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Cardiovascular Implantable Electronic Device Infections due to *Propionibacterium* Species

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Abstract

Introduction—*Propionibacterium* species are part of the normal skin flora and often considered contaminants when identified in cultures. However, they can cause life-threatening infections, including prosthetic cardiovascular device infections. Clinical presentation and management of cardiovascular implantable electronic device (CIED) infection due to *Propionibacterium* species has not been well described.

Methods—Retrospective review of all cases of CIED infection due to *Propionibacterium* species admitted to Mayo Clinic between January 1, 1990 and December 31, 2014. Patient charts were reviewed for clinical, microbiological, and imaging data. Descriptive analysis was performed.

Results—We identified 14 patients with CIED infection due to *Propionibacterium* species, accounting for 2.3% of all CIED infections. Patients were predominantly male (n=12, 86%). The median age at admission was 58.5 years [range, 22–83]. Twelve patients had implantable cardioverter-defibrillators (ICDs) and 2 had permanent pacemaker (PPM) systems. Twelve patients had generator pocket infection (86%). Two patients met clinical criteria for CIED-related infective endocarditis (CIED-IE). Median time between last device manipulation and infection was 9 months [range, 1–98]. All patients were treated with complete device removal and antibiotic therapy. Six-month follow-up data were available for 10 patients (71%), with no relapses documented.

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Conclusion—CIED infections due to *Propionibacterium* species accounted for 2.3% of all device infections over a 25-year period. The most common infectious syndrome was generator pocket infection with delayed onset. There was an unanticipated predominance of ICDs in this cohort. Cure was achieved in all cases with complete device removal and antibiotic therapy.

Keywords

Cardiovascular Implantable Electronic Device (CIED); infection; *Propionibacterium* species; CIED-related infective endocarditis (CIED-IE)

Introduction

Propionibacterium species are anaerobic, biofilm-forming, Gram-positive bacilli that are a ubiquitous part of the human skin flora and are commonly considered contaminants in cultures [1]. However, *Propionibacterium* species can cause significant infections, especially in the setting of prosthetic devices (eg, cardiac valves, prosthetic joints, and central nervous system ventricular shunts) [1–3].

Current literature on the infection of cardiovascular implantable electronic devices (CIEDs) by *Propionibacterium* species is scarce and limited to only case reports [4–7]. Therefore, the ability of these organisms to cause CIED infections is not widely appreciated. In addition, these organisms are slow to grow in routine bacterial cultures and often require prolonged incubation [8]. This may further limit their identification as causative organisms of CIED infection because cultures may be discarded before slow-growing organisms, such as *Propionibacterium* species, are identified. A better understanding of the clinical manifestations and management of CIED infection due to *Propionibacterium* species is needed, as device infections are associated with significant morbidity, mortality, and financial cost [9]. We therefore describe an institutional case series of CIED infections due to *Propionibacterium* species that highlights our diagnostic and therapeutic approaches over the past 25 years.

Methods

Study population

We retrospectively reviewed all cases of adults (≥ 18 years of age) with CIED infection due to *Propionibacterium* species treated at Mayo Clinic in Rochester, Minnesota, from January 1, 1990 to December 31, 2014. Patient charts were reviewed for clinical, microbiological, and imaging data. All patients consented to the use of their medical records for research purposes. The study protocol was approved by the Mayo Clinic Institutional Review Board.

Definitions

CIED infections were classified into 3 different clinical syndromes [10, 11]: 1) pocket infection: defined by the presence of local signs of inflammation at the generation pocket, including erythema, warmth, fluctuance, erosion, tenderness, purulent drainage, or lead erosion with positive cultures from pocket tissue or device material yielding *Propionibacterium* species. 2) CIED-related blood stream infection (BSI): defined as

positive blood cultures for *Propionibacterium* species in the absence of alternative source of infection and resolution of blood stream infection after device explantation. 3) CIED-related infective endocarditis (CIED-IE): defined as positive blood cultures for *Propionibacterium* species, and the presence of intracardiac (device lead or valve) vegetation documented by echocardiography, or if the modified Duke's Criteria for IE [12] were met. Patients with negative blood cultures who presented with systemic symptoms of infection and had unexplained intracardiac vegetation on echocardiography were included if the cardiac device lead tip culture yielded *Propionibacterium* species. Vegetation was defined as an oscillating intracardiac mass on the device lead or cardiac valve confirmed by echocardiography in more than 1 plane.

