

# Clinical Profile of Monomicrobial *Corynebacterium* Hip and Knee Periprosthetic Joint Infections

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**Background.** *Corynebacterium* periprosthetic joint infection (PJI) is a poorly described infectious syndrome. Prior studies included cases of polymicrobial infections. This series describes the clinical characteristics, management, and outcomes of monomicrobial *Corynebacterium* PJI.

**Methods.** We queried the Mayo Clinic Total Joint Registry for cases of monomicrobial *Corynebacterium* knee and hip PJI in adults (age  $\geq 18$  years) between 2010 and 2019.

**Results.** A total of 20 (1%) out of 2067 PJI cases met our inclusion criteria. Most were males (55%), and the median age was 64 years. Seventy percent had chronic symptoms ( $>4$  weeks). PJI was delayed to late ( $>3$  months postimplantation) in 90%. Three species were identified: *C. striatum* (70%), *C. jeikeium* (20%), and *C. amycolatum* (10%). All tested isolates were susceptible to vancomycin (100%) and linezolid (100%), and most had a minimum inhibitory concentration  $\leq 0.06$  mcg/mL to daptomycin (75%). Other agents were less reliable, with high resistance to oral agents commonly used for suppression. Nineteen patients were treated: 37% debridement and implant retention (DAIR), 47% 2-stage exchange, and 16% resection without reimplantation. Of these, failure occurred in 29%, 11%, and 0%, respectively.

**Conclusions.** *Corynebacterium* PJIs pose a therapeutic challenge due to limited antimicrobial armamentarium and undefined optimal surgical intervention. Vancomycin and linezolid remain the most reliable agents for treatment. DAIR may be attempted for acute PJI, but verification of durable chronic suppression options will be critical for this approach.

**Keywords.** *Corynebacterium amycolatum*; *Corynebacterium jeikeium*; *Corynebacterium* species; *Corynebacterium striatum*; periprosthetic joint infection.

*Corynebacterium* species are part of the normal skin flora and are frequently dismissed as clinically insignificant when isolated in cultures [1]. However, *Corynebacterium* spp. can also cause diseases such as endocarditis, bloodstream infections, bone and joint infections, skin and soft tissue infections, respiratory tract infections, and hardware-associated infections [2–6]. *Corynebacterium* spp. may be isolated in up to 5% of cases of periprosthetic joint infections (PJIs) and the only organism isolated in 2% [7].

Accurate identification of the microbiologic etiology is the cornerstone in managing PJI. Recognizing *Corynebacterium*

spp. as the causative agent of PJI is critical due to its challenging antimicrobial susceptibility pattern and limited oral antibiotic options. Our study aimed to describe the clinical characteristics, management, and outcomes of monomicrobial *Corynebacterium* PJI.

## METHODS

We conducted a case series study of patients age 18 years and older diagnosed with hip and knee *Corynebacterium* PJI between January 1, 2010, and December 31, 2019, at a quaternary medical center. We queried the Mayo Clinic Total Joint Registry (TJR) and its accompanying PJI database for cases in which *Corynebacterium* spp. were isolated in cultures (see [Supplementary Figure 1](#) for inclusion flowchart). We excluded patients with polymicrobial infection to be certain that *Corynebacterium* spp. was the causative pathogen. We also excluded patients who did not meet PJI criteria as defined below. We reviewed and extracted the electronic medical record of all patients who met the criteria for clinical characteristics, medical and surgical management, and outcomes. Clinical factors such as age, comorbidities, duration of symptoms, and history of prior PJIs were assessed at the time of surgical management.

Received 21 February 2022; editorial decision 4 April 2022; accepted 11 April 2022; published online 14 April 2022

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<https://doi.org/10.1093/ofid/ofac193>

## Definitions

PJI was defined using the 2018 International Consensus Meeting (ICM) on musculoskeletal infection criteria for diagnosing hip and knee PJI [8]. This definition provides a scoring system based on major and minor criteria (Supplementary Table 1). Failure of therapy was defined by the occurrence of any of the following outcomes: (1) recurrence of PJI, (2) unplanned re-operation secondary to an infection, or (3) infection-related death after surgical management and index hospitalization.

Chronic suppression was defined as oral antibiotics prescribed after 6 weeks of therapeutic intravenous (IV) antibiotics to suppress any residual infection and prevent flare-ups in the long term. These are typically employed following debridement, antibiotics, irrigation, and retention (DAIR) procedures at our institution. Secondary prophylaxis was defined as antibiotics prescribed after infection eradication to prevent future recurrences in patients undergoing reimplantation. Secondary prophylaxis is not routinely prescribed in our institution but is provided on a case-by-case basis, often in patients presumed to be at high risk for reinfection.

Symptoms were considered acute if present for  $\leq 4$  weeks and chronic if present for  $> 4$  weeks [9]. PJI was considered early if it occurred  $< 3$  months, delayed if occurred within 3–12 months, and late if occurred  $> 12$  months from last arthroplasty or revision [10].

