Vascular complications and surgical interventions after world's largest Q fever outbreak

Pieter P. H. L. Broos, MD,[a] Julia C. J. P. Hagenaars, MD, PhD,[b] Linda M. Kampschreur, MD, PhD,[c] Peter C. Wever, MD, PhD,[d] Chantal P. Bleeker-Rovers, MD, PhD,[e] Olivier H. J. Koning, MD, PhD,[b] Joep A. W. Teijink, MD, PhD,[a] and **Marjolijn C. A. Wegdam-Blans, MD, PhD,[f]** *Eindhoven, 's-Hertogenbosch, Utrecht, Nijmegen, and Veldhoven, The Netherlands*

Objective: **Since chronic Q fever often develops insidiously, and symptoms are not always recognized at an early stage, complications are often present at the time of diagnosis. We describe complications associated with vascular chronic Q fever as found in the largest cohort of chronic Q fever patients so far.**
Methods: **Patients with proven or probable chronic Q fever with a focus of infection in an aortic aneurysm or vascular graft were included in this study, using the Dutch national chronic Q fever database.**
Results: **A total of 122 patients were diagnosed with vascular chronic Q fever between April 2008 and June 2012. The infection affected a vascular graft in 62 patients (50.8%) and an aneurysm in 53 patients (43.7%). Seven patients (5.7%) had a different vascular focus. Thirty-six patients (29.5%) presented with acute complications, and 35 of these patients (97.2%) underwent surgery. Following diagnosis and start of antibiotic treatment, 26 patients (21.3%) presented with a variety of complications requiring surgical treatment during a mean follow-up of 14.1 ± 9.1 months. The overall mortality rate was 23.7%. Among these patients, mortality was associated with chronic Q fever in 18 patients (62.1%).**
Conclusions: **The management of vascular infections with *C. burnetii* tends to be complicated. Diagnosis is often difficult due to asymptomatic presentation. Patients undergo challenging surgical corrections and long-term antibiotic treatment. Complication rates and mortality are high in this patient cohort. (J Vasc Surg 2015;62:1273-80.)**

Coxiella burnetii is the causative agent of Q fever, a zoonotic disease, with an extensive animal reservoir. Humans get infected mainly from inhalation of infectious aerosols. Q fever is endemic in every part of the world except New Zealand. Farm animals, such as dairy sheep and goats, are the primary source of human infection.[1]

Acute and chronic Q fever infections have different clinical presentations and serological profiles, and require different treatment strategies. Acute Q fever commonly presents as a flu-like illness with a typically abrupt onset of fever, cough, and headache, which can be complicated by an atypical pneumonia, or as hepatitis. But mostly, acute Q fever remains asymptomatic and is self-limiting.[2,3] Approximately 1% to 5% of infections evolve into chronic Q fever. There is no well-defined incubation period for chronic Q fever; it can become manifest from months to years after initial exposure.[4] Patients at high risk of developing chronic Q fever include patients with an aortic aneurysm, prosthetic vascular graft, cardiac valvulopathy, or compromised immune system.[5,6] Worldwide, endocarditis is the main manifestation of chronic Q fever infection, occurring in 60% to 80% of all cases, followed by vascular infections.[7] Vascular chronic Q fever infections involve patients with *C. burnetii*-infected aneurysms or vascular grafts.

Between 2007 and 2010, a large outbreak of acute Q fever occurred in the Netherlands, with over 4000 reported cases.[8] Dairy goats were identified as the source of infection, as high loads of bacteria were shed during abortions caused by *C. burnetii* infections. Thus, the environment was highly contaminated with aerosols containing *C. burnetii*.

In case reports and small case series, reported complications of vascular chronic Q fever infections are regularly severe. It is often not described whether these complications are present at initial presentation or develop during progression of illness.[9-11] Using the national database, with about 300 patients included, we are able to follow patients and to distinguish between acute and late complications. The purpose of this study was, therefore, to identify and to quantify the important symptoms and complications of patients with vascular infection with *C. burnetii* and to give clinicians, especially in (previously) epidemic areas, tools for accurate diagnosis and therapeutic interventions.

From the Department of Vascular Surgery, Catharina Hospital, Eindhoven[a]; the Department of Surgery, Jeroen Bosch Hospital, 's-Hertogenbosch[b]; the Division of Medicine, Department of Internal Medicine and Infectious Diseases, University Medical Center, Utrecht[c]; the Department of Medical Microbiology and Infection Control, Jeroen Bosch Hospital, 's-Hertogenbosch[d]; the Department of Internal Medicine, Division of Infectious Diseases, Radboud University Medical Center, Nijmegen[e]; and the Department of Medical Microbiology, Laboratory for Pathology and Medical Microbiology (PAMM), Veldhoven,[f] The Netherlands.

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Correspondence: Pieter P. H. L. Broos, MD, Department of Vascular Surgery, Catharina Hospital, Michelangelaan 2, PO Box 1350, 5602 ZA Eindhoven, The Netherlands (e-mail: pieter.broos@catharinaziekenhuis.nl).

