other than the incision which was open or manipulated during an operation and at least one of the following:
1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site. 2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localized pain, or tenderness, unless site is culture-negative. 3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination. 4. Diagnosis of a deep incisional SSI by a surgeon or attending physician.	1. Purulent drainage from a drain that is placed through a stab wound‡ into the organ/space. 2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space. 3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination. 4. Diagnosis of an organ/space SSI by a surgeon or attending physician.

Note: Adapted from *Guideline for prevention of surgical site infection* (1999). Criteria for superficial incisional SSI (involving only the skin and subcutaneous tissue) not reported.

2.2.2. Causative pathogenic agents

    i.   Staphylococcal species

The vast majority (60-80%) of infections following TJA operations are caused by gram-positive Staphylococci species, including methicillin-sensitive *Staphylococcus aureus* (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA)[6]. MRSA is typically associated with poorer health outcomes, compared to MSSA. Infections due to *S. aureus* are predominately endogenous in origin, meaning that infection emanates from the patient's own microbial flora. Anatomically, *S. aureus* colonizes in the nostrils and on the skin; bacterial colonization is the considered the most important predictor of subsequent infection. For example, TJA recipients with pre-surgical nasal colonization have markedly increased odds of developing postoperative infection[7]. There are other various risk factors that can increase the odds of colonization, including diabetic status, the receipt of hemodialysis, and a suppressed immune state[8].

On a molecular level, *S. aureus* is a mechanistically elegant, bacterial adversary. Included in its arsenal are surface proteins the facilitate adhesion to and colonization of host tissues, such as those that surround the implanted prosthetic in TJA recipients, as well as a class of proteins known as invasins that allow the bacteria to spread throughout these tissues. Particularly in patients with prosthetic implants, *S. aureus* can accumulate on a biofilm on the implant surface or penetrate into the porous bone tissue[9]. Additionally, bacterial cells secrete toxins, including hemolysins and leukotoxins, which effectively lyse cell membranes of host tissue and immune cells, allowing bacteria to further colonize nearby tissue. As surface proteins, invasins, and toxins actively promote the spread of *S. aureus* throughout the tissue, other virulence factors play a defensive role in evading the host immune system. Protein A and another protein known as coagulase coat the bacterial cell membrane and inhibit phagocytosis. Coagulase

induces blood clotting in a way that forms a protective barrier around the microorganism; therefore macrophages and other responding immune cells cannot engulf it[10]. Certain strains of *S. aureus* known as coagulase-negative *S. aureus* (CoNS) lack the ability to synthesize coagulase; CoNS bacteria are generally categorized as less virulent that MRSA and MSSA. *S. aureus* also evades neutrophils by secreting proteins that can block neutrophil recognition of antigenic sequences, allowing the foreign invader to remain undetected while it continues to spread. For *S. aureus,* the adaptive immune response usually occurs within 7-10 days and will manifest as swelling, tenderness, neat, and pain near the prosthetic implant[10].

ii.   Gram-negative enteric bacilli

Although gram-positive species predominate as the causative pathogens in infections following TJA, there has been an observed increase in the number of infections due to gram-negative bacilli (GNB)[11]. GNB comprise several species of bacteria, including *Escherichia coli*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and various enterococci species[12]. Many of these microorganisms exhibit some form of antimicrobial resistance, and are thus categorically considered quite virulent relative to other pathogens. Early and appropriate treatment of GNB infection results in reduced mortality and morbidity; however, within the context of TJA in which diagnosis often delayed, infections caused by GNB can be extensively detrimental. Therefore, though GNB are most frequently associated with other categories of HAI, such as respiratory tract infections, catheter-associated urinary tract infections, and bloodstream bacteremia[12], recent evidence suggests that GNB may soon play a larger pathogenic role in the category of surgical site infections. As such, prevalence of GNB isolated from SSI following total joint arthroplasty should be carefully monitored in future microbial surveillance.

