TREATMENT HUMAN GRANULOCYTOTROPIC ANAPLASMOSIS

No prospective studies of therapy for HGA have been conducted. However, doxycycline (100 mg PO twice daily) is effective. Rifampin therapy is associated with improvement of HGA in pregnant women and children. Most treated patients defervesce within 24–48 h.

Prevention HGA prevention requires tick avoidance. Transmission can be documented as few as 4 h after a tick bite.

Q FEVER

The agent of Q fever is *Coxiella burnetii*, a small intracellular prokaryote that only recently was grown in cell-free medium. *C. burnetii*, a pleomorphic coccobacillus with a gram-negative cell wall, survives in harsh environments; it escapes intracellular killing in macrophages by inhibiting the final step in phagosome maturation (cathepsin fusion) and has adapted to the acidic phagolysosome by producing superoxide dismutase. Infection with *C. burnetii* induces a range of immunomodulatory responses, from immunosuppression in chronic Q fever to the production of autoantibodies, particularly those to smooth muscle and cardiac muscle.

Q fever encompasses two broad clinical syndromes: acute and chronic infection. The host's immune response (rather than the particular strain) most likely determines whether chronic Q fever develops. *C. burnetii* survives in monocytes from patients with chronic Q fever but not in monocytes from patients with acute Q fever or from uninfected subjects. Impairment of the bactericidal activity of the *C. burnetii*–infected monocyte is associated with overproduction of interleukin 10. The CD4+/CD8+ ratio is decreased in Q fever endocarditis. Very few organisms and a strong cellular response are observed in patients with acute Q fever, while many organisms and a moderate cellular response occur in chronic Q fever. Immune control of *C. burnetii* is T cell–dependent, but 80–90% of bone marrow aspirates obtained years after recovery from Q fever contain *C. burnetii* DNA. *C. burnetii*'s ready multiplication within trophoblasts accounts for the high concentrations it can reach in the placenta.

Epidemiology Q fever is a zoonosis. The primary sources of human infection are infected cattle, sheep, and goats. However, cats, rabbits, pigeons, and dogs also serve as sources for transmission of *C. burnetii* to humans. The wildlife reservoir is extensive and includes ticks, coyotes, gray foxes, skunks, raccoons, rabbits, deer, mice, bears, birds, and opossums. In female animals *C. burnetii* localizes to the uterus and mammary glands. Infection is reactivated during pregnancy and after radiotherapy in mouse models. High concentrations of *C. burnetii* are found in the placenta. At the time of parturition, the bacteria are released into the air, and infection follows inhalation of aerosolized organisms by a susceptible host. Windstorms can generate *C. burnetii* aerosols months after soil contamination during parturition. Individuals up to 18 km from the source have been infected. Because it is easily dispersed as an aerosol, *C. burnetii* is a potential agent of bioterrorism (Chap. 261e), with a high infectivity rate and pneumonia as the major manifestation.

Determining the source of an outbreak of Q fever can be challenging. An outbreak of Q fever at a horse-boarding ranch in Colorado in 2005 was due to spread of infection from two herds of goats that had been acquired by the owners. PCR testing confirmed the presence of *C. burnetii* in the soil and among the goats. Of 138 persons who lived within 1 mile of the ranch and who were also tested, 11 (8%) had evidence of *C. burnetii* infection, and 8 of these 11 individuals had no direct contact with the ranch.

Persons at risk for Q fever include abattoir workers, veterinarians, farmers, and other individuals who have contact with infected animals (particularly newborn animals) or products of conception. The organism is shed in milk for weeks to months after parturition. The ingestion of contaminated milk in some geographic areas probably represents a major route of transmission to humans. A recent outbreak of Q fever associated with ingestion of raw milk confirms the oral route of transmission. In rare instances, person-to-person transmission follows labor and childbirth in an infected woman, autopsy of an infected individual, or blood transfusion. Some evidence suggests that *C. burnetii* can be sexually transmitted among humans. Crushing an infected tick between the fingers has resulted in Q fever; the implication is that percutaneous transmission can occur.

