Ref: Ro J Infect Dis. 2019;22(2)
DOI: 10.37897/RJID.2019.2.2

Clinical and evolutive aspects of *Coxiella burnetii* infection

Maria Cristina Hoara[1], Simin-Aysel Florescu[1,2], Sebastian Alexandru Piscu[1], Gratiela Tardei[1], Petre Iacob Calistru[1,2]

[1]"Dr. Victor Babes" Clinical Hospital for Infectious and Tropical Diseases, Bucharest, Romania
[2]"Dr. Victor Babes" Infectious and Tropical Diseases Clinic, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

Introduction. *Coxiella burnetii* is the etiological agent of Q fever, a zoonosis that is still subject of „Query". Formerly classified as a *Rickettsia, C. burnetii* is a highly infectious obligate intracellular bacteria, whose main animal reservoirs are cattle, sheep and goats. Commonly following transmission through inhalation of aerosols containing the pathogen spread during animal parturition, Q fever may present as a self-limited febrile illness, pneumonia or acute hepatitis. Nevertheless, the possibility of evolving towards a chronic form exists under certain circumstances, mainly involving previously affected heart valves or blood vessels. Diagnosis is usually serologically based and Doxycycline represents the most frequent choice of antibiotherapy.
Objectives. The aim of this study is to analyse the clinical and laboratory settings that led to diagnosis of acute or chronic Q fever, the treatment regimens applied and consecutive outcome within the group of patients defined below.
Materials and methods. The present paper represents an observational descriptive study performed on a group composed of 24 patients admitted in our hospital along 2018 and diagnosed with confirmed or probable acute or chronic Q fever. Both male and female subjects regardless of their age were included, under the condition of meeting the CDC case definition, by integrating the serological results into the clinical context.
Results and conclusions. A suggestive epidemiological frame was rarely proven. Out of the 24 subjects with ages between 34 and 80 years old, of which only 2 were women, 22 had acute Q fever, manifested mostly as a combination of atypical pneumonia and hepatitis (9 cases, representing 41. Only 2 of the acute Q fever cases had a confirmed diagnosis. Frequent complaints were fever (all cases), chills, headaches and vomiting. Only 28% of the radiologically confirmed pneumonias were accompanied by dry cough, whilst only 21% of the hepatitis cases associated jaundice. Biologically, although leukocytosis was more weakly correlated with acute disease activity, all patients exhibited a moderate to high inflammatory response (through C reactive protein). Considering the latency of specific antibodies' dosage results, the decision of initiating treatment was based on a clinical support. Antibiotherapy consisted of Doxycyclin, alone or in combinations meant to cover a larger spectrum, given the usually nonspecific symptoms and the initially low clinical suspicion for Q fever. Clinical evolution was favorable in all cases. Regarding the two patients with chronic Q fever, manifested as blood culture-negative endocarditis, of which only one was confirmed according to the CDC definition, both had presented valvular lesions before developing IE and had no history of acute infection with *C. burnetii.* In the first case, under empirical infective endocarditis agents (Ceftriaxone and Vancomycin), acute heart failure and necessity of surgical replacement of the affected valve occured, only afterwards being followed by the elevated phase I IgG level that brought diagnostic confirmation. Meanwhile, the second patient did receive a combination with Doxycycline, followed by favorable clinical evolution during admission.

Keywords: *Coxiella burnetii,* Q fever, Doxycyclin

INTRODUCTION

Coxiella burnetii is the etiological agent of Q fever, a disease whose name reminds of the question („Query") Derrick asked himself back in 1935, following the observation of a febrile syndrome outbreak among workers at a slaughterhouse in Brisbane, without an explainable cause at that time. Subsequently, two teams of researchers identified

Corresponding author:
Maria Cristina Hoara, MD
E-mail: cristina_hoara@yahoo.com

Article History:
Received: 31 May 2019
Accepted: 20 June 2019

the causal agent almost simultaneously, initially classified as a *Rickettsia*: **Burnet** and Freeman, in Australia and Davis and **Cox**, in the US. Currently, the intracellular pathogen has been reclassified as a gammaproteobacteria, being more closely related to *Legionella spp*. Morphologically, *C. burnetii* has the characteristics of a pleomorphic cocobacillus, which forms highly resistant spores in the environment, also having a Gram-negative cell wall. What is particular about it is the undergoing of antigenic phase variation, through the change in composition of the surface lipopolysaccharide, which has an implication in attributing the serological response to the acute and chronic form of the disease, respectively (3,4,5).

