

# Risk of Treatment Failure for Prosthetic Joint Infections: Retrospective Chart Review in an Outpatient Parenteral Antimicrobial Therapy Program

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## ABSTRACT

**Background:** Prosthetic joint infections (PJIs) are a major complication of total joint replacement surgeries. Treatment includes surgical intervention with prolonged courses of IV antibiotics in outpatient parenteral antimicrobial therapy (OPAT) programs. The risk of PJI treatment failure is high and may be associated with various clinical factors.

**Objectives:** To determine the rate of PJI treatment failure and to identify potential risk factors for failure in patients admitted to an OPAT program.

**Methods:** A retrospective chart review was conducted for adult patients with PJI admitted to an OPAT program between July 1, 2013, and July 1, 2019. Treatment courses were deemed to have failed according to predetermined criteria.  $\chi^2$  tests and multiple linear regression were used to examine associations of comorbidities, pathogens, and antimicrobial regimens with treatment failure.

**Results:** In total, 100 patients associated with 137 PJI treatment courses in the OPAT program were included. Of these, 28 patients accounted for 65 of the treatment courses. Methicillin-susceptible *Staphylococcus aureus* was the most frequently isolated pathogen (31/137 or 22.6% of treatment courses). Patient comorbidities included body mass index of at least 30 kg/m<sup>2</sup> (58% of patients) and diabetes (41% of patients). The overall rate of treatment failure was 56.2% (77/137 treatment courses). Selected risk factors associated with treatment failure or success were diabetes (50.9% versus 29.8%; odds ratio [OR] 4.03, 95% confidence interval [CI] 1.38–12.88,  $p = 0.013$ ) and depression (32.1% versus 14.9%; OR 5.02, 95% CI 1.30–22.89,  $p = 0.025$ ).

**Conclusions:** The overall rate of PJI treatment failure in the study population was high. Patients with diabetes and depression experienced higher incidences of failure. Future investigations of comprehensive PJI management should be considered to ensure successful treatment and to minimize excessive use of health care resources.

**Keywords:** outpatient, IV therapy, prosthetic joint infection, treatment failure, antimicrobial, duration of therapy, comorbidities

## RÉSUMÉ

**Contexte :** Les infections des prothèses articulaires (IPA) sont une complication majeure des arthroplasties totales. Le traitement comprend une intervention chirurgicale avec des séries prolongées d'antibiotiques IV dans le cadre de programmes de traitement antimicrobien parentéral ambulatoire (*outpatient parenteral antimicrobial therapy*; OPAT). Le risque d'échec du traitement des IPA est élevé et peut être associé à divers facteurs cliniques.

**Objectifs :** Déterminer le taux d'échec du traitement des IPA et identifier les facteurs de risque chez les patients admis dans un programme OPAT.

**Méthodes :** Un examen rétrospectif des dossiers de patients adultes atteints d'une IPA admis dans un programme OPAT entre le 1<sup>er</sup> juillet 2013 et le 1<sup>er</sup> juillet 2019 a été mené. L'échec d'un traitement était défini selon des critères prédéterminés. Des tests  $\chi^2$  et une régression linéaire multiple ont été utilisés pour examiner les associations de comorbidités, d'agents pathogènes et de régimes antimicrobiens avec l'échec du traitement.

**Résultats :** Au total, 100 patients associés à 137 séries de traitements des IPA au sein du programme OPAT étaient inclus. Parmi ceux-ci, 28 patients représentaient 65 des séries de traitement. Le *Staphylococcus aureus* sensible à la méthicilline était l'agent pathogène le plus fréquemment isolé (31/137 soit 22,6 % des séries de traitement). Les comorbidités des patients comprenaient un indice de la masse corporelle d'au moins 30 kg/m<sup>2</sup> (58 % des patients) et un diabète (41 % des patients). Le taux global d'échec thérapeutique était de 56,2 % (77/137 séries de traitement). Les facteurs de risque sélectionnés associés à l'échec ou à la réussite du traitement étaient le diabète (50,9 % contre 29,8 %; rapport de cotes [RC] 4,03, intervalle de confiance à 95 % 1.38-12.88,  $p = 0,013$ ) et la dépression (32,1 % contre 14,9 %; RC 5,02, IC à 95 % 1.30-22.89,  $p = 0,025$ ).

**Conclusions :** Le taux global d'échec du traitement de l'IPA dans la population étudiée était élevé. L'incidence des échecs chez les patients atteints de diabète et de dépression était plus élevée. Des enquêtes futures sur la prise en charge globale de l'IPA devraient être envisagées pour garantir la réussite du traitement et réduire au minimum l'utilisation excessive des ressources de soins de santé.

