

Q fever presenting as recurrent, culture-negative endocarditis with aortic prosthetic valve failure: A case report and review of the literature

Abeer N AlShukairi MD¹, Muhammad G Morshed PhD^{2,3}, Neil E Reiner MD FRCPC FACP^{1,4,5}

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The present report describes a case of recurrent, culture-negative endocarditis presenting with aortic prosthetic valve dysfunction in a 62-year-old man who required four valve replacement surgeries. On each occasion, he presented with valve failure. Fever was only documented during his first presentation. Furthermore, no vegetations were detectable on his aortic valve at transesophageal echocardiography. On the occasion of his most recent presentation, a detailed history of animal exposure – including hunting and skinning deer, moose and other large animals with his bare hands – was the only clue to his diagnosis. Serum antibodies against *Coxiella burnetii* were strongly positive, and *C burnetii* DNA was detected by polymerase chain reaction from his resected aortic valve tissue. Q fever is a worldwide zoonotic infection with diverse reservoirs. This diagnosis should be considered when evaluating unexplained prosthetic valve dysfunction, particularly in the setting of animal exposure.

Key Words: *Coxiella burnetii*; Endocarditis; Prosthetic valve; Q fever

CASE PRESENTATION

A 62-year-old man was evaluated for recurrent prosthetic valve dysfunction in the Infectious Diseases Clinic at Vancouver General Hospital (Vancouver, British Columbia) in July 2004. He had his first bioprosthetic aortic valve replacement for presumed rheumatic aortic valve disease in August 1982, and required repair of an aortic paravalvular leak in November 1982. The patient was asymptomatic until June 2001, when he had fever and transthoracic echocardiographic evidence of aortic prosthetic valve regurgitation and no vegetations. He underwent a second bioprosthetic aortic valve replacement. Bacterial, mycobacterial and fungal cultures from the resected valve tissue were negative. Despite this, he received an empirical six-week course of vancomycin and ceftriaxone as recommended for culture-negative endocarditis. For the next 20 months, his condition was stable, until February 2003, when he presented with clinical evidence of congestive heart failure and transthoracic echocardiographic signs of severe aortic regurgitation with paravalvular leak. Again, no vegetations were apparent, and fever was not documented during this episode. This led to a third aortic valve replacement, and on this occasion a metallic St Jude valve was used (23 AGFN-756,

Une fièvre Q se présentant sous forme d'endocardite récurrente négative à la culture accompagnée d'une insuffisance de la prothèse aortique : Un rapport de cas et une analyse bibliographique

Le présent rapport décrit le cas d'un homme de 62 ans atteint d'une endocardite récurrente négative à la culture accompagnée d'un dysfonctionnement de la prothèse aortique qui a dû subir quatre chirurgies de remplacement valvulaire. À chaque occasion, il présentait une insuffisance valvulaire. On n'a documenté de la fièvre qu'à la première consultation. De plus, à l'échocardiographie transœsophagienne, aucunes végétations n'étaient décelables sur la valvule aortique. Lors de la consultation la plus récente, une anamnèse détaillée de son exposition aux animaux, y compris la chasse et le dépeçage à mains nues de cerfs, d'originaux et d'autres gros animaux, a procuré le seul indice diagnostique. Les anticorps sériques contre le *Coxiella burnetii* étaient fortement positifs et de l'ADN du *C burnetii* a été décelé dans des tissus aortiques réséqués par réaction en chaîne de la polymérase. La fièvre Q est une zoonose auprès de divers réservoirs sur la scène mondiale. Ce diagnostic devrait être envisagé lors de l'évaluation d'un dysfonctionnement inexplicable de la prothèse aortique, notamment en cas d'exposition à des animaux.

serial number 81845443, St Jude Medical Inc, USA). Intraoperatively, friable valves were noted. Bacterial, mycobacterial and fungal cultures of blood and resected valve tissue were again negative. Following a second six-week course of ceftriaxone for culture-negative endocarditis, he remained asymptomatic, with normal transthoracic echocardiographic prosthetic aortic valve hemodynamics for one year. In June 2004, he developed recurrent left-sided failure, and transesophageal echocardiography showed evidence of aortic valve regurgitation, paravalvular leak, moderate mitral regurgitation and no vegetations.

