Chapter 26

Q FEVER

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INTRODUCTION

Q fever is a zoonotic disease caused by *Coxiella burnetii*, a rickettsia-like organism of low virulence but remarkable infectivity. A single organism may initiate infection. In addition, despite the fact that *C burnetii* is unable to grow or replicate outside host cells, there is a sporelike form of the organism that is extremely resistant to heat, pressure, desiccation, and many standard antiseptic compounds; this allows *C burnetii* to persist in the environment for long periods (weeks or months) under harsh conditions. This persistence, coupled with a primary mode of transmission by inhalation of infected aerosols, allows for the development of acute infection following only indirect exposure to an infected source. In contrast to this high degree of inherent resilience and transmissibility, the acute clinical disease associated with Q fever infection is usually a benign, although a temporarily incapacitating, illness in humans. Even without treatment, the vast majority of patients recover. Chronic disease as a result of Q fever is rare, although it is frequently fatal.

The primary reservoir for natural human infection is livestock, particularly parturient females, and the distribution is worldwide. Outbreaks of Q fever are infrequently reported, however, and the disease may be endemic in areas where cases are rarely or never reported. Humans who work in animal husbandry, especially those who assist during parturition (eg, calving or lambing) are at risk for acquiring Q fever. However, a definite risk also exists for persons who live in close proximity to, or who pass through, an area where animal birthing is occurring, even if this occurred months previously.

MILITARY RELEVANCE

Since the disease was described in 1937, thousands of cases involving military personnel of many countries have been reported (an excellent review was published in 1978[1]), and infection with *C burnetii* should be considered a possibility whenever troops are present in an area with infected animals.

American soldiers in Italy during World War II were affected, with 5 confirmed outbreaks of Q fever during the winter of 1944 and spring of 1945,[2] usually in troops occupying farm buildings recently or concurrently inhabited by farm animals.[3] This degree of close contact with farm animals was not an absolute requirement for infection, however: approximately 1,700 cases occurred in late spring, 1945, at an airbase in southern Italy as a result of sheep and goats herded in pastures nearby.[4] During World War II, cases of acute Q fever were also identified in soldiers in Virginia shortly after debarking from a 9-day voyage from Naples, Italy,[4,5] and a single case was identified in a soldier stationed in Panama.[6]

Hundreds of cases consistent with Q fever were observed in German soldiers in Serbia and southern Yugoslavia during World War II. Outbreaks occurred in the apparent absence of disease in the indigenous population. The disease was most commonly referred to as “Balkengrippe”; infection with *C burnetii* was not confirmed by laboratory testing, but the clinical and epidemiological features of the illness described were most consistent with Q fever. Similar cases were observed in German troops during World War II in Italy, Crimea, Greece, Ukraine, and Corsica.[1]

An outbreak of acute Q fever associated with an epidemic of spontaneous abortion in sheep and goats occurred in 78 British troops stationed in Cyprus, from December 1974 to June 1975[7]; Swedish troops were also affected.[8] Q fever outbreaks have also been described[1] among Swiss soldiers in 1948, Greek soldiers from 1946 to 1956, and Royal Air Force airmen on the Isle of Man in 1958. These outbreaks occurred in the soldiers’ home countries when the troops were stationed or training in close proximity to sheep or goats, particularly parturient animals. Outbreaks attributed to sheep or goat exposure in deployed soldiers have been described[1] in American airmen in Libya in 1951 and French soldiers in Algeria in 1955.

Among American military personnel in the Persian Gulf War, one case of meningoencephalitis associated with acute Q fever was reported, with the onset of symptoms 2 weeks after return from the Persian Gulf.[9] One other soldier, with acute Q fever pneumonia, was diagnosed in Saudi Arabia in March 1991.[10] This occurred in a first sergeant in an engineering battalion. Subsequent epidemiological evaluation and serologic testing of the unit identified three additional acute seroconversions among soldiers of the same battalion.[11] Exposure to sheep, goats, or camels was identified in all of these infections acquired in Saudi Arabia.

Q fever is probably endemic in Somalia,[12] and serologic evidence of acute Q fever was identified in two American soldiers evaluated in Somalia for fever of unknown origin.[11,13]

These reports all underscore the importance of considering the diagnosis of Q fever in a febrile soldier in or recently returned from an area where the disease may be present. This is particularly true if the soldier has been in close proximity to or in an area previously occupied by animals which may harbor *C burnetii*.

