Ref: Ro J Infect Dis. 2023;26(1)
DOI: 10.37897/RJID.2023.1.5

An unexpected case of *Coxiella burnetii* endocarditis

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ABSTRACT

Introduction. *Coxiella burnetii* is the causative agent of Q fever, a zoonosis that is usually associated with cattle, sheep, goats and their bodily fluids, mainly milk or amniotic fluid. The disease manifests most commonly as an upper respiratory tract infection or pneumonia, but, in less common cases can lead to endocarditis, hepatitis, meningo-encephalitis and osteomyelitis. In the acute stage, patients usually have a self-limited febrile illness, which can progress to the chronic form of Q fever, most commonly with endocarditis.
Endocarditis is the main manifestation of chronic Q fever and it usually affects patients with risk factors, such as prosthetic valves, abnormal native valves or other cardiac disease history, but it can also be seen in patients with no prior medical history, like the one we describe. The diagnosis is confirmed using the same Duke Criteria used in infectious endocarditis, with one major criterion being either a positive blood culture or PCR for C. burnetii, or a positive IgG phase I serological test [>1:6400). The preferred treatment regimen is doxycycline plus hydroxychloroquine, maintained for a minimum of 18 months, along with regular follow-ups for serology testing and side-effects evaluation.

Case presentation. We describe the case of a 53-year old male with no medical history who presented in our clinic for a 2-week evolution of fever, chills and weight loss. The physical examination revealed no pathological findings. The trans-esophageal cardiac echography showed small vegetations on the mitral valve and the serological test for *Coxiella burnetii* was positive, thus allowing us to confirm the diagnosis of *Coxiella burnetii* endocarditis and start treatment with Doxycycline and Hydroxychloroquine.

Conclusions. *Coxiella burnetii* must be taken into account as a possible diagnosis for culture-negative endocarditis, even in patients with no cardiological medical history and no environmental risk factors.

Keywords: endocarditis, *Coxiella burnetii,* Q fever, Duke criteria

INTRODUCTION

Coxiella burnetii is a Gram-negative, obligate intracellular coccobacillus, morphologically similar to Rickettsia, resistant to environmental factors and certain disinfectants. Human infection occurs usually by inhalation of bacteria from the air, via infectious animal excretions. It is most commonly associated with cattle, sheep, goats, but can also be linked to birds, cats, dogs, horses or wild animals [1]. Other than being a zoonosis, *C. burnetii* has also been isolated from human milk and placenta, thus proving the possibility of vertical and horizontal transmission between humans [2]. There have also been cases of transmission by blood transfusions [3] or fetal delivery from Coxiella-infected women [4]. That aside, Q fever is regarded as an occupational disease as is usually affects people in direct contact with animals or animal secretions, such as farmers, veterinarians or workers in abattoirs. Another risk fac-

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Article History:
Received: 20 March 2023
Accepted: 28 March 2023

tor in the general population is the drinking of unpasteurized milk coming from infected livestock. The infectious dose for *C. burnetii* is very low, only 1-10 bacteria being able to infect 50% of experimental subjects, thus making it one of the most infectious known organisms [5].

Following infection with *Coxiella burnetii,* about half of patients remain asymptomatic, while the other 50% develop symptomatic acute Q fever, manifesting as a nonspecific febrile illness that can occur in conjunction with pneumonia or hepatitis. The most frequent symptoms described are fever, fatigue, chills, headache, sweats and myalgia [6]. The most common laboratory findings are increased liver enzyme levels. Other pathologic findings might include leukocytosis, mild thrombocytopenia or hyperbilirubinemia. The radiological findings on the chest X-ray are consistent with pneumonia, the most common being segmental or lobar consolidation, either one sided or bilateral, being unable to differentiate Q fever pneumonia from other causes of community-acquired pneumonia [7].

