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Cross-sectional Study

Brucella cardiac implantable electronic device infection: A single-center case series

Fatehi Elzein [a,*], Eid Alsufyani [a], Yahya Al Hebaishi [b], Mohammed Mosaad [b], Moayad Alqurashi [a], Ahmed Al Fagih [b]

[a] Infectious Diseases Unit, Prince Sultan Military Medical City, P.O. Box 7897, Riyadh, 11159, Saudi Arabia
[b] Prince Sultan Cardiac Center, Riyadh, Saudi Arabia

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ABSTRACT

Background: Cardiac implantable electronic devices (CIEDs), including implantable cardiac defibrillators, pacemakers, and cardiac resynchronization therapy devices, are lifesaving. However, device infections can lead to morbidity and mortality. **The aim** of this study was to describe the outcome of *Brucella* CIED infections treated at our center, and to identify risk factors for *Brucella* infection in patients with CIEDs. **Study Settings**: Single-center study, Prince Sultan Military Medical City, Riyadh, KSA.

Methods: This case series included all *Brucella*-related CIED infections treated at a tertiary care center between 2009 and 2020. Data on patient demographics, clinical manifestations, predisposing factors, microbiology, treatment regimens, and outcomes were reviewed.

Results: Fifteen patients met the *Brucella* CIED infection criteria. The mean age was 62.2 years, and 80% were males. Common comorbidities included hypertension (73%), diabetes mellitus (67%), ischemic heart disease (47%), and chronic kidney disease (60%). The mean time to infection following the device implantation was 4.8 years (range: 5 months to 13 years). Fever was detected in 53% of patients, device site swelling in 47%, purulent discharge in 33%, and pain in 27%. The blood culture and serology results were positive in 73% and 80% of patients, respectively. All patients were treated with antibiotics, and the infected device was removed. Seven (46.6%) patients underwent reimplantation with a new device. One patient with dual *Brucella* and methicillin-sensitive *Staphylococcus aureus* infection died, and the other 14 patients recovered, with no recurrent infections reported to date.

Conclusion: Brucella should be considered in CIED infections, particularly in endemic areas. Proper treatment and device removal are essential for good outcomes.

Researchregistry 6959

1. Introduction

Brucellosis is the most common zoonotic infection and is caused by an intracellular nonmotile gram-negative aerobic coccobacillus. Infection is frequently acquired by consuming unpasteurized milk, direct contact with infected animals, and inhaling or ingesting raw animal products [1]. Most patients present with an acute febrile illness, with or without organomegaly. However, chronic infection is detected in approximately 14% of cases, of which approximately 26% are osteoarticular brucellosis and 5% are neuroborreliosis. Although the incidence of Brucella endocarditis is rare, only occurring in 0.7–2% of cases of brucellosis, Brucella endocarditis accounts for 80% of *Brucella*-related deaths [2,3].

Cardiac implantable electronic device (CIED) infection is associated with increased all-cause mortality and morbidity and decreased quality of life [4,5]. The incidence of CIED infection is 1–2% over the lifetime of a device [6]. The risk of re-infection in patients with a device infection history is high [7], with incidence rates of up to 12.12/1000 device-years after device replacement, underscoring the importance of infection control measures in preventing primary infections. Of these, antibiotic prophylaxis decreases the re-infection rate by 70% [7]. *Brucella* CIED infections are extremely rare. In a 30-year review including

Abbreviations: CIED, cardiac implantable electronic device; MSSA, methicillin-sensitive *Staphylococcus aureus*.

* Corresponding author.
E-mail address: felzein@psmmc.med.sa (F. Elzein).

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5287 patients with a CIED, only 23 patients (0.38%) developed endocarditis, and only one patient had a *Brucella* infection requiring device and lead removal with antibiotic therapy [8]. A recent study from the Middle East, an area endemic for brucellosis, found only 22 CIED infections over 17 years, and only one case of *Brucella melitensis* CIED infection [9].