The potential of *C burnetii* as a biological warfare threat is directly related to its infectivity. It has been estimated that 50 kg of dried, powdered *C burnetii* would produce casualties a rate equal to that of similar amounts of anthrax or tularemia organisms.[14] Q fever has been evaluated as a potential biological warfare agent by the United States,[15] but munitions and stocks (except that required for vaccine research) were publicly destroyed by executive order of President Richard M. Nixon between May 1971 and May 1972.[16]

HISTORY

Q fever was first described in 1937 by Edward Derrick,[17] while he was the Director of Microbiology and Pathology for the Queensland (Australia) Health Department at Brisbane. In 1935, he was contacted about a febrile illness that had been occurring among abattoir workers in Brisbane. When routine blood cultures and serologic testing did not reveal a diagnosis, Derrick suspected that he was dealing with a new illness. He thoroughly described the clinical characteristics and designated the disease Q (for query) fever. Derrick's laboratory investigation demonstrated that it was possible to transmit the disease to animals by inoculating guinea pigs and mice with the blood of humans suffering from acute Q fever. Although Derrick had initially concluded that the infectious agent was a virus, studies of a guinea pig liver emulsion sent to MacFarlane Burnet in Melbourne subsequently indicated that the causative organism was a rickettsia,[18] according to the terminology used at that time.

Interestingly, Derrick may not have been the first to transfer the disease to laboratory animals. Hideyo Noguchi, working at the Rockefeller Institute in New York City in 1925, may have passed *C burnetii* to guinea pigs from ticks that had been collected at Saw Tooth Canyon by Ralph Parker at the Rocky Mountain Laboratory in Hamilton, Montana.[19] This agent, however, was ultimately lost in animal passage.

About the same time that the investigations were being done in Australia, Gordon Davis was studying Rocky Mountain Spotted Fever at the Rocky Mountain Laboratory. He observed that a febrile illness resulted when ticks collected from the area around the nearby Nine Mile Creek were allowed to feed on guinea pigs.[20] The disease produced in guinea pigs did not, however, resemble Rocky Mountain Spotted Fever. Herald Cox was subsequently able to characterize the organism (then called the "Nine Mile Agent") as similar to rickettsia and to cultivate this organism in the yolk sac membrane of embryonated hen eggs.[21] The relation of Q fever to the Nine Mile Agent was established by Rolla Dyer, director of the National Institutes of Health at the time, after the spleens of infected mice were sent to him by Burnet. In an event that presaged the problems of transmission of Q fever in laboratory workers, Dyer himself acquired acute Q fever during a visit to Hamilton in 1938.[22]

The work of Ralph Parker, also at the Rocky Mountain Laboratory, indicated that ticks are the reservoir of the "Nine Mile Agent." Derrick had also suspected tick transmission from a primary reservoir, and from a secondary reservoir of domestic animals. The significance of exposure to parturient animals was not, however, recognized until 1950.

The causative agent of Q fever was ultimately designated *Coxiella burnetii* to recognize the outstanding contributions of both Cox and Burnet to the isolation and characterization of this new pathogen.[23] The disease, following clinical description and microbiological characterization of the etiologic agent, has been identified in at least 51 countries on 5 continents.[24]

THE INFECTIOUS AGENT

Coxiella burnetii is classified in the family Rickettsiaceae, but is not included in the genus *Rickettsia* and therefore is not a true rickettsia. It is not closely related to any other bacterial species when comparative 16s ribosomal ribonucleic acid (RNA) analysis is performed,[25] thus the genus *Coxiella* has only one species. The closest relative according to 16s ribosomal RNA analysis is *Legionella*,[25,26] but *Legionella* has different growth characteristics (*Legionella*, being a facultative intracellular parasite,

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Fig. 26-1. Electron micrograph of *Coxiella burnetii* in the phagolysosome of an infected yolk sac cell, demonstrating both large (LCV) and small (SCV) cell variants. The bar in the lower right corner represents 0.6 µm. After Renografin (manufactured by Squibb Diagnostics, Princeton, NJ) purification, the cells were fixed with primary fixative and stained with potassium permanganate. The phagolysosome contains many pleomorphic *C burnetii* organisms. Multiplication by binary transverse fission with septa formation (arrows) is seen.

The LCVs resemble Gram-negative bacteria, with outer and cytoplasmic membranes separated by a periplasmic space. The LCV is more metabolically active than the SCV, has less peptidoglycan in the cell wall, and is capable of production of the sporelike form. The loose outer membrane, increased periplasmic space, and bleb formation of some of the LCVs probably indicate that they are undergoing deterioration or have been damaged during preparation. The SCVs appear as extremely dense organisms and are heat-resistant, relatively dormant structures which have the ability to survive in an adverse environment. Reprinted with permission from McCaul TF, Williams JC. Developmental cycle of *Coxiella burnetii*: Structure and morphogenesis of vegetative and sporogenic differentiations. *J Bacteriol*. 1981;147:1067.

is able to survive and multiply extracellularly) and causes a different clinical syndrome.