On detailed questioning, he denied any history of fever, anorexia or weight loss. There was also no history of ingestion of unpasteurized dairy products. His only travel history was within British Columbia, where he spent considerable time hunting deer and moose. He gave a clear history of skinning and butchering the 'kill' with unprotected hands. There was also a history of exposure to a parturient cat at home, five years before his current presentation. On physical examination, he had a temperature of 36.7°C and a blood pressure of 158/90 mmHg. He was not tachycardic. There were no peripheral signs of infective endocarditis, such as clubbing, splinter

¹Department of Medicine, Faculty of Medicine; ²Department of Pathology and Laboratory Medicine, University of British Columbia; ³Laboratory Services, BC Centre for Disease Control; ⁴Department of Microbiology and Immunology, Faculty of Science, University of British Columbia; ⁵Vancouver Coastal Health Research Institute, Vancouver, British Columbia

Correspondence: Dr Neil E Reiner, Division of Infectious Diseases, University of British Columbia, Room 452D, HP/E, 2733 Heather Street, Vancouver, British Columbia V5Z 3J5. Telephone 604-875-4011, fax 604-875-4013, e-mail ethan@interchange.ubc.ca

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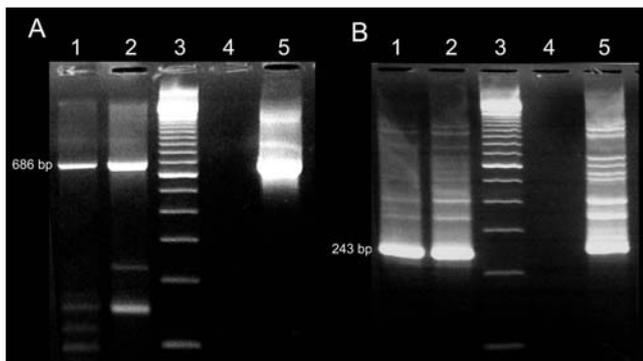


Figure 1) Nested polymerase chain reaction produced a 686 base pair (bp) outer amplicon (A) and a 243 bp inner amplicon (B) using primers based on the *Coxiella burnetii* transposase gene. Lanes 1 and 2 were loaded with material from resected heart valve tissue; Lane 3 – 100 bp ladder; Lane 4 – negative control; Lane 5 – positive control

hemorrhages, Osler's nodes, Janeway's lesions or splenomegaly. Auscultation of the precordium did not reveal any cardiac murmurs. Chest examination was significant for basal bilateral fine crackles. Laboratory investigations showed a total white blood cell count of 8.3×10^9 (normal range 4×10^9 to 11×10^9), hemoglobin level of 124 g/L (normal range 135 g/L to 175 g/L) and platelet count of 209×10^9 (normal range 125×10^9 to 350×10^9). The erythrocyte sedimentation rate was 32 mm/h (normal range 0 mm/h to 10 mm/h) and C-reactive protein concentration was 28 mg/L (normal range 0 mg/L to 6 mg/L). Serological testing for brucellosis, bartonellosis and Q fever was ordered at this time, and the patient was advised to return for follow-up in two weeks. However, his condition deteriorated suddenly, and he presented with cardiogenic shock with pulmonary edema, one week before his scheduled follow-up. He was taken to the operating room on an emergency basis and underwent a fourth prosthetic aortic valve replacement on July 14, 2004. Intraoperatively, dehiscence of his prosthetic valve was noted. A St Jude mitral prosthesis was inverted and inserted in the aortic valve annulus (33 MECJ-502, serial number 822892544, St Jude Medical Inc, USA).