The geographical distribution of *C. burnetii* covers almost the entire globe, excepting the Arctic, Antarctic and New Zealand. Considering both the main way of infection transmission, namely by inhalation of contaminated aerosols especially during animal parturition (the pathogen being intensely concentrated in the placenta), as well as the small infective dose needed to contract the disease, we discuss about a potential bioterrorism agent. The main animal reservoirs are sheep, goats and cattle, fact that shows the occupational character of Q fever – veterinarians, farmers and workers at the slaughterhouse, who come into direct contact with often asymptomatic infected animals, are frequently involved. However, other animal species, such as fish, birds, pigs, dogs, cats, but also wildlife should not be forgotten, all of which are in turn infected by bite or contamination with the debris of ticks or other arthropods, within which the bacteria persists (3,4,5).

In spite of the facts presented above, an epidemiological link between a case suspected of Q fever and the source of infection is rarely established, as the disease can also be transmitted indirectly through contaminated straw or dust, multiple outbreaks involving residents living a few kilometers away from a farm or along an animal freight road. In addition, animals also eliminate the microorganism through urine, feces and milk, which explains a second possibility of contracting the infection, namely the ingestion of unpasteurized dairy products. Other less commonly cited transmission methods involve skin penetration of *C. burnetii* by crushing an infected tick, blood transfusions, sexual contact, maternal-fetal passage, contact between family members, participation at an autopsy or birth assistance of an infected person (4,5).

The first phase of the disease, acute Q fever, appears after an incubation period ranging from 1 to 39 days – depending on the infective dose, with an average of 20 days. According to the host, bacterial strain and infective dose, the infection can be both asymptomatic, especially amongst children and women (more often in pregnant women), which could be explained by steroid hormones influentions, as well as clinically manifest. The most common clinical form developed is a self-limited febrile illness (pseudogripal syndrome) that lasts for 1 to 3 weeks, its features consisting of sudden onset of high fever, chills, fatigue, myalgia, nausea, vomiting, diarrhea and a frequently severe retroorbital headache that can be accompanied by photophobia. This latter fact sometimes leads to lumbar puncture and rare occurrence of *C. burnetii* in CSF has been cited in literature (4,11).

Another clinical expression of the disease is pneumonia. In addition to the aforementioned picture, dry cough and pleuritic chest pain are rarely experienced, meeting the criteria of atypical pneumonia. Radiologically, imaging aspects can range from pleural-based opacities, which are difficult to differentiate from another bacterial focal pneumonia, to bilateral multifocal opacities – associated in literature with exposure to biological products resulting from parturition of domestic cats but increased reticular markings can also be found. A third clinical form of acute disease may be hepatitis, usually without jaundice, biologically accompanied by often minimal-to-moderate hepatocytolysis (transaminase levels increased by 2-3 times above normal), but that can also reach levels found in acute viral hepatitis; hepatosplenomegaly is inconsistent and the histopathological mark is represented by the „doughnut-like" granulomas. Amongst other clinical expressions of acute infection are acute endocarditis, pericarditis and aseptic meningitis. Other paraclinical features of this phase are identification of a frequently normal number of leukocytes (only one-quarter to one-third of cases develop leukocytosis), an inflammatory syndrome quantified by the C-reactive protein (which correlates with disease activity) and change in platelet count – about a quarter of patients have thrombocy-

topenia, while thrombocytosis may occur in convalescence (4,5,11).

In the absence of appropriate antibiotic therapy, certain categories of people are at risk for chronic Q fever, regardless of the presence or lack of symptoms during the acute phase. Thus, immunocompromised hosts, pregnant women, those diagnosed with valvulopathies or vascular aneurysms, carriers of valvular, vascular or joint prostheses may develop chronic Q fever, most commonly manifested as endocarditis, vascular or joint infection of the previously affected areas. In these situations, the usual absence of fever is particular. Regarding the IE, the vegetations developed reflect the intracellular multiplication of the microorganism, having small size and a nodular aspect, being difficult to visualize with transthoracic echocardiography; in addition, the hemocultures are negative. In up to a third of cases, arterial embolism may occur. Furthermore, hepatosplenomegaly frequently accompanies the clinical picture and sometimes a purple rash may occur. Biologically, the chronic phase is characterized by inflammatory syndrome, hypergammaglobulinemia and intra-infectious anemia (4,5).

