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DEVICES

Atypical pathogens associated with cardiac implantable electronic device infections

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Abstract

Background: Cardiovascular implantable electronic device (CIED) infections are associated with significant morbidity and mortality making the identification of the causative organism critical. The vast majority of CIED infections are caused by *Staphylococcal* species. CIED infections associated with atypical pathogens are rare and have not been systematically investigated. The objective of this study is to characterize the clinical course, management and outcome in patients with CIED infection secondary to atypical pathogens.

Methods: Medical records of all patients who underwent CIED system extraction at the University of Chicago Medical Center between January 2010 and November 2020 were retrospectively reviewed to identify patients with CIED infection. Demographic, clinical, infection-related and outcome data were collected. CIED infections were divided into typical and atypical groups based on the pathogens isolated.

Results: Among 356 CIED extraction procedures, 130 (37%) were performed for CIED infection. Atypical pathogens were found in 5.4% (n = 7) and included *Pantoea species* (n = 2), *Kocuria species* (n = 1), *Cutibacterium acnes* (n = 1), *Corynebacterium tuberculostearicum* (n = 1), *Corynebacterium striatum* (n = 1), *Stenotrophomonas maltophilia* (n = 1), and *Pseudozyma ahidis* (n = 1). All patients with atypical CIED infections were successfully treated with total system removal and tailored antibiotic therapy. There were no infection-related deaths.

Conclusions: CIED infections with atypical pathogens were rare and associated with good outcome if diagnosed early and treated with total system removal and tailored antimicrobial therapy. Atypical pathogens cultured from blood, tissue or hardware in patients with CIED infection should be considered pathogens and not contaminants.

KEYWORDS
atypical microorganisms, cardiac implantable electronic device infection, lead extraction

1 | INTRODUCTION

The rate of cardiac implantable electronic device (CIED) infection has increased over the last two decades and is associated with significant morbidity and mortality.[1,2,3] Early recognition and prompt system removal, including lead extraction, are recommended in most situations. Additionally, identification of the causative pathogenic microorganism is critical to guide appropriate antimicrobial therapy.

The vast majority of CIED infections are caused by *Staphylococcal* species (*Staphylococcus aureus and coagulase-negative staphylococci*) and represent between 60% and 80% of cases.[3,4] Not only are staphylococcal CIED system infections highly virulent, but CIED infection secondary to methicillin-resistant staphylococci has become an important cause of CIED infection-related mortality.[5] Other gram-positive cocci such as *Enterococcus* and Streptococcus species, gram-negative bacilli including *Escherichia coli*, *Enterobacter* and *Pseudomonas* species, and fungi such as *Candida albicans*, have previously been reported as pathogens and account for less than 15%-20% of cases.[6] CIED infections associated with atypical pathogens are exceedingly rare and have not been systematically studied. The objective of this study is to characterize the predisposing factors, clinical course, management and outcome in patients with CIED infection secondary to atypical pathogens.

2 | METHODS

2.1 | Subjects

Medical records of all patients who underwent CIED system extraction at the University of Chicago Medical Center between January 2010 and November 2020 were retrospectively reviewed to identify patients with CIED infection. Data collection and analysis was approved by The University of Chicago Institutional Review Board. Demographic data including age, gender and ethnicity as well as clinical characteristics such as, type of CIED, duration of implant, indication for CIED implantation, and underlying comorbidities were collected. Infection specific data such as presenting clinical symptoms, lab investigations, blood, pocket, generator and lead culture results, echocardiographic findings, and outcome and follow-up details were extracted from medical records.

2.2 | Definition of typical and atypical CIED infection

Typical CIED infection was defined as infection due to commonly implicated organisms[3] such as *Staphylococcus aureus and Coagulase negative staphylococcus species*, *Streptococcus* species, *Enterococcus* species, specific *Enterobacterales* (*Escherichia coli*, *Klebsiella* species, *Citrobacter* species, *Enterobacter* species, *Proteus* species, *Serratia* species), *Pseudomonas* species, and *Candida* species.

Atypical CIED infection was defined as infection due a pathogen rarely or previously not associated with CIED infections in humans. This included fastidious organisms such as the *HACEK* group (*Haemophilus species*, *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eeikenella corrodens*, *Kingella kingae*) as well as pathogens rarely identified in CIED infections such as nontuberculous mycobacteria and fungi other than *Candida*. Of note, skin organisms such as *Corynebacterium* species, *Micrococcus* species, or *Cutibacterium* (formerly *Propionibacterium*) species were also considered pathogens given their infrequent association with CIED infections in isolation.

