CHRONIC Q FEVER Chronic Q fever almost always implies endocarditis and usually occurs in patients with previous valvular heart disease, immunosuppression, or chronic renal insufficiency. Fever is usually absent or low grade. Valvular vegetations are detected in only 12% of patients by transthoracic echocardiography, but the rate of detection is higher (21–50%) with transesophageal echocardiography. The vegetations in chronic Q fever endocarditis differ from those in bacterial endocarditis, manifesting as endothelium-covered nodules on the valves. A high index of suspicion is necessary for timely diagnosis. Patients with chronic Q fever are often ill for >1 year before the diagnosis is made. The disease should be suspected in all patients with culture-negative endocarditis. In addition, all patients with valvular heart disease and an unexplained purpuric eruption, renal insufficiency, stroke, and/or progressive heart failure should be tested for *C. burnetii* infection. Patients with chronic Q fever have hepatomegaly and/or splenomegaly, which—in combination with rheumatoid factor, elevated erythrocyte sedimentation rate, high C-reactive protein level, and/or increased γ-globulin concentrations (up to 60–70 g/L)—suggests this diagnosis. Other manifestations of chronic Q fever include infection of vascular prostheses, aneurysms, and bone as well as chronic sternal wound infection. Unusual manifestations include chronic thrombocytopenia, mixed cryoglobulinemia, and livedo reticularis.

Diagnosis Isolation of *C. burnetii* from buffy-coat blood samples or tissue specimens by a shell-vial technique is easy but requires a biosafety level 3 laboratory. PCR detects *C. burnetii* DNA in tissue specimens, including paraffin-embedded samples. Serology is the most commonly used diagnostic tool. Indirect immunofluorescence is sensitive and specific and is the method of choice. Rheumatoid factor should be adsorbed from the specimen before testing. With chronic infection, the titer to phase I antigen is usually much higher than that to phase II antigen (i.e., *C. burnetii* that has truncated lipopolysaccharide associated with gene deletions during laboratory passages), and the diagnosis should not be based on serology alone. Rather, the entire clinical setting must be taken into consideration. An anti–phase I IgG titer of ≥6400 would be considered a major criterion for the diagnosis of chronic Q fever, while a titer of ≥800 but ≤6400 would be a minor criterion. In acute Q fever, a fourfold rise in titer can be demonstrated between acute- and convalescent-phase serum samples.

Fluorodeoxyglucose positron emission tomography combined with CT (FDG-PET/CT) can be useful because it can detect not only valvular infection but also intravascular infection elsewhere as well as osteomyelitis.

TREATMENT Q FEVER

ANTIBIOTICS

Treatment of acute Q fever with doxycycline (100 mg twice daily for 14 days) is usually successful. Quinolones also are effective. When Q fever is diagnosed during pregnancy, treatment with trimethoprim-sulfamethoxazole (TMP-SMX) is recommended for the duration of the pregnancy. One study showed no intrauterine fetal deaths and substantial reduction of obstetric complications in a group of Q fever patients treated with TMP-SMX.

The treatment of chronic Q fever is difficult and requires careful follow-up. Addition of hydroxychloroquine (to alkalinize the phagolysosome) renders doxycycline bactericidal against *C. burnetii*, and this combination is currently the favored regimen. Treatment with doxycycline (100 mg bid) and hydroxychloroquine (200 mg tid; plasma concentration maintained at 0.8–1.2 μg/mL) for 18 months is superior to a regimen of doxycycline and ofloxacin. Among 21 patients who received doxycycline and hydroxychloroquine, 1 died of a surgical complication, 2 were still being treated at the end of the study, 1 was still being evaluated, and 17 were cured. The mean duration of treatment was 31 months. In the ofloxacin and doxycycline group of 14 patients, 1 had died, 1 was still being treated, 7 had relapsed, and 5 had been cured by the end of the study. Optimal management of Q fever endocarditis entails determining the MIC of doxycycline for the patient's isolate and measuring serum doxycycline levels. A serum level–to–doxycycline MIC ratio of ≥1 is associated with a rapid decline in phase I antibodies with the doxycycline-hydroxychloroquine regimen. Patients treated with this regimen must be advised about photosensitivity and retinal toxicity risks. The doxycycline-hydroxychloroquine regimen was successful in one patient with HIV infection and Q fever endocarditis. The Jarisch-Herxheimer reaction occasionally complicates the treatment of chronic Q fever. Treatment of *C. burnetii*–infected aortic aneurysms is the same as that for Q fever endocarditis. Surgical intervention is often required.

If doxycycline-hydroxychloroquine cannot be used, the regimen chosen should include at least two antibiotics active against *C. burnetii*. Rifampin (300 mg once daily) combined with doxycycline (100 mg twice daily) or ciprofloxacin (750 mg twice daily) has been used successfully. The management of patients with Q fever endocarditis is complex and should preferably be undertaken by individuals with experience in managing this illness. Monitoring of antibody titers on a quarterly basis is an essential part of the management of these patients. Thus the laboratory should be contacted and asked to save all serum samples from such patients so that the current sample can be run with the previous one. There is incomplete agreement on the antibody titer at which therapy can be stopped. However, it is reasonable to discontinue treatment if IgG antibody levels have decreased by fourfold at 1 year, if IgM antibody to phase II has disappeared, and if the patient is clinically stable.

Patients with acute Q fever and lesions of native heart valves (e.g., bicuspid aortic valve), prosthetic valves, or prosthetic intravascular material should undergo serologic monitoring every 4 months for 2 years. If the phase I IgG titer is >800, further investigation is warranted. Some authorities recommend that patients with valvulopathy and acute Q fever receive doxycycline and hydroxychloroquine to prevent chronic Q fever. For women who exhibit a serologic profile of chronic Q fever after childbirth, hydroxychloroquine and doxycycline should be given for 1 year.

BIOLOGIC MODIFYING AGENTS

Interferon γ was successful in the treatment of a 3-year-old boy with prolonged fever, abdominal pain, and thrombocytopenia due to *C. burnetii* that had not been eradicated with conventional antibiotic therapy. Many patients with granulomatous hepatitis due to Q fever have a prolonged febrile illness that is unresponsive to antibiotics. For these individuals, treatment with prednisone (0.5 mg/kg) has resulted in defervescence within 2–15 days. After defervescence, the glucocorticoid dose is tapered over the next month.

Prevention A whole-cell vaccine (Q-Vax) licensed in Australia effectively prevents Q fever in abattoir workers. Before administration of the vaccine, skin testing with intradermal diluted *C. burnetii* vaccine is performed, serologic testing is undertaken, and a history of possible Q fever is sought. Vaccine is given only to patients with no history of Q fever and negative results in serologic and skin testing.

Good animal-husbandry practices are important in preventing widespread contamination of the environment by *C. burnetii*. These practices include isolating aborting animals for up to 14 days, raising feed bunks to prevent contamination of feed by excreta, destroying aborted materials (by burning and burying fetal membranes and stillborn animals), and wearing masks and gloves when handling aborted materials. Vaccination of sheep and goats and a culling program were effective in the Netherlands outbreak. Only seronegative pregnant animals should be used in research settings, and only seronegative animals should be permitted in petting zoos.

During an outbreak of Q fever and for 4 weeks after it ceases, blood donations should not be accepted from individuals who live in the affected area.

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