2. Methods

This was a single-center retrospective cohort study conducted in a tertiary level cardiac care center in Saudi Arabia. All patients diagnosed with *Brucella* CIED infection who were treated at the center between 2009 and 2020 were included. Patients with other CIED infections were excluded because they were followed up in other referral centers and had incomplete data. Data were collected from the medical records, infectious disease datasheets, the electrophysiology laboratory and echocardiography database, and microbiological records. The data included demographic characteristics, risk factors, clinical presentation, laboratory investigations, echocardiographic features, and microbiological findings, including *Brucella* serology and blood cultures, the treatment course (medical and surgical), and outcomes. The device infection was categorized as lead infection, pocket site infection, or endocarditis. A pocket site infection was identified when local signs of inflammation at the device pocket were observed, including erythema, warmth, fluctuant swelling, wound dehiscence, erosion, tenderness, or purulent discharge. The diagnosis of CIED endocarditis was based on the Duke criteria [10], and a diagnosis of *Brucella* infection was based on bacterial isolation in blood or tissue cultures or a positive *Brucella* serology. An immunocapture assay for detecting anti-*Brucella* antibodies using the *Brucella abortus* antigen was performed using Brucellacapt® (Vircell Microbiologists, Granada, Spain). Titers of $\geq$1/320 were considered positive. The data was collected and reported in line with STROCSS criteria [11].

The study was approved by the hospital institutional review board. Informed consent was waived due to the retrospective nature of the study.

3. Results

A total of 134 cases of device-related infection were diagnosed in or referred to the center for device removal and were included in the analysis, of which 11.1% (15/134) were associated with brucellosis. Table 1 outlines the demographics, clinical manifestations, predisposing factors, microbiology, treatment regimens, and outcomes of the brucellosis patients. The mean age was 62.2 (range: 49–88 years), and 80% were male. The mean time to infection following device implantation was 4.8 years (range: 1–13 years). Fever was detected in 53% of patients, device site swelling in 47%, discharge in 33%, pain in 27%, and anemia in 27%. The mean C-reactive protein level and erythrocyte sedimentation rate were 36.3 mg/L and 30.2 mm/h, respectively.

Blood culture and serology results were positive in 73% and 80% of patients, respectively. Four patients had a positive *Brucella* culture from the pocket site (Table 2). Only 60% of patients had a risk factor for brucellosis, such as animal contact or raw milk ingestion, recorded. One patient had concomitant methicillin-sensitive *Staphylococcus aureus* (MSSA) bacteremia. The most commonly infected CIEDs were cardiac resynchronization therapy defibrillators and implantable cardioverter defibrillators, while pacemakers were the least common type of CIED infected. Most patients (67%) had combined pocket and lead infection endocarditis, and five had infection at only one of the two sites. In one patient, the pocket site culture was positive, but the blood culture and serology tests were negative. Tricuspid valve endocarditis was detected in one patient, and extracardiac complications were reported in two patients with Brucella spondylodiscitis.

The most common treatment regimens were gentamycin, doxycycline, and rifampicin, and gentamycin, doxycycline, and cotrimoxazole.

Table 1
Demographic and clinical features of brucella CIED infection.

Characteristic	Number/(%)
Age [mean], range	62.2 (49–88) years
Male	12 (80)
BMI [mean]	25 (20.5–36.8)
Diabetes	10 (66.6)
Hypertension	11 (73.3)
IHD	7 (46.6)
Chronic kidney disease including dialysis	9 (60)
Previous history of Brucellosis	1 (6.6)
Risk factor for Brucella	9 (60)
Clinical features	
Mean time to device infection	4.8 (1–13years)
Fever	8 (53.3)
Anemia	4 (26.6)
Pain at site of device	4 (26.6)
Swelling of site of device	7 (46.6)
Discharge from the site	5 (33.3)
Dyspnea	2 (13.3)
Fatigue	3 (20)
Night sweat	2 (13.3)
Anorexia	1 (6.6)
Weight loss	1 (6.6)
Arthralgia	1 (6.6)
Average ESR	30.2 mm/h
Average CRP	36.3 mg/l
Type of CIED	
PM	3 (20)
ICD	5 (33.3)
CRT-D	7 (46.6)
Pocket site infection only	3 (20)
Lead endocarditis only	2 (13.3)
Pocket site and lead endocarditis	10 (66.6)
Valve involved	1 (6.6)
Management	
Removal of device	15 (100)
Re-implant of new device	7 (46.6)
Mean follow up	40 months(9.0–77.4)
Mortality	1 (6.6)

Abbreviations: CIED: cardiovascular implantable electronic devices, BMI: Body Mass Index, IHD: Ischemic heart disease, PM: Pacemaker, ICD: Implantable Cardioverter Defibrillator, CRTD: cardiac resynchronization therapy-defibrillator. ESR: Erythrocyte sedimentation rate. CRP: C-reactive protein.