TABLE 1. Percentage of acute Q fever patients with selected clinical and laboratory findings

Clinical or laboratory finding	% Of patients		% Of patients
Clinical		**Laboratory**	
Fever	88–100	Normal leukocyte count	90
Fatigue	97–100	Thrombocytopenia	25
Chills	68–88	Increased transaminases	45-85
Headache	68–98	Increased bilirubin	9-14.3
Myalgia	47–69	Increased alkaline phosphatase	27.7-57
Sweats	31–98	Increased γ-glutamyl transferase	25-75
Cough	24–90	Increased creatine phosphokinase	29
Nausea	22–49	Increased lactate-dehydrogenase	33.3-40
Vomiting	13–42	Increased creatinine	29-40
Chest pain	10–45	Elevated erythrocyte sedimentation rate	43-87.5
Diarrhea	5–22	Smooth muscle antibodies	65
Skin rash	5–21	Antiphospholipase antibodies	50
Myocarditis	0.5–1		
Pericarditis	1		
Meningo-encephalitis	1		
Death	1–2		

Source: Modified from Maurin M, Raoult D. Q fever. *Clin Microbiol Rev.* 1999;12:518

Chronic Q fever occurs in <5% of persons with acute infection and may occur months, years and even decades after the initial infection [6]. Endocarditis is the most common form of chronic Q fever, comprising 60-78% of all cases [7]. The other possible chronic manifestations are osteomyelitis or vascular infections. The patients that have the highest risk for chronic Q fever and particularly endocarditis are men older than 50, with predisposing heart conditions- native valve defects, artificial valves, with immunosuppressive conditions that show a rapid rise in phase I IgG antibodies after the acute infection.

CASE REPORT

A 53-year-old male with no previous medical history, no direct contact with animals, working as a scenographer in a theater, smoker, is referred to our clinic on the 8th of September for fatigue, weight loss, fever and chills going on for 3 weeks. For these symptoms his GP prescribed him Levofloxacin 750 mg q24h for 7 days, Paracetamol and Ibuprofen, that alleviated the symptoms during the previous week before addressing our clinic (01st-07th September 2022). During this timeframe, the patient was admitted to a Cardiology ward, where a TEE (transesophageal echocardiography) was ordered, revealing small, 2-3 mm vegetations, with preserved motility, attached to the mitral valve cusps, showing no signs of mitral failure. At the time of admittance to our clinic, the patient had only mild symptoms-sub-fever- 37,7°C, chills, fatigue and a 5 kg weight loss during the past 2 weeks. The clinical examination was normal, including cardiac auscultation, which revealed no pathological heart murmurs and no signs of cardiac failure. The laboratory tests also had normal values, with 6000 leukocytes/μL, 337000 thrombocytes/μL, a negative inflammatory syndrome (Fibrinogen 323 mg/dL, CRP 0.22 mg/dL). Creatinine, liver function tests, ionogram and coagulation panel were also normal. The chest X-ray revealed a small interstitial infiltrate in the middle right lobe.

At this moment, taking into account the previous echocardiography examination, the Duke score was calculated to assess the risk of endocarditis, and the patient met one major criteria (echocardiography), and one minor criteria (fever), thus eliciting a possible diagnosis of endocarditis. A wide-spectrum antibiotic treatment was started, with Ceftriaxone 2g q24h iv and Vancomycin 1g q12h iv while also investigating for more signs that would allow us to have a definite diagnosis.

We started by drawing 5 blood cultures, on fastidious antimicrobial neutralizing media (both aerobic and anaerobic) during the next 3 days, all of them showing no bacterial growth. An ophthalmology exam was asked, to search for potential conjunctival hemorrhages and Roth spots but the exam showed none. A cerebral-thorax-abdomen CT scan was ordered next, to determine possible arterial emboli, septic infarcts or intracranial hemorrhages, but none could be determined. The pathological findings noticed on the CT scan were small subpleural hyperdense nodules in both lungs and mild hepatomegaly. The urine dipstick was also normal, with no hematuria or proteinuria, and thus no glomerulonephritis. Osler nodes and Janeway lesions were also absent on the clinical exam and so our initial endocarditis diagnosis was put to question. At this point, a blood sample for *Coxiella burnetii* serology was also drawn and sent to an external laboratory for testing, with the results pending for 7 days.

Taking into account the findings of the chest X-ray and the thorax CT scan, a differential diagnosis of interstitial pneumonia was also considered. Meanwhile, the patient developed an allergic reaction to Ceftriaxone and therefore it was switched to Meropenem 1g iv q8h, along with Vancomycin 1g iv q12h.

The patient had only mild symptoms for the following days, mostly fatigue, dry cough and headache that were treated with Paracetamol 500 mg q12h po. He also received treatment with Apixaban 5 mg q12h po to decrease the thrombotic risk.

On the 21st of September, the *Coxiella burnetii* serology results became available, showing a marked positive result for both phase II IgG (>1:32768) and phase I IgG (>1:8192). At this point, the diagnosis of *Coxiella burnetii* infectious endocarditis was confirmed, with 2 major and 1 minor Duke criteria.