Subsequently, the results of the patient's serology for Q fever were reported as strongly positive. Immunofluorescence assay technique was used to determine antibody against *C. burnetii*. The phase II titre of anti-*C. burnetii* immunoglobulin (Ig) G antibodies was higher than that of phase I (1:65,536 versus 1:32,768) in his primary specimen, which suggested an acute infection (titres under 1:256 indicate past exposure and titres over 1:256 indicate recent or active infection). *C. burnetii* DNA was also detected from his resected valve tissue by polymerase chain reaction (Figure 1), which further validated the presence of active infection. Histopathology of resected aortic valve tissue showed fibrous thickening of the valve cusp associated with degenerative changes, a focal inflammatory infiltrate of neutrophils, histiocytes and lymphocytes. Special stains for fungi and bacteria were negative. The postoperative course was complicated by a prolonged stay in the intensive care unit secondary to cardiac tamponade and intrapulmonary hematoma. Doxycycline 100 mg twice daily and hydroxychloroquine 400 mg once daily were administered postoperatively. After a prolonged hospital stay, the patient was discharged home with normal hemodynamics and aortic prosthetic valve function. Discharge medications included oral

TABLE 1
Follow-up results of indirect immunofluorescence assay immunoglobulin G

Date	Phase I	Phase II
July 2004	1:32,768	1:32,768
August 2004	1:16,384	1:32,768
January 2005	1:8192	1:16,384
April 2005	1:16,384	1:32,768
October 2005	1:32,768	1:65,536
January 2006	1:32,768	1:131,072
April 2006	1:16,384	1:65,536

ciprofloxacin 500 mg and doxycycline 100 mg, both twice daily. Rifampin was not used because of the patient's requirement for warfarin treatment and the concern about drug interactions. Follow-up *C. burnetii* serology in January 2005 revealed a transient decrease in titre with phase I IgG 1:8192 and phase II IgG 1:16,384. However, a rise in titre was noted with phase I IgG 1:16,384 and phase II IgG 1:32,768 in April 2005. Based on these results, the ciprofloxacin was replaced with hydroxychloroquine 400 mg once daily. A further rise in titre was noted, with phase I IgG 1:32,768 and phase II IgG 1:65,536 in October 2005, and the hydroxychloroquine was changed to 600 mg daily. In January 2006, his titre was still increasing, with phase I IgG 1:32,768 and phase II IgG 1:131,072. His latest serology in April 2006 revealed a decline in his titre, with phase I IgG 1:16,384 and phase II IgG 1:65,536 (Table 1). He has since remained asymptomatic, with normal prosthetic valve hemodynamics.

DISCUSSION

We describe a case of recurrent, culture-negative endocarditis with multiple episodes of prosthetic aortic valve dysfunction secondary to unrecognized chronic *C. burnetii* infection spanning a period of at least three years. The diagnosis of Q fever infection was confirmed by high titre anti-*C. burnetii* phase II antibodies, as well as by the detection of *C. burnetii* DNA in resected valve tissue by polymerase chain reaction. The true prevalence of Q fever may be underestimated because this disease can be asymptomatic in infected individuals (1). Q fever is found worldwide, and this zoonotic infection has many different reservoirs, including arthropods (mainly ticks), birds and mammals (2). The sources of human infection are usually cattle, sheep, goats and farm animals. There have been reports of transmission of disease through contact with other animals, such as dogs, cats, rabbits, pigeons and rats. *C. burnetii* can be found in the urine, feces and milk of infected mammals (3). In British Columbia, data on *C. burnetii* in animals are sparse: one of 10 mice (*Peromyscus maniculatus*) showed antibodies against *C. burnetii* from a farm area where a goat was aborted due to *C. burnetii* infection (M Morshed, personal communication). Q fever can also develop in the absence of direct animal contact. Meiklejohn et al (4) described an outbreak of Q fever among personnel involved in perinatal research at the University of Colorado Health Sciences Center in Denver, Colorado (USA). Only 41 of the 137 seropositive individuals were caring for pregnant sheep. Q fever cases were not observed after the removal of sheep from the facility.