## RESULTS

A total of 2067 PJI cases were identified during the study period, of which 20 cases (1%) met our criteria for monomicrobial *Corynebacterium* PJI and were included in our study. A summary of their clinical profile is provided in Table 1. A more detailed description of each patient is available in Table 2. Most

**Table 1. Clinical Profile of Patients Presenting With Periprosthetic Joint Infection Secondary to *Corynebacterium* spp. (n = 20)**

Demographics	
Median age at primary arthroplasty [IQR], y	60 [50–69]
Median age at current PJI [IQR], y	64 [58–71]
Gender (males), No. (%)	11 (55)
Median body mass index [IQR], kg/m <sup>2</sup>	32 [27–36]
Primary arthroplasty	
Joint, No. (%)	
Knee	15 (75)
Hip	5 (25)
Revision arthroplasty before current PJI, No. (%)	
Septic revisions	6 (30)
Aseptic revisions	4 (20)
Current infection	
Median time from last arthroplasty to PJI [IQR], mo	20 [9–32]
Chronic suppressive antibiotics at time of current PJI, No. (%)	
Minocycline	2 (10)
Trimethoprim-sulfamethoxazole	1 (5)
Cephalexin	1 (5)

**Table 1. Continued**

Clinical presentation (n = 20), No. (%)	
Fevers	4 (20)
Chills	4 (20)
Pain	18 (90)
Joint swelling	9 (45)
Joint erythema	2 (10)
Nonhealing wound	1 (5)
Wound drainage	2 (10)
Sinus tract	1 (5)
Medical history	
Comorbidities (n = 20), No. (%)	
Hypertension	12 (60)
Obese (BMI $\geq 30$ kg/m <sup>2</sup> )	12 (60)
Diabetes mellitus	8 (45)
Heart failure	4 (20)
Peripheral arterial disease	2 (10)
Coronary artery disease	6 (30)
Chronic lower extremity edema	5 (25)
Chronic nonhealing lower extremity ulcer	3 (15)
Chronic kidney disease	6 (30)
Solid organ malignancy	3 (15)
Liver cirrhosis	1 (5)
Asplenia	1 (5)
Prior PJI affecting same joint	6 (30)
DAIR for prior PJI	5 (25)
2-stage exchange for prior PJI	1 (5)
Laboratory results at time of PJI diagnosis	
Mean white blood cell count $\pm$ SD, $\times 10^9$ /L	7.94 $\pm$ 2.39
Serum C-reactive protein, No. (%)	
Median level [IQR], mg/L	32 [17–68]
Above reference ( $\leq 8$ mg/L), No. (%)	19 (95)
Serum sedimentation rate, No. (%)	
Median level [IQR], mm/h	39 [27–65]
Above reference (0–22 mm/h), No. (%)	16 (80)
Synovial analysis, No. (%)	
Median synovial white blood cells [IQR], cells/ $\mu$ L	30 733 [15 563–41 237]
Median synovial polymorphonuclear cell [IQR], %	91 [89–92]
Microbiology	
<i>Corynebacterium</i> spp. isolated, No. (%)	
<i>C. striatum</i>	14 (70)
<i>C. jeikeium</i>	4 (20)
<i>C. amycolatum</i>	2 (10)
Management	
Surgical management, No. (%)	
2-stage exchange	9 (45)
DAIR	7 (35)
Resection arthroplasty without reimplantation	3 (15)
None (lost to follow-up without management)	1 (5)
Intravenous antibiotic therapy, No. (%)	
Vancomycin	15 (75)
Daptomycin	3 (15)
Meropenem	1 (5)
Ertapenem	3 (15)
None (lost to follow-up without management)	1 (5)
Median IV antibiotic duration following surgery [IQR], wk	6 [6.0–6.4]
Median time from resection arthroplasty to reimplantation [IQR], wk	12 [12–16]

**Table 1. Continued**

Median time from end of antibiotic therapy to reimplantation [IQR], wk	8 [6–9]
Oral suppressive or secondary prophylactic following therapy, No. (%)	14 (70)
Follow-up and outcome	
Median follow-up duration from surgical management [IQR], mo	23 [12–46]
Clinical outcome, No. (%)	
Cure	16 (80)
Fail	3 (15)
Lost to follow-up without management	1 (5)

Abbreviations: BMI, body mass index; DAIR, debridement and implant retention; IQR, interquartile range; IV, intravenous; PJI, periprosthetic joint infection.

patients were males (55%; n = 11). Ninety-five percent (n = 19) self-identified as White. At diagnosis, the median age (interquartile range [IQR]) was 64 (58–71) years. The most common comorbidities were hypertension and obesity, diabetes mellitus, and coronary artery disease.

### Clinical Presentation

Most of our patients presented with joint pain (90%; n = 18) and/or swelling (45%; n = 9). Other symptoms are listed in [Table 1](#) and were less common. PJI involved the knee in 75% (n = 15) and the hip in 25% (n = 5). PJI followed primary arthroplasties in 50% (n = 10) of patients and revision arthroplasties in the other half. Thirty percent (n = 6) of patients had a history of revision arthroplasty for prior episodes of PJI. These were due to microorganisms other than *Corynebacterium* spp. except for 1 patient with a prior episode of *C. striatum* PJI at an outside facility. The median time from last arthroplasty surgery to PJI (IQR) was 20 (9–32) months, with 90% (n = 18) presenting as delayed or late infections. For the 6 patients with prior PJI, the median time from the previous infection (IQR) was 14 (9–25) months.