2.3 | Identification of pathogens and antimicrobial management

All patients who presented with CIED infection had a minimum of two sets of blood cultures drawn prior to initiation of antimicrobial therapy. At the time of system removal, all hardware (leads, generator) as well as a swab or tissue from the CIED pocket were sent for culture and sensitivity analysis. An atypical organism was considered pathogenic if it was cultured from blood (minimum one set of blood cultures) or cultured from hardware (explanted generator and/or leads) or if it was the only organism identified in the blood, CIED system component or CIED pocket. This definition was used to distinguish true pathogens from presumed contaminants. Advanced laboratory methods such as 16S Ribosomal DNA sequence analysis as well as matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) were utilized for diagnosis in some patients.

The duration and choice of antimicrobial therapy was determined based on culture and sensitivity results, the presence or absence of positive blood cultures and the presence or absence of lead or valvular vegetations. Infectious disease consultation was obtained in the majority of patients.

2.4 | Data analysis and statistics

Data are expressed as mean and standard deviation, or median and interquartile range as appropriate. The main focus of the report was to characterize CIED infections with atypical organisms. Given the overall rarity of atypical CIED infections, non-parametric statistical tests including Mann-Whitney *U* test and Fisher's exact test were used to evaluate differences in means and proportions, respectively, between those with typical and atypical CIED infections. p-values $< .05$ were considered significant. All analyses were performed using the statistical software STATA v. 13.0 (StataCorp, College Station, Texas, USA).

3 | RESULTS

3.1 | Demographic data

From January 2010 to November 2020, 356 CIED extraction procedures were performed at our center. Of those, 130 (37%) were performed due to CIED infection. Atypical pathogens were identified in

seven (5.4 %) patients. The clinical characteristics of these 130 patients are summarized in Table 1. The majority of the study population consisted of men; approximately 30% of the study population was African-American. Over 50% of the CIED infections occurred in patients with implantable cardioverter-defibrillators (ICD) or cardiac resynchronization therapy with a defibrillator (CRT-D) devices. As expected, the study patients had many cardiovascular comorbidities. While patients with CIED infection due to typical pathogens had a higher prevalence of diabetes mellitus, there were no other major differences between the two groups.

3.2 | Pathogens associated with typical CIED infections

Coagulase-negative staphylococcus was the most commonly isolated pathogen accounting for 51% of cases (n = 66) followed by *Staphylococcus aureus* in 35% (n = 46). Other gram-positive organisms isolated included *Streptococcus* species in 1.5% (n = 2), and *Enterococcus faecalis* in 8% (n = 10). Gram negative organisms such as *Eischerichia coli*, *Enterobacter* species, *Pseudomonas* species, *Serratia* species, and *Klebsiella* species were identified in 12% (n = 16). *Candida* species were isolated in 3% (n = 3). Polymicrobial infection was noted in approximately 19% (n = 25). Only one patient had culture negative CIED infection.

3.3 | Pathogens associated with atypical CIED infections

Seven unique pathogens were identified in seven patients: *Pantoea species* (n = 2), *Kocuria* species (n = 1), *Cutibacterium acnes* (n = 1), *Corynebacterium tuberculostearicum* (n = 1), *Corynebacterium striatum* (n = 1), *Stenotrophomonas maltophilia* (n = 1), and *Pseudozyma ahidis* (n = 1). The clinical details of these and other reported patients with atypical CIED infection due to similar organisms are summarized in Table 2.

3.4 | *Panteoa* species

3.4.1 | Patient 1

A 52-year-old obese man with end stage renal disease and non-ischemic cardiomyopathy presented with a systemic ICD infection with two sets of positive blood cultures growing undifferentiated *Pantoea*. Transesophageal echocardiography (TEE) revealed a 3.5 cm vegetation on his ICD lead. Prior to presentation, he had been treated with intravenous vancomycin and cefepime for 12 weeks without success. He underwent extraction of his CIED system. Hardware cultures grew undifferentiated *Pantoea species* and *Staphylococcus haemolyticus*. Both organisms were sensitive to several antibiotics. He was treated with oral trimethoprim-sulfamethoxazole for 3 months. At 4 months follow-up after his system extraction, the patient had no recurrent signs or symptoms of infection. He refused another ICD implant.

3.4.2 | Patient 2

A 26-year-old man with non-ischemic cardiomyopathy, history of ICD implant 2 years prior to presentation, and severe left ventricular dysfunction (on intravenous milrinone therapy via a peripherally inserted central catheter [PICC]) developed upper respiratory tract infection (URI) symptoms, cough, fever and rigors 3-4 weeks prior to presentation. He denied erythema, pain, or swelling at the PICC insertion site. He was hospitalized and was noted to be in septic shock. The PICC was removed and sent for culture (PICC culture was negative). Two sets of blood cultures grew *Pantoea agglomerans* and he was treated with meropenem for 48 h followed by intravenous ceftriaxone. His blood cultures also grew a yeast (*Pseudozyma ahidis*) which was treated initially with intravenous micafungin. A TEE was performed and was notable for a bicuspid aortic valve without any significant stenosis or regurgitation and a 0.95 cm mobile vegetation on his ICD lead. He subsequently underwent extraction of his single chamber transvenous ICD system which was followed by a 6-week course of intravenous ceftriaxone and oral voriconazole. His ICD lead culture was negative. The patient was discharged home with a wearable defibrillator. At 24 months of follow-up, he continues to do well without any symptoms and signs of infection. He has refused another implant.

