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Outcomes of *Enterobacter cloacae*-Associated Periprosthetic Joint Infection Following Hip Arthroplasties

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Background: Periprosthetic joint infections (PJIs) represent a serious complication following total hip arthroplasty (THA) and are associated with significant morbidity. While recent data suggest that *Enterobacter cloacae* is an emerging source of PJI, characteristics and outcomes of *E. cloacae*-associated infections are rarely described. The study aimed to present and describe the findings and outcomes of *E. cloacae*-associated PJI in our department.

Methods: This is a retrospective descriptive study of patients who underwent revision THA for *E. cloacae*-associated PJI between 2011 and 2020 and has a minimum follow-up of 2 years. Outcomes included organism characteristics as well as clinical outcomes, represented by the number of reoperations needed for PJI eradication and the Musculoskeletal Infection Society (MSIS) outcome reporting tool score. Of 108 revision THAs, 12 patients (11.1%) were diagnosed with *E. cloacae*-associated PJI.

Results: The majority of cases had a polymicrobial PJI (n=8, 66.7%). Five *E. cloacae* strains (41.7%) were gentamicin-resistant. Six patients (50.0%) underwent 2 or more revisions, while 3 of them (25.0%) required 4 or more revisions until their PJI was resolved. When utilizing the MSIS outcome score, the first surgical intervention was considered successful (MSIS score tiers 1 and 2) for 5 patients (41.7%) and failed (tiers 3 and 4) for 7 patients (58.3%).

Conclusions: *E. cloacae* is emerging as a common source of PJI following hip arthroplasty procedures. The findings of our study suggest that this pathogen is primarily of polymicrobial nature and represents high virulence and poor postoperative outcomes, as represented by both an increased number of required revision procedures and high rates of patients with MSIS outcome scores of 3 and 4. When managing patients with *E. cloacae*-associated PJI, surgeons should consider these characteristics and inform patients regarding predicted outcomes.

Keywords: *Periprosthetic joint infections, Enterobacter cloacae, Postoperative complications, Revision surgery*

Periprosthetic joint infections (PJIs) represent a catastrophic complication following total joint arthroplasty, with reported incidences of 1%–2% and 4% in primary and revision total joint arthroplasties, respectively.[1,2] As a result of the associated comorbidities and poor outcomes, as well as the financial burden placed on healthcare systems worldwide, the management of this complication warrants full consideration.[3,4] To date, much of the existing literature focuses on PJI prophylaxis. While the rates of PJI have remained relatively constant over time,[5,6]

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ongoing efforts are being made to identify and optimize PJI risk factors and to improve protocols for PJI prevention.[7-10] However, understanding the clinical sequelae and outcomes also has a significant clinical impact on managing patient expectations and providing appropriate patient education to allow for shared decision-making.

While the most frequent pathogens reported in acute PJIs include gram-positive cocci,[11] gram-negative bacilli are reported to be isolated only in approximately 10% of cases.[12] For example, *Enterobacter cloacae* is a gram-negative nosocomial pathogen historically known to infect various medical devices[13] and was previously implicated in patients with immunodeficiency and prolonged hospital stays. Nonetheless, there is a growing body of evidence to suggest that this pathogen is emerging as a common source of infections following orthopedic procedures.[13-16] Understanding the appropriate medical and surgical management of PJIs associated with this pathogen is of notable clinical importance, mainly due to its reported bacterial virulence and growing antimicrobial resistance.[17] Currently, there is a paucity of literature describing the clinical presentation and outcomes associated with *E. cloacae*-associated PJIs.[15,16] Studies that have reported on this pathogen are limited due to short follow-up period.[15] The purpose of the current study was to present and describe the outcomes, findings, and characteristics of *E. cloacae*-associated PJI in our orthopedic department.

METHODS

Study Design

The present study received approval from Institutional Review Board of Tel Aviv Medical Center (No. TLV-0268-21). Informed consent was waived. This is a retrospective review of patients who underwent revision total hip arthroplasty (rTHA) due to PJI in a large, tertiary care university-affiliated medical center between October 1, 2011, and September 30, 2020. Included in our study were patients 18 years of age and older who were diagnosed with *E. cloacae*-associated PJI and had a minimum of 2 years of follow-up after surgery. We excluded patients who did not meet follow-up criteria.