The median duration of symptoms (IQR) was 132 (48–299) days. Thirty percent (n = 6) of patients presented with acute symptoms ( $\leq 4$  weeks) compared with 70% (n = 14) with chronic symptoms ( $> 4$  weeks).

Only 1 patient had a sinus tract on presentation. This patient had a history of recurrent PJIs involving the same knee, requiring multiple surgical interventions. His most recent prior PJI was secondary to *Serratia marcescens* and was managed with DAIR and chronic antimicrobial suppression with trimethoprim-sulfamethoxazole. He had a complicated course with a chronic draining sinus tract. Later, he presented with increased drainage over 8 weeks and was diagnosed with *C. jeikeium* PJI.

Twenty percent (n = 4) of patients developed *Corynebacterium* PJI while on oral suppressive antibiotics for prior PJIs, including minocycline, cephalexin, and trimethoprim-sulfamethoxazole.

Synovial fluid analysis was performed in 80% (n = 16) of patients. In 14 patients, the synovial white blood cell count (WBC) was  $> 3000$  cells per  $\mu\text{L}$  (median WBC [IQR], 30 733 [15 563–41 237] cells per  $\mu\text{L}$ ). The synovial polymorphonuclear percentage ranged from 75% to 97%, with a median (IQR) of 91% (89%–92%). Serum erythrocyte sedimentation rate (ESR) (normal, 0–22 mm/h) and C-reactive protein (CRP; normal,  $\leq 8$  mg/L) were above the cutoff in 80% (n = 16) and 95% (n = 19), respectively. The median CRP (IQR) was 32 (17–68) mg/L, and the median ESR (IQR) was 39 (27–65) mm/h.

### Microbiology

In our cohort, 60% (n = 12) of patients had growth of *Corynebacterium* spp. from synovial fluid aspirate, and 85% (n = 17) from an intraoperative joint specimen. Seventy percent (n = 14) of patients had growth of the same *Corynebacterium* spp. in  $\geq 2$  intra-articular specimens and met the major criteria for PJI. The remaining 30% (n = 6) had monomicrobial growth of *Corynebacterium* spp. from only 1 specimen. In the latter group, 1 patient had a sinus tract communicating with the joint and so met major criteria for PJI. This patient had growth of *Corynebacterium* spp. from a single deep intraoperative sample. The remaining 5 patients all met minor criteria for PJI based on serum inflammatory markers and synovial fluid analysis ([Supplementary Table 2](#)). Two patients had growth of *Corynebacterium* spp. from prosthesis sonicate fluid culture. Three patients had growth from synovial aspirate alone, where growth was only from broth in 1 patient and not specified in 2 patients. Three different species were identified in our cohort. *C. striatum* was the most commonly encountered spp., recovered from 70% of patients (n = 14). One patient had 2 *C. striatum* isolates with a different minimum inhibitory concentration (MIC) to penicillin. *C. jeikeium* and *C. amycolatum* were isolated in 20% (n = 4) and 10% (n = 2), respectively.

### Management

Except for 1 patient lost to follow-up, all 19 other patients were followed for management, outlined in [Table 3](#).

Thirty-seven percent (n = 7) of patients underwent DAIR, of whom 2 had acute early infection, 3 had an acute late infection, and 2 had a chronic late infection. Resection arthroplasty was performed in 63% (n = 12), of whom 11 had chronic delayed or late infection and 1 had an acute late infection. Following resection arthroplasty, 75% underwent reimplantation (n = 9), while 25% remained without reimplantation (n = 3).

Antimicrobial susceptibility testing (AST) was performed on 18 isolates from 85% (n = 17) of patients. The default AST in our laboratory includes penicillin, ceftriaxone, meropenem, and vancomycin. Additional antibiotic testing can be done at the request of the treating physician. [Table 4](#) lists susceptibility interpretations for agents with established guidelines, and