The antibiotic treatment with Meropenem and Vancomycin was switched to Doxycycline 100 mg q12h po and Hydroxychloroquine 200 mg q8h po and a new laboratory evaluation was ordered. Once again, the lab values were within normal parameters, except a mild eosinophilia (600/ µL) and an ALT 72 IU/L [upper normal limit 63 IU/L). The next day, the patient was discharged with the recommendation of continuing the treatment for at least 18 months, with regular follow-ups at 1, 3, 6, 12, 18 months to check for treatment side-effects and for the serologic response.

The patient was able to return for the first follow-up visit after 2 months, when a marked decrease in both phase I and phase II *Coxiella burnetii* IgG was observed.

TABLE 2. Duke Criteria for C. Burnetii endocarditis

A. Definite Positive culture, PCR, or immunochemistry for *Coxiella burnetii* of a cardiac valve
B. Major Criteria ***Microbiology*** Positive culture or PCR of blood or an embolus for *C. burnetii* or serology with IgG phase I antibodies ≥1 : 6400 Evidence of Endocardial Involvement Echocardiogram positive for IE: oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of alternative anatomic explanation; or abscess; or new partial dehiscence of prosthetic valve; or new valvular regurgitation [worsening or changing of preexisting murmur not sufficient) PET scan showing a specific valve fixation and mycotic aneurysm
C. Minor Criteria Predisposing heart condition [known or found on echography) Fever, temperature >38°C Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm [see at PET scan), intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, or rheumatoid factor Serologic evidence: IgG phase I antibodies ≥1:800 <1:6400
Diagnosis Definite 1 A criterion 2 B criteria 1 B and 3 C criteria [including microbiologic evidence and cardiac predisposition) **Diagnosis Possible** 1 B criterion, 2 C criteria [including 1 microbiologic evidence and cardiac predisposition) 3 C criteria (including positive serology and cardiac predisposition)

IE – Infective endocarditis; IgG – immunoglobulin G; PCR – polymerase chain reaction; PET – positron emission tomography.

Modified from Raoult D. Chronic Q fever: expert opinion versus literature analysis and consensus. *J Infect.* 2012;65:102–108.

TABLE 3. Serological response

	14th September 2022	21th November 2022
IgG phase II	1:32768	1:512
IgG phase I	1:8192	1:64
IgM phase II	1:12288	1:16
IgM phase I	1:384	1:128

DISCUSSIONS

Coxiella burnetii infection is still considered an occupational disease, as the main reservoir is represented by cattle, sheep, goats or other animals. Nevertheless, a link between physical contact with animals and Q fever is rarely made. Infectious secretions, such as milk, manure, or placenta (after parturition) contaminate the environment and viable bacteria can be found in the soil for up to 5 months [8]. Most commonly, human transmission takes place via inhalation of infective aerosols that originate directly from birth fluids of infected ani-

mals [7]. An outbreak of Q fever in Switzerland affected more than 350 people living along a road sometimes crossed by sheep, showing that their secretions may infect large numbers of people even in the absence of direct physical contact [9]. Previous studies have thus shown that infective animal secretions can travel as far as 15 km and still carry infective potential and be a potential threat to passers-by. In a previous outbreak, (United Kingdom, Birmingham, 1989) Q fever was diagnosed in 147 patients that lived 18 km away from the farm that housed the infected animals. Still, there was no evidence of direct contact with animals or animal products in any of the patients [10]. Taking this into account, a diagnosis of acute Q fever should also be considered in patients with influenza-like syndrome that do not recall recent direct contact with animals, such as the patient we presented.

EPIDEMIOLOGY

The male to female ratio for Q fever cases in Europe was 2.4:1 according to the national ECDC surveillance for 2015-2018, with most cases diagnosed between April and September. The countries with the highest rates of infection were Spain (0.7 cases/ 100.000), Romania (0.6 cases/100,000) and Hungary (0.5 cases/100,000) [11]. In 2021, the number of cases reported was the lowest recorded in the past 5 years, probably because of diagnostic failures due to the COVID-19 pandemic (460 total cases in 2021, 523 in 2020, 951 in 2019). Also, a statistic regarding infected animals was released, showing that up to 24.6% of tested goats, 12.2%, of tested cattle and 10% of tested sheep had a positive *Coxiella burnetii* serology [11].