**Mots-clés :** ambulatoire, traitement IV, infection de prothèse articulaire, échec thérapeutique, antimicrobien, durée du traitement, comorbidités

## INTRODUCTION

Prosthetic joint replacement is an effective intervention to restore function and improve quality of life for patients with arthritic or dysfunctional joints. In Canada, the number of joint replacement surgeries is expected to rise as the population ages. In its 2018-2019 report, the Canadian Joint Replacement Registry documented a 20% increase in hip and knee replacements over the previous 5 years and annual inpatient costs of \$1.4 billion.<sup>1</sup> Although replaced joints should last 15–20 years before replacement is needed, some patients require early revisions, with associated inpatient costs of \$42.1 million annually.<sup>2</sup> The most common problem leading to early revision surgery is prosthetic joint infection (PJI), accounting for over 30% of cases.<sup>1,2</sup> PJI represents a serious complication of prosthetic joint replacement, resulting in readmission to hospital, prolonged length of stay, joint failure, and increased morbidity and mortality.<sup>3,4</sup> Management of PJI includes revision surgery, source control, and prolonged courses of IV or highly bioavailable oral antibiotics.<sup>1,5,6</sup> Unfortunately, there is a high risk of relapse or re-infection following PJI treatment. In a retrospective study published in 2019, 33% of patients treated for hip or knee PJI experienced treatment failure within 4 years of revision surgery.<sup>7</sup> Both modifiable and nonmodifiable risk factors for PJI treatment failure have been reported in other studies.<sup>8-17</sup>

Risk factors associated with PJI treatment failure in previous studies have included infection due to *Staphylococcus aureus* or gram-negative bacilli, polymicrobial infections, pre-existing liver disease, obesity, smoking, and presence of a communicating sinus tract.<sup>7-16</sup> The risk of treatment failure among patients with retained implants is higher, with one study reporting a failure rate of 45% in patients with late PJI.<sup>17</sup>

To facilitate outpatient care in the community, patients requiring long-duration IV antibiotic therapy are enrolled in outpatient parenteral antimicrobial therapy (OPAT) programs. Unfortunately, there is a paucity of studies investigating PJI management in the OPAT setting, because previous studies investigating risk factors for treatment failure in such programs have included only small numbers of patients with PJI.<sup>18-20</sup> In Winnipeg, Manitoba, the Community IV Program (CIVP) provides OPAT services to patients requiring IV antimicrobials for an extended duration.

The purposes of this study were to determine the rate of PJI treatment failure and to identify risk factors for such failure in the Winnipeg OPAT population. Although previous studies have identified and reported rates of PJI treatment failure and associated risk factors, these data may not be reflective of Winnipeg's OPAT population. The frequency of specific pathogens and antibiotic data such as chosen regimens, duration of treatment, rationale for change in or early discontinuation of IV treatment, and use

of oral antibiotics for infection suppression after IV treatment were also assessed.

## METHODS

This retrospective chart review involved evaluation of the medical records of patients admitted to an OPAT program for treatment of PJI. A list of all patients treated from July 1, 2013, to July 1, 2019, was obtained from the Winnipeg CIVP's electronic medical record (EMR) system. The International Classification of Diseases, Ninth Revision (ICD-9), code 996.66 (for infection and inflammatory reaction due to internal joint prosthesis) was used to screen for PJI-related OPAT admissions. An admission was defined as the patient receiving a referral to the OPAT program for PJI treatment and receiving at least one dose of IV antibiotics through the program.

Patients were included in the study if they were 18 years of age or older when admitted to the OPAT program. Patients were excluded if they had amputation of the implicated limb before OPAT admission, if they had an infection involving nonjoint hardware, or if there was no documentation of the admission in the patient's EMR. If patients had more than one admission to the OPAT program within the study period, each admission was recorded as a separate treatment course. Separate treatment courses occurred if the patient was readmitted to the OPAT program after rehospitalization for any reason that disrupted the previous OPAT treatment course or if the patient was readmitted to the OPAT program at least 2 weeks after completing a previous IV antibiotic treatment course.

Patient data and potential risk factors for PJI treatment failure (Appendix 1, available from <https://www.cjhp-online.ca/index.php/cjhp/issue/view/213>) were extracted through a chart review of documentation in the OPAT EMR system. This documentation included demographic data (age, sex, body mass index [BMI]), and estimated glomerular filtration rate), comorbidities, and use of immunosuppressant medications during the OPAT admission. Underlying comorbidities were determined through initial assessment by the OPAT nurse.

