

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Clinical presentation of acute Q fever in Spain: seasonal and geographical differences



Elena Espejo^{a,*}, Aída Gil-Díaz^b, José Antonio Oteo^c, Renato Castillo-Rueda^b, Lara García-Alvarez^c, Sergio Santana-Báez^b, Feliu Bella^a

^a Consorci Sanitari de Terrassa, Ctra. Torrebonica s/n, 08227 Terrassa, Spain

^b Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain

^c Hospital San Pedro-CIBIR, Logroño, Spain

ARTICLE INFO

Article history:

Received 7 March 2014

Received in revised form 27 May 2014

Accepted 14 June 2014

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:

Coxiella burnetii

Geographical differences

Seasonal variation

Zoonosis

SUMMARY

Objectives: The aims of this study were to improve our understanding of the clinical forms of presentation of acute Q fever in Spain and to determine any possible relationships with geographical and seasonal factors.

Methods: This was a retrospective study of 183 cases of acute Q fever from three Spanish regions, Catalonia, Canary Islands, and La Rioja.

Results: The main clinical form of presentation was hepatitis (49.2%), followed by isolate febrile syndrome (31.7%) and pneumonia (19.1%). The proportion of cases presenting as pneumonia was significantly higher in La Rioja (40.7%) than in Catalonia (18.3%) or the Canary Islands (12.9%) ($p = 0.001$). In Catalonia and the Canary Islands, most cases (52.1% and 57.6%, respectively) were diagnosed between March and June, whereas in La Rioja, most cases (51.8%) occurred between November and February. Overall, the proportion of cases presenting as pneumonia was significantly higher in the period from November to February (32.6%) than in the periods March–June (16.0%) and July–October (13.0%) ($p = 0.01$).

Conclusions: Our results suggest the existence of seasonal differences in the presentation of acute Q fever in Spain, with a higher proportion of pneumonic forms in the colder months. Furthermore, we confirmed the existence of geographical differences, with a higher proportion of pneumonic forms in the region of La Rioja, in the north of the country.

© 2014 The Authors. Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/3.0/>).

1. Introduction

Q fever is a worldwide zoonosis caused by *Coxiella burnetii*.^{1–3} Livestock, and to a lesser degree various wild mammals and domestic animals, such as dogs and cats, constitute the main reservoirs of this microorganism.³ Infected animals shed *C. burnetii* in their feces, urine, milk, and birth products.^{1,4} Shedding to the environment occurs mainly during parturition and abortion.^{2,5,6} The contaminated products form aerosols that can be spread several kilometers by the wind.⁷ Thus, Q fever may occur in urban areas, mainly as sporadic cases, but also as outbreaks.⁸ Outbreaks usually occur in rural areas, often in relation to the transfer or handling of cattle, sheep, or goats.^{9,10}

Inhalation of infectious aerosol particles constitutes the major route of acquiring the disease, while ingestion of raw dairy products is a minor route of transmission. Acquisition through the skin or mucosal contact with contaminated products and vertical transmission are very rare.^{1,2}

Asymptomatic infection is common.^{1,10} Among the symptomatic patients, Q fever may present with acute or chronic clinical manifestations, with endocarditis being the main manifestation of the chronic form.^{1,11} Acute Q fever usually presents with fever, chills, and headache that may be accompanied by pneumonia and/or hepatitis. Meningoencephalitis, pericarditis, and myocarditis are among the rare clinical manifestations.^{1,12–18}

Regional variations in acute disease presentation have been reported.^{1,2} The aims of this study were to improve our understanding of the clinical forms of presentation of acute Q fever in Spain and to determine their possible relationships with geographical and seasonal factors.

* Corresponding author. Tel.: +34 937839488; fax: +34 937003614.

E-mail addresses: 12088eea@comb.cat, eespejo@cst.cat (E. Espejo).

