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Original Research Article

Microbiology of Cardiac Implantable Electronic Device Infections in Saudi Arabia

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Abstract

***Background and Objectives*:** The rates of Cardiac implantable electronic device (CIED) infections are increasing worldwide due to the increased use of these devices. (CIED) infection is a serious complication that is associated with increased mortality, morbidity and healthcare costs. There is a need to investigate data on the microbiology of CIED infections since it is poorly documented in Saudi Arabia. We aimed to determine microbiological findings of CIED infections in our region. ***Methods and Results*:** The study was carried out in cardiology departments at different centers in Saudi Arabia. Our population consisted of all patients with device-related infections over a period of eleven years from January 2009 to December 2020 .It was resulting in 137 patients with device infection. Blood cultures and device material swabs were obtained. *Staphylococcus aureus* was the most common isolated pathogen (37.2%). particularly, coagulase-negative *Staphylococcus aureus* in 15.3% of cases, Methicillin-susceptible *Staphylococcus aureus* (MSSA) in 13.9% of cases and Methicillin-resistant *Staphylococcus aureus* (MRSA) in 8% of cases. *Brucella* accounted for 9.5% of cases. Negative cultures of CIED infections seemed to be a critical issue over the studied years. ***Conclusion*:** *Staphylococcus aureus* was the most frequently isolated pathogen and *Brucella* is a considerable pathogen for CIED infections in our country.

Keywords: Cardiac Implantable Electronic Device, Pacemaker, Defibrillator, CIED Infection, CIED Microbiology, retrospective study.

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1. INTRODUCTION

The use of cardiac implantable electronic devices (CIEDs) continues to grow worldwide [1-4]. The rate of device implantations is increasing with the aging of the general population, the increase in the number of patients with heart diseases, the technological advances of these devices, and expanding of clinical indications [5, 6]. Although the use of these devices enhances outcomes in patients with cardiovascular disease, it is associated with critical complications including infections [7].

Device-related infection constitutes a worrisome risk. Infections are increasing worldwide for all device types, partly related to the growing number of CIED implants due to widening indications, technological advancements of these devices, aging of the general population and increasing numbers of generator replacements [8-10].

CIED infection is a serious complication that is associated with increased mortality and morbidity as well as increased healthcare costs [11, 12]. This is due to the treatment of infections which involves potential risks including device removal and replacement, complications of long-term vascular access, adverse antibiotic reactions, healthcare- associated infection, and involvement of antimicrobial-resistant microorganisms [13, 14].

Cardiac implantable electronic device (CIED) infection may be pocket infection that defined as an

infection limited to the pocket of the device and is clinically suspected in the presence of local signs of inflammation at the generator pocket, including erythema, warmth, pain and swelling, adherence of skin to the device, and erosion of skin with a draining sinus [13, 15-17] or infective endocarditis that defined as infection extending to the electrode leads, cardiac valve leaflets or endocardial surface and causing bloodstream infection and/or endocarditis. It is clinically confirmed by imaging valvular or lead vegetations in more than one echocardiographic plane, and positive blood and/or lead tip cultures [13, 15-17]. The modified Duke criteria [18] and the ESC 2015 criteria [19] are the standardized diagnostic tool for CIED endocarditis.

Patients may become infected at the time of implantation or within 6 months of the most recent device-related procedure and this is described as early CIED infection, or they may get infected after 6 months or later after the most recent device-related procedure and this is described as late CIED infection.

The aim of this study was to describe the microbiological findings of the CIED infections observed at different centers in Saudi Arabia during a period of an eleven years.

2. METHODOLOGY

Study Population:

It is a retrospective cohort study carried out in cardiology departments at different centers in Saudi Arabia. Our population consisted of all patients with device-related infections, of both gender and all ages, over eleven years from January 2009 to December 2020. They were selected among CIED implantation procedures, both first implantation and reoperation.

