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Ten-year experience of Q fever endocarditis in a tertiary cardiac center in Saudi Arabia

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ABSTRACT

Background: Q fever endocarditis (QFE) is considered rare in the Middle East, with only a few cases reported in Saudi Arabia. The aim of this study is to report on the experience of our centre on QFE.
Methods: We searched the medical records for cases of QFE at our cardiac center from 2009–2018. Demographic data, clinical features, serology and echocardiography results, treatments, and outcomes were assessed.
Results: Five hundred and two cases of infective endocarditis were detected over the 10 years period. Among the 234 patients with blood culture-negative endocarditis (BCNE), 19 (8.10%) had QFE. All patients had a previously diagnosed congenital heart disease except for one patient with rheumatic heart disease. Eleven patients had received a bovine jugular vein-related implant, e.g., a Melody valve (seven patients) or Contegra conduit (four patients). Coinfection was detected in three patients, and immunologic and embolic phenomena were observed in five patients. All patients received a combination of hydroxychloroquine and doxycycline, with good outcomes. Only two patients required surgery while on treatment. Two patients died several months after treatment; the cause of death was not identified.
Conclusion: This study indicates that Q fever exists in our population. The majority of the patients had congenital heart disease (CHD) and underwent bovine jugular vein implants. Patients with CHD are at increased risk of infective endocarditis. Bovine jugular vein implants increase the risk of infective and possibly QFE. Proper exclusion of Q fever is warranted in all BCNE and possibly in culture-positive endocarditis cases in areas endemic to Q fever.
Key points: We presented the largest series of Q fever endocarditis cases in Saudi Arabia. We showed that Q fever is not rare in the Middle East and suggest that it should be considered in all blood culture-negative endocarditis cases.

Introduction

Q fever is a worldwide zoonotic disease. Its causative bacterium—*Coxiella burnetii*—is an obligate intracellular Gram-negative coccobacillus that survives by concealing itself in macrophages in the reticuloendothelial system and monocytes in the blood. Initially described by Derrick in 1937 (Derrick, 1937), Q fever is not well known, although accumulating studies from specialized centers and the designation of *C. burnetii* as a bioterrorism agent by the Centers for Disease Control and Prevention have heightened its familiarity (Eldin et al., 2017).

Q fever is usually acquired through the aerosol inhalation of animal products, particularly products of conception. Other routes of transmission include the consumption of infected milk and dairy products (Raoult et al., 2005a). The prevalence rate of Q fever in camels in Saudi Arabia exceeds 51% (Jarelnabi et al., 2018). Camels appear to harbor high concentrations of *C. burnetii,* which they shed through milk, blood, feces, and urine (Mohammed et al., 2014). The high prevalence of Q fever in camels, coupled with the

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widespread habit of raw camel milk intake, highlights the key role camels may play in the transmission of human disease in Saudi Arabia.

There is a scarcity of data on Q fever in Saudi Arabia and the Middle East. Three epidemiological studies from different regions of Saudi Arabia reported 174 patients of infective endocarditis over a period of ten years. QFE endocarditis was not detected or tested for, in any of these patients (Al-Tawfiq and Sufi, 2009; Nashmi and Memish, 2007; Assiri, 2011). The first reports on Q fever in humans in Saudi Arabia were published in 1966 and 1968 (Gelpi, 1966). American soldiers deployed to Iraq in 1995 had 10.6 seroconversions per 1,000 person-months (Royal et al., 2013). Less is known about Q fever than brucellosis, although both are endemic to Saudi Arabia and share similar transmission routes. Q fever also remains a neglected disease in the Middle East despite its endemicity in animals in Lebanon, Egypt, Morocco, and Tunisia (Jaff and Wilson, 2016).

Q fever is asymptomatic in >60% of patients. Acute symptoms include a flu-like illness, pneumonia, and hepatitis. The severity of acute illness may be strain-related. Fortunately, only 1–2% of acute cases progress to chronic infection, whose main manifestation is endocarditis (70% of chronic cases). Other manifestations include intravascular infection, osteomyelitis, and chronic hepatitis (de Lange et al., 2018). The estimated risk of developing endocarditis from a valvular dysfunction is 39%; male patients >40 years-old also have a high risk, especially in the presence of bicuspid valves and/or a high immunoglobulin G (IgG) antiphospholipid (APL) titer >90 units (Million et al., 2013).

