

Vascular chronic Q fever: quality of life

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SUMMARY

The aim of this study was to evaluate the quality of life in patients with vascular chronic Q fever at time of diagnosis and during follow-up. Based upon the SF-36 questionnaire, the mean physical and mental health of each patient were assessed at 3-month intervals for up to 18 months. A total of 26 patients were included in the study. At time of diagnosis, the mean physical health and mental health score was 50·6 [95% confidence interval (CI) 46·7–54·4] and 44·6 (95% CI 41·6–47·5), respectively. During treatment, the mean physical health score declined significantly by 1·7 points each 3 months ($P < 0\cdot001$) to 40·8 (95% CI 34·4–45·1). The mean mental health score significantly and steadily increased towards 51·2 (95% CI 46·9–54·3) during follow-up ($P = 0\cdot026$). A total of 23% of patients were cured after 18 months of follow-up. In conclusion, quality of life at time of diagnosis for patients with vascular chronic Q fever is lower compared to a similar group of patients, matched for age and gender, with an aortic abdominal aneurysmal disease, and physical health decreases further after starting treatment. Considering the low percentage of cure, the current treatment of vascular chronic Q fever patients may require a separate strategy from that of endocarditis in order to increase survival.

Key words: Health statistics, infectious disease, Q fever, zoonoses.

INTRODUCTION

Q fever is a zoonotic disease caused by *Coxiella burnetii*, an intracellular, Gram-negative bacterium. The disease manifests in countries throughout the world, e.g.

France, The Netherlands, UK, Italy, Spain, Germany, Israel, Greece, Canada and Australia [1]. The reservoir of the bacterium is found in a wide variety of animals including goats, cattle, sheep and household pets. These animals can shed *C. burnetii* in their faeces, urine, milk and birth products. Humans are most likely to be infected with the bacterium through inhalation of contaminated aerosols [1, 2]. Unfortunately, Q fever is often underdiagnosed in humans, due to poor recognition by clinicians.

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Two clinical polymorphisms of infection with *C. burnetii* are described; acute Q fever and chronic Q fever. The acute Q fever infection remains asymptomatic in most patients (60%), while symptomatic patients present with a mild influenza-like illness, atypical pneumonia or hepatitis [2]. This form of Q fever is usually self-limiting [2, 3]. Chronic Q fever is a more severe clinical polymorphism. This form of Q fever develops from several months to years after the primary infection [2]. Until recently, the main clinical manifestation of chronic Q fever was Q fever endocarditis [1–3]. In the wake of the Dutch 2007–2010 Q fever outbreak, the prevalence of chronic Q fever in patients with abdominal aortic and/or iliac disease and a previous Q fever infection was 30·8%, which is much higher compared to patients with a history of cardiac valve surgery (7·8% in seropositive patients) [4–6]. The clinical presentation of patients with abdominal aortic and/or iliac disease and chronic Q fever infection (vascular chronic Q fever) can be life threatening. The disease can present as an aneurysm-related acute complication like a symptomatic, ruptured or mycotic aneurysm, aorta-duodenal fistula, aorta-caval fistula and spondylodiscitis [5, 7]. A mortality rate of 25–60% has been reported [8]. Currently, patients with vascular chronic Q fever are treated according to the therapeutic guidelines published for patients with Q fever endocarditis [9–12]. Surgical debridement of the infected aneurysm or graft and placement of an analogous prosthesis (Dacron aortic or bifurcation) or autologous tissue (spiral vein reconstruction) is suggested to be fundamental in the treatment of vascular chronic Q fever [7, 8, 12–15].

Clinical aspects and therapeutic management of the disease will influence the quality of life of these patients. Only a few reports have been published evaluating the quality of life in patients with Q fever and typically they measure the health status at a single time point after the acute Q fever infection [16–19]. Moreover, these reports evaluated patients with acute Q fever but none focus on chronic Q fever patients. Therefore, the aim of the present study was to evaluate the quality of life in patients with vascular chronic Q fever at time of diagnosis and during long-term treatment with an 18-month follow-up in the wake of the Dutch 2007–2010 Q fever outbreak.

