Predictors of Treatment Failure for Hip and Knee Prosthetic Joint Infections in the Setting of 1- and 2-Stage Exchange Arthroplasty: A Multicenter Retrospective Cohort

Christopher E. Kandel,1 Richard Jenkinson,2,3 Nick Daneman,4 David Backstein,5,6 Bettina E. Hansen,1,7 Matthew P. Muller,4 Kevin C. Katz,5,10 Jessica Widdifield,1,11 Earl Bogoch,2,13 Sarah Ward,1,13 Abhilash Sajja,4 Felipe Garcia Jeldes,15 and Allison McGeer1,16

1Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada, 2Division of Orthopaedic Surgery, Department of Surgery, University of Toronto, Toronto, Ontario, Canada, 3Division of Orthopaedic Surgery, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada, 4Division of Infectious Diseases, Sunnybrook Health Sciences Centre, Toronto, Ontario Canada, 5Division of Orthopaedics, Sinai Health System, Toronto, Ontario, Canada, 6Musculoskeletal Centre of Excellence, University of Toronto, Toronto, Ontario, Canada, 7Division of Gastroenterology, Toronto General Hospital, University Health Network, Toronto, Ontario, Canada, 8Unity Health Network, University of Toronto, Toronto, Ontario, Canada, 9North York General Hospital, Toronto, Ontario, Canada, 10Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada, 11Sunnybrook Research Institute, Holland Bone & Joint Program, Toronto, Ontario, Canada, 12ICES, Toronto, Ontario, Canada, 13Division of Orthopedics, Department of Surgery, St. Michael’s Hospital, University of Toronto, Toronto, Ontario, Canada, 14Physician Assistant Program, Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada, 15Department of Microbiology, CHU de Québec - Université Laval, Quebec City, Quebec, Canada, and 16Si Sinai Health System, University of Toronto, Ontario, Canada

Background. Prosthetic hip and knee joint infections (PJIs) are challenging to eradicate despite prosthesis removal and antibiotic therapy. There is a need to understand risk factors for PJI treatment failure in the setting of prosthesis removal.

Methods. A retrospective cohort of individuals who underwent prosthesis removal for a PJI at 5 hospitals in Toronto, Canada, from 2010 to 2014 was created. Treatment failure was defined as recurrent PJI, amputation, death, or chronic antibiotic suppression. Potential risk factors for treatment failure were abstracted by chart review and assessed using a Cox proportional hazards model.

Results. A total of 533 individuals with prosthesis removal were followed for a median (interquartile range) of 814 (235–1530) days. A 1-stage exchange was performed in 19% (103/533), whereas a 2-stage procedure was completed in 88% (377/430). Treatment failure occurred in 24.8% (132/533) at 2 years; 53% (56/105) of recurrent PJIs were caused by a different bacterial species. At 4 years, treatment failure occurred in 36% of 1-stage and 32% of 2-stage procedures (P = .06). Characteristics associated with treatment failure included liver disease (adjusted hazard ratio [aHR], 3.12; 95% confidence interval [CI], 2.09–4.66), the presence of a sinus tract (aHR, 1.53; 95% CI, 1.12–2.10), preceding debridement with prosthesis retention (aHR, 1.68; 95% CI, 1.13–2.51), a 1-stage procedure (aHR, 1.72; 95% CI, 1.28–2.32), and infection due to Gram-negative bacilli (aHR, 1.35; 95% CI, 1.04–1.76).

Conclusions. Failure of PJI therapy is common, and risk factors are not easily modified. Improvements in treatment paradigms are needed, along with efforts to reduce orthopedic surgical site infections.

Keywords. prostatic joint infection; surgical site infection; revision arthroplasty.

Prosthetic joint infections (PJIs) are a feared complication of hip and knee arthroplasty and are associated with substantial morbidity through revision operations, prolonged courses of antibiotics, and joint function loss [1, 2]. PJIs are increasing in parallel with the rising number of hip and knee joint replacements occurring in aging populations [3, 4]. Treatment of PJIs usually requires an operative intervention in conjunction with prolonged courses of antibiotics that are guided by the causative microorganism and procedure performed [5]. To date, the most common operative approach in North America involves prosthesis removal followed by re-implantation, performed either concurrently—a 1-stage procedure—or subsequently—a 2-stage procedure [5].

