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RESEARCH ARTICLE

Clinical characteristics, microbiology, and outcomes of infective endocarditis in Qatar

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ABSTRACT

Background: Infective endocarditis (IE) is a serious and potentially life-threatening disease. The epidemiology, treatment options, and outcomes have changed considerably over the last two decades. The aim of the study was to describe the epidemiology, clinical characteristics, and outcomes of patients with IE in Qatar.

Methods: Patients were identified from Hamad Medical Corporation hospitals' electronic records, the national referral center for the State of Qatar. We included those aged ≥18 years with Duke Criteria-based diagnosis of IE during the period from January 2015 to September 2017. Demographic and clinical data were retrieved. Descriptive statistics were performed, and logistic regression analysis was used to describe the relationship between patient characteristics and all-cause in-hospital mortality. All potentially relevant variables were included in the univariate analysis, while those with $p < 0.1$ in the univariate logistic regression model were included in the multivariate analysis. For the final model, we calculated odds ratios (OR) adjusted for each of the variables included, along with their 95% confidence intervals (95% CI). Data were analyzed using STATA software version 15 (StataCorp, College Station, Texas, USA). The study was approved by the Institutional Research Board with a waiver for informed consent.

Results: Fifty-seven cases were included, of which 70% were males. The mean age was 51 years (± 16.8 years). Eleven (19%) were associated with prosthetic valves, and 6 (11%) with implantable cardiac devices. Fever (84%), dyspnea (46%), and heart failure (37%) were the most common presentations. Only 58% of patients had known preexisting valvular heart disease

or an intracardiac device. Skin infections (10 patients, 18%) were the most prevalent portals of infection, followed by venous catheters, recent valve surgery, and implantable cardiac devices. *Staphylococci* were implicated in 19 (34%) and *Streptococcaceae* in 9 (16%) patients, whereas 21 (37%) patients were culture negative. Left-side IE (49 patients, 86%) was predominant. Acute kidney injury (AKI) (17 patients, 30%) and heart failure (11 patients, 19%) were common complications. The majority of patients received targeted antimicrobial therapy with at least two active agents. Only 9 (16%) patients underwent surgical intervention. Fourteen (25%) patients died of any cause before hospital discharge. Logistic regression analysis identified septic shock [OR 57.8, 95% CI 2.6 – 1360.2; $p < 0.01$] and AKI OR 33.9, 95% CI 2.9 – 398.1; $p < 0.01$) as the only risk factors independently associated with in-hospital mortality.

Conclusion: Staphylococci are the most common microbiological cause of IE in Qatar. Surgical intervention is uncommon, and mortality is relatively high. Our findings suggest that efforts should be directed toward improving IE prevention strategies in high-risk patients, encouraging early microbiological investigations and improving medical and surgical management.

Keywords: infective endocarditis, Qatar, epidemiology, outcomes, microbiology, mortality

INTRODUCTION

Despite considerable progress over the past few decades, infective endocarditis (IE) continues to be associated with multiple complications, including embolic events, aortic root or myocardial abscesses, organ failure, and acute renal failure. All-cause mortality can be as high as 37%.[1,2] In the developed world, IE's epidemiology has changed over the past few decades with a shift toward older patient age, degenerative valve disease, prosthetic valves, and implantable devices replacing rheumatic heart disease as the most frequent predisposing cardiac conditions.[3 – 5] This change can largely be explained by the general improvement in healthcare provisions in most parts of the world, leading to decreased incidence of rheumatic heart disease and improved survival in patients with chronic medical conditions. Moreover, healthcare exposure and intravascular lines have become increasingly associated with IE.[6 – 8] However, these pattern changes have not been reported in developing countries.[9] In addition, the spectrum of causative organisms has also changed over the years with *Staphylococcus aureus* has become increasingly more common, followed by Streptococcus viridans group, *Enterococcus* species, and *Coagulase-negative Staphylococci*.[8] Gram-negative bacteria and fungi have also become more common causes of IE.[10,11] This finding could be explained by the global increase of risk factors for *S. aureus*-associated IE, such as healthcare contact and invasive procedures.

