A Case of Acute Fever with Thrombocytopenia: Diagnostic and Clinical Review of Acute Q Fever Infections

Morgan C. Scully

Metro Infectious Disease Consultants, Huntsville, AL 35801, USA; morgan.c.scully@gmail.com

Submitted: 22 June 2021, accepted: 14 September 2021, published: 31 December 2021

Abstract: Q (Query) fever is a zoonotic illness caused by the bacterium *Coxiella burnetti*, which is transmitted to humans via host animals, usually cattle, sheep and goats. Acute Q fever often presents as a flu-like illness or atypical pneumonia that is nonspecific and often self-limiting. The identification of acute infection is clinically important due to the high morbidity and mortality associated with chronic infection. We present a case of a 43-year-old female who lived in the vicinity of cattle and goats and presented with an acute febrile illness found to be secondary to acute Q fever infection. Exposure to Q fever in the United States is frequently not associated with a classical occupational exposure and should be considered in those living in areas near to possible host animals. We discuss clinical presentation and clues to diagnosis, as well as relevant epidemiology. This case highlights important considerations for risk stratification for chronic infection and follow-up in acute Q fever patients.

Keywords: Q fever; *Coxiella burnetti*; Culture negative Endocarditis

How to cite: Scully, M.C. A Case of Acute Fever with Thrombocytopenia: Diagnostic and Clinical Review of Acute Q Fever Infections. *Priv. Pract. Infect. Dis.*, 2021, 1(2): 7; doi:10.35995/ppid1020007.

Case Report

A 43-year-old female with a past medical history of migraine headaches presented to the hospital in May of 2021 with approximately 4 to 5 days of fevers, fatigue and chills. She also reported headache, nausea and had one episode of vomiting. She reported that approximately 4 weeks prior to symptoms she removed a tick from her left shin. It did not appear engorged, and she did not report the development of any rash. She reported taking no medication on a regular basis. She resided in a

rural area in North Central Alabama with cattle present in the fields next to her home. She also visited her sisters property frequently, which had cattle, goats and chickens. The patient did not actively care for any of the animals, but occasionally helped feed the chickens. She had been sexually active with one male partner for the last 3 years. She did not report any recent travel history. There was no known family history of autoimmune disease or malignancy.

Initial work-up in the emergency room showed a urinalysis with moderate blood, large protein, negative nitrites, moderate leukocytes with 49 white blood cells and large bacteria. A COVID-19 PCR nasopharyngeal swab was negative. Initial blood work was significant for mild hyponatremia, with a sodium level of 132 mmol per liter, alkaline phosphatase of 160 EnzU per liter, aspartate aminotransferase (AST) of 66 EnzU per liter, alanine aminotransferase (ALT) of 24 EnzU per liter, a white blood cell count of 46,800 per cubic millimeter and platelets of 62,000 per cubic millimeter. Initial computed tomography (CT) imaging of the abdomen and pelvis with intravenous contrast showed no significant abnormality. She was admitted to the hospital with a presumed diagnosis of a urinary tract infection and started on intravenous ceftriaxone. Oral doxycycline was added due to her history of recent tick bite. Serologies for tickborne illnesses, including *Rickettsia rickettsii*, *Ehrlichia chaffeenis*, *Anaplasma phagocytophilum*, *Babesia microti* and *Borrelia burgdorferi*, were also sent, and the results were negative. Her initial blood cultures showed no growth after 5 days. Her urine culture grew at 100,000 colony-forming units per mL of *E. coli,* which were sensitive to ceftriaxone.

