Acute Q Fever

Evans R. Fernández Pérez, MD
Dahlia Rizk, DO

Query (Q) fever is a bacterial zoonosis that is underreported worldwide. In 1999, Q fever was added to the list of notifiable diseases in the United States; however, the exact prevalence is unknown. Q fever in humans usually is asymptomatic or mistaken for an acute viral illness. In general, most patients with acute Q fever will recover without treatment; however, the chronic form can lead to substantial morbidity and mortality.[1] This article describes the case of a woman with acute Q fever associated with hepatitis. Epidemiology, clinical manifestations, diagnosis, and treatment of acute Q fever are discussed.

CASE PRESENTATION

Initial Presentation and History

A 65-year-old woman with a past medical history of hypothyroidism reported a 3-day history of progressive right upper quadrant pain, generalized weakness, retro-ocular pain, and sudden onset of fever and chills. Her only medications included levothyroxine sodium 50 mg daily. She had no known allergies and no prior hospitalizations. She had no headache, photophobia, stiff neck, coryza, skin rash, cough, or arthritis. She denied smoking, alcohol use, illegal drug use, or any history of transfusion or surgeries, and had no known contact with ill individuals. Neither collagen vascular diseases nor malignancies were present in her family history. Two months prior to admission, she visited a rural area in the Dominican Republic for 4 weeks. She had no insect bites or animal contacts and consumed no unpasteurized products during that time.

Physical Examination

Physical examination revealed a healthy-appearing elderly woman who was mildly dehydrated and in no apparent distress. She had a temperature of 101.5°F (38.6°C), was tachycardic (heart rate, 108 bpm), normotensive (blood pressure, 140/85 mm Hg), and was breathing normally (14 breaths/min). Examination of the head and neck was unremarkable, with no evidence of scleral icterus or lymphadenopathy. Results of the funduscopic examination were within normal limits. The lungs were clear, but examination of the heart revealed a grade 1/6 blowing systolic murmur at the apex. Abdominal examination revealed mild right upper quadrant tenderness but no hepatosplenomegaly. No skin rash, petechiae, or purpura were present. There was no edema in the extremities, and the neurologic examination was unremarkable.

Laboratory and Imaging Studies

The patient's laboratory results showed normal electrolyte levels and elevated liver enzymes (**Table 1**). Results of the complete blood count, urinalysis, and lumbar puncture were within normal limits. In addition, the chest radiograph was normal. Acute cholecystitis was ruled out by ultrasonography and hepatobiliary scan.

Continued Clinical Course

The patient was admitted to the general medicine service, where supportive treatment was given with antipyretics and intravenous hydration. Her fevers continued to spike daily from 100°F to 104°F without any clear source of infection. The patient had a mildly elevated erythrocyte sedimentation rate and C-reactive protein level. Results of a peripheral blood smear were normal, with no evidence of malaria. Serologic testing was negative for infection with cytomegalovirus, rubella virus, influenza virus, *Toxoplasma gondii*, HIV, dengue virus, *Brucella*, and hepatitis A, B, and C viruses. Serologies for autoimmune hepatitis also were negative (Table 1). Stool culture for *Salmonella* and *Campylobacter* species remained sterile. A tuberculin skin test was negative, and no growth on multiple blood cultures was observed after 7 days.

The diagnostic evaluation was unrevealing following 1 week of rigorous inpatient investigation. An echocardiogram was performed on hospital day 9 to rule out endocarditis and showed only a dilated left ventricle, mild mitral regurgitation, and no evidence of

Dr. Fernández is an internal medicine resident, Beth Israel Medical Center. Dr. Rizk is associate professor of medicine, Albert Einstein College of Medicine, and director of the hospitalist program, Beth Israel Medical Center, New York, NY.

Table 1. Serum Laboratory Results for the Case Patient

Variable	Result	Normal Range
Sodium (mEq/L)	134	134–145
Potassium (mEq/L)	3.6	3.5–5.0
Magnesium (mg/dL)	1.9	1.5–2.4
Total calcium (mg/dL)	8.8	9.0–10.5
Bicarbonate (mEq/L)	24	23–28
Creatinine (mg/dL)	0.7	0.7–1.3
Blood urea nitrogen (mg/dL)	16	8–20
Glucose (mg/dL)	94	70–105
Aspartate aminotransferase (IU/L)	125	0–35
Alanine aminotransferase (IU/L)	107	0–35
Total bilirubin (mg/dL)	0.5	0.3–1.2
Amylase (IU/L)	40	0–130
Lipase (IU/L)	43	0–95
Autoimmune markers		
ALKM	Negative	
ANA	1:160	
ASMA	1:20	
AAA	Negative	

AAA = anti-actin antibody; ALKM = anti–liver-kidney microsomal antibody; ANA = antinuclear antibody; ASMA = anti–smooth muscle antibody.

vegetations. Computed tomography scans of the chest, abdomen, and pelvis were relevant only for diffuse fatty liver. Gallium scanning showed only hepatomegaly. Serology for *Coxiella burnetii* was ordered. After 2 weeks, the patient still was febrile, and a bone marrow biopsy was performed yielding unremarkable results. Serology for *C. burnetii* was consistent with acute Q fever (**Table 2**) (hospital day 16).