**Table 2. Clinical Profile of 20 Patients With Periprosthetic Joint Infection Secondary to *Corynebacterium* spp.**

Patient	Age at PJI/ Gender	BMI	Comorbidities	Primary Arthroplasty	Revision	Micro at Prior PJI <sup>a</sup>	Prior Suppressive ABX	Time to PJI, mo <sup>b</sup>	Temporal Classification	Micro at Current PJI	No. of Specimens With Growth	Specimen Type
1	79/M	25.8	CAD, chronic LLE ulcer	L knee	...	...	...	25.7	Late	<i>C. striatum</i>	≥2	SF/IO
2	91/M	32.2	CKD, obesity	L knee	Aseptic	...	MIN	51.6	Late	<i>C. striatum</i>	≥2	IO
3	60/M	32.3	DM, obesity	R knee	...	...	...	0.5	Early	<i>C. striatum</i>	≥2	IO
4	82/F	36	CAD, DM, CHF, PAD, CKD, obesity, R leg HL, R leg radiation therapy	R knee	Aseptic	...	...	94.3	Late	<i>C. striatum</i>	≥2	SF
5	40/F	34.6	Teratologic right hip dislocation, obesity	R hip	Aseptic	...	...	0.6	Early	<i>C. amycolatum</i>	≥2	SF/IO
6	59/M	62	CHF, obesity, RLE lymphedema	R knee	Septic-DAIR	<i>S. marcescens</i>	SXT	36.5	Late	<i>C. jeikeium</i>	1	IO
7	75/M	36.4	CAD, obesity	L knee	Septic-2-stage	CoNS	...	19.4	Late	<i>C. striatum</i>	≥2	SF/IO
8	58/F	29.8	CKD	R knee	Septic-DAIR	Negative	MIN	11.8	Delayed	<i>C. striatum</i>	≥2	SF/IO
9	65/F	37	Livercirrhosis, DM, CHF, chronic RLE ulcer, CKD, obesity	L knee	...	...	...	33.4	Late	<i>C. striatum</i>	1	SF <sup>c</sup>
10	50/M	21.9	Klipperl-trenaunay syndrome, asplenia	L knee	...	...	...	30.0	Late	<i>C. jeikeium</i>	1	SF
11	59/M	42.4	CAD, DM, CHF, chronic LLE ulcer, CKD, obesity	L knee	Septic-DAIR	MSSA	LEX	31.8	Late	<i>C. striatum</i>	≥2	SF/IO
12	63/F	20	RA, Crohn's disease, immunosuppressive medications	R hip	Septic-DAIR	<i>P. mirabilis</i>	...	30.4	Late	<i>C. striatum</i>	≥2	IO
13	55/F	25.5	RA, Marfan syndrome, immunosuppressive medications	R knee	...	...	...	12.2	Late	<i>C. jeikeium</i>	1	IO <sup>d</sup>
14	69/M	32	Obesity	L hip	Aseptic	...	...	6.4	Delayed	<i>C. amycolatum</i>	≥2	IO
15	68/F	33.5	RA, Sjogren syndrome, obesity	R knee	...	...	...	13.3	Late	<i>C. jeikeium</i>	1	IO <sup>d</sup>
16	57/M	31.3	DM, CKD, COPD, obesity, cerebellar ataxia, developmental delay	L hip	...	...	...	9.7	Delayed	<i>C. striatum</i>	≥2	SF/IO
17	85/M	27.9	CAD, DM, metastatic colon CA	R knee	...	...	...	8.2	Delayed	<i>C. striatum</i>	≥2	SF/IO
18	69/F	26.1	PAD, CKD, localized bladder CA, radiation to pelvis	R hip	...	...	...	47.2	Late	<i>C. striatum</i>	≥2	IO
19	65/M	42.8	DM, CIDP, immunosuppressive medications, obesity	R knee	Septic-DAIR	<i>C. striatum</i>	...	20.7	Late	<i>C. striatum</i>	≥2	SF/IO
20	51/F	NR	Breast CA	R knee	...	...	...	5.2	Delayed	<i>C. striatum</i>	1	SF

Abbreviations: ABX, antibiotics; BMI, body mass index; CA, cancer; CAD, coronary artery disease; CHF, congestive heart failure; CIDP, chronic inflammatory demyelinating polyneuropathy; CKD, chronic kidney disease; CoNS, coagulase-negative staphylococci; DAIR, debridement, antibiotic, and implant retention; DM, diabetes mellitus; F, female; HL, Hodgkin's lymphoma; IO, intraoperative; L, left; LEX, cephalosporin; LLE, left lower extremity; M, male; MIN, minocycline; MSSA, methicillin-susceptible *Staphylococcus aureus*; NR, not reported; PAD, peripheral arterial disease; R, right; RA, rheumatoid arthritis; RLE, right lower extremity; SF, synovial fluid; SXT, trimethoprim-sulfamethoxazole.

<sup>a</sup>Stands for prior PJI episodes affecting the same joint as current PJI.

<sup>b</sup>Time from last arthroplasty surgery to current PJI.

<sup>c</sup>Growth from broth only.

<sup>d</sup>Prosthesis sonicate fluid culture.

