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Antimicrobial therapies for Q fever

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Summary

Q fever is caused by the bacterium *Coxiella burnetii* and has both acute and chronic forms. The acute disease is a febrile illness often with headache and myalgia that can be self-limiting whereas the chronic disease typically presents as endocarditis and can be life threatening. The normal therapy for the acute disease is a two week course of doxycycline, whereas chronic disease requires 18-24 months of doxycycline in combination with hydroxychloroquine. Alternative treatments are used for pregnant women, young children, and those who cannot tolerate doxycycline. Doxycycline resistance is rare but has been reported. Co-trimoxazole is a currently recommended alternative treatment, but quinolones, rifampin, and newer macrolides may also provide some benefit.

Keywords

Coxiella burnetii; Q fever; antibacterial agents; doxycycline; pregnancy; disease management

Q fever diagnosis and treatment

Q fever is a zoonotic disease caused by infection with the intracellular bacterium *Coxiella burnetii*. This gram-negative bacterium has a nearly worldwide distribution and infects a wide variety of animals, including mammals, birds, reptiles, and arthropods [1]. The most common reservoir species leading to human exposure are thought to be domesticated livestock, specifically goats, sheep, and cattle. Livestock animals do not commonly suffer from acute disease when infected, but *C. burnetii* can replicate to high density in the placenta and lead to reproductive failure in these animals [2]. When *C. burnetii* is introduced into previously naïve sheep flocks and goat herds, “abortion storms” can occur and these are often the first indication of the presence of *C. burnetii* in the animals. During birth, large numbers of *C. burnetii* can be released into the environment and this often leads to human infections [3].

C. burnetii is transmitted to humans by inhalation of aerosols that contain the bacteria. These aerosols are often derived from dried animal waste products or birthing fluids. Inhalation is thought to result in infection of monocytic cells in the lung [4]. *C. burnetii* is taken up through the endocytic pathway and remains in an acidic vacuole where it replicates

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slowly [5]. Over time, large numbers of *C. burnetii* can grow in infected vacuoles, and cell egress can release infectious bacteria for further rounds of infection. Humans will typically show symptoms 7-21 days after initial infection, with higher doses having shorter incubation times [6]. It has been estimated that >50% of human infections could be asymptomatic, with concomitant seroconversion [7].

Symptomatic infections can present in both an acute and a chronic form. Acute Q fever is a febrile illness that is often accompanied by fatigue, headache, and myalgia [8]. The disease can resolve without treatment and the median duration of fever in untreated patients is 9-14 days [6,9]. More serious presentations that can occur with acute Q fever are pneumonia and hepatitis [10]. It is fatal in rare cases. Q fever can also present in a chronic form that can take place months or years after the initial infection. Patients with chronic Q fever may or may not recall an episode of symptomatic acute Q fever. Chronic Q fever requires growth of *C. burnetii* in an opportune location in the body. The most common presentation for chronic Q fever is culture negative infectious endocarditis, but vascular infections in chronic Q fever can also be a common manifestation, with fatal aortic aneurysms possible [11,12]. The presence of a pre-existing valvulopathy is the most common risk factor associated with chronic Q fever endocarditis [13,14].

Because of the ability of *C. burnetii* to replicate to high density in the placenta, there are a special set of risks associated with Q fever during pregnancy. Premature birth, stillbirth, intrauterine growth retardation, and low birth weight have all been described as adverse pregnancy outcomes due to Q fever [15-18]. Infection during pregnancy can result in a chronic infection where the bacteria are not cleared and persist in the placenta throughout the pregnancy. The bacteria may also remain after the pregnancy is completed, and could renew replication in subsequent pregnancies [19]. Delivery of babies from *C. burnetii* infected mothers can also create a risk for health care workers, as the generation of *C. burnetii*-containing aerosols is possible [20].

Diagnostic strategies

Diagnosis of acute Q fever relies on a combination of PCR and serology. In the first 1-2 weeks after symptom onset, antibodies against *C. burnetii* will not be present, but *C. burnetii* DNA can be detected in blood and serum using PCR [21]. A positive PCR result will confirm the diagnosis, but negative PCR is inconclusive. For diagnosis by serology, serum should be collected during the acute phase of the disease and a convalescent sample taken 3-4 weeks later. *C. burnetii* exists in two distinct phases and phase-specific antibodies can be informative. Phase 1 *C. burnetii* is the virulent form, whereas Phase 2 *C. burnetii* emerges after long-term culture and has low virulence in animal infections [22]. For unknown reasons, antibodies against Phase 2 *C. burnetii* are the first to arise in human infections. A four-fold increase in titer of IgG antibodies against Phase 2 *C. burnetii* between acute and convalescent samples will confirm the diagnosis of acute Q fever [23]. The indirect fluorescent antibody test (IFA) is used to measure antibody titers. A negative titer on the acute sample does not rule out acute Q fever as the sample may have been taken prior to the appearance of antibodies. IgG antibody titers against Phase 1 *C. burnetii* are typically lower than anti-Phase 2 IgG titers in acute Q fever [24].

Diagnosis of chronic Q fever can be made by the detection of *C. burnetii* in blood or tissue by PCR in the absence of an acute infection. However, many patients are PCR negative and serology is critical for most diagnoses. In chronic Q fever, Phase 1 antibody titers will become elevated and an IgG titer ≥1:1024 against Phase 1 *C. burnetii* is evidence of chronic Q fever. High Phase 1 titer along with the presence of definite endocarditis according to the modified Duke criteria, or an identifiable infection at another location, is considered confirmation of chronic Q fever [23,25]. It has been suggested that high Phase 1 titers in the absence of a confirmed location of infection, but with other clinical signs should be considered probable chronic Q fever [25].