Table 1
Clinical presentation of acute Q fever according to seasonal period

Presentation form	Period			p-Value ^a
	November–February (43 cases), n (%)	March–June (94 cases), n (%)	July–October (48 cases), n (%)	
Pneumonia	14 (32.6)	15 (16.0)	6 (13.0)	0.010
Hepatitis	19 (44.2)	46 (48.9)	25 (54.4)	0.45
Isolated fever	10 (23.2)	33 (35.1)	15 (32.6)	0.17

^a Cases diagnosed between November and February compared with cases diagnosed in other periods.

2. Materials and methods

The study was conducted in three Spanish hospitals, located in separate regions: (1) Terrassa Hospital, located in Catalonia (northeast of Spain) serving a population of about 200 000 inhabitants, with a mainly urban distribution; (2) San Pedro Hospital, located in La Rioja region (north of Spain, adjacent to the Basque Country) serving a population of about 300 000 inhabitants, with a predominantly suburban and rural distribution; (3) Dr. Negrín Gran Canaria University Hospital, located in the Canary Islands (Atlantic Ocean, 200 km from Africa) serving a population of about 450 000 inhabitants with a balanced urban, suburban, and rural distribution.

We reviewed the clinical records of all adult patients who had acute Q fever diagnosed between 1995 and 2009 in Terrassa (Catalonia) and La Rioja, and between 2005 and 2009 in Gran Canaria, where the prevalence of Q fever is higher.¹⁹

Criteria for inclusion in the study were fever (axillary temperature ≥ 38 °C) plus a serological diagnosis of Q fever by means of immunofluorescence assay (IFA), on the basis of any of the following criteria: (1) seroconversion, defined as the appearance of phase II IgG antibodies against *C. burnetii* at a titer $\geq 1/160$ in the convalescent phase following a negative antibody titer in the acute phase; (2) a four-fold or greater rise between acute-phase and convalescent-phase serum samples; (3) a titer of IgG antibodies $\geq 1/320$ in a single determination plus a positive IgM titer; (4) a titer of IgG antibodies $\geq 1/320$ in a single determination in the absence of an alternative diagnosis. The case was considered confirmed when serological criterion 1, 2, or 3 was met, and as probable when criterion 4 was met.

The clinical and epidemiological data were recorded. A chest X-ray was obtained in every case. The following criteria were used to classify the clinical presentation: (1) the patient was considered to have pneumonia if there was a lung infiltrate on chest radiograph; (2) the patient was considered to have hepatitis if the aspartate aminotransferase level and/or alanine aminotransferase level was more than twice as high as the reference value, without lung involvement on chest X ray; (3) isolated febrile syndrome was identified when fever was present without lung or hepatic involvement or another focus of infection.

To study seasonal differences, cases were grouped into three periods, according to the date of presentation: November to February, March to June, and July to October. This clustering was performed taking into account that the months of November to February are those with a lower average temperature in most Spanish regions.

A descriptive analysis was performed using means and standard deviations (SD). Statistical comparisons of categorical variables were made by Chi-square test. A *p*-value of 0.05 or less was considered statistically significant. Statistical analyses were performed using EpiData v. 3.1.

3. Results

Acute Q fever was diagnosed in 183 patients (164 confirmed cases and 19 probable cases), 147 of whom were male (80.3%). The mean patient age was 42.1 years (SD 15.3 years). Seventy-one cases were from Catalonia, 27 from La Rioja, and 85 from Gran Canaria. Sixty-three patients (34.3%) lived in a rural area: 21.1% of those in Catalonia, 40.7% of those in La Rioja, and 43.5% of those in Gran Canaria. No epidemic outbreaks were recorded.

The clinical presentation of Q fever was pneumonia in 35 cases (19.1%), hepatitis in 90 cases (49.2%), and isolated febrile syndrome in 58 cases (31.7%). Of these, three had pericarditis and one had myocarditis. Non-specific clinical manifestations were headache in 107 cases (58.5%), arthromyalgia in 69 cases (37.7%), nausea or vomiting in 32 cases (17.5%), diarrhea in 20 cases (10.9%), abdominal pain in 14 cases (7.7%), and pharyngodynia in five cases (2.7%). One hundred and ten patients were admitted to the hospital, and two patients required admission to the intensive care unit. Two patients died from complications of their underlying disease (liver cirrhosis and end-stage renal disease).