Endocarditis is the most common manifestation of chronic Q fever. Older individuals and immunocompromised patients

are at greater risk for developing chronic Q fever (5). Pre-existing valvular heart disease and prosthetic valves are recognized risk factors for Q fever endocarditis (6-8). Siegman-Igra et al (5) reviewed 408 cases of Q fever endocarditis between 1949 and 1994. Underlying valvular heart disease was almost invariably present, and 38% of patients had prosthetic valves (5). Q fever endocarditis is rarely reported in Canada. Haldane et al (9) described five cases of Q fever endocarditis in Nova Scotia between 1981 and 1982. Four patients had underlying valvular heart disease, including two patients who had prosthetic valves.

C burnetii is not a true rickettsia-like organism, but rather a gamma proteobacteria (order Legionellales), with its closest relationship among pathogenic bacteria being *Legionella pneumophila*. *C burnetii* is a pleomorphic Gram-negative intracellular coccobacillus with distinct characteristics that contribute to its pathogenicity. It infects and multiplies in macrophages and survives within phagolysosomes. The organism also undergoes sporulation in the environment, where it can withstand harsh conditions for extended periods of time (10). *C burnetii* and *Bartonella* species appear to be the most common etiological agents of culture-negative endocarditis caused by fastidious or difficult-to-grow organisms. Compared with culture-positive cases, the etiological diagnosis of culture-negative endocarditis is delayed, resulting in an increased risk of valve destruction, septic emboli and higher mortality (11).

Endocarditis is a particularly severe and often fatal form of chronic Q fever infection. The mortality from Q fever endocarditis was 24% in one case series (12). Compounding the diagnostic difficulties in Q fever endocarditis is the nonspecific nature of the clinical symptoms with which patients present. Constitutional symptoms, congestive heart failure and valvular dysfunction may be the initial presenting symptoms (13). In a review of 19 cases of Q fever endocarditis (8), only five patients had fever, while 10 patients presented with heart failure and valvular dysfunction. Houpiikian et al (14) described the changing clinical presentation of 15 cases of Q fever endocarditis between 1999 and 2000 compared with 15 cases reported in 1987. Significant decreases were found in the prevalence of heart failure, anemia, leukopenia and abnormal liver function test results in patients who had Q fever endocarditis after 1997 (14). Because *C burnetii* is an intracellular pathogen, it does not grow in conventional blood cultures and requires special cell culture conditions (11). Vegetations are seen infrequently on echocardiography. Among the 19 cases of Q fever endocarditis reviewed by Salamand et al (8), transthoracic and transesophageal echocardiography were considered positive for vegetations in only six cases.

In another review of 63 cases of apparently culture-negative endocarditis (15), organisms were identified among 31 cases using serology, microscopy, culture or polymerase chain reaction of resected valves. Diagnosis of Q fever endocarditis can be confirmed readily by serology (16). There are several serological tests available for the diagnosis of Q fever, including complement fixation, indirect immunofluorescence assay (IFA) and ELISA. Although a complement fixation titre of 1:200 has been considered to be diagnostic for Q fever endocarditis (10), other more sensitive assays are available, such as IFA. Indirect immunofluorescence offers good sensitivity and specificity and it is considered the reference test of choice for the diagnosis of *Coxiella* endocarditis (17). In the revised Duke criteria of infective endocarditis, an IgG anti-phase I antibody IFA

titre of over 1:800 is used for the diagnosis of Q fever endocarditis (16). In contrast, Houpiikian and Raoult (11), in their review of practice guidelines for the diagnosis of culture-negative infective endocarditis, suggested that a cut-off of over 1:1600 (phase I IgG IFA) be used for the diagnosis of Q fever endocarditis. They cited that this titre provided a positive predictive value of 98% (11,18). Thus, there is a general consensus that IgG IFA phase I titres of at least 1:800 are highly indicative of Q fever endocarditis. In addition to a role in diagnosis, phase II IFA titres are also useful in monitoring response to treatment of Q fever (17).