CIED implantation procedures in Saudi Arabia are standardized through a national referral program. All centers adhere to these standards. All centers used preoperative antibiotics for patients undergoing CIED implantations or reoperations. Local guidelines determined the type and dosage of antibiotics.

The diagnosis of CIED-related infection was confirmed by clinical examinations associated with laboratory examinations. Both infection types, pocket infection and systemic infection were included. Local infection was defined as an infection limited to the pocket of the device and was clinically suspected in the presence of local signs of inflammation at the generator pocket, including erythema, warmth, pain and swelling, adherence of skin to the device, and erosion of skin with a draining sinus, as previously described [13, 15-17] infective endocarditis was defined as infection extending to the electrode leads, cardiac valve leaflets or endocardial surface and causing bloodstream infection and/or endocarditis. It was clinically confirmed by imaging valvular or lead vegetations in more than one echocardiographic plane, and positive blood and/or lead tip cultures [13, 15-17]. The modified Duke criteria [18] and the ESC 2015 criteria [19] were used as the standardized diagnostic tool for CIED endocarditis.

Cultures were obtained from blood, device pocket swab, extracted lead tips and any attached fibrotic tissue and before the extraction procedures and before the initiation of antibiotic therapy where possible from all infected patients.

Treatment of patients generally followed published practice guidelines and physician discretion [17]. While most patients had extraction of all hardware of the device by either laser-assisted device removal, percutaneous or open surgical means, some were treated with only local debridement or chronic antibiotic suppression. Patients received antibiotic therapy guided by antimicrobial susceptibilities.

The study was approved by Biomedical Ethics Unit at King Abdulaziz University Hospital.

Data Collection:

An extensive review of the medical files of all included patients that developed infection was performed. Data were obtained from 3 centers in Saudi Arabia. The data recorded were defined and comprised of:

- **Clinical data:** Patient's demographics, age at implant, baseline rhythm and an indication of device implant, type of device, manufacturer, type of procedure, implant location, implant time (skin incision, to skin closure), peri-operative antibiotics, an outcome, at last, follow up, hospital stay and mortality.
- **Data related to devising infection:** Culture result, organism isolated and sensitivity profile, antibiotic treatment (type and duration), the timing of device extraction, and outcome.

Statistical Methods

Data are presented as mean+SD, number, percentage, or odds ratio (OR) with a 95% confidence interval (CI). Mann-Whitney tests and Chi-square tests were used to compare categorical and continuous variables. All statistical analyses were performed using IBM SPSS for windows ver.24 statistics software. P value of ≤ 0.05 was considered statistically significant.

3. RESULT

Epidemiology:

The study included a total of 137 patients who had CIED infection, of whom 75.2% were male patients and 24.8% were female patients. A total of 56 patients received an ICD system (40.9%), 41 patients received an PPM system (29.9%), 36 patients received a CRT-D system (26.3%), and only 4 patients received a CRT-P

system (2.9%). The mean (±SD) age of patients was 53±16 years. Among 137 patients with CIED infection, 87 (%63.5) patients had chronic kidney disease, 82 (59.9%) patients had diabetes mellitus, 89 (65%) patients had hypertension and 59 (43.1%) patients had coronary artery disease. The majority of the participants with infection had a pocket infection (73.7%) whereas endocarditis occurred in 68 patients (49.6%). 94 patients had infection after the first CIED implantation with a percentage of 68.6%, whereas 43 patients had infection after replacement with a percentage of 31.4%. Preop antibiotics were obtained in all patients before implanting. The median time from the last surgical intervention involving the device to the onset of infection symptoms in all operations was 730 days. The median length of hospitalization was 27±23 days. Moreover, most of the patients had positive blood cultures (64.2%) and the most common isolated organisms were coagulase-negative Staphylococcus aureus (15.3%), and Methicillin-susceptible Staphylococcus aureus (13.9%). In 34.3%, microbial data were unrevealing (negative cultures) (table 1).