2.2.3 *Treatment protocol.*

Upon official diagnosis SSI, the process of infection management and remediation may begin. The time at which the infection is diagnosed heavily guides the course of treatment. For patients with a diagnostic delay less than 30 days from index surgery, or an estimation of less than 3 weeks from symptom onset, debridement of the infected bone/tissue and retention of the implant is an acceptable treatment option[13]. It should be noted that retention of the original implant may contribute to a higher risk of infection relapse, and should therefore only be considered for patients in which infection was detected early and for whom additional surgery is exceptionally risky. For patients that present with infection greater than 30 days after surgery, a more intensive course of action is required. As with earlier diagnoses, the tissue and bone surrounding the joint is sufficiently debrided and scourged of biofilm[13,14]. However, in delayed cases, effective infection control paradigm mandates the subsequent removal of the prosthetic implant and replacement with an antibiotic-laden cement spacer that acts a temporary placeholder. Though rare, in extensively severe cases infection the best course of action may in fact be amputation of afflicted limbs. Figure 2 details the decision process of determining if implant retention a possibility.
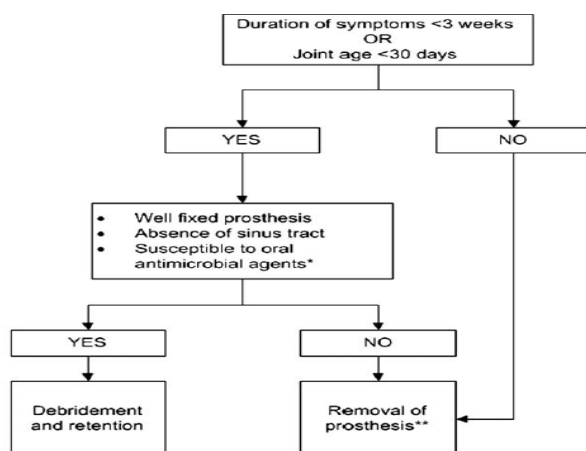
Figure 2. Decision diagram in determining the proper course of treatment following infection diagnosis[13].

Following surgical remediation, six to eight weeks of appropriate antibiotics are intravenously administered to clear any remaining infection. Current recommendations for clinicians regarding antibiotic delivery and duration can be found in Figure 3. Finally, once the patient has been declared free of infection, the process may begin anew with a revision TJA procedure, with hopes of a better outcome than the initial attempt. Though the degrees of infection severity may vary, the treatment protocol for each is inarguably tedious, additionally invasive, and usually a source of great frustration for the patient and provider alike.

Microorganism	Preferred Treatment[a]	Alternative Treatment[a]	Comments
Staphylococci, oxacillin-susceptible	Nafcillin[b] sodium 1.5–2 g IV q4-6 h or Cefazolin 1–2 g IV q8 h or Ceftriaxone[c] 1–2 g IV q24 h	Vancomycin IV 15 mg/kg q12 h or Daptomycin 6 mg/kg IV q 24 h or Linezolid 600 mg PO/IV every 12 h	See recommended use of rifampin as a companion drug for rifampin-susceptible PJI treated with debridement and retention or 1-stage exchange in text
Staphylococci, oxacillin-resistant	Vancomycin[d] IV 15 mg/kg q12 h	Daptomycin 6 mg/kg IV q24 h or Linezolid 600 mg PO/IV q12 h	See recommended use of rifampin as a companion drug for rifampin-susceptible PJI treated with debridement and retention or 1-stage exchange in text
Enterococcus spp, penicillin-susceptible	Penicillin G 20–24 million units IV q24 h continuously or in 6 divided doses or Ampicillin sodium 12 g IV q24 h continuously or in 6 divided doses	Vancomycin 15 mg/kg IV q12 h or Daptomycin 6 mg/kg IV q24 h or Linezolid 600 mg PO or IV q12 h	4–6 wk. Aminoglycoside optional Vancomycin should be used only in case of penicillin allergy
Enterococcus spp, penicillin-resistant	Vancomycin 15 mg/kg IV q12 h	Linezolid 600 mg PO or IV q12 h or Daptomycin 6 mg IV q24 h	4–6 wk. Addition of aminoglycoside optional
Pseudomonas aeruginosa	Cefepime 2 g IV q12 h or Meropenem[e] 1 g IV q8 h	Ciprofloxacin 750 mg PO bid or 400 mg IV q12 h or Ceftazidime 2 g IV q8 h	4–6 wk Addition of aminoglycoside optional Use of 2 active drugs could be considered based on clinical circumstance of patient. If aminoglycoside in spacer, and organism aminoglycoside susceptible than double coverage being provided with recommended IV or oral monotherapy
Enterobacter spp	Cefepime 2 g IV q12 h or Ertapenem 1 g IV q24 h	Ciprofloxacin 750 mg PO or 400 mg IV q12 h	4–6 wk.
Enterobacteriaceae	IV β-lactam based on in vitro susceptibilities or Ciprofloxacin 750 mg PO bid		4–6 wk
β-hemolytic streptococci	Penicillin G 20–24 million units IV q24 h continuously or in 6 divided doses or Ceftriaxone 2 g IV q24 h	Vancomycin 15 mg/kg IV q12 h	4–6 wk Vancomycin only in case of allergy

Figure 3. Recommended course of antibiotic treatment according to causative pathogen[13].