PATIENTS AND METHODS

Patients

From November 2009 to January 2014, all patients with vascular chronic Q fever were included in a

multidisciplinary treatment programme in the Jeroen Bosch Hospital and Bernhoven Hospital. Both hospitals are located in the south of The Netherlands, at the centre of the Dutch 2007–2010 Q fever outbreak. Excluded were all patients who died at time of diagnosis or before the first questionnaire was sent out (before July 2011). We also excluded patients for whom the first questionnaire was completed more than 6 months after the start of therapy, to rule out any influence of therapy on the outcome of the first questionnaire, resulting in January 2011 as the start of the inclusion period for this cohort. The case definition of vascular chronic Q fever is defined as any patient with an abdominal and/or iliac aneurysm or central vascular graft and a serological profile indicating a chronic Q fever infection, i.e. an IgG phase I titre of $\geq 1:1024$ measured using immunofluorescence assay (Focus Diagnostics Inc., USA) [13]. Each patient with vascular chronic Q fever in the multidisciplinary treatment programme was also eligible for inclusion in our study to evaluate quality of life. All eligible patients were asked to participate in our quality of life study. Patients received an information letter, a reply form and the first questionnaire, the Short Form 36 (SF-36) shortly after the diagnosis. Patients were asked to return the completed questionnaire with the reply form or just the reply form stating their refusal to participate. Patients who did not respond received a reminder and finally a telephone call requesting their participation in the study.

SF-36

The first questionnaire (SF-36) was sent out on July 2011. During follow-up, the questionnaires were sent every 3 months for a period of 18 months. The official Dutch translation of the SF-36 obtained from Quality Metric (USA), was used in this study. The SF-36 contains 36 items that measure different health domains of the participants. These include physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (V), social functioning (SF), role emotion (RE) and mental health (MH), which all contribute to two scores about the physical health and the mental health of a patient [20]. The SF-36 is used worldwide as an empirically validated questionnaire for quality of life developed in 1988 by Ware *et al.* [20].

Outcome measures

The primary outcome measure was quality of life (expressed by the physical health score and mental health score) of all patients with vascular chronic Q

fever at time of diagnosis and during an 18-month follow-up. The physical health and mental health scores of each patient were assessed at time of diagnosis ($T=0$) and every 3 months ($T=3$, $T=6$, etc.). The outcome measures were scored on a scale of 0–100, in which a score of 0–39 is well below average, 40–45 is below average and 46–100 is at or above average compared to the general population [20].

Statistical analyses

The primary outcome measures (physical health and mental health scores) were expressed as mean and 95% confidence interval. Differences between groups were calculated using two-sample t test. As significance did not change if multiple testing corrections were made, only uncorrected P values are reported. The longitudinal development of both physical and mental health status scores over 18 months was analysed using generalized estimating equations (GEE), which is a longitudinal linear regression technique. This method is appropriate for longitudinal analysis as the repeated observations within individuals are taken into account. GEE involves a pooled analysis of cross-sectional (between-subject) and longitudinal (within-subject) relationships and results in a single regression coefficient (b) representing the population average difference in the outcome variable over time that incorporates between-subject and within-subject correlations and uses all data available [21, 22]. An exchangeable correlation structure was assumed in all GEE analyses. All analyses were conducted using IBM SPSS Statistics for Windows, v. 19.0 (IBM Corp., USA).

The study protocol is registered in Clinicaltrial.gov, a protocol registration system (registration no.: NCT01450501; ID: 50-51800-98-013). The study obtained approval from the local ethics committees of the Jeroen Bosch Hospital and Hospital Bernhoven; approval of a regional medical research ethics committee was not necessary for this study (regular clinical practice was performed and no emotionally invasive questions were asked).

RESULTS

Between November 2009 and January 2014, a total of 69 patients were included in our multidisciplinary treatment programme. Twelve of the 69 patients died before the first round of questionnaires was mailed in July 2011 (17%). A total of 57 patients

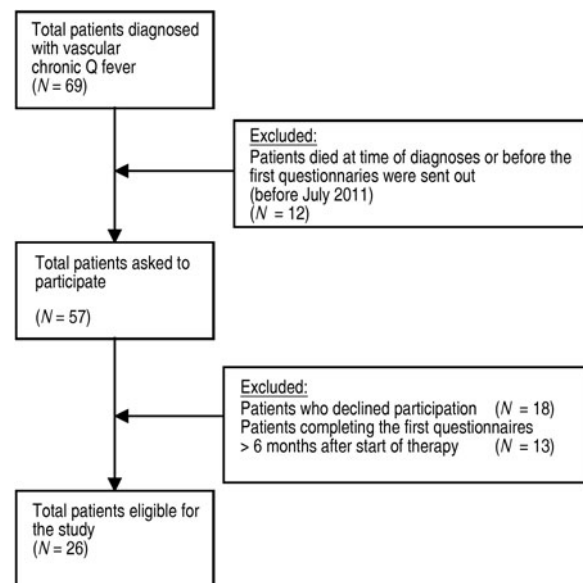


Fig. 1. Flowchart of all 69 patients with vascular chronic Q fever.