After 72 h of intravenous antibiotic therapy with ceftriaxone and oral doxycycline, the patient continued to have high fevers of up to 39.2 °C. Additionally, she had progressive transaminitis with an alanine aminotransferase (ALT) of up to 85 EnzU per liter, aspartate aminotransferase (AST) of 99 EnzU per liter and an alkaline phosphatase of 216 EnzU per liter. Her platelets remained low at 42,000 per cubic millimeter. Given her persistent fever despite the appropriate antibiotic treatment for a urinary tract infection, as well as her transaminitis and thrombocytopenia, her initial diagnosis was reconsidered, and additional work-up was performed. An HIV antibody/antigen test, cytomegalovirus virus serology, Epstein–Barr virus serology, Brucellosis serology, Q fever serology and Leptospirosis serology were sent. A CT of the chest was also obtained with contrast, which showed no significant abnormality. On hospital day 7, the patient felt an overall improvement, and her fevers had resolved. Her platelets slowly improved to 143,000 per cubic millimeter. Her Q fever serology returned positive for IgM phase II antibody at a titer of 1:1024, as well as IgG phase II antibody at a titer of 1:64. All other serologies returned negative. A transthoracic echocardiogram was performed in the hospital, which showed no evidence of endocarditis or valvular abnormalities. A diagnosis of acute Q fever was made, and she was discharged home to complete a 2-week course of doxycycline.

On follow-up, approximately 5 days after discharge, her platelet count was elevated at 522,000 per cubic millimeter. At that time, repeat Q fever antibodies showed a progressive increase in her IgM phase II antibody at 1:2048 and her IgG phase II antibody at 1:1024. She was feeling well, showing no fevers or residual symptoms. A follow-up appointment was scheduled to monitor her Q fever serology.

Discussion

Epidemiology

Q (Query) fever is a zoonotic infection caused by the bacterium *Coxiella burnetti,* a Gram-negative intracellular organism. It is highly infectious to humans, and exposure to a single organism can cause disease [1]. The bacterium is present in many host animals, including cattle, sheep, goats, dogs, ticks and, rarely, cats. There is also serologic evidence of possible infection in pigs, horses and wild animals, but this is not thought to contribute to human disease [2]. In a review of human outbreaks, the most common source of infection was found to be infected sheep or goats [3]. The infection is often asymptomatic in host animals, but it can cause abortions, stillbirths, premature delivery, endometritis, mastitis and infertility [2]. The bacteria are exerted in feces, milk, amniotic fluid and

products of conception, and are often transmitted to humans via inhalation [3]. Although frequently considered an occupational disease in those who work closely with animals, including veterinarians, slaughterhouse works and farmers, direct contact with a birthing animal is not required for infection [4]. In the United States, from 2000 to 2010, approximately 60% of cases were reported without a known livestock contact [4]. *Coxiella burnetti* is a robust organism and able to live in the environment for up to 10 months via sporulation [5]. Therefore, exposure is often from the inhalation of dust particles harboring organisms that are able to travel up to several miles through wind dispersal [3]. There have also been cases reported from US military members while deployed to Iraq and Afghanistan without any other known exposure, which have thought to have been caused by inhalation from contaminated soil particles [1].

Livestock vaccination against *Coxiella burnetii* is a potential tool for infection control. A phase I inactivated whole bacteria vaccine in animals (Coxevac) has been shown to decrease bacterial shedding and the number of abortions among herds and flocks. However, the efficacy is diminished in pregnant animals and those previously infected [2]. A killed whole cell vaccine is available for human use but is only licensed in Australia. It can cause severe reactions in those previously infected with *Coxiella burnetii* and, therefore, screening is requiring prior to administration [2]. It may be beneficial for those at high risk for exposure, including farmers veterinarians and lab researchers.

Clinical Manifestations

Acute Q fever usually manifests as a nonspecific febrile illness with concurrent fatigue, headache, myalgia and, sometimes, pneumonia and hepatitis [4]. Laboratory findings often show elevated liver enzymes in up to 85% of cases and elevated leukocyte counts in up to 25% of cases [4]. One interesting laboratory abnormality in Q fever that may provide a clue to diagnosis, and was also present in our patient, is an initial thrombocytopenia followed by subsequent thrombocytosis [4,5].

Chronic Q fever is thought to develop in <5% of patients with acute infection and most commonly presents as endocarditis [4]. Q fever should be considered in cases of culture-negative endocarditis and is usually diagnosed serologically. Vegetations are often found beneath endothelial surfaces and tend to be smaller overall than other causes of endocarditis [6]. Data regarding the incidence of Q fever among culture-negative endocarditis cases are lacking in the United States [6]. A recent study from a French laboratory found Q fever as an etiology in 37% of 740 culture-negative endocarditis cases [7].