2.3 Identified risk factors in the extant literature.

The predisposition to SSI following TJA is facilitated by a complex array of risk factors, both patient-centric and healthcare provider-related in origin. Patient-related factors include increased age, male sex, smoking status, higher American Society of Anesthesiologist (ASA) score, previous operation history, and existing comorbidities such as diabetes mellitus, obesity, and rheumatoid arthritis[15-23]. Identified healthcare-associated factors include hospital case volume, length of operation, length of hospitalization, and the administration of antibiotic prophylaxis[15,17,18,20]. The implementation of surveillance networks such as the National Healthcare Safety Network (NHSN) has been decidedly helpful in elucidating healthcare-association factors that may predict infection. Such networks dictate strict standards for documenting relevant, comprehensive intricacies concerning treatment in healthcare facilities. For instance, the length of operation in minutes, the exact specification of antibiotic prophylaxis administered perioperatively, and detailed assessments of patient health (i.e., lab data, ASA score) are all procedure-related data elements collected by NHSN and analogous networks that may have been otherwise unavailable. Finally, though many risk factors have been independently implicated throughout the literature, the interplay between both patient and hospital factors, and the resulting impact on risk for SSI, remains yet to be clearly understood. Therefore, future research should not only build on the existing knowledge of infection risk factors following total joint arthroplasty, but should additionally investigate novel ways in which these risk factors may interact or compound.

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CHAPTER III: Original Research Manuscript

Surgical Site Infection Following Total Joint Arthroplasty: An Examination of Microbial Isolates, Predisposing Patient Factors, and Diagnostic Delay.

ABSTRACT.

Background: Although device-associated total joint arthroplasty (TJA) has the potential to greatly improve recipient quality of life, the occurrence of surgical site infection (SSI) thereafter can render drastically debilitating and costly consequences.

Methods: A retrospective cohort design was used to analyze hospital discharge data from the State Inpatient Database (State of California, years 2009-2011). Descriptive statistics were conducted to establish microbial prevalence and multivariate logistic regression was conducted to examine associations between various patient-centric risk factors and the development of SSI. Interaction terms were evaluated for model inclusion. Finally, elapsed time from TJA operation to infection diagnosis was assessed according to site of TJA, pathogen virulence, and pre-existing comorbidities.

Results: During retrospective review, 1769 infections were detected. The incident rate of infection was 2.70 infections per 100,000 person-days. Staphylococci species were the most prevalent microorganisms (79%), including methicillin-resistant *S. aureus* (MRSA 24%) and methicillin-susceptible *S. aureus* (MSSA 40%). Polymicrobial aetiology was identified in 5% of infections. The multivariate logistic model revealed increased odds of infection were found for knee vs. hip operations (OR = 1.50; 95% CI = 1.41 − 1.60), for male sex (OR = 1.70; 95% CI = 1.60 − 1.80), for increasing length of hospitalization (OR = 1.10; 95% CI = 1.09 − 1.11), and for comorbidities including obesity (OR = 3.99; 95% CI = 3.16 − 5.04), diabetes (OR = 1.45; 95% CI = 1.29 − 1.63), and rheumatoid arthritis (OR = 1.49; 95% CI =

1.19 – 1.87). Diagnostic delay differed significantly according to pathogen virulence, but not with comorbid status and site of TJA.

Conclusions: Staphylococci species were the most prevalent microbes identified in infected patients. Anatomical site of TJA, male sex, length of hospitalization, and existing comorbidities were significantly associated with increased odds of surgical site infection following operative TJA. Surveillance networks continue to be fundamental for understanding and reducing the burden of SSI as a subset of healthcare-associated infections.

KEYWORDS: healthcare-associated infections, total joint arthroplasty, surveillance

Introduction.

Though there are numerous benefits associated with total joint arthroplasty (TJA) operations, the development of subsequent surgical site infection (SSI) can be catastrophically detrimental to both the patient and the healthcare system. The occurrence of SSI as a postoperative complication results in increased patient morbidity, length of hospitalization, and augmented healthcare costs in estimation of $1.6 billion annually[1, 2]. Further, the growing number of TJA procedures in the United States and abroad will only serve to amplify these debilitating and costly impacts[3]. Understanding the associations between various patient- and provider-mediated risk factors and the contraction of SSI through epidemiologic investigations is a requisite first step in mitigating the deleterious effects of such infections.