Current treatments

Treatment with antimicrobial agents is recommended for both acute and chronic Q fever [23]. For acute Q fever, a variety of treatments have been used, but doxycycline is considered the reference treatment. Doxycycline has been shown to result in a mean time to defervescence of 2-3 days after the start of treatment [26,27], whereas untreated patients resolve the fever after a mean of 12.5 days [9]. The β-lactams have very little effect on *C. burnetii* [9,26], but some success has been reported with macrolides, co-trimoxazole, quinolones, and rifampin (see below), but none of these are as effective as doxycycline. Recent guidelines for treatment and management of Q fever from the US Centers for Disease Control and Q fever working group recommend a primary treatment for acute Q fever in adults of 100 mg doxycycline twice a day for two weeks [23].

Treatment of chronic Q fever has historically been much more difficult. Doxycycline has been the most effective, but relapses after extended treatment were common in the 1980's and 1990's [28]. Combinations of doxycycline and other classes of antibiotics have been tried with a variety of results, but even after extended treatments (3 years) the reappearance of *C. burnetii* and increasing antibody titers were observed [29]. The possibility was considered that relapses were so common because *C. burnetii* replicates in host cell phagolysomoes that have pH of around 4.5. The low pH in the intracellular compartments could reduce the efficacy of the drugs and prevent bactericidal activity [30,31]. It was demonstrated using *in vitro* experiments that the combination of doxycycline and chloroquine had much more bactericidal activity than doxycycline alone [32]. Chloroquine is a lysosomotropic agent that increases the pH of the phagolysome. These findings led to the combination of hydroxychloroquine and doxycycline as a primary treatment for chronic Q fever [33]. The hydroxyl derivative of chloroquine will also raise the pH of lysosomal compartments and allow doxycycline to have bactericidal activity against *C. burnetii*. The combination of doxycycline and hydroxychloroquine has been shown to be effective at reducing poor outcomes of Q fever endocarditis patients [28,33].

Current recommendations for treatment of chronic Q fever are 100 mg doxycycline twice per day combined with hydroxychloroquine three times per day at 200 mg per dose for at least 18 months [23,33]. Two daily 100 mg doses of doxycycline have been shown to result in serum concentrations of 2-5 mg/L [34,35]. There is evidence that doses resulting in serum concentrations higher than 5 mg/L can lead to faster decline in anti-*C. burnetii* antibodies [36], but controlled studies evaluating doxycycline dosage have not been reported.

The usage of doxycycline plus hydroxychloroquine has reduced the time of treatment in chronic Q fever patients to 18 months for those with native heart valves and 24 months for patients with prosthetic valves. Although still a very long treatment period for a bacterial disease, the use of hydroxychloroquine has reduced treatment times that were previously as long as five years [29]. Long-term treatment with doxycycline and hydroxychloroquine are not without potential complications. Both of these drugs can cause photosensitivity [37], and long term use of hydroxychloroquine can lead to retinopathy [38]. A baseline ophthalmic evaluation is recommended for patients beginning long term hydroxychloroquine with follow-up examinations every six months while on therapy [23,38]. Allergic reactions to both drugs have been reported [28].

Although the incidence of Q fever increases with age and most cases are in adults, children can be infected with *C. burnetii* and have symptomatic Q fever [39]. Treatment for children with acute Q fever is recommended and current treatment guidelines for children over 8 years old call for a two week treatment of doxycycline at a dose of 2.2 mg/kg twice per day (not to exceed 100 mg per dose) [23]. For children under 8 years old, treatment with doxycycline raises additional questions because of the perceived risk of dental staining. Therefore for children under 8, a mixture of trimethoprim and sulfamethoxazole at a 1:5 ratio (co-trimoxazole) is recommended by the CDC [23]. A dose range for the trimethoprim component of 4-20 mg/kg (800 mg maximum per dose) is recommended.

Pregnancy

Pregnancy represents a challenge for Q fever treatment. *C. burnetii* infection of ruminants can result in premature birth, weak offspring, or stillbirth [40]. In humans, Q fever during pregnancy has been associated with spontaneous abortions, intrauterine growth retardation, and intrauterine fetal death [15-18]. Many women develop a serologic profile of chronic Q fever during pregnancy, and viable bacteria can be isolated from patients at the end of pregnancy, even after treatment [19]. However, studies from Germany and the Netherlands have suggested that Q fever during pregnancy does not create increased risk for fetal complications, and emphasize the need to balance the risk of treatment with the potential for poor fetal outcome [41,42]. The current recommendation from the CDC is to treat women with acute Q fever with co-trimoxazole up until the final six weeks of pregnancy, and to give doxycycline and hydroxychloroquine postpartum for 12 months to women that develop a serologic profile of chronic Q fever (Phase 1 IgG titer ≥1:1024) [23]. Doxycycline is contraindicated during pregnancy because of risk to the fetus. The US Food and Drug Administration places doxycycline in pregnancy category D, indicating there is positive evidence of risk to the fetus if doxycycline is taken during pregnancy. Co-trimoxazole has a category C rating, indicating that adverse effects have been observed in animal studies, but adequate studies in humans have not been reported.