Information was collected about the prosthetic joint affected (knee, hip, or other) and the diagnostic indicators of PJI (specifically, presence of a sinus tract, purulence in affected joint, and at least 2 positive results on joint culture yielding the same organism). Any diagnostic indicator not documented in the chart was deemed not present. Data were also collected about the initial hospitalization, including duration of hospital stay and the date and type of surgical intervention. Microbiological data collected included all pathogens detected and the presence of bacteremia. Data collected about antimicrobial treatment included the type of antimicrobial regimen initiated in hospital and in the OPAT program, the intended and actual duration of treatment, and

the reasons for stopping or switching regimens. Use of long-term oral antibiotic therapy after the IV treatment course was also recorded, including intended duration of oral treatment.

Treatment courses that met any of the following criteria were classified as “treatment failure”: readmission to the OPAT program for infection of the same joint, additional surgery outside of the original treatment plan, extension of IV antibiotic treatment beyond 8 weeks, persistence of symptoms, readmission to hospital for reasons related to the infection, and loss to follow-up before completion of treatment (Appendix 2, available from <https://www.cjhp-online.ca/index.php/cjhp/issue/view/213>). Treatment courses that did not meet these criteria were classified as “treatment success”. To compare patient comorbidities in relation to treatment failure and success, each patient and their comorbidities were categorized into either the “treatment failure” or the “treatment success” group. For patients with failure of at least one treatment course, their comorbidities were categorized into the “treatment failure” group, and if they experienced only successful treatment courses, their comorbidities were categorized into the “treatment success” group.

The study was approved by the University of Manitoba Health Research Ethics Board and the Health Sciences Centre Research Impact Committee. The data were collected and analyzed by a single investigator (D.F.). Descriptive statistics were used, with dichotomous data represented as counts and percentages and non-normally distributed continuous data represented as median values and interquartile ranges (IQRs). The  $\chi^2$  test was used to examine associations between comorbidities, surgical interventions, pathogens, and antimicrobial regimens and treatment failure. The rate of treatment failure was determined by dividing the number of treatment courses that met any of the criteria for treatment failure by the total number of PJI treatment courses.

A post hoc analysis was performed using R software, version 4.2.0. This analysis involved a multiple logistic regression model to examine comorbidities for significant association with treatment failure. Odds ratios and confidence intervals (CIs) were determined, as well as the McFadden pseudo  $R^2$  score to determine model fit. McFadden suggested that  $R^2$  values between 0.2 and 0.4 represent a good fit of the model.<sup>21</sup>

## RESULTS

### Demographic Characteristics

For the period between July 1, 2013, and July 1, 2019, a total of 179 separate PJI treatment courses were identified by searching the EMR system. Of these, 42 were excluded: 18 courses had infection of nonjoint hardware, 16 courses had missing EMR documentation, and 8 courses occurred completely outside the study period. The remaining 137 PJI treatment courses, associated with 100 patients, were included in this study. Twenty-eight of the patients had more

than one treatment course through the OPAT program and accounted for 65 (47.4%) of the included courses. Of the 28 patients with multiple treatment courses, 26 (92.9%) had infections in the same joint and 12 (42.9%) had infections with the same pathogen. The median age of all 100 patients was 65 years, and the most common comorbidities were BMI of 30 kg/m<sup>2</sup> or more (58%), diabetes mellitus (41%), smoking (25%), and depression (24%) (Table 1).

### PJI Diagnosis and Surgical Intervention

Patients most commonly experienced PJI in the knee (52% of patients) and hip (41% of patients). Among the 137 treatment courses, the corresponding PJI was characterized by presence of a sinus tract in 23 (16.8%) cases, purulence in the affected joint in 55 (40.1%), and at least 2 positive culture results yielding the same organisms in 76 (55.5%). The most common pathogens isolated were gram-positive cocci (76/137 [55.5%]) (Table 2). *Staphylococcus aureus* was identified in association with 34 (24.8%) of the 137 treatment courses, with methicillin-sensitive *S. aureus* accounting for 31 of these cases. Bacteremia occurred in association with 15 (10.9%) of the treatment courses.

The most common initial surgical interventions to treat PJI were irrigation and debridement (for 65 [47.4%] of the 137 OPAT admissions) and 2-stage revision (49 [35.8%]). Single-stage revision (4 [2.9%]) and other surgeries (9 [6.6%]) were less common. For 10 treatment courses (7.3%), no surgical intervention was performed.