It is estimated that SSI account for approximately 20-30% of all health-care associated infections[4]. Currently, the incident rate of SSI for TJA procedures ranges from 0.72 to 2.71 infections per 100 arthroplasties performed[5-8]; however, these rates almost certainly underestimate the true population incidence as the majority of SSI occur *after* hospital discharge, with some cases remaining undocumented. The magnitude of this incident rate is associated with several previously identified risk factors, both patient-related and healthcare-associated in nature. Patient-related factors include increased age, male sex, smoking status, higher American Society of Anesthesiologist (ASA) score, previous operation history, and existing comorbidities such as diabetes mellitus, obesity, and rheumatoid arthritis[6-14]. Identified healthcare-associated factors include hospital case volume, length of operation, length of hospitalization, and the administration of antibiotic prophylaxis[6, 8, 9, 11]. While some of these factors are non-modifiable (e.g., age, sex), many are to some degree malleable. Therefore, efforts to reduce SSI following TJA operations may be most effectively pursued by targeting preventive measures towards these select modifiable sources of risk.

Sequentially, it is directly pertinent to the surveillance of healthcare-associated infections to identify which microorganisms are most commonly responsible for SSI development. Currently, the vast majority (60-80%) of infections following TJA are caused by gram-positive Staphylococci species, including methicillin-sensitive *Staphylococcus aureus* (MSSA), methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermis* (MRSE), and coagulase-negative staphylococci (CoNS)[5, 15]. However, while staphylococcal species predominate as the causative pathogens of TJA postoperative infection, evidence suggests that other species may be emerging as prevalent bacterial threats. For example, increases in the proportion of infections caused by gram-negative bacilli (GNB) have been observed[16]. Temporal changes are not only limited to species prevalence, but extend also to the diversity of coexisting microbial species at the site of infection.

Although most infections are monomicrobial (i.e, only one species present), trends from the past decade indicate an increase in the number of polymicrobial infections (i.e., multiple species of microbes) following TJA operations[16]. Patients with polymicrobial infections generally have poorer health outcomes, as compared to monomicrobial infections[17]. This temporal shift in pathogenic prevalence and diversity, particularly with regard to resistant species, may have important implications for antibiotics prescribed both prophylactically and for infection management and remediation.

Though a growing body of infection control literature exists examining the risk factors for the absolute occurrence of SSI, less is known about how these implicated risk factors are associated with the *timing* of SSI symptom onset and detection. Conventionally, infection diagnosis after TJA is categorized as early (less than three months), delayed (three months to two years), or late (greater than two years), respective to index date of surgery[18]. Certain factors may influence the likelihood that an infection will be diagnosed as either early, delayed, or late. Previous research has indicated that the procedure type may account for differential timing in detection among TJA recipients, with 25% of total knee arthroplasties diagnosed as delayed, in contrast to only 9% delayed detection among total hip arthroplasties[19, 20]. Pathogen virulence may also have implications for the delay from surgery to diagnosis. More virulent pathogens such as *S. aureus* and gram-negative bacilli may induce more severe and proximally manifesting symptoms than less virulent species (i.e., coagulase-negative staphylococci, enterococci, and streptococci). The severity of symptoms stemming from more virulent pathogens may prompt patients to seek healthcare sooner, ultimately leading to an earlier diagnosis of SSI. The time-from-surgery at which infections are detected is intrinsic to determining the appropriate course for management and treatment[20, 21]. Therefore, more research is needed that examines the relationship between relevant risk factors and the time to SSI detection.

The aims of the current epidemiologic study were 1) to determine the prevalence of microorganisms identified in cases of infection, 2) to examine the associations between various patient characteristics and the outcome of SSI in TJA recipients, and 3) to investigate the associations between procedure type, pathogen virulence, and existing comorbidities and the diagnostic delay from surgery to SSI detection.

Methods.

This retrospective cohort study utilized hospital discharge data from the State Inpatient Database (SID) aggregated by the Healthcare Utilization Project (HCUP). Participating hospitals report inpatient discharge data on a yearly basis; all discharge data is reported, regardless of payment source or insurance affiliation. In this way, a surveillance system is created that yields a fairly representative sample of all inpatient services, including patient characteristics, diagnoses and procedures, and details about hospitalization. For the current study, data from the State of California (years 2009-2011) were analyzed. Particularly, the California SID was selected because of its thoroughness and inclusion of revisit linkage variables, which enabled the identification of patient readmission across multiple years and hospitals. The appropriate Institutional Review Board approval for this study was obtained prior to data management and analysis.

Study Sample.

Records of all TJA operations performed in the years 2009-2011 were reviewed retrospectively. Total hip arthroplasty and total knee arthroplasty procedures were identified through their respective International Classification of Disease 9th Revision (ICD-9) procedure codes. For the purposes of this study, only records indicating primary TJA operations were included for analysis. Documentation of codes used for data management and sample inclusion can be found in Appendix A.

