ORIGINAL ARTICLE

Incidence, Secular Trends, and Outcomes of Prosthetic Joint Infection: A Population-Based Study, Olmsted County, Minnesota, 1969–2007

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CONTEXT. The epidemiology of prosthetic joint infection (PJI) in a population-based cohort has not been studied in the United States.

OBJECTIVES. To provide an accurate assessment of the true incidence, secular trends, clinical manifestations, microbiology, and treatment outcomes of PJI in a population-based cohort.

DESIGN. Historical cohort study.

SETTING. Olmsted County, Minnesota.

PARTICIPANTS. Residents who underwent total knee arthroplasty (TKA) or total hip arthroplasty (THA) between January 1, 1969, and December 31, 2007.

METHODS. Incidence rates and trends in PJI were assessed using the Kaplan-Meier method and log-rank test, as were treatment outcomes among PJI case patients.

RESULTS. A total of 7,375 THAs or TKAs were implanted in residents of Olmsted County during the study period. Seventy-five discrete joints in 70 individuals developed PJI, during a mean ± SD follow-up of 6.8 ± 6.1 years. The cumulative incidence of PJI was 0.5%, 0.8%, and 1.4% after 1, 5, and 10 years after arthroplasty, respectively. Overall, the rate of survival free of clinical failure after treatment of PJI was 76.8% (95% confidence interval [CI], 64.3–85.2) and 65.2% (95% CI, 33.1–76.2) at 3 and 5 years, respectively. The incidence and treatment outcomes did not significantly differ by decade of implantation, patient age at implantation, gender, or joint location.

CONCLUSIONS. The incidence of PJI is relatively low in a population-based cohort and is a function of age of the prosthesis. Incidence trends and outcomes have not significantly changed over the past 40 years.

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About 1,000,000 prosthetic joints are implanted each year in the United States. The number is projected to increase to more than 4 million by 2030.[1,2] Prosthetic joint infection (PJI) is a rare but serious complication of total joint arthroplasty and may result in permanent prosthesis removal or, rarely, loss of limb or life.[3] The cost of medical and surgical management of each PJI is in excess of $50,000.[4,5]

The epidemiology of PJI at the population level has not been studied in the United States. Data on the incidence, microbiology, risk factors, and outcomes are derived from single-center cohorts or convenient cohorts that are susceptible to significant referral bias. Moreover, most studies have been limited by methodological problems, including lack of explicit case or risk factor definitions, incomplete case ascertainment, and incomplete follow-up.[6-12]

Olmsted County is located in southeastern Minnesota, and its population consists largely of middle-class white individuals with characteristics similar to those of the general US non-Hispanic white population.[13] According to the 2000 census, the population of Olmsted County was 124,277.[14] Residents derive their healthcare services, including joint arthroplasties and management of PJI, largely from Mayo Clinic, Rochester, and the Olmsted Medical Center, Rochester. The Rochester Epidemiology Project (REP) allows the linkage of the medical records for local residents who encounter the healthcare system within the county, regardless of the pro-

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vider. Medical histories, diagnoses, surgical interventions, and other key information can thus be accurately obtained for incidence data and population-based analytic studies. The REP is uniquely positioned to study the natural history of diseases in a defined population.[13] This study will thus serve to provide an accurate assessment of the true incidence, secular trends, clinical manifestations, microbiology, and outcomes of PJI in a US population-based cohort and will serve as a source of comparison for previous hospital-based studies.

METHODS

This is a historical population-based cohort study of all Olmsted County residents who underwent total knee arthroplasty (TKA) or total hip arthroplasty (THA) between January 1, 1969, and December 31, 2007. The subgroup of total patients who received joints and who experienced infection of their prosthesis constituted cases (Box 1). Once the diagnoses of the study population and potential case patients were confirmed and residency established, the complete (inpatient and outpatient) medical record was reviewed and pertinent information abstracted. For every identified case patient, the clinical presentation, specific microorganisms responsible for the PJI, type of antimicrobial agent used, duration of treatment, and modality of surgical management were recorded. All case patients were followed passively through their medical record from the date of diagnosis until death, occurrence of clinical failure, or loss to follow-up. All aspects of this study were reviewed and approved by the institutional review boards at Mayo Clinic and Olmsted Medical Center.

