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Diagnosis and Management of Q Fever — United States, 2013

Recommendations from CDC and the Q Fever Working Group

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U.S. Department of Health and Human Services
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Front cover photo: A girl plays with goats, one of the primary reservoirs of Coxiella burnetii, the bacterium that causes the zoonotic disease Q fev

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Diagnosis and Management of Q Fever — United States, 2013

Recommendations from CDC and the Q Fever Working Group

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Summary

Q fever, a zoonotic disease caused by the bacteria *Coxiella burnetii*, can cause acute or chronic illness in humans. Transmission primarily through inhalation of aerosols from contaminated soil or animal waste. No licensed vaccine is available in the Because many human infections result in nonspecific or benign constitutional symptoms, establishing a diagnosis of challenging for clinicians. This report provides the first national recommendations issued by CDC for Q fever recognitio laboratory diagnosis, treatment, management, and reporting for health-care personnel and public health professionals. The treatment of acute and chronic phases of Q fever illness in children, adults, and pregnant women, as well as managemen exposures. These recommendations will be reviewed approximately every 5 years and updated to include new publishe

Introduction

Q fever, first described in 1937, is a worldwide zoonosis that has long been considered an underreported and underdiagnosed illness because symptoms frequently are nonspecific, making diagnosis challenging (1–3). The causative organism, *Coxiella burnetii*, is an intracellular bacterium that tends to infect mononuclear phagocytes but can infect other cell types as well. Infection in humans usually occurs by inhalation of bacteria from air that is contaminated by excreta of infected animals. Other modes of transmission to humans, including tick bites, ingestion of unpasteurized milk or dairy products, and human-to-human transmission, are rare (1). Laboratory diagnosis relies mainly on serology, and doxycycline is the mos effective treatment for acute illness. No vaccine is available commercially in the United States.

Q fever was designated a nationally notifiable disease in the United States in 1999. Since then, reports of Q fever have increased, with 167 cases reported in 2008, an increas greater than ninefold compared with 2000, in which 17 cases were reported (4). The national seroprevalence of Q fever is estimated to be 3.1% based on data from the National Health and Nutrition Examination Survey (2003–2004), and human infections have been reported from every state in the United States (5). Q fever infections in humans and animals have been reported from every world region except Antarctica (6).

Q fever has acute and chronic stages that correspond to two distinct antigenic phases of antibody response. During an acute infection, an antibody response to *C. burnetii* phase II antigen is predominant and is higher than the response to the phase

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antigen, whereas a chronic infection is associated with a rising phase I immunoglobulin G (IgG) titer. Although acute Q fever symptoms in humans vary, the condition typically is characterized by a nonspecific febrile illness, hepatitis, or pneumonia. Asymptomatic infections followed by seroconversion have been reported in up to 60% of cases identified during outbreak investigations (4–8). Onset of symptoms usually occurs within 2–3 weeks of exposure, and symptomatic patients might be ill for weeks or months if untreated.

Chronic Q fever can manifest within a few months or several years after acute infection and can follow symptomatic or asymptomatic infections. Chronic disease is rare (<5% of patients with acute infections) and typically is characterized by endocarditis in patients with preexisting risk factors such as valvular or vascular defects (9). Unlike acute Q fever, which has a low mortality rate (<2%), chronic Q fever endocarditis is always fatal if untreated (10). Routine blood cultures are negative in patients with chronic Q fever endocarditis. Diagnosis of chronic Q fever endocarditis can be extremely difficult because vegetative lesions are visualized by echocardiography in approximately 12% of patients (6).

