Prevalence of Chronic Q Fever in Patients with a History of Cardiac Valve Surgery in an Area Where *C. burnetii* Is Epidemic

Linda M. Kampschreur, Jan Jelrik Oosterheert, Andy I. M. Hoepelman, Peter J. Lestra
de, Nicole H. M. Renders, Peter Elsm
e, and Peter C. WEVER

Division of Medicine, Department of Internal Medicine and Infectious Diseases, University Medical Centre Utrecht, Utrecht, Department of Internal Medicine, Jeroen Bosch Hospital, ’s-Hertogenbosch, Department of Medical Microbiology and Infection Control, Jeroen Bosch Hospital, ’s-Hertogenbosch, and Department of Cardiology, Jeroen Bosch Hospital, ’s-Hertogenbosch, The Netherlands

Chronic Q fever develops in 1 to 5% of patients infected with *C. burnetii*. The risk for chronic Q fever endocarditis has been estimated to be ~39% in case of preexisting valvulopathy and is potentially even higher for valvular prostheses. Since 2007, The Netherlands has faced the largest Q fever outbreak ever reported, allowing a more precise risk estimate of chronic Q fever in high-risk groups. Patients with a history of cardiac valve surgery were selected for microbiological screening through a cardiology outpatient clinic in the area where Q fever is epidemic. Blood samples were analyzed for phase I and II IgG against *C. burnetii*, and if titers were above a defined cutoff level, *C. burnetii* PCR was performed. Chronic Q fever was considered proven if *C. burnetii* PCR was positive and probable if the phase I IgG titer was ≥1:1,024. Among 568 patients, the seroprevalence of *C. burnetii* antibodies (IgG titer greater than or equal to 1:32) was 20.4% (*n* = 116). Proven or probable chronic Q fever was identified among 7.8% of seropositive patients (*n* = 9). Valve characteristics did not influence the risk for chronic Q fever. Patients with chronic Q fever were significantly older than patients with past Q fever. In conclusion, screening of high-risk groups is a proper instrument for early detection of chronic Q fever cases. The estimated prevalence of chronic Q fever is 7.8% among seropositive patients with a history of cardiac valve surgery, which is substantially higher than that in nonselected populations but lower than that previously reported. Older age seems to increase vulnerability to chronic Q fever in this population.

Q fever is a zoonosis caused by *C. burnetii*, an intracellular Gram-negative coccobacillus. Q fever has acute and chronic manifestations. Acute Q fever mostly presents as a self-limiting flu-like illness, sometimes complicated by pneumonia or arthritis. However, most patients, 50 to 60%, remain asymptomatic, which makes *C. burnetii* infections often undetected (14, 17). After acute Q fever, 10 to 20% of patients have persisting fatigue complaints, also known as Q fever fatigue syndrome (QFS) (13). Chronic Q fever develops in 1 to 5% of patients with *C. burnetii* infection and can become manifest even years after primary infection. The most common manifestations are endocarditis, mycotic vascular aneurysm, and vascular prosthesis infection (1, 5, 10, 17). Chronic Q fever mostly affects patients with preexistent valvular disease, vascular prosthesis, and aortic aneurysm, immunocompromised patients, and pregnant women (5, 14, 22, 23). Diagnosis of chronic Q fever relies on serology, PCR, and culture. Chronic Q fever is considered proven if *C. burnetii* is detected by PCR or culture in blood or tissue in combination with a corresponding serological profile in the absence of acute infection. However, PCR and culture on blood specimens both have low sensitivity for the diagnosis of chronic Q fever (6, 16). Serological diagnosis is based on the antigenic variation of *C. burnetii* (20). During acute infection, IgM and IgG antibodies against phase II antigens (phase II IgM and IgG) are detected first, followed by IgM and IgG antibodies against phase I antigens (phase I IgM and IgG). Persisting high titers of phase I IgG and, to a lesser extent, phase II IgG are indicative of chronic *C. burnetii* infection (3, 4, 20).