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METHODS

Dutch national chronic Q fever database. In order to monitor chronic Q fever cases in the Netherlands, the Dutch Q Fever Consensus Group established the Dutch national chronic Q fever database, in which information about all chronic Q fever cases is collected. All Dutch hospitals that treated chronic Q fever patients were actively approached to include patients in the database. In all patients with acute Q fever and a central vascular disease, such as an aneurysm or central vascular graft, a routine follow-up was performed to identify a chronic Q fever infection early in time and years after initial infection. The trial was conducted according to the Declaration of Helsinki and approved by local medical ethics committees. Patient informed consent was not required because data were stored anonymously. Patients 18 years or older who were diagnosed with proven, probable, or possible chronic Q fever, according to the Dutch consensus guideline, were included in the database. Proven chronic Q fever is diagnosed in patients with positive *C. burnetii* polymerase chain reaction (PCR) in blood or tissue, or in patients with patients with phase I IgG ≥1:1024, in combination with definite endocarditis, or evidence of infection of aneurysm or vascular graft on computed tomography (CT), positron emission tomography-computed tomography (PET/CT), ultrasound (US) or magnetic resonance imaging. Probable chronic Q fever is diagnosed in those patients with phase I IgG ≥1:1024 who have established risk factors for chronic Q fever, but without positive PCR in blood or tissue, or without definite endocarditis, or evidence of infection of aneurysm or vascular graft on CT, PET/CT, US, or magnetic resonance imaging. Patients with phase I IgG ≥1:1024 without manifestations meeting the criteria for proven or probable chronic Q fever were diagnosed with possible chronic Q fever. Wegdam-Blans et al published more details regarding the Dutch chronic Q fever consensus guideline.[12]

Microbiological analysis. In the Netherlands, routine microbiological work-up for the diagnosis of chronic Q fever consists of serology, using an IgG phase I/phase II indirect fluorescent antibody test (IFAT; Focus Diagnostics, Cypress, Calif) and PCR for *C. burnetii* DNA on plasma or serum and, if available, tissue. Titration of antibody levels was carried out at the different hospital sites, with dilutions according to a binary scale and a detection cut-off titer of 1:32. PCR for *C. burnetii* DNA was performed using the same in-house assay in all Dutch laboratories (NucliSENS easyMAG; bioMérieux, Boxtel, The Netherlands).[13]

Patients. For this analysis, we used information about all patients with vascular chronic Q fever until the end of May, 2012. Vascular chronic Q fever was defined as proven or probable chronic Q fever, with a focus of infection in an aneurysm, artery, or vascular graft. These patients were also classified as having Q fever vascular infection, according to the French expert-based guideline.[14] Surveillance and treatment of each individual patient was ultimately left to the discretion of the treating physicians.

Table I. Baseline characteristics and risk factors of 122 patients with vascular chronic Q fever

Patient characteristics and risk factors for Q fever	*%*	*No./Total No. (N = 122)*
Median age, years	71.5	IQR, 64.5-76.6
Male gender	78.7	96/122
Diagnosis acute Q fever		
Proven	14.8	18/122
Possible	11.5	14/122
Unknown	73.8	90/122
Vascular history	79.5	97/122
Aneurysm	68.9	84/122
Treated aneurysm	72.6	61/84
Infrarenal vascular graft	78.7	48/61
Suprarenal vascular graft	1.6	1/61
Thoracic vascular graft	19.7	12/61
Untreated aneurysm	27.4	23/84
Peripheral vascular disease	4.9	9/122
Peripheral artery bypass graft	4.1	5/122
Cerebral vascular incident	3.3	4/122
No vascular history	20.5	25/122
Diagnosis vascular chronic Q fever		
Proven	85.2	104/122
Probable	14.8	18/122

IQR, Interquartile range.

Definitions and outcome. We described the vascular complications related to chronic Q fever that required surgery. We distinguished between acute and late complications. Acute complications were defined as complications at the time of diagnosis or before diagnosis that caused serious deterioration in the patient's health status. Late complications were defined as complications after diagnosis that caused serious deterioration in the patient's health status. Other outcome variables were: overall survival and cause of death. For deceased patients, we assessed the cause of death and whether mortality was related to vascular chronic Q fever. Death associated with vascular chronic Q fever was defined as definitely (directly caused by vascular complications), probably (gastrointestinal bleeding in case of suspected arterio-intestinal fistula, clinical deterioration in case of antibiotic refusal, or severe side effects of medication), possibly (coinciding severe comorbidities, unknown cause of mortality), or not associated (other obvious cause of mortality like malignancy).[15]

Data collection and storage. Information on patient characteristics, imaging results, laboratory results, antibiotic therapy, and outcomes were collected from patient records provided by the hospitals that participated in the database. All data were stored and coded using SPSS Version 18 (SPSS Inc, Chicago, Ill).

Statistical methods. Categorical variables are presented as frequencies with percentages. Continuous variables are presented as mean ± standard deviation or as median and interquartile range (IQR) in case of skewed data. Kaplan-Meier and log-rank test were used to