C burnetii must occupy an intracellular environment in order to grow or reproduce, similar to true rickettsia, although, as previously stated, the organism has a sporelike form that is very resistant to heat and desiccation.[27] This sporelike form may be observed in human tissue.[28] The particular cytological niche occupied by *C burnetii* is the usually very destructive environment of the phagolysosome of eukaryotic cells (Figure 26-1), which has a strongly acidic milieu (normal pH is 4.5) and numerous digestive enzymes. While inhabiting the phagolysosome, *C burnetii* usually lives in relatively peaceful coexistence with the host, causing little direct damage to the cell, at least initially.

Replication occurs by binary fission within the host cell; the dormant, sporelike form, is produced under certain circumstances.[29] Dormant *C burnetii* can be stimulated to a brief period of growth by exposure to an acidic environment.[30] Sustained growth and replication of *C burnetii* outside a host cell is not possible.

Phase variation has been described with *C burnetii* maintained in the laboratory.[31] The virulent organism, which is associated with natural infection and a smooth lipopolysaccharide (LPS), is designated as Phase I. This phase is resistant to complement and is a potent immunogen. Serial passage of *C burnetii* in eggs eventually results in the bacterium's conversion to Phase II, which has a rough LPS and is much less virulent than Phase I. This phase is sensitive to complement and is a poor immunogen. The conversion from Phase I to Phase II is irreversible[32] and is the result of a mutation caused by a chromosomal deletion.

Coxiella burnetii also contains several plasmids, and dissimilar plasmid types may be associated with different manifestations of disease.[33] The cell wall of a Phase I *C burnetii* organism contains, in association with lipopolysaccharide, an immunomodulatory complex,[34] which produces toxic reactions in mice (eg, hepatomegaly, splenomegaly, liver necrosis) and lymphocyte hyporesponsiveness in vitro.

THE DISEASE

Epidemiology

Coxiella burnetii is extremely infectious. Under experimental conditions, a *single organism* is capable of producing infection and disease in humans.[35]

The host range of *C burnetii* is very diverse and includes a large number of mammalian species and arthropods. Among these, however, man is the only host identified that normally experiences an illness as a result of infection. A number of differ-

ent strains of *C burnetii* have been identified worldwide, and different clinical manifestations and complications may be associated with the various strains.

Humans have been infected most commonly by contact with domestic livestock, particularly goats, cattle, and sheep. The risk of infection is substantially increased if humans are exposed to these animals at parturition. During gestation, the proliferation of *C burnetii* in the placenta facilitates aerosolization of large numbers of the pathogen during parturition. *Coxiella* organisms thus produced may persist in the local environment, and produce infection, for weeks or months afterwards.

C burnetii is also shed in the urine and feces of infected animals, in addition to being present in the blood and tissues. Survival of the organism on inanimate surfaces, such as straw, hay, or clothing, allows for transmission to individuals who are not in direct contact with infected animals; for example,

- soldiers sleeping in barns previously occupied by infected animals,[3]
- laundry workers handling infected clothing,[36]
- coworkers of an individual with an infected cat in the home,[37] and
- residents of an urban community living along a road utilized by farm vehicles.[38]

Investigation of outbreaks of Q fever frequently report a significant proportion of patients who have no identifiable risk factor. Human-to-human transmission has been reported,[39] but it is a very rare event.

As mentioned previously, the distribution of *C burnetii* is worldwide.[24] With the exception of a few countries (New Zealand is an example), Q fever cases have been identified practically everywhere that an attempt has been made to identify evidence of infection, either in man or in animals.

In the United states, the epidemiology of Q fever is variable. Sporadic but regularly occurring cases have been observed[40] in areas with endemic foci in cattle, and clusters of cases have been described[41] in areas with infected dairy herds. Livestock is not the only source of Q fever infections in this country: a small outbreak in Maine associated with exposure to a parturient cat has been described,[42] similar to an outbreak in Nova Scotia, Canada.[43] Since 1985, outbreaks of Q fever in the United States have been reported in five states among differing groups of individuals:

- slaughterhouse workers in California[44];
- faculty, laboratory workers, and staff exposed to sheep at a medical school in Colorado[45];
- individuals exposed to sheep at a sheep research station in Idaho[46];
- laboratory animal personnel in Arkansas working with parturient sheep[47]; and
- workers in an animal research laboratory in South Carolina who handled and performed surgery on sheep.[48]

Although reported outbreaks[49,50] of Q fever in the United States have been relatively uncommon in recent years, underreporting undoubtedly occurs. For example, although the first 2 cases of Q fever from 2 adjacent rural counties in Michigan were reported in 1984, a study[51] published just 4 years later showed that 15% of the general population surveyed in those 2 counties and 43% of goat owners were seropositive.