Improvements in echocardiographic imaging have resulted in better diagnostic sensitivity and specificity.[12] An increasing recognition of the potential role of nuclear imaging techniques such as radiolabeled leukocyte scintigraphy and 18F-fluorodeoxyglucose positron emission tomographic computed tomographic (FDG-PET/CT) has led some guideline writing committees to include them in their diagnostic criteria for IE.[13,14]

Newer antimicrobial agents and approaches have become established for the treatment of some forms of IE. Examples include daptomycin for methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant Enterococcus species[15] and ampicillin/ceftriaxone combination for the treatment of *E. faecalis* IE.[16] The initial promise of glycopeptide/β-lactam combinations for MRSA bloodstream infections was not supported by the results of a subsequent randomized clinical trial.[17,18] Successful outcomes have also been reported with ceftaroline for MRSA IE.[19]

Data on IE in Qatar are limited to four individual cases of infective endocarditis caused by *Brucella* species and a single case caused by *Streptococcus pneumoniae*.[20,21] An abstract was presented at an international cardiology conference in the year 2014, describing a decrease in the incidence of IE over two time points. However, the abstract does not provide any clinical or microbiological details of the cases.[22] We sought to investigate the epidemiology, clinical characteristics, microbiological profile, and outcomes of IE in Qatar and compare those with data reported from other countries and regions.

METHODS

Hamad Medical Corporation (HMC) is a governmental tertiary care center that provides medical and surgical care for IE in Qatar. Patients were identified from the hospitals' electronic coding records using the Inter-

national Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Those aged ≥18 years and were discharged with a diagnosis of IE during the period between January 1, 2015, and September 30, 2017, were included. In concordance with current international guidelines, patients in whom the modified Duke criteria for definite or possible IE were not fulfilled were excluded.[10,13]

Demographic (age and gender), clinical data (comorbidities, clinical presentations, preexisting valvular disease), laboratory results, echocardiographic findings, antimicrobial therapy, surgical interventions, complications, and mortality data were retrieved. Cases were categorized as native valve, prosthetic valve, or cardiac device-related endocarditis. Acute kidney injury (AKI) was defined as an increase in serum creatinine concentration by ≥44.2 μmol/L or by ≥50% compared with baseline. Early surgery was defined as surgical intervention within two months from the diagnosis of IE. Degenerative valve disease conditions included aortic valve sclerosis or calcification, mitral annulus calcification, and chordal calcification.[23,24] This study was approved by the Institutional Research Board with a waiver for informed consent.

Statistical analysis

Descriptive statistics are given as mean ± standard deviation (SD) or numbers and percentages, as appropriate. Logistic regression analysis was used to describe the relationship between patient characteristics and all-cause in-hospital mortality (any death happened before hospital discharge). All potentially relevant variables were included in the univariate analysis, while those with $p < 0.1$ in the univariate logistic regression model were included in the multivariate analysis. For the final model, we calculated the odds ratios (OR) adjusted for each of the variables included, along with their 95% confidence intervals (95% CI). Statistical analysis were performed using Stata software version 15 (StataCorp, College Station, Texas, USA).

RESULTS

A total of 85 patients were discharged with the IE diagnosis during the study period, of which 28 cases were excluded (20 did not fulfill the modified Duke criteria for definite or possible IE, three were younger than 18 years, and five had alternative diagnoses).

Fifty-seven cases were included, of which 40 (70%) were males. The overall mean age was 51 (±16.8) years (Table 1).

Degenerative valvular disease (12 patients, 21%) was the most common underlying cardiac condition. IE involved native valves (38 patients, 70%), prosthetic valves (11 patients, 19%), or implantable cardiac devices (6 patients, 11%). Important comorbidities included diabetes mellitus (31 patients, 54%), and systemic hypertension (24 patients, 42%). Only 6 (11%) patients were on regular hemodialysis. Among those with an identifiable probable portal of entry, skin infections (10 patients, 18%) were the most prevalent. None of the cases was associated with intravenous drug use (Table 1).

Fever was a presenting symptom in the majority of patients (48 patients, 84%). Dyspnea (26 patients, 46%), heart failure (21 patients, 37%), and generalized fatigue (19 patients, 33%) were also common. Left-side IE (49 patients, 86%) was predominant. Most cases involved native valves (46 patients, 81%). IE occurred mostly on the mitral (27 patients, 47%) or aortic valves (21 patients, 39%) (Table 1).

Approximately one-third (21 patients, 37%) of cases had persistently negative blood cultures (Table 2). *Staphylococci* (19 patients, 53%) and *Streptococci* (9 patients, 25%) were the most common organisms identified when a microbiological etiology was confirmed. Nearly one-third of all staphylococcal cases were caused by methicillin-resistant *S. aureus* (6 patients, 32%). Only a minority of cases were caused by Gram-negative bacilli or *Candia* species (Table 2).