Risk factors for PJI treatment failure identified in previous studies include a longer duration of symptoms before surgery, infection due to Staphylococcus aureus, prior revision arthroplasty, soft tissue integrity, and use of vancomycin [6–11]. These have been identified from cohorts typically involving homogenous patient populations under the care of a limited number of physicians [6, 7, 9–11]. Moreover, the duration of follow-up was often short, resulting in underestimates of the risk of treatment failure [6]. There is a need to assess risk factors for treatment failure over the long term in larger cohorts spanning multiple hospitals. The purpose of this study was to...
evaluate the characteristics associated with PJI treatment failure after operative intervention involving prosthesis removal in 5 hospitals in Toronto, Ontario, from 2010 until 2014.

METHODS

Patient Population
The study population included individuals at least 18 years of age and older who underwent a 1- or 2-stage procedure intended as definitive treatment of a prosthetic hip or knee joint infection at 1 of 5 hospitals (4 academic and 1 community) in Toronto, Ontario, Canada, between January 1, 2010, and December 31, 2014. Eligible patients were identified by reviewing listings of all orthopedic surgery procedures whose description contained any of the following words/phrases: revision, incision, debridement, first-stage procedure, second-stage procedure, single stage, or excision. Patients were excluded if follow-up was <30 days from hospital discharge or the only procedure recorded was the second stage of a 2-stage procedure. Three chart abstractors (Kandel, Garcia Jeldes, Sajja) independently reviewed the medical records to confirm the existence of a PJI using the definition of the Musculoskeletal Infection Society, which incorporates clinical, microbiological, histopathological, and biochemical criteria [12]. This study was approved by the research ethics boards of all participating institutions.

Predictors of Failure
Characteristics potentially associated with PJI treatment failure were abstracted through chart review, including patient (age, medical comorbidities, and prescribed antibiotics), joint (age of prosthesis, indication for initial arthroplasty, and previous revisions), infection (causative microorganism, duration of infectious symptoms, and antecedent antimicrobials), and surgical characteristics (procedure performed and spacer type). Underlying chronic medical conditions were as defined by the attending physician in the hospital chart, with the exception of chronic kidney disease—which was defined by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines as evidence of kidney damage or reduced function present for 3 months—and inflammatory arthritis, which required the receipt of a disease-modifying antirheumatic drug [13].

Microbiology
The causative microorganism for a PJI was defined as an organism isolated from at least 2 intraoperative specimens. If cultures were negative or not collected, preoperative arthrocentesis or operative specimens from prior debridement procedures were considered [12]. Each hospital cultured intraoperative specimens both directly onto multiple agar plates and into enrichment broth with 14-day incubation. Recurrent PJIs were categorized as relapse or reinfection according to whether the bacterial species was the same or different, respectively. If a recurrent PJI was culture negative or culture results were not available it was categorized as “unknown.” Coagulase-negative staphylococci were not identified to the species level; if coagulase-negative staphylococci were the cause of the initial and recurrent PJI, it was classified as a relapse.

Primary Outcome
PJI treatment failure was defined as any 1 of recurrent PJI, receipt of chronic antibiotics for the purpose of infection suppression, excision arthroplasty, limb amputation occurring at any point during follow-up, or death in the 30 days after a surgical procedure [14, 15]. The definition of chronic antibiotic suppression was the intended provision of indefinite oral antibiotics at any time after a definitive operative intervention for a PJI (single-stage procedure, second stage of a 2-stage procedure, or after a spacer insertion when no further surgery was anticipated). The date of failure was defined as the date that a microbiologic specimen was obtained or operative procedure performed that confirmed the diagnosis of recurrent infection or the date of excision arthroplasty, amputation, or death. Treatment outcomes were also categorized according to the Musculoskeletal Infection Society consensus criteria [15].

Statistical Analysis
Data were entered in duplicate and cleaned. All statistical analyses were carried out using R, version 3.4.4. Descriptive statistics for the cohort are presented as proportions and medians with interquartile ranges (IQRs) for categorical and continuous variables, respectively. A Cox proportional hazards model was used to assess factors associated with treatment success once model assumptions were satisfied. A priori, the following covariates were included in the model, as they have been previously shown to be associated with PJI treatment outcome: age, sex, indication for initial arthroplasty (categorized into trauma and other), previous operation for the current PJI, the causative microorganism (categorized into Staphylococcus aureus, Gram-negative bacilli, and other), presence of a sinus tract, and whether the infection was a complication of primary joint replacement or a revision surgery [6–11]. Age was included in the multivariable model with a restricted cubic spline with 3 knots, as a linear relationship with treatment failure was not observed [16]. A sandwich-type variance estimator was used to account for hospital-level clustering [17]. Separate analyses were run for 2-stage procedures only, by time of treatment failure (separated into acute [3 months], subacute [3–24 months], and late [>24 months]), by joint, and by complete vs partial prosthesis removal (with complete defined as 2-stage procedures and 1-stage procedures in which all prosthetic components were excised).