Pathogenesis

Human infection with *C burnetii* is usually the result of inhalation of infected aerosols. Following this, the organisms are phagocytized by host cells, predominately unstimulated macrophages. This uptake of *C burnetii* by host phagocytic cells is not energy dependent, but is probably the result of contact by the pathogen with an existing receptor. After phagocytosis by host cells, conditions within the phagolysosome trigger growth and multiplication of *C burnetii*, with little initial damage to the host cell. Eventually the cytoplasm becomes engorged with *C burnetii* organisms and lysis of the host cell occurs. Dissemination of the pathogen occurs as a result of circulation of organisms free in the plasma, on the surface of cells, and carried by circulating macrophages.

In animals, infection frequently lasts for the life of the animal, in a more-or-less dormant state, with periodic increases in organism numbers during periods of relative immunosuppression, particularly parturition,[52] but also in laboratory animals treated with adrenocorticosteroids[53] or irradiation.[54] *C burnetii* causes little overt disease in animals (and no apparent disease in ticks), except that luxuriant growth in the placenta may increase the rate of spontaneous abortion in some species. Edema and thrombohemorrhagic lesions may be identified in the placentas of infected animals.

There is little host reaction at the initial portal of entry, either in the lung following inhalation of aero-

sol or in the skin following a tick bite. Q fever develops without formation of a primary infectious focus in the area of the tick bite, and the organism does not infect the vascular endothelium as do true rickettsial pathogens.

In man, polyclonal production of antibody represents the initial immune response to *C burnetii*, but humoral immunity alone is ineffective for control of the organism, although the presence of antibody does contribute significantly to antibody-dependent cellular cytotoxicity later in the course of the infection. Passive transfer of immune serum to laboratory animals does not improve clearance of organisms from the spleen.[55] Pretreatment of laboratory animals with cyclophosphamide, an antineoplastic agent that severely inhibits production of antibody, does not adversely affect the course of infection.[56] *C burnetii* organisms that have been opsonized, however, are much more efficiently destroyed by host phagocytic cells than are unopsonized organisms. Control of the infection by the host eventually results from the development of specific cell-mediated immunity, with killing by activated macrophage and natural killer cells. This process may result in a granulomatous reaction without the scarring and tissue reaction observed with true granulomata.

The host immune response in man appears to be modified by the *C burnetii* organism itself in chronic infection, in that the lymphocytes of patients with Q fever endocarditis exhibit profound hyporesponsiveness to *C burnetii* antigen, although they retain their reactivity to other antigens.[57]

The presence of LPS on the cell surface of *C burnetii* protects the pathogen from host microbicidal activities. The phase variation previously described is the result of alteration of the LPS, with the virulent Phase I organism having a smooth LPS. The Phase II organism, the result of serial passage of *C burnetii* in eggs, has a rough LPS, is much less immunogenic than the Phase I, and is less virulent.[58] Phase I organisms are resistant to the lytic action of complement, while Phase II organisms are sensitive to the alternate pathway of complement.[59]

Clinical Disease in Domestic Animals

Except for spontaneous abortion, illness in domestic animals as a result of *C burnetii* infection is unusual, although the organism has a propensity for proliferation in the female reproductive system—particularly the uterus and the mammary glands. Differences between the manifestations in domestic animals, however, are worthy of comment.

In sheep, the infection tends to be transient, followed by spontaneous remission. Infected sheep will usually cease shedding the pathogen after a few months and no longer be infectious to other animals in the flock, except during parturition. Although *C burnetii* has frequently been recovered from the placentas of sheep and has been associated with epidemic abortions, shedding in the milk is rare.

By contrast, chronic shedding—over months or years—of *Coxiella* in the milk of lactating cows can be expected. This aspect of the infection can facilitate maintenance of *Coxiella* in a herd, particularly a dairy herd. Infection in cows is also associated with an increased incidence of spontaneous abortion and may be associated with infertility.

Goats also show an increased disposition for abortion during epizootics of Q fever, and infection in a herd may be maintained by chronic shedding.

