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Case Report

# Culture-negative polymicrobial chronic Q fever prosthetic valve infective endocarditis utilizing 16S ribosomal RNA polymerase chain reaction on explanted valvular tissue

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ABSTRACT

*Coxiella burnetti* is the causative organism of the zoonotic infection Q fever, of which endocarditis is one of the most common manifestations of the chronic form. Polymicrobial endocarditis with Q fever is extremely rare and is yet to be described among an Australasian cohort.

*Summary:* We present the case of a 32-year-old gardener with culture-negative chronic Q fever prosthetic valve endocarditis concomitant with another bacterial pathogen, leading to aortic root abscess formation, requiring a Bentall procedure, extracorporeal membrane oxygenation, and prolonged antimicrobial therapy, with a fatal outcome. Unique to our case, Q fever was identified early, and the second pathogen was only detected on 16S ribosomal RNA (rRNA) polymerase chain reaction of explanted valvular tissue.

Given the high risk for morbidity, we recommend that screening for Q fever in endemic areas among patients with infective endocarditis from other etiologies be considered. In addition, this case highlights the role for Q fever vaccination of the at-risk population with underlying valvulopathy. Furthermore, clinicians should be aware of polymicrobial infective endocarditis and suspicious in case of patients with atypical clinical features.



## Case

A 32-year-old White former army officer and rural landscape gardener was admitted with complaints of acute chest pain and dyspnea on a background of several weeks of constitutional symptoms and pharyngitis.

Three years before presentation, he was treated for culture-negative infective endocarditis, requiring an aortic annulus repair, bovine pericardial patch, bioprosthetic aortic valve replacement, and mitral valve repair. A 16S rRNA polymerase chain reaction (PCR) performed on aortic valve tissue determined a 99% sequence similarity to a *Streptococcus spp*. He was treated with 4 weeks of intravenous (IV) ceftriaxone and vancomycin, after which he recovered and was discharged.

He remained well until 6 months before presentation, where in the context of an acute febrile illness, a diagnosis of acute Q fever was suspected by a community practitioner, and he received a 2-week course of oral doxycycline. Echocardiography was not performed, and he was subsequently lost to follow-up.

His social history was notable for 5 units of daily alcohol, a 4-pack year history of tobacco smoking, noninjectable recreational drug use, and wild pig and kangaroo hunting.

On admission, physical examination revealed evidence of upper limb splinter hemorrhages and an ejection systolic murmur loudest over the aortic area. Pathology results detected a C-reactive protein level of 50 mg/dl and total white blood cell count of 17,900/mm$^3$. Admission electrocardiogram showed first-degree heart block with a PR interval of 209 ms. Transthoracic echocardiography (TTE)

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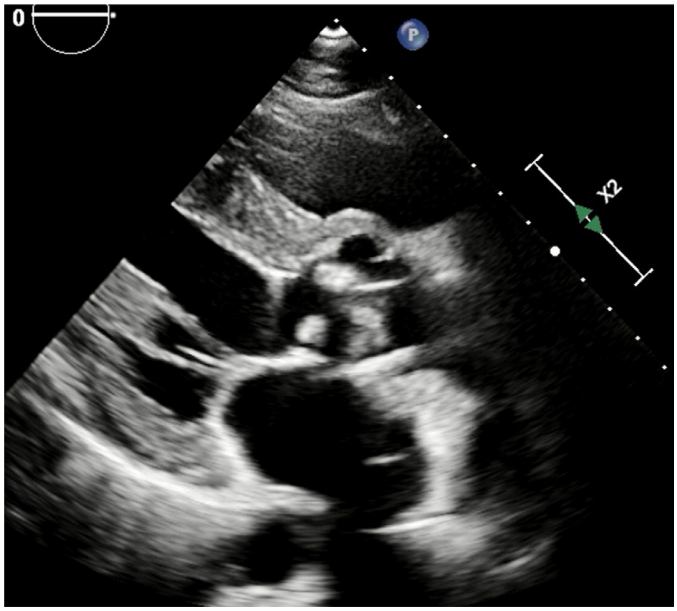


**Figure 1.** Admission transthoracic echocardiogram (parasternal long access view) - aortic valve vegetation/root abscess cavities.

displayed a vegetation on the bioprosthetic aortic valve and an aortic root abscess around the entire circumference of the aortic annulus (Figure 1). He was commenced on IV vancomycin and ceftriaxone on the suspicion of a recurrent streptococcal infection, given his history and pharyngitis.

Multiple blood and mycobacterial cultures drawn throughout his admission were negative; however, *C. burnetti* serology returned suggestive of chronic Q fever (immunoglobulin G [IgG] phase I titer >51,200; IgG phase II titer >51,200). Q fever PCR using two *Coxiella* specific gene targets (Com1 and htpAB) on peripheral blood was negative. Therapeutic oral doxycycline and hydroxychloroquine were added at day 9 to management and vancomycin ceased.

During his inpatient stay, our patient was noted to have several concerning features of deterioration, including recurrent episodes of nonsustained ventricular tachycardia alongside transient bilateral visual loss and peripheral sensory changes, suggestive of microemboli.

A total of 15 days after presentation, he underwent aortic root replacement, coronary ostial reimplanation, and metallic aortic valve replacement. Surgical findings included a circumferential peri-annular abscess extending down to muscular and membranous intraventricular septum with microabscess formation. Intraoperatively, he required cardioversion for recurrent tachyarrhythmia and commenced venoarterial extracorporeal membrane oxygenation (ECMO) a day later in the context of presumed septic shock and high-output cardiac failure.