Most patients received at least two intravenous antimicrobial agents (Table 3). Surgical intervention was performed for only a small proportion (9 patients, 16%) of patients.

The most commonly observed complications were AKI (17 patients, 30%), congestive heart failure (11 patients, 19%), and septic shock (10 patients, 18%). One-quarter (14 patients, 25%) of patients died of any cause during the same hospital admission. The mean (SD) duration of hospital stay was 35 (±30.1) days. Logistic regression analysis identified septic shock [OR 57.8, 95% CI 2.6–1360.2; $p = 0.01$] and AKI (OR 33.9, 95% CI 2.9–398.1; $p < 0.01$) as the only risk factors independently associated with in-hospital mortality (Table 4).

Table 1. Baseline characteristics of 57 patients with IE in Qatar

	Variable	Number (%)
Demographics	Male gender	40 (70%)
	Age in years (mean ± SD)	51 (± 16.8)
Underlying Cardiac condition	Degenerative valvular disease	12 (21%)
	Prosthetic valves	11 (19%)
	Intracardiac device	8 (14%)
	Bicuspid aortic valve	1 (2%)
	Congenital heart disease	1 (2%)
	No previously known underlying heart disease	24 (42%)
Underlying comorbidities	Hypertension	24 (42%)
	Diabetes mellitus	31 (54%)
	Chronic kidney disease	11 (19%)
	Hemodialysis	6 (11%)
Suspected port of infection	Dental procedures	3 (5%)
	Intravenous catheters	6 (11%)
	Valve surgery within ≤ 2 months	6 (11%)
	Pacemaker/implantable cardiac device	6 (11%)
	Skin and soft tissue infection	10 (18%)
	Intravenous drug use	0
Clinical Presentation	Fever	48 (84%)
	Dyspnea	26 (46%)
	Heart failure	21 (37%)
	Fatigue	19 (33%)
	Stroke	5 (9%)
	Chest pain	6 (10%)
	Shock	2 (4%)
	Cardiac arrest	1 (2%)
	Polyarthralgia	2 (4%)
Valvular involvement	Aortic valve	21 (37%)
	Mitral valve	27 (47%)
	Aortic and mitral valves	1 (2%)
	Tricuspid valve	1 (2%)
	Undefined	7 (12%)

DISCUSSION

The small number of cases in our study shows that IE is infrequent but not rare in Qatar. Similar to previous reports, IE in Qatar affected mostly middle-aged men with a male-to-female ratio of 2.3.[4,25] The average patient age in our study (51 ± 16.8 years) is comparable to that reported from some European countries, such as Finland and Greece (54.4 ± 17.3, 54.4 ± 17.1, respectively)[26,27]. However, it is higher than the mean age reported from other developing countries such as Oman, Tunisia, and Pakistan.[9,25,28] The predominance of those older than 50 years in IE reports from developed countries is likely, at least in part, to reflect the declining incidence of rheumatic heart disease in these regions.[29–33]

The degenerative valvular disease was the most common predisposing cardiac condition in our population. Our observation is consistent with reports from North America, Argentina, and Europe.[31–33] This observation could be explained by the increasing proportion of older adults in the general population with a subsequent rise in degenerative valvular lesions. In addition, more patients have prosthetic valves, intracardiac electronic devices, or long-term intravenous lines.[2,34] More than one-third (42%) of patients with IE in our study had no previously known cardiac abnormalities. Contrary to traditional teaching, clinicians should actively consider IE in patients presenting with consistent clinical features, even in the absence of known valvular disease or prosthetic cardiac devices.[27,34–36]