Statistical Analysis

Patient characteristics, clinical manifestations, microbiology, antimicrobial treatment, and surgical treatment modalities were summarized using descriptive statistics, including counts and percentages or means and standard deviations as appropriate. All patients who underwent an arthroplasty were followed prospectively until their last medical visit or first occurrence of PJI. The incidence of PJI was computed and expressed in the following 2 ways: (1) as the rate, per 1,000 person-joint-years, and (2) as the cumulative incidence (%) of PJI, using the Kaplan-Meier method (1 minus the "survival" estimate). With both sets of estimates, the rates of PJI were reported at 1, 2, 5, and 10 years after joint implantation for the overall cohort, as well as by decade of implantation, patient age, gender, and joint location (hip vs knee). For these factors, Kaplan-Meier plots are shown visually to compare survival rates over time across categories, which were also formally compared with a log-rank test. Among the subgroup with subsequent PJI, the rate of survival free from clinical failure was also assessed using Kaplan-Meier methods similar to those described above. All analyses were carried out using the SAS statistical software package (ver 9.2; SAS Institute). A P value less than .05 was considered statistically significant.

Box 1: Definition of Terms

Prosthetic joint infection (PJI) was said to be present if:

1. Two or more cultures from joint aspirates or intraoperative cultures yield the same microorganism

   or

2. Purulence surrounding the prosthesis is observed at the time of debridement or removal of the prosthesis

   or

3. Acute inflammation consistent with infection is present on histopathology examination in conjunction with at least 1 positive culture

   or

4. A sinus tract is present that communicates with the prosthesis.

Olmsted County resident:

Any person residing in Olmsted County for at least 1 year before total joint replacement surgery.

Index arthroplasty:

Total joint replacement surgery preceding first episode of PJI (could be a primary or revision arthroplasty).

Episode of PJI:

First occurrence of infection on specific prosthetic joint (site and side). Infections on different joints in the same individual are included, but secondary infections on a specific joint are excluded.

Clinical failure:

Outcome of PJI classified as relapse, reinfection, superinfection, death from infection, or indeterminate joint failure requiring revision surgery.

RESULTS

Patient Selection

A total of 302 potentially eligible cases of PJI were identified from the surgical index of the REP. One hundred eighty-six were excluded after chart review, as the discharge diagnosis of PJI did not meet our case definition. The discharge diagnosis was not supported by any surgical findings, microbiology, or histopathology reports. The status of 2 patients could not be verified because their medical records were not available for review. Of the 114 confirmed occurrences of PJI, 19 did not meet residency requirements (16 had not resided in Olmsted County for at least 365 days before the index arthroplasty, and 3 were residents only by virtue of being institutionalized). Nineteen Olmsted residents, diagnosed with PJI in the county, were excluded because the index arthroplasty was performed elsewhere. One patient had arthroplasty before 1969.

Incidence

A total of 7,375 THAs or TKAs were implanted in residents of Olmsted County during the study period. We excluded $n = 8$ without any follow-up information available, leaving an analysis cohort consisting of 7,367 arthroplasties from 5,456 unique subjects. Seventy-five discrete joints in 70 individuals developed infection, during a mean ± SD follow-up of 6.8 ± 6.1 years. Figure 1 illustrates the overall survival of THAs and TKAs free of infection for all residents over the study period. The overall unadjusted incidence rate (IR) of PJI was 1.50 per 1,000 person-joint-years (95% confidence interval [CI], 1.18–1.87). The highest IR was within the first year after arthroplasty (4.9/1,000 person-joint-years [95% CI, 3.3–6.8]), with a decline to 3.5/1,000 person-joint-years (95% CI, 2.6–4.7), 2.0/1,000 person-joint-years (95% CI, 1.5–2.6), and 1.6/1,000 person-joint-years (95% CI, 1.3–2.1) at 2, 5, and 10 years, respectively. The cumulative incidence of PJI expressed as a percentage of total knees and hips implanted was 0.5% (95% CI, 0.3–0.7), 0.7% (95% CI, 0.5–0.9), 0.8% (95% CI, 0.6–1.1), and 1.4% (95% CI, 1.0–1.8) at 1, 2, 5, and 10 years after implantation, respectively. From univariate analysis, gender, age at implantation, joint location, and year of implantation were not significantly associated with developing a PJI. Results of these analyses are summarized in Table 1.

Characteristics of Patients with PJI

Of the 70 subjects with new PJI, 43 (61.4%) were females and 27 (38.6%) males. Age at the time of infection ranged from 41.6 to 95.0 years, with an average ± SD of 72.6 ± 12.2 years. Among PJI subjects in whom race was known, 41 (93.2%) of 44 were Caucasian. Sixty percent of PJI episodes occurred within 2 years of primary joint implantation (71% within 2 years of index arthroplasty). Forty three (57%) of the 75 were knee infections and 32 (43%) hip infections. The most common underlying joint diseases were degenerative joint disease ($n = 41$; 55%), fracture ($n = 16$; 21%), and rheumatoid arthritis ($n = 12$; 16%). A majority of the affected joints ($n = 47$; 63%) were preceded by an invasive procedure before the index arthroplasty. Fifteen (20%) had undergone at least 1 revision surgery. The clinical manifestations of PJI in this cohort are summarized in Table 2.