When evaluating patients with unexplained prosthetic valve dysfunction – as the current case illustrates – it is of the utmost importance to obtain a detailed history of contact with animals. In addition, a high index of clinical suspicion for Q fever endocarditis is required in the setting of culture-negative, prosthetic valve endocarditis. Issartel et al (19) reported a case of unexplained severe mitral regurgitation. The diagnosis of Q fever was confirmed by *C burnetii* serology, polymerase chain reaction, positive culture of valve tissue on human embryonic lung fibroblasts and immunohistochemistry (19). Nosedá et al (20) reported a case of unexplained culture-negative endocarditis requiring mitral valve replacement, followed five years later by another episode of culture-negative endocarditis. In the second episode of endocarditis, Q fever was considered and *C burnetii* antibody titre was high. Retrospective review of the resected valves from the first episode of endocarditis, using the Giemsa and Machiavello stains, revealed coccobacilli, consistent with *C burnetii* infection (20).

The optimal choice and duration of antibiotics for Q fever endocarditis have not been established. Levy et al (21) evaluated different antibiotic regimens for the treatment of 32 cases of Q fever endocarditis. The combination of doxycycline and quinolones appeared to be more effective than doxycycline alone in reducing mortality. On the basis of clinical, serological and valve tissue culture results, no treatment regimen was found to cure Q fever endocarditis within two years, even with a combination of antibiotics. The investigators advised a minimum duration of treatment of three years, with therapy combining a quinolone with doxycycline (21). In addition, limited experience appeared to suggest that a combination of doxycycline plus hydroxychloroquine was superior to doxycycline alone in preventing the development of endocarditis in the management of acute Q fever (6). In a meta-analysis of 408 cases of Q fever endocarditis, Siegman-Igra et al (5) reported that the death rate was significantly lower among patients who received a tetracycline in combination with rifampin, ciprofloxacin or trimethoprim-sulfamethoxazole (18%) compared with patients treated with a tetracycline alone (44%). Despite prolonged and combined medical therapy, valve dysfunction may be a late sequelae necessitating valve replacement. In a series (8) evaluating 19 cases of Q fever endocarditis (including 10 with prosthetic valves), early valve replacement was carried out in 15 patients for hemodynamic instability, hemolytic anemia and perivalvular abscess. Three of the four patients who initially received medical therapy alone subsequently required surgery to correct due to failure of the bioprosthesis. Of the 16 patients for whom long-term follow-up was available, none showed signs of recurrence. All patients were treated with combined doxycycline/hydrochloroquine or a quinolone for a mean duration of 24 months. The mean follow-up time was 40 months (8). Whether aggressive and

early surgical therapy for Q fever prosthetic valve endocarditis may decrease the frequency of late relapse is not known and requires further study. Irrespective of therapeutic regimen and duration of treatment, patients with Q fever endocarditis require prolonged follow-up because of the possibility of late relapse (13). In vitro studies have evaluated factors contributing to antibiotic failure and late relapse of Q fever endocarditis. The acidic environment of the phagolysosome where *C burnetii* resides inhibits antibiotic activity. The addition of amantadine and chloroquine to *C burnetii*-infected cells decreases the acidity of the phagolysosome and enhances the activity of doxycycline. The combination of doxycycline with amantadine or chloroquine may be more effective in sterilizing Q fever endocarditis compared with doxycycline monotherapy (22).

In conclusion, Q fever should be considered when evaluating patients with unexplained prosthetic valve dysfunction,

even in the absence of constitutional manifestations. A detailed history of exposure to animals, including pets, is crucial. Serology for *C burnetii* should be requested in all such cases. It would be of interest to have population-based data for *C burnetii* serology to evaluate titres in asymptomatic individuals with a history of exposure to pets. Further studies are required to evaluate the optimal antibiotic regimen and duration of therapy for Q fever endocarditis. The role of early surgery for prosthetic valve Q fever endocarditis in preventing relapses needs to be determined.

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