3.5 | *Kocuria* species

An 86-year-old man with previous cardiac arrest and ischemic cardiomyopathy presented with erythema, skin thinning and fixation over his CIED pocket, 10 years after initial CRT-D implant (Figure 1). Blood cultures were negative and he had no systemic symptoms. He underwent total system extraction and was treated empirically with intravenous vancomycin and cefazolin. ICD lead culture was positive for *Kocuria species* with no other organisms identified. A source for *Kocuria* infection was not found. He was switched to a 10-day course of oral dicloxacillin and was discharged with a wearable defibrillator. At 6 months of follow-up his pocket area had completely healed. He subsequently underwent another CRT-D implant at an outside hospital and has done well without reinfection.

3.6 | Cutibacterium acnes

A 17-year-old boy with a malignant flecainide, nadolol, and sympathectomy refractory catecholaminergic polymorphic tachycardia phenotype caused by a large deletion in exon three of *RYR2* underwent a dual chamber transvenous ICD implantation.[7] Six weeks later, he reported copious serosanguineous discharge from the ICD incision. He denied any history of fever. The patient was admitted and underwent system removal. He was discharged home on oral augmentin. Hardware and

TABLE 1 Characteristics of patients with CIED infection

	Patients with Typical Pathogens (n = 123)	Patients with Atypical Pathogens (n = 7)	*p* value
Demographics			
Age (years)	65 ± 15	53 ± 25	.19
Men	85 (69%)	7 (86%)	.67
Race			
Caucasian	63 (51%)	3 (43%)	
African American	48 (39%)	2 (28%)	.66
Asian	10 (8%)	1 (14%)	
Clinical characteristic			
CIED dwell time (weeks)	253 ± 228	257 ±192	.80
Ischemic cardiomyopathy	56 (45%)	2 (29%)	.32
Non-ischemic cardiomyopathy	55 (45%)	3 (43%)	.62
ARVC	0	1	.05
Ventricular tachycardia or fibrillation	25 (20 %)	2 (29 %)	.48
Previous open heart surgery	39 (32 %)	1 (14 %)	.30
Complete or high grade AVB	33 (27 %)	0	.12
Sick sinus syndrome	13 (11 %)	0	.47
Congenital heart disease	1 (0.8 %)	1 (14 %)	.10
Valvular heart disease	12 (10 %)	1 (14 %)	.53
Peripheral vascular disease	10 (8 %)	0	.56
Atrial fibrillation	52 (42 %)	3 (43 %)	.63
History of cerebrovascular accident	13 (11 %)	0	.47
Pulmonary hypertension	5 (4 %)	0	.75
Systemic hypertension	73 (59 %)	3 (43 %)	.31
Diabetes mellitus	50 (41 %)	0	.03
Past or current tobacco use	57 (46 %)	4 (57 %)	.60
Chronic obstructive pulmonary disease	23 (19 %)	0	.24
Obstructive sleep apnea	12 (10 %)	1 (14 %)	.53
Laboratory & clinical data			
WBC count at presentation (cells/μL)	8.7 ± 4.6	6.5 ± 1.9	.19
Platelet count at presentation (1000/μL)	212 ± 92	208 ± 129	.53
Glomerular filtration rate (mL/min/1.73m^2)	61 ± 30	60 ± 44	.96
Left ventricular ejection fraction (%)	39 ± 16	42 ± 20	.76
Type of Device			
Permanent pacemaker	36 (30%)	1 (14 %)	
Implantable cardioverter-defibrillator	47 (38%)	3 (43 %)	
S-ICD	1 (1%)	0	
CRT-D	35 (28%)	2 (29%)	.22
Other	4 (3%)	0	
Infection characteristics			
Positive blood cultures	67 (45%)	2 (29%)	.25
Positive hardware cultures	93 (76%)	5 (71%)	.68
Septic shock	22 (18 %)	0	.60
Endocarditis	36 (29%)	4 (57%)	.20
Pocket infection	59 (48%)	4 (57%)	.72
Duration of antibiotic therapy (weeks)	4 ± 2.2	5 ± 2.5	.30
Days between infection diagnosis and extraction	27 ± 53	26 ± 46	.23
Infection-related deaths	22 (18%)	0	1.0

Abbreviations: AVB, atrioventricular block; ARVC, arrhythmogenic right ventricular cardiomyopathy; CIED, cardiac implantable electronic device; WBC, white blood cell; S-ICD, subcutaneous implantable cardioverter defibrillator; CRT-D, cardiac resynchronization therapy with a defibrillator.
Values are n (%), mean ± standard deviation.