### Antimicrobial Use

IV antimicrobials commonly initiated in hospital included cefazolin (37 [27.0%] of the 137 OPAT admissions) and vancomycin (30 [21.9%]). After hospital discharge, the most common initial IV antimicrobials administered in the OPAT program were ceftriaxone (65 [47.4%] of the 137 treatment courses) and vancomycin (41 [29.9%]). Oral and IV combination regimens were used in 11 treatment courses (8.0%). In 3 treatment courses (2.2%), oral rifampin was used with ceftriaxone. The overall median duration of IV antimicrobial treatment was 53 days (IQR 45–77 days).

Antimicrobial regimens were changed during OPAT treatment in 21 courses (15.3%), most commonly because of adverse drug reactions (9/21 [43%]) and physician-defined clinical treatment failure (4/21 [19%]). IV antibiotic treatment was stopped early in 18 courses (13.1%). The most common reasons for early discontinuation were adverse drug reaction (7/18 [39%]), readmission to hospital (5/18 [28%]), and patient non-adherence (5/18 [28%]).

Oral antibiotic therapy was initiated after 69 IV treatment courses (50.4%). The most common duration for oral antibiotic therapy was 1 year (17 [24.6%]), with lifelong suppressive therapy recommended after 4 treatment courses (5.8%). The duration of oral antibiotic therapy was not specified for 18 courses (26.1%).

**TABLE 1. Unadjusted Risk Factors for Treatment Failure**

Risk Factor	Group; No. (%) of Patients <sup>a</sup>			p Value <sup>b</sup>
	All (n = 100)	Failure (n = 53)	Success (n = 47)	
Age (years) (median and IQR)	65 (59–71)	62 (56–68)	68 (59–74)	
Obesity (BMI ≥ 30 kg/m <sup>2</sup> )	58 (58)	30 (56.6)	28 (59.6)	0.76
eGFR (mL/min/1.73 m <sup>2</sup> )				
≥ 60	82 (82)	46 (86.8)	36 (76.6)	0.19
45–59	12 (12)	6 (11.3)	6 (12.8)	0.82
30–44	5 (5)	0 (0)	5 (10.6)	0.015
Sex, female	45 (45)	27 (50.9)	18 (38.3)	0.20
Concurrent condition				
Chronic liver disease	5 (5)	5 (9.4)	0 (0)	0.031
Diabetes mellitus	41 (41)	27 (50.9)	14 (29.8)	0.032
COPD	13 (13)	7 (13.2)	6 (12.8)	0.95
History of ischemic heart disease	14 (14)	5 (9.4)	9 (19.1)	0.16
Heart failure	9 (9)	5 (9.4)	4 (8.5)	0.87
Peripheral vascular disease	6 (6)	3 (5.7)	3 (6.4)	0.88
Rheumatoid arthritis	14 (14)	10 (18.9)	4 (8.5)	0.14
Active malignancy	2 (2)	1 (1.9)	1 (2.1)	0.93
Lymphedema	2 (2)	2 (3.8)	0 (0)	0.17
History of MRSA infection	8 (8)	7 (13.2)	1 (2.1)	0.042
Active smoker	25 (25)	16 (30.2)	9 (19.1)	0.20
Depression	24 (24)	17 (32.1)	7 (14.9)	0.045
Gout	14 (14)	5 (9.4)	9 (19.1)	0.16
Immunosuppressive agents				
Corticosteroid > 30 days	4 (4)	2 (3.8)	2 (4.3)	0.90
Methotrexate	3 (3)	2 (3.8)	1 (2.1)	0.63
TNF inhibitor	1 (1)	0 (0)	1 (2.1)	0.29

BMI = body mass index, COPD = chronic obstructive pulmonary disease, eGFR = estimated glomerular filtration rate, IQR = interquartile range, MRSA = methicillin-resistant *Staphylococcus aureus*, TNF = tumour necrosis factor.

<sup>a</sup>Except where indicated otherwise.

<sup>b</sup> $\chi^2$  test.

### Treatment Failure

As shown in Figure 1, 77 of the 137 treatment courses met at least one criterion for treatment failure, resulting in a 56.2% failure rate. Thirty-six courses (26.3%) met 2 or more criteria for treatment failure. Of the 100 patients included in the study, 53 (53%) had at least one course that resulted in treatment failure. The most common reasons for treatment failure (Figure 2) were extension of IV antibiotic therapy beyond 8 weeks (49 [35.8%] of 137 treatment courses) and readmission to the OPAT program for infection of the same joint (46 [33.6%] of 137 treatment courses).