Usually, the diagnosis of the two forms of disease is established by correlating the clinical suspicion with the specific serological response, quantified by immunofluorescence. There are two groups of antibodies – phase I, associated with chronic infection, respectively phase II, corresponding to acute infection. Both groups contain IgM and IgG antibodies. However, molecular tests – PCR, isolation of *C. burnetii* from cell cultures or high performance imaging – CT, MRI, 18F-FDG-PET/CT can also be performed (4,5). It is classically considered that seroconversion in acute Q fever occurs 7-15 days after the onset of symptoms, 90% of patients developing antibodies by the third week, which increase until a serum peak during weeks 4 to 8, decreasing gradually over a year (11). However, a recent serological study highlights the marked interindividual variability of the immune response. Phase II IgG is usually the first synthesized antibody, but any of the four can be detected as early as the disease emerges or on the contrary, even after 150 days since symptoms onset (6). As a result, the current indication for initiation of antibiotic therapy is given by clinical suspicion, as serology may be negative in the first few days of the disease. In addition, it appears that the prompt administration of antibiotic medication does not prevent seroconversion and does not affect the elevation of antibody titers, which allows retroactive diagnosis (7).

Moreover, Q fever is the subject of some contradictory scientific opinions regarding the serological diagnostic criteria, relative to the immunoglobulin titers from which the disease can be asserted. This paper was guided by the latest CDC case definition (2009) of *C. burnetii* infection (8). As a result, regarding the acute phase of the disease, the laboratory criteria can either confirm the diagnosis or just support it. In the first situation, the 4-fold increase of the phase II IgG titer by IFA on serum samples collected 3-6 weeks apart, in convalescence (ideally, the first sample is collected during the first week from onset and the samples are analyzed simultaneously using the same kit), identification of bacterial genetic material by PCR, isolation of the pathogen from cell cultures or use of immunohistochemical detection techniques confirms a case of acute Q fever, in the context of a suggestive clinical picture or an epidemiological connection between the person concerned and another lab-confirmed case. On the other hand, a single phase II IgG determination in a titer of at least 1:128 by IFA supports the diagnosis, defining the probable case of acute Q fever, in the presence of the described symptomatology. This situation is mostly encountered, partly due to patients' lack of asking for medical attendance from the first days of symptoms, but also due to the small initial clinical suspicion, which leads to missing the ideal time for collecting the first serum sample, in order to test paired sera. Also, other methods of detecting antibodies which support the diagnosis of acute infection are ELISA and latex agglutination. An important mention is the CDC's recommendation of not using phase II IgM antibodies for acute phase diagnosis, given their long persistence and higher risk of cross-reactivity with immunoglobulins specific to other microorganisms, such as *Legionella spp*. and *Bartonella spp.* (7,8).

The diagnosis of the chronic disease stage is debated even more. According to the 2009 CDC case definition, chronic Q fever is confirmed in the presence of whether blood culture negative-endocarditis, suspicion of infection of an aneurysm or vascular prosthesis, respectively of an osteoarthritis or

osteomyelitis, if the phase I IgG titer is at least 1:800 through IFA (in fact, also a major criterion according to the Duke modified criteria set) or if the pathogen is identified by PCR, IHC or cell cultures. Classically, it is considered that although the phase II IgG titer remains high at this point, phase I antibodies exceed. A recent study considers such condition as an oversimplification, given the high variability of serological response among individuals[2]. A probable case of chronic infection involves a titer of at least 1:128 of phase I IgG, but less than 1:800, with CDC being the only set of criteria that assigns titres below 1: 800 to a potential case. Alternative proposals belong to experts in the field – Raoult et al. (2012), respectively „Dutch consensus" but discussing them is not an objective of this paper (4,8).

Regarding the treatment of *C. burnetii* infection, during acute phase Doxycycline is most effective at an oral dose of 100 mg x 2/day for two weeks; macrolides, fluoroqinolones and cotrimoxazole are kept as alternatives. Important to note is that in patients with valvular lesions or prostheses, prophylaxis of chronic impairment is required with double therapy – Doxycycline (in the same dose) and Hydroxychloroquine 200 mg x 3 / day for 1 year. Moreover, some authors suggest performing a transesophageal echocardiography in all cases of acute Q fever, in order to discover valvulopathies predisposing to IE and apply the prophylactic treatment. The effect of Hydroxychloroquine is not antibacterial, but that of alkalinizing the acid pH of the phagolysosome within which *C. burnetii* multiplies, thus potentiating the antibiotic's mechanism of action. During chronic phase the same double therapy is performed, but continued for a minimum of 18 months in native valve IE, vascular or osteoarticular infection and for up to 2 years in IE developed on valvular prosthesis (4,5,11).