Outcome Assessment.

The primary outcome of interest was the development of surgical site infection. The medical records of TJA patients were prospectively monitored for a period of 12 months. Previous research has indicated that one year is an appropriate surveillance time for identifying postoperative infections, corroborated by infection classification criteria for implant-associated operations. Infections were defined as patients who underwent TJA and were subsequently readmitted with a surgical site infection code within 12 months of index surgery. Non-infections were defined as TJA recipients that did not readmit for surgical site infection within 12 months of index surgery. ICD-9 codes were used to determine if the principal diagnosis was infection or inflammation resulting from prosthetic implant, and for identification of the causal microorganism (see Appendix A). All diagnoses on record were evaluated in order to determine the principal diagnosis. Individuals that underwent TJA in the terminal year of the study timeframe (2011) that did not develop SSI prior to the end of the year were excluded from risk factor analysis, as their records could not be prospectively monitored for an entire 12 months.

Patient Characteristics.

Patient characteristics were extracted from discharge reports for the inpatient stay associated with the initial TJA operation. Patient demographics such as age, sex, and race, as well as general patient health and comorbidities were considered relevant for analysis. Temporal variables such as length of hospitalization and time lapse from surgery to infection detection were elucidated, and continuous variables were evaluated for normality. All data management and statistical analyses were conducted using SAS 9.4 (SAS, Cary, NC).

Statistical Analyses.

Descriptive statistics were conducted to determine frequencies of patient characteristics and the incident rate of SSI. Incident rate (IR) was calculated as:

$$IR = \frac{new\ cases\ of\ SSI}{total\ number\ of\ persondays\ at\ risk}$$

This IR is calculated from a preliminary sample ($n = 222,078$) including TJA recipients that were eventually excluded from the analyses for microbial prevalence, patient risk factors, and diagnostic delay.

Microbial Prevalence.

Descriptive statistics were used to determine the prevalence of microorganisms indicated on patient records for the inpatient stay at the time of SSI discovery. All additional diagnoses on the patient chart were evaluated for microbial identification by their corresponding ICD-9 codes. Polymicrobial aetiology was flagged as the presence of more than one pathogen on the patient record. Fisher's exact test was conducted to compare the distribution of microbial prevalence by anatomical site of TJA (hip vs. knee).

Patient Risk Factors.

Logistic regression analyses were conducted to examine the association between patient characteristics and the outcome of SSI. Univariate analysis was conducted to determine the independent association of each risk factor with infection. All risk factors that were significantly associated with the outcome as well as with other risk factors were evaluated as potential sources of confounding and effect modification. Characteristics with significant associations in univariate analysis were included in the

multivariate logistic regression model in order to calculate adjusted odds ratios. Interaction terms were also assessed. Akaike Information Criterion (AIC) and Hosmer-Lemeshow goodness-of-fit statistics were given consideration for determining best-fit model selection.

Diagnostic Delay.

Among patients that developed SSI, Wilcoxon rank sum non-parametric *t*-test for independent samples was used to compare median diagnostic delay across anatomical site of TJA (hip vs. knee), pathogen virulence (less virulent vs. more virulent), and comorbid status (no comorbidities vs. one or more comorbidities). Diagnostic delay was defined as the difference from the time of initial TJA operation to time of infection diagnosis.

Results.

For this sample, 1769 surgical site infections were diagnosed. The incident rate of infection for this sample was 2.70 infections per 100,000 person-days at risk.

Microbial Prevalence.

Microbial isolates were identified in 46% of infections. Staphylococci species were implicated in the vast majority (78.9%) of infections, including 39.6% methicillin-susceptible *Staphylococcus aureus* (MSSA) and 24.3% methicillin-resistant *Staphylococcus aureus* (MRSA). Approximately 10.5% of infections were caused by gram-negative bacilli (GNB), comprised of *Eschrichia coli* (1.3%), *Pseudomonas* species (4.5%), and unspecified GNB (4.7%). Polymicrobial infections were identified in 4.7% of all SSI. Frequencies of microorganisms for all infections and according to anatomical site of TJA are reported in Table 1. Further, the distribution of microbial prevalence differed significantly between hip and knee operations. (p < 0.0001).