**Table 3. Management Approach of 20 Patients With Periprosthetic Joint Infection Secondary to *Corynebacterium* spp.**

Symptom Duration	SX	IV ABX	Iv Abx Duration, wk	Supp/Pro ABX Duration, mo	Time From Surgery to Reimplantation, wk	Time From End ABX to Reimplantation, wk	Micro Eradication	O/C	SX at Failure	Micro at Failure	Follow-up Duration, mo
1	Acute	DAIR	VAN <sup>a</sup>	6	DOX <sup>b</sup>	11	...	Reinfection	2-stage exchange with ABX spacer	<i>C. striatum</i>	12
2	Acute	DAIR	VAN <sup>a</sup>	2	AMC <sup>a</sup> + MIN <sup>a</sup>	Indefinite	...	Cure	...	...	7
3	Acute	DAIR	VAN <sup>a</sup>	7	MIN <sup>b</sup>	13	...	Cure	...	...	18
4	Chronic	DAIR	VAN <sup>a</sup>	7	LZD <sup>a</sup> ->VAN <sup>a</sup>	Indefinite	...	Cure	...	...	4
5	Acute	DAIR	DAP <sup>a</sup>	4	DOX <sup>a</sup> ->SXT <sup>a</sup> ->AMX <sup>c</sup>	11	...	Cure	...	...	23
6	Chronic	DAIR	DAP + ETP <sup>a</sup>	6	SXT <sup>b</sup> + MIN <sup>a</sup>	Indefinite	...	Chronic sinus tract	DAIR	Negative	6
7	Acute	DAIR	VAN <sup>a</sup>	6	DOX <sup>b</sup>	Indefinite	...	Cure	...	...	11
8	Chronic	2-stage exchange	VAN <sup>a</sup>	6	MIN <sup>b</sup> ->DOX <sup>b</sup>	29	8	Cure	...	...	79
9	Chronic	2-stage exchange	VAN <sup>b</sup>	6	...	...	16	Reinfection	DAIR	Negative	24
10	Chronic	2-stage exchange	VAN <sup>b</sup>	6	MIN <sup>b</sup>	6	20	Cure	...	...	75
11	Chronic	2-stage exchange	VAN <sup>b</sup>	6	CFR <sup>b</sup>	3	16	Cure	...	...	39
12	Chronic	2-stage exchange	VAN + ETP <sup>a</sup>	14	DOX <sup>b</sup>	Indefinite	16	Cure	...	...	15
13	Chronic	2-stage exchange	VAN <sup>a</sup>	6	...	...	12	Cure	...	...	6
14	Chronic	2-stage exchange	VAN <sup>a</sup>	6	MIN <sup>b</sup>	23	12	Cure	...	...	67
15	Chronic	2-stage exchange	DAP + ETP <sup>a</sup>	6	...	...	16	Cure	...	...	15
16	Chronic	2-stage exchange	VAN <sup>a</sup>	6	...	...	12	Cure	...	...	55
17	Chronic	Resection arthroplasty with articulating spacer	VAN <sup>a</sup>	8	PEN <sup>c</sup>	Indefinite	...	Cure	...	...	29
18	Acute	Resection arthroplasty with no spacer but residual cerclage wires	MEM <sup>a</sup>	7	MIN <sup>a</sup>	57	...	Cure	...	...	54
19	Chronic	Resection arthroplasty with articulating spacer	VAN <sup>a</sup>	6	...	...	...	Cure	...	...	31
20	Chronic	Lost to f/u	Lost to f/u	...	...	...	...	...	...	...	...

Abbreviations: ABX, antibiotics; AMC, amoxicillin-clavulanate; AMX, amoxicillin; CFR, ceftazidime; DAIR, debridement, antibiotic, and implant retention; DAP, daupromycin; DOX, doxycycline; ETP, eritapanem; IV, intravenous; LZD, linezolid; MEM, meropenem; MIN, minocycline; PEN, penicillin; Supp/Pro, suppressive/prophylactic; SX, surgery; SXT, trimethoprim-sulfamethoxazole; VAN, vancomycin.

<sup>a</sup>Antibiotic guided by antimicrobial susceptibilities.

<sup>b</sup>Antibiotic was not guided by antimicrobial susceptibilities.

<sup>c</sup>Isolate intermediately susceptible to penicillin.

<sup>d</sup>Microbiological eradication confirmed via intraoperative cultures at time of reimplantation.

<sup>e</sup>Microbiological eradication confirmed via follow-up arthrocentesis.

**Table 4. Antimicrobial Susceptibility of *Corynebacterium* Species Causing PJI**

Organism	PEN	CRO	VAN	MEM	DOX	SXT	CLI	LZD	CIP	ERY	RIF	GEN	TET
<i>C. striatum</i> (n = 13)	0/13	0/13	13/13	5/13	0/5	0/5	1/3	5/5	0/3	1/3	3/3	1/1	0/1
<i>C. jeikeium</i> (n = 3)	0/3	0/3	3/3	0/3	1/1	0/1	...	1/1	...	...	...	...	...
<i>C. amycolatum</i> (n = 2)	0/2	1/2	2/2	0/2	1/1	1/1	0/1	1/1	...	...	...	...	...

Susceptibilities reported as total number of susceptible isolates/total number of tested isolates. The default AST in our laboratory includes penicillin, ceftriaxone, meropenem, and vancomycin. Additional antibiotic testing was requested for 7 isolates and included doxycycline, trimethoprim-sulfamethoxazole, clindamycin, linezolid, ciprofloxacin, erythromycin, rifampin, and gentamicin. Additionally, susceptibilities to agents without interpretative guidelines such as amoxicillin-clavulanate, moxifloxacin, levofloxacin, daptomycin, tigecycline, and minocycline were occasionally ordered (refer to [Supplementary Table 2](#) for MICs).

Abbreviations: CIP, ciprofloxacin; CLI, clindamycin; CRO, ceftriaxone; DOX, doxycycline; ERY, erythromycin; GEN, gentamicin; LZD, linezolid; MEM, meropenem; MIC, minimum inhibitory concentration; PEN, penicillin; RIF, rifampin; SXT, trimethoprim sulfamethoxazole; TET, tetracycline; VAN, vancomycin.