Endocarditis is also observed in patients with acute Q fever. In a previous study, 12 (7.6%) of 1,569 patients with acute Q fever developed endocarditis, all of whom had a history of valvular heart disease (Fenollar et al., 2001). This emphasizes the importance of screening patients with acute Q fever for valvular heart disease in areas in which endocarditis is the principal presentation (Fenollar et al., 2001). Patients screened and offered combination treatment have a markedly lower risk of progression to chronic disease than those not treated or treated with a single drug. Hence, recent guidelines recommend screening, treatment, and follow-up of patients with valvulopathy and acute Q fever (Million et al., 2013).

Very few reports in Saudi Arabia have focused on Q fever endocarditis (QFE). A recent molecular study of the excised cardiac valve in two cases of QFE in Saudi Arabia identified a new genotype of *C. burnetii*—MST51 (Angelakis et al., 2014). Before this, only three cases, including one pediatric case, had been reported (Al-Hajjar et al., 1997).

This study describes a cluster of QFE cases at a single tertiary center in Saudi Arabia.

Methods

We retrospectively reviewed all QFE cases diagnosed at our center during 2009–2018. The Prince Sultan Cardiac Centre in Riyadh is one of the main cardiac centers in the Kingdom of Saudi Arabia and has 186 beds. Both adults and children and medical and surgical patients are admitted. A registry of all patients admitted with endocarditis was reviewed using an infectious disease consult database and echocardiogram records. Patients with identified microorganisms were excluded, excepting those with Q fever dual infection. Also excluded were patients with blood culture-negative endocarditis (BCNE) who were not tested for Q fever. Ultimately, our study comprised patients with established Q fever. The ethical committee of our hospital approved the study.

Data collected included the following: patient demographics, risk factors for Q fever, past history of cardiac surgery, symptoms and findings at presentation, underlying cardiac abnormalities, investigations performed, surgical intervention, anticoagulant or antiplatelet treatment, anti-microbial therapy type and duration, and patient outcomes.

QFE was diagnosed based on the criteria published by Raoult (2012). The definite criteria were microorganism isolation, positive polymerase chain reaction (PCR) results, and positive immunohistochemistry for a cardiac valve. The major criteria included a positive culture or PCR result for a blood sample or embolus and an IgG1 level ≥6400 mg/dL. Evidence of endocardial involvement was also a major criterion. A definitive diagnosis required fulfilment of one of the definite criteria, two of the major criteria, or one major criterion plus three minor criteria. Other cases were considered as a 'possible diagnosis'.

Results

A total of five hundred and two patients with endocarditis were admitted to our hospital between September 2009 and December 2018. Of these, 234 (46.6%) had BCNE. Serology for Q fever (QF) was performed in 77 patients, 24 of whom had positive serology results for *C. burnetii* infection. Enzyme immunoassay (EIA) QF serology was performed at the Bioscientia Institute for Medical Diagnostics, Germany and indirect immunofluorescence test (IIFT) at the Mayo clinic, USA. Patients 6 and 7 were tested by complement fixation test (CFT). Five of the 24 patients were excluded from the study owing to suspicion of acute infection on serology. Among the remaining 19 patients, all of whom had Q fever endocarditis, 17 were men (89.4 %) and the average age was 19.52 (range, 12–47) years.

None of the patients fulfilled the definite QFE criteria since PCR analysis of the tissues, culturing, and immunohistochemistry were not performed. All patients had confirmatory echocardiographic signs of endocarditis (17 on transthoracic and two on transesophageal echocardiogram) (Table 1). Based on the diagnostic criteria, three patients had a possible diagnosis of infective endocarditis (IE), while 16 had a definitive IE diagnosis.

All patients had an underlying predisposing condition. Eleven patients had repaired tetralogy of Fallot, five had pulmonary valve pathology, and one had prosthetic mitral and aortic valves. All patients had undergone corrective reconstruction surgery (Table 2). A Melody valve (Medtronic Inc., Minneapolis, MN, USA) was inserted in seven patients and a

Table 1
Demographic and clinical characteristics.