Table 1: Characters of patients with device infections (n=137).

Parameter		**Freq (%)/ Mean±SD**
Age		58±16
Sex	Female	34 (24.8%)
	Male	103 (75.2%)
BMI		29.4±6.9
CKD	Not found	50 (36.5%)
	Found	87 (63.5%)
DM	Not found	55 (40.1%)
	Found	82 (59.9%)
HTN	Not found	48 (35%)
	Found	89 (65%)
CHD	Not found	78 (56.9%)
	Found	59 (43.1%)
Type of Device	ICD	56 (40.9%)
	CRT-D	36 (26.3%)
	CRT-P	4 (2.9%)
	PPM	41 (29.9%)
Denovo/repeated	Denovo	94 (68.6%)
	Repeated	43 (31.4%)
Pocket	No	36 (26.3%)
	Yes	101 (73.7%)
IE	No	69 (50.4%)
	Yes	68 (49.6%)
Received preop antibiotics	Yes	137 (100%)
Duration from implantation till infection		38.2±44.1
Blood culture	Negative	49 (35.8%)
	Positive	88 (64.2%)
Vegetations on echo	None	71 (53%)
	Lead	57 (42.5%)
	Valvular	6 (4.5%)
hospital stay in Days		27±23
Mortality	No	130 (94.9%)
	Yes	7 (5.1%)

Microbiology:

In this cohort, the most common isolated organism that was identified in the majority of CIED infectionswas Staphylococcus aureus (37.2%). Of this, coagulase-negative Staphylococcus aureus was more commonly observed (15.3%) than other organisms. Methicillin-susceptible Staphylococcus aureus (MSSA) was the pathogen in 13.9% of CIED infections and Methicillin-resistant Staphylococcus aureus (MRSA) accounted for 8% of all CIED infections. However, Brucella was the pathogen in 9.5% of CIED infections as the third most commonly isolated organism.

In 34.3% of infections, patients had no bacterial or other micro-organism growth from all tested cultures (negative cultures).

Gram-negative bacteria were identified in 21.8% of CIED infections in this cohort as the following percentages: Klebsiella pneumoniae (5.8%), Pseudomonas aeruginosa (5.8%), Acinetobacter baumannii (2.2%), Escherichia coli (1.5%), Serratia

marcescens (1.5%), Enterobacter cloacae (1.5%), Aeromonas sobria (0.7%), Enterobacter aerognes (0.7%), Morganella morganii (0.7%), Proteus mirabilis (0.7%), and Salmonella enteritidis (0.7%). The remaining pathogens in patients with CIED infections were related to Candida Albicans (0.7%), Enterococcus faecalis (0.7%), Group B streptococcal (0.7%), and Staphylococcus epidermidis (0.7%). Table 2 and Figure 1 summarize the distribution of isolated organisms in CIED infections.

The trends of microorganisms in CIED infections over time are shown in Figure 2. the proportions of CIED infections related to negative cultures seem to be a critical issue over the period time from 2009 to 2020. There was an increase in the proportions of CIED infections related to coagulase-negative Staphylococcus aureus from an average of 0.7% in 2010 to 2.9% in 2014. After a decrease to 0.7% in 2015, it then reached the highest level of 3.65% in 2016 then decreased to 0.7% in 2020. As for the proportions of CIED infections related to Methicillin-susceptible Staphylococcus aureus, there was an increasing trend detected to a peak of 3.65% in 2015. However, in 2020, the percentage decreased to 0.7%. Notably, there was another peak of 2.9% in 2018. Methicillin-resistant Staphylococcus aureus was detected only in 2013, 2015, 2018 and 2019 with an average of 0.7%, 2.2%, 2.9%, and 1.46% respectively. The proportions of CIED infections related to Brucella increased from 0 in 2009–2013 to a peak of 2.2% in 2015, and this decreased in 2016 to only 0.7%. In 2017, there was an increase to 2.2%, however, it decreased over the following time reaching 1.46% in 2019. The proportions of other microorganisms did not seem to have significant change over the period time, between 2009 and 2020, (Figure 2).

