

Q fever endocarditis after right ventricle to pulmonary artery conduit insertion: Case series and review of the literature

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ABSTRACT

Q fever (QF) is rarely reported in children. Awareness of the disease and newer diagnostic modalities have resulted in increasing recognition of unusual manifestations. We present three cases of QF endocarditis after right ventricle to pulmonary artery conduit insertion in children.

Keywords: Conduits, *Coxiella burnetii*, endocarditis, Q fever

INTRODUCTION

Q fever (QF) is a zoonotic disease that is caused by the obligate intracellular bacteria *Coxiella burnetii*. Edward Derrick first described the illness Q (for query, owing to the elusiveness of its etiology) fever in 1937 during a cluster of acute febrile illness in abattoir workers in Brisbane, Queensland, Australia.^[1] QF affects all ages, but is mostly reported in those aged 30–70 years. Chronic QF is rare in children, and blood culture-negative endocarditis is the usual manifestation of chronic QF mostly occurring in patients who have had prior valvular damage or who are immunocompromised. Here, we present three cases of QF endocarditis (QFE) after right ventricle to pulmonary artery (PA) conduit insertion in children.

CASE REPORTS

Case 1

AA is a 15-year-old boy with truncus arteriosus Type 1, who underwent Rastelli operation during early infancy. This was followed later with stenting of the right ventricular (RV) outflow tract. At the age of 10 years, he underwent placement of a 25-mm bovine valved conduit. Four years later, he presented with a 2-month

history of fever, and on examination, he had massive splenomegaly. All blood cultures for bacteria and fungi were negative and serological analysis for Brucella species was negative. Transthoracic echocardiography showed a small subvalvular vegetation in the conduit. In view of massive splenomegaly and negative blood cultures, QFE was suspected, and blood samples were sent to the research laboratory of Dr. Didier Raoult in France for serology. Serological investigations showed an antiphase I immunoglobulin G (IgG) titer of 3000 (normal titer <800), which represented chronic QF. Further, detailed history-taking ruled out any known QF infection in the past, but it was documented that he had contact with farm animals and drank unpasteurized camel's milk. Once the diagnosis was documented, he was started on doxycycline and hydroxychloroquine, along with a brief course of isoniazid 300 mg once daily for 3 months. After 1 month of treatment, his infected valved conduit was replaced with a 27-mm Carpentier-Edwards valve.

Case 2

AB is a 12-year-old girl, who had been operated for Tetralogy of Fallot during infancy, and 5 years later,

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she had right ventricle to PA conduit with a 14 mm Hancock valved conduit for RV outflow obstruction. Three years later, she presented with a prolonged history of fever and hepatosplenomegaly. All blood cultures for bacteria and fungi were negative. Results of serological analysis for *Brucella* species were negative. Transthoracic echocardiogram showed no vegetations. Her QF serological investigations showed antiphase I IgG titer of 2000 (normal titer <800), which represented chronic QF. Further, detailed history-taking ruled out any known QF infection in the past, contact with farm animals, or consumption of unpasteurized milk. She was started on hydroxychloroquine and doxycycline. Since she developed allergic reactions to these drugs, she was shifted to moxifloxacin and rifampicin and planned to continue this for 2-year duration. One month after starting treatment, the right ventricle to PA conduit was replaced with an 18-mm aortic valved homograft.

Case 3

AC is a 3-year-old girl, a case of Tetralogy of Fallot with pulmonary atresia and major aortopulmonary collaterals. At the age of 1 year, she underwent closure of ventricular septal defect, right ventricle to PA conduit insertion (14 mm Contegra), and ligation of major aortopulmonary collateral arteries. Two years later, she presented with persistent fever and hepatosplenomegaly. Detailed history-taking ruled out any known QF infection in the past, contact with farm animals, or consumption of unpasteurized milk. All her blood cultures were negative for bacteria and fungi. Her serological analysis for *Brucella* species was negative. Her erythrocyte sedimentation rate (ESR) and liver enzymes were elevated. Transthoracic echocardiogram showed a small vegetation in the Contegra conduit. Her QF serological investigations showed antiphase I IgG titer of 1500 (normal titer <800), which represented chronic QF. She was commenced on doxycycline and hydroxychloroquine therapy, under advice from the infectious diseases team. Now, she is scheduled for replacement of the Contegra conduit.

Most *C. burnetii* infections are due to inhalation of aerosols or dust contaminated with dried birth fluids or excreta from infected animals. Less frequent routes of infection include ingesting contaminated milk, tick bite, or fomite transmission. Person-to-person and mother-to-fetus transmissions have been reported, and the incubation period is 2–3 weeks. Approximately 60% of cases are asymptomatic. Patients with acute infection can be asymptomatic or can present with a flu-like illness, pneumonia, or hepatitis. Approximately 5% of patients develop chronic QF, months or years after initial infection. Differential diagnosis includes any febrile illness with constitutional symptoms such as Brucellosis and influenza.

QFE is one of the main causes of culture-negative endocarditis.^[1] It is important to note that the clinical presentation of endocarditis due to atypical organisms, such as *C. burnetii*, is usually insidious, lacks the typical features of bacterial endocarditis, and often results in delayed diagnosis. Despite increasing awareness, recent studies demonstrate a mean delay of 7 months from symptom onset to diagnosis.^[1]

There are many peripheral manifestations of QFE that can provide essential clues as to the diagnosis. Specifically, hepatomegaly and splenomegaly are evident on physical examination in up to one-half of cases.^[1] Mild hepatitis is usually seen, and ESR will be significantly elevated. Many hematological abnormalities are also observed in up to 50% of cases, with the most frequent being anemia.