Time to infection was calculated from the last device manipulation date, if available. Late infection was defined as infection after 1 year of device placement or system manipulation.

Descriptive statistics on baseline data were defined as count (percentage), mean ($\pm$ SD), or median [range], as appropriate.

Results

Fourteen patients with CIED infection due to *Propionibacterium* species were identified between January 1, 1990 and December 31, 2014, accounting for 2.3% of all CIED infections (n=618) over the study period. Patients were predominately male (n=12; 86%), median age was 58.5 years [range, 22–83], and median BMI was 27.5 [range, 20–38]. All patients had the device placed using a left pectoral approach. Twelve patients (86%) had an implantable cardioverter defibrillator (ICD); 2 patients (14%) had permanent pacemakers (PPMs). Median time between device placement and infection was 9 months [range, 1–98]. Patient demographics, device characteristics, clinical presentation, and management of each case are summarized in Table 1.

Five patients (36%) presented with late infection. The most common presenting clinical syndrome was pocket infection (12 patients [86%]), and 2 patients met the clinical criteria for CIED-IE (cases 1 and 3). All patients but one had signs of infection at generator pocket site on presentation. Two patients only presented with systemic symptoms (Table 2).

Culture specimens were obtained from the generator pocket, device lead, and blood. *Propionibacterium acne* was recovered in 7 cases (50%), *Propionibacterium avidum* in 1 case (7%), and the remaining 6 species (43%) could not be further identified. Three patients with polymicrobial infection (*Propionibacterium* species and coagulase-negative staphylococcus in each case) were included in this series. All 3 cases were pocket infections, and mixed cultures were obtained from generator pocket samples.

Echocardiography was performed in 8 patients (57%); 3 patients had transthoracic echocardiography, 4 had transesophageal echocardiography, and 1 patient had both performed. There was echocardiographic evidence of intracardiac vegetation in 3 patients; 2 had lead vegetations, and 1 had vegetations on a device lead and tricuspid valve. Case 13 had lead vegetation, but did not meet clinical criteria for CIED-IE. Peripheral emboli and metastatic infections were not observed in any patients.

All patients underwent device removal; 12 patients had complete system removal on initial intervention, and 2 patients (14%) had intraoperative complications leading to partial removal. This was followed up by another procedure to remove retained material. Median time to positive culture of a device generator pocket/lead was 4 days [range, 3–6]. Blood cultures were positive in 1 patient, but the time to positivity information was unavailable. Thirteen patients (93%) underwent new device placement. Median time between device removal and reimplantation was 8 days [range, 6–18].

In vitro susceptibility results were available for only 5 isolates (cases 1, 2, 7, 13, and 14), and all isolates were penicillin susceptible (MIC = 1). Details of in-hospital antimicrobial therapy were available for 12 patients; 10 patients (83%) received vancomycin or a regimen including vancomycin, and 2 patients (17%) received cefazolin. Antimicrobial therapy prescribed for the post-hospitalization period were available in 11 patients; 6 patients (55%) received vancomycin or a regimen that included vancomycin, 4 patients (36%) received oral therapy (2 linezolid, 2 cephalexin), and 1 patient (9%) didn't receive any antibiotics after discharge. Antibiotic therapy is described in detail for each patient in Table 1. Overall, median duration of antibiotic therapy was 15 days [range, 10–38]. Six-month follow-up data were available for 10 patients (71%). None of these patients had CIED infection relapse.