RESULTS
There were 568 individuals with 573 prosthetic hip or knee joint infections for which a 1-stage or 2-stage procedure was performed for the treatment of a PJI over the 5-year study period. Of these,
28 (4.9%) patients were excluded because only a second-stage procedure was identified, 4 (0.7%) for follow-up of <30 days, and 8 (1.4%) for amputation, excision, or fusion, leaving 533 for analysis. The median age at the time of index procedure (IQR) was 66 (59–75) years, the most common indication for joint replacement was osteoarthritis (421/533, 79%), the majority of PJIs occurred after primary rather than revision arthroplasty (340/533, 64%), and 9 (2%) occurred within 28 days of the primary arthroplasty (Table 1). Procedures were performed by 28 surgeons, with 21 performing >5 operations. Four hundred thirty patients with a PJI (176 hip joints, 41%) underwent the first of a planned 2-stage procedure, with 88% (377/430) ultimately receiving a second stage a median (IQR) of 118 (90–189) days later and 15% (56/377) undergoing at least 1 additional surgical intervention after the first stage. A 1-stage procedure was performed for the remaining 103 PJIs (75/103 hip, 73%), with complete prosthesis exchange occurring in 36% (37/103). Of the incomplete 1-stage procedures for hip PJIs only, the acetabulum was revised in 63% (35/56). For knee PJIs, the tibial component alone was revised in 40% (4/10). The median duration of follow-up (IQR) was 814 (235–1530) days.

PJIs were monomicrobial in 67% (359/533), polymicrobial in 9% (46/533), and culture-negative in 24% (128/533). The most commonly isolated organisms were coagulase-negative staphylococci (32%), followed by S. aureus (19%), Gram-negative bacilli (10%), and enterococci (8%). The proportions of PJI treatment failures by organism were similar (Table 2). Prescribed antibiotic regimens were available for 96.8% (516/533) of the cohort. Overall, vancomycin was the most commonly prescribed antibiotic for treatment, in 56% (288/516) of participants. For culture-negative infections, vancomycin or cefazolin was used in 80% (102/128); when a Gram-negative bacillus was identified, a fluoroquinolone was used in 54% (29/54); and when a Staphylococcus spp. was identified, adjunctive rifampin was used in 19% (51/269). In the setting of a 2-stage procedure without any intervening operation, the median duration of prescribed antibiotics (IQR) was 44 (42–56) days. For single-stage procedures without chronic antibiotic suppression, the median duration (IQR) was 56 (42–90) days.

Table 1. Characteristics of Individuals Undergoing Prosthesis Removal for the Treatment of a Prosthetic Hip or Knee Joint Infection at 5 Hospitals in Toronto, Ontario, Canada, Between 2010 and 2014

