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Retrospective study of post-operative infections in implantable cardiac devices in a cardiac tertiary care center

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BACKGROUND: The rise in the incidence of implantation is one of the main causes behind the increased rate of CIED infection, which is considered as a serious life-threatening complication.The need of risk factor assessment has become a necessity to prevent further complications and provide prompt management.

OBJECTIVES: Identify the risk factors of infection postoperatively among patients who have implantable cardiac devices.

DESIGN: A retrospective case-control study.

SETTINGS: Cardiac center for adults

PATIENTS AND METHODS: The study included all adult patients (≥ 14 years of age) of all nationalities who underwent cardiac electronic device implantation that was managed in the cardiac center between January 2012 to December 2018.

MAIN OUTCOME MEASURES: Cardiac device infection and associated risk factors.

SAMPLE SIZE: 213, including 23 (10.8%) infected case patients and 190 (89.2%) non-infected controls.

RESULTS: The mean (SD) age of non-infected patients was 45.0 (12.7) years compared with 61.7 (13.7) for infected patients (P<.0001). Anticoagulant use, hypertension, dysplipdemia and age were the most common patient-related risk factors associated with infection. For procedural and post- procedural risk factors, the risk of infection increased as the number of leads and length of procedure increased. The device most often related to infection was the pacemaker. In the multivariate analysis, longer procedure, greater number of leads, older age, anticoagulant use, and implanted pacemaker device were independently associated with infection.

CONCLUSION: We advise the prompt use of strict preoperative antiseptic prophylaxis measures and follow-up for post-implant patients along with patient education for early signs of infections, which will lead to improvement of both diagnosis and treatment quality for our patients in addition to reducing the economic impact on the health care system by minimizing infectious complications.

LIMITATIONS: Single tertiary center study, small sample size.

CONFLICT OF INTEREST: None.

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Sudden cardiac death (SCD) is defined as an unexpected natural death due to cardiac etiology with an onset of symptoms of 1 hour in patients with known or unknown history of cardiac illness.[1] The worldwide health burden of SCD is increasing as the risk factors of cardiac diseases are increasing at a faster rate.[2] Multiple randomized controlled trials have proven that implantable cardioverter defibrillators (ICDs) areeffective as a life-saving preventive measure for individuals at risk of SCD.[3] Indications for cardiac implantable electronic devices (CIEDs) indications are increasing, such as in cases of tachyarrhythmia and bradyarrhythmia and in heart failure patients.[4] CIEDs include ICDs, permanent pacemakers and cardiac resynchronization therapy devices with or without defibrillators.[5,6]

In a period of 15 years, between 1993 and 2008 almost 4.2 million patients in the United States underwent implantation of a CIED.[7] The increasing number of CIED implantations is one of the main causes behind the increased rate of infection worldwide.[8] Risk factors for CIED infection are patient-related, device-related, and procedure-related. Patient comorbidities such as renal failure, diabetes, hypertension, heart diseases, anticoagulation use, antiplatelet use, immunodeficiencies, dyslipidemia, smoking, male sex and ethnicity are considered as risk factors.[8,9] Procedure and device-related risk factors include: procedure length and number of leads. In addition to pre- and post-procedural measures such as antibiotic prophylaxis, length of hospitalization and catheterization of hospitalized patients.[10,11]

The causative microorganisms of these infections include gram-positive and gram-negative bacteria. Gram-positive bacteria are the main etiology, constituting 67.2% to 92.5% of the total number of infections while the rest (18%) are caused by gram-negative bacteria.[12] Twelve to 49% of symptomatic patients that present with infection will have negative blood cultures.[13] Therefore, assessing the clinical manifestations of patients is challenging. Symptoms depend on the infection stage: early or advanced. Patients with early infection will present with erythema, fever, pain and a warm sensation at the affected site, while wound dehiscence, erosion, device drainage and even sepsis can be seen in advanced cases.[14] Based on the International CIED criteria, it is important for diagnosis to note the site of implantation for any swelling, erythema, warmth or tenderness and discharge along with pocket or lead erosion.[15] Intracardiac echocardiography and positron emission tomography and computed tomography (PET/ CT) are used to assess for vegetations of endocarditis and sepsis.[16]