Clinical Disease in Humans

Man is the only host susceptible to infection by *C burnetii* that commonly develops an illness as a result of the infection. The incubation period varies from 10 to 40 days, with the duration of the incubation period being inversely correlated with the magnitude of the inoculum.[35] A higher inoculum also increases the severity of the disease. Q fever in humans may be manifested by asymptomatic seroconversion, acute illness, or chronic disease. The frequency of these manifestations parallels this order in decreasing magnitude. In epidemiological surveys, most seropositive individuals do not recall having the illness. The frequency of chronic disease (usually endocarditis) compared with acute disease is difficult to determine precisely due to underreporting of acute infection but is probably less than 1% of the total infected population.

The tendency for *C burnetii* to produce asymptomatic seroconversion has been documented in several publications. In one study,[35] experimental infection in humans showed that in 2 of 4 volunteers infected with a single organism by aerosol, a diagnosis could be established by serologic conversion without clinical illness. Asymptomatic seroconversion did not occur with higher infecting doses (5–1,500 organisms). In an outbreak in Canada attributed to indirect exposure to contaminated clothing, 6 (37.5%) of 16 individuals diagnosed by seroconversion did not have an associated illness.[37] In Switzerland in 1983, during the course of a serosurvey to investigate a large outbreak of Q fever, more than half of the 415 serologically con-

firmed patients were asymptomatic or minimally ill.[60] These reports underscore the value of an epidemiological investigation when even a single case of acute Q fever is recognized.

Infection with *C burnetii* has been reported[61] to persist in humans, as it does in animals, in an asymptomatic state. Phase I *C burnetii* has been recovered from the placentas of asymptomatic women infected from 1 to 6 months,[62] to 3 years[63] previously. Infection with Q fever may rarely affect the outcome of pregnancy adversely.[64]

Acute Q Fever

There is no characteristic illness for acute Q fever, and manifestations may vary considerably between locations where the disease is acquired.

When symptomatic, the onset of Q fever may be abrupt or insidious, with fever, chills (including frank rigors), and headache being the most common signs and symptoms (Table 26-1). The headache is usually described as severe, throbbing, and frontal or retro-orbital in location. Diaphoresis, malaise, fatigue, and anorexia are also very common. Weight loss of 7 kg or more during the course of acute illness has been reported with surprising frequency, particularly when other general symptoms lasted more than 2 weeks.[2,65] Myalgias are also a frequent complaint, while arthralgias are relatively unusual. Cough tends to appear later in the illness than some of the other more common symptoms, such as fever, chills, and headache, and may not be a prominent complaint. Chest pain occurs in a minority of patients and may be pleuritic or a vague substernal discomfort.

Relatively infrequent symptoms include sore throat, gastrointestinal upset, and neck stiffness, although this last symptom has been severe enough in reported cases of acute Q fever to warrant a lumbar puncture to exclude bacterial meningitis. Although nonspecific evanescent skin eruptions have been reported,[66,67] there is no characteristic rash.

Most patients appear mildly to moderately ill—when the onset is abrupt, Q fever has been mistaken for influenza. The temperature tends to fluctuate, with peaks of 39°C to 40°C, and in approximately one fourth of the cases is biphasic; in two thirds of patients with acute disease, the febrile period lasts 13 days or less. The duration of fever is usually longer in older patients.[68]

Neurological symptoms are not uncommon and in one study[65] were observed in up to 23% of acute cases. Encephalopathic symptoms, hallucinations (visual and auditory), expressive dysphasia, hemi-

TABLE 26-1

SIGNS AND SYMPTOMS IN ACUTE Q FEVER

Signs and Symptoms	Frequency (%)
Onset*	
Gradual	30–70
Abrupt	30–70
Fever	80–100
Chills, rigors	75–100
Headache, retro-orbital pain	50–100
Diaphoresis	40–100
Malaise	50–100
Weakness, fatigue	40–85
Anorexia	35–45
Weight loss ($\geq$ 7 kg)	50–80
Myalgias	45–85
Arthralgias	10–20
Chest pain	40–50
Cough	50–60
Sore throat	5–35
Nausea, vomiting	15–20
Diarrhea	5–20
Neck stiffness	5–7
Neurological signs	10–35

*Some report gradual onset; others, abrupt onset; coincidentally, the frequency is the same.