The reported estimated risk of progression from acute *C. burnetii* infection to endocarditis in patients with any cardiac valvulopathy is ~39% and is thought to be even higher for patients with cardiac valve prosthesis (5, 15). In contrast, a recent Dutch report showed a very low risk of progression to chronic Q fever endocarditis in case of clinically insignificant valvular disease (11). Chronic Q fever endocarditis has high morbidity and mortality, up to 60%, if left untreated. Long-term antibiotic treatment can reduce mortality to less than 5% (15). An early diagnosis and subsequent initiation of adequate treatment are therefore mandatory. The recommended treatment for chronic Q fever endocarditis is a combination of doxycycline and hydroxychloroquine for at least 18 months for native valves and 24 months for prosthetic valves (15, 19).

From 2007 on, there has been an expanding outbreak of Q fever in the south of The Netherlands, with over 4,000 notified cases of acute Q fever (24). As the majority of patients have mild or asymptomatic acute infection, the actual incidence is probably much higher. In 2010, the epidemic dampened, although increasing numbers of chronic Q fever patients were seen (2, 24). This large outbreak allows a more precise risk estimate of chronic Q fever and evaluation of a screening program in patients with cardiac valve disease. We therefore studied the prevalence of chronic Q fever in this area where Q fever is epidemic in patients with a history of cardiac valve surgery.

These data were presented in oral presentations at the Dutch Society for Microbiology [NVMM] Spring Meeting and the An-
nal Meeting of the Dutch Society of Internal Medicine [NIV] in April 2011 and in poster presentations at the Dutch Society of Cardiology [NVVC] meeting in April 2011 and the 21st European Congress of Clinical Microbiology and Infectious Diseases [ECCMID] in May 2011.)

**MATERIALS AND METHODS**

**Patient enrollment.** Patients with a history of cardiac valve surgery were selected from the cardiology outpatient clinic of the Jeroen Bosch Hospital in ’s-Hertogenbosch, The Netherlands, which is located in the center of the area where Q fever is epidemic. Our screening was approved by a local medical ethics review committee. We included all patients ages ≥18 years listed under the registration code “follow-up after cardiac valve surgery” on 1 November 2010. We excluded one patient who had received valve prosthesis because of valvular damage due to chronic Q fever endocarditis.

All patients identified to be alive at the start of our screening were sent an information letter and an invitation for microbiological screening from November 2010 to January 2011. Patients with probable or proven chronic Q fever (see “Definitions” below) were further evaluated at the internal medicine outpatient clinic. The extent of this evaluation was individually assessed but consisted at least of anamnesis, physical examination, and echocardiography. All patients with antibodies against *C. burnetii* as a result of either chronic Q fever or past infection (see “Definitions” below) were approached for follow-up microbiological analysis after 3 months, to examine the development of antibody titer.

After this time period, follow-up was individually determined depending on the outcome of microbiological analysis.

**Microbiological screening.** Screening was performed on serum and EDTA-plasma samples obtained by venipuncture. First, sera were screened for phase I and II IgG with immunofluorescence assay (IFA; Focus Diagnostics, Inc., Cypress, CA) according to the manufacturer’s instructions using a detection cutoff titer of ≥1:32. If one or both antibodies were present at or above this cutoff, exact titers of phase I and II IgM and IgG were determined. Real-time PCR for *C. burnetii* DNA was performed on EDTA-plasma if the phase I IgG titer was ≥1:512 (6, 21). This cutoff, which is below the chronic Q fever definition cutoff titer of 1:1,024 (see “Definitions” below), was chosen to increase the probability of capturing all cases of chronic Q fever. As the acute Q fever epidemic had virtually subsided on 1 November 2010, our screening program was not designed to identify cases of acute Q fever or asymptomatic primary infection.

**Definitions.** A titer of greater than or equal to 1:800 for IgG antibodies specific for phase I antigen using an in-house IFA has been internationally accepted for the serological diagnosis of probable chronic Q fever (3, 15). Recently, an increase of this cutoff to a titer of greater than or equal to 1:1,600 has been proposed, on the basis of new clinical data suggesting considerable overdiagnosis with the cutoff titer of greater than or equal to 1:800 (7). In The Netherlands, essentially all laboratories use the commercial IFA from Focus Diagnostics, Inc. Chronic Q fever was considered probable in this high-risk group if the phase I IgG titer was ≥1:1,024 using the commercial IFA and proven in case of a positive *C. burnetii* PCR result on blood or tissue in combination with a corresponding serological profile (26). Patients with a phase I IgG titer of <1:1,024 and a negative result by *C. burnetii* PCR (if performed) are considered to have past *C. burnetii* infection.