In a population-based study of trends of CIED infection in three decades (1988-2015), the incidence of CIED infection has been increasing for the last two decades.[17] CIED infections are considered as a serious life-threatening complication after the implantation due to the poor prognosis. To correctly manage the infection, complete removal of the implanted device is required in addition to antibiotic therapy for at least 14 days before any new implantation. However, in the case of systemic infections 4-6 weeks of antibiotics are required.[18] Preventive measures must be taken before, during and after the procedure. These measures include pre-procedural antibiotic prophylaxis, proper skin preparation during the procedure and post-procedural regular follow-ups to check on the incision and device function. To conclude, as the incidence of infection of CIEDs is greatly increasing and exceeding that of implantation, the need for risk factor assessment has become a necessity to prevent further complications and provide prompt management. Hence, the need for a detailed risk factor-based analysis is crucial to control and reduce the number of infected patients.
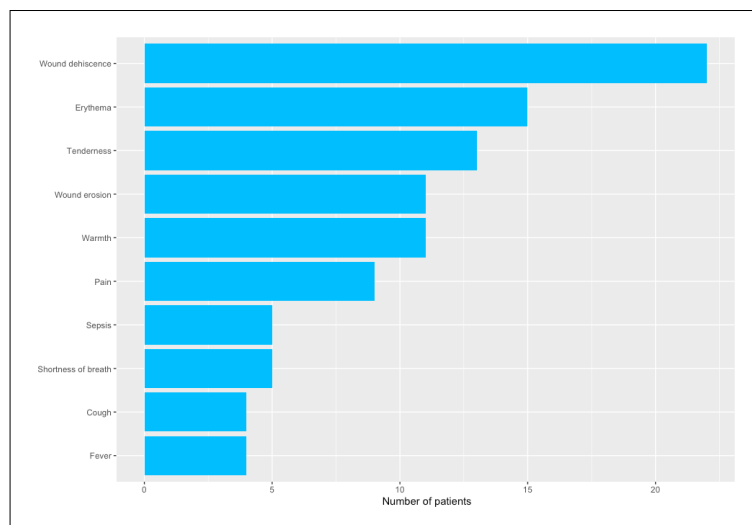
PATIENTS AND METHODS

Study design, setting and participants
The study design was a retrospective case-control study with the ratio 1:8 (infected:non-infected) conducted at the Cardiac Center in Adult Cardiology in Riyadh, Saudi Arabia between January 2012 to December 2018. We chose the study design based on the primary objective, which is to assess the risk factors for device infection postoperatively among those patients who have cardiac electronic device implantation. The study included infected patients (cases) and non-infected adult patients (≥14 years of age) (controls) who underwent cardiac electronic device implantation from all nationalities that were managed and seen in the cardiac center. Our cases (infected) were defined as those who underwent a device implantation and presented with clinical picture of infection (erythema, warmth, fluctuance, wound dehiscence, tenderness, purulent drainage, or erosion of generator or lead through skin) as clear local signs of inflammation and/ or symptoms of fever, shortness of breath, cough, sepsis. We excluded 10 infected patients who did the implantation outside the hospital and those who were under the age of 14 years. The study was approved by King Abdullah International Medical Research Centre (KAIMRC) (Study number RC19/330/R Riyadh, Saudi Arabia).

Table 1. Patient clinical and demographic characteristics (n=213).

	Infected (n=23)	Not infected (n=190)	P value
Age (years) (mean, SD)	60.2 (15.2)	45.7 (13.1)	<.0001
Male	14 (60.9)	130 (68.4)	.5
Female	9 (39.1%)	60 (31.6%)	.5
Saudi	23 (100%)	179 (94.2%)	.6
Non-Saudi	0	11 (5.8%)	.6
Length of stay (days)	6 (11)	3 (7)	.05
Length of procedure (min)	103 (53)	60 (42)	<.0001

Data are number (%) or mean (standard deviation) or median (interquartile range) for length of stay and length of procedure.

Figure 1. Clinical presentation of patients with infection (n=23).

Data collection methods

The retrospective data was collected through patients' electronic health records (EHR) from an adult cardiac registry that is used to record the supporting cardiovascular service lines. Also, the critical care information system was used to acquire the needed information that was not available in the EHRs. We collected demographic information (age, nationality, gender and date of birth), dates of implantation, discharge and admission after the infection, clinical presentation for the infected patients (hyperthermia, pain, warmth, erosion, drainage. etc), preoperative data (risk factors: diabetes mellitus, obesity, anticoagulant use, antiplatelet use. and others), procedural data (type of implantable device and num-

ber of leads, length of procedure), investigations used (ECG, chest X-ray, ECHO and blood test), and antibiotic treatment (piperacillin/tazobactam, vancomycin, ciprofloxacin, augmentin, cefepime, gentamicin).