Table 1. Baseline characteristics of 26 patients with vascular chronic Q fever who participated in the study to evaluate quality of life.

Baseline characteristics	All patients with vascular chronic Q fever ($N = 26$)
Gender, n (% male)	23 (89)
Mean age, (years, s.d.)	69.3 \pm 8.0
Co-morbidity (%)	
Diabetes mellitus	11.5
Cerebrovascular incidents	7.7
Myocardial infarction	38.5
Kidney dysfunction	11.5
Pulmonary diseases	7.7
Cardiac valve pathology (%)	11.5
Mortality (%)	11.5

were asked to participate. Eighteen (32%) of these patients declined to participate, while 13 (23%) patients were excluded because the first questionnaire was completed more than 6 months after the start of therapy. A total of 26 (46%) patients were eligible for the study and completed the first questionnaire (see Fig. 1). Table 1 gives the baseline characteristics of all patients included in the study. Mean age of the study group was 69.3 years (s.d. \pm 8.0). At 15 months, 16/26 (62%) patients completed the questionnaires, as did 14/26 (54%) at 18 months. Of all included patients, 6/26 (23%) were cured after a mean follow-up of 18 months.

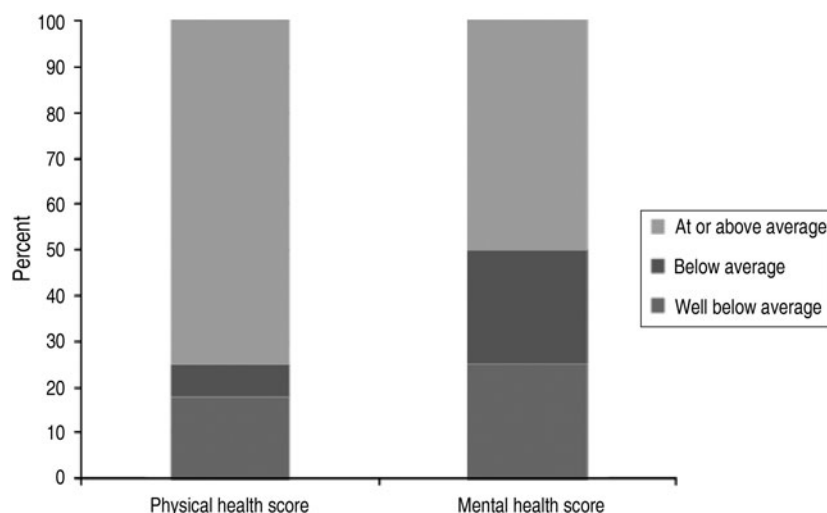


Fig. 2. Distribution of physical and mental health scores at time of diagnoses in all 26 patients with vascular chronic Q fever included in the study. Scores are divided into three categories: at or above average; below average; and well below average.

Table 2. Mean physical health and mean mental health scores with 95% confidence intervals of all included 26 patients at each time point ($T=0$, $T=3$, $T=6$, etc.)

Time (months)	No. of patients completing the questionnaire	Mean physical health score (0–100, 95% CI)	Estimated mean physical health score	Mean mental health score (0–100, 95% CI)	Estimated mean mental health score
$T=0$	26	50.6 (46.7–54.4)	50.6	44.6 (41.6–47.5)	44.6
$T=3$	22	36.9 (33.4–39.2)	48.9	42.9 (39.3–45.9)	45.4
$T=6$	21	41.3 (35.3–45.2)	47.2	49.4 (44.4–54.3)	46.2
$T=9$	19	34.6 (30.5–37.8)	45.5	46.5 (42.5–50.2)	47.1
$T=12$	14	36.4 (32.2–40.0)	43.8	45.8 (41.9–49.3)	47.9
$T=15$	16	36.0 (30.8–38.4)	42.1	48.4 (44.9–50.1)	48.7
$T=18$	14	40.8 (34.4–45.1)	40.4	51.2 (46.9–54.3)	49.5

CI, Confidence interval.