Diagnosis of *E. cloacae*-Associated PJI

PJI diagnosis was made using the revised criteria as defined by the Musculoskeletal Infection Society (MSIS).[18] During the rTHA procedure, intraoperative tissue samples were collected and sent for culture analysis. The different types of tissue samples included one or more of the following: synovium, periprosthetic membrane, bone, hematoma, and synovial fluid. Analysis of samples, including characterization of the microbial strains and antibiotics-resistance profile, was done in the microbiological laboratory. *E. cloacae*-associated PJI was diagnosed if a patient had two or more positive cultures from at least five separate tissue samples.

Data Collection

The data query was performed by the quality control unit. Data were assessed by reviewing the electronic medical records. Data collected included sex, age, medical history and comorbidities, body mass index, Charlson comorbidity index (CCI), and indication of index surgery. We also collected laboratory data, type (i.e., single-stage revision, two-stage revision, etc.), total number of rTHA, microbiological characteristics of the causing pathogens (i.e., poly- or mono-microbial, antibiotics susceptibilities), and antibiotic treatment (type and duration). Lengths of hospital stay, readmissions, and mortality were additionally extracted. The duration of follow-up was the time between the date of *E. cloacae* PJI diagnosis and the last visit to the surgeon. Type of infection was determined by the time from primary surgery to infection diagnosis and was divided to very early (< 1 months), early (1–3 months), and delayed (> 3 months), as previously suggested by Tande and Patel.[19] The decision regarding the initial type of surgical treatment was made by considering the PJI type (i.e., timing of PJI diagnosis) and other implant- and patient-related characteristics.[20] Generally, for very early PJI (< 1 month), debridement, antibiotics and implant retention (DAIR) were utilized; patients diagnosed with an early (1–3 months) or delayed PJIs (> 3 months) were treated with a single- or two-stage revision, based on implant stability, alongside other patient-related characteristics including bone and soft-tissue status. A similar analysis was done for revision total knee arthroplasties. However, no cases of *E. cloacae*-associated PJI were identified.

Primary Outcome

MSIS outcome reporting tool[21] was utilized to evaluate the surgical outcome. Under this tool, outcomes of the first surgical procedure could range from Tier 1 to Tier 4 as follows: Tier 1, infection control with no continued antibiotic therapy; Tier 2, infection control with the need of suppressive antibiotic to control infection; Tier 3, any requirement for additional surgical intervention, sub-classified from 3A to 3F (3A, aseptic revision > 1 year from PJI treatment initiation; 3B, septic revision [including DAIR] >1 year from PJI treatment initiation; 3C, aseptic revision ≤ 1 year from PJI treatment initiation; 3D, septic revision ≤ 1 year from

PJI treatment initiation; 3E, amputation, resection arthroplasty, or arthrodesis; and 3F, retained spacer); and Tier 4, mortality ≤ 1 year (4A) or > 1 year (4B) from PJI treatment initiation. Successful surgical therapy was defined as MSIS tiers 1 and 2, while failure was defined as MSIS tiers 3 and 4.

Statistical Analysis

Descriptive statistics were calculated. The average, median, standard deviation, and range were used to describe quantitative variables, and frequency and percentage were used for qualitative variables.

RESULTS

Study Population

Of the 108 cases of rTHA for PJI performed at our institution during the study period, 12 (11.1%) had an *E. cloacae*-associated PJI. The median age at diagnosis was 70.3 years (range, 40–90). Ten of the patients (83.3%) were female. Ten patients (83.3%) presented with comorbidities. Seven patients (58.3%) had at least 2 comorbidities and 2 patients (16.7%) had no comorbidities. The majority of patients had an ASA score of 3–4 (n = 9, 75.0%) and a CCI score defined as moderate (n = 3, 25.0%) or severe (n = 6, 50.0%) (Table 1).

Clinical Characteristics

Hip hemiarthroplasty was the index surgery in 4 of the patients (33%), while 8 patients (67%) underwent total hip arthroplasty (THA) as their primary surgery. The most common indication for primary surgery was hip fragility fracture (n = 6, 50.0%), followed by osteoarthritis (n = 2, 16.7%), conversion from cephalomedullary nail (n = 2, 16.7%), and developmental dysplasia of the hip (n = 2, 16.7%). Eight patients (66.7%) developed PJI within 30 days of primary surgery, while the other 4 patients (33.3%) developed PJI within 1 to 3 months postoperatively (Table 2). The most common clinical manifestations were pain (n = 11, 91.7%), loss of function (n = 9, 75.0%), wound inflammation (warmth and erythema) (n = 8, 66.7%), and joint effusion (n = 3, 25.0%). Two patients (16.7%) had continuous wound drainage more than 1 week after surgery. However, sinus track was ruled out for both of them intraoperatively as the fascia was intact.