PAPER OBJECTIVES

This paper proposes a comparative analysis between individuals and related to the literature data of the epidemiological, clinical and laboratory contexts that led to diagnosis of acute or chronic Q fever, the treatment regimens applied, as well as the subsequent clinical evolution in a group of patients admitted into the "Dr. Victor Babes" Clinical Hospital for Infectious and Tropical Diseases in Bucharest during the year 2018.

MATERIALS AND METHODS

The type of study performed is a descriptive observational one. The study group comprises 24 patients of both sexes, aged between 34 and 80 years old, hospitalized during January-December 2018 within the infectious diseases compartments of our hospital. The case selection was based on a set of criteria, as follows:

a. Inclusion criteria:
- hospitalization during 2018;
- Q fever diagnosis established during 2018;
- diagnosis of a confirmed or probable case of acute or chronic Q fever established according to the CDC case definition (2009).

b. Exclusion criteria:
- one-day admission, having an established diagnosis before 2018 (patients that came for control);
- diagnosis that does not meet the CDC case definition – whether cases with compatible serologies, but clinically suggestive for another more likely diagnosis – possible cross-reactivities, or clinically suggestive cases for Q fever, but inadequate serology titers in order to support the diagnosis.

RESULTS AND DISCUSSIONS

Compared to other European countries, according to a recent ECDC report for 2016, Romania is part of a group situated on the second position as average number of confirmed cases (50), being outpaced by countries such as France, Spain and Germany (9). In 2017, ECDC centralized 48 cases from our country, increasing compared to previous years (10). The batch of 24 patients in this study thus agrees with the data presented, given that the cases identified in other profile clinics within the country during 2018 are not included.

Returning to this paper, regarding the **epidemiological context**, Figure 1 shows that most of the subjects were men (22 cases, respectively 91.6%), which does not necessarily correlate with a tropism of *C. burnetii* for male patients, but rather with an increased prevalence of asymptomatic infection

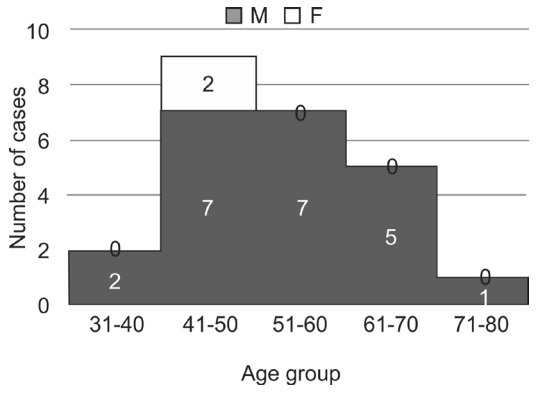


FIGURE 1. *Distribution of cases according to age category and sex*

among women, as it has been explained in the first part of the paper. Age segment between 41 to 50 years old was mostly affected (9 cases), closely followed by the 51 to 60 years old one (7 cases); no cases were registered among children (Figure 1), who are frequently asymptomatic, as presented earlier. Furthermore, 58% of individuals were residents of an urban area, which is a slightly surprising finding, given the lack of regular contact with animals that constitute the main reservoir of the pathogen. On the other hand, though, it shouldn't be forgotten that the disease cand also be transmitted by pets or by oral means through consumption of dairy products from local producers; the ubiquitous character of *C. burnetii*, which can be carried away over long distances through air currents has an impact on the large coverage of this illness, as well.

The possible source of infection was documented in only 7 patients, as follows: possession of goats, sheep, cattle in one case, possession of pets in another one, presence of other domestic animals within the household (4 situations) and last but not least, a case of cheese consumption; the product had been bought from a shepherd in a rural area 2 weeks prior to symptoms onset. Instead, no case of occupational exposure was documented.