Infections can also occur in aortic aneurysms and vascular grafts, and present as osteomyelitis, granulomatous hepatitis and chronic pulmonary disease [1]. Symptoms include persistent fever, fatigue, malaise and weight loss [4]. Even with treatment, mortality is high in chronic infection, with a 3-year mortality of 25% in vascular infections and 7% in endocarditis [4]. The progression of the disease from acute to chronic infection is not well understood, but risk factors of developing chronic disease include pregnancy, immunosuppression, valvulopathy and vascular abnormalities [4]. Previous studies have estimated that the risk of endocarditis developing after acute Q fever in patients with underlying valvulopathy is approximately 40% [8]. Therefore, it is also recommended that all patients diagnosed with acute Q fever undergo baseline echocardiography to assess the risk of chronic infection and decide on treatment duration, as shown in Figure 1 [4,8]. Recent data also show that 75% of chronic Q fever patients developed disease within 6 months of acute infection [8]. A strategy for follow-up serology testing is, therefore, recommended in all acute Q fever patients. The Centers for Disease Control (CDC) recommendations include repeat testing at 6 months to evaluate for chronic disease in low-risk patients and at 3, 6, 12, 18 and 24 months for patients with underlying valvular or vascular abnormalities, as shown in Figure 1 [4].

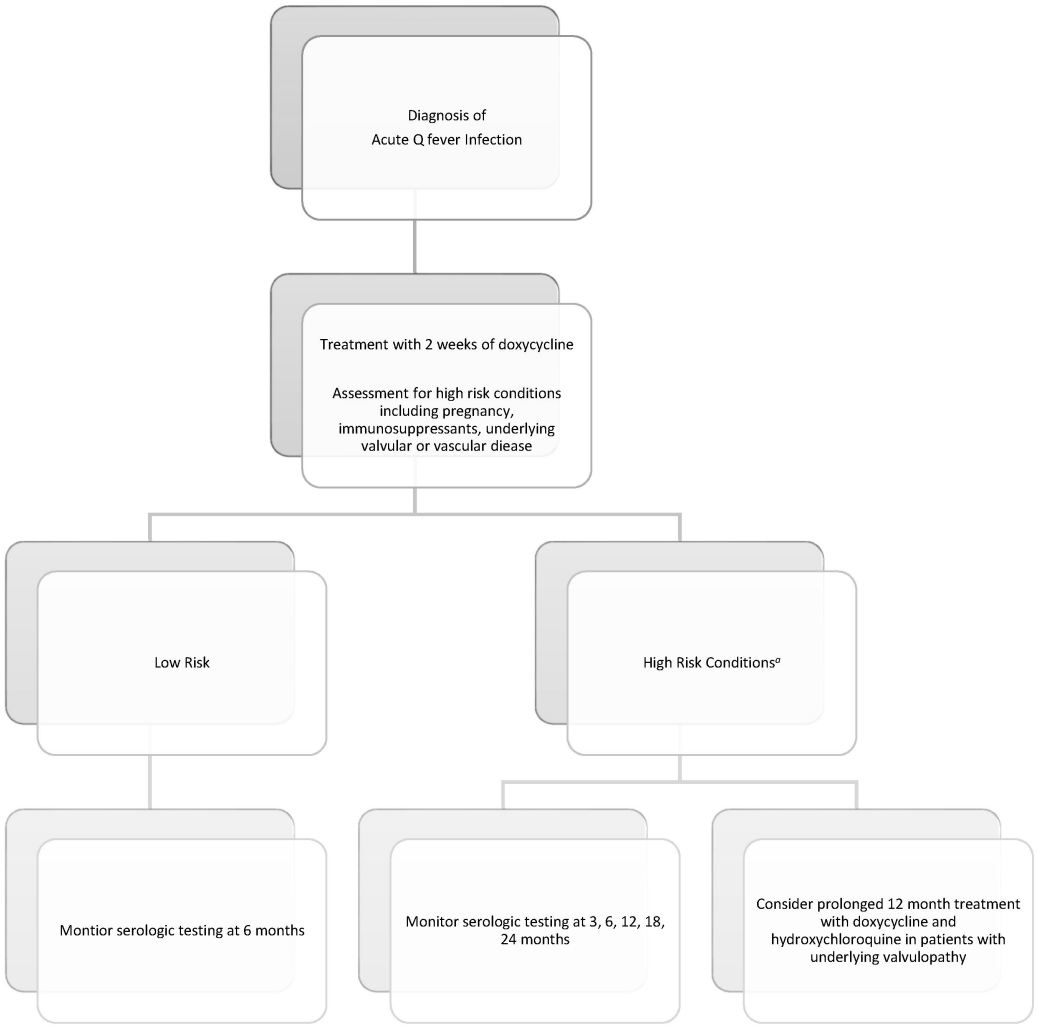

Figure 1: Treatment and monitoring of acute Q fever infection. [a] High-risk conditions include pregnancy, immunosuppression, underlying valvular or vascular disease.

Diagnostic Testing

Diagnosis of both acute and chronic Q fever is usually made by serologic testing, with immunofluorescence assay being the most commonly used method due to its high sensitivity and specificity [1]. For acute infections, most patients seroconvert within 7 to 15 days after symptom onset [4]. Polymerase chain reaction testing is also available to assist with diagnosis during acute infection [4]. Serologic testing differentiates the two different antigenic forms of the *Coxiella burnetti* organism. The bacteria have two separate surface lipopolysaccharide forms, phase I and phase II [2]. As summarized in Table 1, both IgM and IgG phase II antibodies are found predominantly in acute infection, while phase I antibodies develop in high levels in chronic infection only [2]. This means that serologic testing is useful in monitoring for the development of chronic Q fever after acute disease.

Table 1: Important clinical findings.

