

# Retrospective Examination of Q Fever Endocarditis: An Underdiagnosed Disease in the Mainland of China

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## Abstract

**Background:** Q fever endocarditis, a chronic illness caused by *Coxiella burnetii*, can be fatal if misdiagnosed or left untreated. Despite a relatively high positive rate of Q fever serology in healthy individuals in the mainland of China, very few cases of Q fever endocarditis have been reported. This study summarized cases of Q fever endocarditis among blood culture negative endocarditis (BCNE) patients and discussed factors attributing to the low diagnostic rate.

**Methods:** We identified confirmed cases of Q fever endocarditis among 637 consecutive patients with infective endocarditis (IE) in the Peking Union Medical College Hospital between 2006 and 2016. The clinical findings for each confirmed case were recorded. BCNE patients were also examined and each BCNE patient's Q fever risk factors were identified. The risk factors and presence of Q fever serologic testing between BCNE patients suspected and unsuspected of Q fever were compared using the Chi-squared or Chi-squared with Yates' correction for continuity.

**Results:** Among the IE patients examined, there were 147 BCNE patients, of whom only 11 patients (7.5%) were suspected of Q fever and undergone serological testing for *C. burnetii*. Six out of 11 suspected cases were diagnosed as Q fever endocarditis. For the remaining 136 BCNE patients, none of them was suspected of Q fever nor underwent relevant testing. Risk factors for Q fever endocarditis were comparable between suspected and unsuspected patients, with the most common risk factors being valvulopathy in both groups. However, significantly more patients had consulted the Infectious Diseases Division and undergone comprehensive diagnostic tests in the suspected group than the unsuspected group (100% vs. 63%,  $P = 0.03$ ).

**Conclusions:** Q fever endocarditis is a serious yet treatable condition. Lacking awareness of the disease may prevent BCNE patients from being identified, despite having Q fever risk factors. Increasing awareness and guideline adherence are crucial in avoiding misdiagnosing and missed diagnosing of the disease.

**Key words:** Blood Culture; Endocarditis; Q Fever

## INTRODUCTION

Q fever endocarditis is a chronic infection caused by the zoonosis *Coxiella burnetii*. Q fever infections can be common in regions where people are in close contact with livestock. However, only a small proportion of those who have acute Q fever develop the chronic form. Chronic Q fever has nonspecific manifestations, and diagnosis often occurs after serological testing and nonspecific cardiac findings.

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If left untreated, Q fever endocarditis can be severe and potentially fatal.<sup>[1]</sup> Large numbers of patients with Q fever endocarditis have been reported in Europe. Reviews of Q fever endocarditis reported a prevalence of one in one million per year,<sup>[2]</sup> and of 5% in all infective endocarditis (IE).<sup>[3]</sup> Scott *et al.* reported that Q fever endocarditis accounts for about 1% of all cases of endocarditis in the United States.<sup>[4]</sup> The literature has reported numerous cases in Western Europe and the United States, and Australia; however, there are very few reports in the literature on Q fever endocarditis in China. This study summarizes cases of Q fever endocarditis diagnosed in blood culture negative endocarditis (BCNE) patients in the Peking Union Medical College Hospital (PUMCH), compares the risk factor for Q fever among suspected and unsuspected patients, and discusses factors that may contribute to the low diagnostic rate.

## METHODS

### Patients and procedures

Six hundred and thirty-seven consecutive cases of IE, between January 2006 and August 2016, were identified from the PUMCH database and examined for cases of Q fever endocarditis. Before 2006, Q fever serological diagnostic testing available to our facility was the complement fixation method. The complement fixation method has been documented to be less specific, lack sensitivity, and be detected later than the immunofluorescence antibody assay (IFAA).<sup>[5]</sup> For this study, we focused on cases after 2006, where IFAA to detect Phase I and II *C. burnetii* antibodies from the serum was accessible. All IFAAs were done at the State Key Laboratory of Pathogen and Biosecurity of the Institute of Microbiology and Epidemiology at the Academy of Military Medical Sciences (Beijing, China). All Q fever endocarditis patients must satisfy the modified Duke criteria for IE<sup>[3]</sup> and have significant levels of immunoglobulin (Ig) G titer antibodies against *C. burnetii* (Phase I IgG titer >1:800).<sup>[6]</sup>

The PUMCH Institutional Review Board approved all procedures of this study, and each patient provided written informed consent for this study. The Q fever endocarditis patients' demographics, initial presentation, cardiovascular manifestations, other clinical features, laboratory results, serology, treatment, and follow-up were collected from each patient's medical record. Since Q fever endocarditis patients are known to have uncommon presentations, the patients' initial presentation and present history was particularly noted, and a short patient description was written for each patient. Echocardiograms, aerobic and anaerobic pathogen blood cultures were performed in all patients. No blood or resected cardiac tissue culture for *C. burnetii* was performed in these patients.

