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1257 8.6.42 *Coxiella burnetii* infections (Q fever) Strickman D, et al. (1995). In vitro effectiveness of azithromycin against doxycycline-resistant and -susceptible strains of *Rickettsia tsutsugamushi*, etiologic agent of scrub typhus. *Antimicrob Agents Chemother*, 39, 2406–10. Watt G, et al. (1996). Scrub typhus infections poorly responsive to anti-biotics in northern Thailand. *Lancet*, 348, 86–9.

8.6.42 *Coxiella burnetii*

infections (Q fever) Thomas J. Marrie ESSENTIALS Q fever is a zoonosis caused by *Coxiella burnetii*, an intracellular Gram-negative spore-forming bacterium, the common animal reservoirs of which are cattle, sheep, and goats. Rats and mice have been implicated as reservoirs in some areas. In French Guiana the three-toed sloth is the reservoir. *C. burnetii* is trophic for the endometrium and mammary glands of female animals, and during pregnancy the organism reaches very high concentrations in the placenta such that at the time of parturition organisms are aerosolized and contamination of the environment occurs. Inhalation of even one microorganism can result in infection. Clinical features—there are two main forms of the disease:

(1) acute—can present as inapparent infection, self-limited febrile illness, pneumonia, and hepatitis, or less commonly with a variety of organ-specific manifestations such as encephalitis, pericarditis, and pancreatitis; Q fever in pregnancy is associated with a high rate of abortion or neonatal death. (2) Chronic—most often ‘culture-negative’ endocarditis or infection of aortic aneurysms, but occasionally osteomyelitis. Diagnosis, treatment, and prevention—diagnosis is confirmed by serological testing: in acute disease antibodies to phase II antigen are higher than those to phase I, whereas the reverse is true in chronic disease. Acute Q fever is treated with doxycycline or a quinolone; chronic disease with long-term doxycycline and hydroxychloroquine; and Q fever in pregnancy with co-trimoxazole for the duration of the pregnancy and—for those post-partum women with a chronic Q fever serological profile—1 year of doxycycline and hydroxychloroquine after delivery. Vaccination should be offered to those whose occupation places them at high risk for *C. burnetii* infection. History In August 1935, Dr Edward Holbrook Derrick, Director of the Laboratory of Microbiology and Pathology of the Queensland Health Department in Brisbane, Australia, was asked to investigate an outbreak of undiagnosed febrile illness among workers at the Cannon Hill abattoir. Derrick realized that he was dealing with a type

of fever that had not been previously described—he named it Q (for query) fever. Two years later, Sir Frank Macfarlane Burnet in Australia and Herald Rea Cox in the United States of America isolated the microorganism responsible for Q fever. *Coxiella burnetii* This microorganism, the sole species of its genus, has a Gram-negative cell wall and measures $0.3 \times 0.7 \mu\text{m}$ (Fig. 8.6.42.1). It is an obligate phagolysosomal parasite of eukaryotes that sporulates, stains well with Gimenez's stain, and multiplies by transverse binary fission. *C. burnetii* undergoes phase variation akin to the smooth to rough transition in some enteric Gram-negative bacilli. In nature and laboratory animals it exists in the phase I state. Repeated passage of phase I virulent organisms in embryonated chicken eggs leads to the conversion from phase I virulent to phase II avirulent forms. Antibodies to phase I antigens usually predominate in chronic Q fever, while phase II antibodies are higher than phase I antibodies in acute Q fever. The genome of *C. burnetii* strain Nine Mile Phase I has 1 995 275 base pairs. There are many genes with potential roles in adhesion, invasion, intracellular trafficking, host-cell modulation, and detoxification. *C. burnetii* can now be grown in a cell-free medium, an advance that should lead to further insight into this complex microorganism. Immune control of *C. burnetii* is T-cell dependent but it does not eliminate *C. burnetii* from infected humans. In 80–90% of bone marrow aspirates from those who have recovered from Q fever, polymerase chain reaction (PCR) assays for *C. burnetii* DNA are positive. The use of microarrays allows insight into the complexity of the host-microorganism interaction in illnesses such as Q fever. In one such experiment 335 genes in the *C. burnetii*-infected human monocytic leukaemia cell line THP-1 were up- or down-regulated at least twofold. Fig. 8.6.42.1 Transmission electron micrograph showing *C. burnetii* cells within a macrophage in the heart valve of a patient with Q fever endocarditis. The dark material in the centre of each cell is condensed DNA. Magnification $\times 15\ 000$.