Table 2: Frequency & percentages of isolated organisms (n=137).

Isolated organism	**Freq/ (%)**
Acinetobacter baumannii	3 (2.2%)
Aeromonas sobria	1 (0.7%)
Brucella	13 (9.5%)
Candida Albicans	1 (0.7%)
Coagulase negative*Staphylococcusaureus*	21 (15.3%)
Escherichia coli	2 (1.5%)
Enterobacter aerognes	1 (0.7%)
Enterobacter cloacae	2 (1.5%)
Enterococcus faecalis	1 (0.7%)
Group B streptococcal	1 (0.7%)
Klebsiella pneumoniae	8 (5.8%)
Morganella morganii	1 (0.7%)
Methicillin-resistant *Staphylococcus aureus*	11 (8%)
Methicillin-susceptible *Staphylococcus aureus*	19 (13.9%)
No Growth	47 (34.3%)
Proteus mirabilis	1 (0.7%)
Pseudomonas aeruginosa	8 (5.8%)
Salmonella enteritidis	1 (0.7%)
Serratia marcescens	2 (1.5%)
Staphylococcus epidermidis	1 (0.7%)

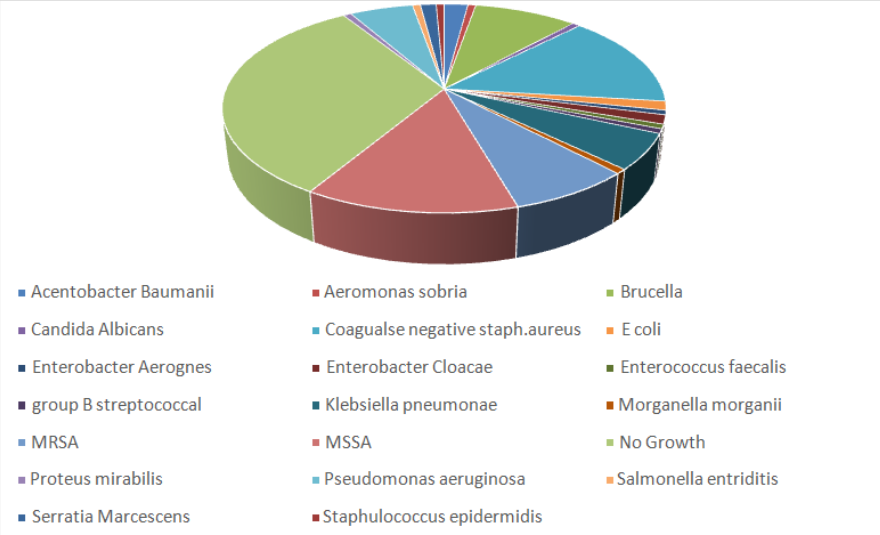

Figure 1: Isolated organisms of CIED infections

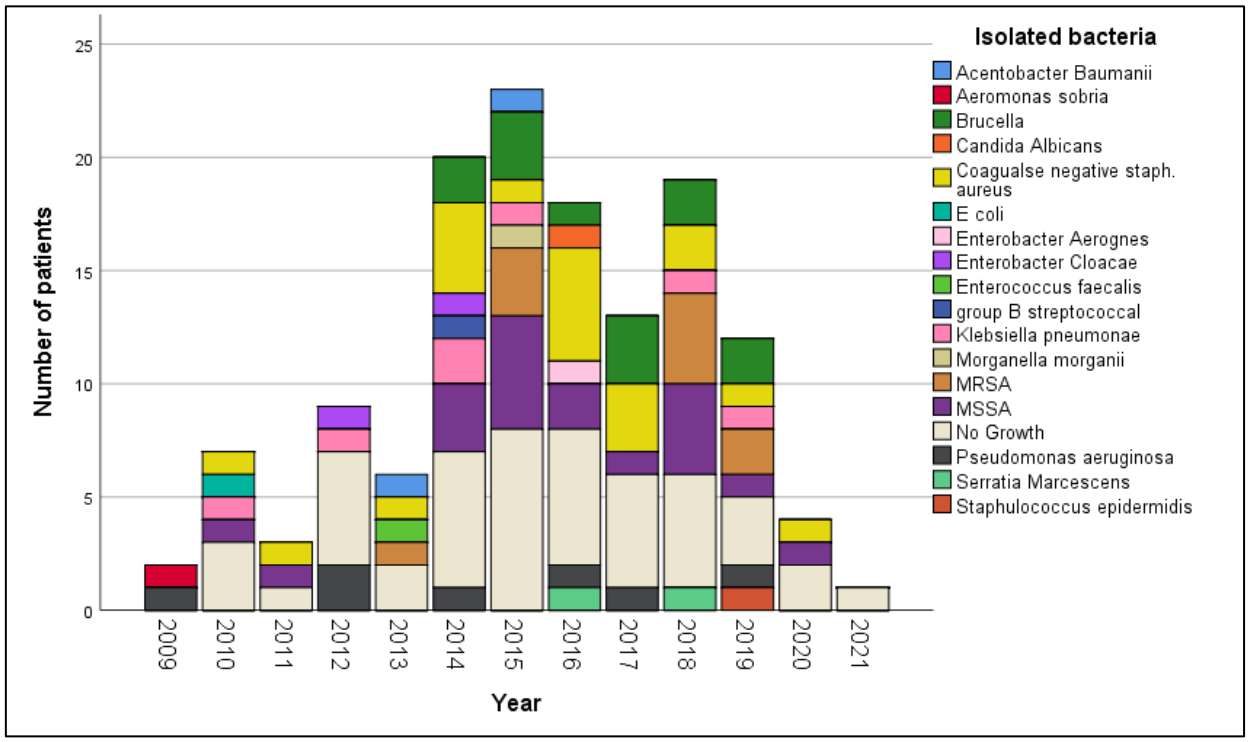

Figure 2: Trends of isolated organisms per year (n=137)

4. DISCUSSION

To our knowledge, our study is the first study to investigate the microbiology associated with CIED infections in Saudi Arabia.

In our study, the majority of infections (37.9%) were caused by Staphylococcus species which is consistent with previous reports [20-26]. However, the rates of coagulase-negative staphylococcal infections seemed to be more widespread as seen in some studies. Sohail *et al.