As regards the seasonal distribution, 94 cases (51.4%) were diagnosed between March and June, 46 cases (25.0%) between July and October, and 43 cases (23.5%) between November and February. The clinical presentation in the form of pneumonia was significantly more frequent in the period from November to February than in the rest of the year (Table 1).

Table 2
Seasonal distribution and clinical presentation in each region

	Region			p-Value ^a
	Catalonia (71 cases), n (%)	Gran Canaria (85 cases), n (%)	La Rioja (27 cases), n (%)	
Period				
November–February	13 (18.3)	16 (18.8)	14 (51.8)	0.0001
March–June	37 (52.1)	49 (57.6)	8 (29.6)	0.014
July–October	21 (29.5)	20 (23.5)	5 (18.5)	0.39
Clinical presentation				
Pneumonia	13 (18.3)	11 (12.9)	11 (40.7)	0.001
Other presentations	58 (81.7)	74 (87.1)	16 (59.3)	
Patients admitted to hospital	61	27	22	
Pneumonia	12 (19.7)	8 (29.6)	10 (45.5)	0.03
Other presentations	49 (80.3)	19 (70.4)	12 (54.5)	

^a Cases from La Rioja compared with cases from Catalonia or Gran Canaria.

Table 2 shows the seasonal distribution and the clinical presentation of acute Q fever in the three regions. Of note, the proportion of cases that occurred between November and February was significantly higher in La Rioja than in the other two regions. Likewise, the proportion of cases with pneumonia was significantly higher in this region than in the other two, and this difference remained when considering only cases admitted to hospital.

4. Discussion

Coinciding with other Spanish series of Q fever,^{19–23} more than half of the cases in our study occurred in the spring months. This has been attributed to the fact that most births in cattle and sheep take place during these months, a condition that is known to release large amounts of *C. burnetii*.^{5,9} However, it is noteworthy that most cases from La Rioja were diagnosed between November and February. One possible explanation for this is that the reproduction of sheep in this region is usually planned so that deliveries occur in the run-up to the Christmas holidays, when a suckling kid is traditionally eaten.

A predominance of males was observed in the three participating hospitals, which is common in most series of Q fever.^{6,7,12–14,19–29} This has been attributed to an increased risk of occupational exposure for men, but it is likely that hormonal factors also play a role.³⁰

It is known that there are regional variations in the predominant presenting form of acute Q fever.³⁰ It has been suggested that the clinical form could be related to differences in the infecting strain,³¹ the inoculation dose, host factors, or the route of infection.¹ Pneumonia would predominate in cases acquired by inhalation of infectious aerosol particles, whereas hepatitis would predominate in cases acquired by ingestion of contaminated dairy products.³²

Our finding of an increased number of cases of Q fever pneumonia during the colder months suggests a possible relationship between clinical presentation and temperature or other seasonal factors. It is conceivable that the cold and winter viral infections increase the susceptibility of the respiratory mucosa to *C. burnetii*, as with other pathogens such as *Streptococcus pneumoniae*. In the vast majority of studies on Q fever from Spain, febrile forms without pneumonia predominate,^{19–21,24–28} with the exception of the series from the Basque Country, in the Spanish north coast region, where pneumonic forms predominate.^{22,23,29} In this regard, our finding of a significantly higher proportion of pneumonia in La Rioja, a region in the north, bordering the Basque Country, is noteworthy. Moreover, it is likely that some of the reported differences are biased due to the observer. So, pneumonic forms predominate in the series from pneumology services, and febrile forms, with or without hepatitis, are more frequent in the series from internal medicine and infectious diseases services, especially in centers with a specific protocol for the study of fever of intermediate duration, which includes carrying out Q fever serology.^{20,24,33}

The main limitations of our study are its retrospective nature and the fact that only cases from three Spanish regions were included.