[Supplementary Table 3](#) includes the MIC distribution of all tested agents. All 19 patients received a course of therapeutic intravenous antibiotics. This consisted of monotherapy with vancomycin in 74% (n = 14), daptomycin in 5% (n = 1), and meropenem in 5% (n = 1). The remainder received combination antimicrobial therapy with daptomycin and ertapenem in 11% (n = 2), and vancomycin and ertapenem in 5% (n = 1). The decision to use combination therapy in 3 patients was due to the treating physicians' concern that other unidentified pathogens may be involved. Two of these patients had monomicrobial *Corynebacterium* growth from 1 specimen only, so their role as primary pathogens was unclear. The third patient had *Corynebacterium* growth from  $\geq 2$  specimens but was kept on a broader regimen due to a prior episode of PJI with *P. mirabilis*. Therapy was AST-guided in 17 patients, while the remaining 2 patients were treated empirically. After surgical intervention, the median duration of IV antibiotics (IQR) was 6 (6–6.4) weeks.

Of those who underwent 2-stage exchange, the median time from resection to reimplantation (IQR) was 12 (12–16) weeks, and the median time from the end of therapeutic IV antibiotics to reimplantation (IQR) was 8 (6–9) weeks. Following reimplantation, 56% (n = 5) of patients in this group were prescribed secondary prophylaxis with oral antibiotics including minocycline, doxycycline, penicillin V.K., and cefadroxil.

Chronic suppressive antibiotics were instituted in 100% of patients following DAIR (7/7). In addition, 67% (2/3) of patients undergoing resection arthroplasty without reimplantation were considered high-risk for infection relapse and were transitioned to chronic suppressive antibiotics following therapy. The agents used for suppression included doxycycline (n = 2), minocycline (n = 3), linezolid (n = 1), amoxicillin-clavulanate (n = 1), amoxicillin (n = 1), and trimethoprim-sulfamethoxazole (n = 1).

#### Follow-up and Outcome

The median follow-up duration from surgical intervention (IQR) was 23 (12–46) months for the 19 treated patients. Eighty-four percent (n = 16) of patients had symptom resolution during follow-up and remained infection-free after that.

Based on our definition, the remaining 16% (n = 3) of patients met clinical failure.

Seven patients underwent DAIR as primary management, and failure occurred in 2 patients (29%). One patient was initially managed with DAIR after presenting with acute late infection and AST-guided IV antibiotics for PJI secondary to *C. striatum*. The *C. striatum* isolate was resistant to tetracycline (MIC >8 mcg/mL) but not tested against doxycycline. Regardless, doxycycline was chosen as a suppressive agent due to a lack of other oral options. He developed signs of reinfection during follow-up and underwent a 2-stage exchange with intraoperative cultures, again demonstrating *C. striatum*. He remained symptom-free after his 2-stage exchange procedure. The second patient who failed in this group presented with chronic late PJI with *C. jeikeium* and had a chronic sinus tract. He had a complicated history of recurrent PJIs, multiple prior surgical interventions, and lower extremity lymphedema. The patient opted for DAIR and antimicrobial suppression instead of a more radical approach such as permanent resection or amputation. He was maintained on suppression with minocycline (MIC, 1 mcg/mL) following DAIR. He was also on trimethoprim-sulfamethoxazole for prior *Serratia marcescens* PJI. He underwent a second DAIR due to persistent drainage, but intraoperative cultures were negative. He continued to have a chronically draining sinus tract but was functional and pain-free.

Antimicrobial suppression following DAIR was challenging. Two of our patients were suppressed with amoxicillin and amoxicillin-clavulanate. The former had a *C. striatum* strain intermediately susceptible to penicillin. The patient was switched to amoxicillin after developing photosensitivity with doxycycline and trimethoprim-sulfamethoxazole. The latter was on minocycline (*Corynebacterium* MIC, 8 mcg/mL) suppression for *S. aureus* PJI in the contralateral knee, and amoxicillin-clavulanate (MIC,  $\leq 2/1$  mcg/mL) was added to suppress *C. amycolatum* PJI. Both patients were cured and remained infection-free during follow-up. One patient was maintained on linezolid suppression and subsequently developed acute kidney injury, hepatitis, and lactic acidosis, all considered related to linezolid. The patient was switched to IV vancomycin and

had clinical improvement. The patient presented again with asystole, hypotension, and lactic acidosis within a month and was transitioned to comfort care without workup or treatment and died. Finally, of the 2 patients maintained on doxycycline suppression, MICs for doxycycline were unavailable. Susceptibility to the tetracycline group is not routinely performed at our institution. However, 1 patient had an isolate that was tested for tetracycline and was resistant. As previously discussed, this patient failed doxycycline suppression and had recurrence of *Corynebacterium* PJI.

Nine patients underwent a 2-stage exchange as primary surgical management; 1 had an unsuccessful outcome (11%). This patient had PJI secondary to *C. striatum*, and his IV antimicrobial therapy was empiric due to a lack of AST. He had negative intraoperative cultures during reimplantation and was not maintained on secondary prophylaxis. He then developed signs of reinfection and underwent DAIR, but his intraoperative cultures remained negative. He remained symptom-free after his DAIR procedure.

Three patients underwent permanent resection arthroplasty without reimplantation. All were cured without recurrence of infection.