Need for alternative therapies

Although doxycycline is effective for Q fever treatment, there are reasons to seek alternative therapies. *Coxiella burnetii* is considered a category B agent of bioterrorism by the CDC. It is possible to produce large quantities of organisms and these would be quite stable in storage and transport. The organisms are highly infectious and transmitted by inhalation.

Dispersal of concentrated aerosols over a large area would be expected to infect large numbers of people [43]. For these reasons, the US biological weapons program tested *C. burnetii* on human subjects in the 1950's and 1960's as part of "Project Whitecoat" [6,44]. In these studies, *C. burnetii* was found to be able to infect humans at a very low dose of less than 10 organisms, and aerosol dispersal was effective for human infection [6]. Although use of *C. burnetii* as a weapon would not be expected to cause widespread fatalities, it is thought that significant impairment of physical activity could be achieved, along with associated alarm in the population and significant long-term morbidity for a subset of victims [43]. Recent advances in microbiological techniques make it conceivable that *C. burnetii* could be modified for greater virulence or made to have antibiotic resistance [45].

In addition to the potential of engineered antibiotic resistance in *C. burnetii*, natural resistance to doxycycline is also a concern. Although resistance to doxycycline does not appear to be a common occurrence, doxycycline resistant isolates do exist. In 2005, 3 isolates with doxycycline minimum inhibitory concentrations (MICs) of greater than 8 μg/ml were reported [46]. This included one from an endocarditis patient that died during treatment with doxycycline, one isolate from a goat, and a third from a human acute Q fever case. The genome sequence from the resistant isolate obtained from the endocarditis patient is available [47], but no potential mechanisms of resistance have been described. The extent of doxycycline resistance is not known. It can be difficult to obtain human isolates and testing for doxycycline resistance is not commonly performed. However, advent of newer assays based on real-time PCR have allowed more testing of new isolates in recent years [48].

Pregnancy also presents a need for more alternative therapies for Q fever. The reference treatment of doxycycline is not acceptable for use in pregnancy due to risk to the fetus, and negative effects of co-trimoxazole have not been ruled out [23,49]. Not all studies of Q fever during pregnancy have found a large impact on fetal health, suggesting that strain and host factors may influence whether acute Q fever can impair fetal growth and development [41,42,50]. This raises questions about the universal need for treatment during pregnancy, and the risk/benefit calculation that must be made. Safer alternative therapies would be beneficial.

The current protocol of using doxycycline plus hydroxychloroquine to treat chronic Q fever represents a significant improvement over previous therapies. Examination of Q fever endocarditis outcomes in France from 1983 to 2006 shows that use of the combination therapy has coincided with reduced mortality and a reduced need for heart valve replacement [28]. However, relapses can still occur and the treatment recommendation of antimicrobial therapy for at least 18 months is one of the longest treatment regimens used for a bacterial infection. Alternative or adjuvant therapies would be beneficial for Q fever endocarditis with the goal of shortening the duration of therapy and reducing relapse events.

Alternatives for Q fever treatment

A number of different antibiotic therapies have been investigated for Q fever (Table 1). Some have been given intentionally for Q fever treatment, or given as an empiric treatment

before a diagnosis was made, or investigated for efficacy against *C. burnetii* in vitro. Randomized, controlled studies evaluating different treatments have not been reported for acute or chronic Q fever. Current treatment recommendations are based on combinations of case studies, retrospective cohort studies, and *in vitro* data. Many of the *in vitro* studies were performed by counting the number of visually infected cells under the microscope [51,52], but more recent studies have evaluated growth using real-time PCR [48]. The quinolones have been used with some success [51]. In vitro, gatifloxacin has been shown to be highly effective, and moxifloxacin, gemifloxacin, levofloxacin, pefloxacin, and ofloxacin also have some inhibition of *C. burnetii* growth [52-56]. Ciprofloxacin has some antimicrobial effect, but not as strong as the other quinolones [52,54]. A more recent study using real-time PCR to get a better quantitative assessment of *C. burnetii* growth found very little effect for ciprofloxacin [48]. The β-lactam antibiotics, including penicillin, amoxicillin, and cephalosporins, appear to have little effect on the growth of *C. burnetii* [9,26,48,57].

In vivo use of quinolones has primarily been associated with Q fever endocarditis. Combinations of quinolones and doxycycline were mainly used before 1999 [28]. The drugs ofloxacin and pefloxacin showed some benefit for chronic Q fever when used in conjunction with doxycycline, but success was limited and required at least three years of treatment [29]. In 1999 a study was published that compared the combination of doxycycline and hydroxychloroquine to the combination of doxycycline and ofloxacin [33]. It was thought that this combination would be more effective due to the ability of hydroxychloroquine to raise the pH of the phagolysosomes where *C. burnetii* replicates and allow more effective doxycycline activity [32]. Indeed, the doxycycline/hydroxychloroquine combination allowed a reduced duration of treatment and had fewer relapses [33]. Although before 1999 doxycycline in combination with quinolones was considered a reference treatment, this combination has not been widely used since that time [28].

Rifampin has been used with some success against *C. burnetii*. *In vitro* studies have found it to be very effective [48,57]. Rifampin is usually used in combination with other drugs because the risk of developing drug resistance is high. Before the common usage of hydroxychloroquine, a combination of rifampin plus doxycycline was sometimes used for the treatment of Q fever endocarditis [28,29]. Rifampin has also been used to treat Q fever during pregnancy [58,59]. A combination of rifampin and erythromycin has resulted in a successful delivery and recovery from a human placental infection [58]. Rifampin is placed in pregnancy category C by the US FDA.