### Risk Factors for Treatment Failure

Patient comorbidities associated with treatment failure, as indicated by unadjusted  $\chi^2$  analysis, are shown in Table 1. The risk factors associated with treatment failure were diabetes mellitus (50.9% versus 29.8%;  $p = 0.032$ ), chronic liver disease (9.4% versus 0%;  $p = 0.031$ ), history of infection or colonization with methicillin-resistant *S. aureus* (MRSA)

(13.2% versus 2.1%;  $p = 0.042$ ), and depression (32.1% versus 14.9%;  $p = 0.045$ ). There was no significant association of treatment failure with immunosuppressive therapy during OPAT treatment.

There was no significant difference in terms of treatment failure versus success for PJI of the knee (31/53 [58.5%] versus 21/47 [44.7%];  $p = 0.17$ ), the hip (20/53 [37.7%] versus 21/47 [44.7%];  $p = 0.48$ ), or other types of joints (2/53 [3.8%] versus 5/47 [10.6%];  $p = 0.18$ ). Diagnostic criteria, including presence of sinus tract, purulence in the affected joint, and at least 2 positive cultures yielding the same organism, were not significantly associated with treatment failure.

Pathogens associated with treatment failure are shown in Table 2. Gram-positive cocci were associated with treatment failure (63.6% for treatment failure versus 45.0% for treatment success;  $p = 0.029$ ), but there was no significant association for gram-negative, anaerobic, or polymicrobial infections. Culture-negative infections were associated with treatment success (16.7% versus 5.2%;  $p = 0.028$ ). The

**TABLE 2. Frequency of Pathogens Associated with Failure of Treatment for Prosthetic Joint Infection**

Pathogen	Group; No. (%) of Infections			p Value <sup>b</sup>
	All Infections <sup>a</sup> (n = 137)	Failure (n = 77)	Success (n = 60)	
Gram positive	76 (55.5)	49 (63.6)	27 (45.0)	0.029
<i>Staphylococcus aureus</i>	34 (24.8)	23 (29.9)	11 (18.3)	0.12
MSSA	31 (22.6)	22 (28.6)	9 (15.0)	0.06
MRSA	3 (2.2)	1 (1.3)	2 (3.3)	0.49
Coagulase-negative <i>Staphylococcus</i>	19 (13.9)	13 (16.9)	6 (10.0)	0.25
<i>S. simulans</i>	1 (0.7)	1 (1.3)	0 (0)	0.38
<i>S. epidermidis</i>	6 (4.4)	5 (6.5)	1 (1.7)	0.17
MRSE	8 (5.8)	4 (5.2)	4 (6.7)	0.72
Resistant <i>S. haemolyticus</i>	4 (2.9)	3 (3.9)	1 (1.7)	0.44
<i>Streptococcus</i>	18 (13.1)	9 (11.7)	9 (15.0)	0.57
GAS	3 (2.2)	2 (2.6)	1 (1.7)	0.71
GBS	3 (2.2)	1 (1.3)	2 (3.3)	0.42
Group C/G streptococci	3 (2.2)	1 (1.3)	2 (3.3)	0.42
Viridans streptococci	8 (5.8)	5 (6.5)	3 (5.0)	0.71
<i>S. pneumoniae</i>	1 (0.7)	0 (0)	1 (1.7)	0.26
<i>Enterococcus</i>	5 (3.6)	4 (5.2)	1 (1.7)	0.27
<i>E. faecalis</i>	3 (2.2)	2 (2.6)	1 (1.7)	0.71
VRE	2 (1.5)	2 (2.6)	0 (0)	0.21
Gram-negative	7 (5.1)	3 (3.9)	4 (6.7)	0.46
<i>Escherichia coli</i>	4 (2.9)	2 (2.6)	2 (3.3)	0.80
Multidrug-resistant <i>E. coli</i>	1 (0.7)	0 (0)	1 (1.7)	0.26
<i>Proteus</i>	2 (1.5)	1 (1.3)	1 (1.7)	0.86
Anaerobes	4 (2.9)	1 (1.3)	3 (5.0)	0.20
<i>Cutibacterium</i>	1 (0.7)	0 (0)	1 (1.7)	0.26
Other	3 (2.2)	1 (1.3)	2 (3.3)	0.42
Polymicrobial	31 (22.6)	18 (23.4)	13 (21.7)	0.81
Other	1 (0.7)	0 (0)	1 (1.7)	0.26
Culture negative	14 (10.2)	4 (5.2)	10 (16.7)	0.028

GAS = group A *Streptococcus*, GBS = group B *Streptococcus*, MRSA = methicillin-resistant *Staphylococcus aureus*, MRSE = methicillin-resistant *Staphylococcus epidermidis*, MSSA = methicillin-susceptible *Staphylococcus aureus*, VRE = vancomycin-resistant *Enterococcus*.