Discussion

We describe the largest series of CIED infections due to *Propionibacterium* species to date. *Propionibacterium* species accounted for 2.3% of all CIED infections (n=618) over a 25 year study period, signifying the infrequency of this infection. Median time from last device manipulation (including de novo placement) to clinical infection was 9 months, approximately 4 months longer than what has been previously described for ICDs [11]. This is likely due to low virulence of *Propionibacterium* species leading to indolent infection. This has been well described in prosthetic joint infections [13, 14] as well as prosthetic valve endocarditis, in which the median time to infection from valve placement was approximately 4 years [2], assuming that valve contamination with *Propionibacterium* species occurred at the time of valve placement.

The majority of infections occurred in males with an ICD (n= 11, 79%). The predominance of males in *Propionibacterium* species-related infections has been well documented [1, 2, 13]. Kanafani et al [13] suggested that a tropism of *Propionibacterium* species to cause infections in males is related to higher testosterone levels, which increase the population of these organisms on the skin. The predominance of ICD infections in this cohort was somewhat unexpected, considering that the majority of implanted CIEDs are PPMs [9]. While the precise reason for this disproportionate involvement of ICDs is unclear, it may be due to the larger size of ICD generators. Prior research has demonstrated that biofilm formation is an important virulence factor for invasive *Propionibacterium acnes* infections [15]; thus, the larger size of the ICD generator may provide additional surface area for microbial adherence and multiplication. However, the size of this cohort is too small to draw any conclusions regarding biofilm formation on different types of CIEDs.

The most common clinical infection syndrome in our series was generator pocket infection. *Propionibacterium* species are the most commonly isolated organisms from generator pockets either following de novo implantation or device replacement [16, 17]. In a prospective study of 100 patients undergoing either de novo implantation or replacement (for noninfectious causes) of a PPM, device generator pocket swab cultures were positive for *Propionibacterium* species in 42% [17]. Mason et al. [16] have demonstrated that the presence of positive culture from a generator pocket at the time of device replacement (for noninfectious causes) was not a marker for future infection. Currently, there is neither a culture method nor a biological marker to separate generator pocket infection (rare—rates of CIED pocket infection have been reported as low as 0.13% [18]) from colonization (as common as 42% [17]). A study from the Cleveland Clinic suggests that the time to culture positivity may help separate true-positive from false-positive culture results in *Propionibacterium*-related prosthetic joint infections (5 days vs 9 days, respectively) [19]. Median time to culture positivity in our series was 4 days. Whether this distinguishes infection from contamination would be merely speculative, as there are no studies comparing median time to culture positivity of CIED infections due to *Propionibacterium* species. The presence of an organism on multiple culture sets might be beneficial in distinguishing infection from a contaminant. Eight patients with pocket infection (n=12) had 1 culture set positive for *Propionibacterium* species (Table 1). Newer techniques such as device ultrasonication have been associated with higher sensitivity for bacteriologic diagnosis of CIED device pocket infection [16]. Using conventional culture methods, the rate of culture-negative CIED pocket infection at our institution between 1991 and 2003 was approximately 7% [11]. Whether the use of ultrasonication or extending the incubation period of culture could have reflected an increase in the incidence of CIED infection due to *Propionibacterium* species necessitates further research.

Two patients in this series (cases 1 and 3) had CIED-IE. In reviewing the literature, we identified 4 more cases of *Propionibacterium* CIED-related IE [4–7]; demographics, device type/status, clinical presentation, and management of reviewed cases are illustrated in Table 3. Common characteristics included the lack of signs of infection at pocket site which were present in 1/6 cases only. In agreement with previous literature, patients with CIED-IE are less likely to have signs of infection at device generator pocket site [20]. *Propionibacterium* species do not readily grow on blood cultures, even when intracardiac material is involved. In a review of 70 cases of IE caused by *Propionibacterium* species, 38% of patients had negative blood cultures [2]. The previous factors highlight why diagnosis is difficult and often subject to delay. Time from symptom onset to diagnosis for all identified cases of *Propionibacterium* CIED-related IE (mean, 74 days [±83]) was twice longer than what is previously described for CIED-IE (mean, 36 days [±117]) [21]. Delay in diagnosis may lead to undesirable complications. This is best demonstrated with the case by Santo et al. [6] the patient had a 4-month diagnosis delay from the first positive blood culture, underwent 3 hospitalizations, and developed a pulmonary embolism before a diagnosis was made. In a review of 522 positive blood cultures for *Propionibacterium acnes*, 18 (3.5%) had clinically significant BSI [8]. This highlights that not all blood cultures positive for *Propionibacterium* species are contaminants and BSI should be put into consideration particularly in the presence of an intravascular/intracardiac prosthetic material.