TABLE 1. Microbial Isolates from All Surgical Site Infections (SSI) and According to Anatomical Site

Microorganisms	All SSI = 831 (%)	Hip SSI = 276 (%)	Knee SSI = 555 (%)
Gram-positive cocci:			
Methicillin-resistant *Staphylococcus aureus* (MRSA)	202 (24.3%)	76 (27.5%)	126 (22.7%)
Methicillin-sensitive *Staphylococcus aureus* (MSSA)	329 (39.6%)	114 (41.3%)	215 (38.7%)
Unspecified *Staphylococcus aureus*	125 (15.0%)	37 (13.4%)	88 (25.9%)
Streptococcus species	63 (7.6%)	12 (4.3%)	51 (9.2%)
Gram-negative bacilli (GNB)			
Escherichia coli	11 (1.3%)	1 (0.4%)	10 (1.8%)
Pseudomonas species	37 (4.5%)	8 (2.9%)	29 (5.2%)
Unspecified GNB	39 (4.7%)	17 (6.2%)	22 (4.0%)
Other/unspecified	25 (3.0%)	11 (4.0%)	14 (2.5%)
Polymicrobial aetiology[†]	39 (4.7%)	10 (3.6%)	26 (5.2%)

Note. † Organisms from polymicrobial infections are also represented in their respective species categories above. Estimates reflect counts and percentages for records with non-missing microbial data only (46% of total infections); therefore, counts do not accumulate to the total 1769 infections identified in record review.

Patient Risk Factors.

A total of 146,492 TJA operations were identified through retrospective review (34% total hip arthroplasty, 66% total knee arthroplasty) and included in the final analytic sample. Median age was 67.0 years (IQR 60.0 – 75.0), and the majority of TJA recipients were female (60.1%). Most recipients were Caucasian (77.7%). Median length of hospitalization for the inpatient stay surrounding the procedure was 3.0 days (IQR 3.0 – 4.0).

Univariate analysis revealed that all risk factors were significantly associated with the outcome of SSI (Table 2). Although many variables were significantly associated with both the outcome and additional patient characteristics, none were deemed to be sources of confounding. Forward selection identified 4 statistically significant interaction terms. Models containing all possible combinations of these interaction terms were evaluated. The final model that yielded minimum the AIC value and $p >$ 0.05 for the Hosmer-Lemeshow χ^2 goodness-of-fit test contained 3 interaction terms: obesity x TJA site, obesity x sex, and obesity x length of hospitalization.

TABLE 2. Patient Characteristics of Total Sample and According to Infection Status

Variable	Total (n = 146,492)	No SSI (n = 144,723)	SSI (n = 1769)	P Value
Sex[†]				
Male	56,131 (39.3%)	85,793 (60.8%)	871 (49.9%)	<0.0001
Female[§]	86,664 (60.1%)	55,257 (39.2%)	874 (50.1%)	
Race[†]				
White	106,558 (77.7%)	105,289 (98.8%)	1,269 (1.2%)	0.0019
Non-white[a]	30,549 (22.3%)	30,117 (98.6%)	432 (1.4%)	
Site of TJA[†]				
Knee	96,879 (65.9%)	95,608 (98.7%)	1,271 (1.3%)	<0.0001
Hip[§]	50,083 (34.1%)	49,585 (99.0%)	498 (1.0%)	
Obesity[†]	29,496 (20.1%)	28,981 (98.2%)	515 (1.8%)	<0.0001
Diabetes[†]	25,323 (17.2%)	24,868 (98.2%)	455 (1.8%)	<0.0001
Rheumatoid arthritis[†]	5,063 (3.5%)	4,978 (3.4%)	85 (1.7%)	0.0017
Hypertension[†]	91,077 (62.0%)	89,905 (98.7%)	1,172 (1.3%)	0.0002
Age[†] (years) Median (IQR)	67.0 (60.0 – 75)	67.0 (60.0 – 75)	67.0 (58.0 74.0)	<0.0001
Length of hospitalization[†] (days) Median (IQR)	3.0 (3.0 – 4.0)	3.0 (3.0 – 4.0)	3.0 (3.0 – 4.0)	<0.0001

Note. § Indicates referent group. † Variable significant in univariate analysis. Due to missing data, frequencies may not add up to 100%.

After logistic regression in the multivariate model, all variables but hypertension and race remained significantly associated with the outcome of SSI (Table 3). Increased odds of infection were found for knee vs. hip operations (OR = 1.50; 95% CI = 1.41 – 1.60), for male sex (OR = 1.70; 95% CI = 1.60 – 1.80), for increasing length of hospitalization (OR = 1.10; 95% CI = 1.09 – 1.11), and for comorbidities including obesity (OR = 3.99; 95% CI = 3.16 – 5.04), diabetes (OR = 1.45; 95% CI = 1.29 – 1.63), and rheumatoid arthritis (OR = 1.49; 95% CI = 1.19 – 1.87). Increasing age was determined to be very slightly protective against SSI (OR= 0.99; 95% CI = 0.98 – 0.99).