Data sources: (1) Robbins FC, Ragan CA. Q fever in the Mediterranean area: Report of its occurrence in Allied troops, I: Clinical features of the disease. *Am J Hyg*. 1946;44:6–22. (2) Feinstein M, Yesner R, Marks JL. Epidemics of Q fever among troops returning from Italy in the spring of 1945, I: Clinical aspects of the epidemic at Camp Patrick Henry, Virginia. *Am J Hyg*. 1946;44:72–87. (3) Marrie TJ, Langille D, Papukna V, Yates L. Truckin' pneumonia—An outbreak of Q fever in a truck repair plant probably due to aerosols from clothing contaminated by contact with a newborn kitten. *Epidem Inf*. 1989;102:119–127. (4) Langley JM, Marrie TJ, Covert A, et al. Poker players pneumonia: An urban outbreak of Q fever following exposure to a parturient cat. *N Engl J Med.* 1988;319:354–356. (5) Raoult D, Marrie TJ. State-of-the-art clinical lecture: Q fever. *Clin Inf Dis.* 1995;20:489–496. (6) Clark WH, Lennette EH, Railsback OC, Romer MS. Q fever in California. *Arch Intern Med*. 1951;88:155–161. (7) Dupont HT, Raoult D, Brouqui P, et al. Epidemiologic features and clinical presentation of acute Q fever in hospitalized patients: 323 French cases. *Am J Med*. 1992;93:427–434. (8) Tselentis Y, Gikas A, Kofteridis D, et al. Q fever in the Greek island of Crete: Epidemiologic, clinical, and therapeutic data from 98 cases. *Clin Inf Dis*. 1995;20:1311–1316.

facial pain resembling trigeminal neuralgia, diplopia, and dysarthria were also reported. Other manifestations involving the central nervous system, such as encephalitis, encephalomyelitis, optic neuritis, or myelopathy may also occur,[9,69,70] particularly late in the acute illness.

Physical findings in acute Q fever are as nonspecific as the clinical symptomatology. Rales are probably the most commonly observed physical finding; evidence of pleural effusion (including friction rub) and consolidation may also be noted, but not in the majority of infections. Although hepatomegaly, splenomegaly, jaundice, pharyngeal injection, and hepatic and splenic tenderness have all been reported, they are relatively unusual in acute infection.

Reports of abnormalities on chest X-ray examination vary with locale, but abnormalities are probably seen in 50% to 60% of patients.[71] An abnormal chest radiograph may be seen in the absence of pulmonary symptoms, while a normal chest radiograph may be observed in a patient with pulmonary symptoms. The most common abnormality observed in a recent report from England was a unilateral, homogenous infiltrate involving one or two lobes,[71] although lobar consolidation and pleural effusions[72] may also be seen. Rounded opacities and hilar adenopathy are not uncommon,[43] at least in Canada, and the diagnosis of Q fever should be at least be considered when these abnormalities are observed in the setting of acute pneumonia.

Laboratory abnormalities of routine tests most commonly involve tests of liver function, and patients with acute Q fever may present with a clinical picture of acute hepatitis. Depending on the locale, reported elevations of aspartate aminotransferase, alanine transferase, or both, in the range of 2- to 3-fold higher than the upper limit of normal, are observed in 50% to 75% of patients, while elevation of the alkaline phosphatase is observed in 10% to 15% of patients. The total bilirubin can be expected to be elevated in 10% to 15% of patients with acute Q fever. The white blood cell count is usually normal; the erythrocyte sedimentation rate is elevated in one third of patients.[65] Mild anemia or thrombocytopenia may also be observed.

Complications recorded in a recent outbreak involving 147 symptomatic cases of Q fever included 2 of acute endocarditis, 2 of renal failure, and 1 of reactive polyarthropathy.[65] Persistent nonspecific symptoms, such as fatigue and malaise, were reported in 32% of the patients in this series, while weight loss (defined as $\geq$ 7 kg) was identified in 71%, although none developed serologic evidence suggestive of chronic Q fever. An interesting epidemiological feature identified in the study was a significantly higher percentage of smokers in the affected group than in the general population of the area surveyed.