Propionibacterium species are susceptible to a wide range of antimicrobial agents. Vancomycin is often used as first-line empiric therapy for CIED infections due its activity against coagulase-negative staphylococci. In a study of 28 *Propionibacterium acnes* isolates, penicillins and cephalosporins had the lowest MIC values in vitro [22]. The majority of patients in this series received vancomycin, either as monotherapy or in combination. Three patients with penicillin-susceptible strains received vancomycin, which we attributed to delayed culture results.

Current 2010 AHA CIED infection management guidelines [18] recommend aggressive treatment with complete device removal and antibiotic therapy. This recommendation applies to infections limited to the generator pocket as conservative management (antimicrobial therapy without device removal) has shown higher rates of treatment failure and recurrent infections [18]. Duration of antimicrobial therapy should be 10 to 14 days after CIED removal for device pocket infections, and at least 14 days after CIED removal for CIED-BSI. The duration of antibiotic therapy should be extended for at least 4–6 weeks for complicated infections (valve vegetations, or septic emboli) [18]. All cases in this series were treated with complete device removal and antibiotic therapy; all patients with adequate follow-up data were cured, with no infection recurrences at 6 months of follow-up.

Conclusion

CIED infections due to *Propionibacterium* species accounted for 2.3% of all device infections over a 25-year period at our institution. The most common infectious syndrome was generator pocket infection. There was an unanticipated predominance of ICDs infection. CIED-IE occurred in only 2 cases. Cure was achieved in all 14 cases with complete device removal and antibiotic therapy. No CIED infection relapses occurred at 6-month follow-up.

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Demographics, Device Type/Status, Clinical Presentation, and Management of *Propionibacterium* Species CIED Infections