Particular attention was also paid to the BCNE patients as these patients may have risk factors warranting Q fever screening. Previous studies have identified the following presentations (1) cardiac valvulopathy or valvular prostheses defects, (2) fever without leukocytosis, (3) immunocompromised,

(4) periprosthetic leak in the absence of vegetations - place BCNE patients at risk of Q fever endocarditis.<sup>[6,7]</sup> Patients suspected of BCNE but not fulfilling the modified Duke Criteria<sup>[3,8]</sup> were excluded. The presence of Q fever risk factors was analyzed in all BCNE patients from 2006 to 2016 [Figure 1]. The reasons why some but not all patients were selected for Q fever screening were noted to understand guideline adherence and daily practice.<sup>[3,8]</sup>

### Statistical analysis

Standard descriptive statistics (including mean and standard deviation) were used to describe Q fever endocarditis patients. The differences in clinical risk factors between suspected and unsuspected BCNE patients were analyzed with Chi-squared test or Chi-squared test with Yates' correction for continuity. The level of significance was set at  $P < 0.05$ . Statistical analyses were performed with SPSS version 18.0 (SPSS Inc., Chicago, Illinois, USA).

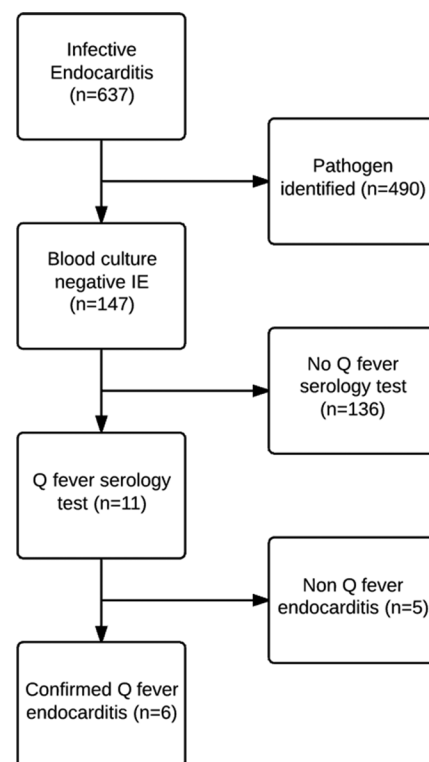
## RESULTS

### Patient demographics and initial presentation

Of the 637 cases of IE, six cases of Q fever endocarditis were found. All identified Q fever endocarditis patients were Han Chinese males and their ages ranged from 22 to 61 years old. Demographic and clinical data of the six patients were summarized in Tables 1 and 2.

#### Patient 1

A 41-year-old male cattle and sheep herdsman presenting with fever and jaundice was admitted in March 2008. The patient previously had splenectomy due to hepatosplenomegaly.



**Figure 1:** Flowchart of the infective blood culture negative endocarditis and Q fever endocarditis patient selection process.

**Table 1: Clinical findings and relative incidence of finding in Q fever endocarditis patients**

Findings	Normal value or range (unit)	Number of patients with indicated findings (%)*	Reference reports <sup>[9]</sup>
Clinical findings			
Fever	–	6 (100)	N/A
Cardiac failure	–	4 (67)	N/A
Clubbing	–	4*	N/A
Arterial embolism	–	1 (17)	N/A
Hepatomegaly	–	2 (33)	N/A
Splenomegaly	–	3 (50)	N/A
Purpuric rash	–	1 (17)	N/A
Valvulopathy			
Aortic	–	5 (83)	N/A
Mitral	–	3 (50)	N/A
Laboratory findings			
Leukocyte			
Leukocytosis	4.0–10.0 ( $\times 10^9/L$ )	0	N/A
Leukopenia		1 (17)	N/A
Anemia	110–160 (g/L)	3 (50)	40–55% with anemia
Elevated creatine	53–132 ( $\mu\text{mol/L}$ )	1 (17)	65–73% elevated
Thrombocytopenia	100–360 ( $\times 10^9/L$ )	1 (1)	26–56% with thrombocytopenia
Elevated transaminase			
AST	5–37 (U/L)	4 (67)	40–83% elevated
ALT	5–40 (U/L)	3 (50)	N/A
Hyperbilirubinemia (TBIL)	5.1–22.2 ( $\mu\text{mol/L}$ )	0	N/A
ALP	27–107 (U/L)	3 (50)	88% elevated
Elevated ESR	0–20 (mm/h)	5 (83)	N/A
Elevated LDH	97–270 (U/L)	3 (50)	94% elevated
Elevated gamma globulin	7–17 (g/L)	1*	35% present
Antinuclear antibody	<1:40	0*	60% present
Rheumatoid factor	0–20 (U/ml)	2*	40% present
Smooth muscle antibodies	<1:20	0*	N/A