section 8 Infectious diseases 1258 Recently adipose tissue has been shown to be the reservoir for *C. burnetii* during bacterial latency. *C. burnetii* has survived for 586 days in tick faeces at room temperature, 160 days or more in water, 30–40 days in dried cheese made from contaminated milk, and up to 150 days in soil. Epidemiology Q fever is a zoonosis. There is an extensive wildlife and arthropod (mainly ticks) reservoir of *C. burnetii*. This reservoir might differ from area to area; for example in Spain, European rabbits serve this function while in Nova Scotia Canada, cats are the prime reservoirs; rats in Netherlands, three-toed sloth in French Guinea and mice in China are the reservoirs in those countries. Domestic animals are infected through inhaling contaminated aerosols or by ingesting infected material. These animals rarely become ill, but abortion and stillbirths may occur. *C. burnetii* localizes in the uterus and mammary glands of infected animals. During pregnancy there is reactivation of *C. burnetii* and it multiplies in the placenta, reaching 109 infective doses per gram of tissue. The organisms are shed into the environment at the time of parturition. Humans become infected after inhaling organisms aerosolized at the time of parturition, or later when organisms in dust are stirred up on a windy day. Infections have occurred up to 18 km downwind from a source. Infected cattle, sheep, goats, and cats are the animals primarily responsible for transmitting *C. burnetii* to humans. There have been several outbreaks of Q fever in hospitals and research institutes due to the transportation of infected sheep to research laboratories. Some studies have suggested that ingestion of contaminated raw milk is a risk factor for the acquisition of Q fever. Percutaneous infection, such as when an infected tick is crushed between the fingers, can occur but is rare. Transmission via a contaminated blood transfusion has rarely occurred. Vertical transmission from mother to child has been infrequently reported. A 2007 review documents 74 cases of Q fever in pregnant women. The authors found

that Q fever was present in 1 in 540 pregnancies in an area of endemic Q fever in southern France. Person-to-person transmission has been documented on a few occasions, including sexual transmission. To date, 45 countries on five continents have reported cases of Q fever. Q fever is estimated to cost \$A1 million in Australia each year and results in the loss of more than 1700 weeks of work. There are several studies where young age seems to be protective of infection with *C. burnetii*. In a large outbreak of Q fever in Switzerland, symptomatic infection was five times more likely to occur in those over 15 years of age compared with those younger than 15. In many outbreaks of Q fever, men were affected more commonly than women. It had been assumed that this was due to the fact that certain occupations in which men predominate were more likely to be associated with Q fever. However, in France, despite similar exposures, the male to female ratio is 2.45:1. The explanation for this gender difference is that female sex hormones are protective against Q fever infection. Currently Q fever is common in several European countries with recent outbreaks in Germany and the Netherlands. There are a considerable number of sporadic cases of Q fever in England, France, and Spain. The outbreak in the Netherlands is the largest to date, with over 4000 cases from 2007 to 2010, and many lessons have been learned from it. In 2007 a total of 168 individual human Q fever cases were notified, occurring after visits to dairy farms with abortion problems. The outbreak was concentrated around a single village, where a case-control study found that contact with manure, hay, and straw were risk factors. Moreover, people living in the eastern part of the village close to ruminant farms, one of which was a dairy goat farm with a recent history of abortion problems, were at higher risk than people living in other parts of the village. In 2008, 1000 human cases were notified, with average age 51 years (range 7–87 years), and 21% were hospitalized. In April 2009 a further sharp increase in human cases was observed, resulting in the total number of 2355. Pneumonia accounted for 68% of the cases and hepatitis for 15%. The gender ratio was 1 female to 1.7 males. In general, 59% of the notified human cases in 2009 lived within a 5-km zone around the notified dairy goat, dairy sheep farm, while 12% of the Dutch population lived within such as zones. Genotyping of *C. burnetii* isolates found that one unique genotype predominated in dairy goat herds and one sheep herd, and this genotype was similar to the human isolates. Overall 10 different genotypes were identified. Systematic culling of gestating ewes and goats on infected farms as well as other measures stopped the outbreak. More than 50 000 animals on 88 farms were culled. The incidence of Q fever in the United States is 0.38 cases per million with a 2% fatality rate. Fatal cases were underreported by case reports by a factor of 14 and by 5.2 for death certificates. Ingestion of raw milk was twice as common among cases as compared with the national average. The incidence in Germany is 1.4 cases per million. In contrast the rate per 100 000 is 2.5 in France, 2.8 in Australia, 0.02 in South Korea and in one city in French Guiana it is 37–150 per 100 000. Clinical features Humans are the only species known consistently to develop illness following infection with *C. burnetii*. There is an incubation period of about 2 weeks (range 2–29 days) following inhalation of *C. burnetii*. A dose–response effect has been demonstrated experimentally and clinically. *C. burnetii* is one of the most infectious agents known; a single microorganism is able to initiate infection in humans. The resulting illness can be divided into acute and chronic varieties. Acute Q fever Self-limiting febrile illness The most common manifestation of acute Q fever is a self-limiting febrile illness that is dismissed as a ‘cold’. Serosurveys reveal that in most endemic areas 5–10% of the population have antibodies to *C. burnetii* but never remember the illness that resulted in seroconversion. Q fever pneumonia This is the most commonly recognized manifestation of acute Q fever in some geographical locations. There is often a seasonal distribution, most of the cases occurring between February and May (consistent with the birthing season in the small ruminant reservoirs).