*, reported that 42% and 29% of infections were caused by Coagulase- negative staphylococci and Staphylococcus aureus, respectively [20]. coagulase-negative staphylococci species contribute to of 37.6% of infections while Methicillin-resistant staphylococci were the pathogens in 33.8% of all CIED infections and accounted for 49.4% of all staphylococcal infections [23]. Our results showed that coagulase-negative Staphylococcus aureus and Methicillin-susceptible Staphylococcus aureus, in 15.3% and 13.9% of patients, respectively, were the leading pathogens for CIED infections.

Nonstaphylococcal infections such as Gram-negative bacilli, enterococci, streptococci, anaerobes, fungi, mycobacteria, and polymicrobial contribute only a minor percentage of CIED infections [20, 22-24, 27].

However, our results showed that in 9.5% of infection cases Brucella was the leading causative pathogen of CIED infections, as the third pathogen causing CIED infections in our study. Brucella is one of the rare pathogens worldwide, but it is still endemic in several areas, especially in the Middle East Area [28]. In our country, although the declining incidence rate of brucellosis over the last few years, it remains high [29, 30]. Regarding CIED infections, several studies worldwide didn't reveal any CIED infection cases associated with Brucella [21-24]. However, a study from the Middle East, found one case of Brucella melitensis CIED infection out of 22 CIED infection cases over 17 years [31].