The patient was started on doxycycline, began to defervesce, and was discharged home asymptomatic and afebrile after 3 weeks of hospitalization. One week after discharge, the patient was in stable condition with normalized liver function, and subsequent Q fever serology was obtained. Of note, there was a fourfold increase in antibody titer between the acute and convalescent phase 2 IgG serum samples obtained within a 14-day period—1:512 for the first titer compared with 1:2048 for the second titer. The Department of Health was notified, and the test results were confirmed.

DISCUSSION

Epidemiology

First described in Australia in 1935, Q fever is a zoonotic infection caused by the pathogen *C. burnetii*.

Table 2. Serology for *Coxiella burnetii* for the Case Patient

Variable	Result
IgG phase 2 screen	Positive
IgG phase 2 titers	1:512
IgM phase 2 screen	Positive
IgM phase 2 titers	1:8192
IgG phase 1 screen	Negative
IgM phase 1 screen	Negative

C. burnetii is a strictly intracellular gram-negative bacterium[1] that is highly infectious when aerosolized and inhaled. This bacterium is present worldwide and has many different reservoirs, including mammals, birds, and arthropods.[1] The most commonly identified sources of human infection are livestock, which shed *C. burnetii* in urine, feces, milk, and birth byproducts.[2] A single bacterium is sufficient to infect experimental animals and likely causes the disease in humans, who are the only symptomatic host.[3] At highest risk for infection are veterinarians, farmers, stockyard and abattoir workers, as well as laboratory personnel. The disease is virtually nonexistent in urban areas but can be spread in a rural community by contaminated dust, hay, and clothing.[3] Therefore, direct contact with infected animals is not required for human infection. The organism is resistant to heat, drying, and many common disinfectants, enabling the bacteria to survive for long periods in the environment.[4] Sporadic cases of human infection also have resulted from transplacental transmission,[5] sexual transmission,[6] and from blood transfusions. In 2002, 61 cases of Q fever were reported to the Centers for Disease Control and Prevention (incidence rate, 0.05 per 100,000 population) (**Figure**). In 2001, 26 cases were reported.

Pathogenesis

After inhalation of airborne particles, the organism multiplies in the lungs and is disseminated to other organs.[7] In mammals, the usual host cell of *C. burnetii* is the macrophage, where the bacteria adapt to survive and multiply by binary fission within the acidic environment of its phagolysosome.[8,9] Within the phagolysosome, *C. burnetii* undergoes sporogenic differentiation. The spore-like forms are eventually released by exocytosis or by lysis of the host cells resulting in spreading of the organism to other mononuclear phagocytes.[10]

C. burnetii exhibits a host-dependent antigenic variation called phase variation 1 and 2. This phenomenon is due to mutational changes in the lipopolysaccharides of the bacterium.[11] The highly infectious phase 1