**Statistics.** Clinical and microbiological data for all patients with *C. burnetii* antibodies were collected, stored, and analyzed in an SPPS (version 18.0)-based database. Qualitative data were compared by use of Fisher’s exact test. Mean values were compared by use of the independent-samples *t* test. Results were expressed as means or percentages, with, respectively, standard deviation (SDs) or *P* values. The significance level was set at a *P* value of ≤0.05.

**RESULTS**

Assessment for patients listed under the registration code “follow-up after cardiac valve surgery” on 1 November 2010 revealed 715 patients. Patients had been under follow-up care after valve surgery for a maximum duration of 33 years. Of the 715 patients, 49 had died in the previous 3 years. The 666 remaining patients were invited for screening by letter. In all, 568 patients (85.3%) responded and supplied blood samples for microbiological analysis. Eighty-three patients (12.5%) did not participate, 4 patients (0.6%) moved elsewhere, and 11 patients (1.7%) had died during enrollment of the study. Phase I and/or phase II IgG (IgG titer greater than or equal to 1:32) was detected in 116/568 patients (20.4%), indicating chronic or past *C. burnetii* infection. Only five seropositive patients (4.3%) had had a notified case of acute Q fever in the preceding years. Nine of 116 patients (7.8%) had proven or probable chronic Q fever (Fig. 1). These nine patients represent 1.6% of the total screened population. Results of their microbiological analysis are presented in Table 1. Four of 116 patients (3.4%) had proven chronic Q fever, based on a positive *C. burnetii* PCR result in plasma, and 5/116 patients (4.3%) had probable chronic Q fever, based on a phase I IgG titer of ≥1:1,024. In six patients, long-term antibiotic treatment, consisting of a combination of doxycycline and hydroxychloroquine, was initiated. Three patients refused antibiotic treatment, because of older age and fear of side effects. One patient who had probable chronic Q fever at initial screening progressed to PCR-positive proven chronic Q fever during follow-up, after refusal of antibiotic therapy. All probable and proven chronic Q fever patients were invited to the outpatient clinic for individual further evaluation and workup. One patient complained of fatigue and exertional dyspnea, and another patient complained of fatigue only. The remaining seven patients (77.8%) had no complaints. All patients were offered transesophageal echocardiogram (TEE). Two patients refused; they underwent transthoracic echocardiogram (TTE). Echocardiogram showed slight deterioration of mitral valve prosthetic function in one patient, who also showed increased intensity around this valve on positron emission tomography-computed tomography (PET-CT). Echocardiogram in the remaining eight chronic Q fever patients showed no abnormalities. PET-CT revealed an aneurysm, without increased intensity, in one patient but was unremarkable in all others.

Past *C. burnetii* infection with no indication of chronic infection was detected in 107/116 (92.2%) patients. All 107 patients had phase II IgG antibodies. Results of phase I and phase II IgG titrations are presented in Table 2. Microbiological analysis of 101 follow-up blood samples after 3 months did not reveal development of chronic Q fever in any of these patients. Phase II IgG titers declined in 53 patients (52.5%), remained the same in 34 patients (33.7%), and increased in 14 patients (13.9%; maximum titer, 1:4,096). Among the 14 patients with increasing phase II IgG titers, 2 had a low-positive phase II IgM titer at initial screening. This could theoretically indicate a recent *C. burnetii* infection, but this seems unlikely, since the Q fever outbreak had virtually subsided at the time of initial screening (24). Phase I IgG titers declined in 7 patients (6.9%), remained the same in 74 patients (73.3%), and increased in 21 patients (20.1%; maximum titer, 1:256). Most of the increased phase I titers at follow-up were 1:32 or 1:64, which had been negative at first screening. One patient had died in the 3-month period (the outcome of the initial screen-
ing for this patient was a phase II IgG titer of 1:512 and a negative phase I IgG result), while four other patients did not participate in follow-up. All patients with increased phase I or phase II IgG titers at the first follow-up were subsequently screened again 6 months after initial screening. No progression to chronic Q fever was observed in any of these patients.