| Characteristic                        | Overall Cohort (n = 533) | 1-Stage (n = 103) | 2-Stage (n = 430) |
|---------------------------------------|---------------------------|-------------------|-------------------|
| Age, median (IQR), y                  | 66 (59–75)                | 67 (58–79)        | 66 (59–75)        |
| Male sex                              | 264 (50)                  | 54 (52)           | 215 (50)          |
| Joint type                            |                           |                   |                   |
| Hip                                   | 251 (47)                  | 75 (73)           | 176 (41)          |
| Knee                                  | 282 (53)                  | 28 (27)           | 254 (59)          |
| Arthroplasty indication               |                           |                   |                   |
| Osteoarthritis                        | 421 (79)                  | 76 (74)           | 345 (80)          |
| Trauma                                | 63 (12)                   | 13 (13)           | 50 (12)           |
| Inflammatory arthritis                | 18 (3)                    | 6 (6)             | 12 (3)            |
| Other                                 | 31 (6)                    | 8 (8)             | 23 (6)            |
| Prosthetic joint status<sup>b</sup>   |                           |                   |                   |
| Primary                               | 340 (64)                  | 66 (64)           | 274 (64)          |
| Revision                              | 193 (36)                  | 37 (36)           | 156 (36)          |
| Previous failed debridement           | 99 (19)                   | 2 (2)             | 97 (23)           |
| Knee spacer type (n = 254)            |                           |                   |                   |
| Dynamic                               | NA                        | NA                | 189 (74)          |
| Static                                | NA                        | NA                | 65 (26)           |
| Sinus tract present                   | 161 (30)                  | 18 (18)           | 143 (33)          |
| Vancomycin in cement                  | 355 (67)                  | 31 (30)           | 324 (75)          |
| Duration of symptoms                  |                           |                   |                   |
| Chronic (>21 d)                       | 480 (90)                  | 83 (81)           | 397 (92)          |
| Culture negative                      | 128 (24)                  | 17 (17)           | 111 (26)          |
| Organism known in advance             | 271 (37)                  | 32 (31)           | 173 (41)          |
| Comorbidity                           |                           |                   |                   |
| Diabetes                              | 214 (40)                  | 39 (38)           | 175 (41)          |
| Heart disease                         | 124 (23)                  | 24 (23)           | 100 (23)          |
| Kidney disease                        | 95 (18)                   | 16 (18)           | 79 (18)           |
| Liver disease                         | 52 (10)                   | 6 (6)             | 46 (11)           |

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: IQR, interquartile range; NA, not applicable; PJI, prosthetic joint infection.

<sup>b</sup>Includes osteonecrosis, congenital conditions, previous malignancy, and native joint septic arthritis.

<sup>2</sup>Status of the prosthetic joint before the onset of the PJI.
Table 2. Microbiology of Prosthetic Hip and Knee Joint Infections in a Multicenter Retrospective Cohort Undergoing Prosthesis Removal for a Prosthetic Joint Infection at 5 Hospitals in Toronto, Ontario, Canada, Between 2010 and 2014

| Organisms Causing Initial Infection | No. (%) Failing After Prosthesis Removal Surgerya | No. (%) With Recurrent PJIb |
|-------------------------------------|-----------------------------------------------|-----------------------------|
| Coagulase-negative staphylococci    | 52/172 (30)                                   | 11/37 (30)                  |
| Staphylococcus aureus              | 31/101 (31)                                   | 10/21 (48)                  |
| MSSA                                | 27/88 (31)                                    | 9/19 (47)                   |
| MRSA                                | 4/13 (31)                                     | 1/2 (50)                    |
| Enterococcus species               | 15/45 (33)                                    | 2/9 (22)                    |
| Beta-hemolytic streptococci        | 9/23 (38)                                     | 1/5 (20)                    |
| Non-beta-hemolytic streptococci    | 6/20 (30)                                     | 0/4 (0)                     |
| Other Gram-positive bacteria       | 6/37 (16)                                     | 1/3 (33)                    |
| Gram-negative bacilli              | 21/54 (39)                                    | 3/14 (21)c                  |
| Pseudomonas aeruginosa             | 7/12 (58)                                     | 0/3 (0)                     |
| Enterobacter spp.                  | 6/11 (55)                                     | 1/6 (17)                    |
| Escherichia coli                   | 1/10 (10)                                     | 1/1 (100)                   |
| Klebsiella pneumoniae              | 3/7 (43)                                      | 0/2 (0)                     |
| Otherc                            | 7/18 (39)                                     | 2/4 (50)                    |
| Candida species                    | 2/5 (40)                                      | 1/2 (50)                    |

Abbreviations: MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-sensitive Staphylococcus aureus; PJI, prosthetic joint infection.

aNumbers sum to >405 due to polymicrobial infections.
bIncludes only those individuals who received antibiotics with the intent of cure as opposed to suppression of infection with indefinite antibiotics.
cIncludes Corynebacterium spp., Dermabacter hominis, Listeria monocytogenes, Cutibacterium spp., Clostridium spp., and oral anaerobes.
dSum is greater than the total number of prosthetic joint infections due to Gram-negative bacilli on account of polymicrobial infections.
eIncludes Ralstonia spp., Moraxella spp., Seratia marcescens, Proteus spp., Pasteurella spp., Morganella morgani, Capnocytophaga canimorsus, Bacteroides spp., Stenotrophomonas maltophilia, and Actinobacter spp.