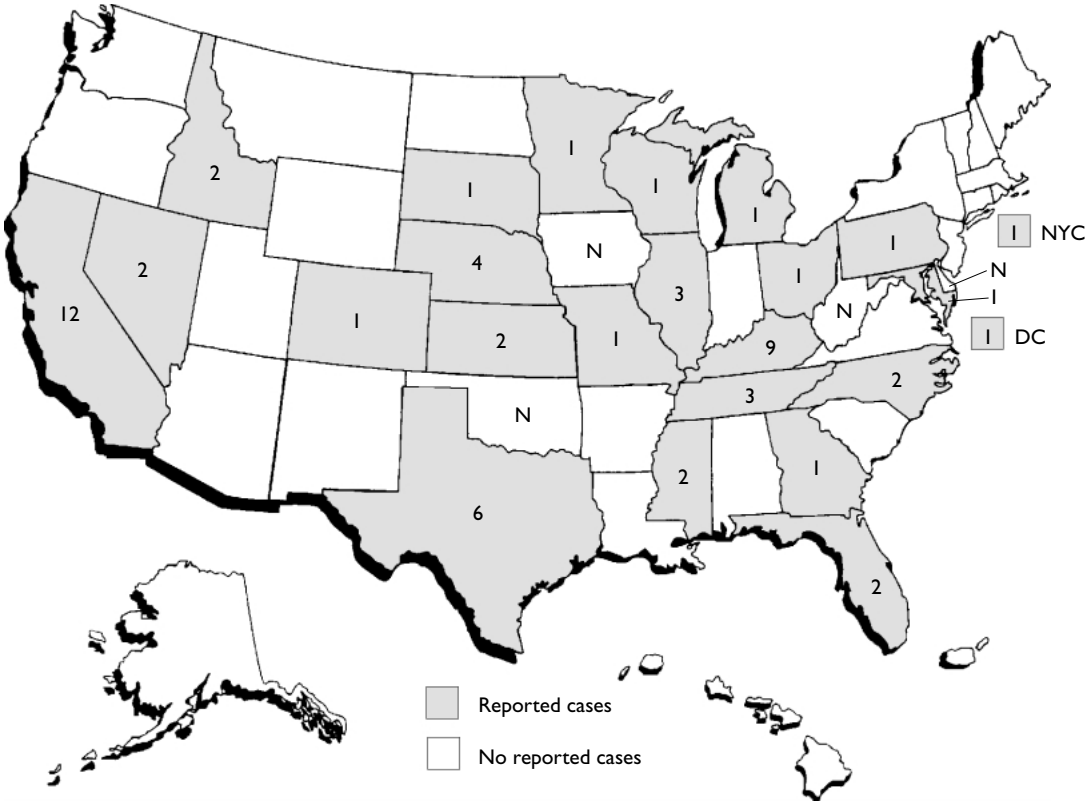

Figure. Reported cases of Q fever in the United States in 2002. Identification and reporting of Q fever are incomplete, and the number of cases reported do not represent the overall distribution or regional prevalence of disease. N = not notifiable. (Adapted from Centers for Disease Control and Prevention. Summary of notifiable diseases, United States, 2002. Available at www.cdc.gov/mmwr/summary.html. Accessed 30 Jun 2004.)

Table 3. Symptom and Relative Frequency for Acute Q Fever

Symptom	Frequency, %
Fever (present in all symptomatic patients)	80–100
Severe headache, retro-orbital pain (may be a useful clue to diagnosis)	75–100
Fatigue, anorexia, weight loss	50–85
Cough	50–60
Myalgia	45–84
Pleuritic chest pain	40–50
Nausea, vomiting	15–20
Diarrhea	5–20

Adapted from New York City Department of Health, Bureau of Communicable Diseases. Medical treatment and response to suspected Q fever: information for health care providers during biologic emergencies. Available at www.nyc.gov/html/doh/html/cd/qfmd.html. Accessed 30 Jun 2004.

antigen is isolated from animals or humans. Repeated passage of phase 1 antigens in cell cultures lead to modification of lipopolysaccharides resulting in an antigenic transition to the phase 2 form, which is avirulent.[1,3,11] This antigenic shift can be measured and is valuable for the differentiation between acute and chronic Q fever.[1]

Clinical Manifestations

The incubation period for Q fever varies between 2 to 5 weeks and is inversely correlated with the number of organisms that initially infect the patient.[12] Illness is characterized by either acute or chronic clinical manifestations. In the acute phase, half of the patients are asymptomatic (**Table 3**).[3,10] Some patients present with a self-limited flu-like illness with abrupt onset of fevers, usually lasting for 1 to 2 weeks. Pneumonia may be present in 1 of 3 ways: pneumonia with fever but no pulmonary symptoms (most common clinical scenario), atypical pneumonia,[13] or rapidly progressive disease (often mimicking Legionnaire's disease). Hepatitis may be present, as in the case patient, and hepatomegaly is common.[3] More severe extrapulmonary disorders

include endocarditis,[14] with a predilection for the aortic valve, myocarditis,[15] pericarditis, aseptic meningitis, and encephalitis.[16] Patients who have had acute Q fever may develop the chronic form 1 to 20 years after initial infection. Chronic infection, usually characterized by endocarditis, is uncommon, occurring in fewer than 2% of acute infections.[1,3] As many as 25% of people with chronic Q fever may die of the disease.[14]

Diagnosis

Unexplained fevers, negative blood cultures, normal leukocyte count, and unexplained elevated hepatic enzymes should raise the suspicion for diagnosis of Q fever, especially in immunocompromised patients. The laboratory findings during acute Q fever are nonspecific, and the diagnosis is confirmed only by serology. Complete blood count usually is normal, and liver function tests often show a slight elevation (2 to 3 times the normal level of transaminases).[1,3] A variety of nonspecific autoimmune antibodies have been identified,[10] especially in patients with Q fever hepatitis. However, the awareness of this autoimmune induction in symptomatic infected patients, particularly with systemic inflammatory diseases such as systemic lupus erythematosus, is paramount and may reflect reactivation and progression of infection or antibiotic therapy refractoriness in previously treated patients.[17] Culturing this organism is possible but dangerous due to its extreme infectivity—a biosafety level 3 laboratory must be available to use this method.