In view of escalating inotropic requirement and fevers, therapy was changed to piperacillin-tazobactam, vancomycin, moxifloxacin, doxycycline, and hydroxychloroquine. Repeat echocardiography was suggestive of an anterior regional wall abnormality consistent with a myocardial perfusion defect.

Day 4 postoperatively, he was afebrile, and therapy rationalized to ceftriaxone, doxycycline, and hydroxychloroquine. ECMO was complicated by persistent circuit thrombosis and subsequently weaned.

Over the next day, he experienced rising inotropic demands, and a TTE displayed worsening septal and apical akinesia. This was followed by a pulseless electrical activity arrest, from which he was not able to be revived.

Tissue from the explanted aortic valve and abscess fluid had no growth on bacterial, mycobacterial, and fungal culture; however, *C. burnetti* DNA was detected on PCR using the Com1 and htpAB gene targets. 16S rRNA PCR that was performed through a conventional Sanger sequencing method identified a mixed sequence indicative of more than one bacterial pathogen. Further molecular sequencing and analysis could not be performed, and the second species was unable to be identified.

Of note, his tests were negative for *Legionella* and *Brucella* serology during his admission, with a low positive *Bartonella* IgG titer of uncertain significance (1:128). Postmortem microscopy of the myocardial tissue displayed extensive necrosis, organizing inflammation, granulation tissue, and fibrosis. Ziehl-Neelsen, Rhodamine auramine, Periodic acid-Schiff, Grocott methenamine silver, and Gram staining of the autopsy sample were negative.

## Discussion

Q fever is the most commonly reported zoonotic disease in Australia (Eastwood et al., 2018). Human transmission of the intracellular Gram-negative coccobacillus *C. burnetti* occurs through aerosolization of infected animal secretions. Proximity to animals and farm work are known occupational hazards. In an Australian setting, serologic evidence of *C. burnetti* has been identified in a range of wildlife, including kangaroos, possums, dingoes, wild pigs, cats, bandicoots, and foxes (Cooper et al., 2012). In addition, kangaroos have been implicated as likely host animals in a sylvatic cycle of coxiellosis involving Australian ticks (Graves and Stenos, 2017).

Approximately 1–5% of all acute Q fever cases progress to chronic infection, of which alongside vascular infection, endocarditis is one of the most frequent manifestations (Deyell et al., 2006; Kampschreur et al., 2014). The probability of endocarditis is greater in those with known valvulopathy or prosthetic cardiac material, where it is recommended that a minimum of 12 months of prophylactic doxycycline alongside concomitant hydroxychloroquine is administered to lower the risk of progression (Million et al., 2013).

Polymicrobial endocarditis involving any pathogen is rare and at increased risk in those with prosthetic valves, a history of injecting drug use, and previous endocarditis (Shah et al., 2015). Polymicrobial endocarditis relating to Q fever is rarer. To our knowledge, there are only 11 cases of dual-pathogen Q fever endocarditis reported to date, all outside Australasia (Kaech et al., 2008; Kampschreur et al., 2011; Raoult et al., 2005; Rovery et al., 2009; Yahav et al., 2015). All described cases had coinfection with a typical endocarditis-causing pathogen: *Streptococcus, Enterococcus*, and *Staphylococcus* spp. Aortic root abscess formation was reported in only one other case (Yahav et al., 2015).

Echocardiography is classically insensitive at diagnosing infective endocarditis in chronic Q fever, with small vegetations seen on valves, if at all. In such cases, a diagnosis of endocarditis may also be made through the use of the modified Dukes criteria with supportive microbiology, such as the identification of *C. burnetti* on PCR in blood or tissue or when serologically significant phase 1 IgG antibody titers ≥1:800 are noted, with fluorodeoxyglucose-positron emission tomography/computed tomography (CT) and cardiac CT recommended as tools to further evaluate for paravalvular infection (Kamprschreur et al., 2015). Microabscess and root abscess formation are rarely described (Deyell et al., 2006). This raised suspicion for a second culprit organism in our case.

Although testing for *C. burnetti* is included in the workup for culture-negative endocarditis, it is not standard practice to investigate for other pathogens when a causative organism has already been identified. However, the indolent progression of valvular damage in chronic Q fever is thought to make patients more susceptible to endocarditis with other organisms (Kampschreur et al., 2012; Paymard et al., 2015). This case is remarkable for the unique

presentation of *C. burnetti* prosthetic valve infective endocarditis, with the suspicion of a second organism established using 16S rRNA PCR on valvular tissue.

We believe *C. burnetti* serologic testing should be considered in all patients from an endemic area with infective endocarditis and pre-existing valvulopathy even where a typical pathogen has been isolated. Furthermore, this case highlights the ongoing need for education of the at-risk population to take appropriate infection-control precautions in high-risk settings, including Q fever vaccination. Furthermore, clinicians should be aware of Q fever polymicrobial infective endocarditis and suspicious of such in patients with atypical clinical features, such as in our case.

## Conflict of interest

The authors declare no conflict of interest.

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## Ethical approval statement

The subject's next of kin was informed about the purposes of the report and signed a consent form. A copy of the written consent is available for review by the editor of this journal.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.05.011.

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