Q fever is an occupational disease in persons whose work involves contact with animals, such as slaughterhouse workers, veterinarians, and farmers, although infection is not limited to these groups. Urban outbreaks and cases with no known exposure or close proximity to livestock have been reported, as have nonoccupational exposures such as through a hobby farm (a small farm that is not a primary source of income) (11). Data collected from Q fever case report forms submitted to CDC during 2000–2010 indicate that 320 of 405 (79%) cases in patients who reported occupational status are recognized in patients who are not in previously defined high-risk occupations, and 243 of 405 (60%) cases are in patients who do not report livestock contact (CDC, unpublished data, 2010). These findings underscore the need for health-care professionals to consider Q fever in the differential diagnosis in patients with a compatible illness, even in the absence of occupational risk or history of direct contact with animal reservoirs. Approximately 200 cases of acute Q fever were reported in U.S. military personnel who had been deployed to Iraq since 2003. Investigations of these cases linked illness to tick bites, sleeping in barns, and living near helicopter zones with environmental exposure resulting from helicopter-generated aerosols (12,13).

The largest known reported Q fever outbreak involved approximately 4,000 human cases and occurred during 2007–2010 in the Netherlands. This outbreak was linked to dairy goat farms near densely populated areas and presumably involved human exposure via a windborne route (14).

Prompt diagnosis and appropriate treatment shortens the illness and reduces the risk for severe complications (15,16). In patients with chronic Q fever illness, early treatment might be lifesaving. Physician awareness of the epidemiologic and clinical characteristics of Q fever is required to make a prompt and correct diagnosis. Information in this report is designed to assist U.S. clinicians with the following:

- Recognize common epidemiologic features and clinical manifestations of Q fever.
- Consider Q fever as the cause of a patient's illness if appropriate.
- Obtain relevant history (e.g., medical history and exposure) and diagnostic tests for Q fever.
- Identify the limitations and utility of laboratory diagnostic testing.
- Make treatment decisions based on epidemiologic and clinical evidence.
- Recognize that doxycycline is the treatment of choice for patients of any age with severe illness.
- Recognize potential severe manifestations of acute and chronic Q fever and understand appropriate strategies to monitor and manage these patients.
- Manage infected children and pregnant women appropriately.
- Provide effective risk communication for persons at high risk for Q fever exposure.
- Report suspect and confirmed cases to appropriate public health officials.

A compilation of the key point summaries for Q fever clinical features, diagnosis, treatment, occupational exposures, and surveillance and reporting are provided (Appendix A).

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reviewed, revised, and refined the recommendations. In 2012, the CDC National Institute of Occupational Safety and Health reviewed the recommendations. When possible, recommendations were based on existing recommendations

- recent travel to areas of higher risk for Q fever, such as rural, agricultural communities (domestic and international), areas with recent outbreaks such as the Netherlands, or regions such as the Middle East where the disease is highly endemic
- sexual contact with a person who has recently had Q fever or contact with contaminated clothing and linens leading to fomite transmission
- Q fever symptoms in a person who has a partner or family member who has received a diagnosis of Q fever
- chronic Q fever symptoms in anyone with a history of acute Q fever infection, particularly persons with valvular heart disease or a vascular graft or arterial aneurysm, immunosuppressed persons, and women who are pregnant

Although a detailed exposure history, including animal

Pregnant Women

Q fever infections in women that occur shortly before conception or during pregnancy might result in miscarriage, stillbirth, premature birth, intrauterine growth retardation, or low birthweight (75). Adverse pregnancy outcomes are likely to be caused by vasculitis or vascular thrombosis resulting in placental insufficiency, although direct infection of the fetus has been documented (76). Of the reports that describe outcomes of infected pregnant women, none have documented an increased risk for congenital malformations because of infection (75,76).

Pregnant women might be less likely to have symptoms of Q fever compared with other adults (e.g., a febrile illness), although they remain at risk for adverse pregnancy outcomes (50). As a result, if a pregnant woman with no history of clinical illness has only a single increased antibody titer, it is difficult for the health-care provider to determine whether the increase is from a previous or current infection. Serosurveys of pregnant women evaluating a possible association between a single, elevated *C. burnetii* antibody titer (which cannot differentiate between previous or current infection) and adverse pregnancy outcomes have reported mixed findings (77–80). A woman with a previous infection (>30 days before conception) with no evidence of progression to chronic disease does not require treatment during pregnancy. However, a Q fever infection during pregnancy requires antibiotic treatment (Table 2), and health-care providers should consider several factors to determine the best treatment approach. Careful assessment of serologic results are useful because the phase II antibody response is increased in patients with an acute infection but decreases during convalescence as the phase I antibody response increases. Factors to consider before initiating treatment include whether the patient had contact with infected livestock, occupational animal contact, or an epidemiological link to another person with Q fever to guide treatment decisions.

