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ORIGINAL ARTICLE

Acute Q fever related in-hospital mortality in the Netherlands

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ABSTRACT

Introduction: A large outbreak of acute Q fever has been reported in the Netherlands with over 3500 cases from 2007 to 2009, during which 749 patients were hospitalised. In foreign cohorts, reported mortality rates in patients hospitalised with acute Q fever, ranged from 0.9 to 2.4%. We analysed mortality among hospitalised patients with acute Q fever in the Netherlands.

Methods: Physicians from hospitals in the afflicted region were asked to provide details about patients who died with a diagnosis of acute Q fever between 2007 and 2009.

Results: Nine patients (seven males, median age 72 years) from six hospitals were reported, who died within approximately one month following hospitalisation for acute Q fever. Six definite acute Q fever cases and three probable cases were identified. Six patients presented with infiltrates on the chest X-ray and a median CURB-65 score of 3. Median time of hospitalisation was 13 days (range 1-33). All patients had serious, often coinciding, underlying conditions including chronic cardiovascular disease, chronic lung disease, diabetes mellitus and malignancy.

Conclusion: The mortality rate of patients hospitalised because of acute Q fever was estimated at approximately 1%. Patients who died with acute Q fever were often male, of older age, and had chronic coinciding underlying conditions, which gives an a priori higher risk of death.

KEYWORDS

Coxiella burnetii, hospitalisation, mortality, Q fever

INTRODUCTION

Q fever is a zoonotic infection, caused by *Coxiella burnetii*, an intracellular gram-negative coccobacillus. There is a large animal reservoir, with goats, sheep and cattle being the most common source of human infections, although infections from birds, pets and arthropods have also been described. When infected, mammals shed *C. burnetii* in urine, faeces, milk and especially birth products. In placental tissues of infected animals, up to 10^9 microorganisms per gram of tissue can be found. Humans get infected from direct contact with infected animals and/or inhalation of contaminated aerosols.[1-5] Most people infected with *C. burnetii* did not have close contact with infected animals, but were infected because of windborne spread of bacteria, which can travel over several kilometres.[3] Rarely, people get infected from drinking contaminated milk and sporadic human-to-human transmission has been described following contact with an infected parturient woman, blood transfusion or sexual intercourse.[2]

Q fever has both acute and chronic manifestations and the presentation of the disease is extremely variable. After infection, most patients (50 to 60%) remain asymptomatic. Typically, symptomatic patients report a flu-like illness with fever, myalgia, fatigue, headache and artralgia, often accompanied by respiratory signs of pneumonia. Mild elevations of transaminases can be present, and severe acute hepatitis may occur. More rarely, pericarditis, myocarditis, meningitis, peripheral neuropathy and haemolytic anaemia accompany an acute Q fever infection.[1-5] Symptoms can last from ten to 90 days, and usually resolve spontaneously. Antibiotic treatment with doxycycline or fluoroquinolones

is only warranted in symptomatic patients to shorten the duration of the fever and to hasten recovery from the pneumonia.[2,3] A significant number of acute Q fever patients subsequently develop a chronic fatigue syndrome, which can last five to ten years after the acute illness.[3,6,7]

Following an acute infection with *C. burnetii*, 1 to 5% of patients progress to chronic infection, which can even develop years after the primary infection. Endocarditis, vascular aneurysm and prosthesis infection are the most common manifestations. Most frequently affected are patients with pre-existent valvular disease and vascular defects (especially aortic aneurysms and aortic stents/prosthesis), immunocompromised patients and pregnant women.[2,3,8]

Diagnosis of Q fever mandates notification to the municipal health authorities in the Netherlands. In the last three consecutive years, there has been a large expanding outbreak of Q fever in the south of the Netherlands: in 2007, a small outbreak of 168 cases was identified, while in 2008 and 2009, the epidemic progressed to 1000 and 2357 cases respectively.[9]

According to the literature, rates of hospital admission in symptomatic patients with acute Q fever range from 2% to as high as 63%.[3] Reported overall mortality rates of acute Q fever range from 0.5 to 2% in French and Australian populations.[2,3] Mortality data for hospitalised patients with acute Q fever range from 0.9 to 2.4% and are available from older reports from the United Kingdom (1979) and France (1992), respectively.[10,11]