Characteristic	# %
Age	12–47 year
Male	17 (89.4)
Female	2 (10.5)
Aspirin use	3 (15.7)
Anticoagulation	1 (5.2)
Animal exposure or raw milk ingestion	3 (15.7)
Predisposing heart condition:	
Congenital heart disease	18 (94.7)
RHD with prosthetic valve	1 (5.2)
Pacemaker	2 (10.5)
Pervious infective endocarditis	1 (5.2)
Clinical feature:	
Fever	12 (63.1)
Weight loss	3 (15.7)
Night sweat	4 (21)
Fatigue	6 (31.5)
Shortness of breath	7 (36.8)
Splenomegaly	14 (73.6)
Hepatomegaly	11 (57.8)
Hepatitis	1 (5.2)
Anemia	16 (84.2)
Glomerulonephritis	3 (15.7)
Septic emboli	2 (10.5)

Table 2
Echocardiographic findings at diagnosis and preceding procedure before QFE.

#	Echocardiography finding at QFE diagnosis	Gradient of PV at diagnosis	Procedure before QFE diagnosis		
			# of surgery	# TPVI	Stent/conduit
1	Flattering echogenic structures at the level of PV, mild Para prosthetic leak	40	3	2	PA stent
2	Tiny oscillating masses seen inside the PV	39	2		
3	There is small echogenic mass seen attached to TV septal leaflet	45	2	1	PA stent
4	Small echogenic mobile mass, attached to PV leaflet	40	2		
5	Mobile mass attached to the pulmonic valve conduit	35	3		Conduit
6	Echogenic mass attached to PV leaflets, PV insufficiency with multiple jets	20	2		PA stent
7	Small calcifications seen at prosthetic pulmonary valve	30	1	1	
8	RV - PA conduit with multiple echogenic masses seen in the conduit	50	3		Conduit
9	Small mobile echogenic structures seen in PV	70	2		
10	Tiny flickering echogenic tissue attached to the PV, mild paravalvular leak	30	2		PA stent
11	Mobile mass attached to the PV	75	2	2	
12	New mobile echogenic mass seen attached to the PV leaflets	45	3	1	Conduit
13	There is echo genic structure seen attached to PV	60	2	1	
14	Mild PR of implanted pulmonary	78	2		
15	Dehiscence of the MV prosthesis, severe PVL, paravalvular regurgitation of AV prosthesis	NA	2		
16	PV thickened with multiple echogenic mobile structure around the valve, severe PVL	28	2		
17	Elongated mobile mass 20 mm seen in the MPA attached to the prosthetic PV	70	3		
18	Mobile mass is present on the prosthetic PV	76	2	1	Stent
19	RV-PA conduit peak gradient is 50 mm Hg	50	4		Conduit

TV, Tricuspid valve; PV, pulmonary valve; RV-PA, Right ventricular to Pulmonary artery; PR, Pulmonary regurgitation; MV, Mitral valve; AV, Aortic valve; MPA, Main pulmonary artery; TPVI, transcatheter pulmonary valve implantation; PM, pacemaker; QF IE, Q fever infective endocarditis; PA, Pulmonary artery; PVL, prosthetic paravalvuler leak; IE, Infective endocarditis.

Contegra pulmonary conduit in four. Two patients had coarctation of the aorta with aortic stenosis, both of whom underwent the Ross procedure where the diseased aortic valve is replaced with the patient's own healthy pulmonary valve. A Melody valve is then inserted in the patient's own pulmonary valve. Seven patients received Edward valve. One patient had a prosthetic valve for rheumatic mitral valve disease. Two patients were on aspirin while another was on warfarin for a prosthetic valve. Sixteen patients were not on aspirin during the 6 months preceding the endocarditis presentation. Three patients had a clear history of animal contact including raw milk ingestion, while 11 denied prior animal exposure.

Fever was present in 12 (63%) patients (subjective fever in five and documented body temperature >38.3 °C in seven). Seven (36.8%) patients denied having a history of fever (Table 1), while 14 of 15 (93.0%) had splenomegaly confirmed by ultrasound. Four patients did not have an abdominal ultrasound. Anemia was documented in 16 (84.2%) patients, with a hemoglobin level <12.0 g/dL. The mean C - reactive protein level and erythrocyte sedimentation rate were 20.85 (range, 2–153) mg/L and 32.92 (range, 1–104) mm/h, respectively (Table 3). All patients had a diagnostic titre for QFE (Table 4).