TABLE 2 Characteristics of patients with atypical CIED infection

Authors	Age (years)	Gender	CIED dwell time (weeks)	Comorbidities	Type of CIED	WBC Count (10^9/L)	Days between diagnosis and extraction	Endocarditis (lead or valve)	Hardware cultures	Blood cultures	Site culture	Antibiotic sensitivity	Antibiotic therapy utilized
Pantoea species													
Kohli et al	52	M	359	NICM, ESRD	ICD	3.4	131	3.5 cm intracardiac vegetation	RV lead: *Pantoea species* and *Staphylococcus haemolyticus*	Positive	–	Both *Pantoea species* and *Staphylococcus species* were pansensitive.	Vancomycin and Cefepime for 12 weeks followed by oral TMP/SM for 3 months
Kohli et al	26	M	208	NICM (EF 21%) on home milrinone therapy, BAV	ICD	5.7	12	0.95 cm mobile vegetation on ICD lead	–	Positive *Pseudozyma aphidis*	–		Meropenem for 48 h, Ceftriaxone for 6 weeks Micafungin for 9 days, Metronidazole for 7 days
Ajam et al[17]	61	F	<1	NICM, DM, HTN	CRT-D	13	A few days	–	–	–	Positive *Co-infection with Stenotrophomonas maltophilia*)	TMP/SM	TMP/SM for 14 days
Kocuria species													
Kohli et al	86	M	538	ICM, VT, AF, OSA	CRT-D	5.3	7	–	ICD lead	–	–		Vancomycin and cefazolin for 72 h Dicloxacillin for 10 days
Cutibacterium acnes													
Kohli et al	17	M	6	Obesity, CPVT	ICD	9.7	7	–	ICD lead	–	Pocket	Penicillin (S) Moxifloxacin (S)	Cephalexin for 4 days Vancomycin + Cefepime for 7 days Oral amoxacillin for 14 days followed by long term suppressive amoxicillin
Chakour et al[33]	48	M	262	SSS	PPM		12	15 x 8 mm mass on the RV lead)	PPM lead	Positive	–	Penicillin (S) Amoxicillin (S) Erythromycin (S)	IV Amoxicillin X 1 month
Noel et al[34]	74	M	104	AV block, DM, HTN	PPM	15	11	6 x 3 cm mass in the right atrium)	□ (PCR)	Positive	–		Amoxicillin □ clavulanic acid Gentamicin, Amoxicillin□ Rifampicin for 6 weeks

(Continues)

TABLE 2 (Continued)

Authors	Age (years)	Gender	CIED dwell time (weeks)	Comorbidities	Type of CIED	WBC Count (10^9/L)	Days between diagnosis and extraction	Endocarditis (lead or valve)	Hardware cultures	Blood cultures	Site culture	Antibiotic sensitivity	Antibiotic therapy utilized
Santo KRE et al[35]	48	F	52	Ebstein's anomaly	PPM	270		Positive	–	Positive	–		Oral first generation cephalosporin IV Ceftriaxone □ Gentamicin Oral doxycycline IV Vancomycin, IV Daptomycin for 6 weeks
Gorospe L et al[36]	59	M			PPM			Positive	Positive	–	–	Penicillin (S)	UNK
						Corynebacterium tuberculostearicum							
Kohli et al	55	F	3	ARVC, VT		ICD	12	–	RA lead and ICD generator	–	–		Cefepime for 96 h Clindamycin for 2 weeks
						Corynebacterium striatum							
Kohli et al	55	M	270	ICM,LVAD, ESRD	ICD	7.5	8	–	RA and ICD leads and LVAD driveline	–	–		Vancoycin for 6 weeks, Oral Cephalexin (long term prophylaxis)
Melero-Bascones, et al[49]	73	M	312		PPM		28	Positive		Positive	Positive	Penicillin (R) Vancomycin (S)	IV Vancomycin (4 weeks) TMP/SM and Rifampin for 2 weeks
Oliva et al[46]	71	F	8		PPM	11	7	Positive	Positive (Sonication)	Positive (CONS)	Positive (CONS)	Penicillin (R) Cefotaxime (R) Gentamicin (R) Erythromycin (R) Levofloxacin (R) Clindamycin (R) Vancomycin (S) Linezolid (S) Daptomycin (S)	Daptomycin for 4 weeks 7 days Linezolid

(Continues)

TABLE 2 (Continued)