Macrolides can have an effect on *C. burnetii* growth but the results of their use has been somewhat mixed. Some *in vitro* studies have found very little inhibition of *C. burnetii* growth in the presence of erythromycin or azithromycin [46,52]. However, in 13 *C. burnetii* isolates that were resistant to erythromycin in vitro, growth inhibition was observed in the presence of telithromycin [46]. Other studies have found inhibition of *C. burnetii* growth by clarithromycin *in vitro*, although it was generally not as effective as doxycycline or some quinolones [53,54,60]. Inhibition of growth at a low MIC using azithromycin *in vitro* has also been reported [60].

In spite of these mixed results using macrolides *in vitro*, studies of Q fever patients treated with macrolides suggest that these drugs can have some benefit. Acute Q fever pneumonia patients given treatment with macrolides have been reported. A study of 11 acute Q fever patients from Spain that were given erythromycin found that all 11 had rapid improvement and were afebrile by the fourth day of treatment [61]. Only 2 of 8 patients on other antibiotics improved during this time frame. Patients not responding to other antibiotics promptly improved after beginning erythromycin treatment [61]. A second study from Spain found that 25 acute Q fever pneumonia patients improved rapidly after treatment with erythromycin, although not as quickly as 23 patients receiving doxycycline treatment [27]. A larger study of 113 Greek acute Q fever patients found that erythromycin, clarithromycin, and roxithromycin were all effective at reducing the duration of fever [26]. Although not as effective as doxycycline, the macrolides were much more effective than β-lactams. Macrolides are an attractive potential alternative therapy for Q fever. Some macrolides are in pregnancy category B, and could be a safer alternative for treatment in some cases. However, it is clear that macrolides are not as effective as doxycycline, and many strains of *C. burnetii* appear to be resistant to erythromycin *in vitro* [46]. This suggests that macrolides should not be a primary choice for Q fever treatment. However, newer macrolides such as clarithromycin and azithromycin could be explored further and represent a possible alternative therapy, especially during pregnancy.

A common contemporary alternative to doxycycline is co-trimoxazole. This drug is a mixture of trimethoprim and sulfamethaxzole at a 1 to 5 ratio. It functions as a folic acid antagonist and blocks DNA synthesis to reduce bacterial replication. Co-trimoxazole is the recommended treatment for pregnant women as it has activity against *C. burnetii*, and when supplemented with folic acid, has a better safety profile in pregnancy than doxycycline [23]. The use of co-trimoxazole for Q fever during pregnancy is based primarily on a study published in 2007 that found benefit with co-trimoxazole therapy for at least 5 weeks during pregnancy [49]. Q fever patients that were put on co-trimoxazole long-term during pregnancy developed fewer obstetric problems than patients that did not receive this treatment. Pregnant patients treated with co-trimoxazole were also less likely to develop a chronic Q fever serologic profile [49]. Although other studies have found that the benefit of long term treatment during pregnancy may not be as large as that found in the 2007 study [41], and questions about the risk of using co-trimoxazole during pregnancy remain, current recommendations are for long-term co-trimoxazole treatment for pregnant Q fever patients [23,49]. Co-trimoxazole has been used sporadically for chronic Q fever, with variable results. Successful clearance of the bacteria has been reported, but also failures. It is recommended that pregnant women with a chronic serologic profile be placed on doxycycline plus hydroxychloroquine after delivery [23,49].

Expert commentary and five-year view

Doxycycline remains the first choice of treatment for acute Q fever, and doxycycline plus hydroxychloroquine is the first choice for chronic Q fever. No alternatives have the efficacy of doxycycline, and it has a long track record in successful treatment of *C. burnetii* infections [28]. A problem with the use of doxycycline for acute Q fever is the diagnostic delay. Q fever is rarely suspected in acute febrile illnesses, although studies have shown that

it may be a fairly common cause of febrile disease [62,63]. If diagnostics are ordered, it usually consists of a serologic assay which provides a single titer. The prevalence of Q fever antibodies in the general population (3.1% in the US) makes it impossible to distinguish between a current infection and past infection based on one titer result [62]. In addition, titers may not be present until 7-10 days after symptom onset. For these reasons, a confirmed diagnosis usually depends on comparison between acute and convalescent serum samples, with a four-fold rise in IgG against Phase 2 *C. burnetii* confirming a diagnosis. This is of course not useful for a treatment decision, as the convalescent sample will be taken in most cases after symptoms have resolved and treatment is not recommended for asymptomatic patients. Thus, the diagnostic delay is an obstacle to timely treatment with doxycycline. The use of PCR can provide a much more timely diagnosis. *C. burnetii* DNA can be detected both in whole blood and serum in the time before IgG antibodies are present in the blood. PCR can therefore provide a positive diagnosis while patients are symptomatic and guide treatment decisions. In the recent Q fever epidemic in the Netherlands, PCR was considered an essential aspect of the diagnostic protocol [21]. Increased use of PCR for Q fever diagnostics could make administration of doxycycline for symptomatic patients more realistic.