The risk for adverse effects on the fetus and the risk that the mother will develop chronic Q fever are highest when an acute infection occurs during the first trimester (81,82). Untreated infection in the first trimester is more likely to result in miscarriage, whereas infection later in pregnancy is more likely to cause premature delivery (75). Women infected with acute Q fever during pregnancy, including those who were asymptomatic or experienced no adverse pregnancy outcomes, might be at risk for recrudescent infection during subsequent pregnancies (83). Therefore, pregnant women with a history of Q fever infection during a previous pregnancy should be monitored closely for recrudescent infection in all subsequent pregnancies.

Health-care providers should educate women of childbearing age who receive a diagnosis of acute Q fever of potential risks to the fetus. These women should be advised to avoid pregnancy for at least 1 month after diagnosis and treatment and should receive a pregnancy test to determine whether long-term antibiotic treatment is needed.

Radiologic Evaluation

Pneumonia is one of the primary clinical manifestations of acute Q fever (6). Chest radiograph abnormalities are seen in the majority of patients with acute Q fever, although patients in the early stages of disease might have normal radiographic findings. Radiographic evaluation of acute Q fever patients

Laboratory Findings

Although up to 25% of patients with acute Q fever have an increased leukocyte count, most patients have normal white blood cell counts. Mild thrombocytopenia in early illness, which occurs in approximately one third of patients, might be followed by subsequent thrombocytosis. Increased erythrocyte sedimentation rate, hyponatremia, hematuria, increased creatine kinase, and increased C-reactive protein levels have been reported.

The most common laboratory abnormalities are increased liver enzyme levels, which are observed in up to 85% of cases (89). Hyperbilirubinemia occurs in one in four patients (26, 90–

involvement might occur and should prompt testing for Q fever in patients with aortic defects (104). Imaging techniques that might prove useful for diagnosis of vascular infections include computed tomography, magnetic resonance imaging, or duplex ultrasound. Fluorodeoxyglucose positron emission tomography combined with computed tomography has high sensitivity

Diagnosis

Acute Q Fever

Because most persons with acute Q fever have nonspecific symptoms, health-care providers typically do not suspect Q fever during the acute stage of the disease. Although a laboratory diagnosis of acute Q fever can be made on the basis of serologic results, the requirement of a fourfold rise in phase II IgG antibody titer between acute and convalescent samples for definitive diagnosis makes this primarily a retrospective diagnosis (Table 3). For a definitive diagnosis in the early stages of acute Q fever illness, serologic testing in combination with PCR is recommended. PCR of whole blood or serum can be positive very early after symptom onset but becomes negative as the antibody titer increases and after administration of

TABLE 3. CDC surveillance case definition and case classification for acute and chronic Q fever

	Acute Q fever	Chronic Q fever
Clinical evidence of infection	Fever and one or more of the following: rigors, severe retrobulbar headache, acute hepatitis, pneumonia, or elevated liver enzymes	Newly recognized culture-negative endocarditis (particularly in a patient with previous valvulopathy or compromised immune system), suspected infection of a vascular aneurysm or vascular prosthesis, or chronic hepatitis, osteomyelitis, osteoarthritis, or pneumonitis in the absence of other known etiology
Laboratory criteria*,†	Laboratory confirmed (one or more of the following):	

might have a higher cross-reactivity. Cross-reactions between Coxiella, Legionella, and Bartonella species have been reported (128,129). However, the cross-reacting antibodies generally have low titers and should not result in misdiagnosis.