Authors	Age (years)	Gender	CIED dwell time (weeks)	Comorbidities	Type of CIED	WBC Count (10^9/L)	Days between diagnosis and extraction	Endocarditis (lead or valve)	Hardware cultures	Blood cultures	Site culture	Antibiotic sensitivity	Antibiotic therapy utilized
Abi et al[47]	51	M	28	High grade AVB	PPM	5.3		Positive	Positive	Positive	–	Penicillin G (S) Gentamicin (S) Tobramycin (S) Erythromycin (S) Lincomycin (S) Linezolid (S) Chloramphenicol (S) Tetracycline (S) Rifampicin (S) Trimetho-prim/Sulfamethoxazole (S) Ofloxacin (S) Teicoplanin (S) Vancomycin (S) Oxacillin (R) Kanamycin (R) Fosfomycin (R) Fusidic Acid (R)	IV Ciprofloxacin □ Vancomycin for 6 weeks
Guererro et al[48]	78	M	24	DM, CRF	PPM	10	24	Positive	–	Positive	–	Daptomycin (S) Penicillin (R) Cephalosporin (R) Clindamycin (R) Fluoroquinolones (R) Trimetho-prim/Sulfamethoxa Doxycycline (S) Gentamicin (S) Linezolid (S)	Daptomycin for 3 weeks
						Stenotrophomonas maltophilia							
Kohli et al	79	M	100	HTN	PCM	6.3	6	No	PPM Generator, RA and RV lead	–	Positive	Levofloxacin (S) Minocycline (S) Trimetho-prim/Sulfamethoxa (S)	Vancomycin for 48 h Cefepime for 96 h , TMP/SM for 6 weeks

(Continues)

TABLE 2 (Continued)

Authors	Age (years)	Gender	CIED dwell time (weeks)	Comorbidities	Type of CIED	WBC Count (10^9/L)	Days between diagnosis and extraction	Endocarditis (lead or valve)	Hardware cultures	Blood cultures	Site culture	Antibiotic sensitivity	Antibiotic therapy utilized
Takigawa et al[51]	72	F	884	AV block, Chronic refractory middle and external otitis	PCM	6.8	102	17 × 7 mm mobile vegetation on RA lead)	–	Positive	Positive	TMP/SM (S) Minomycine (S) Pazufloxacin (S)	Vancomycin Ceftazidime (no response) TMP/SM Minomycine Pazufloxacin
Aktuerk et al[52]	93	M		CRF, IHD, AF, Dementia, HTN, Polymyalgia Rheumatica (steroids)	PCM			–		–	Positive		
Reynaud et al[53]	81	F	68	HTN, AF, Rhizomelic pseudo-polyarthritis (Steroids), CRF	CRT-P			3 mobile vegetations [<10 mm] on TV)	Positive	–	Positive	Ticarcillin-Clavulanic Acid (R) Cephalosporins (R) Carbapenems (R)	IV TMP/SM Moxifloxacin Died 9 days after device extraction.
Ajam M et al[17]	61	F	Few days	NICM, DM, HTN	CRT-D	13	A few days	–	–	–	□ (Also, *Pantoea calida*)	Trimethoprim-sulfamethoxazole (S)	Trimethoprim-sulfamethoxazoleX 14 days
Rostoff et al[54]	22	M	52	D-TGA s/p Senning procedure, AV block, CHF (NYHA IV)	PCM	5.5	A few days	6 × 16 mm vegetation on LV lead)	Positive	Positive	–	Ticarcillin-Clavulanic Acid (S) Trimethoprim-sulfamethoxazole (R) Ciprofloxacin (R) Aminoglycosides (R) β-lactams (R)	TMP/SM amikacin Died 9 days after surgical device and lead extraction.

Abbreviations: WBC, white blood cell; M, male; F, female; NICM, non-ischemic cardiomyopathy; ESRD, end stage renal disease; ICD, implantable cardioverter defibrillator; RV, right ventricle; E F, ejection fraction; CONS, *coagulase negative Staphylococcus*; S, sensitive; R, resistant; ICM, ischemic cardiomyopathy; VT, ventricular tachycardia; VF, ventricular fibrillation; OSA, obstructive sleep apnea; CRT-D, cardiac resynchronization therapy with a defibrillator; CPVT, catecholaminergic polymorphic ventricular tachycardia; SSS, sick sinus syndrome; PPM, permanent pacemaker; AVB, atrioventricular block; DM, diabetes mellitus; HTN, hypertension; PCR, polymerase chain reaction; ARVC, arrhythmogenic right ventricular cardiomyopathy; RV, right ventricle; RA, right atrium; LVAD, left ventricular assist device; CRF, chronic renal failure; AF, atrial fibrillation; CRT-P, cardiac resynchronization therapy with a pacemaker; D-TGA, D-Transposition of great arteries; NYHA, New York Heart Association; LV, left ventricle; TV, tricuspid valve.