<sup>a</sup>Four treatment courses (2 with treatment failure and 2 with treatment success) did not have documented culture results.

<sup>b</sup> $\chi^2$  test.

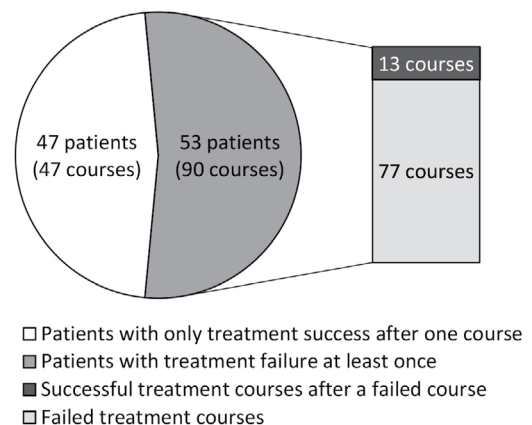
presence of bacteremia was not associated with treatment failure (10/77 [13.0%] versus 5/60 [8.3%];  $p = 0.39$ ).

### Surgical Interventions and Treatment Failure

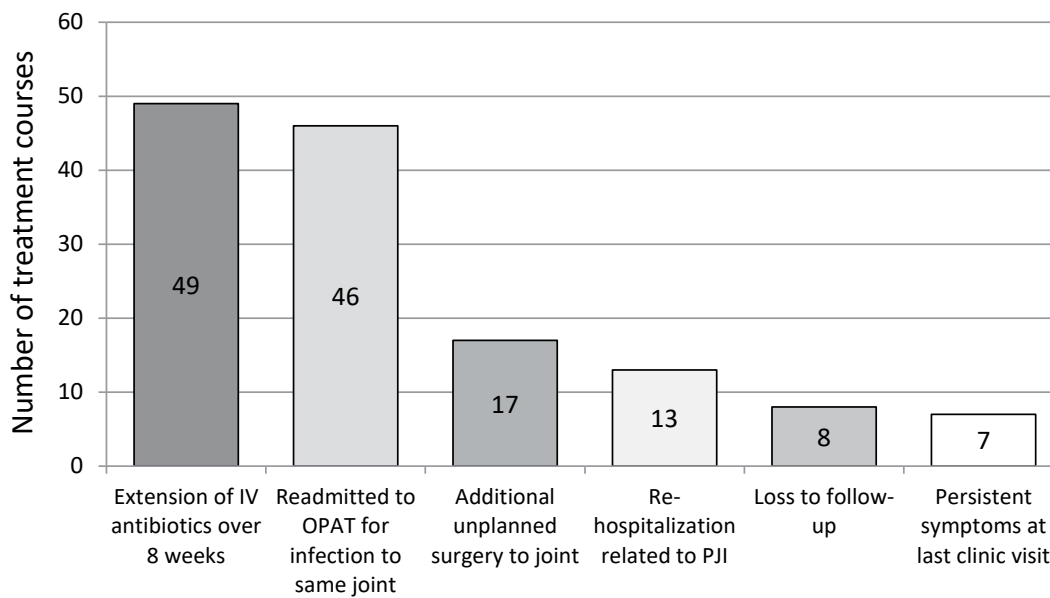
Initial surgical intervention consisting of irrigation and debridement was not associated with treatment failure (41/77 [53.2%] versus 24/60 [40.0%];  $p = 0.12$ ). There was also no association of treatment failure or success with other types of surgeries or with no surgical intervention.