Three patients had dual infections, one of whom had a positive *Brucella* sp. blood culture and a history of raw milk ingestion. Methicillin-sensitive *Staphylococcus aureus* (MSSA) and coagulase-negative staphylococci were isolated from patient 15 and patient 12, respectively. Three patients had evidence of glomerulonephritis, and systemic lupus erythematous (SLE) was suspected. SLE

Table 3
Primary diagnosis type and site of involved valves.

#	Age(Year)	Primary diagnosis	Valve involve	Type of valve with IE	Symptom from last valve	Duration B/T symptom and diagnosis
1	47	TOF, PS	PV	Melody	3 M	3 M
2	24	PS, ASD	PV	Edward	9 Y	2 M
3	18	TOF	PV, TV	Melody	4,9 Y	6 M
4	12	TOF	PV	Edward	5 Y	5 M
5	19	TGA, sub PS, sub AS	PV	Contegra	4,2 Y	3 M
6	20	TOF, PDA	PV	Edward	2.8 Y	8 M
7	12	TOF	PV	Melody	10 M	11 M
8	13	Truncus arteriosus, PFO	PV + conduit	Contegra	2 Y	3 M
9	13	CoA, AS, PDA, bAV (ROSS)	PV	Contegra	9 Y	1,5 M
10	12	TOF	PV	Edward	4 Y	1.4 Y
11	18	CoA, AS, bAV (ROSS)	PV	Melody	1.6 Y	3 M
12	18	(PA-VSD), PDA	PV	Melody	5 Y	1.5 M
13	24	TOF	PV	Melody	4 Y	1,5 M
14	28	PS, VSD, ASD	PV	Edward	11 Y	8 M
15	29	RHD	AV, MV	Metallic	14 Y	2 M
16	14	TOF	PV	Edward	5 Y	2 Y
17	19	TOF	PV	Edward	6 Y	1 Y
18	17	TOF	PV	Melody	6 Y	2 M
19	14	TOF, PA	RV-PA Conduit	Conduit Contegra	8 Y	2 Y

IE, Infective Endocarditis; M, monthes; Y, Year; TOF, Tetralogy of fallot; PS, Pulmonary stenosis; ASD, Atrial septal defect; TGA, Transposition of the great arteries; AS, Aortic stenosis; PDA, Patent ductus arteriosus; PFO, patent foramen ovale; CoA, coarctation of the aorta; bAV bicuspid aortic valve; ROSS, Ross procedure; (PA-VSD) Pulmonary atresia - Ventricular septal defect; VSD, ventricular septal defect; RHD, Rheumatic heart disease; PA, Pulmonary atresia; PV, pulmonary valve; TV, Tricuspid valve; AV, aortic valve; MV, mitral valve; RV-PA, Right ventricular to pulmonary artery; B/T, Between.

Table 4
Clinical features and treatment of QFE patients.

#	Clinical feature	Treatment and outcome			
		Regimen	Duration	Surgery	Relapse/Mortality
1	Fever, Hepatosplenomegaly, Anemia	Doxy/HCQ	18M	Ballooning of PV	No
2	Hepatosplenomegaly, Anemia	Doxy/HCQ	24 M	PVR at end of Tx	No
3	Fever, Splenomegaly, Anemia, GN	Doxy/Cipro.	24M	No	No
4	Hepatosplenomegaly, Anemia, GN	Doxy/HCQ	24 M	PVR at end of Tx	No
5	Fever, Hepatosplenomegaly, Anemia, GN	Doxy/HCQ	18M	No	Died
6	Fever, Hepatosplenomegaly, Anemia	Doxy/HCQ	24 M	No	No
7	Fever, Anemia	Doxy/HCQ	24 M	No	No
8	Fever, Hepatosplenomegaly, Anemia	Doxy	10M	PVR on Tx	Died
9	Hepatosplenomegaly, Anemia	Doxy/HCQ	24 M	No	NA
10	Fever, Hepatosplenomegaly, Anemia	Doxy/HCQ	24 M	No	NA
11	Fever, Splenomegaly, Anemia	Doxy/HCQ	NA	No	NA
12	Fever, Hepatosplenomegaly, Anemia	Doxy/HCQ	NA	No	NA
13	Asymptomatic (tested on echo finding)	Doxy/HCQ	NA	No	NA
14	Asymptomatic (tested on echo finding)	Doxy/HCQ	NA	No	NA
15	Fever, Splenomegaly, Anemia	Cipro./HCQ	8 M	No	Miss F/U
16	Anemia (tested on echo finding)	Doxy/HCQ	24 M	PVR on Tx	No
17	Hepatosplenomegaly, Anemia	Doxy/HCQ	NA	No	NA
18	Fever, Splenomegaly, Anemia	Doxy/HCQ	NA	No	NA
19	Fever, Splenomegaly	Doxy/HCQ	NA	No	NA