Table 2. Microbiology, management, complications, and outcomes of IE in Qatar

	Variable	Number (%)
Microbiology	Staphylococcus species	19 (34%)
	Methicillin-sensitive *S. aureus*	8 (14%)
	Methicillin-resistant *S. aureus*	6 (11%)
	Coagulase-negative staphylococci	5 (9%)
	Streptococcaceae	9 (16%)
	Viridans Streptococci	8 (14%)
	S. pneumoniae	1 (2%)
	Others	8 (13%)
	Enterococcus faecalis	1 (2%)
	Enterococcus gallinarum	1 (2%)
	Pseudomonas aeruginosa	1 (2%)
	Klebsiella species	1 (2%)
	Serratia marcescens	1 (2%)
	Pandoraea species	1 (2%)
	Bacteroides fragilis	1 (2%)
	Candida parapsilosis	1 (2%)
	Culture negative	21 (37%)
Mode of Treatment	Medical only	48 (84%)
	Medical and surgical	9 (16%)
Complication	Acute kidney injury	17 (30%)
	Heart failure	11 (19%)
	Embolic stroke	4 (7%)
	Septic shock	10 (18%)
Outcomes	In-hospital Mortality	14 (25%)
	Length of hospital stay in days (± SD)	35 (± 30.1)

Among the clinical presentations, fever was the most prevalent symptom in our patients (84%), similar to findings from other studies.[18,25,26] Native-valve IE (81%) and left-side IE (86%) were predominant in our study, with the mitral valve being the most commonly involved (47%) followed by the aortic valve (37%). Several studies showed similar findings.[37,38,39] On the other hand, others showed a predominance of the aortic valve.[27,40,41] There is no obvious explanation for this pattern of valve involvement. It could be explained, in part, by very low rates of intravenous drug abusers, central vascular catheters, and implantable cardiac devices in our cohort, which are known risk factors for right-sided infective endocarditis.[42]

Staphylococcus species, especially *S. aureus*, were the most prevalent causative microorganism in our study (25%), followed by the Streptococcus Viridans Group in (14%) of cases. This pattern has been reported in recent studies.[4,36,42–45] Other studies still report the predominance of streptococci.[5,47] MRSA were isolated from 6 (11%) cases reported here. This is higher than those reported from countries with low MRSA rates, where the proportion of IE caused by these organisms ranged between 3.7% and 7%,[48,49] but it is considerably lower than rates reported from countries such as the United States where rates as high as 17.5% were recently reported.[43] The differences in microbiological profiles of IE in different parts of the world is not surprising as it's by large a reflection of background microbiological trends, antimicrobial resistance rates, and antimicrobial prescribing patterns.

A notable finding in our study was the high frequency of culture-negative IE (37%). Previous studies from developing countries showed comparable proportions.[5,11,27,38] In contrast, in other series from developed countries, cultures were negative in only 5% to 15% of IE cases.[4,50] Two most likely explanations for such a high rate of negative cultures in our series are widespread early empiric antibiotics therapy and limited access to specialized culture, serological, and molecular techniques to identify important fastidious microorganisms, such as *Coxiella burnetiid*, *Bartonella* species, and others.[51–54]

In line with data from other parts of the world, major complications observed in our population were AKI,

Table 3. Management of 57 cases of IE from Qatar according to their microbiological etiology

Microbiological Etiology (number)	Native or Prosthetic Device* IE (number)	Definitive Antimicrobial Regimen (number)	Surgical Intervention (number, percentage)	In-hospital mortality (number, percentage)
MSSA (8)	Native valve (5)	cloxacillin (5)	1	2
	Prosthetic device (3)	cloxacillin plus rifampicin (3)	0	1
MRSA (6)	Native valve (3)	vancomycin or daptomycin (3)	0	1
	Prosthetic device (3)	vancomycin or daptomycin, plus rifampicin (3)	0	2
Coagulase-Negative Staphylococci (5)	Native valve (1)	Daptomycin (1)	0	0
	Prosthetic device (4)	vancomycin or daptomycin, plus rifampicin (4)	0	1
Streptococcus viridans (8)	Native valve (8)	Ceftriaxone (8)	0	0
	Prosthetic device (0)			
Negative cultures (21)	Native valve (19)	ceftriaxone plus vancomycin (19)	6 (29%)	2 (11%)
	Prosthetic device (2)	ceftriaxone plus daptomycin (2)	0	0
Others (8)	Native valve (4)	meropenem plus gentamicin (4)	2	1
	Prosthetic device (4)	meropenem plus gentamicin (3) fluconazole (1)	0	1

*Involving prosthetic valves or intracardiac devices.
IE, infective endocarditis; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*

congestive heart failure, and septic shock.[4,55,56] AKI is a well-recognized independent risk factor for short- and long-term mortality in patients with or without acute IE.[57,58] These findings could be explained by the high rate of heart failure with concomitant use of nephrotoxic diuretics and the use of inotropic support in our cohort. Moreover, the most common organisms are *S. aureus* and *Streptococcus* species, which are associated with increased risk of IE-associated glomerulonephritis.[59]