Infections due to *C. burnetii* occur in most geographic locations except New Zealand and Antarctica. Thus Q fever can be associated with travel. The number of reported cases of Q fever in the United States ranges from 28 to 54 per year. More than 70% of these cases occur in males, and April, May, and June are the most common months for acquisition. Q fever continues to be common in Australia, with 30 cases per 1 million population per year. Cases among abattoir workers in Australia declined dramatically as a result of a vaccination program. An outbreak of Q fever began in the Netherlands in 2007, and by 2010 more than 4000 cases had been reported. Pneumonia was a common manifestation in this outbreak. The outbreak was due to a combination of high-density goat farming in areas abutting large urban populations and environmental factors. Farms where spread did not occur had high vegetation densities and lower groundwater concentrations.

The primary manifestations of acute Q fever differ geographically (e.g., pneumonia in Nova Scotia and granulomatous hepatitis in Marseille). These differences could reflect the route of infection (i.e., ingestion of contaminated milk for hepatitis and inhalation of contaminated aerosols for pneumonia) or strain differences. In the Netherlands outbreak, sequelae of infection in pregnant women were rare; this was not the case among pregnant women elsewhere.

Young age seems to be protective against disease caused by *C. burnetii*. In a large outbreak in Switzerland, symptomatic infection occurred five times more often among persons >15 years of age than among younger individuals. In many outbreaks, men are affected more commonly than women; the proposed explanation is that female hormones are partially protective.

Clinical Manifestations • ***ACUTE Q FEVER*** The symptoms of acute Q fever are nonspecific; common among them are fever, extreme fatigue, photophobia, and severe headache that is frequently retro-orbital. Other symptoms include chills, sweats, nausea, vomiting, and diarrhea, each occurring in 5–20% of cases. Cough develops in about half of patients with Q fever pneumonia. Neurologic manifestations of acute Q fever are uncommon; however, in one outbreak in the United Kingdom, 23% of 102 patients had neurologic signs and symptoms as the major manifestation. A nonspecific rash may be evident in 4–18% of patients. The WBC count is usually normal. Thrombocytopenia occurs in ~25% of patients, and reactive thrombocytosis (with platelet counts exceeding 10^6/μL) frequently develops during recovery. Chest radiography can show opacities similar to those seen in pneumonia caused by other pathogens, but multiple rounded opacities in patients in endemic areas suggest a diagnosis of Q fever pneumonia.

Acute Q fever occasionally complicates pregnancy. In one series, it resulted in premature birth in 35% of cases and in abortion or neonatal death in 43%. Neonatal death (previous or current) and lower infant birth weight are three times more likely among women seropositive for *C. burnetii*.

After the usual incubation period of 3–30 days, 1070 patients with acute Q fever in southern France presented with hepatitis (40%), both pneumonia and hepatitis (20%), pneumonia (17%), isolated fever (14%), CNS involvement (2%), and pericarditis or myocarditis (1%). Acalculous cholecystitis, pancreatitis, lymphadenopathy, spontaneous rupture of the spleen, transient hypoplastic anemia, bone marrow necrosis, hemolytic anemia, histiocytic hemophagocytosis, optic neuritis, and erythema nodosum were less common manifestations.

POST–Q FEVER FATIGUE SYNDROME Prolonged fatigue can follow Q fever and can be accompanied by a constellation of symptoms including headaches, sweats, arthralgia, myalgias, blurred vision, muscle fasciculations, and enlarged and painful lymph nodes. Long-term persistence of a noninfective, nonbiodegraded complex of *Coxiella* cell components, with its antigens and specific lipopolysaccharide, has been detected in the affected persons. Patients who develop this syndrome have a higher frequency of carriage of HLA-DRB1*11 and of the 2/2 genotype of the interferon γ intron 1 microsatellite.