Physical and mental health at time of diagnosis

At time of diagnosis, the mean physical health score for all 26 patients was 50.6 [95% confidence interval (CI) 46.7–54.4], which is at or above average compared to the general population. The majority (74.9%) of patients scored at or above average (46–100), 7.2% scored below average (40–45) and 17.9% of all patients scored well below average (0–39). The mean mental health score at time of diagnosis was 44.6 (95% CI 41.6–47.5), which is categorized as below average. A total of 25.0% of all patients scored well below average (0–39), another 25.2% scored below average (40–45) and 49.8% scored at or above average (46–100). A graphic view of the

distribution of physical and mental health scores is shown in Figure 2. At time of diagnosis, the mean quality of life score on the SF-36 (physical and mental health scores combined) was 47.6 (95% CI 44.3–50.6) for all vascular chronic Q fever patients, which is at or above average.

Physical and mental health scores during follow-up

Table 2 shows the mean physical and mental health scores at each time point ($T=0$, $T=3$, $T=6$, etc.) for all included patients ($N=26$). Figure 3 shows the course of the mean physical and mental health scores in time. At time of diagnosis, the mean physical health

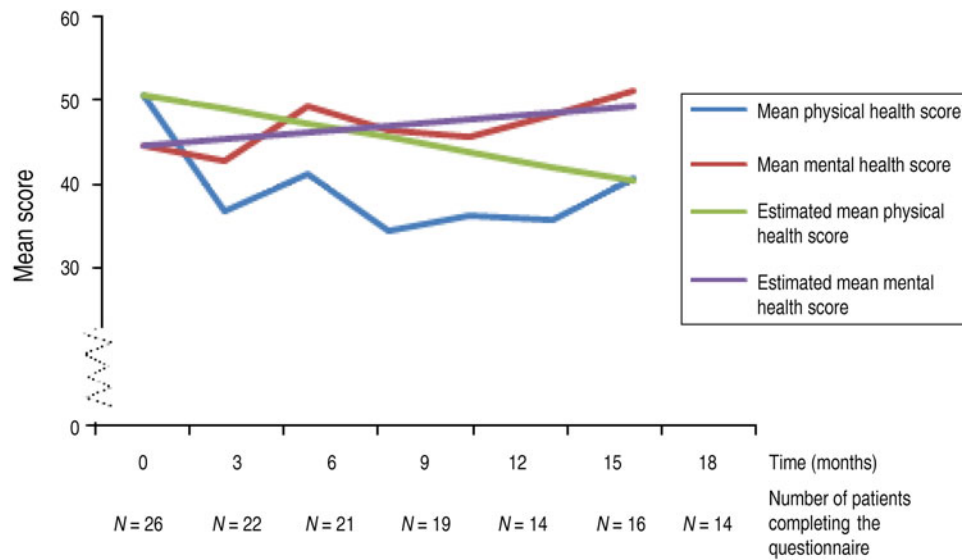


Fig. 3. Mean of physical health score (blue line), mental health score (red line), estimated mean physical health score (green line) and estimated mean mental health score (purple line) of all 26 patients at each time point ($T=0$, $T=3$, $T=6$, etc.) during the 18 months of follow-up.

score was at or above average (50.6, 95% CI 46.7–54.4), but 3 months after diagnosis and start of treatment, the mean score decreased to 36.9 (95% CI 34.4–45.1), which is well below average. During follow-up, the mean physical health score decreased significantly by an average of 1.7 points every 3 months (95% CI 0.9–2.5, $P < 0.001$) and was in the categories well below or below average for at least 1.5 years (see Fig. 3). The score declined and crossed the line towards a score indicating well below average (0–39) at point $T=3$, but at $T=6$ and $T=18$ the score increased slightly and the line touched the threshold for a score below average (40–45) but decreased again afterwards. The mean mental health score was below average at time of diagnosis (44.6, 95% CI 41.6–47.5) and increased to 51.2 (95% CI 46.9–54.3) during the 18 months of follow-up, which is at or above average. The mean mental health score increased significantly by steps of an average of 0.82 every 3 months (95% CI 0.08–1.2, $P = 0.026$).