The onset is nonspecific with fever, fatigue, and headache. The headache may be very severe, occasionally so severe that it

1259 prompts a lumbar puncture. A dry cough of mild to moderate intensity is present in 24–90% of patients. About one-third of patients have pleuritic chest pain. Nausea, vomiting, and diarrhoea occur in 10–30% of patients. Most cases of *C. burnetii* pneumonia are mild; however, about 10% are severe enough to require admission to hospital and, rarely, assisted ventilation is necessary. Death is rare in Q fever pneumonia and is usually due to comorbid illness. The white blood cell count is usually normal, but is elevated in one-third of patients. Liver enzyme levels may be mildly elevated at two to three times normal. Alkaline phosphatase is raised in up to 70% of patients and 28% are hyponatraemic. Reactive thrombocytosis is surprisingly common and microscopic haematuria is a common finding. The chest radiographic manifestations of Q fever pneumonia are usually indistinguishable from those of other bacterial pneumonias (Fig. 8.6.42.2); however, rounded opacities are suggestive of this infection (Fig. 8.6.42.3). Some investigators have reported delayed clearing of the pneumonia; however, in our experience resolution is usually complete within 3 weeks. Hepatitis The liver is probably involved in all patients with acute Q fever. There are three clinical pictures: • Pyrexia of unknown origin with mild to moderate elevation of liver function tests. In some patients, corticosteroid therapy is necessary because patients remain febrile despite appropriate antibiotic therapy. • A hepatitis-like picture: liver biopsy shows distinctive doughnut granulomas consisting of a granuloma with a central lipid vacuole and fibrin deposits (Fig. 8.6.42.4). Prolonged fever unresponsive to antibiotics is common in these patients (Fig. 8.6.42.5). • ‘Incidental hepatitis’. In this setting liver enzymes are elevated but other features dominate the clinical picture—such as pneumonia. Thus, the liver is said to be incidentally involved. Q fever in pregnancy Acute Q fever occasionally complicates pregnancy. In 23 published cases 35% had premature birth, and 43% ended in abortion or neonatal death. In a serosurvey of 4588 pregnant women in Halifax, Nova Scotia, Canada, women seropositive for *C. burnetii* were three times more likely to have a current or previous neonatal death. A study of 1174 pregnant women during the recent outbreak of Q fever in the Netherlands found that antibodies against phase II *C. burnetii* were not significantly associated with preterm delivery, low birth weight babies, and several other outcomes. Adverse outcomes attributable to Q fever were not seen in a recent study from Germany of 11 women with this infection during pregnancy. Whether these differences are due to properties of the infecting strain is not known. In several animal species (other than humans) Q fever is associated with abortions and stillbirths. Clearly, more information is needed on Q fever in pregnancy in humans. Fig. 8.6.42.2 Serial chest radiographs of a 35-year-old patient with Q fever pneumonia. The first radiograph (1 August 1989) shows a round opacity in the right upper lobe, which increases in size over the next 6 days. The pneumonia has completely cleared by 19 September 1989. 8.6.42 *Coxiella burnetii* infections (Q fever)

section 8 Infectious diseases 1260 Neurological manifestations Encephalitis, encephalomyelitis, toxic confusional states, optic neuritis, and demyelinating polyradiculoneuritis are uncommon manifestations of Q fever. Rare manifestations These include myocarditis, pericarditis including constrictive pericarditis, bone marrow necrosis, rhabdomyolysis, glomerulonephritis, lymphadenopathy, pancreatitis, splenic rupture, acalculous cholecystitis, mesenteric panniculitis, erythema nodosum, epididymitis, orchitis, priapism, and erythema annulare centrifugum. Chronic fatigue may be a sequel of Q fever in some patients. Chronic Q fever The usual manifestation of chronic Q fever is that of culture-negative endocarditis. Some 70% of these patients have fever and

