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Chronic Q Fever-Related Dual-Pathogen Endocarditis: Case Series of Three Patients▽

Linda M. Kampschreur,[1]* Jan Jelrik Oosterheert,[1] Cornelia A. de Vries Feyens,[2] Corine E. Delsing,[3] Mirjam H. A. Hermans,[4] Ingrid L. L. van Sluisveld,[5] Peter J. Lestrade,[6] Nicole H. M. Renders,[7] Peter Elsman,[2] and Peter C. Wever[7]

Division of Medicine, Department of Internal Medicine and Infectious Diseases, University Medical Center Utrecht, Utrecht, Netherlands[1]; Department of Cardiology, Jeroen Bosch Hospital, 's-Hertogenbosch, Netherlands[2]; Department of Internal Medicine and Infectious Diseases, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands[3]; Molecular Diagnostics, Jeroen Bosch Hospital, 's-Hertogenbosch, Netherlands[4]; De Peperstoep, Gameren, Netherlands[5]; Department of Internal Medicine, Jeroen Bosch Hospital, 's-Hertogenbosch, Netherlands[6]; and Department of Medical Microbiology and Infection Control, Jeroen Bosch Hospital, 's-Hertogenbosch, Netherlands[7]

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Following *Coxiella burnetii* infection, there is a 1 to 5% risk of chronic Q fever. Endocarditis, mycotic aneurysm, and vascular prosthesis infection are common manifestations. We present three patients with endocarditis by *C. burnetii* concomitant with another bacterial pathogen. Chronic Q fever should therefore be considered in all endocarditis patients in regions where Q fever is endemic.

CASE REPORTS

Case 1. The first patient was a 69-year-old man with a history of acute rheumatoid disease, congenital combined mitral valve insufficiency and stenosis, and severe aortic valve insufficiency, for which he received an aortic valve prosthesis 31 years ago. Two months before presentation, he had been hospitalized because of suspected sepsis and congestive heart failure. At that time, *Coxiella burnetii* serology (immunofluorescence assay; Focus Diagnostics, Inc., Cypress, CA) was found positive and PCR was not yet available. A diagnosis of acute Q fever was suspected (Table 1). Blood, sputum, and urine cultures revealed no other pathogens. He was treated with moxifloxacin for 2 weeks, after which he recovered and was discharged. Two months later, he presented with fever, chills, and dizziness. He also complained of shortness of breath and paroxysmal nocturnal dyspnea. Upon physical examination, he had a systolic murmur at the left fifth intercostal space that had not been reported before. Laboratory results are displayed in Table 2. Under suspicion of endocarditis, treatment with amoxicillin and gentamicin was initiated. Transthoracic echocardiography (TTE) showed progression of mitral valve insufficiency but no vegetations. Multiple blood cultures grew *Streptococcus salivarius.* In addition, *C. burnetii* serology was suggestive of chronic Q fever. PCR for *C. burnetii* was positive on serum of this episode. In retrospect, PCR on serum drawn during the first admission also proved to be PCR positive (Table 1). A diagnosis of dual-pathogen endocarditis with *S. salivarius* and *C. burnetii* was made. Doxycycline and hydroxychloroquine with a planned duration of 24 months were added to the antibiotic regimen. Throughout the 21-month follow-up, medication levels have been adequate. No worsening of mitral valve function was detected with repeated echocardiography. Serology revealed a gradual 4-fold decrease of phase I IgG and the disappearance of phase II IgM. PCR for *C. burnetii* proved negative after 6 months of treatment (Table 1).

Case 2. The second case involved a 71-year-old man with a history of hypertension. Two months before presentation, he had been treated with penicillin for culture-proven meningitis and bacteremia caused by *Streptococcus mitis.* To exclude endocarditis as a cause for *S. mitis* bacteremia, a TTE had been performed which showed mild mitral valve regurgitation but no other abnormalities and no vegetations. He was discharged in fairly good condition. Two months later, he presented with chest pain and a fever. He reported that he suffered from episodes of feeling warm and cold, malaise, and loss of energy. On examination, there was a new systolic murmur on the apex. Laboratory results are shown in Table 2. Serology for *C. burnetii*, requested by the general practitioner 1 week before presentation, revealed titers suggestive of chronic Q fever, which was confirmed by a positive serum PCR for *C. burnetii* (Table 1). TTE showed severe eccentric mitral valve insufficiency with a vegetation on the anterior mitral valve leaflet. Thoracic computed tomography (CT) angiography to rule out aortitis was without abnormalities. A positron emission tomography (PET) scan revealed no other localization for chronic Q fever. Under suspicion of chronic Q fever endocarditis, treatment with doxycycline and hydroxychloroquine was initiated with a planned duration of 18 months. However, after several days, multiple blood cultures again grew *S. mitis*. A diagnosis of dual-pathogen endocarditis with *S. mitis* and *C. burnetii* was made, and treatment with penicillin and gentamicin for 6 weeks was added. He responded well, and 6 months later he performed physical activities without complaints. The phase I IgG antibody titer had dropped to 1:4,096, while the phase II IgM titer dropped to 1:32. Serum PCR became negative at 6 months of treatment (Table 1). Repeated TTE showed no progression of mitral valve insufficiency, regression of vegetations, and good left ventricular function.