Epidemiology	1. Q fever infection can occur without occupational exposure, usually among people who live near infected cattle, goats or sheep and inhale aerosolized dust particles containing the bacterium. 2. Acute infection usually presents as a nonspecific flu-like illness, sometimes with pneumonia, and a clinical clue may be thrombocytopenia followed by thrombocytosis.
Diagnosis	1. Serologic diagnostic testing differentiates between acute and chronic infection, with acute infection causing high levels of IgG and IgM phase II antibodies, and chronic infection causing IgG and IgM phase I antibodies. 2. Patients with acute Q fever infection should be tested for baseline valvular abnormalities to assess their risk of chronic infection, followed by repeat serologic testing depending on their risk.
Treatment	1. Acute infection should be treated with 100 mg doxycycline twice a day for 14 days. A longer duration of therapy with doxycycline and hydroxychloroquine can be considered for patients at high risk for chronic infection. 2. Chronic infection requires serologic testing to ensure response to therapy and should be treated with 100 mg doxycycline twice a day and 200 mg hydroxychloroquine three times a day for at least 18 months.

Treatment

The CDC recommended therapy for patients with acute symptomatic disease is 100 mg doxycycline twice a day for 14 days [4,9]. There is no recommended therapy for patients who are asymptomatic or had prior disease, but could be considered for those at a high risk of chronic infection [9,10]. Treatment with doxycycline is associated with earlier defervescence and improvement in clinical symptoms, and some studies indicate it may help prevent the development of chronic infection [4,9]. Endocarditis has developed in patients even after the treatment of acute infection [10,11]. Therefore, some studies suggest a treatment course of 12 months of doxycycline and hydroxychloroquine in patients with acute Q fever and underlying valvular abnormities to prevent the development of endocarditis and chronic infection [10,11], as shown in Table 1.

The treatment of chronic Q fever is overall more challenging and prolonged. The current expert recommendations are a course of 100 mg doxycycline twice a day and 200 mg hydroxychloroquine three times a day for at least 18 months for native valve infections and 24 months for prosthetic valve infections [4,9]. Q fever endocarditis is often diagnosed at a later stage in illness and, therefore, often requires surgical intervention due to valvular damage [6]. Serologic testing during the treatment of chronic Q fever is recommended, and a serologic cure is a titer of phase I IgG antibody of less than 200 [6].