Most patients (67%) were treated for 12 weeks, but some were treated for longer (Table 3). The implant was removed in all patients, and only 47% (7/15) had reimplantation. Only one patient (with concomitant MSSA bacteremia) died. None of the 14 surviving patients have had a recurrent *Brucella* CIED infection to date, after a mean follow-up period of 40 months (range: 9.0–77.4 months).

4. Discussion

To our knowledge, this is the largest case series of *Brucella*-related CIED infection. Most previous reports of *Brucella* CIED infection have been single case reports. In this study, *Brucella* was responsible for 11.1% of the CIED infections. This is a surprisingly high number as only 13 cases have previously been described in the literature (**Table 4**). Multiple factors may have contributed to this high incidence rate. Despite the declining incidence of brucellosis in certain parts of Saudi Arabia, the incidence rate remains high, particularly among adults aged 40–49 years [12,13]. It is noteworthy that a lack of a history of exposure to *Brucella* does not rule out the possibility of brucellosis. Therefore, in contrast to other centers, at our center all patients with CIED infection are routinely tested for brucellosis. Additionally, cardiac device use is increasing in Saudi Arabia, and 400–500 devices are implanted at the center annually. Moreover, the center is a national referral center for laser lead extraction of infected CIEDs, and so receives referrals of patients with CIED infections from other hospitals throughout the country.

Most patients in this study were middle-aged men. As in previous

Table 2
Diagnosis and treatment of CIED infection.

#	Blood culture	Pocket site culture	Serology	Lead IE	Antibiotic	Duration	Out come
1	Pos.	Neg.	1:1280	Yes	AG, Doxy, SXT	3 M	Missed F/U
2	Pos.	Neg.	1:10240	Yes	AG, Doxy, SXT	3 M	Cured
3	Pos.	Neg.	1:20480	Yes	AG, Doxy, SXT	3 M	Cured
4	Pos.	Neg.	1:10240	Yes	AG, Doxy, Rif	3 M	Cured
5	Pos.	Pos.	1:10240	No	AG, Doxy, Cipro	3 M	Cured
6	Pos.	Pos.	1:10240	No	AG, Doxy, Rif	5 M	Cured
7	Pos.	Pos.	1:10240	Yes	AG, Doxy, Rif	3 M	Cured
8	Neg.	Neg.	1:10240	Yes	AG, Doxy, Rif	3 M	Mortality
9	Neg.	Neg.	1:10240	Yes	AG, Doxy, Rif	3 M	Cured
10	Neg.	Neg.	1:320	Yes	Treated in primary center	NA	Cured
11	Pos.	Neg.	1:10240	Yes	AG, Doxy, SXT	4 M	Cured
12	Pos.	Neg.	1:10240	Yes*	AG, Doxy, Cipro	4 M	Cured
13	Pos.	Neg.	Negative	Yes	Treated in primary center	NA	Missed F/U
14	Pos.	Neg.	Negative	Yes	AG, Doxy, Rif	3 M	Cured
15	No	Pos.	1:160	No	AG, Doxy, SXT	3 M	Cured

Abbreviations: CIED: cardiovascular implantable electronic devices, IE: Infective endocarditis, AG: Aminoglycosides, SXT: Co-trimoxazole, Cipro: Ciprofloxacin, Rif: Rifampicin, F/U: Follow up, *Tricuspid valve endocarditis, NA: Not available.

Table 3
Type of device, indication, timing of infection and management.