Microbiological Characteristics

Intraoperative samples were monomicrobial in 4 cases (33%) and polymicrobial in 8 cases (67%). *Staphylococcus* species (n = 5, 41.7%) was the most common bacteria associated with *E. cloacae* PJI, followed by *Pseudomonas aeruginosa* (n = 4, 33.3%), *Enterococcus faecalis* (n = 2, 16.7%), *Klebsiella Pneumoniae* (n = 2, 16.7%), and other gram-negative bacteria (n = 2, 16.7%). Six *E. cloacae* strains (50.0%) were resistant to trimethoprim-sulfamethoxazole, while 5 strains (41.7%) were resistant to gentamicin and ceftriaxone (Table 3).

Antibiotic Treatment and Medical Management

All patients were treated with an initial empiric course of intravenous antibiotics until culture results were available. Upon discharge, treatment was converted to oral antibiotics if a suitable antibiotic agent was appropriate. Patients who required a long-term intravenous treatment received a peripheral inserted central catheter (PICC) line (n = 5, 41.7%). Three patients (25.0%) received a single antibiotic

Table 1. Patient Characteristics

Variable	*Enterobacter cloacae*-associated PJI (n = 12)
Female sex	10 (83.3)
Age (yr)	70.3 (40–90)
Comorbidity	
BMI > 30 kg/m^2	3 (25.0)
Smoking	3 (25.0)
Diabetes mellitus	5 (41.7)
Chronic renal failure	2 (16.7)
Hypertension	8 (66.7)
Peripheral vascular disease	1 (8.3)
Ischemic heart disease	2 (16.7)
Congestive heart failure	2 (16.7)
ASA score	
1–2	3 (25.0)
3–4	9 (75.0)
CCI score	
Mild (0–2)	3 (25.0)
Moderate (3–4)	3 (25.0)
Severe (> 5)	6 (50.0)
Follow-up duration (yr)	5.0 (2.3–11.4)

Values are presented as number (%) or median (range).
PJI: periprosthetic joint infection, BMI: body mass index, ASA: American Society of Anesthesiology, CCI: Charlson comorbidity index.

Table 2. Clinical Characteristics

Variable	*Enterobacter cloacae*-associated PJI (n = 12)
Primary surgery	
Hip hemiarthroplasty	4 (33.3)
Total hip replacement	8 (66.7)
Indication for primary surgery	
Hip fragility fracture	6 (50.0)
Conversion from failed CMN	2 (16.7)
Osteoarthritis	2 (16.7)
DDH	2 (16.7)
Type of infection*	
Very early (< 1 mo)	8 (66.7)
Early (1–3 mo)	4 (33.3)
Delayed (3–12 mo)	0

Values are presented as number (%).
PJI: periprosthetic joint infection, CMN: cephalomedullary nail, DDH: developmental dysplasia of the hip.
*Determined by the time from primary surgery to infection diagnosis.

Table 3. Microbiological Characteristics

Variable	*Enterobacter cloacae*-associated PJI (n = 12)
Microbial culture	
Monomicrobial	4 (33.3)
Polymicrobial	8 (66.7)
Associated bacteria	
Staphylococcus species	5 (41.7)
Pseudomonas aeruginosa	4 (33.3)
Enterococcus faecalis	2 (16.7)
Klebsiella pneumoniae	2 (16.7)
Other gram-negative bacteria	2 (16.7)
E. cloacae drug resistance	
Trimethoprim/sulfamethoxazole	6 (50.0)
Ceftriaxone	5 (41.7)
Gentamicin	5 (41.7)
Ceftazidime	4 (33.3)
Chloramphenicol	4 (33.3)
Cefuroxime	3 (25.0)
Amoxicillin	2 (16.7)
Piperacillin/tazobactam	2 (16.7)
Cefazolin	1 (8.3)
Ciprofloxacin	1 (8.3)
Ertapenem	1 (8.3)
Imipenem	1 (8.3)
Meropenem	1 (8.3)
Tobramycin	1 (8.3)

Values are presented as number (%).
PJI: periprosthetic joint infection.