In the Netherlands, 749 patients are known to the national health services to have been hospitalised with acute Q fever from 2007 to 2009.[9] This number is presumably not completely accurate, as it is extracted from questionnaires sent to the general practitioners of notified acute Q fever patients. Extrapolation of the previously published mortality rates for hospitalised patients with acute Q fever allows for an estimation of seven to 18 deaths in this three-year period in the Netherlands. However, although Q fever itself has been a notifiable disease in the Netherlands since 1978, there is no requirement to notify deaths attributable to this disease. Therefore, there are no accurate data about mortality rates during the Q fever epidemic in the last three years in the Netherlands. In the present report, we assess the mortality rate among hospitalised patients with an acute Q fever infection and, in addition, evaluate epidemiological characteristics of these patients. Death due to chronic Q fever has not yet been evaluated as it can be expected that this condition still has to develop in a significant number of patients at risk.

METHODS

Q fever in the Netherlands is mostly restricted to the middle and southern areas of the country. By October 2009, clinicians and microbiologists from 12 hospitals in the afflicted regions were asked to provide details about patients who were admitted at their hospital and died with a diagnosis of acute Q fever. If an acute Q fever-related death was reported, we requested information about patient characteristics, comorbidity, performed diagnostic procedures (chest X-ray, polymerase chain reaction (PCR), serology), severity of pneumonia and antimicrobial treatment.

Until 2008, laboratory diagnosis of acute Q fever in the Netherlands was mainly established by serological testing for antibodies to phase I and phase II antigens of *C. burnetii*. The most commonly used tests are the indirect immunofluorescence assay (IFA; Focus Diagnostics, Inc., Cypress, CA, USA), complement fixation test (CFT; Siemens Healthcare Diagnostics GmbH, Eschborn, Germany) and enzyme-linked immunosorbent assay (ELISA; Institut Virion\Serion GmbH, Würzburg, Germany). Appearance of phase II IgM and IgG antibodies indicates an acute Q fever infection. Seroconversion usually takes place seven to 15 days after onset of clinical symptoms.[12]

Since 2009, PCR on serum has become an important tool in the diagnosis of Q fever. PCR for *C. burnetii* allows the diagnosis of acute Q fever early after onset of disease, before seroconversion has taken place.[13] Adhering to recently published Dutch guidelines, the diagnosis of acute Q fever was considered definitive on the basis of either a positive serum PCR or a seroconversion or fourfold increase in antibody titres to *C. burnetii* as detected by either IFA or CFT in two consecutive serum samples. The diagnosis was considered possible when there were clinical signs compatible with an acute Q fever infection in concordance with the presence of antibodies to *C. burnetii* as detected by either IFA or CFT in a single serum sample.[14]

When pneumonia was suspected and confirmed on chest X-ray, the CURB-65 score was used as an index for the severity of pneumonia. The CURB-65 score is a clinical method of predicting the mortality of community-acquired pneumonia (CAP). It consists of five criteria, scoring 1 point each: confusion of new onset, urea >7 mmol/l, respiratory rate ≥30 breaths, blood pressure systolic <90 mmHg or diastolic ≤60 mmHg and age ≥65 years. A CURB-65 score of 0 gives a less than 1% 30-day mortality risk, score of 1 a 3% risk, score of 2 a 13% risk, score of 3 a 17% risk, score of 4 a 42% risk and score of 5 a 57% risk.[15]

RESULTS

Survey results

Nine patients who had died following hospitalisation with acute Q fever were identified: seven males and two females (78 *vs* 22%), admitted in six different hospitals. All patients were at least 55 years or older. Median age at

time of death was 72 years (range 55 to 86). All patients had serious, often coinciding, underlying conditions including chronic cardiovascular disease (five patients; 56%), chronic lung disease (seven patients; 78%), diabetes mellitus (four patients; 44%) or malignancy (two patients; 22%) (*table 1*). Median time of hospitalisation before death was 13 days (range 1 to 33). There were no reported deaths due to acute Q fever in 2007. Two patients died in 2008 and seven patients in 2009 (*figure 1*).