### Antimicrobials and Treatment Failure

There were no associations of IV antimicrobial therapy with treatment failure, whether IV monotherapy, IV combination therapy, or oral-IV combination regimens. The median



**FIGURE 1.** Patient outcomes and antibiotic treatment courses.



**FIGURE 2.** Incidence of treatments for prosthetic joint infection (PJI) that met criteria for treatment failure. A total of 36 courses (26.3%) met multiple criteria for treatment failure. OPAT = outpatient parenteral antimicrobial therapy.

duration of IV antimicrobial treatment was 71 days (IQR 46–95 days) for courses with treatment failure and 50 days (IQR 44–54 days) for courses with treatment success. When we excluded treatment courses defined as failure based on extension of IV antibiotic therapy beyond 8 weeks, the median duration of IV antimicrobial treatment was 63 days (IQR 44–86 days) for courses with treatment failure. Among patients with treatment failure due to extension of IV antibiotics beyond 8 weeks, the median duration of IV treatment extension beyond the 8-week mark was 28 days (IQR 18–62 days). Among patients who experienced treatment failure, the longest duration of IV antibiotic therapy occurred for PJI of the knee (median 81 days, IQR 50–110 days), whereas the median duration was 63 days (IQR 42–82 days) for hip PJI and 68 days (IQR 55–99 days) for PJIs affecting other joints.

### Post Hoc Analysis

The multiple logistic regression analysis showed that diabetes ( $p = 0.013$ ) and depression ( $p = 0.025$ ) were significantly associated with treatment failure (Table 3). The McFadden pseudo  $R^2$  score was 0.31, representing good model fit.

## DISCUSSION

In Canada, PJI associated with hip and knee replacements accounted for over 30% of cases in which early revision surgery was required.<sup>1,2</sup> Early revision surgeries due to PJIs were also associated with higher average cost and longer length of hospital stay compared with non-PJI cases.<sup>2</sup> Additionally, the Canadian Institute for Health Information indicated that diabetes was a comorbidity in 24% of patients requiring early revisions due to PJI, compared with 12.7%–17% of early

**TABLE 3. Logistic Regression Analysis of Association with Treatment Failure**

Factor	Odds Ratio (95% CI)	$p$ Value
Sex, female	1.47 (4.16–5.14)	0.54
Chronic liver disease	$3.14 \times 10^7$ (0– $\infty$ )	0.99
Diabetes mellitus	4.03 (1.38–12.88)	0.013
COPD	2.76 (0.55–14.9)	0.22
History of ischemic heart disease	0.47 (0.09–2.21)	0.35
Heart failure	2.75 (0.50–16.56)	0.25
Peripheral vascular disease	2.04 (0.19–19.36)	0.53
Rheumatoid arthritis	6.09 (0.80–68.71)	0.09
Active malignancy	1.54 (0.02–142.61)	0.86
Lymphedema	$3.23 \times 10^7$ (0– $\infty$ )	0.99
History of MRSA infection	3.42 (0.39–75.98)	0.32
Active smoker	0.60 (0.14–2.33)	0.47
Depression	5.02 (1.30–22.89)	0.025
Gout	0.52 (0.08–2.77)	0.46
Corticosteroid > 30 days	0.05 (1.01 $\times 10^{-3}$ –1.13)	0.07
Methotrexate	5.35 (0.20–376.35)	0.37
TNF inhibitor	$1.75 \times 10^{-9}$ (0– $\infty$ )	> 0.99

CI = confidence interval, COPD = chronic obstructive pulmonary disease, MRSA = methicillin-resistant *Staphylococcus aureus*, TNF = tumour necrosis factor,  $\infty$  = infinity.

revisions due to other causes.<sup>2</sup> In our study of patients with PJI treated within the OPAT program, the treatment failure rate was 56.2%, which highlights the difficulty of eradicating PJI and the increased burden of infection. Risk factors associated with treatment failure were diabetes, depression, chronic liver disease, history of MRSA infection/colonization, and presence of gram-positive cocci.

In previous studies, the rate of PJI treatment failure has ranged from 12.2% to 63%,<sup>15-17,22-41</sup> including 33% after 4 years in patients treated with 1- or 2-stage exchange arthroplasty,<sup>7</sup> 42.1% in streptococcal PJI,<sup>15</sup> and 45% in late-acute PJI.<sup>17</sup> Most of these previous studies were retrospective and focused on subpopulations (such as patients who underwent specific surgical interventions or had particular pathogens) or investigated time to PJI relative to initial joint replacement surgery. The rate of treatment failure in our study (56.2%) was higher than the failure rates in most other studies,<sup>15-17,22-28,36-41</sup> but the difference is difficult to interpret because of differences in the criteria used to define treatment failure and the heterogeneous patient populations.