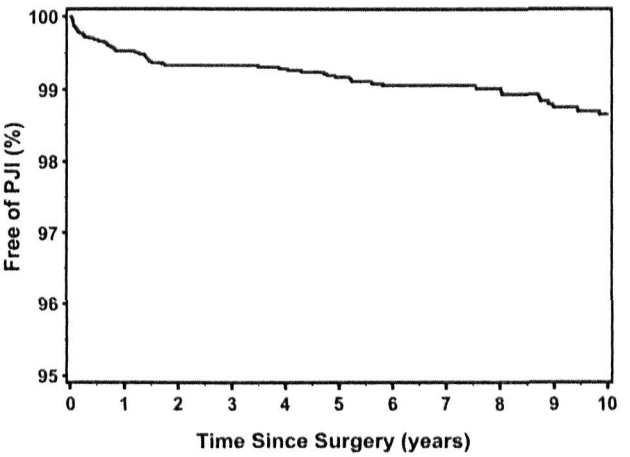

FIGURE 1. Kaplan-Meier plot of overall survival of total hip or knee arthroplasty free of prosthetic joint infection (PJI) for residents of Olmsted County, Minnesota, 1969–2007. $N = 7,367$.

Microbiology

The most common microorganisms causing PJI were staphylococci, accounting for 39 (52.0%) infections. *Staphylococcus aureus* was isolated in 21 (28.0%) episodes, only 2 of which were methicillin resistant. Eighteen (24.0%) infections were attributable to coagulase-negative staphylococci, 3 (4.0%) of which were further identified as *Staphylococcus lugdunensis.* Eight (10.7%) patients experienced polymicrobial infection, and 6 (8.0%) persons had a culture-negative PJI. Only 1 nonbacterial infection occurred, in a patient with *Coccidiodes imitis* knee infection (Table 3). Perioperative blood cultures were positive for the offending microorganism in 14/56 (25.0%) episodes. Methicillin-susceptible *S. aureus* (MSSA) bacteremia was the most common, occurring in 10 (58.8%) of 17 episodes, followed by *Streptococcus* bacteremia, in 3 (30%) of 10 episodes.

Treatment

More than half of PJI episodes (41/75; 54.7%) underwent debridement and retention of the prosthesis as the initial surgical management strategy. Sixteen (21.3%) episodes were treated by 2-stage exchange surgery, while 5 (6.7%) had no surgical intervention. Other modalities of surgical management included resection arthroplasty ($n = 6$), external arthrodesis ($n = 4$), 1-stage surgery with oral antibiotic sup-

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TABLE 1. Cumulative Incidence of Prosthetic Joint Infection at 2 and 5 Years after Arthroplasty by Age, Gender, Joint Location, and Year of Primary Arthroplasty

Group	2-year cumulative incidence, % (95% CI)	5-year cumulative incidence, % (95% CI)
Overall	0.67 (0.50–0.90)	0.84 (0.64–1.11)
Age, years		
<60	0.55 (0.26–1.18)	0.79 (0.41–1.57)
60–69	0.50 (0.26–0.97)	0.77 (0.43–1.37)
70–79	0.83 (0.52–1.33)	0.96 (0.62–1.53)
80+	0.74 (0.41–1.39)	0.74 (0.41–1.73)
Gender		
Female	0.67 (0.46–0.97)	0.74 (0.52–1.08)
Male	0.68 (0.42–1.12)	1.02 (0.66–1.59)
Joint location		
Hip	0.52 (0.33–0.83)	0.65 (0.42–1.04)
Knee	0.83 (0.57–1.21)	1.03 (0.72–1.47)
Year of implantation		
1969–1989	0.32 (0.14–0.72)	0.39 (0.18–0.83)
1990–1999	0.99 (0.62–1.57)	1.18 (0.77–1.82)
2000+	0.69 (0.45–1.07)	0.96 (0.61–1.50)

NOTE. CI, confidence interval.

pression ($n = 2$), and amputation ($n = 1$). All but 6 patients had adjunctive parenteral antibiotic therapy for a mean ± SD duration of 27.8 ± 12.9 days. The most prescribed antibiotics were cephalosporins ($n = 36$; 47.9%), vancomycin ($n = 18$; 24.0%), and penicillins ($n = 13$; 17.3%). For patients with retained prosthesis, long-term oral antibiotic suppression was administered for a mean ± SD duration of 26.2 ± 24.5 months during a maximum 5-year follow-up period. Oral antibiotic choices were cephalosporins ($n = 19$; 25.3%), penicillins ($n = 15$; 20.0%), tetracyclines ($n = 10$; 13.5%), and fluoroquinolones ($n = 8$; 10.7%).