#	Primary indication for device	Device Type	Time to infection from implant	Explanted	Re-implant	Time to Re-implant
1	secondary prevention	ICD	1 Y	Yes	NO	
2	primary prevention	ICD	5 M	Yes	No	
3	primary prevention	CRTD	7 Y	Yes	No	
4	primary prevention	CRTD	4 Y	Yes	No	
5	primary prevention	ICD	3 Y	Yes	Right side	2 Months
6	complete heart block	PM	13 Y	Yes	INTRACARDIAC	16 Days
7	primary prevention	CRTD	4 Y	Yes	Right side	3 Years
8	primary prevention	CRTD	5 Y	Yes	NO	
9	complete heart block	PM	4 Y	Yes	INTRACARDIAC	8 Days
10	primary prevention	ICD	11 Y	Yes	Right side	5 Months
11	primary prevention	CRTD	3 Y	Yes	NO	
12	primary prevention	CRTD	5 Y	Yes	NO	
13	primary prevention	CRTD	2 Y	Yes	NO	
14	complete heart block	PM	8 Y	Yes	Right side	1 Month
15	primary prevention	ICD	2 Y	Yes	Right side	1 Month

Abbreviations: PM: Pacemaker, ICD: Implantable Cardioverter Defibrillator, CRTD: cardiac resynchronization therapy-defibrillator.

studies, hypertension, diabetes mellitus, ischemic heart disease, and chronic kidney disease were the major predisposing factors. CIED may present as a pocket site infection or lead endocarditis with or without bacteremia. Occasionally, systematic manifestations occur without focal signs or bacteremia [5]. In this study, over half the patients had *Brucella* infection at multiple sites. Two patients had an extracardiac infection with complicated spondylodiscitis, which underscores the importance of identifying all the infection sites. Positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with computed tomography (^{18}F-FDG PET/CT)is useful for detecting endocarditis and distant infections. The sensitivity, specificity, and overall diagnostic accuracy of ^{18}F-FDG PET/CT for CIED infection are estimated to be 87%, 94%, and94%, respectively [14].

Staphylococci, either coagulase-negative or *Staphylococcus aureus,* account for 60–80% of CIED infections [15]. However, brucellosis is extremely rare, despite remaining an important pathogen to consider in endemic areas [16]. Both *Brucella* and staphylococci are capable of multilayered biofilm formation [17]. Several *Brucella* proteins, including SP41, are involved in the adhesion to different cell types or the extracellular matrix [18]. As a result, *Brucella* readily binds to collagen, fibronectin, vitronectin, and other extracellular matrix proteins. Biofilm formation and the intracellular location of *Brucella* species account for the chronicity of infection and the need for device extraction, together with prolonged antibiotic treatment. Brucella endocarditis requires prolonged treatment, with most patients receiving antibiotics for 3–6 months [19]. Device extraction followed by reimplantation is essential [19]. A study reported that the mortality rate for Brucella endocarditis patients was 32.7% in a group that was provided only medical therapy compared to 6.7% in the group provided medical and surgical therapy ($p < 0.001$) [20]. Therefore, all devices should be extracted within 72 h to lower mortality and decrease the hospital stay length.

In this study, one patient had a dual *Brucella* and MSSA bacteremia. Dual *Brucella* and other bacterial endocarditis have been described previously [21]. *Streptococcus viridans* and *Coxiella burnetti* have also been reported in patients with Brucella endocarditis, highlighting the importance of diagnosing *Brucella* infection in predisposed patients in endemic areas, even if other organisms are isolated. Both *Brucella* blood or tissue culture and *Brucella* serology should be performed if an infection is suspected. While most patients in this case series were positive on both blood culture and serology, three patients had culture-negative, serology-positive brucellosis, and a further three patients had culture-positive, serology-negative brucellosis. In one patient, both blood culture and serology tests were negative, and the diagnosis was established only on the pocket site tissue culture. These cases underscore the importance of testing cultures from multiple sites in all patients.

4.1. Limitations

Our study has several limitations. The study was retrospective and was conducted at a single specialized center. This specialized nature of the center and referral of patients from other hospitals could have contributed to the high number of cases. Patients with other bacterial infection were not included so we were unable to compare risk factors for infection and outcome in patients with *Brucella* CIED infection

Table 4
Published articles on CIED Brucella Infection.