For many years, chronic Q fever was a very difficult disease to treat, and there were many examples of relapse and treatment failures [10,28]. For these reasons various alternative therapies have been explored. The advent of the combination of doxycycline plus hydroxychloroquine as a treatment for Q fever endocarditis in the 1990's has been very beneficial to patients as this has reduced relapses and the need for valve replacements [33]. However, this treatment still requires 18 months of antibiotic therapy, and some patients cannot tolerate doxycycline. Hydroxychloroquine can also cause ocular toxicity and may not be tolerated due to an impaired visual field. Although not common, isolates resistant to doxycycline have been reported [46,47]. It is therefore worthwhile to search for alternative treatments for Q fever endocarditis. Quinolones, rifampin, co-trimoxazole, and telithromycin have all been used on Q fever endocarditis patients [28], but these strategies have all been replaced by the doxycycline/hydroxychloroquine protocol [33]. A suitable alternative will need to have bactericidal activity and be tolerated for fairly long-term use.

An open question for Q fever treatment is the value of treating acute fever in preventing the later development of Q fever endocarditis. Rapid diagnosis and treatment of acute Q fever may not only be important for the relief of symptoms of the acute disease but could also have a role in preventing evolution of chronic disease. There could also be a benefit for high risk patients in longer term treatment after the normal two-week course of doxycycline. A recent report has evaluated the benefit of screening acute Q fever patients for valvulopathies and treating all patients with significant valvulopathies with doxycycline/ hydroxychloroquine for 12 months [64]. This study found 31/72 acute Q fever patients had a significant valvulopathy. Eighteen of the 31 patients with acute Q fever and valvulopathy received doxycycline/hydroxychloroquine for 1 year and did not develop endocarditis during the follow-up period (1-4 years). The 13 patients that had acute Q fever and valvulopathy but did not receive prophylactic antibiotic treatment all developed endocarditis within one year. This study emphasizes the risk of endocarditis for acute Q fever patients

with valvulopathy [14,64], and shows that it is possible to prevent endocarditis with doxycycline/hydroxychloroquine therapy. However, in other contexts, the benefit of screening every acute fever patient for valvulopathy may not be as significant [65]. Other patient groups may have lower incidence of valvulopathy and certain strains of *C. burnetii* may have more or less propensity for endocarditis [14].

The need for long-term treatment for Q fever during pregnancy is based on a limited number of patients. The rationale comes primarily from a study of 53 patients in France that had high rates of obstetric complications without therapy, but a very significant reduction with long-term (5 weeks or more) co-trimoxazole treatment [49]. Other studies have also found negative implications of Q fever during pregnancy [15-18]. However, a recent study from Germany of 11 women with Q fever during pregnancy found none with obstetric complications related to the infection, even though only 3 received long-term co-trimoxazole [41]. In the Netherlands, a serosurvey of pregnant women in a region that had high incidence of Q fever during 2007-2008 found 37 women with both IgM and IgG antibodies against Phase 2 *C. burnetii*, suggesting a recent infection [42]. The incidence of fetal complications was the same in this seropositive group as that found in seronegative mothers from the same region, suggesting that *C. burnetii* infection in these cases did not lead to adverse pregnancy outcomes [42]. Reasons for differences in the incidence of adverse pregnancy outcomes related to Q fever are not currently known. One possibility is that *C. burnetii* strain differences can impact the effect on pregnancy [50]. Because long-term treatment with antibiotics poses some risk to the fetus, it will be important to better understand the risks of *C. burnetii* infection for the fetus so that risk/benefit calculations can be weighed more effectively. Evaluation of genotype-specific impact on pregnancy could shed light on this matter.

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References

1. McQuiston JH, Childs JE. Q fever in humans and animals in the United States. Vector Borne & Zoonotic Diseases. 2002; 2(3):179–191. [PubMed: 12737547]
2. Hatchette T, Campbell N, Hudson R, Raoult D, Marrie TJ. Natural history of Q fever in goats. Vector Borne Zoonotic Dis. 2003; 3(1):11–15. [PubMed: 12804376]
3. van der Hoek W, Dijkstra F, Schimmer B, et al. Q fever in the Netherlands: an update on the epidemiology and control measures. Euro surveillance : bulletin europeen sur les maladies transmissibles = European communicable disease bulletin. 2010; 15(12)
4. Graham JG, MacDonald LJ, Hussain SK, Sharma UM, Kurten RC, Voth DE. Virulent Coxiella burnetii pathotypes productively infect primary human alveolar macrophages. Cellular microbiology. 2013; 15(6):1012–1025. [PubMed: 23279051]
5. Voth DE, Heinzen RA. Lounging in a lysosome: the intracellular lifestyle of Coxiella burnetii. Cellular microbiology. 2007; 9(4):829–840. [PubMed: 17381428]
6. Benenson AS, Tigertt WD. Studies on Q fever in man. Transactions of the Association of American Physicians. 1956; 69:98–104. [PubMed: 13380951] [•The very low infectious dose of *C. burnetii* for humans via inhalation of aerosols is defined in this study.]