nearly all have abnormal native or prosthetic heart valves. Hepatomegaly and/or splenomegaly occur in about one-half of these patients and one-third have finger clubbing. A purpuric rash due to immune complex-induced leucocytoclastic vasculitis and arterial embolism occurs in about 20% of patients. Hyperglobulinaemia (up to 60 g/ litre) is common and is a useful clue to chronic Q fever in a patient with the clinical picture of culture-negative endocarditis. Other manifestations of chronic Q fever include osteomyelitis, infection of aortic aneurysm, and infection of vascular prosthetic grafts. The strains of *C. burnetii* that cause chronic Q fever do not differ from those that cause acute Q fever. Peripheral blood lymphocytes from patients with Q fever endocarditis are unresponsive to *C. burnetii* antigens in vitro, while responding normally to other antigens. Positron emission scanning has emerged as a useful tool in the diagnosis and management of patients with Q fever. The site of infection, heart valve, aorta, bone, or joint can be visualized. Diagnosis A strong clinical suspicion based on the epidemiology and clinical features as outlined earlier is the cornerstone of the diagnosis of Q fever. This suspicion is confirmed by determining a fourfold or

Fig. 8.6.42.3 Portable anteroposterior chest radiograph of a 72-year-old man with Q fever pneumonia. This radiographic picture is indistinguishable from pneumonia due to any other microbial agent. Fig. 8.6.42.4 Liver biopsy showing characteristic doughnut granuloma. The hole in the centre of the granuloma is lipid that has been dissolved during the fixation process.

1261 greater increase in antibody titre between acute and 2- to 3-week convalescent serum samples. A variety of serological tests are available including complement fixation, microimmunofluorescence (IFA), and enzyme immunoassay. The immunofluorescence antibody test is the best test. In acute Q fever the antibody titre to phase II antigen is higher than that to phase I antigen, while the reverse occurs in chronic Q fever. In chronic Q fever, antibody phase I titres are extremely high, in the order of 1:8192 and higher. In acute Q fever, antibody titres to phase I antigen are rarely in excess of 1:512 (usually 1:8 to 1:32), while peak antibody titres to phase II antigen are between 1:1024 and 1:2048. The microorganism can be isolated in embryonated eggs or in tissue culture; however, a biosafety level 3 laboratory is required. The PCR can be used to amplify *C. burnetii* DNA from tissues or other biological specimens. Good laboratory practice, with known positive and negative controls is extremely important in the diagnosis of Q fever. Three different laboratories (in France, the United Kingdom, and Australia) tested the same serum samples using an IFA test. However, the antigen used in the test differed in each laboratory—Nine Mile strain in France; Nine Mile strain clone 4 as phase II antigen and Henzerling strain as phase I antigen in Australia; patient Lane strain ST 12 group for phase I and II antigens in the United Kingdom. Concordance was only 35%. The Australian and United Kingdom results had the greatest concordance and French and United Kingdom results the lowest. Serological testing revealed no chronic serological profiles when tested in either France or Australia but 10 when tested in the United Kingdom. Serological results from a patient with treated Q fever endocarditis suggested treated (France), chronic (United Kingdom), and borderline chronic (Australia) infection. How the antigens were prepared can also make a difference in the test results, and this paper does not indicate whether the strains were grown in tissue culture or egg yolk sac. Treatment Acute Q fever is treated with a 2-week course of tetracycline or doxycycline. Quinolones can also be used. Any patients who develop acute Q fever and have lesions of their native valves (e.g. congenital bicuspid aortic valve), prosthetic valves, or prosthetic intravascular material should have serological monitoring every 4 months for 2 years, and if the phase I IgG titre exceeds 1:800 further investigation is warranted. Some authorities recommend

Fig. 8.6.42.5 Fever in Q fever hepatitis. This patient had been febrile for 6 weeks before he was transferred to this hospital and had liver biopsy done and diagnosis of Q fever hepatitis made. 8.6.42 Coxiella burnetii infections (Q

fever)

Revision #1

Created 2026-01-22 16:45:53 UTC by Omar Ayman

Updated 2026-01-22 16:45:53 UTC by Omar Ayman