Chronic Q Fever

Chronic infection with *C burnetii* is usually manifested by infective endocarditis, which is also the most severe complication of Q fever. In addition, a report[73] from France of 92 cases published in 1993 also listed hepatitis, infected vascular prostheses and aneurysms, osteomyelitis, pulmonary infection, cutaneous infection, and an asymptomatic form. In addition, 7 of the 92 patients described in this report experienced fever only. Also noted was the observation that although 81% of patients had an identifiable risk factor, only 31% lived in a rural area. In addition, some form of immunodeficiency was observed in 20% of the patients, raising the possibility that chronic Q fever occurs as a result of reactivation of latent infection.[73] Inflammatory pseudotumor of the lung as a chronic complication of Q fever has also been reported.[74,75]

In Q fever endocarditis, fever has been recorded in 85% of patients, along with other systemic symptoms, such as chills, headache, myalgias, and weight loss, in a recent study[73] of 84 cases. Fever was not as prominent, however, in chronic compared to acute Q fever. Other frequently reported clinical features of Q fever endocarditis in this very large series included congestive heart failure (76%), splenomegaly (42%), hepatomegaly (41%), clubbing (21%), and cutaneous signs, often the result of a leukocytoclastic vasculitis (22%). Approximately 90% of patients in this study had preexisting valvular heart disease; more than half had a vascular prosthesis.

Routine blood cultures in Q fever endocarditis are negative, and Q fever should be considered when culture-negative endocarditis is encountered. The diagnosis of infective endocarditis secondary to Q fever is confirmed by serologic testing: antibody to Phase I organisms is usually higher than that for Phase II, and, more significantly, immunoglobulin A (IgA) antibody to *C burnetii* is also present.[76]

Diagnosis

Diagnosis of Q fever is usually accomplished by serologic testing because culture of *C burnetii* is potentially hazardous to laboratory personnel and requires animal inoculation or cell culture.

A number of serologic methods are used, including complement fixation (CF), indirect fluorescent antibody (IFA), macroagglutination and microagglutination, and enzyme-linked immunosorbent assay (ELISA). Significant antibody titers are usually not identifiable until 2 to 3 weeks into the illness. In 1987, the sensitivities of the different antibody assay methods were reported[77] as 94% for ELISA, 91% for IFA, and 78% for CF. Following infection, significant antibody titers may be present for years, particularly with more sensitive assays, such as the ELISA.

Of the methods currently utilized for the diagnosis of Q fever, the ELISA is the most sensitive and the easiest to perform. The utility of the ELISA for epidemiological screening and diagnosis of Q fever has recently been confirmed.[78] This assay, performed at the United States Army Research Institute of Infectious Diseases, Fort Detrick, Frederick, Maryland, can establish a diagnosis of acute Q fever from a single serum specimen, with a sensitivity of 80% to 84% in early convalescence and 100% in intermediate and late convalescence.[79] In general, antibodies to the rough Phase II organism are identified earlier in the illness, during the first few months following infection, followed by a decline in antibody to Phase II organisms and a rise in antibody to the smooth, virulent Phase I organism. Antibodies of the IgM type are usually observed within the first 6 to 12 months following infection, with persistence of IgG antibodies afterward.

Polymerase chain reaction (PCR) may also be useful in the future for the diagnosis of Q fever,[80–83] but remains to be validated in acute clinical cases.

TREATMENT

The treatment of Q fever was the subject of an excellent review that was published in 1993.[84] Tetracyclines have been the mainstay of therapy since the 1950s. When initiated within the first few days of illness, treatment with a tetracycline shortens the course of the disease. Attempted prophylaxis with a tetracycline (20 g of oxytetracycline administered over 5–6 d), however, has produced mixed results.[35] Initiation of the antibiotic early in the incubation period (24 h after exposure) merely prolonged the incubation period, while initiation of therapy late in the incubation period prevented the development of disease.

Macrolide antibiotics, such as erythromycin, are also effective for the treatment of acute Q fever.[72,85] A new macrolide, azithromycin, has also demonstrated efficacy in a few cases, but experience is very limited.[86]

When chronic Q fever infection is manifested by infective endocarditis, treatment is very difficult; the mortality is 24% even when patients receive appropriate treatment.[73] At least 2 years of therapy are required, usually with a tetracycline combined with rifampin or a quinolone, although trimethoprim-sulfamethoxazole has also been used.[84] Quinolones alone or in combination have also been effective. Most recently, the addition of hydroxychloroquine to tetracycline has shown promising results both in vitro[87] and in a small number of patients.[88]

PROPHYLAXIS

Q fever can be prevented by immunization. Vaccine prophylaxis for Q fever has been studied and used almost since the discovery that the responsible organism could be propagated in the yolk sac of eggs. Immunization with formalin-killed *C burnetii* confers protection against Q fever in laboratory personnel,[89] abattoir workers,[90,91] and human volunteers experimentally exposed to aerosolized *C burneti.*[92] In Australian abattoir workers, the results of efficacy studies were impressive: a single injection of 30 µg of vaccine antigen (Q-Vax, manufactured by CSL Ltd., Parkville, Victoria, Australia) conferred protective immunity that began 2 weeks after immunization and persisted for at least 5 years.[90] Protection depends primarily on cell-mediated immunity, the presence of which may be detected by positive skin test reactions and in vitro lymphocyte transformation in response to *C burnetii* antigen,[93] although these tests are not positive in all individuals previously infected with *C burnetii*.