Parameter	β	P Value	OR	95% CI
TABLE 3. Multivariate Logistic Regression Analysis Between Infections and Non-Infections				
Age[†]	-0.01	<0.0001	0.99	(0.98 – 0.99)
Race	0.02	0.6947	1.02	(0.91 – 1.15)
Sex[†]	0.53	<0.0001	1.70	(1.60 – 1.80)
Site of TJA[†]	0.41	<0.0001	1.50	(1.41 – 1.60)
Obesity[†]	1.38	<0.0001	3.99	(3.16 – 5.04)
Diabetes[†]	0.37	<0.0001	1.45	(1.29 – 1.63)
Hypertension	0.07	0.2032	1.07	(0.96 – 1.20)
Rheumatoid arthritis[†]	0.40	0.0006	1.49	(1.19 – 1.87)
Length of hospitalization[†]	0.09	<0.0001	1.10	(1.09 – 1.11)

Note. † Indicates patient characteristics that remained significant in multivariate model.

Diagnostic Delay.

Median time delay from surgery to infection diagnosis was significantly greater for less virulent pathogens (60 days, IQR = 27 – 160) compared to more virulent pathogens (38 days, IQR = 20 – 98)

(p < 0.0001). Diagnostic delay did not differ with comorbid status (no comorbidities vs. one or more comorbidities) or anatomical site of TJA operation (hip vs. knee).

Discussion.

For the majority of recipients, TJA is a highly beneficial operation that improves range of motion, mobility, and quality of life generally. However, for the small subset of patients who go on to develop subsequent surgical site infection, the operative experience becomes tainted by further pain and debilitation, frustration, and augmented healthcare costs. And while advances in infection prevention and control continue to emerge, this epidemiological study and others demonstrate that SSI remains a notable occurrence following total joint arthroplasty operations.

Microbial Prevalence.

The overall cumulative rate of infection for this sample was 1.2%, similar to rates previously established throughout the extant literature[5-8]. The incident rate of infection was 2.70 infection per 100,000 person-days of follow-up time. In congruence with microbial prevalence determined in other studies[5,16], Staphylococci species were the most common microorganisms isolated from infected patients. Methicillin-susceptible *Staphylococcus aureus* (MSSA) was the most prevalent pathogen (39.6%), followed by methicillin-resistant *Staphylococcus aureus* (MRSA; 24.3%). These findings demonstrate that antibiotic-resistant species continue to present a notable threat with regards to health-care associated infections; therefore, special consideration should be given to which antibiotics are prescribed prophylactically and perioperatively. For this sample, the proportion of polymicrobial infections was comparatively small (5%) compared to those found in other studies (46%)[16]. The distribution of pathogens differed significantly in hip and knee operations, however, the biological mechanisms for this finding are unclear. A worthwhile addendum to this analysis would be to

investigate which patient characteristics are associated with the susceptibility to specific microbes; that is, could patient attributes potentially predict the causative microorganism in cases of infection?

Patient Risk Factors.

The patient characteristics investigated in this study were age, sex, race, anatomical site of TJA, length of hospital stay associated with the TJA operation, and patient comorbidities existing at the time of surgery. Patients who received joint replacement at the knee had 1.5 times the odds of developing surgical site infection as compared to those who underwent joint replacement at the hip (95% CI = 1.41 – 1.60). Length of inpatient stay surrounding the initial arthroplasty operation was also statistically significant (OR = 1.10; 95% CI = 1.09 – 1.11). Though the magnitude of this association was relatively small compared to the contributions from other risk factors, it aligns with previous findings. A longer hospitalization may result from complications during or immediately after surgery, as well as patient vulnerabilities that may necessitate a longer period of observation post-operation. It would not be imprudent to infer that such complications and vulnerabilities might supplement the odds of developing infection.

When regressed in the multivariate model, all comorbidities except hypertension were significantly associated with SSI. Of these comorbidities, obesity had the largest associative measure (OR = 3.99, 95% CI = 3.16 – 5.04). In fact, the relationship between obesity and the outcome of SSI was the strongest relative to all other patient characteristics analyzed. Further, all significant interaction terms that improved model fit contained an obesity component. This finding has substantial implications for practice and prevention. Obesity not only contributes heavily to the risk of SSI development, but perhaps more encouraging, is largely modifiable. Obese status should be given due consideration when evaluating a patient for TJA operation potential. With acknowledgement that the lack of mobility that

often necessitates TJA may add to or exacerbate patient obesity, healthcare providers should suggest that patients take safe measures to reduce BMI to a non-obese status, when possible.