In our patients, the in-hospital mortality was 25%, which is within the mortality rate range of 15% – 30% reported in other case series.[3,8,19] Although, this rate is higher than rates reported in other studies.[4,56,60] Only 9 (16%) patients in our cohort underwent early surgical intervention. Notably, out of 11 who died during the same hospitalization, only 4 (36%) had undergone surgical intervention. In general, 25% – 50% of patients with acute IE may require surgical intervention during acute infection. Though potentially lifesaving in many cases, surgical intervention in this setting can be technically challenging and may lead to serious complications., especially in severely ill patients with multiple organ dysfunctions.[4,10,13,61] The risks and benefits of surgery need to be considered carefully on a case-by-case basis. Decisions on whether to proceed with surgery and the best timing should be based on multidisciplinary discussions that involve patients or their representatives.[62]

Several studies identified an association between *S. aureus* bacteremia and higher mortality in IE.[4,63] We did not find an association between any specific microorganism and all-cause mortality [unadjusted OR 1.73, 95% CI 0.49 – 5.99; $p = 0.39$]. This might be due to the relatively small number of cases and the retrospective nature of our study. The average length of hospital stay of 30 days reported here has obvious cost and resource implications. Interventions, such as outpatient parenteral therapy or an early switch to oral antimicrobial therapy, might help to reduce the economic burden and improve patient experience.[25,64]

Table 4. Logistic regression analysis for risk factors for all-cause in-hospital mortality

Variable	Unadjusted Odds Ratio (95% CI)	*p* Value	Adjusted Odds Ratio (95% CI)	*p* Value
Age	1.03 (0.991.07)	0.14	–	–
Male	3.21 (0.6316.29)	0.16	–	–
Diabetes mellitus	2.62 (0.719.63)	0.15	–	–
Chronic kidney disease	3.43 (0.8513.79)	0.08	2.04 (0.0946.3)	0.655
Hemodialysis	3.64 (0.6420.59)	0.14	–	–
Heart failure	1.26 (0.384.23)	0.71	–	–
Acute kidney injury	22.61 (4.84105.55)	0.00	33.9 (2.9398.1)	<0.01
Fever	1.17 (0.216.39)	0.86	–	–
Septic shock	75.60 (7.85727.76)	0.00	57.8 (2.51360.2)	0.01
Skin infection	1.63 (0.269.99)	0.60	–	–
Early valve surgery	0.58 (0.065.48)	0.64	–	–
Intracardiac device	1.63 (0.269.99)	0.60	–	–
Valvular abscess formation	0.73 (0.143.92)	0.71	–	–
Native-Valve IE	1.59 (0.298.420)	0.59	–	–
Prosthetic-valve IE	0.29 (0.0.032.53)	0.26	–	–
Aortic valve IE	0.34 (0.081.41)	0.14	–	–
Mitral valve IE	1.53 (0.4.55.17)	0.49	–	–
Multi-valve IE	1.68 (0.367.85)	0.51	–	–
Gram-Positive bacteria	0.87 (0.262.91)	0.82	–	–
Staphylococcus spp. IE	1.73 (0.495.99)	0.39	–	–
Streptococcus spp. IE	0.34 (0.042.96)	0.33	–	–
Culture-Negative IE	0.31 (0.110.85)	0.02	1.66 (0.1419.85)	0.14

CI, confidence interval; IE, infective endocarditis

Our study is limited by its relatively small sample size and its retrospective nature. However, to the best of our knowledge, it is the first such study from Qatar and is larger than many studies reported from the region.

In summary, IE is an uncommon but important clinical problem in Qatar. Skin infections are an important risk for IE in Qatar. A considerable proportion of patients with IE have no known preexisting cardiac conditions. *Staphylococci* are the most frequently confirmed bacterial etiology of IE in Qatar, but nearly one-third of cases are culture negative. Only a small proportion of patients with IE undergo surgical intervention, and the overall mortality is high. These findings suggest that efforts should be directed toward improving IE prevention strategies in high-risk patients, encouraging early microbiological investigations and improving medical and surgical management.

Conflict of interest

No conflict of interest to declare.

Ethical issues

The study was approved by the Research Committee and Medical Research Centre at the Hamad Medical Corporation.

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