Clinical data, characteristics of valve surgery, and cardiovascular (risk) factors of all patients with probable or proven chronic *C. burnetii* infection and past *C. burnetii* infection are listed in Table 3. There were no significant differences in clinical features and location, year, and type of valve surgery between these two groups. Patients with chronic Q fever were significantly older than patients with past *C. burnetii* infection.

**DISCUSSION**

Using a targeted screening program in a high-risk population for development of Q fever endocarditis in an area where Q fever is epidemic, we found a seroprevalence of antibodies against *C. burnetii* antigens of 20.4%. In comparison, in May 2009, amid the

---

**TABLE 1** Microbiological results in nine patients with a history of cardiac valve surgery and proven or probable chronic Q fever at initial screening and after 3 months of follow-up

| Patient | Initial results | Result after 3 mo of follow-up |
|---------|-----------------|-------------------------------|
| Phase II IgG titer | Phase I IgG titer | PCR | Antibiotic treatment | Phase II IgG titer | Phase I IgG titer | PCR |
| 1 | 1:65,536 | 1:32,768 | + | Yes | 1:32,768 | 1:16,384 | – |
| 2 | 1:2,048 | 1:1,024 | – | Refused | 1:4,096 | 1:4,096 | – |
| 3 | 1:16,384 | 1:32,768 | – | Refused | 1:16,384 | 1:16,384 | – |
| 4 | 1:4,096 | 1:2,048 | – | Refused | 1:4,096 | 1:4,096 | – |
| 5 | 1:16,384 | 1:16,384 | – | Yes | 1:16,384 | 1:16,384 | – |
| 6 | 1:32,768 | 1:32,768 | – | Refused | 1:8,192 | 1:4,096 | + |
| 7 | 1:32,768 | 1:65,536 | + | Yes | 1:32,768 | 1:16,384 | + |
| 8 | 1:16,384 | 1:16,384 | – | Yes | 1:16,384 | 1:16,384 | – |
| 9 | 1:4,096 | 1:512 | + | Yes | 1:2,048 | 1:2,048 | + |

* Antibody titers were determined by immunofluorescence assay. –, negative; +, positive.

---

**TABLE 2** Coxiella burnetii phase I and phase II IgG titers in patients with a history of cardiac valve surgery and past *C. burnetii* infection

| Titer | No. (%) of patients ($n = 107$) |
|-------|---------------------------------|
| Phase I IgG | Phase II IgG |
| Negative | 85 (79.4) | 0 |
| 1:32 | 6 (5.6) | 29 (27.1) |
| 1:64 | 7 (6.5) | 24 (22.4) |
| 1:128 | 3 (2.8) | 19 (17.8) |
| 1:256 | 3 (2.8) | 13 (12.1) |
| 1:512 | 3 (2.8) | 9 (8.4) |
| 1:1,024 | 0 | 5 (4.7) |
| 1:2,048 | 0 | 5 (4.7) |
| $\geq$1:4,096 | 0 | 3 (2.8) |

* Antibody titers were determined by immunofluorescence assay.
A response rate of 85.3%, a seroprevalence rate of 20.4% (of which only 4.3% had a notified acute Q fever episode in the past), and a chronic Q fever prevalence rate of 1.6% in the total screened population indicate that our screening program is a proper instrument for early detection of chronic Q fever in this high-risk group of patients. Mild damage of the prosthetic valves was seen in only one patient. Eight patients (88.9%) did not show any sign of valvular damage or vegetation on echocardiogram, and seven patients (77.8%) with proven chronic Q fever had no symptoms. One patient who had refused treatment progressed, however, from probable chronic Q fever to proven disease during follow-up. We think, therefore, that targeted screening and subsequent long-term antibiotic treatment allow prevention of serious morbidity and mortality. As the sensitivity of blood PCR for detection of chronic Q fever is far from optimal (6), both probable and proven chronic Q fever cases were managed similarly and offered long-term antibiotic treatment.