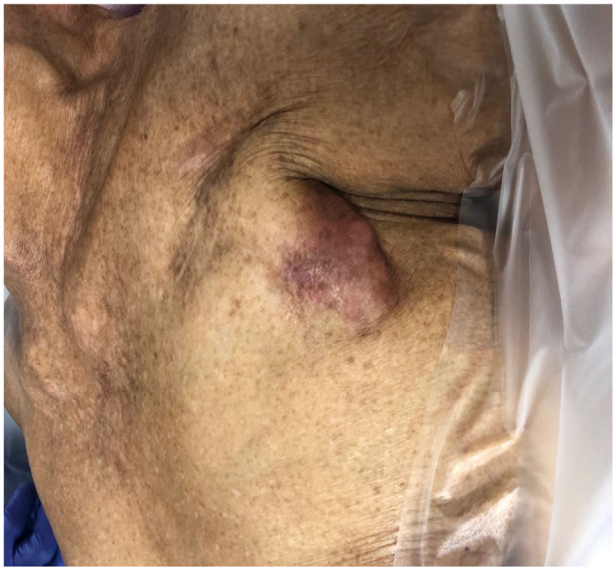

FIGURE 1 Cardiac implantable electronic device (CIED) pocket infection secondary to *Kocuria species*. Erythema, thinning and fixation of the skin overlying the CIED pocket are seen predominantly over the lower lateral border of the CIED pocket. Implantable cardioverter defibrillator (ICD) lead and pocket cultures were positive for *Kocuria species* with no other organisms identified [Color figure can be viewed at wileyonlinelibrary.com]

pocket-tissue cultures grew *Cutibacterium acnes*. He was treated with oral amoxicillin therapy for 14 days which was followed by long term suppressive therapy with the same drug. Over 24 months of follow-up, he has done well without recurrence of infection. Another ICD was implanted on the contralateral side.

3.7 | Corynebacterium tuberculostearicum

A 55-year-old woman with a history of arrhythmogenic right ventricular cardiomyopathy and sustained monomorphic ventricular tachycardia underwent dual chamber ICD implantation in 2006. She underwent pulse generator change in July 2013 during which a capsulectomy was performed and an antibiotic-eluting pouch was utilized. She began to notice worsening pain, swelling, redness, and drainage at the site without any fever 3 weeks after the procedure (Figure 2). She underwent system extraction. The ICD generator and the right atrial (RA) lead both grew *Corynebacterium tuberculostearicum* which was treated with oral clindamycin for 2 weeks. No other organisms were isolated. A subcutaneous defibrillator was implanted 3 days after extraction of the old system. Over 48 months of follow-up, the patient has not had any recurrent signs or symptoms of infection.

3.8 | Corynebacterium striatum

A 55-year-old man with ischemic cardiomyopathy, history of dual chamber ICD implant in 2018, end stage renal disease and left ventricular assist device (LVAD) as destination therapy, presented with atypical chest pain, generalized weakness, and worsening dyspnea for a week. He endorsed tenderness and drainage around the LVAD driveline insertion site. He denied fever. He had a history of chronic LVAD driveline site infection with *Corynebacterium* species and a recent admission for *Corynebacterium striatum* bacteremia that was being treated with oral cephalexin. A TEE was performed and showed a moderate sized mobile echo density on the TV adjacent to the ICD lead. He underwent extraction of the CIED system which was followed by a 6-week course of intravenous vancomycin. Cultures from the RA and ICD leads grew *Corynebacterium striatum*. Long-term oral cephalexin was recommended. The patient died 2 months after the procedure due to intracranial complications resulting from a fall on oral anticoagulation. No recurrent signs or symptoms of infection were reported.

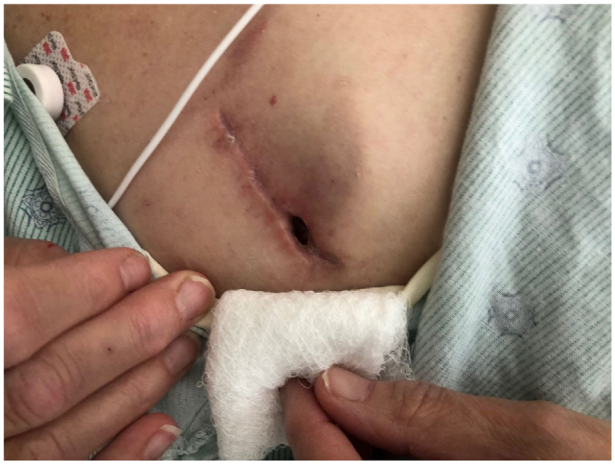

FIGURE 2 Cardiac implantable electronic device (CIED) pocket infection secondary to *Corynebacterium tuberculostearicum*. Discoloration of the skin adjacent to the surgical incision is visible. The lateral border of the incision is open 3 weeks after dual chamber ICD generator change. The implantable cardioverter defibrillator (ICD) generator and the right atrial (RA) lead both grew *Corynebacterium tuberculostearicum* [Color figure can be viewed at wileyonlinelibrary.com]