Because early doxycycline treatment (within the first 3 days of symptoms) is most effective, treatment of a patient suspected of having Q fever should be based on clinical findings and should not be delayed while awaiting laboratory confirmation. No evidence indicates that early administration of doxycycline blunts the antibody response or prevents seroconversion (130, 131).

Nucleic Acid Detection

Rapid, sensitive, and quantitative PCR techniques have been developed for Q fever testing. Multiple gene targets have been used, and physicians should be aware that they can differ in sensitivity and specificity (132).

Either whole blood collected in anticoagulant-treated tubes or serum can be used for PCR testing. Whole blood might have a higher concentration of C. burnetii DNA than serum but is also likely to have more PCR inhibitors. For PCR results to be useful, the clinical sample must be obtained in the acute phase of infection (optimally during the first 2 weeks of symptom onset) and either before or shortly after (within 24–48 hours) antibiotic administration. When appropriate samples are drawn (i.e., during the acute phase and before or shortly after antibiotic administration), PCR results are positive in almost all patients with early acute Q fever before the antibody response develops (133).

Chronic Q Fever

The Duke criteria, a set of validated diagnostic criteria for infective endocarditis, were revised in 2000 to include redefined Q fever serologic parameters (134). That revision defined a phase I IgG antibody titer >1:800 or a single positive blood culture for C. burnetii as a major criterion for infective endocarditis. The Duke Endocarditis Service also advocated for use of TEEs as the initial diagnostic test of choice in patients categorized as having possible infective endocarditis, those with suspected complicated infective endocarditis, and those with suspected prosthetic valve infective endocarditis (Appendix B). A patient with a phase I IgG antibody titer >1:800 or a single positive blood culture for C. burnetii and one of the following minor criteria would be classified as having possible infective endocarditis, thereby warranting use of an initial TEE: predisposition, predisposing heart condition or injection drug use, fever, vascular phenomena, immunologic phenomena, or microbiologic evidence.

Serologic Testing

Chronic Q fever is diagnosed primarily by serologic testing. Establishing an identifiable nidus of chronic infection (e.g., endocarditis, vascular infection, or osteomyelitis) is required, as is laboratory confirmation. The distinct antigenic phases to which humans develop antibodies play an important role in the diagnosis. In contrast to acute Q fever infection, chronic infection is associated with continued increasing phase I IgG titers (typically 1:1024) that might be higher than phase II IgG. However, there are reports of chronic Q fever patients who retain extremely high phase II IgG antibody titers that equal or exceed their phase I IgG titers (asing phase I IgG

refrigerated and shipped by express shipping on frozen gel packs separated from the specimen by packing material. Samples can be frozen in a non–frost-free freezer and shipped on dry ice to the laboratory.

Blood. Whole blood for PCR testing should be collected before antibiotic administration in EDTA-treated anticoagulant tubes and shipped refrigerated on frozen gel packs by overnight shipping. If samples are to be prepared for other laboratory tests, the buffy coat can be saved for DNA amplification and stored frozen in a non–frost-free freezer.

Tissue. Heart valve tissue is the most commonly evaluated specimen used for confirmation of chronic Q fever. Fresh tissue specimens, which are the most effective and have the widest range of diagnostic techniques, should be refrigerated if they are being transported within 24 hours, and they should be shipped on frozen gel packs. If transport does not occur within 24 hours, specimens should be frozen in a non–frost-free freezer and shipped on dry ice for either culture or PCR analysis. In preparation for transport, fresh tissue should not be immersed in saline but should be placed on a gauze pad moistened with sterile saline and placed in a sterile collection cup. PCR, immunohistochemistry staining, and culture isolation for C. burnetii can be attempted on fresh tissue. Should culture attempts be performed, biopsy specimens should be kept at -80°C (-112°F) before shipping and shipped on dry ice.