In conclusion, our results suggest the existence of seasonal differences in the presentation of Q fever in Spain, with a higher proportion of pneumonic forms in the winter months. Furthermore, we confirmed the existence of geographical differences, with a higher proportion of pneumonic forms in the region of La Rioja, in the north of the country.

Funding sources: None declared.

Conflict of interest: The authors declare that they have no conflict of interest.

References

- Maurin M, Raoult D. Q fever. *Clin Microbiol Rev* 1999;**12**:518–53.
- Parker NR, Barralet JH, Bell AM. Q fever. *Lancet* 2006;**367**:679–88.
- Porter SR, Czapliski G, Mainil J, Guattéo R, Saegerman C. Q fever: current state of knowledge and perspectives of research of a neglected zoonosis. *Int J Microbiol* 2011;248418. <http://dx.doi.org/10.1155/2011/248418>.
- Stoker MG, Marmion BP. The spread of Q fever from animals to man: the natural history of a rickettsial disease. *Bull World Health Organ* 1955;**13**:781–806.
- Woldehiwet Z. Q fever (coxiellosis): epidemiology and pathogenesis. *Res Vet Sci* 2004;**77**:93–100.
- Kováčová E, Kazar J, Šimková A. Clinical and serological analysis of a Q fever outbreak in Western Slovakia with four-year follow-up. *Eur J Clin Microbiol Infect Dis* 1998;**17**:867–9.
- Tissot-Dupont H, Amadei MA, Nezri M, Raoult D. Wind in November, Q fever in December. *Emerg Infect Dis* 2004;**10**:1264–9.
- Hawker JI, Ayres JG, Blair I, Evans MR, Smith DL, Smith EG, et al. A large outbreak of Q fever in the West Midlands: windborne spread into a metropolitan area? *Commun Dis Public Health* 1998;**1**:180–7.
- Welsh HH, Lennette EH, Abinanti FR, Winn JF. Air-borne transmission of Q fever: the role of partition in the generation of infective aerosols. *Ann N Y Acad Sci* 1958;**70**:528–40.
- Dupuis G, Petite J, Péter O, Vouilloz M. An important outbreak of human Q fever in a Swiss alpine valley. *Int J Epidemiol* 1987;**16**:282–7.
- Brouqui P, Tissot Dupont H, Drancourt M, Berland Y, Etienne J, et al. Chronic Q fever. Ninety-two cases from France, including 27 cases without endocarditis. *Arch Intern Med* 1993;**153**:642–8.
- Tissot Dupont H, Raoult D, Brouqui P, Janbon F, Peyramond D, Weiller PJ, et al. Epidemiologic features and clinical presentation of acute Q fever in hospitalized patients: 323 French cases. *Am J Med* 1992;**93**:427–34.
- Raoult D, Tissot-Dupont H, Foucault C, Gouvernet J, Fournier PE, Bernit E, et al. Q Fever 1985–1998. Clinical and epidemiological features of 1383 infections. *Medicine (Baltimore)* 2000;**79**:109–23.
- Sampere M, Font B, Font J, Sanfeliu I, Segura F. Q Fever in adults: review of 66 clinical cases. *Eur J Clin Microbiol Infect Dis* 2003;**22**:108–10.
- Marrie TJ. Coxiella burnetii pneumonia. *Eur Respir J* 2003;**21**:713–9.
- Levy PY, Carrieri P, Raoult D. Coxiella burnetii pericarditis: report of 15 cases and review. *Clin Infect Dis* 1999;**29**:393–7.
- Fournier PE, Etienne J, Harle JR, Habib G, Raoult D. Myocarditis, a rare but severe manifestation of Q fever: report of 8 cases and review of the literature. *Clin Infect Dis* 2001;**32**:1440–7.