#	Articles	Year	Age (Y)/ G	device Type	Infective Endocarditis	Blood Culture	Pocket site culture	serology	Time to infection	Removal	Reimplant	Abx	Duration	Out come
1	Dhand et al. (31)	2007	66 M	ICD	No	Neg.	Pos.	NA	2.5 Y	Yes	1 Week	AG/D/ Cip	6 Weeks	cured
2	Jamil (32)N et al.	2018	82 M	PM	Yes	Neg.	Pos.	NA	2 Y	Yes	1 Week	AG/D/Rif	12 Weeks	cured
3	Tsyba (33) et al.	2018	41 M	PM	Yes	Neg.	Pos.	Pos.	8 Y	Yes	No	AG/D/Rif	12 Weeks	cured
4	Dourakis et al. (34)	2007	70 M	PM + TV	Yes	Pos.	Neg.	Pos.	7 Y	Yes	Same time	D/Rif/ Cip	12 Weeks	cured
5	Al-Adsani et al. (35)	2018	70 M	PM	Yes	Pos.	Neg.	NA	1 Y	No	No	AG/D/ Ri/B	12 Weeks	cured
6	Ibrahima et al.(36)	2019	52 F	PM	NA	Neg.	Pos.	Pos.	NA	Yes	No	AG/D/Rif	12 Weeks	cured
7	de la Fuente et al.(37)	1997	63 M	PM	No	Neg.	Pos.	Neg.	1.4 Y	Yes	1 Week	AG/D/Rif	6 Weeks	cured
8	Gungor O et al.(38)	2012	61 M	PM	No	Pos.	Pos.	NA	2 Y	Yes	No	D/Rif	6 Weeks	cured
9	Elmardi et al.(15)*	2016	54 F	CRTD	No	Neg.	Neg.	Pos.	7 Y	Yes	No	Unknown	Unknown	cured
			52 M	ICD	No	Neg.	Neg.	NA	1 Y	Yes	No	AG/D/B	Unknown	cured
10	Almajed et al.(14)	2010	38 M	PM	Yes	Pos.	Neg.	Pos.	20 Y	Yes	No	D/Rif	6 Weeks	cured
11	Miragliotta et al.(39)	2005	70F	PM	No	Pos.	Pos.	Pos.	4 Y	Yes	Same time	Min/Rif/ Cipro	12 Weeks	cured
12	Ulkar et al. (40)	2001	68 M	PM	No	Neg.	Neg.	Pos.	8 Y	Yes	Unknown	Unknown	Unknown	Cured

Abbreviations: Y: Year, G: Gender, Abx: Antibiotic, M: male, F: Female, PM: Pacemaker, ICD: Implantable Cardioverter Defibrillator, CRTD: cardiac resynchronization therapy-defibrillator, TV = Tricuspid valve, AG: Aminoglycoside, D: Doxycycline, R: Rifampicin, Min: Minocycline, Cipro: Ciprofloxacin, B: Bactrim, NA: Not available. Pos. = Positive, Neg. = Negative,* Included in the current study.

compared to other types of CIED infection.

5. Conclusion

Brucella CIED infection is infrequent yet increasing and should be considered in all patients living in or visiting endemic areas, particularly in individuals with negative cultures for other organisms. The presence of other bacterial isolates should not rule out a *Brucella* diagnosis, as dual infection can occur. Prompt removal of the device and appropriate antibiotic therapy improve the prognosis. Patients with CIEDs living in endemic areas ought to be informed of the risk of *Brucella* CIED infection and advised how to avoid contracting brucellosis.

Provenance and peer review

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Ethical Approval

Ethical approval was obtained from PSMMC ethical committee.

Consent

Consent was waved in view of retrospective nature of the study.

Author contribution

Dr. Elzein, formed the study concept, revised the data, interpreted results and wrote the manuscript.

Dr. Ahmed Al Fagih and Dr. Yahya Al Hebaishi were the physicians following the patients and contributed to the manuscript writing and revisions. Dr. Mohammed Mosaad Collected, analysed the data and revised the manuscript.

Dr. Eid Alsufyani collected, analysed, and tabulated the data. He contributed to writing and revising the manuscript.

Registration of research studies

1. Name of the registry: Research Registry.
2. Unique Identifying number or registration ID: *researchregistry6959*.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry#home/

Guarantor

Dr Fatehi E Elzein.

Declaration of competing interest

No conflict of interest.

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