Formalin-fixed paraffin-embedded blocks for PCR and immunohistochemistry can be stored and shipped at room temperature and should never be frozen. During warmer months, the blocks should be shipped refrigerated with a frozen gel pack to prevent melting. Formalin-fixed wet tissue should be stored and shipped at room temperature. Length of time in formalin might adversely affect assay results. If sending glass slides with sections from paraffin-embedded blocks, 10–12 treated (e.g., with silane or poly-L-lysine) glass slides with sections of affected tissue cut at a thickness of 3 µm (or greater than 5 µm) should be submitted. These may be shipped

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heart valve defects (143,144); health-care providers should use their clinical judgment to determine the most appropriate tools for assessment of risk (Figure).

Chronic Q Fever in Adults

Management of chronic Q fever is evaluated through both
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1. Use a fit-tested N-95 (or comparable) respirator and eye protection (e.g., goggles or face shield).
2. Contain and dispose of contaminated waste (e.g., dressings or birth products) in accordance with facility-specific guidelines for infectious waste.
3. Place the patient in an airborne infection isolation room or a private room if one is not available during the procedure. The patient does not need to wear a face mask, because Q fever is not transmitted by sneezing or coughing.
4. Handle used patient-care equipment in a way that prevents contamination of skin and clothing. Ensure that used equipment has been cleaned and reprocessed appropriately.
5. Ensure that procedures are in place for cleaning and disinfecting environmental surfaces in the patient care environment (see #5 in the Research Facility Safety Standards section that follows for chemical disinfectant recommendations).

Precautions used in addition to standard precautions are only recommended during an aerosol-generating procedure. Procedures that do not generate aerosols, such as drawing blood or giving physical examinations, do not pose a risk for transmission of Q fever. Transmission through coughing or sneezing is not a documented route of infection, and there is no evidence that Q fever is transmitted by any type of casual contact (e.g., hugging, shaking hands, kissing, or sharing food).

Laboratory transmission of *C. burnetii* is primarily a concern when bacteria are propagated using specialized techniques (i.e., tissue culture), during lapses in standard precautions leading to specimen aerosolization, and through protocols involving passage through animals. Handling of usual biomedical specimens, including routine blood culture testing, from humans or animals collected in medical or veterinary settings is not considered an exposure risk for Q fever and can be processed by routine standard precautions and handling techniques.

Laboratory safety and containment recommendations for *C. burnetii* should be followed as described in the CDC Biosafety in Microbiological and Biomedical Laboratories (163). Samples known or suspected to contain viable *C. burnetii* (i.e., birth products or other biologic material from infected animals or humans) should be handled in a BSL-3 facility and rendered nonviable or destroyed. Appropriate personal protective equipment (PPE) can be effective at reducing the risk for exposure in handling these types of specimens. In the BSL-3 laboratory, attire worn while working with viable *C. burnetii* should be sterilized after use. Protective eyewear such as splatter-proof safety goggles or face shields, disposable gloves, and shoe covers also should be worn, and showering after working with *C. burnetii* under BSL-3 conditions is recommended. In laboratories that work with viable *C. burnetii* organisms in culture media or live animals, unvaccinated workers should wear respiratory protection such as an N95 respirator. An N95 respirator filters at least 95% of airborne particles when used correctly but might not completely eliminate infection risk. A powered air purifying respirator with P100 filtration also can be used in research laboratories that experiment with *C. burnetii*, particularly by employees unable to wear an N95 respirator. Whether this higher level

risk, the risk for chronic Q fever development is still present regardless of whether symptomatic or asymptomatic infection occurs. Because of the limited treatment duration in the 1956 study, the lack of additional studies verifying its findings, and use of oxytetracycline instead of doxycycline, the benefit of prophylactic antimicrobial agents is questionable and therefore not recommended.

A daily fever monitoring log should be kept for a minimum of 3 weeks after exposure to *C. burnetii*. The incubation period for Q fever is dose dependent. The majority of infected persons have symptom onset 2–3 weeks after exposure, although onset can occur up to 6 weeks after exposure. If fever occurs during the monitoring period, immediate treatment with doxycycline should be administered and testing should be performed. Treatment within 24 hours of fever onset is extremely effective in shortening illness duration and symptom severity (16,130). Baseline serologic testing can be performed to evaluate previous infection status with a convalescent sample drawn 6 weeks later to determine whether asymptomatic seroconversion has occurred. Although asymptomatic infections do not routinely require treatment, even asymptomatic infection carries a risk for progression to chronic disease in groups at high risk; therefore, treatment for asymptomatic infection might be considered in these groups. Determination of infection status might provide useful data to guide future health management.