Clinical and microbiological diagnosis of acute Q fever

An overview of the clinical and microbiological features is presented in *table 1*. Six patients presented with evident infiltrates on chest X-ray and a median CURB-65 score on admission of 3 (range 1 to 3). The other three patients had no evident infiltrative changes on the chest X-ray, and as a result no CURB-65 score was calculated. One of them suffered from acute myeloid leukaemia and chemotherapy-induced neutropenia, which could explain the absence of infiltrative changes. Another patient suffered from metastastic lung carcinoma hindering detection of any infiltrative changes. Median C-reactive protein (CRP) level and white blood cell count (WBC) at hospital admission were 100 mg/l (range 43 to 267) and 10.2 x 10^9/l (range 4.0 to 14.0, after exclusion of the patient with chemotherapy-induced neutropenia), respectively.

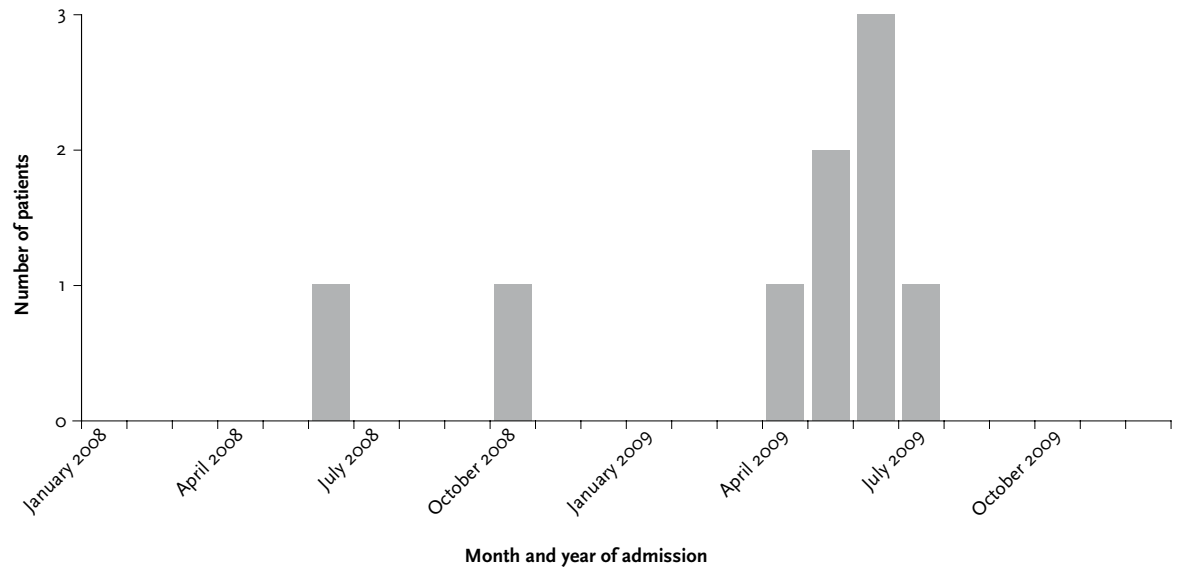
A definite laboratory diagnosis of acute Q fever was made by positive serum PCR for *C. burnetii* in four

Table 1. *Overview of patient characteristics, clinical and microbiological features and antimicrobial treatment of nine fatal acute Q fever cases*