\*Some patient data unavailable; exact percentages not calculated. AST: Aspartate transaminase; ALT: Alanine transaminase; ALP: Alkaline phosphatase; LDH: Lactate dehydrogenase; ESR: Erythrocyte sedimentation rate; TBIL: Total bilirubin; N/A: Not available.

He occasionally consumed moderate amounts of alcohol (approximately 100 ml of liquor daily) over the past 15 years. His hepatitis screening, for the hepatitis B, C, and D virus antibodies, returned negative.

#### Patient 2

A 22-year-old male college student with intermittent cough, fever, and episodic chest pain for 1 year was admitted in March 2010. He was diagnosed at a local hospital with viral myocarditis, acute hepatitis, and pneumonia. The patient denied having a history of heart disease or viral hepatitis.

#### Patient 3

A 61-year-old male civil servant was admitted in July 2009 for a fever and rash lasting 4 months. He began experiencing afternoon fever accompanied by chills, fatigue, sleep hyperhidrosis, and weight loss.

#### Patient 4

A 54-year-old taxicab driver was admitted in May 2012 for intermittent fever. He had undergone bioprosthetic aortic valve replacement due to chronic fever and congenital bicuspid aortic malformation 2 years prior in a local hospital.

However, his fever relapsed 10 months after the operation, and five routine blood cultures were all negative.

#### Patient 5

A 55-year-old veterinarian with chronic exposure to livestock (including cattle, sheep, and swine) was admitted in February 2015 due to fever, low appetite and weight loss for 6 months. On admission, he was also diagnosed with rheumatic heart disease. Aortic and mitral stenosis and regurgitation were found.

#### Patient 6

A 58-year-old man admitted in March 2014 due to recurring fever lasting over four years. In 2010 he underwent anti-tuberculosis treatment. Over the next few years, vegetations were found, and he was placed on various antibiotics. He underwent aortic and mitral valvuloplasty, however, 8 months after the operation his recurring fever continued, and perivalvular leaks was found.

### Cardiovascular manifestations

Four patients had congestive heart failure, ranging from Class I to III, according to the New York Heart Association

classification. One patient had previous rheumatic heart disease. Transthoracic echocardiography was performed in all patients. In five patients, the vegetation was seen on the aortic leaflet while in one patient the vegetation was seen on the papillary muscle of the mitral valve. For all patients, the vegetation was also accompanied by some degree of insufficiency and regurgitation.

### Other clinical features and laboratory results

Other clinical features were noted and can be found in Table 1. All patients presented with fever and two patients had a high-grade fever. All patients repeatedly had negative blood cultures, on average 4.4 times per person. Elevated liver enzymes, leukocytosis, leukopenia, anemia, and an increased erythrocyte sedimentation rate were observed as well. One patient (case 3) had impaired T-cell function with weight loss, hepatosplenomegaly, acropachy, and rash.

### Serology, treatment, and follow-up

To confirm the diagnosis of Q fever endocarditis, all six patients received serological testing for *C. burnetii* antigens by IFAA. All patients showed elevated IgG Phase I and Phase II antibody titers. The values upon initial diagnosis can be found in Table 1.