The total duration of antimicrobial suppression or secondary prophylaxis varied. Four patients were maintained on oral suppression and 2 on oral secondary prophylaxis until the last day of follow-up and were meant to continue indefinitely. One patient in the DAIR group discontinued prophylaxis after a subsequent 2-stage exchange for reinfection with *C. striatum*. Repeat intraoperative cultures at the time of reimplantation remained negative, and further oral antibiotics were considered of no benefit due to resistance. On the other hand, 7 patients discontinued their antibiotics during follow-up, with no episodes of treatment failure in this group. The latter group's median duration for suppression and prophylaxis (IQR) was 11 (11–12) and 23 (6–29) months, respectively.

Three of our patients died during follow-up. None were directly related to PJI, outside of the case of lactic acidosis, possibly related to previous linezolid exposure.

## DISCUSSION

We highlight several important observations on monomicrobial *Corynebacterium* PJI in our study. Our findings can be compared with prior series while keeping in mind that earlier publications included polymicrobial infections; hence, other pathogens might have altered the clinical course in these studies and may account for some differences in observations [9, 11–13].

We found a very low prevalence of monomicrobial *Corynebacterium* PJI at our institution, consistent with previous literature [7]. Previous studies from other centers from the United States, Russia, Argentina, Uruguay, and Germany

also reported a low prevalence of *Corynebacterium* in hip and knee PJI ( $\leq 2.5\%$  detection rate) [13, 14]. These prior reports, however, were not restricted to monomicrobial cases. The pathogenic role of *Corynebacterium* may be questioned in 6 of our patients, who had growth from only 1 intraoperative or synovial aspirate specimen. However, all of them met the 2018 ICM PJI definition. We also checked and confirmed that they met the 2011 Musculoskeletal Infection Society (MSIS) and 2021 European Bone and Joint Infection Society (EBJIS) PJI criteria [15, 16]. While we think it is unlikely, it remains possible that these 6 patients represent culture-negative infection with *Corynebacterium* spp. reflecting contamination.

*Corynebacterium* PJI typically presents with indolent chronic symptoms. Most of our patients experienced PJI-related symptoms for weeks to months before presentation, particularly joint pain. The majority also had delayed or late infections. Patients rarely presented with systemic symptoms and had a low prevalence of sinus tract infections despite the chronic nature of infection (5%;  $n = 1$ ). The chronicity of symptoms was similarly observed in other series on *Corynebacterium* PJI [9, 11]. On the other hand, 1 distinguishing finding in prior series is that a good proportion of *Corynebacterium* PJIs presented as early infections ( $< 3$  months postimplantation), up to 71% in a study by Chauvelot et al. from France [9, 17]. This same study also reported a sinus tract infection in 73% of patients [9]. A notable limitation from the study by Chauvelot et al. is that 60% of included cases were polymicrobial [9].

*C. striatum* is the most common species identified in PJI cases. This species accounted for 70% of our isolates. Its relative prevalence is reflected in the current literature on *Corynebacterium* PJI [9, 11, 13]. We also detected *C. jeikeium* and *C. amycolatum*, both of which have also been previously described to cause PJI [18]. Although not detected in our study, other *Corynebacterium* spp. can cause PJI, including *C. tuberculoostearicum* and *C. simulans* [9].

The management of *Corynebacterium* PJI is quite challenging due to a limited armamentarium of effective antibiotics to treat and suppress infection, which is an important take-home message. The optimal management approach for *Corynebacterium* PJI has not been defined. For nonstaphylococcal PJI, The Infectious Diseases Society of America (IDSA) recommends using 4–6 weeks of pathogen-specific IV or highly bioavailable oral antibiotic therapy following DAIR and resection arthroplasty with or without reimplantation [10]. Chronic suppressive antibiotic therapy can be reserved for patients with implant retention. The median duration of IV antibiotics in our series and the use of antibiotic suppression align well with these recommendations. In addition, secondary prophylaxis with prolonged courses of oral antibiotics following reimplantation was common in our series.

To date, vancomycin and linezolid remain the most effective agents against *Corynebacterium* infections, and our AST results

show reliable susceptibilities to both. Most tested isolates also exhibited low MICs to daptomycin. On the other hand, susceptibility to other potential agents such as beta-lactams, tetracyclines, trimethoprim-sulfamethoxazole, and fluoroquinolones is unpredictable and needs confirmation before use given the high frequency of resistance. This again highlights the challenge of choosing an effective oral agent for suppression following IV therapy. Our AST results are compatible with those reported by Chauvelot et al., except for higher susceptibilities to tetracycline detected in their series [9]. In line with the findings above, IV vancomycin is the most reported antibiotic for treating *Corynebacterium* PJI [9, 11–13] and is the drug of choice in our center.