Outcomes of Patients with PJI

Seventy-five episodes of PJI were passively followed for a mean ± SD duration of 3.1 ± 1.8 years after diagnosis. Overall, the rate of survival free of clinical failure after treatment of PJI was 76.8% (95% CI, 64.3–85.1) and 65.2% (95% CI, 33.1–76.2) at 3 and 5 years, respectively (Figure 2*A*). There was not an overall difference in success rate across the various treatment types ($P = .22$), although the rate of survival free of clinical failure was marginally (but not significantly) higher in the 2-stage exchange group when compared to only those treated with debridement/retention of prosthesis ($P = .069$; Figure 2*B*).

DISCUSSION

This is the first population-based epidemiologic study of PJI in the United States. We began our case finding from March 10, 1969, when Dr. Mark B. Coventry performed the first Food and Drug Administration–approved total hip replacement surgery in the United States at Rochester Methodist Hospital, Rochester, Minnesota. All incident cases of PJI in Olmsted County from this date forth were included, thus limiting sampling bias associated with case selection. We applied the same strict reference standard to all cases to minimize measurement bias. Every potential case was reviewed, referring to original microbiology, pathology, and surgical reports to confirm the diagnosis. We also applied strict residency status requirements that excluded patients who had not lived in Olmsted County for a year before arthroplasty and/or had their prostheses implanted elsewhere.

The limitations of this study are inherent to its retrospective nature. The details and accuracy of the clinical data collected are largely dependent on the written record and could not otherwise be verified by the investigators. The other limitation is the unexpectedly small sample size. This is a reflection of the true low incidence of PJI in this population, as well as our strict inclusion/exclusion criteria. The latter decision was taken a priori, to ensure that we had as "clean" a population-based cohort as possible, even at the expense of potentially generating enough power to show statistically significant differences in incidence or outcomes between various subgroups of the study population. Findings of this study can be gen-

TABLE 2. Clinical Features of 75 Episodes of Prosthetic Joint Infection

Symptom/sign	Present (%)	Absent (%)
Pain/tenderness	70 (94.6)	4 (5.4)
Swelling/effusion	35 (48.6)	37 (51.4)
Redness/erythema	28 (38.9)	44 (61.1)
Differential warmth	25 (34.2)	48 (65.8)
Fever	27 (36.5)	47 (63.5)
Purulent drainage/sinus tract	29 (39.7)	44 (60.3)

NOTE. Percent expressed as proportion of the total. When the total is <75, it implies data missing or undocumented in the chart.

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TABLE 3. Microbiology of 75 Episodes of Prosthetic Joint Infection

Microorganism/class	No. (%)
MSSA	19 (25.3)
MRSA	2 (2.6)
Coagulase-negative staphylococci	18 (24.0)
Streptococci	13 (17.3)
Enterococci	3 (4.0)
Gram-positive bacilli	2 (2.7)
Gram-negative bacilli	1 (1.3)
Anaerobes	2 (2.7)
Polymicrobial	8 (10.6)
Culture negative	6 (8.0)
Fungi	1 (1.3)

NOTE. MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*.

eralized to a predominantly middle-class white US population. The extent to which socioeconomic factors and race/ethnicity affect outcomes in total joint arthroplasties is unknown. The major findings of our study are thus discussed in the context of the strengths and limitations outlined above.

Joint infection is a time-dependent outcome following arthroplasty; the cumulative incidence increases with age of the implant. The cumulative incidence of PJI was 0.7% at 2 years of implantation and increased only slightly to 0.8% after 5 years. Our study confirms that the greatest hazard occurs in the first 2 years after primary or revision arthroplasty, with about 60%–70% of infections occurring during this period. This is in keeping with the widely held view that the mechanism of PJI is predominantly perioperative contamination of the implant, which manifests as early infection (within 3 months) or may be delayed for up to 2 years as a result of biofilm formation, with the microorganisms assuming a dormant planktonic state under adverse conditions.