Table 1

Case (Year of Diagnosis)	Age/Sex	Comorbidities	Device/ Chamber	Total Device Procedures Prior to Infection	Last Device Manipulation (Time to Infection, Months)	Initial Presentation	Echocardiog- raphy (Vegetation Site)	Culture Results (Pocket/ Lead/ Blood)	Antibiotic Therapy (In-hospital / Discharge)	Treatment/Outco- me (Follow-up Months)
1 (1994)	62/M	CAD, CHF	PPM/Single	3	N/A (3)	Fever, chills, sweating, malaise, murmur	TTE+TEE (V+L')	P • /L ₊ ^{1/1} /B ₊ ^{N/A}	N/A	Complete removal/Cured (1)
2 * (1995)	50/F	None	ICD/Dual	1	Initial placement (1)	Erythema, swelling, drainage, pus, IOP at generator pocket	N/A	P ₊ ^{3/4} /L ₊ ^{1/1} /B ₋ ^{0/2}	N/A	Complete removal/Cured (131)
3 (2002)	50/M	Lymphoma, CHF	ICD/Dual	2	System upgrade (36)	Fever, chills, hypotension, tachycardia, malaise, erythema, pain, swelling, IOP at generator pocket	TEE (L')	P ₋ ^{0/6} /L ₊ ^{1/1} /B ₋ ^{0/4}	Vancomycin~/Vancomycin~	Complete removal/Cured (19)
4 * (2003)	68/M	CAD, CHF	ICD/Dual	2	N/A (11)	Lead erosion	N/A	P ₊ ^{1/1} /L ₊ ^{1/1} /B ₋ ^{0/2}	Cefazolin/Cephalexin	Complete removal/Cured (21)
5 * (2004)	22/M	None	ICD/Dual	1	Initial placement (10)	Erythema, pain, pus, lead erosion, IOP at generator pocket	N/A	P ₊ ^{2/2} /L ₊ ^{1/1} /B ₋ ^{0/2}	Vancomycin/Vancomycin	Complete removal/Cured (109)
6 (2005)	76/M	CAD, Hx of leukemia	ICD/Single	2	Generator change (3)	Erythema, swelling, drainage, pus, IOP at generator pocket	TEE (Negative)	P • /L ₊ ^{1/1} /B ₋ ^{0/7}	Vancomycin/N/A	Complete removal^/Cured (0)
7 (2005)	83/M	Hx of bladder Cancer, CAD, splenectomy, CHF	ICD/Dual	4	Lead change (1)	Erythema, warmth, drainage, IOP at generator pocket	N/A	P ₊ ^{1/1} /L ₋ ^{0/2} /B ₋ ^{0/1}	Vancomycin/Linezolid(PO)	Complete removal/Cured (6)
8 (2007)	78/M	CAD, CHF	ICD/Single	1	Initial placement (9)	Erythema, pain, swelling, warmth, tenderness, drainage, IOP at generator pocket	N/A	P ₊ ^{2/3} /L ₋ ^{0/2} /B ₋ ^{0/2}	Vancomycin~/Cephalexin	Complete removal/Cured (15)
9 (2008)	48/M	Giant cell myocarditis, CHF	ICD/Dual	2	Generator change (36)	Erythema, swelling, warmth, tenderness, IOP at generator pocket	TEE (Negative)	P ₊ ^{1/1} /L ₋ ^{0/2} /B ₋ ^{0/4}	Vancomycin/Vancomycin	Complete removal^/Cured (82)
10 (2008)	47/M	CHF	ICD/Single	2	System upgrade (98)	Erythema, swelling	TTE (Negative)	P ₊ ^{2/4} /L ₋ ^{0/3} /B ₋ ^{0/7}	Cefazolin/None	Complete removal/Cured (79)
11 (2008)	68/M	CAD, CHF	ICD/Dual	2	System upgrade (2)	Lead erosion	TTE (Negative)	P ₋ ^{0/2} /L ₊ ^{2/3} /B ₋ ^{0/2}	Vancomycin/Linezolid (PO)	Complete removal/Cured (0)
12 (2010)	55/M	CAD	ICD/Dual	1	Initial placement (14)	Erythema, pain, tenderness, pus, IOP at generator pocket	TTE (Negative)	P ₊ ^{1/4} /L ₋ ^{0/3} /B ₋ ^{0/2}	Vancomycin~/Vancomycin~	Complete removal/Cured (0)
13 (2010)	79/F	Hx of melanoma	PPM/Dual	2	Generator change (15)	Erythema, pain, pus, IOP at generator pocket	TEE (L')	P ₋ ^{0/3} /L ₊ ^{2/2} /B ₋ ^{0/4}	Vancomycin/Vancomycin	Complete removal/Cured (56)
14 (2013)	52/M	None	ICD/Dual	3	Generator change (3)	Swelling, IOP at generator pocket	N/A	P ₊ ^{2/3} /L ₋ ^{0/1} /B ₋ ^{0/2}	Vancomycin/Vancomycin	Complete removal/Cured (17)

* Cases with mixed infection “*Propionibacterium* species + *CONS*.” Total device procedures prior to infection: all device-related procedures including previous/initial placement.

Hx, history of; CAD, coronary artery disease; CHF, congestive heart failure; IOP, intraoperative purulence; PPM, permanent pacemaker; ICD, implantable cardioverter defibrillator; TTE, transthoracic echocardiogram; TEE, transesophageal echocardiogram; V, valve; L', lead vegetation; ~, in combination with other antibiotics; ^, intraoperative complication requiring a second procedure; P, pocket; L, lead; B, blood; ##, number of positive cultures for *Propionibacterium* species/number of cultures taken; +, positive; -, negative; •, N/A; Ab, antibiotics.