Figure 1. Prosthetic joint infection treatment success over time for 1- and 2-stage procedures using a Cox proportional hazard model adjusted for age, sex, surgical procedure, organism, medical comorbidities, presence of a sinus tract, prior debridement, joint status, and arthroplasty indication for the overall cohort (A) and conditional on the operative procedure performed (B).
Overall, treatment failure was 13.1% (95% confidence interval [CI], 10.2%–16%) within 6 months of the index operation, 24.8% (95% CI, 20.8%–28.6%) by 2 years, and 33.0% (95% CI, 28.1%–37.5%) by 4 years (Figure 1). For single-stage procedures, the failure rate at 6 months was 22% (95% CI, 15%–32%), by 2 years it was 29% (95% CI, 21%–40%), and by 4 years it rose to 36% (95% CI, 27%–47%), whereas the corresponding values for 2-stage exchanges were 11% (95% CI, 8%–14%), 24% (95% CI, 20%–28%), and 32% (95% CI, 27%–38%). Rates of failure were similar between hip (28%, 70/251) and knee joint (29%, 82/282) PJIIs. Failure was most often the result of a recurrent PJI (105/150, 70%), followed by antimicrobial suppression (32/150, 21%). Of the recurrent PJIIs, re-infection occurred in 53% (56/105) and relapse in 23% (24/105); the remaining 25 (24%) infections were culture-negative. Death within 30 days of a surgical procedure occurred in 2% (10/533). When applying the Musculoskeletal Infection Society criteria, the optimal outcome of infection eradication without the need for chronic antimicrobials occurred in 64% (343/533), whereas a repeat operation occurred in 26% (140/533) (Table 3).

On multivariable analysis, the following characteristics were associated with treatment failure: liver disease (adjusted hazard ratio [aHR], 3.12; 95% CI, 2.09–4.66), the presence of a sinus tract (aHR, 1.53; 95% CI, 1.12–2.10), prior failed debridement with prosthesis retention (aHR, 1.68; 95% CI, 1.13–2.51), a 1-stage procedure (aHR, 1.72; 95% CI, 1.28–2.32), and infection with a Gram-negative bacillus (aHR, 1.35; 95% CI, 1.04–1.76) (Table 4). When excluding those who received chronic antibiotic suppression, an empiric antibiotic regimen having activity against all the causative pathogens did not impact treatment failure (HR, 0.98; 95% CI, 0.84–1.13).

There were no significant changes in the findings when restricting the analysis to PJI interventions involving removal of all prosthetic components or to PJIIs treated with a 2-stage procedure, and there was no difference between PJI relapse or reinfection (data not shown). Inclusion of the second-stage procedure as a time-varying covariate did not change the risk factors identified. No factors examined were significantly associated with late treatment failure (occurring at >24 months).

DISCUSSION

Among a cohort of 533 individuals with a hip or knee PJI treated with a 1- or 2-stage exchange arthroplasty at 1 of 5 hospitals in Toronto, Ontario, the 2-year failure rate was 25%. This high failure rate is similar to that found in other studies with different patient populations, reflecting the difficulty of successful PJI therapy despite prosthesis removal [9, 18, 19]. The majority of treatment failures occur within 2 years after surgical intervention. Patient, microbiologic, and procedure-related factors were found to be associated with treatment failure.

Table 3. Prosthetic Joint Infection Treatment Outcomes According to Musculoskeletal Infection Society Categorization Scheme [15]

| Outcome Tier | Frequency (%) |
|--------------|---------------|
| Tier 1: Infection control without antibiotics | 343 (64) |
| Tier 2: Infection control with antibiotics | 40 (8) |
| Tier 3: Reoperation or spacer retention | 140 (26) |
| A: Aseptic revision >1 y after PJI treatment | 11 (2) |
| B: Septic revision >1 y after PJI treatment | 35 (7)* |
| C: Aseptic revision ≤1 y after PJI treatment | 6 (1) |
| D: Septic revision ≤1 y after PJI treatment | 50 (9)* |
| E: Amputation, excision, arthrodesis | 13 (2) |
| F: Retained spacer | 25 (5) |
| Tier 4: Death | 10 (2) |
| A: Death ≤1 y after PJI treatment | 9 (2) |
| B: Death >1 y after PJI treatment | 1 (0.2) |

Abbreviation: PJI, prosthetic joint infection.

*For Tiers 3B and 3D, the number of recurrent PJIIs due to the same bacterial species was 21 and due to a different species was 33.
when a prosthesis retention approach is adopted [29]. Similarly, we found that liver disease was associated with treatment failure in the setting of prosthesis removal.