Statistical analysis

Means and proportions of the study participants were calculated to characterize the study participants, overall and in groups. The primary outcome variable was having infection after undergoing a cardiac electronic device implantation. To determine the factors associated with having infection, the two groups (infected and non-infected) were compared using the chi square or Fisher exact test for categorical factors and t test or Mann-Whitney U Test for continuous variables as appropriate. Then, a multivariate logistic regression model was used to determine which of the risk factors were independently associated with increased/decreased incidence of infections. In the multivariate logistic regression model, infection was modeled as the dependent variable, and all potential risk factors as the independent variables. Covariates were chosen on the basis of univariate testing and physician input. Level of significance was declared at α=.05. Statistical analysis was conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Of 213 adults (≥14 years of age, 190 (89.2%) were uninfected patients and 23 (10.8%) were infected. For all study subjects the mean (SD) age was 47.2 (14) years (**Table 1**). The medianand 25th/75th quartiles were 3 (2.0, 9.0) for length of stay and the maximum was 61 days.The majority (n=165, 77.4%) were admitted for less than 10 days. Only 48 (22.5%) were admitted for a period longer than 10 days 69.7 (37%) was the mean length of the procedure (device implantation) (**Table 1**).

Our 23 infected patients most commonly presented with wound dehiscence (95.6%) (**Figure 1**). There was no report of drainage of the device in our 23 patients. Comparing the infected patients (n=23, 10.8%) with non-infected patients 190 (89.2%), anticoagulant use, hypertension, previous surgery and dyslipidemia were associated with having infection (**Table 2**). For procedure-related risk factors, the type of implantable device, the length of procedure and the number of leads were all associated with the acquisition of infection. None of the 23 infected patients had any immunodeficiencies (**Table 2**).

In the multivariate logistic regression, longer procedure, greater number of leads, older age, anticoagulant use, and implanted pacemaker device were inde-

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pendently associated with infection **(Table 3)**.

DISCUSSION

This retrospective case-control analysis studied the risk factors and clinical presentation that can present with a device infection postoperatively among those patients who have cardiac electronic device implantation. Our main demographic finding in gender ratio was that there were many more males than females with 67.6% male patients and 32.4% female. Considering the risk factors for cardiac diseases, a male majority is the norm. As for infected patients, as expected, there were 14 males and 9 females. In a retrospective case-control design study done by Sohail from January 1991 to December 2003, both their case and control groups described a male predominance (76%) in cases and controls.[14] The summary statistics for our population mean age of our population were similar to those in another study.[19] At the time of implantation the mean age was 47.2 (14) years for controls and 60.2 (15.2) years for cases. Gil et al reported a mean age of infected patients of 60.5 (9.3) years.

The presenting clinical features of our infected patients were wound dehiscence, erythema, tenderness, wound erosion, warmth, pain, sepsis, shortness of breath, cough and fever. The most commonly described symptoms were wound dehiscence 22 (95.6%) and erythema 15 (65.2%) respectively. Chua et al[20] reported the most common clinical features were pocket erythema (n=67, 55%) and local pocket pain (n=68, 55%) for 123 patients with ICD infections at the Cleveland Clinic Foundation.

Patient-related risk factors associated with infection were anticoagulant use 17 (73.9%), hypertension, previous surgery and antiplatelet use all found in 16 (69.6%). In a study in Saudi Arabia by Al-Khadra of 47 patients on oral anticoagulation, at week 6 post-implantation all evaluated patients had well-healed scars with excellent device pacing.[21] In a case-control study in Atlanta (United States) anticoagulant use and renal dysfunction were the most significant risk factors related to device infection.[22] In our study, only 5 of 23 cases had renal dysfunction. Diabetes, a main healthcare burden in Saudi Arabia, was present in only 13 (56.5%) of our infected patients and 73 (38.4%) of our non-infected implantation patients. The rate of diabetes was 58.3% in a single-centered study of 108 patients who had ICD implantation in Riyadh, Saudi Arabia, from December 2007 through January 2010.[23]

The device used in most infected patients in our study was the implantable cardiac defibrillator (n=10 (43.5%) followed by biventricular pacemakers (n=7,

Table 2. Risk factors for device infection in infected patients compared with non-infected patients.