Our study highlights the limitations of estimating the incidence density for PJI (number of new infections per person-joint-years). Those estimates assume a constant risk over follow-up time, which is clearly not the case. We note how drastic the IR changes depending on how much follow-up time you allow per person-joint-year (4.9 and 1.6 per 1,000 person-joint-years at 1 and 10 years, respectively). These results become difficult to explain and can be misleading.

The secular trends of PJI noted in this study may be considered paradoxical. Our study shows no statistically significant difference in incidence of PJI rates over 4 decades of implantation. The incidence of PJI is influenced by a number of factors. These include preoperative morbidities such as obesity and diabetes mellitus and intraoperative factors such as aseptic technique, surgical skills, and operating room environment. We hypothesize that some of these factors, acting in opposing directions, counterbalanced each other, resulting in no net statistically significant secular trend in the incidence of PJI. Our findings may also be an artifact of the small numbers of case patients. We did not notice any trends that associate PJI with age of patient at time of prosthesis implantation, gender, or site of implant (hip vs knee).

Staphylococci have been consistently isolated as the predominant pathogen in PJI. The major difference between this population-based cohort and previous studies, however, is the very high bacteremia (59%) associated with *S. aureus* joint infections. Hematogenous seeding of total joint prosthesis is not unusual, especially with *S. aureus*, but rates this high have not previously been reported. There are several plausible explanations for this phenomenon. We postulate that our patients tend to present to their healthcare providers earlier, with joint pain and systemic symptoms (fever and other constitutional symptoms), and are less likely to have consumed antibiotics before evaluation. The healthcare providers are therefore more likely to sample their blood for microbiologic cultures, compared to the usual chronic PJI host.

Overall, 3 out of every 4 infected prosthetic joints were

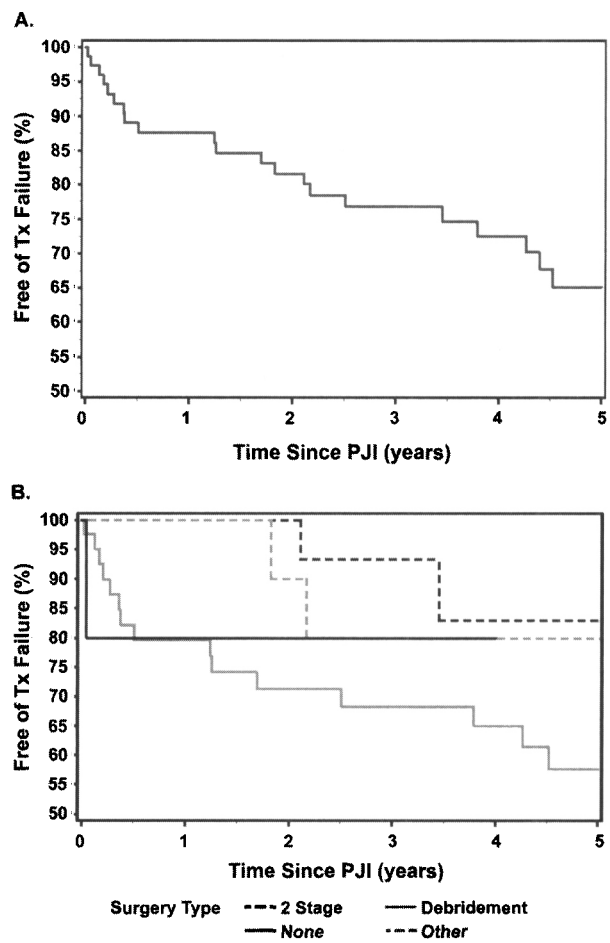

FIGURE 2. *A*, Kaplan-Meier plot of overall outcome free of treatment failure for all patients with prosthetic joint infection (PJI). $N = 75$. *B*, Kaplan-Meier plot of outcome free of treatment failure for patients with PJI by type of initial surgical strategy. $N = 75$; $P = .221$.

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free of clinical failure 3 years after diagnosis and treatment. Two-stage exchange surgery is associated with a more favorable 3-year outcome (>93%) compared to debridement and prosthesis retention (68%). There was no significant difference in success rates over the 4 decades.

CONCLUSIONS

The incidence of PJI is time dependent, with the greatest hazard within 2 years of arthroplasty. The 5-year cumulative incidence of PJI in this population is less than 1% and has not significantly changed over the past 40 years. Staphylococci are the predominant pathogens, but streptococci also play an important role in this population. *Staphylococcus aureus* PJI is often associated with bacteremia. Two-stage exchange surgery has better outcomes free of clinical failure compared to debridement with prosthesis retention. The findings of our study highlight important similarities and major differences between the epidemiology of PJI in a population-based cohort and a hospital-based sample.

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