treatment. Eight patients (66.7%) received a combination of 2 antibiotics and 1 patient (8.3%) received a combination of 3 antibiotics. The majority of patients (n = 11, 91.7%) were treated with a beta-lactam. A carbapenem was used in 5 cases (41.7%): meropenem (n = 3, 25.0%) and imipenem (n = 2, 16.7%). Five cases (41.7%) were treated with cephalosporin: ceftazidime (n = 4, 33.3%) and ceftriaxone (n = 1, 8.3%). One patient (8.3%) was treated with ampicillin, a penicillin. A fluoroquinolone was most frequently combined with beta-lactams (ciprofloxacin, n = 5, 41.7%). The other combined agents were vancomycin (n = 3, 25.0%) and rifampin (n = 1, 8.3%). After excluding 2 patients who died during hospitalization, the median duration of antibiotic treatment was 6 weeks (range, 6 to 12 weeks) (Table 4).

Surgical Management and Clinical Outcomes

The initial surgical treatment was debridement, antibiotics, irrigation, and prosthesis retention (DAIR) for 7 patients (58.3%) and single-stage revision for 5 patients (41.7%). Six patients (50.0%) had a single revision, 2 patients (16.7%) underwent 2 revisions, 1 patient (8.3%) underwent 3 revisions, and 3 patients (25.0%) underwent a total of 4 or more revisions (Table 4). Of the 12 patients who were surgically treated for *E. cloacae*-associated PJI, 5 (41.7%) were categorized as tier 1 according to the MSIS outcome reporting tool and were considered successfully treated. Three patients (25.0%) were categorized as tier 3, as 2 patients (16.7%) finally underwent a two-stage revision and 1 patient (8.3%) underwent a resection arthroplasty (Girdlestone procedure). Two patients (16.7%) died within 30 days from surgery and 2 patients (16.7%) died more than 1 year after surgery, thus categorized as tier 4A and 4B, respectively (Table 4).

Table 4. Characteristics of Surgical and Medical Treatment

Characteristics	*Enterobacter cloacae*-associated PJI (n = 12)
Initial surgical revision procedure	
DAIR	7 (58.3)
One-stage revision	5 (41.7)
Number of revisions	
1	6 (50.0)
2	2 (16.7)
3	1 (8.3)
≥ 4	3 (25.0)
Duration of antibiotic treatment (wk)*	
6	5 (41.7)
8	1 (8.3)
12	4 (33.3)
MSIS score	
Tier 1	5 (41.7)
Tier 2	0
Tier 3	3 (25.0)
Tier 4A	2 (16.7)
Tier 4B	2 (16.7)

Values are presented as number (%).
PJI: periprosthetic joint infection, DAIR: debridement, antibiotics, irrigation, and prosthesis retention, MSIS: Musculoskeletal Infection Society.
*Available for 10 patients, after excluding 2 patients who died during hospitalization.

DISCUSSION

PJIs are reported as one of the leading indications for revisions following primary THA and total knee arthroplasty.[22] PJIs have important financial ramifications on healthcare systems. Along with an expected increase in the incidence of arthroplasty procedures, annual hospital costs for PJI of the hip and knee are increasing and are estimated to be $1.85 billion by the year 2030.[23,24] As a result of the financial burden placed on orthopedic departments in addition to patient-related morbidity associated with this complication, it is important for surgeons to understand the presentation and management of certain pathogens in order to maximize patient outcomes. To date, limited reports have described the course and the characteristics associated with *E. cloacae*-associated PJI.

Our study had severable notable findings regarding *E. cloacae*-associated PJIs: (1) these infections were associated solely with PJI following hip arthroplasties only and not with PJI following knee arthroplasties; (2) they presented very-early or early PJI (< 3 months from primary surgery); (3) these infections were of polymicrobial nature and with high rates of gentamicin resistance; and (4) they had poor outcomes as represented by both high rates of patients necessitating 2 or more revisions and high rates of patients with MSIS outcome score of 3 or 4.

When assessing revisions due to PJI of both hip and knee arthroplasties, *E. cloacae* was present only for hip surgeries. A previous review by Tsai et al.[25] on the microbiological profiles of PJI following hip and knee arthroplasties reported that enteric gram-negative bacteria were more commonly identified in hip PJI than knee PJI. As *E. cloacae* occurs as microflora and is normally found in the intestinal tract, the authors proposed that the proximity between the hip and the gastrointestinal tract could explain this result. Aboltin et al.[26] observed similar conclusions regarding a more prevalent colonization of the hip area with gut-derived organisms. Further research aimed to better identify the common organism associated with PJI of the hip or knee is needed to improve perioperative optimization of antibiotic prophylactic protocols.