3.9 | Stenotrophomonas maltophilia

A 79-year-old man with a history of hypertension and complete heart block treated with permanent pacemaker (PPM) implantation in 2017, noted increasing irritation around his pacemaker incision site. He presented with pacemaker erosion and treatment was initiated with intravenous cefepime and vancomycin. He denied any fever or symptoms suggestive of systemic infection. The transvenous PPM system was subsequently extracted and replaced with a leadless pacemaker (Micra, Medtronic, Minneapolis, **Minnesota**, USA). The generator, RA lead and right ventricular (RV) lead cultures grew *Stenotrophomonas maltophilia* which was treated with oral trimethoprim-sulfamethoxazole for 6 weeks with resolution of symptoms. At 12 months of follow-up, he is doing well without any recurrent signs or symptoms of infection.

4 | DISCUSSION

Descriptions of CIED infections with atypical microorganisms are limited to anecdotal case reports and to the best of our knowledge, this is the first study to systematically evaluate the clinical presentation, management and outcome in patients with CIED infection secondary to atypical pathogens.

The main findings in this paper are as follows: (1) Atypical pathogens accounted for 5% of CIED infections over a 10-year period (2) CIED infections secondary to atypical pathogens were associated with a good outcome if diagnosed early and treated with total system removal and tailored antimicrobial therapy. (3) This is the first report of CIED infection associated with *Kocuria* species, *Pseudozyma aphidis*, and isolated *Corynebacterium tuberculostearicum*.

The microbiology of CIED infection has changed over the last two decades. Hussein et al, reported the microbiology of CIED infection in a modern cohort of patients and found a significant rise in CIED infection secondary to methicillin-resistant staphylococcus aureus (MRSA). MRSA infections accounted for 34% of all CIED infections and 49% of all staphylococcal infections; atypical pathogens were found in less than 0.2%, however, an increasing trend was noted during the study period.[6] CIED infection secondary to MRSA was associated with high mortality, especially in elderly patients with bacteremia.[5] A high proportion of culture negative CIED infections which were not further characterized, lack of use of advanced laboratory methods such as 16S Ribosomal DNA sequence analysis and MALDI-TOF MS, and a different geographic location may account for the difference in prevalence of atypical CIED infections reported by Hussein et al and us.[6]

Because CIED infections with atypical pathogens are rare, little is known about their presentation and outcome. Recent advancements in laboratory technology have allowed for microbial identification and diagnosis that was not previously possible. As a result, organisms historically not associated with CIED infections have now been isolated though the use of 16S ribosomal DNA sequencing as well as MALDI-TOF mass spectrometry. This is not unique to CIED infections; atypical pathogens have been identified through these means for multiple other types of infections, expanding our understanding of these organisms as pathogenic and not simple contaminants.[8,9,10]

In our study, both patients with CIED infection due to *Pantoea* species presented with bacteremia. *Pantoea* species, which are members of *Enterobacterales* family, are gram-negative bacilli that are frequently found in soil and vegetation.[11] Recent studies have also reported isolation of *Pantoea* species from the skin of healthy humans.[12] In both immunocompetent and immunocompromised humans, *Pantoea* species are a rare cause of sepsis[13] which at times can be multidrug resistant.[14] One of our patients had no obvious risk factors for infection but the other had an long term PICC line which placed him at higher risk as *Pantoea* species have been associated with central venous catheter-associated infections.[15] Cardiovascular infections with *Pantoea* species are exceedingly rare and only one patient with mitral valve endocarditis[16] and another with CIED pocket infection have been reported to date.[17] Most of the patients with *Pantoea* infection, including the two in our study, have done well following appropriate culture and sensitivity guided antimicrobial therapy. However, care should be exercised while using carbapenems as approximately 21% of *Pantoea agglomerans* isolates were noted to be carbapenem resistant in a recent series.[18]

One of these patients was also co-infected with *Pseudozyma aphidis* which is a rare fungal cause of infection in immunocompromised patients, particularly in those with hematological and oncological disorders. A bloodstream infection via possible gastrointestinal translocation has been suggested as a source in a handful of patients that have been reported. Most of the reported patients responded to either voriconazole, posaconazole, or amphotericin B.[19] CIED infection with *Pseudozyma aphidis* has not been reported to date.