Several assays are available to determine the presence of Q fever. Antibody detection by indirect fluorescent antibody or enzyme-linked immunosorbent assay are the most commonly referenced methods. The presence of IgG, IgM, and IgA antibodies to both phase 1 and 2 antigens are initially assayed.

Acute and convalescent IgG antibody titers show a fourfold rise within 2 to 3 months after onset of illness. In acute Q fever, antibodies to phase 2 antigens predominate. In chronic Q fever, the reverse occurs, resulting in phase 1 titers that are higher than phase 2 titers.[3,10,17] A serum sample with phase 2 IgG titer of 1:200 or higher and phase 2 IgM titer of 1:50 or higher indicates a recent Q fever infection (specificity and positive predictive value of 100%),[18] usually within the last 6 to 8 months. An IgG titer of 1:1600 or greater against phase 1 antigen are indicative of chronic infection.[18]

Currently a phase 1 IgG titer of more than 1:800 (98% positive predictive value) or a single positive blood culture for *C. burnetii* is part of the microbiologic major criteria of the modified Duke criteria for the diagnosis of Q fever endocarditis.[19]

Differential Diagnosis

Because the clinical manifestations are nonspecific early on, Q fever can resemble many infections such as acute viral infections, salmonellosis, malaria, brucellosis, and tick-borne diseases. When Q fever presents as a pneumonic illness, it is similar to other atypical pneumonias such as those caused by chlamydia, legionella, or viruses, in which the hallmark is the absence of bacterial pathogens on Gram stain and culture. Granulomatous hepatitis may be present during the acute phase of Q fever[20] and must be differentiated from other common causes, such as sarcoidosis, systemic infections (ie, military tuberculosis), autoimmune disorders (ie, Wegner's granulomatosis), and drug reactions. The hepatic granuloma characteristically has a ring of fibrinoid necrosis surrounding a central lipid vacuole (fibrin ring or "doughnut" granuloma).[21] The fibrin ring granuloma, however, are not diagnostic of Q fever, and similar lesions can be seen in patients with other disorders such as boutonneuse fever, toxoplasmosis, and allopurinol hypersensitivity.[21,22]

Treatment

The prognosis for patients with acute Q fever is excellent, with a case fatality rate of approximately 1% in hospitalized patients.[3] While antimicrobial therapy is indicated, most patients with acute Q fever improve. When Q fever is diagnosed, however, the administration of antibiotics is appropriate to help the patient recover promptly and to reduce the likelihood of progression to chronic disease, which is far more resistant to treatment. Antibiotic therapy should last 14 to 21 days for acute Q fever and several years for chronic disease.[1,3]

Doxycycline is the treatment of choice for acute Q fever and early use can shorten the duration of fever.[23] Alternative therapies include quinolones, chloramphenicol, macrolides, rifampin, and hydroxychloroquine. The latter 2 drugs have mainly been used in combination with doxycycline in the treatment of Q fever endocarditis. Prophylaxis with an inactivated whole cell vaccine has been effectively used in occupational settings in Australia and eastern Europe; however, the vaccine is not licensed for general use in the United States.

Q Fever As a Biologic Weapon

The Centers for Disease Control and Prevention classifies *C. burnetii* as a category B biologic agent because it is moderately easy to disseminate and can cause moderate morbidity and mortality. Because of its environmental resistance and remarkable infectivity, *C. burnetii* has the potential to be used as a biologic

weapon in a terrorist attack. The most likely scenario would be spreading of the organism in an aerosol form that could be inhaled by targeted populations. However, because of its low virulence and inability to cause acute fatal disease, *C. burnetii* may not be effective as a biologic weapon.

CONCLUSION

Q fever may mimic several conditions. A high degree of clinical alertness is a prerequisite for the diagnosis of *C. burnetii* infection, which can be confirmed by serology. Finally, the disease should be suspected in patients who present with unexplained prolonged or recurrent fever and evidence of atypical pneumonia, endocarditis, or abnormal liver chemistry studies in the absence of viral hepatitis after exposure to arthropods or animal hosts or aerosols in endemic areas. **HP**

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