GN, Glomerulonephritis; Doxy, Doxycycline; HCQ, Hydroxychloroquine; Cipro, Ciprofloxacin; M, Months; NA, Not applicable; PV, Pulmonary valve; PVR, pulmonary valve replacement; TX, Treatment; F/U, Follow up; * serology done by CFT complement fixation test.

markers including antinuclear antibodies were negative in two of the patients. One patient was diagnosed with SLE on renal biopsy despite the absence of clinical and serological markers.

All patients excepting two received a combination of doxycycline and hydroxychloroquine. In one patient, the regimen was changed to ciprofloxacin and doxycycline owing to hydroxychloroquine-related side effects. Another patient was shifted to ciprofloxacin and hydroxychloroquine following doxycycline-induced dysphagia. The duration of treatment was 18–24 months. Eight patients were still undergoing treatment at the time of the study. Five patients required surgery, three during the treatment and two after completing the treatment. One patient who underwent doxycycline monotherapy and surgery died of multiorgan failure 20 months following diagnosis. He was poorly compliant to treatment. Another patient died one year later following a complex cardiac surgery and renal failure. None of the patients who completed the treatment relapsed (Table 5).

Table 5
Serology results for Q fever.

#	IgG		IgM		Method
	Phase I	Phase II	Phase I	Phase II	
1	1:64000	1:64000	1:1024	1:1024	EIA
2	1:16000	1:16000	1:256	1:16	EIA
3	1:16384	1:16384	1: 2048	1:128	IIF
4	1:32768	1: 4096	1: 2048	1:64	IIF
5	1:2048	1:1024	1: 768	1:384	EIA
6	1:256	1:128	1: 48	1: 96	CFT
7	1:200	1:200	negative	Negative	CFT
8	1:1024	1:1024	1:96	1:24	EIA
9	1:32768	1:16384	1:16	1:16	IIF
10	1: 32000	1:16000	1:128	1:16	EIA
11	1:4096	1:16384	1: 2048	1:16	IIF
12	1:2048	1:16000	1:1024	1:128	EIA
13	1:32000	1:64000	1:512	1:32	EIA
14	1:16000	1:16000	1:1024	1:64	EIA
15	1:32768	1:16384	1:1024	1:16	IIF
16	1:1024	1:1024	1:192	1:192	IIF
17	1:32768	1:32768	1:64	1:16	IIF
18	1:16384	1:16384	1: 2048	1:256	IIF
19	1:16000	1:16000	1:512	1:256	EIA

CFT: Complete fixation test, EIA: enzyme immune assay, IIF: Indirect Immunofluorescence.

Discussion

This study described a cluster of QFE cases at a single tertiary center in Saudi Arabia. To the best of our knowledge, this is the largest retrospective series on QFE in the Middle East. It is also the largest QFE series involving bovine jugular vein grafts such as Melody valves and Contegra conduits. Among the 502 patients with endocarditis, 234 (46.6%) had BCNE, which is consistent with the rates of BCNE in the Mediterranean basin (46–69%) (Gouriet et al., 2018). The rates of Q fever in all endocarditis and BCNE patients in our study were only 3.7% and 8.0%, respectively; however, this is probably an underestimation since many of the BCNE patients did not undergo serology.

Endocarditis occurs in 70% of chronic Q fever cases, but only 0.76% of acute Q fever cases. However, Q fever accounts for 10% of all BCNE cases. QFE follows in 40% of patients with underlying valvulopathy (Fenollar et al., 2001). Vascular infection is fatal if a combination of medical and surgical treatment is not provided. For reasons unclear, it is prevalent in certain cohorts such as the Dutch (56.7%), while none of the patients from French Guyana developed vascular infection (Edouard et al., 2014; Kampschreur et al., 2014). None of our patients had a vascular infection. While acute Q fever can be strain-related, chronic Q fever can involve all strains (Kampschreur et al., 2014).