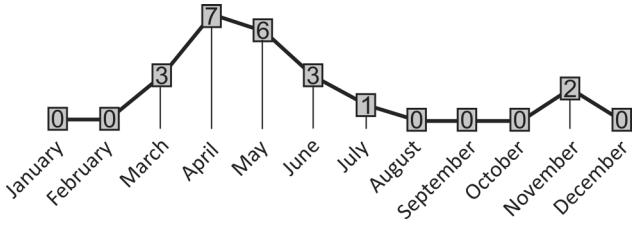


FIGURE 2. *Seasonal distribution of the 22 acute Q fever cases*

By analysing the seasonal distribution of the acute Q fever cases, it was observed that most of them (20 individuals) had occured during spring and early summer – from March until June (Figure 2); this finding is consistent with ECDC graphic data for the 2013-2017 period, which reveal a certain pattern with peaks in cases count along April and May (10).

Regarding the causes of immunosuppression that were identified within the group (in 11 patients), they consisted mainly in alcoholism and diabetes. The aspect of immunodepression matters in Q fever, as in most infectious diseases, both due to the increased risk of acquiring the infection and its more symptomatic character, but especially because of the higher chronicization potential.

Moving to the **clinical context**, the batch was divided into two groups according to disease stage, having 22 individuals with acute Q fever and only two with chronic form (both with blood culture-negative endocarditis). Regarding the first category, the disease was serologically confirmed in only two cases, whereas the other 20 were probable ones. This finding is not at all surprising given the discussion around the CDC case definition carried earlier, but may also be due to a study limitation, such as dosing phase II IgG antibodies from the second serum elsewhere, at a private laboratory, which implies that data were not available for collecting considering the retrospective nature of this study. Only one case of IE was confirmed in the laboratory.

Regarding the clinical forms of acute infection that were identified, as shown below (Figure 3), the concomitance of pneumonia and hepatitis predominated (9 cases, representing 41%), followed by penumonia and hepatitis alone (considered from a transaminase level increase of at least 2 times above the upper normal value), representing 18% each; another 18 percent corresponded to the self-limited febrile illness cases. Last but not least, a less common clinical manifestation was also found in a male patient - acute pericarditis.

The clinical manifestations associated with the acute condition were mostly general (fever, chills, myalgia, nausea); 7 patients experienced headache, but lacked the retroorbital character or photophobia often described. In addition, of the 14 subjects who developed interstitial pneumonia (increased reticu-

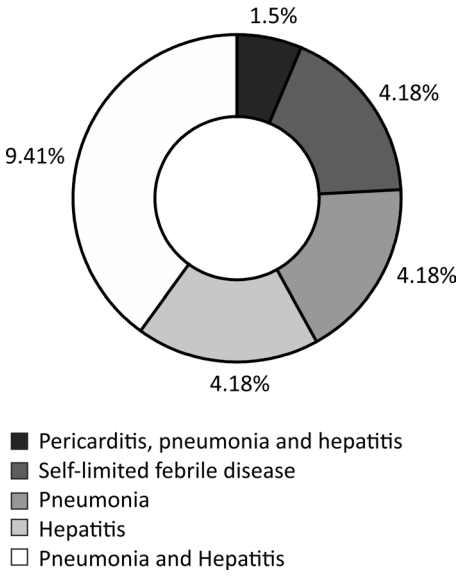


FIGURE 3. *Acute Q fever clinical forms idientified within the group*

lar markings were the only radiological changes encountered), only 4 experienced dry cough (28%); among the 14 cases of hepatitis, only 3 were accompanied by scleral icterus (21%), results that confirm the data found in literature. Also, 78% of hepatitis involved clinically or ultrasound-detected hepatosplenomegaly.

By bringing the **laboratory findings** into discussion, leukocytosis was noticed in less than half of the acute Q fever cases, which indicates its weaker correlation with this particular bacterial infection. 86% of patients developed at least minimal hepatocytolysis (defined as any level elevation of alanine aminotransferase above the upper normal limit); thrombocytopenia was identified in 31% of cases. All these data are similar to those cited in the first part of the paper (Figure 4). Despite the frequently normal leukocyte count, however, the clinician is guided towards a bacterial etiology by the high C-reactive protein level. All individuals experiencing acute Q fever included in the group had an increase of CRP starting from a moderate 5 mg/dl up to a maximum of 40 mg/dl, as it can be seen in Figure 5. On the other hand, another useful inflammatory marker – procalcitonin, reached a significantly increased level (>2 ng/ml) in 7 of the 10 situations in which it was used, without another objectified concomitant bacterial infection; this result is in contradiction with informations provided by the studies published so far. Moreover, regarding the case of oral infection by cheese consumption, manifested through pneumonia and hepatitis, procalcitonin rose to a value of almost 22 ng/ml, an indirect sign of sepsis. However, the patient's further clinical evolution was favorable.