Infections due to Gram-negative bacilli were associated with a higher hazard of treatment failure. Similar associations have been identified previously in the setting of both prosthesis retention and removal [6]. We did not, however, find that *Staphylococcus aureus* was associated with PJI treatment failure, which differs from the results of previous studies [30]. This may relate to including only PJIs treated with prosthesis removal, as this association is more pronounced in the setting of prosthesis retention [31]. The virulence factors of *Staphylococcus aureus* and propensity to form a biofilm may contribute to the decreased effectiveness of debridement alone [32]. Accordingly, prosthesis removal may be preferred in PJIs caused by these organisms when there are additional risk factors for treatment failure. Renal failure and underlying inflammatory arthritis are additional risk factors that were not corroborated in this cohort [33]. However, our study was underpowered to detect the previously estimated size of effect of these comorbidities. In addition, our definition of renal disease, which included only those with chronic renal failure according to the KDIGO criteria, was more stringent than that used in previous studies [29].

### Treatment Failure
The newly recommended tiered reporting of outcomes of PJI management is complex but provides a useful illustration of the variability in treatment failure rates likely to be reported based on different definitions of treatment success and durations of follow-up [15, 34]. In our cohort, inclusion of chronic antibiotic suppression as treatment failure increased the overall failure rate to 29% from 22%; similarly, excluding spacer retention as a cause of failure lowered the failure rate by ~5%. It may not be possible to achieve universal consensus on a single definition of failure.

In our study, when an organism was identified in the setting of a recurrent PJI, which occurred in 75% of treatment failures, the majority were different from the initial causative organism. This is similar to a previous study demonstrating that the proportion of recurrent PJIs caused by the same organism was lower in the setting of prosthesis removal as compared with prosthesis retention [35, 36]. Our estimate of the proportion of recurrent infections due to a different organism is conservative, as coagulase-negative staphylococci were classified as the same organism because they were not routinely identified to the species level in our laboratories. Our results suggest that after collection of appropriate microbiological specimens in these patients, it is prudent to provide empiric antibiotic coverage directed not only toward previously detected pathogens, but also more broadly against other common causative pathogens, before adjusting therapy once microbiology results are available.

### Limitations
There are limitations that merit emphasis. Our detection strategy for PJI was imperfect and may have missed some individuals, particularly if operative procedures were miscoded or treatment was provided at a different hospital. These scenarios are likely to include a small number of individuals and will minimally impact the results. In addition, by design, only those individuals who underwent an operation for the treatment of a PJI were included. However, the number of individuals treated with antibiotics alone for a PJI is expected to be small; the majority of those in whom an antibiotic suppression strategy is adopted undergo at least 1 operative intervention [37, 38]. Moreover, individuals treated medically opt to focus on attenuating symptoms, making them different from those for whom

---

Table 4. Univariate and Multivariate Hazard Ratios for Characteristics Associated With Prosthetic Joint Infection Treatment Failure in Patients Undergoing Prosthesis Removal for a Prosthetic Joint Infection at 5 Hospitals in Toronto, Ontario, Canada, Between 2010 and 2014

| Characteristic | Univariate Hazard Ratio (95% Confidence Interval) | P Value | Adjusted Hazard Ratio (95% Confidence Interval) | P Value |
|---------------|-------------------------------------------------|---------|-----------------------------------------------|---------|
| Nonprimary joint | 1.34 (0.75–2.40) | .33 | | |
| Arthroplasty indication | | | | |
| Trauma | 1.38 (0.96–1.99) | .08 | | |
| Failed prior debridement | 1.78 (1.45–2.19) | <.001 | 1.68 (1.13–2.51) | .011 |
| 1-stage procedure | 1.29 (0.99–1.69) | .06 | 1.72 (1.28–2.32) | <.001 |
| Microbiology | | | | |
| *Staphylococcus aureus* | 1.30 (0.82–2.05) | .27 | | |
| Gram-negative bacilli | 1.81 (1.44–2.29) | <.001 | 1.35 (1.04–1.76) | .026 |
| Sinus tract | 1.77 (1.30–2.41) | <.001 | 1.53 (1.12–2.10) | .008 |
| Diabetes mellitus | 1.11 (0.84–1.46) | .45 | | |
| Liver disease | 2.75 (1.93–3.92) | <.001 | 3.12 (2.09–4.66) | <.001 |
| Kidney disease | 1.03 (0.72–1.48) | .86 | | |

*For each characteristic, the comparison is the absence of the characteristic unless a reference is specified. For 1-stage procedures, the reference group is 2-stage procedures.*
the goal is infection eradication [39]. Some characteristics potentially associated with surgical site infection such as smoking and surgeon volume could not be obtained. Despite the size of the cohort, the subgroup analyses should be interpreted with caution. Finally, the retrospective nature of the study increases the possibility that unmeasured confounders might affect our results.