	Infected (n=23)	Not infected (n=190)	P value
Patient-related risk factors			
Anticoagulant use	17 (73.9)	31 (16.3)	<.0001
Antiplatelet use	16 (69.6)	98 (51.6)	.1
Previous surgery	16 (69.6)	90 (47.4)	.04
Hypertension	16 (69.6)	73 (38.4)	.004
Dyslipidemia	14 (60.9)	63 (33.2)	.009
Obesity	13 (56.5)	98 (51.6)	.6
Diabetes mellitus	13 (56.5)	73 (38.4)	.09
Smoking	12 (52.2)	74 (38.9)	.2
Renal failure	5 (21.7)	17 (8.9)	.07
Immunodeficiency	0 (0.00)	8 (4.2)	.6
Procedural, post-procedural risk factors			
Device type: Implantable cardiac defibrillator	10 (43.5)	133 (70.0)	.03
Device type: Biventricular pacemaker	7 (30.4)	34 (17.9)	
Device type: Pacemaker	6 (26.1)	23 (12.1)	
Number of leads	2.0 (0.9)	1.5 (0.8)	.01

Data are number (%) or mean (standard deviation) or median (interquartile range) unless otherwise noted.

30.4%). After the multivariate analysis, it was clear that the pacemaker followed by the ICD formed independent risk factors for infection. In the study in Atlanta, implantable cardiac defibrillators (60%) and pacemakers (40%) were the most frequently reported devices associated with infection.[22] Another important risk factor is the number of leads, as it has been reported in another study that implantation of two or more leads is considered an independent risk factor for CIED infections.[24] Our study supports this as a risk factor since the majority of our infected patients had more than one lead: 6 (26%) with two leads, 8 (34.7%) with three leads and only 9 (39.1%) with one lead.

As for the study's limitations, it was a single tertiary center-based study with small sample size which makes generalization of outcomes not applicable.Due to lack of some information and the poor quality of medical record pool we had some missing data. In the future,

Table 3. Multivariate analysis of risk factors for device infection.

Effect	Beta	Standard error	Odds ratio	95% Conf. interval	P value
Intercept	-12.3317	2.7978	-	-	<.0001
Length procedure	0.0174	0.00864	1.018	(1.00, 1.03)	.0436
Number leads	1.8863	0.9366	6.595	(1.05, 41.35)	.0440
Length of stay	0.0316	0.0306	1.032	(0.97, 1.10)	.3013
Age	0.0920	0.0347	1.096	(1.02, 1.17)	.0080
Gender					
Female vs male	0.1651	0.9082	1.179	(0.20, 6.99)	.8558
Smoking					
Yes vs no	1.4923	0.7977	4.447	(0.93, 21.24)	.0614
Dyslipidemia	0.4192	0.7880	1.521	(0.32, 7.13)	.5947
Diabetes					
Yes vs no	-0.1114	0.7872	0.895	(0.19, 4.19)	.8875
Obesity					
Yes vs no	0.4362	0.7280	1.547	(0.37, 6.44)	.5490
Hypertension					
Yes vs no	0.1754	0.8217	1.192	(0.24, 5.96)	.8310
Renal failure					
Yes vs no	0.7641	0.9742	2.147	(0.32, 14.49)	.4329
Antiplatelet use					
Yes vs no	0.1210	0.8064	1.129	(0.23, 5.48)	.8807
Anticoagulant use					
Yes vs no	2.7500	0.7381	15.643	(3.68, 66.46)	.0002
Previous surgery					
Yes vs no	-0.1952	0.7218	0.823	(0.20, 3.39)	.7868
Implantable device					
Biventricular pacemaker vs pacemaker	-4.5549	1.8352	0.011	(0.0 , 0.38)	.0131
Implantable device					
Implantable cardiac defibrillators vs pacemaker	-1.9098	0.9474	0.148	(0.02, 0.95)	.0438

Model summary measures: Deviance 73.9939, McFadden R square 0.5106, Cox and Snell R square 0.2465, Overall model test: Chi-square 60.2774, df 16
P<.0001

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large multicenter studies should be conducted in Saudi Arabia to gain more knowledge about the topic.

In conclusion, many studies have included the risk factors associated with cardiac device infections. However, unfortunately, there are very limited data on CIED-related infections in the Middle Eastern region. Our study is the first to aim for better understanding of risk factors and clinical presentation related to the patients received at the hospital to improve prompt diagnosis and treatment quality for our patients. The addition of our data will be helpful in better assessing and treating patients with CIED infections to aim for improved outcomes and less economic impact on the health care systems by minimizing the infectious complications. We advise the prompt use of strict preoperative antiseptic prophylaxis measures and the follow-up for post-implant patients along with patient education on the early signs of infections.

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