Summary of Occupational Exposure to Q Fever

- The majority of occupationally related Q fever outbreaks in the United States have occurred among biomedical research facility workers exposed to infected pregnant ewes.
- Workplaces with employees at high risk for *C. burnetii* exposure (e.g., laboratories that experiment with *C. burnetii* and animal research facilities) should institute a Q fever medical surveillance and health education monitoring program. Engineering controls, administrative controls, and use of PPE are recommended when appropriate.
- Use of standard precautions by health-care providers is sufficient to prevent Q fever transmission during routine care. Additional precautions should be used during aerosol-generating procedures.
- Use of postexposure prophylaxis is not recommended for workers after a known or potential exposure; any acute febrile illness that occurs within 6 weeks of exposure warrants immediate treatment and medical evaluation.

Surveillance and Reporting

Q fever is a nationally notifiable disease in the United States. Health-care providers should report suspected or confirmed cases through local or state reporting mechanisms in place for notifiable disease conditions. Many state laboratories have systems in place that automatically report specific diseases, although this varies by state. The most recent human case definition, revised in 2009, provides separate reporting categories for acute and chronic Q fever (Table 3). The CDC case definition is used for national reporting as a public health surveillance tool and is not intended for clinical diagnosis. A medical diagnosis is made to treat a patient and should consider all aspects of the illness. Surveillance case definitions are used for standardization, not patient care.

National surveillance for Q fever in the United States relies on accurate and timely reporting of cases by health-care providers. When health-care providers identify a potential case of acute or chronic Q fever, they should notify the local or state health department, which can assist with obtaining appropriate diagnostic testing. Epidemiologic and clinical patient information is reported through state health departments to CDC on a standard, confidential case report form (Appendix D). When reporting cases of Q fever, clinical signs and symptoms should be included as well as laboratory results. CDC compiles reports of Q fever from state health departments, including diagnosis, date of onset, and basic demographic and geographic data, and reports the summary data.

Although Q fever is a zoonotic disease, infection in animals is not considered reportable to national agricultural authorities. However, many states consider the disease reportable when it is diagnosed in animals. Veterinary health authorities should follow state-specific reporting guidelines.

Summary of Q Fever Surveillance and Reporting

- Human Q fever infection is a notifiable disease in the United States.
- Health-care providers who identify a potential case of Q fever should notify the local/state health department, which can assist with diagnostic testing.
- Surveillance and reporting of Q fever are key components of public health education and disease prevention efforts.

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References

45. CDC. Q fever—California. MMWR 1977;26:86–7.
46. Kanfer E, Price C, MacD

97.

134. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633–8.
135. van der Hoek W, Versteeg B, Meekelenkamp JC, et al. Follow-up of 686 patients with acute Q fever and detection of chronic infection. Clin Infect Dis 2011;52:1431–6.
136. Fenollar F, Fournier PE, Raoult D. Molecular detection of Coxiella burnetii in the sera of patients with Q fever endocarditis or vascular infection. J Clin Microbiol 2004;42:4919–24.
137. Limonard GJ, Nabuurs-Franssen MH, Weers-Pothoff G, et al. One-year follow-up of patients of the ongoing Dutch Q fever outbreak: clinical, serological and echocardiographic findings. Infection 2010;38:471–7.
138. Lepidi H, Houpikian P, Liang Z, Raoult D. Cardiac valves in patients with Q fever endocarditis: microbiological, molecular, and histologic studies. J Infect Dis 2003;187:1097–106.
139. Hamilton LR, George DL, Scoville SL, Hospenthal DR, Griffith ME. PCR for rapid diagnosis of acute Q fever at a combat support hospital in Iraq. Mil Med 2011;176:103–5.
140. Gikas A, Kofteridis D, Manios A, Pediaditis J, Tselentis Y. Newer macrolides as empiric treatment for acute Q fever infection. Antimicrob Agents Chemother 2001;45:3644–6.
141. Dijkstra F, Riphagen-Dalhuisen J, Wijers N, et al. Antibiotic therapy for acute Q fever in the Netherlands in 2007 and 2008 and its relation to hospitalization. Epidemiol Infect 2011;139:1332–41.
142. 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;42:818–21.
143. Healy B, Llewelyn M, Westmoreland D, Lloyd G, Brown N. The value of follow-up after acute Q fever infection. J Infect 2006;52:e109–12.
144. Palmer SR, Young SE. Q-fever endocarditis in England and Wales, 1975–81. Lancet 1982;320:1448–9.
145. Raoult D, Houpikian P, Tissot Dupont H, Riss JM, Arditi-Djiane J, Brouqui P. Treatment of Q fever endocarditis: comparison of 2 regimens containing doxycycline and ofloxacin or hydroxychloroquine. Arch Intern Med 1999;159:167–73.
146. Rolain JM, Mallet MN, Raoult D. Correlation between serum doxycycline concentrations and serologic evolution in patients with Coxiella burnetii endocarditis. J Infect Dis 2003;188:1322–5.
147. Parker NR, Barralet JH, Bell AM. Q fever. Lancet 2006;367:679–88.
148.

Appendix A

Q Fever Key Point Summaries

Acute Clinical Features

- Prolonged fever (>10 days) with a normal leukocyte count, thrombocytopenia, and increased liver enzymes is suggestive of acute Q fever infection.
- Children with Q fever generally have a milder acute illness than adults.
- Children are more likely to have a rash than adults. Rash has been reported in up to 50% of children with acute Q fever.
- Women infected with Q fever during pregnancy are at increased risk for miscarriage and preterm delivery.
- Women of child-bearing age who receive a diagnosis of Q fever can benefit from pregnancy screening and counseling to guide health-care management decisions.

Chronic Clinical Features

- Persons who are at high risk for development of chronic Q fever include persons with preexisting valvular heart disease, vascular grafts, or arterial aneurysms.
- Infection during pregnancy and immunosuppression (e.g., from chemotherapy) are both conditions that have been linked to chronic Q fever development.
- Endocarditis and infections of aneurysms or vascular prostheses are the most common forms of chronic Q fever and generally are fatal if untreated.
- Chronic Q fever is rarely reported in children.
- In contrast with adults, osteomyelitis is one of the most common findings in children with chronic Q fever.

Diagnosis

- Polymerase chain reaction (PCR) of whole blood or serum provides rapid results and can be used to diagnose acute Q fever in approximately the first 2 weeks after symptom onset but before antibiotic administration.
- A fourfold increase in phase II immunoglobulin G (IgG) antibody titer by immunofluorescent assay (IFA) of paired acute and convalescent specimens is the diagnostic gold standard to confirm diagnosis of acute Q fever. A negative acute titer does not rule out Q fever because an IFA is negative during the first stages of acute illness. Most patients seroconvert by the third week of illness.
- A single convalescent sample can be tested using IFA in patients past the acute stage of illness; however, a demonstrated fourfold rise between acute and convalescent samples has much higher sensitivity and specificity than a single elevated, convalescent titer.
- Diagnosis of chronic Q fever requires demonstration of an increased phase I IgG antibody (1:1024) and an identifiable persistent infection (e.g., endocarditis)
- PCR, immunohistochemistry, or culture of affected tissue can provide definitive confirmation of infection by Coxiella burnetii.
- Test specimens can be referred to CDC through state public health laboratories.