Upon diagnosis, all patients were treated with antimicrobial therapy. The specific drugs administered can be found in Table 2. All patients responded well except for patient 4 who continued to exhibit symptoms and high levels of Phase I and II antibodies. The patient experienced decompensated heart failure and later experienced periprosthetic valvular regurgitation and partial dehiscence

[Figure 2a]. He underwent repeat valvuloplasty with a mechanical aortic valve. Histological examination of the bioprosthetic valve revealed fibrosis, inflammatory cell infiltration, and myxomatous degeneration. Histological staining, including hematoxylin and eosin staining, gram staining, periodic acid-Schiff staining, Grocott's methenamine silver staining and acid-fast staining, all returned negative. Two weeks after receiving mechanical valvuloplasty, his titer of Phase I antibody dropped from 1:3200 to 1:800 and the titer of Phase II antibody from 1:1600 to 1:200 [Figure 2b]. He was asymptomatic at the 3-year follow-up after surgery.

Patient follow-up ranged from 24 to 53 months. A follow-up examination was performed every 3–6 months; each time a routine blood test, liver and kidney function test, echocardiogram and serological test were administered.

### Blood culture-negative endocarditis cases

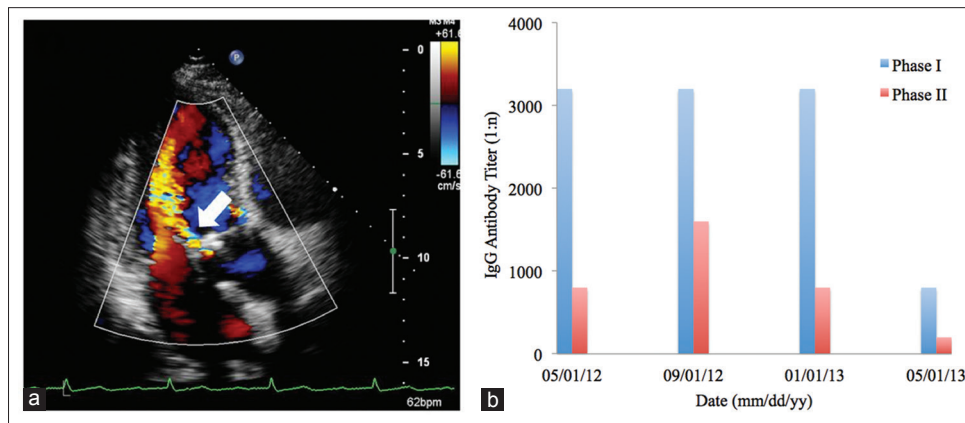
There were 637 cases of IE during the period. Four hundred and ninety cases had causative microorganisms identified through blood culturing or through tissue culturing. The remaining 147 (23.1%) cases were BCNE on unknown cause, of which 11 patients (7.5% of BCNE cases) were suspected of Q fever and underwent Q fever serological analysis by IFAA. The remaining 136 patients were unsuspected of Q fever and did not undergo relevant testing.

To understand the reasoning behind the low Q fever endocarditis diagnostic rate, we examined the clinical characteristics of the BCNE patients. It was found that among the 136 unsuspected patients, many possess risks warranting Q fever suspicion and thus serological testing. Fifty percent

**Table 2: Cases of Q fever endocarditis reported in PUMCH from 2006 to 2016**

Items	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Gender	Male	Male	Male	Male	Male	Male
Age (years)	41	22	61	54	55	58
NYHA classification	2	3	1	2	N/A	3
Symptoms	Fever, cough, jaundice	Fever, cough, chest pain	Fever, erythema	Fever, arterial embolism	Fever, weight loss, cough	Fever, chills, weakness, weight loss
Cardiac findings	Mitral aortic valve deformity, aortic valve vegetation	Vegetations on chordae tendineae of the anterior leaflet of the mitral valve	Aortic valve thickening with vegetations	Vegetations on bioprosthetic aortic valve, mild to moderate aortic perivalvular leakage	Stenosis and Regurgitation of aortic and mitral valves. Aortic valve vegetation	Atrial perivalvular abscess and vegetation. Mitral valve regurgitation
Phase I IgG	1:800	1:1600	1:>5120	1:3200	>1:1600	1:6400
Phase II IgG	1:800	1:800	1:>5120	1:800	>1:1600	N/A
Antimicrobial therapy	Minocycline	Doxycycline + SMZ-TMP	Doxycycline	Minocycline + HCQ	Amikacin + vancomycin	Minocycline + HCQ
Operation	No	No	No	Yes, due to congestive heart failure	Yes	No
Follow-up (months)	53	30	37	36	24	48
Outcome	Cure	Cure	Cure	Bioprostheticvalvuloplasty and cure	Cure	Stable*

\*Reported to be stable upon discharge, further details unknown. NYHA: New York Heart Association; SMZ-TMP: Sulfamethoxazole-trimethoprim; HCQ: Hydroxychloroquine; PUMCH: Peking Union Medical College Hospital; N/A: Not available.