DISCUSSION

To our knowledge, this is the first prospective cohort study to evaluate the quality of life in patients with vascular chronic Q fever at time of diagnosis and during follow-up/treatment. At time of diagnosis the mean SF-36 score (physical and mental health scores combined) in patients with vascular chronic Q fever is lower compared to a similar group, matched for

age and gender, of patients with an aortic abdominal aneurysmal disease described by Aljabri *et al.* [23] (47.6 vs. 66.3, respectively). Aljabri *et al.* used the SF-36 in patients with an aneurysm before and after elective surgery [23]. Their group consisted of 76 patients undergoing an endovascular aortic repair or open reconstruction. The mean age was 72.4 years and 82% were male, which is comparable to our study group. The difference in the mean score on the SF-36 could, therefore, be related to the chronic infection with Q fever. Previous literature concerning the health status of Q fever patients after long-term follow-up emphasizes the negative influence of a Q fever infection on the health status of the patient [16, 18, 19, 24, 25]. Van Loenhout *et al.* demonstrated that the Nijmegen Clinical Screening Instrument (NCSI) as well as the SF-36 can be used to measure health status in acute Q fever patients [16]. The other reports concluded that patients who were exposed to *C. burnetii* (patients with a past resolved Q fever) experienced more complaints of fatigue (chronic fatigue syndrome; CFS), which could also be the case in patients with a chronic Q fever infection and could explain the low score on the SF-36 at time of diagnosis [18, 19, 24]. During follow-up, the most interesting finding was the significant decline in the mean physical health score after diagnosis and/or start of treatment, which for most of the time was in the well below average category during the 1.5 years of follow up. This could be related to the chronic Q fever disease,

its clinical presentation with acute and aspecific complaints or infection with *C. burnetii* itself [1, 2]. Van Loenhout *et al.* reported that patients with acute Q fever had a clinically relevant lower quality of life at 12–26 months after onset of illness [25]. Hachette *et al.* used the SF-36 during follow-up of patients after an acute Q fever infection, their physical health declined significantly during follow-up compared to controls (-5.7 ± 10.0 , $P = 0.0021$) [18]. Although, these are different groups of patients (past resolved *vs.* chronic Q fever patients), the decrease in physical health could be related to the Q fever infection. In our view it is also likely that these findings reflect the negative impact of the treatment on vascular chronic Q fever patients. A large number of patients experienced severe side-effects of doxycycline and hydroxychloroquine or other antibiotics, while the patients who underwent major surgery at the start of treatment needed time to recover physically. The decrease in physical health score during follow-up could also be influenced by a large amount of public attention to chronic Q fever in The Netherlands. Media attention could increase the awareness and/or the perception of symptoms and complaints in these patients and therefore influence physical health.

The mean mental health score on the SF-36 in patients with vascular chronic Q fever at the time of diagnosis is below average, which could be related to the impact of the diagnosis; the knowledge of having a chronic illness and the perspective of long-term antibiotic treatment with possible side-effects. The mental health score increased during follow-up and might be explained by a combination of acceptance of the disease, adjustment to the treatment and perhaps cure of the disease.

Currently, treatment of vascular chronic Q fever relies upon antibiotic treatment (doxycycline and hydroxychloroquine) and major surgery, which are taken from the guidelines for treatment of Q fever endocarditis and from reports stating that surgery is mandatory [1, 8–12, 14, 15]. We found a low cure rate of 23% after 18 months of follow-up in our patients with vascular chronic Q fever and a possible negative impact by treatment (the antibiotic and/or surgical treatment) on the physical health in vascular chronic Q fever patients. Raoult *et al.* reported a relatively higher cure rate of 71% in 21 patients with Q fever endocarditis using the combination strategy of doxycycline and hydroxychloroquine after a mean treatment duration of 31 months [22]. We are interested in following our patients to study the possible changes in quality of life scores after cessation of antibiotic therapy.

A limitation of our study is the high percentage (32%) of patients declining to complete the questionnaire. Additionally, our study included a low number of patients. As a result, the power to detect a significant effect between particular subgroups is limited. Only half ($n = 14$) of all included patients at the start of the study completed the questionnaire at the end (46%), due to loss of follow-up ($n = 2$), patients' deaths ($n = 3$) or refusal of further participation ($n = 7$). However, this study is the largest study of chronic Q fever patients with vascular complications and even with small sample sizes the results indicate additional reduction of the quality of life than that due to treatment alone.

CONCLUSION

The quality of life at time of diagnosis in patients with vascular chronic Q fever is lower compared to a similar group without Q fever. Physical health decreases further after the start of treatment. Considering the low percentage of cure, the current treatment of vascular chronic Q fever patients may require a different strategy from endocarditis in order to increase survival.

DECLARATION OF INTEREST

None.

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