To identify if screening could be limited to subgroups of patients with a history of valve surgery, we compared valve properties, e.g., year of surgery, location, and type, between the group of chronic Q fever patients and patients with past C. burnetii infection. No significant differences were seen. The same results were obtained for cardiovascular (risk) factors. However, patients with suspected chronic Q fever were significantly older than patients with past C. burnetii infection. Although the number of chronic Q fever patients in our study was small, this suggests that older age does raise the risk for development of chronic Q fever in patients with cardiac valve abnormalities, which could be explained by the fact that older age is associated with a diminishing immune response (27). Remarkably, the study population of Fenollar et al. (5), in which the risk for chronic Q fever was estimated at ~39%, had a lower mean age (59.6 years; range, 45 to 74 years) than our study population.

The risk of chronic Q fever in our study could have been overestimated. Only four patients had proven chronic Q fever with a positive C. burnetii PCR result. In the other five patients, only serological evidence for chronic Q fever (phase I IgG titer ≥1:1,024) was found. These patients could have been wrongly diagnosed as having chronic Q fever, thus causing an overestimate of this condition (9). As some patients underwent valve surgery during the Q fever outbreak in The Netherlands, we cannot be sure that patients who had surgery during the time period from 2007 to 2010 did not actually already have chronic Q fever before surgery. Nevertheless, as these patients did have severe valvulopathy requiring surgical intervention at that time, they still had a reported important risk factor for chronic Q fever development (5, 23). Unfortunately, screening for Q fever antibodies before valve surgery in patients from areas where the disease is epidemic is not yet standard care in The Netherlands.

There are also several reasons why the estimated prevalence of chronic Q fever in patients with a history of valvular surgery may be an underestimate. First, chronic Q fever can develop even years after primary infection, while our screening program was executed within 2 years after the peak of the epidemic in 2009. Yet, it is known that 75% of chronic Q fever cases develop within 6 months after primary infection (10). In addition, follow-up of seropositive patients after 3 months and again after 6 months in cases with increased phase I or II IgG titers at first follow-up revealed no additional chronic cases, although this follow-up period is relatively short. Moreover, most patients with past Q fever al-

### TABLE 3
Clinical characteristics, characteristics of valve surgery, and cardiovascular (risk) factors in patients with a history of cardiac valve surgery and chronic Q fever or C. burnetii infection

| Characteristic                      | Chronic Q fever (n=9) | Past Q fever (n=107) | P^d |
|-------------------------------------|-----------------------|----------------------|-----|
| No. (%) of patients by sex          |                       |                      |     |
| Male                                | 6 (66.7)              | 66 (61.7)            | 0.534 |
| No. (%) of patients by year of surgery |                      |                      |     |
| 2010                                | 0                     | 8 (7.5)              |     |
| 2006-2009                           | 4 (44.4)              | 42 (39.3)            |     |
| 2001-2005                           | 3 (33.3)              | 31 (29.0)            |     |
| 1996-2000                           | 0                     | 9 (8.4)              |     |
| Before 1996                         | 2 (22.2)              | 17 (15.9)            |     |
| No. (%) of patients by type of valve surgery |            |                      | 0.978 |
| Biological valve(s)                 | 4 (44.4)              | 30 (28.0)            |     |
| Mechanical valve(s)                 | 4 (44.4)              | 61 (57.0)            |     |
| Bentall procedure                   | 0                     | 5 (4.7)              |     |
| Valve repair(s)                     | 1 (11.1)              | 13 (12.1)            |     |
| No. (%) of patients with:           |                       |                      | 0.795 |
| Coronary disease                    | 5 (55.6)              | 34 (31.8)            | 0.140 |
| History of CABG                     | 4 (44.4)              | 23 (21.5)            | 0.126 |
| History of PTCA                     | 1 (11.1)              | 9 (8.4)              | 0.569 |
| Hypertension                        | 4 (44.4)              | 46 (43.0)            | 0.599 |
| Diabetes                            | 0                     | 12 (11.2)            | 0.595 |
| Dyslipidemia                        | 4 (44.4)              | 30 (28.0)            | 0.248 |
| Immunity disorder                   | 0                     | 0                    |     |

^a CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty. Percentages add up to >100 due to multiple valve surgeries in some patients (1 chronic Q fever patient [11.1%] and 9 past Q fever patients [8.4%]).

^b Probable and proven chronic Q fever.

^c Patients with positive phase I and/or phase II IgG result (titers greater than or equal to 1:32) without evidence of chronic Q fever.