**Figure 2:** Laboratory results from patient 4. (a) Transthoracic echocardiogram showing a severe perivalvular regurgitation of the bioprosthetic aortic valve (arrow). No valvular vegetations were found. (b) Serial serologic testing of immunoglobulin G against *Coxiella burnetii* showed consistently high levels of Phase I and II antibodies prior to the valvuloplasty. The Phase I antibody drop dramatically from 1:3200 to 1:800 and the Phase II from 1:1600 to 1:200 two weeks after the aortic bioprosthesis replacement.

of the patients suspected of Q fever had two or more risk factors, and this percentage was nearly identical (54%,  $n = 74$ ) in the unsuspected patients. The most and second most common risk factors were valvulopathy and fever without leukocytosis, respectively, in both groups. Apart from perivalvular leakage, both groups had a comparable proportion of each Q fever risk factor. Furthermore, all patients suspected of Q fever endocarditis were either admitted to or were consulted by the Infectious Diseases Division while only 63% of the unsuspected patients had consulted the Infectious Diseases Division ( $P = 0.03$ ). None of the unsuspected patients had undergone *C. burnetii* serological testing [Table 3].

## DISCUSSION

To the best of our knowledge, our study reported the most cases of Q fever endocarditis in the mainland of China. The patient characteristics were similar to those reported from Western countries. The patients' were predominately male and mostly over 40-year-old.<sup>[9]</sup> The patients had a high incidence of fever, abnormal liver function as exhibited by elevated liver enzymes, the telltale sign of valvular defects, and routine blood cultures were negative in all the patients.<sup>[7,10]</sup> Vegetative growth seen by echocardiography was observed in all patients despite being present in only about 12% of chronic Q fever patients.<sup>[11]</sup>

In this study, patient 4 failed to respond to combined antimicrobial therapy. Along with his persistently elevated Phase I IgG levels, the patient experienced deterioration in cardiac function and worsening of valve regurgitation. Intriguingly, not only did his symptoms improve rapidly, but his Phase I and II IgG levels fell dramatically after bioprosthesis replacement, suggesting that high levels of IgG may be associated with *C. burnetii* residing in the bioprosthesis.

Compared to tetracycline and rifampin-cotrimoxazole or its combination, doxycycline plus hydroxychloroquine is

an optimal therapeutic regimen with a lower relapse rate.<sup>[12]</sup> In this study, three patients responded well to minocycline, doxycycline or doxycycline-cotrimoxazole therapy and had no symptoms at the 30-month follow-up. It is suggested that follow-up should be conducted every month for the 1<sup>st</sup> year, then every 3 months for 18 months to 4 years,<sup>[13]</sup> and a lifelong treatment of doxycycline may be appropriate. However, whether the serial serological testing can be used as a prognostic index is still controversial.<sup>[9,14]</sup> In a report from Spain, IgG Phase I antibody levels were monitored in patients with Q fever endocarditis to see the association between the IgG titers and prognosis. After three years of follow-up, the reduction of IgG Phase I antibody was rare and not related with cure or relapse.<sup>[14]</sup>

The first confirmed case of Q-fever in China was reported in 1950.<sup>[15]</sup> However, very few cases of Q fever endocarditis from the mainland of China have been reported in the literature. Since the 1980s, there were approximately 28,000 cases of IE in the mainland of China, and only four other cases of Q fever endocarditis were reported.<sup>[13,16]</sup> Thus far, estimating the incidence of Q fever endocarditis in the mainland of China cannot be accurately made, but it is clear that the number of confirmed cases is very low. Despite the few reported Q fever endocarditis cases in the literature, reports have shown that Q fever may be fairly common. Among the 34 Chinese provinces and municipalities, 24 have reported cases of Q fever and outbreaks have also been reported in the Inner Mongolia, Sichuan, Xinjiang, Yunnan, and Tibet Provinces.<sup>[17]</sup> In these regions of China, many individuals' livelihoods involve working with livestock. A serological screening of over 3000 livestock found that the seroprevalence of Q fever was 24.9% in cattle and 13.5% in sheep.<sup>[18]</sup> Based on a seroepidemiological survey, the positive rate of Q fever serology ranges from 1.6% to 28.7% in healthy people living in the Southwestern Chinese Provinces of Guizhou, Sichuan, Yunnan, and Tibet.<sup>[15,19]</sup> The high positive rate of Q fever serology and the low number of Q fever endocarditis cases suggest that Q fever