In Turkey, another study from the Middle East found that out of 5287 patients with CIED, only 23 patients developed endocarditis, and only one patient developed Brucella infection [26] in Saudi Arabia, a recent single-center study revealed that 11.1% of CIED infection cases were associated with brucellosis [32]. Therefore, it is essential to consider Brucella-specific tests like extended blood cultures and serology titer in the laboratory detection of the microorganism to confirm a diagnosis in endemic regions.

Our study showed that 34.3% of infections were negative cultures, similar to other studies, the rate of negative cultures observed in Italy was about 29% [22]. 13.2% of patients were reported to had no bacterial or other micro- organism growth on cultures [23]. The low sensitivity of blood cultures is more likely related to antimicrobial therapy before or during specimen collection. Thus, obtaining culture material

before the initiation of antibiotics should be considered, whenever possible.

Furthermore, the assessment of the trends of isolated microorganisms in CIED infections between 2009 and 2020 showed mostly the absence of significant trends in the epidemiology of these pathogens. However, the proportion of negative cultures of CIED infections seemed to be a critical issue over the years, which could reflect the wide use of antibiotics before obtaining specimens for culturing. The trend of the proportions of culture-negative CIED infections was observed to be increasing over time [23]. Therefore, obtaining culture material before the initiation of antibiotics is essential, to the extent possible. Another observation is that the proportions of CIED infections related to Brucella seemed to have been considerable over time, which could reflect that patients may were living in or visiting endemic areas as it remains an important pathogen.

Microorganisms that caused CIED infections may be arisen either by contamination of leads and/or pulse generator during implantation or subsequent manipulation or bloodstream infection [17]. Contamination may be due to the patient's skin flora at the time of skin incision or exogenously from the health care environment. However, direct lead seeding can occur during bacteremia caused by a remote infectious focus, such as local septic thrombophlebitis, osteomyelitis, pneumonia, surgical site infection, contaminated vascular catheters or bacterial entry via the skin, mouth, gastrointestinal, urinary tract, or respiratory tracts [17, 21]. Fukunaga *et al.*, have shown that of 208 patients with CIED infection, bacteremia was identified in three patients as this might be the result of a secondary seeding [33]. Two patients were reported to have Gram-negative bacteremia that resulting from infection of a peripherally inserted central catheter line and from a vascular port for chemotherapy that was responsible for a secondary seeding of the CIED and two others with peritoneal dialysis catheter infection and pyelonephritis infections, had occurred at a distant site, most probably secondarily seeded the CIED via hematogenous spread [34].

Bacterial adherence to the generator or the leads is facilitated by irregular and hydrophobic surfaces. As surfaces differ in their propensity for bacterial adherence microorganisms also vary in their capacity for bio-film formation. The microorganisms most frequently isolated (Gram-positive bacteria, especially Coagulase-negative Staphylococci and Staphylococcus aureus) are more susceptible to adhere to non-biological material than others [23, 33].Others suggested that host factors may affect the formation of bio-film which include a localized compromised innate immune response in the vicinity of the device, systemically weakened innate immune function, and microbial contamination [35].

5. CONCLUSION

Staphylococcus aureus was the most common pathogens in our population of patients with confirmed CIED infections, especially coagulase-negative species. coagulase-negative Staphylococcus aureus accounted for fifteen and three tenths' percent while methicillin-susceptible staphylococcus aureus accounted for thirteen and nine tenths' percent of CIED infections. Brucella was a considerable pathogen for CIED infections in our country accounted for nine and five tenths' percent. Recommended strategies to be considered in our region include taking Brucella-specific tests into consideration in laboratory detection like extended blood cultures and serology titer as it remains widespread in the country and obtaining blood culture and swab cultures before the initiation of antibiotics to the extent possible for the selection of the appropriate antimicrobial agent.

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