Further on, we will explain how the specific antibodies' dynamic led to diagnosis formulation in the two cases of confirmed acute Q fever (Figures 6 and 7 down below). Thus, in both situations, an increase in phase II IgG titer of more than 4 times between the paired sera determinations was noticed. In the second case, although the initial sample had been collected relatively late (20 days after the first symptoms), containing a significantly elevated antibody titer at that time (phase II IgG = 1:1,024), serological confirmation was yet obtained by subsequently reaching an impressive value – 1:132,000, which meets the requirements of the

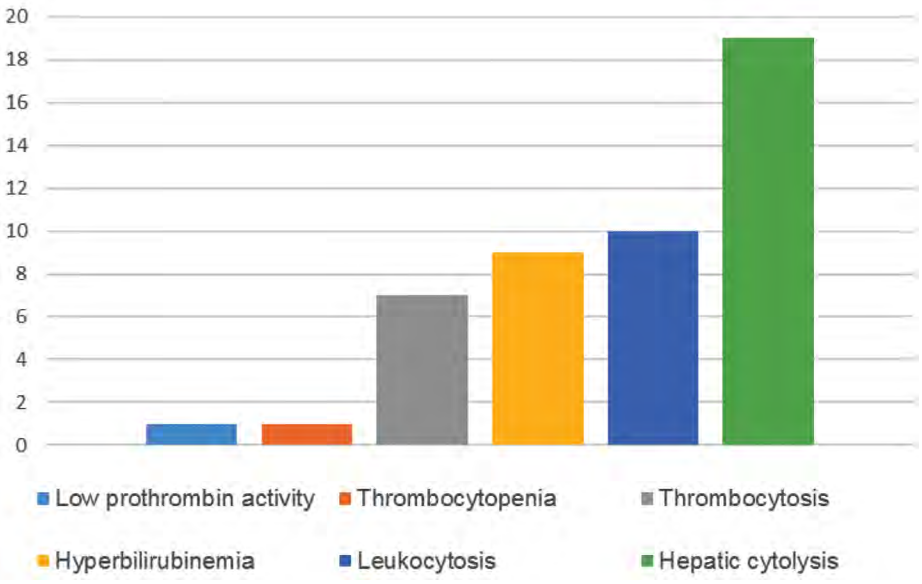


FIGURE 4. *Paraclinic modifications within the acute Q fever group*

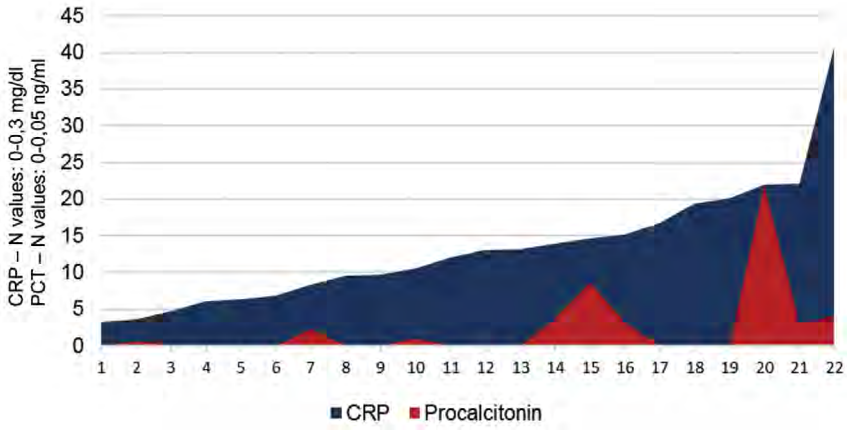
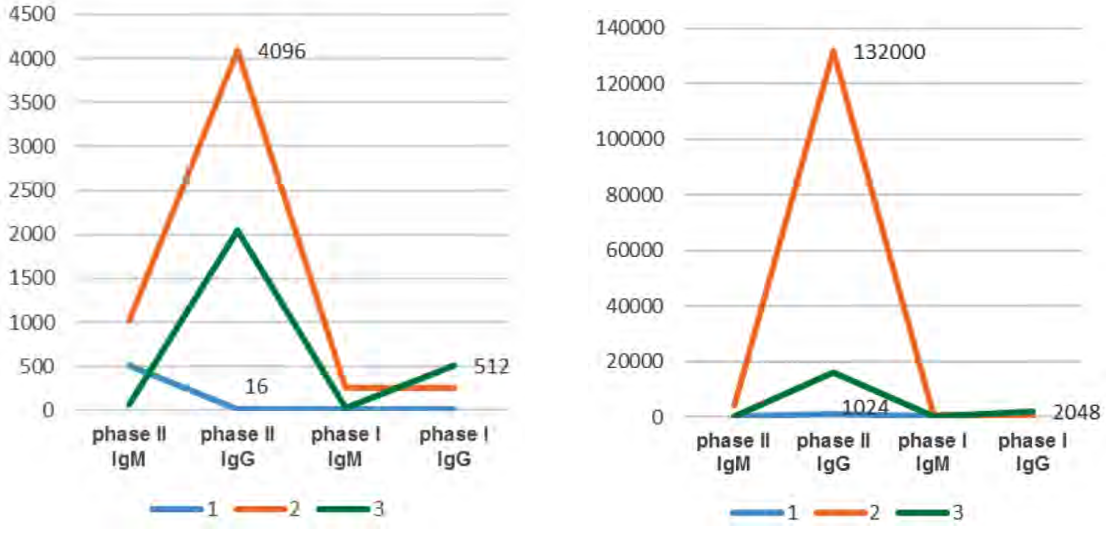