The American Academy of Pediatrics recommends treatment with doxycycline, even for children under the age of 8. An alternative treatment recommendation in children includes 4 to 20 mg trimethoprim-sulfamethoxazole per kg twice a day for 14 days [4,10]. Pregnancy also presents a challenge for the treatment of Q fever as doxycycline is contraindicated during pregnancy due to the risk to the fetus. The current CDC recommendations are to use 800–160 mg trimethoprim-sulfamethoxazole twice a day for the duration of the pregnancy in order to prevent premature birth or stillbirth [4,9]. Due to the risk of hyperbilirubinemia to the infant after delivery, it is also recommended to stop the trimethoprim-sulfamethoxazole 6 weeks prior to delivery. After

delivery, women should have serologic monitoring at 3, 6, 12, 18 and 24 months as they remain at a higher risk for the development of chronic disease [4].

Funding: This research received no external funding.

Conflicts of Interest: The author declares no conflicts of interest.

References

1. Hartzell, J.D.; Wood-Morris, R.N.; Martinez, L.J.; Trotta, R.F. Q fever: Epidemiology, diagnosis, and treatment. *Mayo Clin. Proc.* **2008**, *83*, 574–579. [CrossRef]
2. Porter, S.R.; Czaplicki, 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**, *2011*, 248418. [CrossRef] [PubMed]
3. Clark, N.J.; Magalhaes, R.S. Airborne geographical dispersal of Q fever from livestock holdings to human communities: A systematic review and critical appraisal of evidence. *BMC Infect. Dis.* **2018**, *18*, 218. [CrossRef] [PubMed]
4. Anderson, A.; Bijlmer, H.; Fournier, P.E.; Graves, S.; Hartzell, J.; Kersh, G.J.; Limonard, G.; Marrie, T.J.; Massung, R.F.; McQuiston, J.H.; et al. Diagnosis and management of Q fever—United States, 2013: Recommendations from CDC and the Q Fever Working Group. *Morb. Mortal. Wkly. Rep. Recomm. Rep.* **2013**, *62*, 1–30.
5. Fournier, P.E.; Marrie, T.J.; Raoult, D. Diagnosis of Q fever. *J. Clin. Microbiol.* **1998**, *36*, 1823–1834. [CrossRef] [PubMed]
6. Karakousis, P.C.; Trucksis, M.; Dumler, J.S. Chronic Q Fever in the United States. *J. Clin. Microbiol.* **2006**, *44*, 2283–2287. [CrossRef] [PubMed]
7. Fournier, P.; Thuny, F.; Richet, H.; Lepidi, H.; Casalta, J.; Arzouni, J.; Maurin, M.; Célard, M.; Mainardi, J.-L.; Caus, T.; et al. Comprehensive Diagnostic Strategy for Blood Culture–Negative Endocarditis: A Prospective Study of 819 New Cases. *Clin. Infect. Dis.* **2010**, *51*, 131–140. [CrossRef] [PubMed]
8. Landais, C.; Fenollar, F.; Thuny, F.; Raoult, D. From Acute Q Fever to Endocarditis: Serological Follow-Up Strategy. *Clin. Infect. Dis.* **2007**, *44*, 1337–1340. [CrossRef] [PubMed]
9. Kersh, G.J. Antimicrobial therapies for Q fever. *Expert Rev. Anti-Infect. Ther.* **2013**, *11*, 1207–1214. [CrossRef] [PubMed]
10. Fenollar, F.; Fournier, P.; Carrieri, P.; Habib, G.; Messana, T.; Raoult, D. Risks Factors and Prevention of Q Fever Endocarditis. *Clin. Infect. Dis.* **2001**, *33*, 312–316. [CrossRef] [PubMed]
11. Fenollar, F.; Thuny, F.; Xeridat, B.; Lepidi, H.; Raoult, D. Endocarditis After Acute Q Fever in Patients with Previously Undiagnosed Valvulopathies. *Clin. Infect. Dis.* **2006**, *42*, 818–821. [CrossRef] [PubMed]