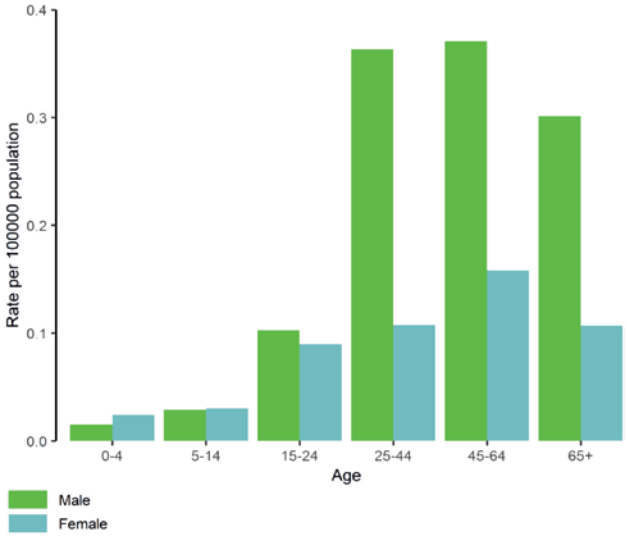

FIGURE 1. Distribution of confirmed Q fever rate per 100,000 population, by age and gender, EU/EEA, 2019 Source: The European Union One Health 2021 Zoonoses Report, 11 November 2022

Coxiella burnetii endocarditis is the most common seen manifestation of chronic Q fever and it usually affects abnormal cardiac valves or prosthetic valves [12]. Risk factors that suggest a higher chance of developing chronic Q fever include male sex, rapid rise in phase I IgG, age older than 50 and positive antiphospholipid antibodies. Rising serology titers (>1:1024) following treatment with doxycycline should warrant further investigation for persistent infection - endocarditis, vascular infection, osteomyelitis. Trans-thoracic echocardiography should be performed as soon as possible to detect possible valvular vegetations, but they can be absent in up to half of the cases [13].

The diagnostic can be confirmed using the Duke criteria, with the major criteria being either signs of endocardial involvement using echocardiography or PET scan or a positive *Coxiella burnetii* blood culture/ PCR/ >1:6400 serology for phase I IgG. It has been noted that higher antibody titers are more commonly associated with a positive endocarditis diagnosis, as it can also be seen in the Duke criteria. A lower antibody titer (higher than 1:800 but lower than 1:6400) is considered a minor criterion, being associated with a positive diagnosis in just 37% of cases, as opposed to the 75% positive predictive value when the titer is >1:3200 [14].

Treatment consists of doxycycline 100 mg q12h and hydroxychloroquine 200 mg q8h for 18 months (native valves) or up to 24 months (prosthetic valves) [15]. Different attempts were made to find alternative treatment schemes, and the outcome of tetracyclines plus hydroxychloroquine was similar to that of tetracyclines plus quinolones [13]. Surgery may also be necessary in the case of infected cardiac prostheses. Follow-up is also recommended because of the risk of side-effects. Hydroxychloroquine may cause retinal toxicity, so an ophthalmic exam should be done every 6 months to prevent damage. Serologic monitoring should also be recommended every 3-6 months to determine the decrease of phase I IgG, which is correlated with a proper therapeutic response. Other markers of successful therapy include the decrease of inflammatory markers, particularly ESR, the correction of anemia or the resolution of hyperglobulinemia [13].

CONCLUSION

Even though Q fever is an occupational disease and is most often diagnosed in people that had physical contact with goats, sheep or cattle, it should also be considered in patients that do not meet the above criteria. As noted before, infectious particles originating from animal dejections can travel for several kilometers and still carry infectious potential, so direct contact is often not needed. Mainly, the ques-

tion patients should be asked is not only if they had physical contact with animals or raw milk but also If they live close to farms, pastures or other areas crossed by animals.

Other than that, if acute Q fever is diagnosed, the progression to endocarditis must always be taken into account, even if the patient has no prior cardiac risk, such as the patient we presented above. For this, phase I IgG should be checked regularly to see if the acute-phase treatment with Doxycycline is effective.

Once Q fever has been diagnosed (either in its acute or chronic form), regular follow-up visits must be scheduled in order to check for the serologic response, as it has been shown that the increase in phase I IgG titers is directly linked to complications.

Conflict of interest: none declared
Financial support: none declared

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