The risk factors for Q fever could not be identified in most of our patients, perhaps owing to the retrospective nature of our study. Similar to previous studies, a few of the patients in our study denied having any risk factors (Armstrong et al., 2018). Because bacterial aerosols can be spread by the wind >30 km (Tissot-Dupont et al., 2004), Q fever can occur in areas that are distant from the main contaminated regions. Thus, the absence of a history of contact with animals should not exclude a diagnosis of Q fever.

Patients with congenital heart disease (CHD) have a greater risk of endocarditis than does the general population (Hascoet et al., 2017). Young CHD patients are tested more frequently than older patients, which may explain in part why most of the patients in our study were young. All of the patients in our study excepting two were men. In Australia, men are five times more likely to develop an infection than women (Hartzell et al., 2008). It has been suggested that female sex hormones have a protective effect (Raoult et al., 2005a).

Remarkably, 58.0% of our patients had undergone a pulmonary bovine jugular vein implant. 7 patients had transcatheter pulmonary valve implantation (TPVI) while 4 had a Contegra conduit (Medtronic Inc., Minneapolis, Minnesota) in the right ventricular outflow tract (RVOT). TPVI was accomplished by using a bovine Melody valve. Since its introduction in 2000, the Melody valve has demonstrated adequate hemodynamic and clinical outcomes. Several studies have confirmed the safety of TPVI and the durability of the implant (Patel et al., 2014). However, these benefits are offset by recent reports showing IE after Melody valve implantation (Hascoet et al., 2017; Patel et al., 2014; Abdelghani et al., 2018; Malekzadeh-Milani et al., 2018). The incidence rate of TPVI-related IE varied between 3.5% and 25% in one systemic review, with an annualized rate of 1.3–9.1% per patient-year (Abdelghani et al., 2018). Most IE cases presented during the first year after TPVI, with 23% presenting after 3 years.

The trauma induced during TPVI could precipitate IE; however, there was no difference in the IE incidence rate between groups that underwent transcatheter implantation versus surgical valve implantation (Sharma et al., 2017). As another possibility, bovine jugular vein grafts (e.g., Melody valves and Contegra conduits) have a higher rate of delayed IE development than do other right ventricle-to-pulmonary artery conduits (median cumulative incidence, 5.4% and 1.2%, respectively; $P < 0.0001$) (Sharma et al., 2017). The risk is also much higher for jugular vein grafts than homografts (hazard ratio, 9.05; 95% confidence interval, 2.6–31.8. An in vitro study showed selective adhesion of bacteria to healthy Melody valve tissue (Jalal et al., 2015). The usual microorganisms involved in post-TPVI infective endocarditis are *Staphylococci* (42% of cases) and *Streptococci* (30% of cases) (Abdelghani et al., 2018). These values are similar to those observed in prosthetic valve endocarditis cases. The likelihood of IE should be weighed against the effectiveness and durability of the valve.

Extensive evaluation of all possible risk factors for infection is recommended prior to valve insertion. Interestingly, abrupt discontinuation of aspirin is a possible risk factor for percutaneous pulmonary valve (PPV)-related IE. Thrombus formation has been observed in cases with Contegra bovine grafts. A thrombus is thought to act as a focus for infection and therefore its formation should be avoided. Anti-aggregant discontinuation is another risk factor for IE ($P = 0.002$) (Malekzadeh-Milani et al., 2015), which is why lifelong prophylaxis with aspirin is advocated (Patel et al., 2014). Only three of our patients were on aspirin prior to infection. Aspirin discontinuation may have increased the risk of endocarditis in our patients; however, in the study by Jewgenow et al., almost 25% of 46 explanted valves contained a thrombus despite aspirin administration (Jewgenow et al., 2019). Therefore, aspirin alone may not effectively prevent thrombosis.