* Corresponding author. Mailing address: Division of Medicine, Department of Internal Medicine and Infectious Diseases, Room F02-107, University Medical Center Utrecht, P.O. Box 85500, 3508 GA Utrecht, Netherlands. Phone: 0031 (0)88-7556228. Fax: 0031 (0)30-2523741. E-mail: l.m.kampschreur@umcutrecht.nl.

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TABLE 1. *C. burnetii* serology (IFA) and PCR[a]

Patient and sampling time	Titer				Serum PCR result
	Phase I IgM	Phase I IgG	Phase II IgM	Phase II IgG	
1					
First admission	1:1,024	1:2,048	1:2,048	1:2,048	Positive
Second admission[b]	1:8,192	1:32,768	1:8,192	1:16,384	Positive
After 6 mo of treatment	1:1,024	1:8,192	1:2,048	1:8,192	
After 12 mo of treatment	1:64	1:4,096	Negative	1:4,096	
After 21 mo of treatment	Negative	1:1,024	Negative	1:2,048	Negative
2					
At admission	1:512	1:65,536	1:256	1:65,536	Positive
After 6 mo of treatment	1:32	1:4,096	1:32	1:4,096	Negative
3					
At admission	1:64	1:4,096	1:64	1:2,048	Negative

[a] IFA, immunofluorescence assay; phase I IgM, IgM antibodies to *Coxiella burnetii* phase I antigens; phase II IgM, IgM antibodies to *C. burnetii* phase II antigens; phase I IgG, IgG antibodies to *C. burnetii* phase I antigens; phase II IgG, IgG antibodies to *C. burnetii* phase II antigens.
[b] Two months after the first admission.

Case 3. The third case was an 88-year-old woman with a history of hypertension and cholecystectomy. Two days before presentation, she had experienced chills, vomiting, and collapse, which recovered spontaneously. At presentation, she had chills, fever, a productive cough, and exertional dyspnea. Physical examination revealed a new systolic murmur at the second intercostal space on the left. Laboratory results are shown in Table 2. Under the suspicion of acute endocarditis, treatment with flucloxacillin and gentamicin was initiated. Multiple blood cultures grew *Staphylococcus aureus*. TTE showed mitral valve insufficiency with possible vegetations under the posterior mitral valve leaflet. Despite antibiotic treatment, her clinical situation rapidly deteriorated and she died of septic shock 7 days after admission. Autopsy was denied. Serological examination performed on the day of death showed evidence of chronic Q fever, while *C. burnetii* PCR on serum was negative (Table 1). Based on the serological profile, a postmortem diagnosis of dual-pathogen endocarditis with *S. aureus* and *C. burnetii* was suspected.

TABLE 2. Results of laboratory tests at presentation[a]

Measurement	Reference value(s)	Result for patient:		
		1	2	3
WBC (10^9/liter)	4.0–10.0	5.5	8.5	18.3
CRP (mg/liter)	<6	15	37	322
Creatinine (μmol/liter)	60–110 (M); 50–100 (F)	104	85	114
GFR (MDRD) (ml/min/1.73 m^2)	>60	61	77	39
AST (U/liter)	<35 (M); <30 (F)	32	26	83
ALT (U/liter)	<45 (M); <35 (F)	18	44	93
Troponin T (μg/liter)	<0.1		<0.05	<0.05
Troponin I (μg/liter)	<0.2	<0.2		
Creatinine kinase (U/liter)	<170 (M); <145 (F)	17	27	62

[a] WBC, white blood cell count; CRP, C-reactive protein; GFR (MDRD), estimated glomerular filtration rate using the modification of diet in renal disease formula; AST, aspartate aminotransferase; ALT, alanine aminotransferase; M, male; F, female.