Chronic infection occurs almost exclusively in two groups: those with preexisting valvular heart disease and those who are immunocompromised.^[2] In one recent series, patients with a valvulopathy and acute QF had a 38.7% chance of going on to develop endocarditis.^[3] Patients with valvular prostheses are at the greatest risk.^[2] The median time to development of chronic QF was 6 months following acute infection, although a latent period of up to 20 years has been reported.

In our series, in one case, there was a mammal contact, but there was no proof of its association with the infection. Furthermore, as we noticed, all our cases had valvulopathy, which is considered one of the risk factors for QF infective endocarditis. One of our patients is the youngest with QFE reported in the literature.

The diagnosis of QFE is usually based on serological investigations, bacterial cultures, and polymerase chain reaction testing. Echocardiography, usually the mainstay of diagnostic imaging in endocarditis, is of limited value in chronic QF. In fact, transthoracic echocardiography reveals abnormalities in only 12% of cases. This is mainly due to the small size and nodular shape of the typical vegetations. While transesophageal echocardiography is far superior in demonstrating lesions, it too has significant limitations. In our series, two out of three patients had small vegetation in the valved conduit.

The diagnosis of QFE is hampered by the inability to culture *C. burnetii* using routine media. The diagnosis of chronic QF, therefore, relies on serological testing. Diagnosis of acute QF is confirmed by serologic evidence of a fourfold increase in phase II IgG through an immunofluorescent assay test between paired sera taken 3–6 weeks apart. A single high-serum phase II IgG titer in the convalescent stage may be considered as evidence of probable infection. Chronic QF is characterized by increased titers against the phase I antigen. An IgG antiphase I antibody titer of 1:800 or greater has a specificity of 99.6% for the diagnosis of chronic QF.

In fact, the Duke's criteria^[4] have been modified to include this serological cutoff as a major criterion for the diagnosis of endocarditis.

In 2014, Yuan studied right-sided infective endocarditis (IE) and reported that the risk of IE was 6.6% in conduits in comparison to 3.7% in prosthetic valve materials. Fifty out of 63 patients had positive serology test, of which one patient tested positive for *C. burnetii*.^[5]

In a recent review done by Patel *et al.*, the incidence of IE was found to be higher in patients with Contegra conduits compared with that in patients with homografts or other bioprosthesis.^[6]

QFE was also associated with porcine bioprosthetic valves as it was found in a case series done by Fernández-Guerrero *et al.* in 1998. In three patients with subacute or chronic course, *C. burnetii* was isolated in all three of them.^[7]

In our three cases presented, all had RV to PA conduit, had similar clinical picture, a high index of suspicion due to blood negative cultures, and all had serology positive for QF infection.

Adherence to standard precautions during care of patients prevents transmission. Symptomatic patients with acute QF should be treated for 2 weeks with doxycycline. Children aged younger than 8 years with mild illness, pregnant women, and patients allergic to doxycycline can be treated with trimethoprim-sulfamethoxazole.

The optimal treatment of QFE has not been completely defined, in part due to the difficulty of its culture and the inapplicability of conventional antibiotic susceptibility assays. In the model developed by Raoult *et al.*,^[8] only doxycycline in combination with chloroquine exhibited bactericidal activity. Specifically, the combination of a fluoroquinolone with either doxycycline or rifampin was successful in controlling infection, although relapse rates were as high as 50% at discontinuation despite prolonged therapy of up to 3 years. More recently, the combination of doxycycline and chloroquine was compared with doxycycline and ofloxacin in a nonrandomized, nonblinded study. The doxycycline and chloroquine group experienced markedly fewer relapses; in fact, no relapses were observed after 18 months of treatment.

Upon completion of therapy, the antibiotics can be discontinued if the patient exhibits clinical improvement in addition to a fourfold decrease in phase I IgG levels and the complete disappearance of phase II IgM titers. Decreases in antibody levels despite specific therapy are very slow, and, in some patients, plateau without decreasing. Raoult^[9] suspects that antiphase I IgA and IgG titers of <1:200 are indicative of cure, at least for endocarditis, and that treatment must be maintained

until that level is reached. This rarely occurs within 2–3 years after initiation of treatment.

QFE is a potentially fatal disease if not diagnosed and treated in time. It has been recommended that patients who are successfully treated for acute QF should have serological follow-up every 4 months for 2 years. In the setting of QFE, due to risk of relapse even after successful treatment, it is recommended that patients should have serological follow-up for at least 5 years because of the possibility of later relapse.^[9]

Acute QF is often a mild or self-limiting illness with a low risk for death. The clinical course of QFE is often severe. Untreated chronic QFE or vascular infection is often fatal. The mortality among cases reported before 1987 was 37%. In a recent series, a mortality rate of only 10% was observed in cases diagnosed in a mean period of 6 months after presentation.^[10]

CONCLUSION

QFE may be one of the causes of blood culture-negative endocarditis. The diagnosis is often significantly delayed or even missed, resulting in significant morbidity and mortality. However, it is imperative that physicians maintain a high index of suspicion, especially among patients with Contegra conduit and those who are immunocompromised. Patients with QFE need prolonged course of antimicrobial therapy and require prolonged follow-up because of the possibility of later relapse.

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Conflicts of interest

There are no conflicts of interest.

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