	Sex	Age	Diagnosis	Days in hospital	CURB-65 score	Comorbidity	Antimicrobial treatment before diagnosis of Q fever	Antimicrobial treatment after diagnosis of acute Q fever	Other pathogens, besides *C. burnetii*
Patient 1	M	79	PCR	22	2	COPD with bronchiectasis, diabetes mellitus, alcohol abuse	Penicillin and ciprofloxacin	Doxycycline and flucloxacillin	Sputum culture: *Staphylococcus aureus*
Patient 2	F	64	PCR	19	3	Chronic heart failure and left ventricular failure, heart valve disease (two valve prosthesis), diabetes mellitus, chronic renal disease	Cefuroxime, after four days switch to doxyxcycline	Moxifloxacin	-
Patient 3	M	82	Serology (IFA)	13	3	COPD, peripheral vascular disease, myocardial infarction	Amoxicillin with clavulanic acid and tobramycine, after two days switch to moxifloxacin	- (diagnosis post-mortem)	Blood culture: *Staphylococcus hominis*
Patient 4	M	86	PCR and serology (CFT)	13	3	Lung fibrosis, CABG, diabetes mellitus	Amoxicillin with clavulanic acid and fluconazole	- (diagnosis post-mortem)	Culture of bronchoalveolar lavage: *Candida lusitaniae*
Patient 5	M	83	PCR	1	1	Dementia, infrarenal aneurysm	Amoxicillin with clavulanic acid	- (diagnosis (4 months) post-mortem)	-
Patient 6	M	55	PCR and serology (IFA)	33	-	Acute myeloid leukaemia, lobectomy lung	Vancomycin, meropenem, ceftazidime, co-trimoxazole, voriconazole and acyclovir	Doxycycline, vancomycin, co-trimoxazole, voriconazole and aciclovir	Considered as colonisation: *Escherichia coli (ESBL), Acinetobacter iwoffii, Acinetobacter baumannii, Candida glabrata*
Patient 7	M	72	PCR	9	3	Hyperthrophic obstructive cardiomyopathy, mitral insufficiency, chronic atrial fibrillation, CVA, COPD	Penicillin and ciprofloxacin, after one day switch to penicillin and doxyxycline	Doxycycline	-
Patient 8	M	56	Serology (CFT)	9	-	Metastastic lung cancer	Doxycycline	Doxycycline	-
Patient 9	F	69	Serology (IFA)	9	-	COPD, diabetes mellitus	Penicillin and ciprofloxacin	Penicillin and ciprofloxacin	-

M = male; F = female; PCR = polymerase chain reaction; IFA = indirect immunofluorescence assay; CFT = complement fixation test; COPD = chronic obstructive pulmonary disease; CABG = coronary artery bypass graft; CVA = cerebral vascular accident; ESBL = extended-spectrum beta-lactamase.

Figure 1. *Month and year of admission of nine fatal acute Q fever cases*



seronegative patients and two seropositive patients. In one patient, who died one day after hospital admission, the definite diagnosis of acute Q fever was established four months post-mortem through PCR on a stored seronegative serum sample. In three patients with clinical signs compatible with an acute Q fever infection, a laboratory diagnosis of possible acute Q fever was made on the basis of positive serology in a single serum sample. As these patients died nine to 13 days after hospital admission, a second serum sample to confirm the diagnosis could not be obtained. Both patients with a definite and a possible diagnosis were included in the overall analysis.

Antimicrobial treatment

Table 1 gives an overview of the prescribed antimicrobials and co-pathogens for the nine patients who died with an acute Q fever infection. Five patients were initially treated with antibiotics with proven activity against *C. burnetii*. The sixth patient switched after two days and the seventh patient after four days of admission to an antibiotic with proven activity against *C. burnetii,* before the actual diagnosis was made. After diagnosis of acute Q fever, antibiotic treatment was switched from ciprofloxacin to doxycycline in one patient and from doxycycline to moxifloxacin in a second patient, while in a third patient doxycycline was added to co-trimoxazole. In the two patients who were never treated with an adequate antibiotic regime for *C. burnetii,* the diagnosis of acute Q fever was made post-mortem.

In cultures of four patients, other pathogens were detected, which influenced the choice of antimicrobial treatment.

DISCUSSION

We identified nine patients who died, within approximately one month following hospital admission, with definite or possible acute Q fever in the period of 2007 to October 2009. With 749 known hospital admissions due to acute Q fever in the Netherlands from 2007 to 2009, the in-hospital mortality rate is approximately 1%, which is relatively low and illustrative of the relatively mild nature of the acute form of this disease. In comparison, the reported overall in-hospital mortality rate of CAP in the Netherlands is 8%.[16] Seven out of the nine patients were males. This is in line with the fact that male sex is a risk factor for symptomatic acute Q fever and the reported incidence of acute Q fever in males and females. In surveys from Australia and France, males are fivefold and 2.5-fold, respectively, more likely to develop symptomatic acute Q fever.[1,2,3,5]

Doxycycline and fluoroquinolones are the antibiotics of choice for acute Q fever. Treatment lessens the duration of fever and hastens recovery of pneumonia, but the effect on mortality has not been investigated. Initiation of treatment three days after symptom onset is reported to be less effective; however, good clinical responses have been observed with treatment up to a week from start of symptoms.[1-3] Five out of nine patients were initially treated with adequate antibiotic regimes for acute Q fever. Two patients started adequate therapy at admission-day two and four, respectively.