Q fever is a zoonotic infection caused by *C. burnetii*, an intracellular Gram-negative coccobacillus. The presentation of the disease is variable, with both acute and chronic manifestations. After acute infection, 40 to 60% of patients remain asymptomatic, while others develop symptoms ranging from a flu-like illness to severe presentations, including pneumonia and hepatitis. Following acute infection, 1 to 5% of patients progress to chronic infection, which can develop even years after the primary infection. Endocarditis, mycotic aneurysm, and vascular prosthesis infection are the most common manifestations (1, 8). Patients with preexistent valvular disease or vascular defects, especially aortic aneurysms and aortic stents and prostheses, immunocompromised patients, and pregnant women, are most frequently affected (1, 2, 5, 8). The estimated risk of transformation from acute infection to Q fever endocarditis in patients with preexisting valvulopathy is approximately 40% (2, 5).

Laboratory diagnosis of chronic Q fever relies on serology and PCR. When cultured in cells, *C. burnetii* exhibits antigenic variation. The virulent variant, named phase I, shifts to an avirulent variant, phase II. During acute infection, antibodies predominantly to phase II antigens are detected first, whereas persisting high levels of antibodies to phase I antigens are indicative of chronic Q fever infection (3, 7, 10). Chronic Q fever is suspected if titers of phase I IgG antibodies are >800 and is evident if culture of *C. burnetii* is positive or *C. burnetii* DNA is detected by PCR in blood or tissue in the absence of acute infection (3, 7). A phase I IgG antibody titer >1:800 or positive culture for *C. burnetii* is included as a major criterion in the modified Duke criteria for diagnosis of infective endocarditis (6, 9).

The most effective antibiotic treatment for chronic Q fever endocarditis consists of a combination of doxycycline and hydroxychloroquine for 18 months for native valves and 24 months for prosthetic valves, until a 4-fold decrease of phase I IgG titers and a complete clearance of phase II IgM is reached. If phase I IgG titers remain higher or phase II IgM titers are detectable, treatment should be extended (7).

Q fever endocarditis is an indolent disease, and symptoms are nonspecific. Often, the diagnosis is made when significant valvular damage has already occurred (2, 5). A diagnosis of

chronic Q fever endocarditis might be missed if other pathogens are first isolated, in case of a so-called dual-pathogen endocarditis. Endocarditis due to a concomitant infection with *C. burnetii* and another causative agent has thus far incidentally been described in seven cases only, all in France, in a time period of at least 13 years (4, 9, 11). Here, we have presented three patients with a *C. burnetii* dual-pathogen endocarditis infection in a 2-year period. This observation is related to one large outbreak of acute Q fever in the southern part of the Netherlands, with approximately 4,000 cases from 2007 onward (12). As a result, chronic Q fever, Q fever endocarditis, and associated Q fever dual-pathogen endocarditis are increasingly diagnosed. Although the epidemic seems to have subsided, it is expected to progress in the years to come.

Although *C. burnetii* diagnostics are included in the modified Duke criteria for diagnosis of infective endocarditis, systematic serological testing for *C. burnetii* is not common practice, especially when another etiological pathogen has already been identified. An adequate diagnosis of Q fever endocarditis has important clinical implications, as this condition requires long-term treatment and follow-up and has poor prognosis if untreated, with mortality approaching 100% and the need for surgery rising up to 60% (7). It is therefore advisable to perform microbiological analysis for *C. burnetii* in patients with suspected endocarditis, especially in areas where Q fever is endemic.

Chronic Q fever is thought to develop after an acute episode due to an ineffective immune response, which results in continuous multiplication of *C. burnetii* in macrophages (2, 10). The exact sequence of events leading to dual-pathogen endocarditis is unclear. Presumably, the initial presence of Q fever endocarditis, and associated indolent progression of valvular damage, makes the patients more susceptible to endocarditis with other pathogens. On the other hand, preexisting valvular lesions put patients at risk for both Q fever endocarditis and bacterial endocarditis due to other pathogens. Both microorganisms require adequate and sufficiently long treatment.

In conclusion, we report three patients who presented with chronic Q fever-related dual-pathogen endocarditis. Q fever endocarditis needs long-term antibiotic treatment and has poor prognosis if left untreated. It is therefore recommended to perform microbiological analysis for *C. burnetii* through serology and serum PCR and, if possible, tissue PCR in patients presenting with endocarditis, especially for those residing in a region with high seroprevalence of Q fever, regardless of other identified pathogens.

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