- Hatchette TF, Marrie TJ. Atypical manifestations of chronic Q fever. *Clin Infect Dis* 2001;**33**:1347–51.
- Bolaños M, Santana OE, Pérez-Arellano JL, Ángel-Moreno A, Moreno G, Burgazzoli JL. Fiebre Q en Gran Canaria. Aportación de 40 nuevos casos. *Enferm Infecc Microbiol Clin* 2003;**21**:20–3.
- Alarcón A, Villanueva JL, Viciano P, López-Cortés L, Torronteras R, Bernabeu M, et al. Q fever: epidemiology, clinical features and prognosis. A study from 1983 to 1999 in the South of Spain. *J Infect* 2003;**47**:110–6.
- Domingo P, Muñoz C, Franquet T, Gurguá M, Sancho F, Vazquez G. Acute Q fever in adult patients: report of 63 sporadic cases in an urban area. *Clin Infect Dis* 1999;**29**:874–9.
- Montejo Baranda M, Corral Carranceja J, Aguirre Errasti C. Q fever in the Basque Country: 1981–1984. *Rev Infect Dis* 1985;**7**:700–1.
- Aguirre Erasti C, Montejo Baranda M, Hernández Almaraz JL, De la Hoz Torres C, Martínez Gutiérrez E, Villate Navarro JL, et al. An outbreak of Q fever in the Basque Country. *Can Med Assoc J* 1984;**131**:48–9.
- Bella F, Espejo E, Mauri M, Alegre MD. Clinical presentation of Australian acute Q fever. *Am J Med* 1994;**96**:397–8.
- Romero-Jiménez MJ, Suárez-Lozano I, Fajardo JM, Benavente A, Menchero A, De la Iglesia A. Hepatitis aislada como forma de presentación de la fiebre Q: características clínicas y epidemiológicas en 109 pacientes. *Enferm Infecc Microbiol Clin* 2003;**21**:193–5.
- Muñoz-Sanz A, Vera A, Rodríguez Vidigal FF. Fiebre Q en Extremadura: una infección emergente. *Enferm Infecc Microbiol Clin* 2007;**25**:230–4.
- Bartolomé J, Marín A, Lorente S, Heredero E, Crespo MD. Fiebre Q aguda: 35 casos en Castilla-La Mancha. *Enferm Infecc Microbiol Clin* 2004;**22**:292–4.
- Ruiz Seco MP, López Rodríguez M, Estébanez Muñoz M, Pagán B, Gómez Cerezo JF, Barbado Hernández FJ. Fiebre Q: 54 nuevos casos de un hospital terciario de Madrid. *Rev Clin Esp* 2011;**211**:240–4.
- García-Clemente M, Seco-García AJ, Gutiérrez-Rodríguez M, Romero-Álvarez P, Fernández-Bustamante J, Rodríguez-Pérez M. Brote epidémico de neumonía por Coxiella burnetii. *Enferm Infecc Microbiol Clin* 2007;**25**:184–6.
- Raoult D, Marrie TJ, Mege JL. Natural history and pathophysiology of Q fever. *Lancet Infect Dis* 2005;**5**:219–26.
- Jado I, Carranza-Rodríguez C, Barandika JF, Toledo A, García-Amil C, Serrano B, et al. Molecular method for the characterization of Coxiella burnetii from clinical and environmental samples: variability of genotypes in Spain. *BMC Microbiol* 2012;**12**:91. <http://dx.doi.org/10.1186/1471-2180-12-91>.
- Marrie TJ, Stein A, Janigan D, Raoult D. Route of infection determines the clinical manifestations of acute Q fever. *J Infect Dis* 1996;**173**:484–7.
- Parra Ruiz J, Peña Monje A, Tomás Jiménez C, Parejo Sánchez MI, Vinuesa García D, Muñoz Medina L, et al. Clinical spectrum of fever of intermediate duration in the south of Spain. *Eur J Clin Microbiol Infect Dis* 2008;**27**:993–5.