^d Fisher’s exact test, unless otherwise indicated.

^e Independent-samples t test (95% confidence interval, 1.225 to 17.698).

Q fever epidemic, C. burnetii IgG seroprevalence was assessed among blood donors in the area with the highest reported Q fever incidence in The Netherlands, showing a seroprevalence of 12.2% for C. burnetii IgG phase II antibodies using a 1-dilution-higher cutoff titer of ≥1:64 (8). Of the seropositive patients, 7.8% had evidence of probable or proven chronic Q fever. A recent report stated that in a group of 686 unselected patients diagnosed with acute Q fever in 2007 and 2008 in The Netherlands, 1.6% progressed to chronic Q fever, which is much lower than the incidence observed in our high-risk population (25). This confirms earlier findings that previous cardiac valve surgery gives a highly increased risk for development of chronic Q fever. Yet, the formerly estimated risk of ~39% for the development of chronic Q fever in patients with cardiac valvulopathies could not be reproduced. This estimate resulted from a retrospective analysis of patients identified by a Q fever reference center over a 16-year time span and may therefore differ from our results (5). Strain-specific clinical features might, however, also be responsible for the discrepancy.
ready had undetectable phase I IgG titers at initial screening (79.4%), which makes development of chronic Q fever less likely, in our opinion. Nevertheless, we cannot exclude the possibility that some patients might develop chronic Q fever in the future, which could cause a (small) difference in the prevalence rates of chronic Q fever reported in our study. Second, we identified 60 patients with a history of cardiac valve surgery who had died in the last 3 years with unknown C. burnetii serostatus. After analysis of their medical records, the possibility that chronic Q fever-related disease contributed to their death could not be excluded in nine cases (15.0%). If, among the deceased patients, these nine patients had actual chronic Q fever, Q fever antibody seroprevalence would decrease to 19.5% and the chronic Q fever prevalence would be 14.6%. A third reason for underestimation of chronic Q fever cases is the possibility that we overestimated the number of past C. burnetii infections by using a detection cutoff titer of $\geq 1:32$ for phase I and II IgG. These titers can also be caused by antibodies cross-reacting to other pathogens or by aspecific reactions (18). Yet, it is also known that, following C. burnetii infection, antibodies to C. burnetii can disappear over time or titers can become very low, leading to an underestimation of the infection rate (12, 25). This was illustrated in our study by one case who had a confirmed acute Q fever episode in 2009 and demonstrated a phase II IgG titer of 1:32 in our screening. Nevertheless, if a cutoff titer for phase II IgG of $\geq 1:128$ had been used in our study, 64/568 patients (11.3%) would still have been seropositive. The prevalence of chronic Q fever in the seropositive group would then have been 14.1% (9/64), which is still markedly lower than the previously reported 39% (5).

In conclusion, targeted screening in a high-risk population seems a proper instrument for early detection of chronic Q fever cases, which potentially allows prevention of serious morbidity and mortality. Therefore, screening for C. burnetii antibodies in patients with a history of valve surgery could also be considered in other outbreak settings. We have found a seroprevalence of Q fever antibodies of 20.4% in patients with a history of valvular surgery. The prevalence of chronic Q fever in seropositive patients was 7.8%, which is substantially lower than that stated in previous reports of patients with cardiac valve disease. In this study, patients with older age and a history of valve surgery seem to be more vulnerable for the development of chronic Q fever.

ACKNOWLEDGMENT

None of the authors has any funding or conflicts of interest to report.