CONCLUSIONS

Prosthetic hip and knee joint infections are challenging to eradicate, with failure rates >20% even in the setting of complete prosthesis removal. Compatible with previous research, most patient risk factors associated with PJI treatment failure were not modifiable. There is an urgent need to improve treatment paradigms and interventions that will improve the treatment of these devastating infections.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

Financial support. This work was supported by the Eliot Phillipson Clinician-Scientist Training Program at the University of Toronto.

Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Gundtoft PH, Pedersen AB, Varnum C, Overgaard S. Increased mortality after prosthetic joint infection in primary THA. Clin Orthop Relat Res 2017; 475:2623–31.
2. Moore AJ, Blom AW, Whitehouse MR, Gooberman-Hill R. Deep prosthetic joint infection: a qualitative study of the impact on patients and their experiences of revision surgery. BMJ Open 2015; 5:e009495.
3. Kuzure S, Ong K, Lau E, et al. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am 2007; 89:780–8.
4. Perfetti DC, Boylan MR, Nazini Q, et al. Have periprosthetic hip infection rates plateaued? J Arthroplasty 2017; 32:2244–7.
5. Osman DR, Berbati EF, Berendt AR, et al; Infectious Diseases Society of America. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2013; 56:e1–e25.
6. Hsieh PH, Lee MS, Hsu KY, et al. Gram-negative periprosthetic joint infections: risk factors and outcome of treatment. Clin Infect Dis 2009; 49:1036–43.
7. Parvizi J, Ghanem A, Ezzam K, et al. Periprosthetic infection: are current treatment strategies adequate? Acta Orthop Belg 2008; 74:793–800.
8. Kühn B, Hartzer RU, Wood CM, et al. Reinfektion after two-stage revision for periprosthetic infection of total knee arthroplasty. Int Orthop 2012; 36:65–71.
9. Mortazavi SM, Vegari D, Ho A, et al. Two-stage exchange arthroplasty for infected total knee arthroplasty: predictors of failure. Clin Orthop Relat Res 2011; 469:3049–54.
10. Massin P, Deloye T, Lhotellier L, et al. Infection recurrence factors in one- and two-stage total knee prosthesis exchanges. Knee Surg Sports Traumatol Arthrosc 2016; 24:3131–9.
11. Cunningham DJ, Karolus JJ, Bolognesi MP, et al. Specific infectious organisms associated with poor outcomes in treatment for hip periprosthetic infection. J Arthroplasty 2017; 32:984–90.e5.
12. Zmistowski B, della Valle C, Bauer TW, et al. Diagnosis of periprosthetic joint infection. J Orthop Res 2014; 32(Suppl 1):S98–107.
13. Inker LA, Astor BC, Fox CH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis 2014; 63:713–35.
14. Diaz-Ledezma C, Higuera CA, Parvizi J. Success after treatment of periprosthetic joint infection: a Delphi-based international multidisciplinary consensus. Clin Orthop Relat Res 2013; 471:2374–82.
15. Fillingham YA, Della Valle CJ, Suleiman LI, et al. Definition of successful infection management and guidelines for reporting of outcomes after surgical treatment of periprosthetic joint infection: from the Workgroup of the Musculoskeletal Infection Society (MSIS). J Bone Joint Surg Am 2019; 101:e69.
16. Ireton Jr, FE. Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis. 2nd ed. Switzerland: Springer International Publishing; 2015.
17. Austin PC. A tutorial on multilevel survival analysis: methods, models and applications. Int Stat Rev 2017; 85:185–203.
18. Bejon P, Berendt A, Atkins BL, et al. Two-stage revision for prosthetic joint infection: predictors of outcome and the role of reimplantation microbiology. J Antimicrob Chemother 2010; 65:659–75.
19. Mahmud T, Lyons MC, Naude DD, et al. Assessing the gold standard: a review of 253 two-stage revisions for infected TKA. Clin Orthop Relat Res 2012; 470:2730–6.