7. Dupuis G, Petite J, Peter O, Vouilloz M. An important outbreak of human Q fever in a Swiss Alpine valley. Int J Epidemiol. 1987; 16(2):282–287. [PubMed: 3301708]
8. Maurin M, Raoult D. Q fever. Clinical Microbiology Reviews. 1999; 12(4):518–553. [PubMed: 10515901]
9. Clark WH, Lennette EH. Treatment of Q fever with antibiotics. Ann N Y Acad Sci. 1952; 55(6): 1004–1018. [PubMed: 13139179]
10. Marrie, TJ. Acute Q fever. In: Marrie, TJ., editor. Q Fever vol. 1. The disease. CRC Press; Boca Raton, FL: 1990. p. 125-160.
11. Botelho-Nevers E, Fournier PE, Richet H, et al. Coxiella burnetii infection of aortic aneurysms or vascular grafts: report of 30 new cases and evaluation of outcome. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology. 2007; 26(9):635–640.
12. Fournier PE, Casalta JP, Piquet P, Tournigand P, Branchereau A, Raoult D. Coxiella burnetii infection of aneurysms or vascular grafts: report of seven cases and review. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 1998; 26(1):116–121. [PubMed: 9455519]
13. Fenollar F, Fournier PE, Carrieri MP, Habib G, Messana T, Raoult D. Risks factors and prevention of Q fever endocarditis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2001; 33(3):312–316. [PubMed: 11438895]
14. Kampschreur LM, Dekker S, Hagenaars JC, et al. Identification of risk factors for chronic Q fever, the Netherlands. Emerg Infect Dis. 2012; 18(4):563–570. [PubMed: 22469535]
15. Ellis ME, Smith CC, Moffat MA. Chronic or fatal Q-fever infection: a review of 16 patients seen in North-East Scotland (1967-80). The Quarterly journal of medicine. 1983; 52(205):54–66. [PubMed: 6878620]
16. Jover-Diaz F, Robert-Gates J, Andreu-Gimenez L, Merino-Sanchez J. Q fever during pregnancy: an emerging cause of prematurity and abortion. Infectious diseases in obstetrics and gynecology. 2001; 9(1):47–49. [PubMed: 11368259]
17. Langley JM, Marrie TJ, Leblanc JC, Almudevar A, Resch L, Raoult D. Coxiella burnetii seropositivity in parturient women is associated with adverse pregnancy outcomes. American journal of obstetrics and gynecology. 2003; 189(1):228–232. [PubMed: 12861167]
18. Stein A, Raoult D. Q fever during pregnancy: a public health problem in southern France. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 1998; 27(3):592–596. [PubMed: 9770161]
19. Raoult D, Fenollar F, Stein A. Q fever during pregnancy: diagnosis, treatment, and follow-up. Arch Intern Med. 2002; 162(6):701–704. [PubMed: 11911725]
20. Raoult D, Stein A. Q fever during pregnancy--a risk for women, fetuses, and obstetricians. The New England journal of medicine. 1994; 330(5):371.
21. Schneeberger PM, Hermans MH, van Hannen EJ, Schellekens JJ, Leenders AC, Wever PC. Real-time PCR with serum samples is indispensable for early diagnosis of acute Q fever. Clinical and vaccine immunology : CVI. 2010; 17(2):286–290. [PubMed: 20032219] [••This study defines the importance of using PCR for timely diagnosis of acute Q fever.]
22. Stoker MG, Fiset P. Phase variation of the Nine Mile and other strains of Rickettsia burneti. Canadian journal of microbiology. 1956; 2(3):310–321. [PubMed: 13316625]
23. CDC. Diagnosis and Management of Q Fever — United States, 2013: Recommendations from CDC and the Q Fever Working Group. MMWR. Morbidity and mortality weekly report. 2013; 62(RR03):1–23. [PubMed: 23302815] [••Comprehensive recommendations for Q fever diagnosis, treatment, and prevention.]
24. Teunis PF, Schimmer B, Notermans DW, et al. Time-course of antibody responses against Coxiella burnetii following acute Q fever. Epidemiol Infect. 2013; 141(1):62–73. [PubMed: 22475210]
25. Wegdam-Blans MC, Kampschreur LM, Delsing CE, et al. Chronic Q fever: review of the literature and a proposal of new diagnostic criteria. The Journal of infection. 2012; 64(3):247–259. [PubMed: 22226692] [••Proposed diagnostic criteria for chronic Q fever based on the experience of the Dutch Q fever epidemic.]