Q fever with Melody valve-related endocarditis is extremely rare. Hence, the presence of this disease in our series is notable. The first case of QFE was reported by Jalal et al. in 2017 (Jalal et al., 2018). In this case, a 13-year-old boy had undergone Melody PPV insertion 4 years before presenting with hepatosplenomegaly detected on a routine follow up. Although his presentation was atypical, Q fever was confirmed via both Q fever serology and blood-specific PCR (Jalal et al., 2018). Corrective RVOT obstruction surgery using a bovine Contegra conduit can predispose a person to Q fever-related IE. This occurred in two patients in the report by Stefanidis et al.; both developed a Q fever infection within 3 years of implantation (Stefanidis et al., 2011). Similarly, the average time between Melody valve insertion in our patients and QFE occurrence was 38 (range, 3–72) months. However, QFE developed 2–9 years after Contegra conduit implantation, and within 6.8 (range, 3–11) years after Edward valve implantation.

Almost all of our patients had pulmonary valve involvement. In contrast, in an Australian series, all confirmed cases had Q fever-related IE of the aortic valve (Armstrong et al., 2018). We note that our patients were younger than those in previous relevant studies, perhaps owing to the many patients with CHD and/or the frequent use of jugular vein grafts in the RVOT. Of note, two of our patients who underwent Ross surgery with a Melody valve in the pulmonary area developed QFE. In this type of surgery, the diseased aortic valve is replaced with the person's own pulmonary valve, which in turn is replaced with a pulmonary homograft. In our patients, endocarditis developed on top of the bovine jugular vein graft in the pulmonary valve. This highlights the inherent predisposition of the jugular vein graft to IE rather than the natural pulmonary tissue placed in the aorta.

QFE usually presents with nonspecific features, resulting in delayed diagnosis. Eleven of our patients were diagnosed 2–8 months after their presentation, while six were diagnosed at 1–2 years. One patient was initially treated empirically with rifampicin for disseminated tuberculosis owing to liver granuloma, which may have contributed to the diagnostic delay. Rifampicin is bacteriostatic and is not routinely used in Q fever treatment (Bental et al., 1995). Granulomatous hepatitis is a known feature of Q fever. Doughnut granulomas with a typical fibrin ring are classically seen in primary Q fever cases. Isolated chronic granulomatous hepatitis is rarely reported, while chronic hepatitis is usually associated with endocarditis (Eldin et al., 2017).

A Q fever infection can be overlooked when another bacterial infection is present. Concomitant infection with endocarditis-associated microorganisms, such as *Streptococci, Enterococci*, and *Staphylococci*, has been reported (Kampschreur et al., 2011). Thus, Q fever should be considered in all patients with endocarditis living in endemic areas, irrespective of other identified infections (Raoult et al., 2005b). One of our patients had both a *Coxiella* and MSSA infection. More interestingly, another patient, who had consumed raw milk, had positive results for both Q fever (confirmatory serology) and *Brucella* sp. (blood cultures). *Coxiella* and *Brucella* have similar modes of transmission and animal reservoirs.

Autoimmune changes associated with QFE can also confound QFE diagnosis. Antiphospholipid and antinuclear antibodies are produced during acute infection. In one study, a very high IgG (APL) titer was associated with a relative risk of 24.9 for endocarditis development in patients with acute Q fever (Million et al., 2015). Fortunately, treatment of acute Q fever with hydroxychloroquine prevents persistent APL and reduces the number of associated complications, including thrombosis (Million et al., 2017). Three of our patients were initially diagnosed with systemic lupus nephritis. One had "full-house" SLE nephritis on biopsy. Infection-related full-house SLE with negative serology has been previously reported (Wen and Chen, 2010).

The usual manifestations of QFE are fever, anemia, and splenomegaly. In a Mayo Clinic series, fever occurred in all QFE patients, none of whom had documented splenomegaly (Scott et al., 2008). In our study, only one-third of the patients had a documented fever, while 92% of the tested patients had splenomegaly. This could be due to the delayed diagnosis in our group.

In summary, we presented the largest series of QFE cases in Saudi Arabia. We show that Q fever occurrence is not rare in the Middle East and suggest that Q fever should be considered in all cases of BCNE, as well as all cases with bovine jugular vein grafts. Explanted valves mounted on paraffin tissue should be tested via PCR for Q fever. We do not know if a single or several genotypes are circulating in Saudi Arabia. Some authorities advocate Q fever screening before new valve implantation. Further studies are needed to define the circulating strains of Q fever in camels and on explanted valves during cardiac surgery.

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Conflict of interest

All authors report no conflicts of interest.

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