**Table 3: Clinical characteristics of blood culture–negative endocarditis patients based on suspicion of Q fever (from 2006 to 2012)**

Characteristics	Patients suspected of Q fever (n = 11)	Patients not suspected of Q fever (n = 136)	$\chi^2$	P
Q fever risk factors, n (%)				
Valvulopathy	8 (55)	96 (71)	0.02	0.88
Fever without leukocytosis	7 (73)	79 (58)	0.13	0.72
Immunocompromised	1 (64)	23 (17)	0.46	0.50
Perivalvular leak	3 (27)	8 (6)	6.73	0.01
Number of risk factors present (%)				
≤1	5 (45)	62 (46)	0.00	0.99
≥2	6 (55)	74 (54)		
Contact with infectious disease division and guideline adherence, n (%)	11 (100)	86 (63)	4.6	0.03

endocarditis may be an underreported and under-identified disease in China.

A few factors may attribute to the low diagnostic rate of Q fever endocarditis among physicians at our facility and even throughout China. First, in our review of BCNE patients, the presence of Q fever risk factors was similar across unsuspected and suspected patient groups, suggesting special attention should be paid to BCNE patients as a whole. Fournier *et al.* reported that among 740 patients with BCNE, 37% had *C. burnetti* as the causative agent.<sup>[20]</sup> In clinical guidelines, serological analysis for *C. burnetti* has been recommended in patients with IE, especially in patients with BCNE.<sup>[3,8]</sup> This study showed that when Q fever endocarditis was suspected among BCNE patients, the diagnostic rate through serological analysis was 55%, comparable to that, 48%, reported in the literature.<sup>[20]</sup> However, in the present study, the serological testing for *C. burnetii* is performed in very few patients with BCNE. Of note, all BCNE cases that underwent serological testing were consulted by physicians in the Infectious Diseases Division. Thus, guideline adherence and awareness may not be as stringent among physicians in divisions other than infectious diseases. This suggests that awareness of Q fever endocarditis presentation, risk factors, and general guidelines is critical in the approach to BCNE patients.

Second, notifiable or reportable disease surveillance is crucial for infectious disease prevention and control. In countries such as the United States,<sup>[6]</sup> and Australia,<sup>[21]</sup> Q fever infection is a notifiable disease with each country's Center for Disease Control or equivalent. In the People's Republic of China, according to the *Chinese Infectious Diseases Prevention Act (2013 update)*,<sup>[22]</sup> there are 39 notifiable diseases and Q fever is not among the list. In addition, Q fever serology testing through IFAA is not accessible to all hospitals. For instance, only one clinical facility, the Academy of Military Medical Sciences, in Northern China, covering a population of approximately 160 million, can conduct serological testing for *C. burnetti*.

Third, empirical antibiotic therapy may have also contributed to the low diagnostic rate of Q fever. Of the 147 cases with BCNE of unknown cause, empirical antibiotic therapy was

given before admission. Empirical therapy consists mainly of gentamicin or vancomycin to target the common etiologies of IE,<sup>[23]</sup> thus, often rendering the diagnostic culturing and sampling inconclusive.<sup>[24]</sup> If there lack systematic testing protocols for uncommon pathogens, proper diagnosis of Q fever can easily be overlooked.

Due to the limited cases of Q fever endocarditis found and few BCNE patients undergoing Q fever serological testing, definitive conclusions cannot be made from this study. However, with the available data, we compared the risk factors to the literature including the IE guidelines released by the United States Center for Diseases Control.<sup>[6]</sup> We found that many patients had clinical indications where a Q fever serological test was recommended but failed to receive one.

In conclusion, this study found a low diagnostic rate of Q fever among BCNE patients. According to serological surveying and screening, Q fever or Q fever endocarditis is underestimated in China. The array of presentations and non-specific symptoms across patients remain the key challenge in diagnosing the disease. We noted limitations, specific to the mainland of China, hindering the identification, and management of this disease, among which we believe physician awareness of the risk factors and adherence to clinical guidelines play crucial roles.

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### Conflicts of interest

There are no conflicts of interest.

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