26. Gikas A, Kofteridis DP, Manios A, Pediaditis J, Tselentis Y. Newer macrolides as empiric treatment for acute Q fever infection. Antimicrobial agents and chemotherapy. 2001; 45(12):3644–3646. [PubMed: 11709360] [•Evaluation of macrolide treatment for acute Q fever patients, showing that newer macrolides are not as effective as doxycycline, but that they offer benefit compared to β-lactams.]
27. Sobradillo V, Zalacain R, Capelastegui A, Uresandi F, Corral J. Antibiotic treatment in pneumonia due to Q fever. Thorax. 1992; 47(4):276–278. [PubMed: 1585291]
28. Million M, Thuny F, Richet H, Raoult D. Long-term outcome of Q fever endocarditis: a 26-year personal survey. The Lancet infectious diseases. 2010; 10(8):527–535. [PubMed: 20637694] [••Description of 104 Q fever endocarditis patients with outcomes provided for multiple treatment regimens.]
29. Levy PY, Drancourt M, Etienne J, et al. Comparison of different antibiotic regimens for therapy of 32 cases of Q fever endocarditis. Antimicrobial agents and chemotherapy. 1991; 35(3):533–537. [PubMed: 2039204]
30. Lam C, Mathison GE. Effect of low intraphagolysosomal pH on antimicrobial activity of antibiotics against ingested staphylococci. Journal of medical microbiology. 1983; 16(3):309–316. [PubMed: 6876137]
31. Raoult D, Drancourt M, Vestris G. Bactericidal effect of doxycycline associated with lysosomotropic agents on Coxiella burnetii in P388D1 cells. Antimicrobial agents and chemotherapy. 1990; 34(8):1512–1514. [PubMed: 2221859]
32. Maurin M, Benoliel AM, Bongrand P, Raoult D. Phagolysosomal alkalinization and the bactericidal effect of antibiotics: the Coxiella burnetii paradigm. The Journal of infectious diseases. 1992; 166(5):1097–1102. [PubMed: 1402021] [•Demonstration that alkalinization of phagolysosomes with chloroquine improves the bactericidal activity of antibiotics.]
33. 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(2):167–173. [PubMed: 9927100] [••First study defining the benefit of doxycycline/hydroxychloroquine combination therapy for Q fever endocarditis.]
34. Beringer PM, Owens H, Nguyen A, Benitez D, Rao A, D'Argenio DZ. Pharmacokinetics of doxycycline in adults with cystic fibrosis. Antimicrobial agents and chemotherapy. 2012; 56(1): 70–74. [PubMed: 22024822]
35. Neuvonen PJ, Gothoni G, Hackman R, Bjorksten K. Interference of iron with the absorption of tetracyclines in man. British medical journal. 1970; 4(5734):532–534. [PubMed: 5483323]
36. Lecaillet A, Mallet MN, Raoult D, Rolain JM. Therapeutic impact of the correlation of doxycycline serum concentrations and the decline of phase I antibodies in Q fever endocarditis. The Journal of antimicrobial chemotherapy. 2009; 63(4):771–774. [PubMed: 19218274]
37. Drucker AM, Rosen CF. Drug-induced photosensitivity: culprit drugs, management and prevention. Drug safety : an international journal of medical toxicology and drug experience. 2011; 34(10):821–837.
38. Tehrani R, Ostrowski RA, Hariman R, Jay WM. Ocular toxicity of hydroxychloroquine. Seminars in ophthalmology. 2008; 23(3):201–209. [PubMed: 18432546]
39. Maltezou HC, Constantopoulou I, Kallergi C, et al. Q fever in children in Greece. Am J Trop Med Hyg. 2004; 70(5):540–544. [PubMed: 15155988]
40. Roest HJ, van Gelderen B, Dinkla A, et al. Q fever in pregnant goats: pathogenesis and excretion of Coxiella burnetii. PloS one. 2012; 7(11):e48949. [PubMed: 23152826]
41. Boden K, Brueckmann A, Wagner-Wiening C, et al. Maternofetal consequences of Coxiella burnetii infection in pregnancy: a case series of two outbreaks. BMC Infect Dis. 2012; 12:359. [PubMed: 23249469] [•An examination of pregnant women with Q fever that found no fetal complications associated with Q fever during pregnancy.]
42. van der Hoek W, Meekelenkamp JC, Leenders AC, Wijers N, Notermans DW, Hukkelhoven CW. Antibodies against Coxiella burnetii and pregnancy outcome during the 2007-2008 Q fever outbreaks in The Netherlands. BMC Infect Dis. 2011; 11:44. [PubMed: 21314933] [•Pregnant

women with antibodies against *C. burnetii* had similar pregnancy outcomes compared to women without *C. burnetii* antibodies.]

43. Madariaga MG, Rezai K, Trenholme GM, Weinstein RA. Q fever: a biological weapon in your backyard. The Lancet infectious diseases. 2003; 3(11):709–721. [PubMed: 14592601]
44. Pittman PR, Norris SL, Coonan KM, McKee KT Jr. An assessment of health status among medical research volunteers who served in the Project Whitecoat program at Fort Detrick, Maryland. Military medicine. 2005; 170(3):183–187. [PubMed: 15828690]
45. Omsland A, Beare PA, Hill J, et al. Isolation from animal tissue and genetic transformation of Coxiella burnetii are facilitated by an improved axenic growth medium. Appl Environ Microbiol. 2011; 77(11):3720–3725. [PubMed: 21478315] [••Demonstration of growth and transformation of *C. burnetii* in the absence of host cells.]
46. Rolain JM, Lambert F, Raoult D. Activity of telithromycin against thirteen new isolates of C. burnetii including three resistant to doxycycline. Ann N Y Acad Sci. 2005; 1063:252–256. [PubMed: 16481522]
47. Rouli L, Rolain JM, El Filali A, Robert C, Raoult D. Genome sequence of Coxiella burnetii 109, a doxycycline-resistant clinical isolate. J Bacteriol. 2012; 194(24):6939. [PubMed: 23209205]
48. Brennan RE, Samuel JE. Evaluation of Coxiella burnetii antibiotic susceptibilities by real-time PCR assay. J Clin Microbiol. 2003; 41(5):1869–1874. [PubMed: 12734219]
49. Carcopino X, Raoult D, Bretelle F, Boubli L, Stein A. Managing Q fever during pregnancy: the benefits of long-term cotrimoxazole therapy. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2007; 45(5):548–555. [PubMed: 17682987] [•This study found fetal complications associated with Q fever during pregnancy that could be alleviated by 5-week course of co-trimoxazole.]
50. Angelakis E, Million M, D'Amato F, et al. Q fever and pregnancy: disease, prevention, and strain specificity. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology. 2013; 32(3):361–368.
51. Yeaman MR, Mitscher LA, Baca OG. In vitro susceptibility of Coxiella burnetii to antibiotics, including several quinolones. Antimicrobial agents and chemotherapy. 1987; 31(7):1079–1084. [PubMed: 3662472]
52. Lever MS, Bewley KR, Dowsett B, Lloyd G. In vitro susceptibility of Coxiella burnetii to azithromycin, doxycycline, ciprofloxacin and a range of newer fluoroquinolones. International journal of antimicrobial agents. 2004; 24(2):194–196. [PubMed: 15288324]
53. Gikas A, Spyridaki I, Scoulica E, Psaroulaki A, Tselentis Y. In vitro susceptibility of Coxiella burnetii to linezolid in comparison with its susceptibilities to quinolones, doxycycline, and clarithromycin. Antimicrobial agents and chemotherapy. 2001; 45(11):3276–3278. [PubMed: 11600400]
54. Gikas A, Spyridaki I, Psaroulaki A, Kofterithis D, Tselentis Y. In vitro susceptibility of Coxiella burnetii to trovafloxacin in comparison with susceptibilities to pefloxacin, ciprofloxacin, ofloxacin, doxycycline, and clarithromycin. Antimicrobial agents and chemotherapy. 1998; 42(10):2747–2748. [PubMed: 9756789]
55. Raoult D, Yeaman MR, Baca OG. Susceptibility of Coxiella burnetii to pefloxacin and ofloxacin in ovo and in persistently infected L929 cells. Antimicrobial agents and chemotherapy. 1989; 33(5): 621–623. [PubMed: 2751278]
56. Rolain JM, Maurin M, Raoult D. Bacteriostatic and bactericidal activities of moxifloxacin against Coxiella burnetii. Antimicrobial agents and chemotherapy. 2001; 45(1):301–302. [PubMed: 11120982]
57. Raoult D, Torres H, Drancourt M. Shell-vial assay: evaluation of a new technique for determining antibiotic susceptibility, tested in 13 isolates of Coxiella burnetii. Antimicrobial agents and chemotherapy. 1991; 35(10):2070–2077. [PubMed: 1759829]
58. Bental T, Fejgin M, Keysary A, et al. Chronic Q fever of pregnancy presenting as Coxiella burnetii placentitis: successful outcome following therapy with erythromycin and rifampin. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 1995; 21(5):1318–1321. [PubMed: 8589167]