FIGURE 5. *Inflammatory changes within the acute Q fever group*

case definition. Still here, a particular attention must be directed towards the important increase in the phase I IgG titer by the third serological determination; this finding justifies careful follow-up of the patient, especially due to an underlying aortic valvulopathy, which implies a high risk of chronicization. Dynamical serological determinations were also performed in 3 other cases, but the delay of the first serum sample drawing (at 10, 15 and 18 days, respectively, after onset of symptoms) led to missing the moment of titer peak and therefore to the incapacity of objectifying its growth with time. Compared with the second confirmed case mentioned above, one can conclude that duration between the onset of disease and seroconversion, as well as between the onset and moment of phase II IgG serum peak, respectively, are subject of great individual variation. Another 17 probable cases of acute infection were detected as a result of a single antibody determination, developing titers starting from the lowest value accepted as diagnostic (1:128) to a maximum level of 1:16,000.

An interesting observation was that in 4 cases of acute Q fever, IgM antibodies against Epstein-Barr virus, as well as specific to Chlamydia and Mycoplasma intracellular bacteria were identified. These serologies had been required in the context of a relatively nonspecific clinical picture. Although this could theoretically reveal concomitant infections, the cross-reactivity hypothesis is more likely, as cited in literature (1). As a result, the clinician must be aware of this possibility and judge the case accordingly. Although the impact on the initial therapy is not significant in the case of a misdiagnosis, Q fever may become chronic within certain risk categories, carrying a potentially increased pathogenic impact over time in the absence of disease recognition, close follow-up and drug prophylaxis.



FIGURES 6 and 7. *The specific antibody dynamics noticed in the two acute Q fever confirmed cases*

Moving to the **therapeutic context**, all patients with acute form benefited from the standard recommendation, namely Doxycycline at a dose of 100 mg x 2/day; nevertheless, it was prescribed alone in only 4 cases (18%), being more frequently introduced in therapeutic combinations. The decision of administering other antibiotics can be explained by the low degree of suspicion for *C. burnetii* infection at the time of admission and assumption of other etiologies as being more likely; Doxycycline was therefore often added later, as a new approach to an unfavorable clinical evolution. In addition, serology results are available only afterwards, supporting the diagnosis retroactively, frequently following the discharge of the patient. However, clinical suspicion placed in a suggestive epidemiological frame dictates the initiation of treatment with Doxycycline. The duration of antibiotic course has varied widely between 7 and 39 days, but we remind that, ideally, the acute Q fever phase should receive treatment for two weeks. The clinical evolution was unanimously favorable.

Reaching to the two chronic Q fever cases, manifested by blood culture-negative endocarditis, first confirmed by a phase I IgG titer greater than 1:16,000, second having a serological result that could only support the diagnosis (1:512), we reiterate the risk of chronicization brought by the presence of cardiac valvulopathies and the possibility that this stage occurs in the absence of acute Q fever documentation, which can pass unnoticed. Herein, both male patients had aortic valvulopathies and held no history of acute disease. As a result, prophylaxis with Doxycycline and Hydroxychloroquine had not been undergone. An important mention is that the patient diagnosed with probable IE had experienced left basal pneumonia and hepatocytolysis not accompanied by leukocytosis two months prior to admission in our hospital, which might have been his acute episode, but not interpreted and treated as such.