20. Sherrell JC, Fehring TK, Oduo S, et al; Periprosthetic Infection Consortium. The Chiritanjan Ranawat Award: fate of two-stage reimplantation after failed irrigation and debridement for periprosthetic knee infection. Clin Orthop Relat Res 2011; 469:18–25.
21. Buller LT, Sabry FY, Easton RW, et al. The preoperative prediction of success following irrigation and debridement with polynethylene exchange for hip and knee prosthetic joint infections. J Arthroplasty 2012; 27:857–64.e1–4.
22. Tornero E, Morata L, Martinez-Pastor JC, et al. Importance of selection and duration of antibiotic regimen in prosthetic joint infections treated with debridement and implant retention. J Antimicrob Chemother 2016; 71:1395–401.
23. Kunutsor SK, Whitehouse MR, Lenguerrand E, et al; INFORM Team. Re-infection outcomes following one- and two-stage surgical revision of infected knee prosthesis: a systematic review and meta-analysis. PLoS One 2016; 11:e0151537.
24. Kunutsor SK, Whitehouse MR, Blom AW, Beswick AD; INFORM Team. Re-infection outcomes following one- and two-stage surgical revision of infected hip prosthesis: a systematic review and meta-analysis. PLoS One 2015; 10:e0139166.
25. Kunutsor SK, Whitehouse MR, Blom AW, et al; Global Infection Orthopaedic Management Collaboration. One- and two-stage surgical revision of periprosthetic joint infection of the hip: a pooled individual participant data analysis of 44 cohort studies. Eur J Epidemiol 2013; 31:933–46.
26. Strange S, Whitehouse MR, Beswick AD, et al. One-stage or two-stage revision surgery for prosthetic hip joint infection—the INFORM trial: a study protocol for a randomised controlled trial. Trials 2016; 17:90.
27. Hoell S, Sieweke A, Goshger G, et al. Eradication rates, risk factors, and implant selection in two-stage revision knee arthroplasty: a mid-term follow-up study. J Orthop Surg Res 2016; 11:93.
28. McPherson EJ, Woodson C, Holtom P, et al. Periprosthetic total hip infection: outcomes using a staging system. Clin Orthop 2002; 8–15.
29. Tornero E, Morata L, Martinez-Pastor JC, et al. KLIC-score for predicting early failure in prosthetic joint infections treated with debridement, implant retention and antibiotics. Clin Microbiol Infect 2013; 31:876.e9–1.e17.
30. Sakellariou VL, Poutsiadas LA, Vasilakakos T, et al. Risk factors for recurrence of periprosthetic knee infection. J Arthroplasty 2015; 30:1618–22.
31. Koyonos L, Zmistowski B, Della Valle CJ, Parvizi J. Infection control rate of irrigation and debridement for periprosthetic joint infection. Clin Orthop Relat Res 2011; 469:3043–8.
32. Palhairi AE, Horswill AR. The staphylococcal biofilm: adhesins, regulation, and host response. Microbiol Spectr 2016; 4(2).
33. Cha MS, Cho SH, Kim DH, et al. Two-stage total knee arthroplasty for prosthetic joint infection. Knee Surg Relat Res 2015; 27:82–9.
34. Tan TL, Goswami K, Fillingham YA, et al. Defining treatment success after 2-stage exchange arthroplasty for periprosthetic joint infection. J Arthroplasty 2018; 33:3541–6.
35. Zmistowski B, Tetzeault MW, Alijanpour P, et al. Recurrent periprosthetic joint infection: persistent or new infection? J Arthroplasty 2013; 28:1468–9.
36. Zmistowski BM, Manrique J, Patel R, Chen AF. Recurrent periprosthetic joint infection following irrigation and debridement with component retention is most often due to identical organisms. J Arthroplasty 2016; 31:148–51.
37. Pradier M, Robineau O, Boucher A, et al. Suppressive antibiotic therapy with oral tetracyclines for prosthetic joint infections: a retrospective study of 78 patients. Infection 2018; 46:39–47.
38. Siqueira MB, Saleh A, Klika AK, et al. Chronic supression of periprosthetic joint infections with oral antibiotics increases infection-free survivorship. J Bone Joint Surg Am 2015; 97:1220–32.
39. Keller SC, Cosgrove SE, Higginb Y, et al. Role of suppressive oral antibiotics in orthopedic hardware infections for those not undergoing two-stage replacement surgery. Open Forum Infect Dis 2016; 3(XX):XXX–XX.