The findings of this study suggest that *E. cloacae*-associated PJI primarily presents < 3 months from surgery, with the majority of our cases diagnosed within 1 month from primary surgery. This observation is consistent with a previous study by Bouige et al.,[15] which also reported that PJI due to *E. cloacae* tends to occur early after the last prosthetic surgery. Understanding the timing of *E. cloacae*-associated PJI is essential in order to effectively diagnose and treat acute PJI, and high index of suspicion of this pathogen is warranted when treating patients with early-onset PJI.

The majority of the infections in our study were polymicrobial. Several previous studies corroborate this finding, reporting polymicrobial infections with *E. cloacae*.[11,12,17,27] Polymicrobial infections are a major concern as additional complications arise when they are involved.[12] Furthermore, polymicrobial infections often require multidrug combination therapy, thus introducing the patient to a potential risk of adverse events and cross-drugs reactions. Regardless, in the past decade, the use of gentamicin as a targeted gram-negative antibiotic prophylaxis prior to THA procedures emerged, with previous studies showing its efficacy in reducing gram-negative-associated PJIs.[28] However, a substantial percentage of *E. cloacae* strains in our study were gentamicin resistant, suggesting that gentamicin may not be efficient in preventing *E. cloacae*-asso-

ciated PJIs. The findings of this study, along with previous findings of increased ciprofloxacin resistance rates among gram-negative bacteria,[15] warrant discussion regarding the optimal perioperative antibiotic prophylaxis of patients undergoing hip arthroplasty procedures.

The initial surgical treatment was considered failed for the majority of the patients in our cohort, reflecting the severity of theses presentations. Similarly, Bouige et al.[15] reported that only 50% of the patients with *E. cloacae*-associated PJI had a favorable outcome. As the majority of the patients in our cohort presented with PJI within 1 month from surgery, the most common initial surgical treatment was DAIR. These findings are in agreement with previous reports suggesting that PJI due to gram-negative pathogens is difficult to treat and is associated with limited success,[29] especially when initially treated with DAIR.[17] Furthermore, the average antibiotic period was greater than 8 weeks for more than half of the patients in the study. This period was particularly long, relative to the recommended guidelines for the management of PJI.[30] Such findings reflect the virulence, morbidity, along with the resistance to treatment associated with this pathogen and should be considered during patient discussion to best manage their expectations.

It is important for surgeons to understand risk factors for revision surgeries and their presentations in order to maximize patient outcomes and relieve the economic burden associated with these adverse events. Our study adds to a small body of evidence to better describe the presentation and characteristics associated with PJI due to *E. cloacae*. Understanding the characteristics and appropriate management of PJIs due to *E. cloacae* may minimize the associated revisions required and the difficulty responding to treatment and may help guide surgeons in their management of PJIs.

We acknowledge that the current study is not without its limitations. The small number of cases could have been susceptible to a sampling bias. As the majority of patients had up to 5 years of follow-up, it was difficult to draw conclusions regarding the characteristics of this pathogen in the long term. However, to the best of our knowledge, this study has the longest follow-up for reporting outcomes of *E. cloacae*-associated PJI. Additionally, the surgical revision procedures were performed by different surgeons, which could have biased our results. Furthermore, while the majority of patients in our cohort underwent DAIR as their initial surgical treatment, a considerable proportion of patients underwent a single-stage revision as their initial surgical treatment, and none of the patients were treated initially with two-stage revision. This may limit the generalizability of our findings, as not all medical center utilize this approach in treating PJI; specifically, a two-stage approach is generally accepted in the United States, while a single-stage revision is more common in Europe.[31] However, when indicated, a single-stage revision was previously reported to have comparable outcomes to two-stage revision.[31-33] Finally, as some of the presentations were polymicrobial, which are inherently more virulent, this may overestimate the morbidity associated with this pathogen. Nonetheless, the fact that the majority of the infections in our study were polymicrobial should serve as important consideration in the management of patients with *E. cloacae*-associated PJIs.

E. cloacae is emerging as a common source of PJI following hip arthroplasty procedures. The findings of our study suggest that this pathogen is primarily of polymicrobial nature and represents high virulence and poor postoperative outcomes, as represented by both an increased number of required revision procedures and high rates of patients with MSIS outcomes scores of 3 and 4. When managing patients with *E. cloacae*-associated PJI, surgeons should consider these characteristics and inform patients regarding predicted outcomes.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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