REFERENCES

1. Botelho-Neves E, et al. 2007. Coxiella burnetii infection of aortic aneurysms or vascular grafts: report of 30 new cases and evaluation of outcome. Eur. J. Clin. Microbiol. Infect. Dis. 26:635–640.
2. Delsing CE, Kullberg BJ, Bleeker-Rovers CP. 2010. Q fever in The Netherlands from 2007 to 2010. Neth. J. Med. 68:382–387.
3. Dupont HT, Thirion X, Raoul D. 1994. Q fever serology: cutoff deter-
4. minimation for microimmunofluorescence. Clin. Diagn. Lab. Immunol. 1:189–196.
5. Dupuis G, et al. 1986. Serological diagnosis of Q fever endocarditis. Eur. Heart J. 7:1062–1066.
6. Fenollar F, et al. 2001. Risks factors and prevention of Q fever endocarditis. Clin. Infect. Dis. 33:312–316.
7. Fenollar F, Fourrier PE, Raoul D. 2004. Molecular detection of Coxiella burnetii in the sera of patients with Q fever endocarditis or vascular infection. J. Clin. Microbiol. 42:4919–4924.
8. Frankel D, Richet H, Renvoise A, Raoul D. 2011. Q fever in France, 1985-2009, Emerg. Infect. Dis. 17:350–356.
9. Hogema BM, et al. 2011. Coxiella burnetii infection among blood donors during the 2009 Q-fever outbreak in The Netherlands. Transfusion 52: 1040–1049.
10. Hung MN, et al. 2011. Serologic assessment of the risk of developing chronic Q fever in cohorts of acutely infected individuals. J. Infect. 62: 39–44.
11. Landais C, Fenollar F, Thuny F, Raoul D. 2007. From acute Q fever to endocarditis: serological follow-up strategy. Clin. Infect. Dis. 44:1337–1340.
12. Limonard GJ, Naber-Ruus Franssen MH, Dekhuijzen PN, Groot CA. 2011. Prevention of Q fever endocarditis. Lancet Infect. Dis. 11:82–83.
13. Limonard GJ, et al. 2010. One-year follow-up of patients of the ongoing Dutch Q fever outbreak: clinical, serological and echocardiographic find-
14.ings. Infection 38:471–477.
15. Marmion BP, Shannon M, Maddocks I, Storm P, Penttila I. 1996. Protracted debility and fatigue after acute Q fever. Lancet 347:977–978.
16. Maurin M, Raoul D. 1999. Q fever. Clin. Microbiol. Rev. 12:518–553.
17. Million M, Thuny F, Richet H, Raoul D. 2010. Long-term outcome of Q fever endocarditis: a 26-year personal survey. Lancet Infect. Dis. 10:527–535.
18. Musso D, Raoul D. 1995. Coxiella burnetii blood cultures from acute and chronic Q-fever patients. J. Clin. Microbiol. 33:3129–3132.
19. Parker NR, Barralet JH, Bell AM. 2006. Q fever. Lancet 367:679–688.
20. Psaroulaki A, et al. 2006. Epidemiological study of Q fever in humans, ruminant animals, and ticks in Cyprus using a geographical information system. Eur. J. Clin. Microbiol. Infect. Dis. 25:576–586.
21. Raoul D, Houpiikan P, Tissot DH, Riss JM, Jriditi-Djiane Brouqui P. 1999. Treatment of Q fever endocarditis: comparison of 2 regimens containing doxycycline and ofloxacin or hydroxychloroquine. Arch. Intern. Med. 159:167–173.
22. Raoul D, Marrie T, Mege J. 2005. Natural history and pathophysiology of Q fever. Lancet Infect. Dis. 5:219–226.
23. Schneeberger PM, et al. 2010. Real-time PCR with serum samples is indispensable for early diagnosis of acute Q fever. Clin. Vaccine Immunol. 17:286–290.
24. Tissot-Dupont H, Raoul D. 2008. Q fever. Infect. Dis. Clin. North Am. 22:505–514, ix.
25. Tissot-Dupont H, Vaillant V, Rey S, Raoul D. 2007. Role of sex, age, previous valve lesion, and pregnancy in the clinical expression and outcome of Q fever after a large outbreak. Clin. Infect. Dis. 44:232–237.
26. van der Hoek W, et al. 2012. Shifting priorities in the aftermath of a Q fever epidemic in 2007 to 2009 in The Netherlands: from acute to chronic infection. Euro Surveill. 17(3):pii=20059. http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20059.
27. van der Hoek W, et al. 2011. Follow-up of 686 patients with acute Q fever and detection of chronic infection. Clin. Infect. Dis. 52:1431–1436.
28. Wegdam-Blans MC, et al. 2012. Q fever: review of the literature and a proposal of new diagnostic criteria. J. Infect. 64:247–259.
29. Weiskopf D, Weinberger B, Grubeck-Loebenstein B. 2009. The aging of the immune system. Transpl. Int. 22:1041–1050.