One patient in our series had CIED infection due to *Kocuria* species which has not been previously reported. *Kocuria* species are gram-positive bacteria which are rarely associated with human disease. To date, only 28 patients with *Kocuria kristinae* infection, the most common pathogenic species, have been reported.[20] These include patients with cholecystitis, peritonitis, abdominal abscess, bacteremia, umbilical sepsis, and urinary tract infection.[20,21] Cardiac involvement in *Kocuria* infections is very rare and only four patients with *Kocuria* endocarditis have been reported.[20,21,22,23,24] *Kocuria* species are often sensitive to vancomycin, linezolid, rifampicin, teicoplanin, cefotaxime, ampicillin/sulbactam, minocycline, and meropenem. Initial treatment of *Kocuria* infections should involve parenteral vancomycin in combination with another antibiotic to which the organism is susceptible.[25]

The patient with *Cutibacterium acnes* CIED infection presented with a pocket-only infection. *Cutibacterium acens* is a gram-positive bacterium that forms part of the normal flora of the skin and oral cavity. Although primarily recognized for its role in acne, *Cutibacterium acnes*, can cause a range of postoperative and device-related infections including those of cardiac shunts and prosthetics.[26,27] *Cutibacterium acnes* native valve endocarditis is rare.[28,29,30,31,32] To date, only four patients with *Cutibacterium acnes* mediated CIED infections have been reported.[33,34,35,36] In most of those cases, the infection was indolent, difficult to diagnose and occurred after a long period following device implantation.

Corynebacterium species are gram-positive rods that colonize the skin and mucosal surfaces of humans. They are frequently isolated from clinical specimens and interpretation of their clinical relevance may be difficult. Lipophilic corynebacteria tend to be involved in infections of hospitalized patients and often show multidrug resistance. *Corynebacterium tuberculostearicum* has been associated with wound infection, urinary tract infection, osteomyelitis and mastitis.[37,38,39] The species is often associated with resistance to multiple antimicrobials.[40] To the best of our knowledge, there are no previous reports of *isolated Corynebacterium tuberculostearicum* mediated CIED infection. *Corynebacterium striatum* is an emerging multidrug resistant nosocomial pathogen capable of causing a variety of infections in immunocompromised and hospitalized patients.[41,42] *Corynebacterium striatum* has been associated with both native and prosthetic valve endocarditis and bone and joint infections.[43,44,45] However, CIED infections with *Corynebacterium striatum* are rare with only four patients reported to date.[46,47,48,49] Our patient had a chronic LVAD driveline site infection

and bacteremia which infected the CIED system. The characteristics of all the reported patients with *Corynebacterium striatum* CIED system infection are summarized in Table 2.

Stenotrophomonas maltophilia, a small, aerobic, gram-negative bacillus is a nosocomial pathogen extensively resistant to multiple antibiotics, and is also a rare cause of endocarditis. Because of its resistance to multiple antibiotics, *Sternotrophomonas maltophilia* endocarditis often results in frequent therapeutic failures and carries a high risk of complications and mortality.[50] CIED infections with *Stenotrophomonas maltophilia* are highly unusual with only five patients reported to date.[17,51,52,53,54] The characteristics of these patients are summarized in Table 2.

Our study had several limitations. This was a single center retrospective observational study from a quaternary care center. It is possible that the prevalence of bacterial colonization in the environment and on mucosal and skin surfaces differs between geographic regions. Our results therefore may not be automatically applicable to other geographic regions. Even though we utilized non-parametric methods of statistical analysis, larger multicenter collaborative efforts can provide datasets that lead to more robust comparisons between patients with typical and atypical CIED infections. Lastly, laboratory methods based on 16S ribosomal DNA sequencing as well as MALDI-TOF mass spectrometry were utilized for diagnosis in some but not all patients in our study. Prospective studies have shown that utilization of DNA analysis identified additional microbial species in 43% of patients with culture positive CIED infection and could therefore play a role in diagnosis of difficult to treat or culture negative CIED infections.[55]

5 | CONCLUSIONS

CIED infections with atypical pathogens were rare and associated with good outcome if diagnosed early and treated with total system removal and tailored antimicrobial therapy. Atypical pathogens cultured from blood, tissue or hardware in patients with CIED infection should be considered pathogens and not contaminants. Large multicenter studies are required to further characterize the determinants and outcomes in patients with atypical CIED infections.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Drs. Kohli and Shahab were involved in data collection. Dr. Kohli carried out the analysis and wrote the initial draft. Drs. Shahab, Hazra, Aziz, Beaser, Upadhyay, Tung and Nayak took part in planning, writing, revising, and reviewing the final draft of this manuscript. All co-authors contributed fully in terms of the design of the study, the evaluation of data, the actual manuscript preparation, and the revision and approval of the final submitted manuscript. The corresponding author confirms that all authors have seen and approved the final text.

DATA AVAILABILITY STATEMENT

Some of the data underlying this article are available in the article. The authors will be happy to share the complete dataset upon request.

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