Treatment and Management

- Because of the delay in seroconversion often necessary to confirm diagnosis, antibiotic treatment should never be withheld pending laboratory tests or discontinued on the basis of a negative acute specimen. In contrast, treatment of chronic Q fever should be initiated only after diagnostic confirmation.
- Treatment for acute or chronic Q fever should only be given in clinically compatible cases and not based on elevated serologic titers alone (see Pregnancy section for exception)
- Doxycycline is the drug of choice, and 2 weeks of treatment is recommended for adults, children aged 8 years, and for severe infections in patients of any age.
- Children aged <8 years with uncomplicated illness may be treated with trimethoprim/sulfamethoxazole or a shorter duration (5 days) of doxycycline.
- Women who are pregnant when acute Q fever is diagnosed should be treated with trimethoprim/sulfamethoxazole throughout the duration of pregnancy.
- Serologic monitoring is recommended following acute Q fever infection to assess possible progression to chronic infection. The recommended schedule for monitoring is based on the patient's risk for chronic infection.

Occupational Exposure

- The majority of occupationally related Q fever outbreaks in the United States have occurred among biomedical research facility workers exposed to infected pregnant ewe

- Workplaces with employees at high risk for *C. burnetii* exposure (e.g., laboratories that experiment with *C. burnetii* and animal research facilities) should institute a Q fever medical surveillance and health education monitoring program. Engineering controls, administrative controls, and use of personal protective equipment are recommended when appropriate.
- Use of standard precautions by health-care providers is sufficient to prevent Q fever transmission during routine care. Additional precautions should be used during aerosol-generating procedures.
- Use of postexposure prophylaxis is not recommended for workers after a known or potential exposure; any acute febrile illness that occurs within 6 weeks of exposure warrants immediate treatment and medical evaluation.

Surveillance and Reporting

- Human Q fever infection is a notifiable disease in the United States.
- Health-care providers who identify a potential case of Q fever should notify the local/state health department, which can assist with diagnostic testing.
- Surveillance and reporting of Q fever are key components of public health education and disease prevention efforts.

Appendix C

Additional Information and Resources

CDC

Rickettsial Zoonoses Branch
http://www.cdc.gov/qfever
http://www.bt.cdc.gov/agent/qfever/clinicians/index.asp
CDC Q Fever Case Report Form
http://www.cdc.gov/qfever/pdfs/qfevercasereport_2010.pdf
Contact CDC
Telephone: 1-800-CDC-INFO (1-800-232-4636)
E-mail:
- Clinicians: coca@cdc.gov
- General public: cdcinfo@cdc.gov

Laboratories that Perform Diagnostic Assays

Association of Public Health Laboratories
http://www.aphl.org/AboutAPHL/publications/Documents/PHPR_2012April_State-Public-Health-Laboratories-Emergency-Contact-Directory.pdf

Laboratory Safety

CDC Select Agent Program
http://www.cdc.gov/phpr/dsat.htm
Biosafety in Microbiological and Biomedical Laboratories
http://www.cdc.gov/biosafety/publications/bmbl5/bmbl5_sect_VIII.pdf

General Q Fever Information

World Organization for Animal Health (OIE)
http://www.oie.int/international-standard-setting/terrestrial-manual/access-online
American Veterinary Medical Association
https://www.avma.org/KB/Resources/Backgrounders/Documents/zu_q_fever.pdf
American Academy of Pediatrics
http://aapredbook.aappublications.org
Herd Management Plan Example
http://liv.mt.gov/content/ah/diseases/reportable/qfeverherdplan.pdf
CDC Q Fever: Frequently Asked Questions
http://liv.mt.gov/content/ah/diseases/reportable/qfeverfaq.pdf

Suggested Reading

Q Fever Comprehensive Overview
Maurin M, Raoult D. Clin Microbiol Rev 1999;12:518–53.
Diagnosis of Q Fever
Fournier PE, Marrie TG, Raoult D. J Clin Microbiol 1998;36:1823–34.
Long-Term Outcome of Q Fever Endocarditis: A 26-Year Personal Survey
Million M, Thuny F, Richet H, Raoult D. Lancet 2010; 10:527–35.

Appendix D

Q Fever Case Report Form

The Morbidity and Mortality Weekly Report (MMWR)

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