All nine patients had serious, often coinciding, underlying conditions including chronic cardiovascular disease, chronic lung disease, diabetes mellitus and malignancy.

In four patients, co-pathogens, besides *C. burnetii,* were detected. It is feasible that these pathogens contributed to some extent to the patients' death and influenced the choice of antimicrobial therapy. In addition, six patients were older than 65 years, which is one of the risk factors that stratifies patients with CAP to a higher risk class in the CURB-65 score.[15] With a score of 3, the median CURB-65 score in the six patients who presented with pneumonia was relatively high, representing a 30-day mortality risk of 17%.

In comparison, median age at time of hospitalisation of 28 patients with non-lethal acute Q fever who had been included in 2008 to 2009 in a prospective observational study on the aetiology of CAP at the Jeroen Bosch Hospital was 55 (range 23 to 96; 25% of patients older than 65 years). This cohort consisted of 19 males and 9 females (68 *vs* 32%). Median CURB-65 score on admission was 0 (range 0 to 4) and median time of hospitalisation was six days (range 2 to 14). Overall, patients in this cohort had far less relevant underlying conditions (three patients (11%) with chronic cardiovascular disease, five patients (18%) with diabetes mellitus, one patient with chronic hepatitis C and one patient with chronic use of methotrexate for chronic arthritis, while no patients with chronic lung disease or malignancy were identified; unpublished data). Likewise, an earlier Dutch report by de Wit *et al.* of 25 non-lethal, hospitalised, acute Q fever cases in the Netherlands, described a CURB-65 score of 0±1 (mean ± SD).[17] These observations indicate that hospitalised patients who eventually died of an acute Q fever infection were at time of presentation already more severely ill than patients who survived.

The aim of this report was to make an estimation of in-hospital acute Q fever related-deaths in the Netherlands and to describe the patient characteristics of the fatalities. It is feasible that death as a result of acute Q fever is underreported. There are as yet no adequate databases of hospitalised acute Q fever patients in the Netherlands and the exact number of patients hospitalised due to acute Q fever is not known. Also, there is no requirement to notify deaths attributable to this disease. Furthermore, it is more than likely that due to its design, our survey was not all-comprehensive. In most hospitals, PCR for *C. burnetii* was not introduced until early 2009. It is, therefore, possible that in 2007 and 2008, seronegative patients may have died from pneumonia or febrile disease caused by *C. burnetii*, in whom the diagnosis could not be established with PCR. These patients are missed in this survey. This is illustrated by the fact that in one seronegative case, diagnosis was made through PCR four months post-mortem. However, even if death to acute Q fever is underreported, this also holds true for non-fatal cases of the disease. For example, Schneeberger *et al.* have previously shown that retrospective PCR analysis on stored serum samples from patients in whom the diagnosis of acute Q fever had not been made using serological techniques allowed this diagnosis to be made in 5/50 (10%) cases.[13] Moreover, especially in 2007 and 2008, many clinicians were still unaware of the existence of a Q fever epidemic. Since there is an evident overlap in symptoms with other febrile diseases, the possibility of acute Q fever could easily be overlooked and, subsequently, no diagnostic tests to detect *C. burnetii* were ordered. Thus, death to acute Q fever as well as acute Q fever itself might be underreported, warranting some caution towards the in-hospital mortality rate reported in this survey.

CONCLUSION

The in-hospital mortality rate of acute Q fever in the Netherlands can be estimated at around 1%, which is relatively low compared with the overall in-hospital mortality rate of CAP and illustrates the relatively mild nature of the acute form of this disease. Patients who died with acute Q fever were often male, of older age, and had chronic coinciding underlying conditions, which gives an a priori higher risk of death. The rate of death cannot be accurately defined, because there is no obligation to register Q fever-related admissions and fatalities in the Netherlands. Better registration is necessary to provide a detailed estimation of mortality because of acute Q fever.

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