To date, it appears there is no universal definition of PJI treatment failure. Diaz-Ledezma and others<sup>42</sup> used a Delphi method to establish criteria for successful PJI treatment, which include (1) healing of the wound and no recurrence of infection, (2) no subsequent surgical intervention for infection, and (3) no PJI-related mortality. Data for these criteria were captured in our study and were used to identify treatment failure. Additionally, use of IV antibiotics beyond 8 weeks was used as a criterion for failure in our study, based on the 2013 Infectious Diseases Society of America guideline recommendations<sup>5</sup> for 2- to 6-week courses of IV antibiotics with allowance for scheduling changes or slight extensions. To our knowledge, no other studies have included prolonged duration of IV antibiotics as a criterion for treatment failure, perhaps overlooking the significant time and resource implications for both patients and OPAT programs. There also appear to be wide variations in antibiotic treatment strategies and durations in the literature and clinical practice, relative to the general guideline recommendations for IV antibiotics (specifically oral rifampin for staphylococcal PJI) for 2–6 weeks.<sup>5</sup> Factors contributing to this variability may be the lack of high-quality randomized studies comparing different durations of IV antibiotic treatment, the unknown efficacy of oral step-down therapy as an alternative to prolonged IV therapy, individual patient or logistic factors affecting optimal duration of treatment, and difficulty in managing comorbid conditions.

Our study also differed from previous literature by primarily focusing on PJI patients admitted to an OPAT program for infection management. These patients tend to constitute a high-risk population needing complex care; this complexity was highlighted by the 28% of patients who needed multiple treatment courses and accounted for 47.4% of the PJI treatment courses. Of note, the pathogens found

in our study reflected PJIs described in previous literature.<sup>7,23-25</sup> However, our study also had a higher proportion of patients with diabetes (41%) than in other studies (8.8% to 26.3%).<sup>15,17,22-28</sup> The higher proportion of patients with diabetes in our study may have contributed to the higher rate of treatment failure that we observed.

Similar to our findings, comorbid conditions such as diabetes and depression have been found to be risk factors for PJI treatment failure.<sup>16,27</sup> In our study, these associations were confirmed as significant through the post hoc logistic regression analysis with a good model fit. Although chronic liver disease and history of MRSA infection were also associated with treatment failure in our study, the number of patients with either of these conditions was small. Diabetes is a well-known risk factor for development of PJI,<sup>2,43</sup> and Cancienne and others<sup>16</sup> found that diabetes was associated with risk of incomplete 2-stage procedures and death within 1 year after removal of an infected hip prosthesis. This situation is concerning, given that the number of Manitobans with a diagnosis of diabetes is expected to increase by 37% from 2018 to 2028,<sup>44</sup> at the same time as demand for hip and knee replacements is anticipated to increase with aging of the population. Physiologically, diabetes or hyperglycemia can lead to biofilm formation, decrease wound healing, impair leukocyte function, and decrease blood flow to the extremities because of microvascular changes.<sup>45</sup> Cancienne and others<sup>16</sup> also found that depression was associated with increased risk of repeat debridement and incomplete 2-stage procedures. Future studies should investigate coinciding treatment and optimization of comorbid risk factors during PJI treatment, as there are no current investigations in the literature.<sup>43</sup>

Our study had several limitations: it was a small, single-centre study, the researchers had EMR access only at the OPAT site, and IV antibiotic therapy duration greater than 8 weeks was used as a criterion for treatment failure. More specifically, this small, single-centre study was restricted to patients with PJI who were admitted to the Winnipeg OPAT program by a limited number of practitioners; as such, patients with PJI who were admitted to centres outside the Winnipeg OPAT may have been missed. In addition, we did not have access to hospital inpatient data for the initial surgery or subsequent hospital admissions. We also did not have access to information about oral antibiotic prescriptions after OPAT treatment, meaning such therapy may have been missed if it was not documented in the OPAT EMR. Finally, use of an arbitrary 8-week threshold criterion for treatment failure made it difficult to compare failure rates in this study with those from other studies.

## CONCLUSION

The failure rate of PJI treatment in the Winnipeg OPAT population was 56.2%, higher than failure rates reported in most other studies. Patients with diabetes, depression,

chronic liver disease, or previous MRSA infection and those with PJIs involving gram-positive cocci experienced higher incidence of treatment failure. Opportunities for future investigations include assessment of the optimal duration of IV antibiotics and the efficacy of oral antibiotic step-down therapy, as these have yet to be defined. As the number of joint replacement surgeries in Canada continues to increase, this study and its high rate of treatment failure emphasize the need for future investigations of comprehensive PJI management to minimize the risk of treatment failure and to reduce excessive utilization of resources at the level of both patients and health care systems.

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