The native aortic valve vegetations' characteristics were described both by transthoracic and transesophageal echocardiography, both lesions associating perianular abscesses. The first man, afebrile (as often cited in chronic Q fever), developed a complication of IE, namely acute heart failure and thus received an indication of valvular prosthesis. Following his transfer into the cardiac surgery department he was lost from track; serological results subsequently occurred and confirmed the diagnosis. As a result, during the short stay in our clinic he received exclusively empirical biterapy for IE (7 days of Ceftriaxone and Vancomycin). The second patient, after a short 4-day empirical treatment, also received Doxycillin for another 11 days, with recommendation of continuing this treatment alone until the serology result emerged. However, he has also been lost from our records, therefore quantifying long-term results became impossible.

CONCLUSIONS

1. Q fever is an increasingly common disease reported both in Europe and in our country, with a potentially negative impact in the event of chronicization;
2. Q fever involves men more often and a careful anamnesis is necessary in order to identify a possible epidemiological context;
3. The acute stage of the disease has a seasonal character, being encountered mainly from March until July;
4. In our clinic, the most common clinical forms of acute disease were interstitial pneumonia and hepatitis, alone or concomitantly, with the predominance of general symptoms to the detriment of local ones; as a result, the clinical diagnosis of acute Q fever is often difficult, given the mainly non-specific manifestations;
5. Acute paraclinical changes usually involve a normal number of leukocytes, minimal to moderate hepatocytolysis syndrome, moderate to severe inflammatory syndrome and, on occasion, thrombocytopenia, features that may further guide the health professional;
6. In both acute and chronic phases diagnosis is predominantly serological, but should be carefully assesed, given the possibility of cross-reactivities;
7. The antibiotic of choice is short term Doxycycline for the acute disease and long term Doxycycline – Hydroxychloroquine double therapy in the case of chronic Q fever, respectively;
8. One-year long prophylaxis using the aforementioned double treatment is important in patients with heart valvular impairment who experience acute Q fever;

9. Clinical course following the acute phase is usually favorable, but frequently implies cardiovascular morbidity in persons with risk factors for the development of chronic form.

Conflict of interest: none declared
Financial support: none declared

REFERENCES

1. Chung-Hsu L et al. High seroprevalence of Mycoplasma pneumoniae IgM in acute Q fever by Enzyme-Linked Immunosorbent Assay. *PLoS,* 8(10): e77640, 2013;
2. Miller H et al. Trends in Q fever serologic testing by immunofluorescence from four large reference laboratories in the United States, 2012–2016. *Scientific Reports,* 8(1): 16670, 2018;
3. Million M, Raoult D. Q fever. In: Hunter's Tropical Medicine and Emerging Infectious Disease, 9th edition. Editors: Magill AJ, Solomon T, Hill DR, Ryan ET. Ed. Saunders, Elsevier, 2012. p. 558;
4. Raoult D, Marrie TJ. *Coxiella burnetii* (Q fever). In: Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases 8th edition. Editors: Bennett JE, Dolin R, Blaser M. Ed. Saunders, Elsevier, Philadelphia, 2015; pp. 2208-2216;
5. Walker DH, Dumler S, Marrie TJ. Rickettsial diseases. In: Harrison's Infectious Diseases, 3rd edition. Editors: Kasper D, Fauci A. Ed. McGraw Hill, USA, 2017; pp. 696-698;
6. Wielders CCH et al. Kinetics of antibody response to *Coxiella burnetii* infection (Q fever): Estimation of the seroresponse onset from antibody levels. *Epidemics,* 13: 37-43, 2015;
7. www.cdc.gov – Morbidity and Mortality Weekly Report - Diagnosis and Management of Q Fever — United States, 2013: Recommendations from CDC and the Q Fever Working Group;
8. www.cdc.gov – Q fever – Case definition;
9. www.ecdc.europa.eu – Surveillance Report – Annual Epidemiological Report for 2016, Q fever – Stockholm, January 2019;
10. www.efsa.europa.eu - The European Union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2017 – November 2018;
11. www.uptodate.ro – Didier R., Clinical manifestations and diagnosis of Q fever.