Table 2Demographic and Clinical Features of Patients With CIED Infection due to *Propionibacterium* Species

Characteristics:	No. (%)
Male	12 (86)
Age at admission, median [range]	58.5 [22–83]
BMI, median [range]	27.5 [20–38]
Permanent pacemaker (PPM)	2 (14)
Implantable cardioverter defibrillator (ICD)	12 (86)
Total procedures prior to infection, median [range]	2 [1–4]
Comorbidities	
Congestive heart failure (CHF)	8 (57)
Coronary artery disease (CAD)	6 (43)
Anticoagulation	5 (36)
Malignancy	3 (21)
Chemotherapy	1 (6)
Autoimmune disease	1 (6)
Immunosuppression drugs	1 (6)
Splenectomy	1 (6)
Diabetes mellitus/Hemodialysis/Liver disease/Graft/Steroids/HIV	0 (0)
Presentation	
Local Finding at Generator Site	
Erythema	10 (71)
Intraoperative purulence	10 (71)
Swelling	7 (50)
Pain	5 (36)
Pus	5 (33)
Drainage	4 (29)
Chills	2 (17)
Warmth	3 (21)
Tender	2 (17)
Erosion	3 (21)
Systemic Symptoms	
Fever	2 (21)
Malaise	2 (21)
Tachycardia	1 (6)
Sweating	1 (6)
Hypotension	1 (6)
Microbiology	
Positive pocket culture	9 (64)
Positive lead culture	8 (57)
Positive blood culture	1 (7)

Characteristics:	No. (%)
Number of positive cultures for <i>Propionibacterium</i> species >1	9 (71)
Treatment	
Duration of Ab therapy (days) Median, [Range]	15 [10–38]
New device	13 (93)

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“Cases from reviewed literature” Demographic Features, Device Type/Status, Clinical Presentation, and Management of CIED-IE due to *Propionibacterium* Species

Table 3

Case	Age/ Gender	Comorbidities	Device	Total Device Procedures Prior to Infection	Time To Infection From Placement (Months)	Symptom Onset (Days)	Initial Presentation	Culture Results (Pocket/ Lead/ Blood)	Number of +BC (Time to + Hours)	Treatment/Outcome (Follow-up Months)
Chua, et al. ⁽⁴⁾	78/M	Hypothyroidism, hypertension	PPM	1	N/A	180	Fever, chills, sweating, fatigue, malaise	P•/L+/B+	N/A	Complete removal+Ab/Cure
Santo, et al. ⁽⁶⁾	48/F	Ebstein anomaly	PPM	2	96	1 st admission: 120 3 rd admission: 150	1 st admission: fever, malaise, chills 3 rd admission: fever, chills, malaise, pleuritic pain	1 st admission: P•/L•/B– 3 rd admission: P•/L–/B+ +	1 st admission: 1/7 (N/A) 3 rd admission: 2/5 (N/A)	1 st admission: Ab/Recurrence (3) 3 rd admission: Lead removal+Ab/Cure(32)
Noel, et al. ⁽⁵⁾	74/M	Type 2 DM, hypertension	PPM	1	24	15	Fatigue, purpura, delirium	P•/L•/B+	1/6 (93)	Complete removal + Ab/Cure (N/A)
Zedtwits-Liebenste in, et al. ⁽⁷⁾	31/M	Tetralogy of Fallot	PPM	3	N/A	2	Fever, murmur	P•/L•/B+	?/5 (N/A)	Ab/Cure (12)

Total Device procedures prior to infection: all device-related procedures including previous/initial placement. Device manipulation: includes all invasive device manipulations i.e lead/generator change, device revision. Ab indicates antibiotics; BC, blood culture; CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus; ICD, implantable cardioverter defibrillator; IOP, intraoperative purulence; PPM, permanent pacemaker; P, pocket; L, lead; B, blood; +, positive; –, negative; •, N/A,.