Linezolid is an effective alternative with proven clinical efficacy against several multiresistant gram-positive pathogens, including *Corynebacterium* spp. [19, 20]. Nonetheless, it is associated with a relatively high incidence of reported adverse events, particularly severe cytopenias. In our series, linezolid was used for suppression in only 1 patient, who subsequently developed lactic acidosis. Lactic acidosis is an uncommon but potentially serious complication of linezolid therapy [21]. A longer duration of therapy (>6 weeks) is considered a risk factor for lactic acidosis [21]. Therefore, physicians remain cautious about prescribing prolonged courses of linezolid. Existing data show that therapeutic drug monitoring may have a role in minimizing linezolid-induced toxicity. The relationship between exposure and toxicity has mainly been established for linezolid-induced thrombocytopenia, and more studies are needed to better define thresholds for other adverse events [22]. Physicians may need to consider linezolid with close monitoring, but a careful risk–benefit discussion with the patient is advised.

IV daptomycin is another alternative or last-resort drug for treating multiresistant gram-positive pathogens [23]. Daptomycin is overall better tolerated than linezolid. Therefore, in our center, IV daptomycin has been used in place of IV vancomycin to treat *Corynebacterium* PJI in patients with contraindication to the latter. IV daptomycin has also been used, yet infrequently, in prior *Corynebacterium* PJI series [9, 13]. All tested isolates in our series had favorable daptomycin MICs except for 1 isolate with MIC  $\geq 256$  mcg/mL. However, the emergence of high-level daptomycin resistance (HLDR; defined as MIC  $\geq 256$  mcg/mL) in clinical *Corynebacterium* isolates after exposure to daptomycin has been reported, similar to other gram-positive pathogens [24]. This has been chiefly described with *C. striatum*, where sequential clinical specimens from few reported cases exhibited emergence of HLDR during daptomycin therapy [23, 25, 26]. It was also demonstrated in vitro, where 90%–100% of *C. striatum* isolates developed HLDR after daptomycin exposure [23, 27]. The emergence of HLDR has also been described in other species, including *C. jeikeium* and *C. amycolatum* [27]. After 24 hours of in vitro

daptomycin exposure, 12% of 119 non-*striatum* isolates developed HLDR [27]. The effect of this phenomenon on clinical outcomes remains unclear. Reported cases of cardiac device infection showed the emergence of HLDR at the time of clinical worsening during or after a course of daptomycin [25, 26]. Whether such events could occur in PJI cases remains to be seen. In our series, 3 patients were treated with daptomycin, 2 of whom were cured, while 1 failed due to chronic sinus tract infection.

Several new antibiotics with good gram-positive activity were made available over the last 2 decades to treat skin and soft tissue infections [28]. These include delafloxacin, omadacycline, tedizolid, dalbavancin, telavancin, oritavancin, and eravacycline, which are available in either oral or IV formulation. Good in vitro activity against *Corynebacterium* spp. has been shown for telavancin, dalbavancin, oritavancin, eravacycline, and tedizolid [9, 27, 29–32]. Unfortunately, the use of these newer drugs against *Corynebacterium* infections is still limited due to lack of clinical experience and the absence of data on in vivo efficacy.

DAIR might be an appropriate approach in patients with acute *Corynebacterium* PJI or early infections who meet other criteria suggested by IDSA guidelines. However, the choice depends on the availability of an oral agent for chronic suppression to follow the 6-week therapeutic course [10]. Resection arthroplasty, with or without reimplantation, may be the best chance for infection eradication, but it can be associated with significant morbidity. Prior series suggest that failure rates can be high with both types of surgical intervention [9, 13]. Pannu et al. reported failure in 40% and 56% of patients with *C. striatum* PJI who underwent DAIR and implant explantation with or without reimplantation, respectively [13]. Chauvelot et al. detected failure in 56% of patients with *Corynebacterium* PJI while reporting optimal surgical intervention in 93% of the entire cohort [9].

In contrast to both series, we found a much lower failure rate. Only 15% (n = 3) of our patients failed during follow-up. This is true despite having a median follow-up that is similar to and longer than that of Pannu et al. and Chauvelot et al., respectively [9, 13]. In our study, DAIR was primarily restricted to patients with acute infections, except for 2 patients with chronic late infections. Therefore, this surgical management could be considered appropriate for certain patients. Factors leading to a higher failure rate in the prior series are unclear. Multiple factors could have played a role, including the polymicrobial nature of some infections in these prior studies.

## CONCLUSIONS

Monomicrobial *Corynebacterium* PJI is a rare entity yet challenging due to limited clinical experience and limited options for antimicrobial therapy and suppression. Nonetheless, we



saw a more favorable outcome than the previous studies; the strict inclusion of monomicrobial infections likely accounts for that. Our study design and sample size remain a significant limitation, and we encourage the reporting of more such cases to enrich the scarce literature. Based on our review, selected patients may benefit from DAIR; however, verification of AST for durable chronic suppression options is critical. We also highlight the need to expand our armamentarium against *Corynebacterium* by testing the efficacy of newer antibiotics made available over the last 2 decades.

### 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.** Not applicable.

**Potential conflicts of interest.** Matthew P. Abdel, MD, declares royalties related to hip and knee implants from Stryker (USA) and is a member of the American Academy of Orthopaedic Surgeons (AAOS) board of directors. Aaron J. Tande, MD, writes a chapter on Uptodate.com on osteomyelitis and receives a small honorarium. All other authors report no potential conflicts. 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.

**Availability of data and material.** Data not publicly available.

**Patient consent.** Our study does not include factors necessitating patient consent.

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