Interestingly, increasing age was found to very slightly protective against infection (OR = 0.99, 95% CI 0.98 – 0.99). This finding contradicts associations elucidated in other studies, in which older age *increases* the odds of SSI or is not significantly associated at all. However, the odds ratio obtained for this sample, though significant, is substantially close to and tightly clustered around OR = 1. Therefore, from a clinically practical perspective, it would be unwise to advocate that increased age is a protective factor. More research is needed to determine a more concrete and universal understanding of the relationship between age and development of SSI after TJA, as well as what other factors may confound this relationship.

Diagnostic Delay.

Prior research suggests that the time lapse from index TJA surgery to detection of SSI may be influenced by a variety of factors. In this sample, diagnostic delay differed significantly according to degree of pathogen virulence, but not by anatomical site of TJA or comorbid status. The severity of symptoms stemming from more virulent pathogens may prompt patients to seek healthcare sooner, which may explain why infections in the sample caused by more virulent microbes such as *S. aureus* and GNB were detected almost a full month sooner than those caused by less virulent organisms. An earlier detection of SSI implies earlier management and treatment administration. Considering that it is treatment paradigm to 1) first remove the infected implant and place an antibiotic-laden spacer until infection has cleared (approximately 6 weeks), and 2) to then perform another TJA surgery for which recovery time approximates an additional 6-8 weeks, expediting this rehabilitation process through earlier detection is undeniably advantageous. It should be noted that this investigation, as well as many

others throughout the literature, use the time of infection diagnosis as a proxy for the time of event occurrence. In reality, symptom onset and clinically detectable levels of infection most likely occur days to weeks prior to diagnosis. Therefore, though time and resource intensive, prospective cohort studies in which biological samples are regularly extracted and examined may illuminate more precisely the exact timing and natural history of surgical site infection following TJA operations, and sequentially, how patient and pathogen characteristics affect this timing.

Strengths and Limitations.

This investigation exhibits many strengths. Firstly, the dataset from which the sample was drawn is deemed to be fairly representative of inpatient visits nationally. Additionally, due to the size and inclusiveness of the data, the sample size of the population of interest (TJA recipients) was relatively large (n = 146,692). Given the small rate of infection that is generally expected for SSI following arthroplasty operations, a large population sample is favorable. Finally, the retrospective study design used for this examination is preferable for investigating comparatively rare disease outcomes.

However, various limitations must also be addressed. The largest drawback of this study is that it limits risk factor assessment to only those patient characteristics available on the medical record. Data pertaining to details surrounding hospitalization (i.e., length of operation and administration of antibiotic prophylaxis) would substantially enhance the predictive potential of the multivariate logistic regression model and more accurately estimate measures of association. This point emphasizes the importance of continued, standardized maintenance of infection surveillance networks such as the National Healthcare Safety Network (NHSN) for all inpatient services. Such networks annotate more comprehensively the procedural factors may be relevant to development of later infection or complications that result from seeking healthcare. Additionally, data from only one state were used. Therefore, it is possible that if a

patient had a TJA operation in-state, and then moved out of state and subsequently developed SSI, that infection would not be included in the current calculated rate. Therefore, this incident rate calculated for this study most likely underestimates the true population rate. Integration of data across all states would greatly strengthen future epidemiological investigations. Finally, the use of forward selection in model determination may have excluded biologically, though not statistically, important interactions.

Conclusions.

Staphylococci species were the most prevalent microbes identified in infected patients. Anatomical site of TJA, male sex, length of hospitalization, and existing comorbidities were significantly associated with increased odds of surgical site infection following operative TJA. Particularly, the modifiable risk factor of comorbid obesity enumerated the largest measure of association for the outcome of infection; therefore, efforts to reduce obesity in TJA candidates may in turn reduce the rate of SSI. Infections caused by more virulent pathogens were detected earlier than those caused by less virulent pathogens, though median time to diagnosis in both categories was still considered early by conventional classification. Finally, surveillance networks continue to be fundamental for understanding the relationship between various patient-centric and healthcare provider-related risk factors, and the potential reduction of surgical site infection as a subset of healthcare-associated infections.

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Appendix A.

Supplemental Table 1. ICD-9 Codes for Data Management.		
Event	**ICD-9 Code**	**Code Description**
Total hip arthroplasty (THA)	81.51	Primary total arthroplasty of the hip
Total knee arthroplasty (TKA)	81.54	Primary total arthroplasty of the knee
Identification of SSI	996.66	Infection and inflammation reaction due to internal joint prosthesis
Identification of SSI	996.67	Infection and inflammation reaction due to other internal orthopedic device implant and graft