59. Hellmeyer L, Schmitz-Ziegler G, Slenczka W, Schmidt S. [Q Fever in pregnancy: a case report and review of the literature]. Zeitschrift fur Geburtshilfe und Neonatologie. 2002; 206(5):193–198. [PubMed: 12395293]

60. Keysary A, Itzhaki A, Rubinstein E, Oron C, Keren G. The in-vitro anti-rickettsial activity of macrolides. The Journal of antimicrobial chemotherapy. 1996; 38(4):727–731. [PubMed: 8937968]

61. Perez-del-Molino A, Aguado JM, Riancho JA, Sampedro I, Matorras P, Gonzalez-Macias J. Erythromycin and the treatment of Coxiella burnetii pneumonia. The Journal of antimicrobial chemotherapy. 1991; 28(3):455–459. [PubMed: 1960125]

62. Anderson AD, Kruszon-Moran D, Loftis AD, et al. Seroprevalence of Q fever in the United States, 2003-2004. Am J Trop Med Hyg. 2009; 81(4):691–694. [PubMed: 19815888]

63. Prabhu M, Nicholson WL, Roche AJ, et al. Q fever, spotted fever group, and typhus group rickettsioses among hospitalized febrile patients in northern Tanzania. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2011; 53(4):e8–15. [PubMed: 21810740]

64. Million M, Walter G, Thuny F, Habib G, Raoult D. Evolution From Acute Q Fever to Endocarditis Is Associated With Underlying Valvulopathy and Age and Can Be Prevented by Prolonged Antibiotic Treatment. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2013

65. Kampschreur LM, Oosterheert JJ, Hoepelman AI, et al. Prevalence of chronic Q fever in patients with a history of cardiac valve surgery in an area where Coxiella burnetii is epidemic. Clinical and vaccine immunology : CVI. 2012; 19(8):1165–1169. [PubMed: 22695158]

Key issues

- Coxiella burnetii infection can result in Q fever, a febrile illness that can include myalgia, fatigue, and severe headache.
- Q fever can present in an acute form, which is a disease that can resolve in less than 14 days, or a chronic form. The chronic form often presents as endocarditis or vascular infection and can be life threatening.
- Acute Q fever is treated with doxycycline and chronic Q fever with doxycycline plus hydroxychloroquine.
- Co-trimoxazole is an alternative antimicrobial that is recommended for children less than 8 years old and for pregnant women diagnosed with Q fever.
- Alternative antibiotics are needed due to the possibility of bioterrorism, doxycycline resistance, risk of current therapies to fetal health, and long course of current therapies.
- Quinolones, co-trimoxazole, rifampin, and some macrolides are possible alternative drug treatments for Q fever, but none perform as well as doxycycline.
- Some benefit may exist in aggressive screening and treatment for pregnant women and patients with valvulopathies, but more study is needed.

Table 1

Antimicrobials used for Q fever

Drug	*In vitro* effect on *C. burnetii*	Acute Q fever treatment	Chronic Q fever treatment	Antimicrobial effect	FDA Pregnancy category
Doxycycline	Low MIC[1]	Most effective treatment	Most effective in combination with hydroxychloroquine	Bactericidal above pH 5.5	D
Co-trimoxazole	Low MIC	Recommended for pregnant women and children <8 yrs	Mixed results	Bactericidal	C
Quinolones	Low MIC	Can be effective	Used with doxycycline prior to 1999, but relapses were common	Bactericidal above pH 5.5	C
Rifampin	Low MIC	Limited data	Used with doxycycline prior to 1999, but relapses were common	Bacteriostatic	C
Macrolides	Mixed results	Some examples of rapid defervescence	Limited data	Bacteriostatic	B or C

[1] minimal inhibitory concentration