These long-lasting indicators of cell-mediated immunity develop in most individuals after natural infection, but are also seen after immunization,[90,93] although to a lesser extent. Conversion from a negative lymphocyte proliferative response to a positive was observed in 11 (85%) of 13 of the individuals vaccinated.[93] In the same study, only 5 (38%) of 13 of vaccinated subjects seroconverted, and 31 (60%) of 52 developed a positive skin test following vaccination. Therefore, although the whole cell Q fever vaccine used in the Australian abattoirs confers protection, there does not appear to be a measurable response reliably associated with protective immunity.

C burnetii formalin-killed whole cell vaccines are generally well tolerated after subcutaneous injection, although some individuals develop severe local reactions at the site of injection. These reactions can involve formation of sterile abscesses that may drain spontaneously or may require surgical incision.[94] The incidence of severe, persistent local reactions is immunologically mediated by a delayed hypersensitivity response, resulting from previous natural infection with *C burnetii* or repeated immunization[92]; the risk of severe local reaction increases with the number of Q fever immunizations. This observation led to the development of an intradermal skin test using 0.02 µg of specific formalin-killed whole cell vaccine to detect presensitized or immune individuals.[95]

Severe local reactions to the vaccine were found to be associated with induration of 5 mm or larger at the skin test site by 7 days after inoculation. Although cumbersome, inconvenient, and costly, this prior screening procedure proved to be very effective in reducing the number of severe local reactions to Q fever vaccine. Subsequent experience with this skin test at the Rocky Mountain Laboratory in Montana showed that there were no severe local reactions in 80 individuals whose skin tests were negative when they were immunized with one or two doses of vaccine. Prior to the availability of skin test screening, severe local reactions occurred in 42 (45%) of 94 vaccinated individuals.[95] Additionally, in Australian abattoirs, more than 4,000 individuals whose skin tests were negative received the formalin-killed vaccine during the course of vaccine efficacy studies, and of these, only 1 developed a significant chronic reaction.[90] The advisability of prior skin testing was further reinforced when severe local reactions were observed in 3 of 10 individuals with a positive skin test to *C burnetii* antigen who mistakenly received a single dose of vaccine.[96]

Although an effective Q fever vaccine is licensed in Australia, all Q fever vaccines used in the United States are currently investigational. Certain groups of individuals should be considered for vaccine prophylaxis, including the following:

- veterinarians, veterinary technicians, and animal care workers who may come into contact with *C burnetii*–infected animals, particularly pregnant animals;
- laboratory investigators, technicians, and other personnel who perform research on live *C burnetii* organisms; and
- abattoir workers who have contact with cattle, sheep, or goats (particularly pregnant animals) that may be infected with *C burnetii*.

Research efforts are currently underway to develop a Q fever vaccine that is safe to administer to anyone, including Q fever–immune individuals. The residue of *C burnetii* organisms following chloroform-methanol extraction (CMR vaccine) has been tested for safety in nonimmune volunteers[97] and is currently being tested for safety in Q fever–immune individuals. Antibiotic prophylaxis of Q fever has been tested with a tetracycline, as was discussed in the treatment section of this chapter.

SUMMARY

Q fever, a zoonotic disease caused by the rickettsia-like organism *Coxiella burnetii*, is important to military medicine primarily because of its exceptional infectivity. The disease is transmitted mainly by inhalation of infected aerosols, and a single organism may cause infection in humans. The disease is worldwide in distribution; the primary reservoir for human infection is livestock, particularly goats, sheep, and cattle. Contact with parturient animals or products of conception poses especially high risk, since the organism is present in very high numbers in this setting. The organism is also very resistant to pressure and desiccation, and may persist in a sporelike form in the environment for months after the source has left the area.

Diagnosis of Q fever is performed by serologic testing. Treatment with tetracyclines is effective. Prevention is possible with a formalin-killed, whole-cell vaccine, but prior skin testing to exclude immune individuals is necessary to avoid severe local reactions to the vaccine. A Q fever vaccine is licensed in Australia, but not in the United States, where all Q fever vaccines are investigational.

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RECOMMENDED READING

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Marrie TJ, ed. *Q Fever: The Disease*. Vol 1. Boca Raton, Fla: CRC Press; 1990.

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